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Dedication

To my mother and father, my wife Heather, and our children Elaina, Alex, and Will for their love and inspiration.
— Habib Samady

Thank you to my wife, Yvonne, for her continued love and support!
— William F. Fearon

Thank you to my wife, Elene, and my children for their support!
— Alan C. Yeung

Thanks to my wife, Gail, and my colleagues at Emory and Stanford Universities.
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It is with great pleasure that I introduce a superb addition to the “modern era” cardiovascular educational literature, the Second Edition of Interventional Cardiology, co-edited by Drs. Samady, Fearon, Yeung, and King. This updated and comprehensive textbook brings to life the full breadth of interventional cardiovascular medicine. It will become a mandatory resource for the broad community of healthcare professionals in this expanding and evolving subspecialty.

During the 40th year anniversary of the first PCTA and the 15th year anniversary of the first TAVR, it is timely to reflect on the dramatic changes that have shaped interventional cardiology over time. The original dream of Andreas Gruentzig in 1977 was to achieve catheter-based percutaneous treatment of vascular disease in alert, awake patients, a dream that was considered heresy by some and fanciful by most cogent observers. Over four decades of determined iteration, refinement, and innovation, the use of less invasive, transcatheter (non-surgical) diagnosis, and therapy has transformed medicine. To extend Gruentzig’s dream to widespread clinical practice required: (1) an evolution in technologies (from balloons to stents with local drug delivery); (2) the development of clinical research methodologies (evidence-based clinical trials and resulting society guidelines); (3) improvements in operator skills with a focus on life-long training; (4) the adoption of new practice management strategies (including optimal use of adjunctive pharmacotherapy and the application of diagnostic intravascular imaging and physiology to direct therapy decisions); (5) an expansion of interventional concepts to new nonvascular clinical targets such as structural heart disease (best embodied by the TAVR breakthrough technology); and (6) acceptance that a multi-disciplinary Heart Team approach should become the standard for optimal diagnosis and treatment of patients with complex cardiovascular disease.

This revised textbook Interventional Cardiology captures the aforementioned evolutionary journey with carefully organized content that is well illustrated and referenced and emphasizes practical aspects of
procedures, techniques, therapies, and clinical care pathways. The 9 sections and 78 chapters provide a remarkable in-depth compendium of the essential body of knowledge in interventional cardiology through 2017. Moreover, important ancillary topics such as medical management of risk factors, an understanding of evidence-based clinical trials, reimbursement and socioeconomic issues, and the principles of interventional device innovation are thoughtfully addressed. The co-editors of this impressive Second Edition of *Interventional Cardiology* should be congratulated for amassing a landmark reference that represents the most up-to-date, all-inclusive, and practical resource of its kind, which undoubtedly will be embraced by interventionalists around the world.

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The first edition of this textbook was published 10 years ago because Alan Yeung and I recognized that the field of interventional cardiology had matured enough to warrant a comprehensive exploration of the discipline. I was serving as chair of the writing group for the American Board of Internal Medicine Interventional Cardiology board at the time and was aware that the questions that we were asking needed a text that could provide answers from experts who were generating those answers. Alan succeeded me as chair of the board test writing group, and the job has increased greatly because of the expansion of the discipline.

To collate much of the current knowledge pertinent to interventional cardiology, we now have enlisted two of our colleagues, Habib Samady and Bill Fearon, who have become leaders in the specialty, to join us in updating or, more appropriately, redoing *Interventional Cardiology*. Of course, no textbook can provide the latest trial results, and in the age of information technology, some even question the value of textbooks. As an editor of *JACC: Cardiovascular Interventions*, I have often said that review papers should be different from book chapters. This is true but should not denigrate book chapters. A book chapter on a targeted subject forces authors to concisely focus attention to what they perceive to be the pertinent knowledge base about that subject. That base of knowledge is necessary if results of new findings are to be correctly interpreted and their influence on practice properly evaluated. History teaches us that we must know what went on before if we are to understand the present. This is the purpose of this book: to provide the current base of knowledge that is necessary but not completely sufficient to become an expert in interventional cardiovascular medicine. To become and remain an expert requires not only the current knowledge but also the continued learning from new evidence. To that end, this book will be accompanied by periodic updates that will be available electronically. We believe that new evidence in isolation, without the background, may often be misleading.

The book is organized into nine sections with chapters geared to the
current needs thoughtfully chosen by the chapter authors. Each chapter is followed by a set of questions that focus on the main points of the topic addressed by the chapter. These questions are not intended to replace courses specifically targeted to the objective of preparing for examinations. Nonetheless, we believe that this method of asking what we have learned from a discussion is a helpful tool. Growth in interventional cardiology training and practice is perhaps best reflected in the largest section of the book, which deals with interventional procedures. In this section, 29 chapters in the first edition have increased to 38 chapters with expanded coverage of radial approach, chronic total occlusion intervention methods, and structural heart disease interventions. New chapters on the MitraClip procedure and atrial appendage occlusion, and three chapters covering patient selection and procedural techniques for transcatheter aortic valve implantation headline all the amazing advances that have occurred in the treatment of structural heart disease. Likewise, important advances in peripheral vascular interventions are emphasized. More than other digestible sources, this book also provides concise explanations of evolving concepts in intravascular physiology and imaging that inform current practice and underlie research and development efforts in stenting and bioabsorbable scaffold technology, as well as evolving pharmacological approaches to control thrombosis, restenosis, and neoatherosclerosis. There are other expanded chapters on healthcare economics and methods for achieving innovation.

This book is intended for all who are being trained in the discipline of interventional cardiology as well as those who practice this specialty and have trouble remembering all the background that relates to the patient whom they are currently treating. (Certainly true for many of us.) The perspectives of the carefully selected authors of these chapters will frequently be of value in making current judgments. In addition, any physician who wants to know the astonishing possibilities of, as well as the limitations of, interventional cardiology will benefit by referring to this volume for guidance.

Spencer B. King III, MD
Part I Knowledge Foundation

1. History of Interventional Cardiology
2. Coronary Anatomy for the Interventionalist
3. Cardiac Anatomy for the Interventionalist
4. Anatomy of Cardiac Valves for the Interventionalist
5. Peripheral Anatomy for the Interventionist
6. The Coronary Circulation
7. Hemodynamic Assessment of Renal Artery Stenosis
8. Valvular Pathophysiology
9. Arterial Disease
10. Ventricular Pathophysiology
History of Interventional Cardiology

Brian W. Kaebnick
Bill D. Gogas
Spencer B. King III

INTRODUCTION

Surveying the landscape of interventional cardiology today, one sees a mature discipline using sophisticated technology and techniques that are backed by the findings of rigorous clinical trials. Many advancements have occurred in the field since the first angioplasty performed by Andreas Gruentzig in 1977. What began as a technique to treat a focal stenosis in patients with stable angina by physicians who performed diagnostic cardiac catheterizations has progressed to complex percutaneous interventions in unstable patients by highly trained and experienced operators. The work in coronary interventions also served as a catalyst for the development of therapies and technology to treat valvular heart disease with percutaneous valve replacement and repair. Understanding the history and development of interventional cardiology provides important insight and perspective to appreciate current practices as well as provide inspiration for future advancement of the field.

EARLY DEVELOPMENTS IN INVASIVE CARDIOLOGY
Many individual achievements provided the foundation for the development of interventional cardiology (Fig. 1-1). Werner Forssmann is credited as performing the first human cardiac catheterization in 1929 while working in Eberswalde, Germany.\(^1\) He was inspired by the works of French physiologists Bernard, Chauveau, and Marey, who measured the intracardiac pressures in horses by directly inserting catheters into the heart. He hypothesized that accessing the heart directly with a catheter would provide a safer mechanism to deliver therapeutic drugs. Unfortunately, he did not have the support of his department chief, who thought such a procedure was reckless and likely fatal. Despite his chief’s disapproval, he was unrelenting in his pursuit and decided to perform the procedure on himself. With the help of an unsuspecting nurse, he cut down to his left brachial vein and inserted a urinary catheter as far as it would go.
He then traveled with the nurse to the basement where the x-ray machine was located and documented the catheter location in the right atrium. His self-experimentation resulted in disciplinary action, and as a result, Forssmann was not able to pursue any further study on the subject.²

Much of the development of right heart catheterization and hemodynamic assessment is credited to the work of Andre Cournand and Dickinson Richards at Bellevue Hospital in New York, which resulted in a 1956 Nobel Prize in Medicine that was shared with Forssmann.

Refinements in right heart catheterization over the next 2 decades eventually led to the desire to better understand left heart hemodynamics and
valvular function through catheterization. After working out much of the
details of accessing the left ventricle in a canine model, Henry Zimmerman
performed the first left heart catheterization on a human in 1950 via a radial
artery approach in Cleveland, Ohio. Early left heart catheterizations
consisted of hemodynamic assessments and injection of contrast into the
ventricle and aorta to assess left ventricular function and valvular disease.
The coronary arteries were indirectly assessed by these methods but were not
adequate for diagnostic quality. The concern was that the contrast media
would cause ischemia and ventricular fibrillation. The need to obtain
diagnostic assessment of coronary blockages, however, was becoming more
important with the advent of coronary artery bypass surgery.

Interestingly, the first direct coronary angiography occurred by mistake in
1958. While performing a routine left heart catheterization at the Cleveland
Clinic, Mason Sones pulled back across the aortic valve and prepared for an
aortogram. As the injection started, Dr. Sones noted the catheter tip was
directly engaged in the right coronary artery and filled the vessel with viscous
diatrizoic acid (Hypaque) contrast media before the catheter was able to be
removed. Fortunately, the patient did not develop ventricular fibrillation but
rather asystole, which was converted to sinus rhythm by having the patient
cough 3 or 4 times. Despite this near-fatal complication, Dr. Sones saw the
potential need for diagnostic angiography and was instrumental in developing
techniques to access and visualize coronary arteries.5,6

DEVELOPMENT OF ANGIOPLASTY

Up to this point in the mid-20th century, advancements in invasive
cardiology had been diagnostic, which still left therapies for coronary artery
and valvular disease in the hands of the surgeons while cardiologists
watched. This relationship, however, would soon change thanks to a
determined and somewhat controversial figure, Charles Dotter. A radiologist
by training, Dotter was well published in the field of angiocardiography and,
by age 32, was professor and chairman of the radiology department at
University of Oregon Medical School. He entered into the field of
interventional radiology by coincidence while attempting an abdominal
aortogram for an assessment of renal artery stenosis in 1963. Dotter advanced
his catheter through a stenotic right iliac artery in order to reach the aorta and,
in the process, recanalized the artery. He presented his findings at the Czechoslovak Radiologic Conference in June 1963 to a very receptive audience, where he concluded “the angiographic catheter can be more than a tool for passive means for diagnostic observation.”

He would return to the United States to further refine his technique of “Dottering” stenotic vessels with Melvin Judkins by designing specialized catheters to serially dilate stenotic lesions. His methods were not well received by surgeons in the United States despite successfully treating many patients and saving them from limb amputation. Even though Dotter had little support back home, his techniques were championed by Werner Porstmann in Berlin and Eberhard Zeitler in Engelskirchen, Germany. Zeitler would later teach Andreas Gruentzig this technique, who would go on to adapt the concept to coronary arteries.

Andreas Gruentzig’s initial training after medical school was in the field of epidemiology, but he soon became interested in peripheral vascular disease while studying at the Ratchow Clinic in Darmstadt, Germany. During his training, he became interested in Dotter’s technique in treating stenotic vessels. Gruentzig then moved to Zurich, Switzerland, to accept a position in the angiology department at the University Hospital. He quickly set out to begin the Dotter technique and invited Zeitler to Zurich to help perform his first dilation.

Despite embolizing plaque to the distal leg and obstructing flow, Gruentzig remained convinced of the promise of the procedure to treat atherosclerosis not only in the peripheral arteries but also in the heart. He recognized that the coronary arteries posed a much different challenge than the large and relatively straight peripheral vessels and that another technique besides serially dilating with a catheter was needed. Gruentzig’s answer to this challenge was a slender, steerable balloon-tipped catheter that could be inflated to expand the lesion.

He set out to design his catheter with his assistant Maria Schlumpf. Early attempts to construct the catheter took place at his kitchen table with the help of Maria’s husband, Walter, and Gruentzig’s wife, Michaela. He soon consulted with Dr. Hoph, a professor of chemistry at University of Zurich, who advised Gruentzig to use polyvinyl chloride to construct his balloon in order to maintain its desired shape and size. After some initial homemade prototypes, Gruentzig partnered with Schneider Needle Company to manufacture his balloon catheter. He tested his catheter in a dog model where
the discrete stenosis in the artery was created with silk ligature. Gruentzig was able to use his catheter to cross the stenosis and perform a balloon dilation to successfully treat the stenosis. He presented this proof of concept at the 1976 American Heart Association meeting to a lackluster response\(^{10}\) (Fig. 1-2).
Undeterred, Gruentzig was determined to use his technique to treat heart disease in humans and tried unsuccessfully to convince surgeons in Zurich to allow him to try his balloon angioplasty technique on patients undergoing bypass surgery. He eventually partnered with a cardiologist, Richard Myler, in San Francisco at St. Mary’s Hospital, who persuaded the cardiac surgeon, Elias Hanna, to test his procedure. After successfully performing the procedure in humans, Gruentzig returned to Zurich to treat patients in hopes of avoiding bypass surgery. His initial attempt was on a patient with complex disease, as well as severe peripheral vascular disease, which his catheter was not able to navigate, and the procedure was aborted. This setback illustrated the need for better lesion and patient selection to ensure success of this new procedure, and thus, Gruentzig started looking for lower risk patients without complex disease.

He soon found his next patient—a 38-year-old man with severe angina and a proximal discrete lesion. After discussing the experimental nature of the procedure with the patient and getting his consent, Gruentzig successfully performed his first balloon angioplasty procedure on September 16, 1977. The patient’s angina was successfully treated, and the patient did well after his procedure. The patient even underwent a follow-up heart catheterization in 1987 that demonstrated a patent vessel free of residual stenosis. Gruentzig successfully performed 4 more balloon angioplasties and presented his case series at the 1977 American Heart Association meeting. This meeting was a much different experience than the 1976 meeting; he presented to packed house and received a standing ovation. He would publish his early findings in *The Lancet* as a Letter to the Editor in February 1978.11

**EARLY ADOPTION OF BALLOON ANGIOPLASTY**

The success of Gruentzig’s balloon angioplasty technique ushered in a paradigm shift in approaching coronary disease, and cardiologists and
radiologists from around the world came to Zurich to learn the technique. Gruentzig knew that in order for his idea to remain successful that his technique must be properly taught to skilled operators rather than disseminated to the masses. He was worried that if careless physicians performed his procedure then fatal outcomes would doom his idea. Thus, Gruentzig established his first teaching course in 1978, where 28 physicians traveled to Zurich to watch him perform cases. While at the course, physicians learned how to perform the procedure, but just as important, they also were educated on the complications, pitfalls, and tricks to rescue a procedure. Gruentzig continued his teaching courses in Zurich, until he was recruited to come to Emory University, where his courses were continued until his untimely death in 1985 and beyond. Many other courses were also created to train the early adaptors of angioplasty. The first balloon angioplasties in the United States occurred simultaneously in San Francisco by Richard Myler and in New York by Simon Stertzer, so that neither individual would be the first to perform the procedure.12

As more physicians were taught balloon angioplasty and brought the technique to their practice, the equipment and techniques began to evolve to overcome some of the limitations of the procedure. Tortuous vessels and the inability to recross a lesion that had shut down during inflation led to the development of over-the-wire systems. John Simpson took this idea further by first crossing the lesion with a wire and then advancing the balloon over the wire. This allowed for the development of lower profile balloons and expanded the technique to stenosis in distal segments. As the technology and operator experience advanced, so did the success of the procedure as well as its ability to challenge bypass surgery. However, there had not been any definitive evidence to compare angioplasty to bypass surgery, a proven therapy. All the evidence for angioplasty consisted of an international registry established by the National Heart, Lung, and Blood Institute (NHLBI). To better understand the optimal treatment of coronary disease, the NHLBI awarded the first randomized controlled trial comparing angioplasty to bypass surgery in 1987.13

The Emory Angioplasty Versus Surgery Trial (EAST) demonstrated equivalent survival rates at 3 and 8 years.14 The EAST trial was followed by the Bypass Angioplasty Revascularization Investigation (BARI) trial, which also demonstrated no significant difference in mortality between the 2 procedures at 5 and 10 years.15-17 The only clinical difference was in the
revascularization rate after intervention, which was high for angioplasty. Despite this difference, these trials suggested that angioplasty was a safe and effective treatment for stable coronary disease.

As a result of the building evidence for balloon angioplasty in stable disease, Jurgen Meyer began investigating its use in acute coronary syndromes. Initially, it was used as an elective procedure performed to treat angina resulting from a residual stenosis after a myocardial infarction or as a rescue therapy for patients who failed thrombolysis. Geoffrey Hartzler then went on to use balloon angioplasty as an alternative to thrombolytic therapy, setting up later trials such as Primary Angioplasty in Myocardial Infarction (PAMI) and Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb), which demonstrated a mortality improvement with angioplasty.\textsuperscript{19,20}

**TECHNOLOGICAL ADVANCEMENTS**

Although the concept of percutaneous intervention with balloon angioplasty was being expanded to more complex lesions, multivessel disease, and acute coronary syndrome, the procedure was not without limitations. Acute complications during the procedure such as vessel dissection and acute closure could occasionally be treated percutaneously with long balloon inflations; however, up to 12% of patients required urgent bypass surgery to rescue the vessel.\textsuperscript{21} Additionally, residual vessel stenosis and restenosis often required repeat interventions and prevented long-term success. These issues drove the need for an adjunctive therapy to help keep the vessel open. Although many new devices were developed for opening coronary obstructions, including atherectomy devices and lasers, they did not materially improve on the balloon. The idea of an endovascular scaffold or stent to maintain vessel patency was thought to be the best solution. Thus, multiple groups concurrently pursued the development of first-generation stent design across the world.

In the United States, an Argentinian-trained radiologist, Julio Palmaz, was inspired to develop a solution to the procedural failures of balloon angioplasty after attending a talk given by Gruentzig at the Society of Interventional Radiology meeting in New Orleans in 1978. He was further exposed to the balloon angioplasty equipment while training at University of
California at Davis, where he would wash the balloons after the procedures. After training, he took a position in San Antonio, Texas, where he had dedicated research time to further develop his stent idea. There, he was introduced to interventional cardiologist Richard Schatz, who helped refine his idea by suggesting an articulation connection of 2 stents to make the device more flexible. The first human implant of the Palmaz-Schatz stent occurred in Brazil in 1986. The stent was further studied in Europe in the BENESTENT and STRESS trials, which demonstrated a reduction of restenosis from 42% to 32%.\textsuperscript{22,23} The US Food and Drug Administration (FDA) gave initial approval to the Palmaz-Schatz stent in 1994 for short lesions in large-caliber vessels >3 mm, but its indications were eventually expanded to smaller vessels, vein grafts, and longer lesions.

In Europe, while working at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, Ulrich Sigwart developed a woven self-expanding helical stent inspired by Chinese finger traps.\textsuperscript{24} This stent was eventually implanted in a patient in 1986 by Dr. Sigwart and Jacques Puel. Further use and development of this stent was put on hold, as Sigwart partnered with MedInvent, a subsidiary of Pfizer, which was currently dealing with ongoing valve failures with their Bjork-Shiley valve. This issue led Sigwart to partner with another company, ACS, and eventually develop a balloon-expandable stent, Multilink, which was more deliverable and steerable. The first human implant of the Multilink stent occurred in London in 1993; the Multilink was approved by the FDA in 1997 and, with slight modifications, is still in use today.

In the United States, Cesare Gianturco, an interventional radiologist, had already worked with Cook Inc. to develop a balloon-expandable coil stent to be used in peripheral arteries. He was interested in applying his coil stent design technology to coronary arteries. In our experimental lab, Gary Roubin and Keith Robinson at the Gruentzig Center tested his stent design in porcine coronary arteries.\textsuperscript{25} The first implant of his stent occurred at Emory Hospital in 1987 as part of a proposal submitted to the FDA for early feasibility. The proposal was designed for the coil stent to be used to treat patients with acute vessel closure during balloon angioplasty rather than sending to emergent bypass surgery. Based on the results of this proposal as well as other studies, the FDA approved commercial use of the stent in 1993.

Despite the success of stents to improve restenosis rate and treat acute closure of the arteries to avoid emergent bypass surgery, the early use of
stents, regardless of design, was plagued by acute stent thrombosis, which limited the widespread adaptation this new technology. To combat this issue, patients were maintained on heparin infusion and transitioned to aspirin and warfarin therapy, which often led to patients having a prolonged hospital course after stenting. Eventually, the strategy of dual antiplatelet therapy was established as the preferred method to prevent stent thrombosis in the mid-1990s.

Ticlopidine was initially used with aspirin, but hematologic disorders such as thrombotic thrombocytopenia purpura and neutropenia limited its use. Fortunately, clopidogrel was approved in 1997 and largely replaced ticlopidine.

In addition to better medical therapy, better procedural techniques and technology resulted in the understanding that stent underexpansion and malapposition were also key factors leading to stent thrombosis. Work by Antonio Colombo of Milan, Italy, and Jonathan Tobis from the University of California demonstrated that high-pressure poststent dilations led to better expansion and less malapposition within the vessel and reduced stent thrombosis risk. The development of intravascular ultrasound allowed for a better assessment of stent expansion and also helped reduce the risk of stent thrombosis.

Vessel restenosis due to intimal hyperplasia still remained a problem, even with properly deployed stents. Initial attempts to combat this process involved the use of radiation in the form of brachytherapy. This technique worked but was cumbersome due to the difficulty of handling radioactive materials in the catheterization lab. The concept then shifted to antiproliferative drugs applied to the stent itself. Many agents were tried to inhibit cell growth but failed to prevent restenosis. These included coating the stent with gold, silicon carbide, and hormone receptor blockers.

Eventually, sirolimus and paclitaxel were found to be effective agents to be applied to stents. The first drug-eluting stent, which was coated with sirolimus, was implanted in 1987. This stent would be further developed into the Cypher Stent (Cordis, San Francisco, CA) and gained approval for clinical use in 2002. Along with the Taxus Stent (Boston Scientific, Marlborough, MA), first-generation drug-eluting stents were compared to bare metal stents and were found to have a decreased rate of in-stent restenosis as well as need for revascularization.
Further advancements in stent technology resulted in more effective agents, such as everolimus and zotarolimus, as well as better techniques in applying the drug to further improve long-term outcomes. Stent technology continues to progress with development of fully resorbable stents called bioresorbable scaffolds.\textsuperscript{33}

**EVOLUTION OF STRUCTURAL CARDIOLOGY**

As the discipline of coronary intervention evolved so did the explorations into transcatheter approaches to valvular diseases. Rubio-Alvares and Limon-Lason performed the first valve intervention in 1952 in Mexico at the Instituto de Cardiologia using a ureteral catheter and a guitar string to slice open a stenosed pulmonary valve.\textsuperscript{34} The idea of catheter-based therapy remained dormant until 1979 when Dr. Semb used a balloon-tipped catheter to perform a balloon valvulotomy of the pulmonic valve.\textsuperscript{35} The concept of balloon angioplasty was later used by Jean Kan at Johns Hopkins University to further refine and develop a dedicated catheter to dilate the valve. Bulldogs served as an animal model due to the breed-specific high rate of congenital pulmonic stenosis. The first human valvuloplasty occurred in 1982, and valvuloplasty has since gone on to be the preferred initial treatment of isolated pulmonic stenosis. Based on the success of pulmonary valvuloplasty, the concept of balloon valvuloplasty was quickly adapted to other stenotic valves.\textsuperscript{36}

Approaching the mitral valve was more challenging due to lack of a direct route like the pulmonary valve. Initially, in 1984, Kanji Inoue used a surgical approach to dilate a stenotic mitral valve with good results. Percutaneous access to the left atrium was first developed by Constantine Cope in 1959 at the New Jersey Veterans Affairs Hospital and was later refined to treat transposition of the great arteries by William Rashkind and William Miller at Children’s Hospital of Philadelphia.\textsuperscript{37} James Lock adapted these techniques to perform the first mitral valvuloplasty procedure in 1984.\textsuperscript{38} Similar to pulmonary valvuloplasty, mitral valvuloplasty has become the preferred initial treatment for rheumatic mitral stenosis over surgery.

Unfortunately, the success of valvuloplasty experienced in the pulmonary
and mitral valves did not translate to treating degenerative calcific aortic valve stenosis. Alain Cribier at the Charles Nicole University in Rouen, France, performed the first aortic balloon valvuloplasty in 1985. 39 Although there was initial improvement in patients, the longevity of the result was impaired by early restenosis and poor long-term survival if surgery was not performed. To effectively treat this disease, more advanced technology would need to be developed. 40

Just as early angioplasty spurred the development of new technology, valvuloplasty has led to new technology to replace and repair dysfunctional valves. Again, the pulmonary valve led a new wave of innovating transcatheter valve replacement therapy. Philipp Bonhoeffer performed the first pulmonary valve replacement in 2000 using a large bovine jugular vein sutured to a platinum stent frame, a precursor to the Medtronic Melody Valve (Medtronic, Edgewater, MD). 41 In a similar fashion, Cribier used his experience in aortic valvuloplasty to develop a balloon-expandable stented valve as a more definitive therapy to treat aortic stenosis. He performed the first transcatheter aortic valve replacement (TAVR) in 2002 using a valve design that would later evolve into the Edwards Sapien Valve (Edwards Lifesciences, Irvine, CA). 42 Based on the PARTNER trial, the Sapien valve achieved commercial use for inoperable patients in 2011 and for high-risk patients in 2012. 43 Currently, the Edwards Sapien Valve and Medtronic CoreValve are among those commercially available for TAVR, with many more valve designs being studied in clinical trials.

Although rheumatic mitral stenosis could be treated with balloon valvuloplasty, mitral regurgitation presented a much more complex pathology to treat. Because the mitral valve has a more complex saddle-shaped anatomy, initial attempts to treat mitral regurgitation investigated methods to repair the valve. Despite many different attempts to percutaneously repair the mitral valve since the 1990s, there remains only 1 commercially available device. The MitraClip (Abbott Vascular, Santa Clara, CA) is based on a surgical edge-to-edge mitral valve repair technique known as the Alfieri stitch. The device approaches the mitral valve from a transseptal puncture and attaches a clip to the anterior and posterior valve leaflets to secure a prolapsed or failed valve segment, thus reducing regurgitation. 44 The MitraClip became commercially available to treat surgically high-risk patients with degenerative mitral valve regurgitation in 2013 after
demonstrating reduction in mitral regurgitation and equivalent survival to surgical repair in the EVEREST and EVEREST II trials.\textsuperscript{45,46} There are no transcatheter mitral valve replacement therapies commercially available; however, there are currently many devices undergoing early feasibility trials in humans.

**INTERVENTIONAL CARDIOLOGY AS A DISCIPLINE**

Initially, the field of interventional cardiology was self-regulated and available only to those who went to one of Gruentzig’s training courses and acquired an angioplasty balloon catheter. As new technology developed outside the control of Gruentzig, the procedure became available to all cardiologists. In 1988 and 1993, the American College of Cardiology issued the first set of guidelines, including indications for balloon angioplasty as well as approximate activity levels needed to maintain competence. As the field continued to expand in the 1990s, so did the knowledge base and skill set needed to be proficient in the discipline. In response to this growth, in 1998, the American Board of Internal Medicine (ABIM) approved the Certificate of Added Qualification in Interventional Cardiology, which required completion of 1 year of additional training within an ABIM-approved fellowship program with a separate board examination.

In addition to the need for specialized training and examinations, new journals, societies, and meetings were created to be resources for continued advancement and education. Many of the first-tier journals quickly developed subspecialty journals, with the first issues of *JACC: Cardiovascular Interventions* and *Circulation: Cardiovascular Interventions* appearing in 2008. These journals, and others, continue to document the continued advancements in the field.

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A thorough knowledge of normal and abnormal coronary anatomy is essential for the interventional cardiologist. The direct application of this knowledge base helps in the selection of the appropriate catheter for coronary engagement in both diagnostic and intervention procedures. Knowledge of anatomy also facilitates the selection and interpretation of angiographic views during cardiac catheterization. Finally, because interventional therapy may be needed in several unusual circumstances, a working knowledge of coronary artery anomalies is also essential. This chapter addresses coronary artery anatomy and related technical issues pertinent to the interventional cardiologist.

NORMAL CORONARY ANATOMY

The coronary arterial system can be divided into the large vessels, or the epicardial coronary arteries, and the small vessels, or the microvasculature. The microvasculature consists of arterioles, which measure less than 200 μm and are poorly visualized with routine coronary angiography. These arterioles feed a broad capillary network that delivers oxygenated blood to the myocardium. They also regulate coronary pressure and flow through their ability to vasodilate and constrict in response to a variety of stimuli. The importance of the microvasculature in determining patient outcomes in both
the acute setting, such as myocardial infarction, and the chronic setting has been highlighted.¹

**The Left Coronary Artery**

Both the right and left coronary artery ostia arise from their respective aortic sinuses. Both ostia are located more than half the distance between the sinotubular junction and aortic valve annulus (Fig. 2-1). The left main coronary artery originates with an elliptic ostium measuring approximately 3.2 ± 1.1 mm × 4.7 ± 1.2 mm.² This coronary artery continues at an acute angle and travels parallel to the aortic sinus wall, coursing between the pulmonary artery and the left atrium in the region of the left atrial appendage. The length of the left main artery ranges from 0 mm (“double-barrel ostium”) to 20 mm. However, in most cases, the length of the left main coronary artery is between 6 and 15 mm, with an average diameter ranging from 3 to 6 mm.³ In two-thirds of cases, the left main coronary artery bifurcates into the left anterior descending (LAD) and circumflex arteries (Fig. 2-2); in one-third of cases, it trifurcates into the LAD artery, the circumflex artery, and a ramus intermedius artery, which follows a course similar to either the first diagonal artery from the LAD artery or first obtuse marginal artery from the circumflex.⁴

**FIGURE 2-1** Anterior (A) and posterior (B) view of the coronary arterial and venous system. AIV, anterior interventricular vein; CFX, circumflex coronary artery; CS, coronary sinus; GCV, great cardiac vein; LAD, left anterior descending artery; MCV,
middle cardiac vein; PDA, posterior descending artery; RCA, right coronary artery; SCV, small cardiac vein.
The LAD artery follows the anterior interventricular sulcus and may pass around the cardiac apex. When it passes around the apex, the LAD travels along the posterior interventricular sulcus and can anastomose with branches from the posterior descending branch of the right coronary artery. The LAD artery has characteristic septal perforating branches that serve the anterior two-thirds and the infra-apical portions of the ventricular septum. A common anatomic variant occurs when the LAD artery terminates before reaching the cardiac apex. In these cases, a large diagonal artery or an unusually large posterior descending artery from the right coronary artery should be anticipated to be present and provide the necessary left ventricular perfusion.

In addition to septal perforators, the next major branches of the LAD artery are the diagonal arteries, which course along the anterolateral free wall of the left ventricle in a diagonal fashion, hence the name. On average, two major diagonal arteries are present, although smaller diagonal vessels can be identified. In addition, small ventricular branches from the LAD can form an anastomotic network with similar branches from the proximal right coronary artery.

The circumflex coronary artery arises at an acute angle from the left main coronary artery and travels in the epicardial fat pad beneath the left atrial appendage, coursing through the left atrioventricular (AV) sulcus. When a posterior descending artery (PDA) arises from the distal circumflex artery, the coronary circulation is defined as either left dominant or codominant. A “codominant” coronary artery system is one in which a PDA arises from both the right and circumflex coronary arteries. Codominant coronary artery systems, seen in less than 10% of patients, are usually characterized by smallish PDA branches, which perfuse the posterior interventricular sulcus toward the apex of the heart. The circumflex artery gives rise to as many as three obtuse marginal arteries that supply the left ventricular lateral wall. In more than 80% of patients, the left circumflex artery transitions to a smaller AV groove artery, which is considered the distal continuation of the true
circumflex artery. Usually, this artery does not pass the crux cordis, but in the 10% of cases with a left-dominant coronary circulation, the AV groove branch is large and of similar diameter to the main circumflex artery, giving rise to both posterolateral branches and a left posterior descending branch.\textsuperscript{8}

**The Right Coronary Artery**

The right coronary artery originates from the right sinus of Valsalva and follows the right AV sulcus around the acute margin of the heart, giving off several major branches (Fig. 2-3). The conus artery is the first major branch, with a separate ostium from the aorta in 50% of cases. The sinoatrial nodal artery is the second major branch, arising from the right coronary artery in 60% of cases and from the left circumflex artery in 40% of cases.\textsuperscript{5}
FIGURE 2-3  A. A dominant left coronary artery in the left anterior oblique and cranial projection showing the continuation of the circumflex, which then gives off posterolateral left ventricular branches and the posterior descending artery. B. A nondominant right coronary artery (RCA) in the right anterior oblique projection demonstrating a right ventricular (RV) marginal branch but no posterior descending or posterolateral left ventricular branches. LAD, left anterior descending artery.

The acute marginal branches of the right coronary artery arise from the proximal to midportion of the vessel, supply the free wall of the right ventricle, and often anastomose to smaller branches of the LAD artery. The distal right coronary artery follows the posterior interventricular sulcus where it bifurcates into the PDA (in 90% of patients) and major posterolateral branches. The PDA continues in the posterior interventricular sulcus and usually terminates in the region of the cardiac apex. The posterolateral artery, a continuation of the right coronary artery, continues in the AV sulcus to the crux of the heart, frequently giving rise to the AV nodal artery. Finally, the posterolateral artery terminates in two or three branches that course toward the cardiac apex. When the right coronary artery is nondominant, it may terminate in the region of the acute margin of the heart (see Fig. 2-3). In the situation of total LAD artery occlusion, many of the branches of the right coronary artery may give rise to LAD artery collateral vessels. The right coronary conus branch artery may become clinically significant when the LAD artery is occluded proximally. In addition, the acute marginal branches of the right coronary artery anastomose with marginal branches from the circumflex artery as well as the septal perforating branches from the LAD artery. The PDA gives rise to branches that anastomose with the distal branches of the LAD artery. This angiographic visualization of the distal LAD artery by collateral arteries is especially important when performing interventions on chronic total occlusions of that artery. Likewise, the distal segments of the right coronary artery can often be visualized by left coronary angiography via collateral filling.

Myocardial bridging is a congenital variant that can occur in all coronary vessels but is most commonly found in the LAD artery. It is defined as a segment of the major epicardial artery tunneling through the myocardium and then resurfacing. Evidence of bridging has been reported in 40% to 80% of autopsy studies, but it is noted less commonly on invasive coronary angiography. The in vivo diagnosis of bridging can be improved with the use
of intravascular ultrasound and/or coronary computed tomographic angiography. The clinical relevance of myocardial bridging is controversial. In most cases, bridges are asymptomatic, benign findings. However, in some patients, they can be responsible for chest pain, arrhythmia, and acute coronary syndromes. In these instances, it is believed that endothelial dysfunction, development of atherosclerosis just proximal to the bridge, left ventricular hypertrophy, and diastolic dysfunction exacerbate the bridge in varying degrees and contribute to the clinical presentation. Symptomatic bridges are typically treated medically. Results of treatment with percutaneous coronary intervention have been poor in general. When medical therapy fails, surgical unroofing of the bridge can be considered.9

The Coronary Venous System

Knowledge of the coronary venous system is becoming increasingly important to the interventionalist to facilitate various noncoronary and electrophysiologic cardiac interventions (Fig. 2-4). The venous circulation of the heart is divided into three systems: the anterior cardiac veins, the coronary sinus and its tributaries, and the thebesian veins. The anterior cardiac veins, which originate from the right ventricular free wall surface of the heart,3,8 drain the right ventricle and empty into the right atrium. The coronary sinus and its tributaries, which course on the surface of the left ventricle, run in parallel to the coronary arterial branches. The major tributary of the coronary sinus is the anterior interventricular branch, which parallels the LAD artery and turns into the great cardiac vein as it enters the AV groove. The coronary sinus enters the right atrium adjacent to the tricuspid valve. Finally, the thebesian veins drain directly into the underlying right-side chambers. Flow is very minimal in these vessels, but these veins could give rise to very small and usually insignificant right-to-left shunts.3,8
FIGURE 2-4 Coronary venous anatomy. The coronary sinus is cannulated with a balloon catheter, wherein contrast injection of the coronary sinus visualizes both the anterior ventricular cardiac vein as well as late-phase filling of the lateral and inferior cardiac veins.

CORONARY ARTERY ANOMALIES

Benign Anomalies

Most coronary artery anomalies are clinically benign incidental findings (Table 2-1). Separate and adjacent ostia of the LAD and left circumflex arteries are the most common anomaly, occurring in 0.41% of cases according to a large series reported from the Mayo Clinic. Separate coronary ostia constitute approximately 30% of all benign coronary anomalies. Of interest, there is an association with a bicuspid aortic valve in these patients. From a practical standpoint, catheter engagement may opacify one vessel and not the other. Occasionally, two separate diagnostic catheters
are needed to complete the angiographic study of this anomalous left coronary artery system.

Table 2-1 Benign Coronary Anomalies (80% of total cases)

<table>
<thead>
<tr>
<th>Type of Anomaly</th>
<th>Incidence (%)</th>
<th>Anomaly (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separate adjacent LAD and LCX ostia</td>
<td>0.41</td>
<td>30.4</td>
</tr>
<tr>
<td>LCX origin from RCA or RSV</td>
<td>0.37</td>
<td>27.7</td>
</tr>
<tr>
<td>Anomalous LCX from PSV</td>
<td>0.004</td>
<td>0.3</td>
</tr>
<tr>
<td>Anomalous origin from aorta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMCA</td>
<td>0.01</td>
<td>1.0</td>
</tr>
<tr>
<td>RCA</td>
<td>0.15</td>
<td>11.2</td>
</tr>
<tr>
<td>Absent LCX</td>
<td>0.003</td>
<td>0.2</td>
</tr>
<tr>
<td>Small fistula</td>
<td>0.12</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Abbreviations: LAD, left anterior descending (artery); LCX, left coronary artery; LMCA, left main coronary artery; PSV, peak systolic velocity; RCA, right coronary artery; RSV, right subclavian vein.

The second most common coronary artery anomaly is the anomalous origin of the circumflex artery from either the right coronary artery or the right sinus of Valsalva.\textsuperscript{10,11} This anomaly, seen in 0.38% of diagnostic angiograms and making up 28% of benign coronary artery anomalies, is characterized by a retroaortic course of the circumflex, with the vessel running posterior to the aortic root. The clinical importance of identifying this anomaly is high for several reasons. First, unless the catheterizing physician has an adequate level of suspicion, this vessel may remain unvisualized. Second, for patients undergoing aortic valve replacement or mitral valve repair or replacement, this artery may be at risk for damage during surgery unless the surgeon is aware of its presence and retroaortic course.
Angiographically, one imaging hallmark is a long left main coronary artery segment, often longer than 15 mm. Also, the retroaortic course of the circumflex around the aorta produces an angiographic “dot” (the end-on view of the vessel as it courses around the aorta) seen on aortography or ventriculography in the right anterior oblique projection. This coronary anomaly is best engaged with an Amplatz or multipurpose catheter in a steep left anterior oblique view.

The third most common benign coronary anomaly is the anomalous origin of the right coronary artery from the left sinus of Valsalva, occurring in 0.15% of cases and constituting 12% of benign coronary anomalies. The remaining benign coronary anomalies include an anomalous origin of the left main coronary artery from the aorta, constituting 1% of anomalies in the benign group, and an absent circumflex artery (seen in approximately 0.03% of all cases), constituting less than 1% of benign coronary anomalies.

Coronary artery fistulas constitute a separate group of benign anomalies and occur when a coronary artery branch communicates directly with another chamber or structure, usually the right ventricle or pulmonary artery. Most fistulas, usually incidental findings during angiography, are small and clinically unimportant and rarely demonstrate the high flow and drainage into a right-side chamber that would produce a significant left-to-right shunt. Small fistulas have been noted to occur in 0.12% to 0.14% of catheterization cases, constituting approximately 10% of all benign coronary anomalies.

**Clinically Serious Anomalies**

Twenty percent of coronary artery anomalies are associated with potentially serious clinical consequences (Table 2-2). The most common anomaly in this group is the origin of the right coronary artery from the left sinus of Valsalva, which occurs in approximately 0.12% of all cases and constitutes 8% of all coronary anomalies. In this case, the right coronary artery has an interarterial course between the aorta and pulmonary artery. This anomaly may be associated with ischemic symptoms and requires surgical revascularization. The course of the vessel produces a bend point anterior to the aorta, resulting in an angiographic dot sign seen on ventriculography or aortography.

| Table 2-2 | Potentially Serious Coronary Anomalies (20% of total cases) |
Anomalous Pathways of the Left Coronary Artery Arising From the Right Aortic Sinus

Another group of coronary anomalies considered to be potentially serious involves the origin of the left main coronary artery (LMCA) from the right sinus of Valsalva (Fig. 2-5). Overall, these anomalies constitute 1.5% of all coronary anomalies and are seen in 0.2% of all catheterization cases. The LMCA from the right sinus of Valsalva has four potential pathways, with one being strongly associated with angina, syncope, or sudden death. Computed tomography coronary angiography has simplified diagnosing the course of the anomalous LMCA, but knowledge of the invasive angiographic findings remains important. The first pathway is a retroaortic course that takes the left main artery posterior to the aortic root. This pathway is characterized by a posterior angiographic dot sign and is considered benign (see Fig. 2-5C).
In the second pathway, the LMCA may cross low and anterior through a “septal” course (see Fig. 2-5A; Figs. 2-6A-C and 2-7). This anomaly is usually benign and characterized by septal perforators coming off of the LMCA, with an intramuscular course passing near the right ventricular outflow tract. As the LMCA curls downward at the bifurcation point to give rise to the circumflex artery, it creates a downward loop, or angiographic “eye” sign.
FIGURE 2-6 A. Long left main coronary artery that supplies only a left anterior descending branch and no circumflex. B. Injection of the right coronary artery with reflux into the anomalous left circumflex faintly filling this vessel. C. Selective injection of the anomalous circumflex coronary artery originating from the right sinus of Valsalva.
FIGURE 2-7 Anterior course of the left main artery originating from the right coronary sinus.

The third pathway in this group involving the LMCA coursing anteriorly over the pulmonary artery and right ventricle demonstrates an upward loop and an upgoing eye sign created by the alignment of the left main and circumflex arteries. This anomaly is also considered benign (see Fig. 2-5B).\textsuperscript{10-13}

The fourth anomalous left main pathway from the right sinus of Valsalva is considered to be serious. Originating in the right sinus, the left coronary artery following an intramural path between the pulmonary artery and aorta creates an anterior dot sign as it bends and exits its intra-arterial segment (see Figs. 2-5D and 2-8). This anomaly has been associated with angina, syncope, and sudden cardiac death. When it is found, surgery is usually required.\textsuperscript{13} The slitlike ostial orifice stretching or narrowing during activity is thought to be the mechanism producing ischemia in these patients.
The anomalous origin of the LMCA, LAD artery, or right coronary artery from the pulmonary artery is another potentially serious coronary anomaly. In these situations, coronary flow is antegrade in the normal coronary artery and retrograde in the anomalous vessel, allowing left-to-right shunting from the coronary artery bed to the pulmonary circulation. When the right coronary artery is involved, the situation is relatively benign. However, an anomalous origin of the LMCA or LAD artery from the pulmonary artery is often associated with angina and ischemic left ventricular dysfunction. Combined, anomalous origins of coronary arteries from the pulmonary artery constitute 0.8% of all coronary anomalies and are seen in 0.04% of cases. Ligation or grafting of the aberrant vessel is the treatment of choice.

Other potentially serious coronary anomalies are rare and include a single
coronary artery supplying the entire ventricle. These occur in 0.05% of catheterization cases, constitute 3.3% of all coronary anomalies, and should be considered potentially serious. There are many variations of single coronary arteries, which have been classified by Lipton et al.\textsuperscript{16}

\section*{CORONARY ARTERY COLLATERAL CIRCULATION}

The coronary collateral circulation is a potential source of blood to the myocardium that develops when blood flow via the normal route is impaired. It is believed that small anastomoses between the branches of the major epicardial coronary arteries exist in a dormant fashion. With the appropriate stimuli, these anastomoses can enlarge and allow adequate blood flow to otherwise ischemic myocardium.

Myocardial ischemia and/or development of a pressure gradient appear to be the most important stimuli to the development or maturation of coronary collateral circulation. The exact mechanism by which this is achieved remains an intense area of investigation. It appears that the increased production of growth factors induced by ischemia results in angiogenesis and/or vasculogenesis.\textsuperscript{17} Others have proposed that the physical forces as a result of a pressure gradient might induce endothelial cells to proliferate.\textsuperscript{17}

The presence of collateral circulation has been shown to have important clinical sequelae in both the acute and chronic settings. For example, in patients with acute myocardial infarction treated with fibrinolytic therapy, the presence of collateral circulation was associated with improved ventricular function, less aneurysm formation, and smaller infarcts.\textsuperscript{18-20} Long-term survival in patients with stable angina and coronary artery disease has been shown to be improved in those with good collateral circulation in comparison to patients with poor collateral circulation.\textsuperscript{21}

Rentrop and colleagues\textsuperscript{22} popularized a standard angiographic technique for assessing collateral circulation. The degree of contrast filling of a diseased vessel after injection of the contralateral vessel was graded on a scale of 0 to 3, where 0 equals no filling, 1 equals filling of side branches of the diseased vessel via collateral channels without visualization of the epicardial segment, 2 equals partial filling of the epicardial segment via collateral channels, and 3
equals complete filling of the epicardial segment of the diseased vessel via collateral channels. This qualitative (and rather insensitive) method for determining the degree of collateral circulation has been replaced by coronary wire-based techniques for measuring pressure- or velocity-derived collateral flow indices.\textsuperscript{23-25}

A number of common collateral connections between the major epicardial arteries have been described,\textsuperscript{7} including intracoronary collaterals or connections from the proximal portion of an occluded artery to the distal portion of the same vessel. These can exist as “bridging” collaterals, which are small channels that develop around an occlusion and allow filling of the distal vessel. Alternatively, larger channels can form from a branch proximal to an occlusion, such as an acute marginal branch off the right coronary artery, and anastomose to a branch distal to the occlusion, such as another acute marginal branch or the PDA. Another example is the Kugel artery, a branch off the proximal right coronary artery that anastomoses to the AV nodal artery, distal to a right coronary artery occlusion, and thereby fills the vessel beyond the blockage.\textsuperscript{26}

Intercoronary collaterals are connections between branches of two of the three major epicardial coronary arteries. Common examples include septal-to-septal collaterals emanating from the posterior descending coronary artery going to the LAD artery, or vice versa; the distal LAD artery and PDA often collateralize each other, as do the obtuse marginal branches of the circumflex and either the posterior left ventricular branches of the right coronary or the diagonal branches of the LAD artery. An important source of collateral flow to the LAD artery that can easily be missed at the time of angiography if not selectively injected with contrast is the conus branch of the right coronary artery.\textsuperscript{27}

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**MULTIPLE CHOICE QUESTIONS**

1. The coronary microvasculature is defined as:
   A. Arterioles that measure less than 200 μm in diameter and are easily visualized on conventional coronary angiography.
   B. Arterioles that measure less than 200 μm in diameter and are not visualized on conventional coronary angiography.
   C. Arterioles that measure greater than 200 μm in diameter and are easily visualized on conventional coronary angiography.
   D. Arterioles that supply deoxygenated blood to the myocardium.
   E. Arterioles that are unable to vasodilate or vasoconstrict in response to stimuli.

2. The right coronary artery:
   A. Originates from the left sinus of Valsalva.
   B. Gives off the conus artery in 90% of cases, whereas the conus artery originates from a separate ostium in the other 10% of cases.
   C. Gives off the sinoatrial nodal artery in 90% of cases.
   D. Gives off the conus artery, which may be an important source of collaterals to an occluded left anterior descending artery.
   E. Gives off the posterior descending branch in 10% of cases.

3. Myocardial bridging:
   A. Has been reported in 40% to 80% of autopsy cases.
   B. Is an acquired variant that can develop in any coronary artery.
   C. Is best diagnosed with coronary angiography.
   D. Causes symptoms in most cases.
   E. Is most commonly treated with surgery when symptomatic.

4. Which of the following statements is true regarding benign coronary anomalies?
A. Separate ostia of the left anterior descending and left circumflex arteries (absence of a left main coronary) are the least common.
B. Many fistulas demonstrate high flow with significant left-to-right shunts.
C. A long left main coronary artery is an imaging hallmark of an anomalous circumflex coming off the right coronary artery.
D. The right coronary artery coming off the left sinus of Valsalva is the most common.
E. A bicuspid aortic valve is associated with an anomalous circumflex coming off of the right coronary artery.

5. Which of the following statements is true regarding the clinically serious coronary anomalies?
   A. These represent 80% of all coronary anomalies.
   B. The left main coronary artery coming off the right sinus of Valsalva has only one known course, which it takes to reach the left ventricle.
   C. Surgery is never required when the left main coronary artery comes off the right sinus of Valsalva.
   D. A single coronary artery supplying the entire left ventricle occurs in 5% of all coronary angiograms and represents 30% of all anomalies.
   E. An anomalous right coronary artery coursing between the pulmonary artery and the aorta may be responsible for ischemic symptoms and can require surgical revascularization.

**ANSWERS**

1. B
2. D
3. A
4. C
5. E
INTRODUCTION

This chapter on cardiac anatomy takes a practical approach for operators who are going to perform various procedures associated with structural heart disease. Rather than assume the traditional approach of describing the gross anatomy of the heart in isolation from the procedures performed, this chapter will attempt to provide useful information (Tips and Tricks) of how the anatomy, as seen by the percutaneous operator, affects the procedure results. Therefore, the emphasis is not only on gross anatomy, but also the anatomy that the interventionalist perceives using different imaging modalities. Whereas a surgeon can see and touch the anatomic structures, a cardiac interventionalist has to rely on indirect methods of visualization, which include fluoroscopy, echocardiography, and intracardiac ultrasound. Magnetic resonance or computed tomography images can be useful for orientation and diagnosis before the procedure (and, more recently, can be used as an overlay on the fluoroscopy monitor in the catheterization lab). However, the focus of this chapter is what the interventionalist has at his or her disposal at the time of the procedure to understand the anatomy. Accurate use of available imaging modalities in the catheterization laboratory and appreciation of relative orientations are important for optimal device sizing.
and placement.

**ORIENTATION**

Fluoroscopy provides a familiar image with the right atrium adjacent to the spine in the anteroposterior (AP) view, to the right in left anterior oblique (LAO) angulation, and anterior to the spine in the right anterior oblique (RAO) projection. The left upper pulmonary vein is just superior to the left atrial appendage and extends outside the cardiac shadow (Fig. 3-1). Transesophageal echocardiography (TEE) provides an image with the left atrium at the top of the screen because it is the closest structure to the probe, whereas the anterior cardiac structures, including the right atrium, are at the bottom of the screen. The left side of the image represents the inferior aspect of the heart leading to the inferior vena cava (IVC), and the right represents the superior aspects, including the superior vena cava (SVC) and aorta, all of which are not presented in the same orientation as the physical anatomy (Fig. 3-2). Rotating a TEE image 90° counterclockwise will orient the image similarly to a fluoroscopic image but with the plane of the image originating posteriorly from the esophagus to the anterior chest. The intracardiac echocardiography (ICE) probe is situated typically in the right atrium facing the atrial septum. The structure closest to the probe, and therefore at the top of the screen, is the right atrium. Similarly to TEE, the IVC is to the left of the screen, and the SVC is on the right. Rotating the ICE image 90° counterclockwise will present an image in the same anatomic orientation as fluoroscopy (see Fig. 3-1). TEE provides multiple tomographic cuts of the heart from different planes and angulations, which can be confusing for the interventionalist with a catheter in hand.
FIGURE 3-1 Anteroposterior fluoroscopy of a 24-mm sizing balloon across the interatrial septum. The wire is in the left upper pulmonary vein (LUPV). LA, left atrium; ICE, intracardiac echocardiography; RA, right atrium. (From El Said HG. Patent Foramen Ovale Morphology and Impact on Percutaneous Device Closure. Pediatr Cardiol 2004;26:62-65, with permission of Springer.)
FIGURE 3-2 A. Transesophageal echocardiography images showing a horizontal and oblique orientation of the omniplane in relation to the atrium. Positioning the probe
in the mid-esophagus with the omniplane at 0° and rotating the probe shows a 4-chamber view of the septum and atria (*echo image 1*). This is a good starting position. B. The height and angle of the omniplane determine the image cut seen on the screen. *Echo image 2*: A high esophageal omniplane position at around 50° will show the ascending aorta, and high atrial septum. *Echo image 3*: A low esophageal image shows the lower atrial septum and the posterior rim. Ao, aorta; Asc, ascending; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RAA, right atrial appendage; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve.

**ATRIAL SEPTAL DEFECTS**

The secundum septal defect is the most common type of atrial septal defect (ASD) and involves the fossa ovalis border and the deficient edge of the ostium secundum. The defect may be circular, oval, or fenestrated, and the septum may be rigid or aneurysmal and floppy. Relative to the long axis of the body, the right atrium lays anterior to the left atrium, and the septum is oriented obliquely in the chest from the posterior right to the anterior left. The IVC enters the right atrium at an angle and is oriented roughly in a line through the inferior-posterior quadrant of the right atrium to the superior-anterior quadrant. In utero, this orientation helps direct returning placental blood from the IVC toward the foramen ovale on the septum (*Fig. 3-3*). The eustachian valve further helps to direct the oxygenated placental blood toward the still patent foramen ovale. A long residual eustachian valve can be misinterpreted as the atrial septum on TEE.
FIGURE 3-3 Pathology sample with the right atrium opened showing the atrial septum and the rims of the fossa ovale: retro-aortic (superior-anterior [SA]), superior vena cava (SVC; superior-posterior [SP]), posterior (P), inferior vena cava (IVC; inferior-posterior [IP]), and atroioventricular (inferior-anterior [IA]). An overlay provides the approximate direction of the quadrants. Asc Ao, ascending aorta; PV, pulmonary valve; TV, tricuspid valve.

The rims surrounding the defect may be deficient in any of the quadrants if they measure less than 5 mm. The retroaortic rim is in the anterior-superior quadrant. The SVC and right pulmonary veins border the posterior-superior quadrant. The posterior free right atrial wall makes up the posterior rim. The tricuspid valve borders the inferior-anterior quadrant, and the IVC is contiguous with the posterior-inferior quadrant (Fig. 3-4).
Other types of septal defects are outside the fossa ovalis and can be close to other cardiac structures. These defects, such as the ostium primum and inferior and superior sinus venosus ASDs, are not correctable by percutaneous techniques and will not be covered in this chapter.\(^1\)

In the AP projection, an ASD is oriented slightly superior to the tricuspid valve. Because the atrial septum is oblique, a guide wire from the IVC will typically pass across an ASD to the left upper pulmonary vein, appearing slightly outside the heart border on fluoroscopy. Care must be taken not to advance the wire into the left atrial appendage oriented inferior and anterior to the pulmonary veins unless the operator is performing a left atrial appendage closure procedure (see Fig. 3-1; Fig. 3-5).\(^2\) A sizing balloon should be used to obtain the stretch diameter and the Doppler stop-flow measurements in the LAO projection to minimize foreshortening. A mobile, aneurysmal septum can be difficult to assess on imaging, and balloon sizing ensures appropriate device size selection, thus reducing the risk of embolization or complications.
FIGURE 3-5 Intracardiac echocardiography (ICE) image of the wire crossing the atrium from the inferior vena cava (IVC; left upper corner). The wire was advanced from the IVC into the right atrium (RA), then across the septum into the distal portion of the left atrium. Note that the orientation of ICE images places the right atrium at the top of the screen, but anatomically on fluoroscopy, the guide wire is traveling superiorly from the IVC through the right atrium to the superior and posterior left upper pulmonary veins.

For a complete rim and defect evaluation using TEE in the midesophageal position, the omniplane transducer is rotated through approximately 0°, 45°, and 90°. Starting at 0°, the TEE shows the anterior-posterior rims including the mitral valve and posterior atrial wall. Rotating from 30° to 45° will show the anterior-superior or retroaortic rim, which is most commonly deficient in up to 42% of patients. Moving the TEE probe at this angle in and out brings into view the superior and inferior margins of the defect (see Fig. 3-2). Further rotation to 90° to 110° will show the SVC and IVC rims (bicaval view) (Fig. 3-6). Three-dimensional echocardiography can outline the defect and the rims surrounding it, making identification of deficient rims easier. This is also helpful after device deployment to judge the level of
impingement on cardiac structures. The pulmonary venous connections can be evaluated by echocardiography and a pulmonary angiogram during the venous phase using a 45° LAO and 35° cranial projection.  

**FIGURE 3-6** Transesophageal echocardiography images of the vertical orientation of the omniplane. Rotating the probe rightward (counterclockwise) and angulating the omniplane to about 110° will yield the bicaval view (top right). Rotating the probe leftward will show the anterior structures including aorta (top left). The **bottom left panel** shows color flow used in assessing flow across the septum. Ao, aorta; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; RA, right atrium; SVC, superior vena cava; TV, tricuspid valve.

To use ICE in the assessment and positioning of a closure device, begin in the right atrial home view, keeping in mind that the most proximal structure at the top of the screen is the right atrium (Fig. 3-7A). This view shows the
right atrium, right ventricle, and tricuspid valve. Placing a 20° retrograde angle on the ICE probe and rotating the probe clockwise will show the aorta in the short axis and the right ventricular outflow (Fig. 3-7B). Additional clockwise steering will also bring the foramen ovale into the field. Continuing to rotate brings the interatrial septum into view and the left atrial appendage in the right bottom of the image. The mitral valve may also be observed with slight right-left rotation of the probe (Fig. 3-7C). Further clockwise rotation will then bring the left pulmonary veins into view with the left upper pulmonary vein (LUPV) to the right of the screen and left inferior pulmonary vein to the left (Fig. 3-7D). Slight clockwise rotation will bring the guide wire into view traversing the septum and along its path in the left atrium. Additional clockwise rotation will then bring the right pulmonary veins into view in the short axis (Fig. 3-7E). Withdrawing the probe to the inferior right atrium and with additional posterior tilt will show the SVC and superior-posterior rim (Fig. 3-7F). Once the device is deployed, moving the probe in and out in the neutral position with slight right-left angulation is done to demonstrate capture of the rims by the occluder.
FIGURE 3-7 A-F. Intracardiac echocardiography images. The most proximal structure at the top of the screen is the right atrium (RA). A. This image shows the RA, right ventricle (RV), and tricuspid valve (TV). B. Placing a 20° retrograde angle and rotating clockwise will show the top right panel and the aorta (AO) in the short axis with the right ventricular outflow. C. This panel shows that turning the probe more clockwise will visualize the foramen ovale. D. Continuing to rotate clockwise brings the pulmonary veins into view as this panel shows. The mitral valve may also be observed with slight right-left rotation of the probe. E. This panel shows that additional clockwise rotation will then bring the right pulmonary veins into view in the short axis. E. Withdrawing the probe to the inferior right atrium and with additional posterior tilt will show the superior vena cava (SVC) and superior-
The orientation of the IVC relative to the atrial septum causes the device delivery sheath to place traction on the occluder inferiorly toward the IVC. During deployment of an Amplatzer septal occluder (St. Jude Medical, Saint Paul, MN), care must be taken to orient the left atrial disk parallel to the septum before pulling it against the septum. If the device is angulated perpendicular to the defect, the left atrial disk may prolapse across the septum and into the right atrium. This is of greater concern with the Amplatzer septal occluder, especially in cases of a deficient retroaortic rim. The TorqueView sheath (St. Jude Medical) typically used with the Amplatzer device may not orient in the ideal plane in horizontal or rotated hearts. The Hausdorf sheath (Cook Medical, Bloomington, IN) has 2 posterior curves and an angled tip designed to maintain the distal part of the sheath and the device parallel to the septum so the disk is less likely to prolapse into the right atrium when there is a large ASD. Once the sheath and left atrial disk are pulled as a unit against the septum, the right atrial disk is deployed. Until the device is released, the deployment cable places traction on the device and angulates the occluder. The tension placed on the device by the cable will press the right disk into the IVC rim and possibly push it across the septum. Conversely, the torque on the superior-anterior aspect of the device with a deficient retroaortic rim may prolapse the device into the right atrium. A clockwise rotation on the delivery sheath for deficient IVC rims and counterclockwise for deficient retroaortic rims may orient the deployed, but unreleased, device more parallel to the septum and capture the rims (Fig. 3-8).
FIGURE 3-8 Transesophageal echocardiography images. On the left is the Amplatzer septal occluder oriented perpendicular to the septum due to the traction on it toward the inferior vena cava (IVC). On the right is the result of clockwise rotation of the delivery sheath, and releasing some of the traction orients the occluder more parallel to the septum. LA, left atrium; RA, right atrium.

Larger closure devices in small or geometrically unfavorable left atria can also make deployment of the left atrial disk challenging. With the delivery sheath in the LUPV, it is possible to deploy the left disk in the proximal pulmonary vein, then gently retract the disk out and oppose it to the defect ensuring the rims are captured. Finally, a deficient retroaortic rim should prompt some caution because it is associated with device-related complications including erosions, arrhythmias, and malposition. A large defect and aneurysmal septum are also risk factors because both of these issues require larger devices to be placed. The risk of erosion is rare, at 0.1% to 0.2%, but should be considered if the patient complains of chest pain, numbness, sudden weakness, dizziness, syncope, shortness of breath, or tachycardia (Fig. 3-9).
FIGURE 3-9 Amplatzer occluder compression superiorly into the aortic root during aortic root injection of contrast. This threatens possible erosion, which has not occurred yet.

PATENT FORAMEN OVALE

Patent foramen ovale (PFO) is present in 20% to 30% of the general population. In utero, the septum primum develops to pass to the left and under the septum secundum, creating a conduit shunting blood in the fetal circulation from the IVC across the interatrial septum into the left heart. The
oxygen saturation of placental blood is only 67%. If the blood were to follow the usual pathway through the right heart and the unaerated fetal lung, the oxygen content would continue to fall and would not be able to sustain organogenesis. This mechanism is so important that it is preserved throughout evolution in all mammals. At birth, the drop in pulmonary pressure closes the tunnel as the left atrial pressure exceeds right atrial pressure, and in most people, the septum primum and septum secundum fuse. PFOs vary in shape, configuration, mobility, and size. An understanding of PFO anatomy is important for device closure procedures. PFO size increases with age in children until maximum growth is achieved. In the adult, there is no evidence that the PFO size changes over time. PFOs usually range in size from 3.4 to 5.8 mm but reportedly can be larger, and may be 3 to 18 mm in length. The variation depends partly on how a PFO is measured (eg, by echocardiography or by balloon sizing at cardiac catheterization).

The PFO has an oval shape and is formed by the crescent-shaped thicker (1 cm) septum secundum superiorly with the thin (1 mm) septum primum passing from the inferior aspect of the atrium, under the septum secundum, then entering the left atrium (Fig. 3-10). It extends superiorly and behind the limbus of the septum secundum (Fig. 3-11). Inferior-posterior to the PFO is the IVC, inferior-anterior is the tricuspid valve, and superior-anterior is the aortic root. The SVC enters the right atrium superior-posterior to the PFO and is about 1.2 cm away (Fig. 3-12). To cross the PFO, a multipurpose catheter and either a 0.035 J or straight-tipped wire may be advanced up the IVC. Probing the septum about 1 cm below the SVC in a line inferior-posterior to the aorta should permit crossing the PFO tunnel as is done during a trans-septal puncture when the foramen ovale is closed (Fig. 3-13).
FIGURE 3-10 A representation of a patent foramen ovale in the open (left) and closed (right) positions.

FIGURE 3-11 The fossa ovale is bordered by the septum secundum superiorly and the septum primum inferiorly. A patent foramen ovale, if present, would be in the location highlighted in blue. LV, left ventricle; RA, right atrium; RV, right ventricle.
FIGURE 3-12 Angiogram of a catheter in the right atrium tenting the septum primum. Contrast is flowing through the patent foramen ovale (PFO) and into the left atrium (seen better on cine images). ICE, intracardiac echocardiography; LA, left atrium; RA, right atrium.

FIGURE 3-13 Posteroanterior projection (left) showing a multipurpose catheter and guide wire across the patent foramen ovale (PFO) tunnel to the left upper pulmonary
Vein. Left anterior oblique cranial projection (right) during fluoroscopy shows a sizing balloon with a waist at the site of the PFO. ICE, intracardiac echocardiography; LUPV, left upper pulmonary vein.

Accurate evaluation of the PFO tunnel length and morphology requires careful echocardiographic assessment. This is needed to assess the length and height of the PFO and the presence and extent of any septal aneurysm. This in turn can influence the choice of device size and to assure there are no other findings such as a secundum ASD, fenestrated septum, septal masses, or septal hypertrophy. To obtain the width of the PFO, it would be necessary to visualize the atrial septum directly en-face. This can be obtained currently only with 3-dimensional echocardiographic imaging. Alternatively, balloon sizing of the PFO can be performed during fluoroscopy, to obtain the stretched diameter and shape of the tunnel. It is important to decrease any foreshortening of the radiographic projection, and the LAO cranial view is usually the preferred projection (Fig. 3-14). The shape and size of the PFO tunnel using a balloon will influence selection of the device and its size to close the PFO. The 2 currently available devices in the United States are the Amplatzer septal occluder, the Gore Cardioform, and the Gore Helex septal occluder (W. L. Gore & Associates, Flagstaff, AZ). These devices are approved by the US Food and Drug Administration (FDA) for closure of ASDs but are not approved for closure of PFOs. At the present time, PFO closure is performed either under an Investigational Device Exemption protocol or used off-label. The Amplatzer septal occluder is self-centering, so sizing is done 1:1 to the defect. The Gore Helex device has a narrow neck and is composed of expanded ePTFE material on a 0.012-inch nickel-titanium wire frame. For a typical small PFO less than 12 mm, we use the 25-mm Helex device because it is soft and well tolerated. Larger PFOs requiring the use of a 30- or 35-mm occluder result in the Helex device having too little compression force. This leaves a large residual shunt in 50% of people. Therefore, we prefer the newer Gore Cardioform, or the Amplatzer septal occluder for PFOs larger than 12 mm in diameter.
FIGURE 3-14 Sizing balloon in the patent foramen ovale (PFO) tunnel outlining the morphology of the tunnel and an intracardiac echocardiography (ICE) image of the PFO showing how the septum primum goes behind and to the left of the septum secundum. (Balloon markings are 15 mm inside edge to inside edge.) LA, left atrium; RA, right atrium; SPV, superior pulmonary vein.

During TEE imaging, the omniplane angle is rotated to the bicaval view (approximately 90-110°) to show the different aspects of the septum and bring the PFO tunnel into view (Figs. 3-15 and 3-16). We currently prefer using ICE for PFO closures, but some centers report using fluoroscopic guidance only, after they have assessed the anatomy with a preprocedure TEE.

FIGURE 3-15 Transesophageal echocardiography image of an atrial septal aneurysm with a patent foramen ovale (PFO; center). The image on the left shows an agitated
saline bubble study, and the image on the right demonstrates color flow across the PFO (arrow). LA, left atrium; RA, right atrium.

FIGURE 3-16 Transesophageal echocardiography image of a patent foramen ovale (PFO) in relationship with the ascending aortic root and aortic rim. This view is helpful in assessing the device position against the aorta, especially if the aortic anatomy is distorted.

A bubble study and color-flow Doppler are applied to assess the channel. The operator can also observe the wire crossing the tunnel and assess the extent of atrial septal aneurysm as well as the septal thickness and aortic morphology (Fig. 3-17).
FIGURE 3-17 Three-dimensional transesophageal echocardiography of an aneurysmal interatrial septum in different planes. LA, left atrium; RA, right atrium.

PFO Morphology and Genetic Sequencing

A proposed classification of PFO morphology is shown in Table 3-1.15 Fenestrations and aneurysmal septal anatomy are associated with larger PFOs and are postulated to increase the risk of paradoxical emboli. In people who
develop platypnea-orthodeoxia later in life, the proposed mechanism is that the anatomy is altered, such as with an enlarged aortic root or with hemidiaphragm paralysis. This in turn deforms the septum to enlarge the PFO and prolong the PFO opening during ventricular systole. The variation in PFO anatomy should influence the choice of the device and its size.

Table 3-1 Proposed Classification of Patent Foramen Ovale (PFO) Anatomy

<table>
<thead>
<tr>
<th>Classification of PFO Anatomic Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>Standard anatomy, no aneurysm</td>
</tr>
<tr>
<td>Complex 1</td>
<td>Presence of septal aneurysm</td>
</tr>
<tr>
<td>2</td>
<td>Tunnel longer than 18 mm</td>
</tr>
<tr>
<td>3</td>
<td>Lipomatous hypertrophy of the septum</td>
</tr>
<tr>
<td>4</td>
<td>Associated with Eustachian valve and Chiari network</td>
</tr>
<tr>
<td>5</td>
<td>Multifenestrated aneurysmal septum or associated with small atrial septal defects</td>
</tr>
<tr>
<td>6</td>
<td>Associated with distorted aortic root anatomy or a shortened or missing septal rim</td>
</tr>
</tbody>
</table>

A recent study of 48 people from 16 families who had PFO-related phenotypes (cryptogenic stroke or migraine with aura) was performed with exome sequencing to assess single nucleotide polymorphisms. There were 3 genes that were associated with the presence of a PFO and 5 genes that were more common in people with a closed foramen ovale. The inheritance suggests that PFO closure is determined by a polygenic basis, which may explain the variety of shapes and sizes of the septum primum and PFO.

**TRANSSEPTAL CATHETERIZATION**

Multiple procedures require crossing the interatrial septum including mitral
valvuloplasty, left atrial appendage procedures, mitral valve clip, closure of mitral paravalvular leaks, and electrophysiologic studies. In complex PFO procedures where the tunnel is long and angulated, a transseptal puncture may permit a more effective placement of a device. In most interventional procedures, the puncture is aimed at the fossa ovalis. This is in contrast to pulmonary venous isolation procedures where the puncture may be angulated toward the pulmonary veins and thus away from the fossa ovalis. See the prior section on ASD and PFO closure for a more detailed description of the anatomy of the fossa ovalis and septum.

The septum is angulated in an oblique fashion from posterior-medially to anterior-laterally toward the left relative to the long axis of the body and is bordered by the posterior atrium on the right, right pulmonary veins on the left, ascending aorta anterior-superiorly, tricuspid valve anterior-inferiorly, and, a few centimeters away, the IVC posterior-inferiorly. The shape of the septum is variable and can be flat in normal atria or convex if the left atrial pressure is elevated as in mitral stenosis. The septum itself may be thickened or aneurysmal, increasing the difficulty associated with transseptal puncture.18

The equipment selection is dependent on the specifics of the anatomy. The standard Brockenbrough needle (BRK) is angled at 19°. For a curved septum, a more angulated needle (BRK-1) angled at 55° may be necessary to keep traction on the septum. Depending on the procedure planned, a Mullins catheter or the Swartz SL catheters (St. Jude Medical) may be needed. The SL0 catheter has a primary curve of 50°, whereas the SL1 has an additional secondary curve of 45° and the SL2 has a primary curve of 90°.19

**The Transseptal Procedure**

A 0.032 J-wire is advanced up the IVC, and the introducer sheath and dilator are advanced over it to the SVC. The wire is removed and the selected needle is advanced up the introducer until the needle is 1 cm inside the distal end of the dilator. The operator will feel the BRK needle curve fit in the introducer sheath’s curve. The sheath is rotated posteriorly to the 4 to 6 o’clock position to avoid the aortic root as it enters the right atrium. The catheter is withdrawn slowly under fluoroscopy until medial steps are observed; these steps are often felt as well. The first step corresponds to the introducer sheath entering the right atrium from the SVC. The needle then is moved medially and
inferiorly within the right atrium. The sheath should be along the medial aspect of the right atrium and posterior to the noncoronary sinus of the aorta. On additional slow withdrawal, the sheath will drop again over the limbus of the septum secundum into the fossa ovalis. This is observed on posteroanterior fluoroscopy as a second medial step. The tip of the introducer sheath is checked in the RAO and LAO projections. In the RAO projection, the tip should be lined up parallel to the spine. In the LAO projection, the tip should point to the left and posterior. Staining of the septum can be helpful to affirm on fluoroscopy the location of the sheath tip relative to other cardiac structures in 3 dimensions. The sheath is held stable, and with a swift movement, the needle is advanced forward to cross the septum. If the septum is aneurysmal or thickened, the needle may not puncture the septum easily. Excessive pressure on the sheath may cause it to slip out of the fossa, or if too much force is applied, the needle may puncture through the septum and then proceed to the posterior wall of the left atrium. Therefore, a bovie or radiofrequency energy may be needed to burn through the septum by applying energy to the back end of the needle for a few seconds as it rests against the tented septum. Contrast may be injected through the needle to confirm crossing into the left atrium, or the needle may be connected to a pressure transducer. Once across the septum, the needle is anchored to maintain access, and the sheath and dilator are advanced slowly together to the mid-left atrium. The needle is removed several inches and the sheath is advanced over the dilator. The dilator is then removed slowly to ensure no air is sucked into the left atrium. A Toray wire (Toray International, Tokyo, Japan) may be advanced to safely maintain wire access to the left atrium. Longer sheaths with a deflecting mechanism, such as an Agilis sheath (St. Jude Medical), may be necessary to achieve the appropriate orientation once across the septum (Fig. 3-18).
FIGURE 3-18 *Left:* Left anterior oblique (LAO) angulation showing an Agilis sheath pointing to the left and posterior across the septum. *Right:* Right anterior oblique (RAO) fluoroscopy showing the transseptal sheath parallel to the spine and pointing into the septum.

TEE or ICE imaging makes transseptal access safer but does require an understanding of the anatomy. Echocardiography can be used to “find” the tip of the transseptal sheath and observe tenting of the septum prior to extending the needle. In TEE, the omniplane is angulated from 0° showing the 4-chamber views to 65° showing the aortic root. If the sheath is observed at the same plane as the aortic root, then the operator will need to rotate the BRK needle clockwise (posteriorly) away from this area or risk a puncture into the aorta. Further angulation to 110° or the bicaval view will show how high up the septum the sheath tip is and allow the operator to monitor the tip location as the catheter is pulled down the septum (Fig. 3-19). Depending on the procedure, the operator may need to position the puncture a certain distance above the mitral valve annulus.
FIGURE 3-19 Transesophageal echocardiography images of the septum showing the aortic root (left), a 4-chamber view (bottom), and a bicaval view (right). Rotating, moving the probe in and out, and angulating the omniplane will show the different parts of the septum and puncture spot. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RAA, right atrial appendage; RV, right ventricle; SVC, superior vena cava.
It is recommended that a patient undergo a full TEE evaluation prior to a transseptal puncture to assess the morphology of the septum, the possible anomalies, and for the presence of thrombus in the left atrial appendage, especially in the setting of atrial fibrillation or mitral stenosis. Once the puncture is done, the needle is connected to pressure to confirm it is not in the pericardial space or aorta before the dilator is advanced.\textsuperscript{21}

ICE may also be used to localize the transseptal puncture. It is typically positioned in the “home view.” The probe is rotated clockwise until the aorta comes into view. It is then rotated further clockwise until the left pulmonary veins come into view (Fig. 3-20). A puncture at this plane will yield a posterior transseptal puncture typical for pulmonary vein isolation procedures. To perform a puncture appropriate for left atrial appendage procedures or mitral valve procedures, the catheter is gently rotated counterclockwise to show the left atrial appendage. The transseptal sheath may need to be rotated clockwise or counterclockwise until tenting is observed in this view. It is important to position the puncture in the correct plane to facilitate the intervention. Additional devices such as a more angulated sheath or an Agilis sheath may be needed for back-up support (Fig. 3-21).

\textbf{FIGURE 3-20} Intracardiac echocardiography images of the septal puncture. A. Transseptal sheath tenting in the same plane as the left pulmonary veins (5 o’clock). B. The septum with the left atrial appendage in view (5 o’clock). LA, left atrium; LAA, left atrial appendage; LPV, left pulmonary vein; RA, right atrium.
PERCUTANEOUS TRANSVENOUS MITRAL VALVULOPLASTY

The technique of percutaneous transvenous mitral valvuloplasty (PTMV) depends on adequate fracturing of the fused, rheumatic mitral leaflets. Success is defined as a final mitral valve area greater than 1.5 cm$^2$ with moderate or less regurgitation. Understanding the anatomic changes that take place in mitral stenosis and the specific valve pathology is important for the success of the procedure and long-term outcomes, as well as for avoiding complications during the procedure. Prior to the intervention, a full evaluation is required by echocardiographic imaging to assess the valve morphology. Although a precise number on the Wilkins score alone may not determine the success or advisability of performing the valvuloplasty, it provides a rough estimate of the severity of calcification and fibrosis, which are predictors of success with the procedure. The extent of mitral regurgitation also is important since it is likely that balloon valvuloplasty will
result in some increase in the degree of regurgitation. The Wilkins score includes leaflet mobility, valve calcification, leaflet thickening, and disease of the subvalvular apparatus. It does not, however, include an important prognostic indicator, that is, commissural calcification. Valvotomy of a highly calcified leaflet and commissure increases the risk of an unsuccessful result or worse: annular tearing and mitral regurgitation (Fig. 3-22). It is also important to identify unusual insertion of the papillary muscles at the leaflet tips and areas of restriction in the valvular apparatus. Finally, mitral stenosis significantly increases the risk for atrial fibrillation and for developing left atrial thrombus. The presence of left atrial thrombus is a relative contraindication to the procedure, and if present, it is safer to postpone the procedure until adequate anticoagulation is achieved (Fig. 3-23). Mitral valvuloplasty has been performed safely in patients with thrombus in the left atrial appendage, but this should be attempted only after 3 months of adequate anticoagulation by operators who have extensive experience with the procedure. However, surgery may be the best option for these patients.

**FIGURE 3-22** “Surgical view” of the normal mitral valve. In a rheumatic valve, the commissures fuse, restricting valve opening and creating the characteristic “hockey stick” appearance on long-axis echocardiography. This view gives the best spatial orientation to perform paravalvular and mitral procedures. It also shows the relationship to the left atrial appendage (LAA) and appropriate direction for advancing the guide wires.
FIGURE 3-23 Thrombus in the left atrium with a rheumatic, restricted mitral valve (MV). This finding on echo would be a contraindication to perform a percutaneous transseptal mitral valvuloplasty (PTMV). AO, aorta; LA, left atrium; LV, left ventricle.

The percutaneous technique has 2 components. The first is a transseptal puncture in the optimal position for the intervention (see Fig. 3-18). The second part is passing the balloon through the mitral valve and performing the commissurotomy.

The presence of a PFO may obviate the need for a transseptal puncture, but due to the orientation of the PFO tunnel, it may not orient the device in the proper direction for crossing the mitral valve. The transseptal puncture should be oriented in the direction just posterior to the left atrial appendage and the inferior part of the fossa ovalis as discussed in the preceding transseptal section (Figs. 3-24 and 3-25). Achieving an appropriate position for the puncture may be more difficult in mitral stenosis patients due to increased left atrial pressures and a convex septum bulging outward into the right atrium. This pushes the interatrial septum and fossa ovalis against the transseptal sheath, making anchoring of the sheath on the septum challenging, and the sheath may slide off (Fig. 3-26). A transseptal puncture in a patient with mitral stenosis is similar to trying to puncture the convex surface of a grapefruit, which makes precise needle tenting on the septum
difficult (Fig. 3-27). Care must be taken not to allow the catheter to slip and puncture anteriorly near the ascending aorta or posteriorly into the transverse sinus and then into the left atrium. This course may be catastrophic because the needle is within the left atrium and the operator may think it is safe to advance the large dilator and sheath. A problem will only be apparent upon removing the 14-Fr commissurotomy balloon when the pericardial effusion develops.

**FIGURE 3-24** Intracardiac echocardiography images of the septum with the left atrial appendage at 5 o’clock (left). Tenting of the septum prior to extending the Brockenbrough needle (right). LA, left atrium; LAA, left atrial appendage; RA, right atrium.
FIGURE 3-25 Gross pathology image showing the position of the left atrium and mitral valve. Dotted line denotes the approximate transseptal puncture direction overlaying the mitral valve opening. The left atrial appendage (LAA) is anterior and lateral to the plane of the interatrial septum.
FIGURE 3-26 Transesophageal echocardiography: Convex septum bulging into the right atrium. The transseptal sheath (arrow) is flat or parallel against the septum in the right atrium (instead of pointing perpendicular to it for an easier puncture). AO, aorta.
FIGURE 3-27 A model of a convex septum. As the Brockenbrough needle is rotated anterior to posterior or from the 4 o’clock to the 8 o’clock position, the needle may “jump” over the bulging foramen ovale.

The most common current method to perform percutaneous mitral valvuloplasty is by use of the Inoue balloon. The balloon is self-centering and distensible, which facilitates precise volume inflation. Once the transseptal puncture is performed, a spring-coil guide wire such as the Toray wire is advanced and safely positioned in the left atrium. The sheath and introducer are then removed from the body (Fig. 3-28). A rigid 14-Fr dilator is then used to dilate both the venipuncture at the skin and the septum making sure the dilator is passed 3 or 4 times to allow smooth Inoue balloon transit. The balloon is then advanced under imaging guidance to the left atrium, and the coil guide wire is withdrawn. Due to the stenotic mitral valve, the left atrium can be quite large, and the heart position in the chest may be more horizontal. By fluoroscopy in the RAO projection, the operator would aim the balloon at an angle almost perpendicular to the long axis of body (Fig. 3-29). Care must be taken under imaging to ensure the balloon is not entangled with the subvalvular apparatus. In the RAO projection, the balloon is advanced with the stylet manipulated slightly (about 1 cm) in or out to keep the balloon horizontal and coaxial with the mitral valve. In the RAO view, the balloon is checked for freedom of movement in the left ventricle before fully inflating it. Under TEE, the angle appears to be more oblique to almost inferior, whereas under ICE, due to the orientation of the probe, it will appear to be almost parallel to the long access of the body (Fig. 3-30).²⁷,²⁸
FIGURE 3-28 Anteroposterior fluoroscopy of the Toray looped guide wire in the left atrium (LA). The procedure was performed through a patent foramen ovale (PFO), and at the conclusion of the valvuloplasty, a sizing balloon was used to evaluate the PFO channel. RA, right atrium.
**FIGURE 3-29** Right anterior oblique 30° fluoroscopy. *Top left:* Fluoroscopy of the Inoue balloon crossing the mitral valve at an angle almost perpendicular to the long axis of the body (the catheter then proceeds inferiorly as it moves to the apex of the left ventricle). *Top right:* Distal portion of the balloon is inflated and the balloon is pulled back to the mitral valve under fluoroscopic and echocardiographic guidance. *Bottom left:* The proximal component is inflated with a waist visualized at the site of the mitral valve under echocardiography. *Bottom right:* The balloon is further inflated to the volume set by the inflating syringe.
Once the distal part of the balloon is well inflated, the balloon is pulled back against the mitral valve and the proximal portion is inflated. At this point, a waist should be observable by fluoroscopy and echocardiography. Further inflation will obliterate the waist. The balloon is then deflated and pulled back into the left atrium. The mitral valve gradient and the degree of regurgitation are assessed and the procedure is repeated in a step-wise fashion at 1-mm increments of the balloon diameter until an optimal result is obtained or mitral regurgitation is increased.29

**TRANSCATHETER AORTIC VALVE REPLACEMENT**

Transcatheter aortic valve replacement (TAVR) is associated with several chronic comorbid conditions and prior interventions that may alter the native anatomy. The process of implanting a prosthetic valve in the aortic position requires a detailed understanding of the anatomy of the left ventricular outflow tract, valve, aorta and surrounding structures. In addition, the individual approach taken for the procedure (transfemoral, transapical, transaortic) requires its own considerations, as outlined below.
The aortic valve is typically tricuspid but can exist in other configurations, the most common of which is bicuspid, which occurs in 1% to 2% of the population. A bicuspid valve is the most common indication for intervention in younger patients. The most likely leaflets to fuse in bicuspid valves are the left and right coronary cusps, followed by fused right and noncoronary cusps. A bicuspid valve is often accompanied by aortopathy with subsequent aneurysm formation, so attention has to be paid to the aorta (Fig. 3-31). Rheumatic disease of the aortic valve is less common and produces both a restricted and insufficient valve. Degenerative disease of trileaflet aortic valves increases in prevalence with age, reaching about 2% after age 65 and is associated with atherosclerotic coronary and vascular disease. Aortic sclerosis is a common associated condition occurring in 20% to 30% of all patients older than age 65 years. Currently, transcatheter aortic valve implants are indicated in the United States only for calcified degenerative valves. This is partly due to the need for annular calcification to anchor the current prostheses. Balloon valvuloplasty alone has limited long-term benefit for calcification of trileaflet valves compared to rheumatic aortic stenosis where the commissures are fused and respond better to balloon dilatation. Balloon valvuloplasty in bicuspid and degenerative valves causes stretching of the aortic wall at the nonfused comissures, and much of the early restenosis is due to aortic recoiling.

![Figure 3-31](image)

**FIGURE 3-31** A normal trileaflet aortic valve (left), a bicuspid valve (center), and a degenerative trileaflet aortic valve (right).

The aortic root continues from the left ventricular outflow tract and is separated from it by the aortic valve. The aortic root is made up of the valve leaflets, the sinus, coronary ostia, and contains several anatomic and virtual annuli, which will be described later. The root occupies the center of the heart
when viewed from the short axis (see Fig. 3-25; Fig. 3-32). The most anterior part of the root, looking from the frontal plane, contains the right coronary cusp. This lays posterior-lateral and just inferior to the right ventricular outflow tract. The continuation of the aorta then travels medially along the roof of the right atrium to the arch. The posterior right aspect of the root contains the noncoronary or posterior cusp and forms the fibrous continuity with the mitral valve’s anterior leaflet (Fig. 3-33). This is important to consider when implanting the aortic prosthesis because the fibrous continuity cannot support an implant and placing the prosthesis too far into the ventricle risks displacement, disruption of the mitral valve leaflet, or damage to the chordae tendineae. The rest of the aortic root sits against the ventricular septum, which is made up mostly of the muscular septum, and forms the border against the tricuspid valve and right infundibulum. The membranous component of the ventricular septum sits just below the right and noncoronary aortic cusps and is attached to the interleaflet fibrous triangle made up of the fibrous wall between the right and noncoronary aortic cusps (Fig. 3-34). It separates superiorly the aortic vestibule, which is inferior to the aortic orifice and is composed of fibrous instead of muscular walls, from the right atrium and superior right ventricle. It is possible to injure the septum with instrumentation during a procedure in the left ventricular outflow tract. In cases of heavy subaortic and annular calcification, the septum can be punctured during balloon valvuloplasty producing a ventricular septal defect (Fig. 3-35). Care must be taken to position the percutaneous aortic valve device in patients with an existing prosthetic mitral valve. Because the prosthetic mitral annulus is not compliant and is intimately involved with the aortic annulus, forces applied to the outflow tract will be transmitted away from the aortic-mitral continuity and onto the ventricular septum (Fig. 3-36).
FIGURE 3-32 Transesophageal echocardiography image in the short axis showing the aortic root in the middle, left atrium (LA), right atrium (RA), right ventricle (RV), right ventricular outflow tract (RVOT), and pulmonary artery (Pa).
FIGURE 3-33 Gross pathology image of the left ventricle opened along the long axis. The trigon between the right and noncoronary cusp houses the central fibrous body on the ventricular septum. The anterior leaflet of the mitral valve is continuous with the noncoronary or posterior cusp of the aortic valve.
FIGURE 3-34 The base of the fibrous triangle is made up of the membranous septum and the fibrous trigone and continues on to become the fibrous continuity of the anterior leaflet of the mitral valve.
FIGURE 3-35 A percutaneous prosthetic valve was deployed in the usual position, but heavy left ventricular outflow tract (LVOT) calcification (blue arrow) was compressed against the septal wall during balloon expansion, resulting in rupture through the septum that produced a ventricular septal defect. LV, left ventricle; RA, right atrium; RV, right ventricle; VSD, ventricular septal defect.
FIGURE 3-36 Computed tomography of a patient with a prosthetic mitral valve. Forces applied to the fibrous continuity are resisted by the prosthetic mitral ring and are transferred onto the ventricular septum as well as anteriorly (red arrow).

On the aortic side of the valve, the sinus of Valsalva expands outward, forming a bulb that attaches to the ascending aorta at the sinotubular junction. Attention should be paid to the shape and height of the sinus. A flat sinus may not have enough space during deployment of a balloon-expandable percutaneous aortic valve for the native valve leaflets to be tucked inside the sinus. Instead, a heavily calcified leaflet in a small sinus of Valsalva may be pushed flat along the walls and potentially obstruct a coronary ostium (Fig. 3-37). This possibility, due to a shorter and smaller sinus, is greater in women.
FIGURE 3-37 Computed tomography of a heavily calcified aortic valve leaflet, leaflet length, and coronary ostial height.

The course of the coronary arteries may be variable, which has implications for the procedure and may lead to compression by the implant. If there is an anomalous coronary course, there is a small chance of coronary compression during device expansion. A coronary angiogram prior to the implant is also important to look for coronary artery stenosis. The principal anatomic considerations for coronary occlusion following a TAVR procedure are the height of the coronary ostia, the diameter of the annulus, the diameter and shape of the sinus of Valsalva, and the size of the calcification on the left coronary leaflet. A sinus of Valsalva diameter less than 30 mm and left main coronary ostium less than 12 mm in height measured from the nadir of the cusp are associated with an increased risk for coronary occlusion.\textsuperscript{33} While angiographically the right coronary artery ostium appears to be lower than the left due to the angulation of the heart relative to the longitudinal axis of the body, it is actually further away from the aortic valve, so right coronary artery occlusions are much less common during TAVR.\textsuperscript{34} The risk of coronary occlusion is not changed by the approach or by annular calcification.\textsuperscript{33} The presence of a bulky nodule at the edges of the native leaflets, however, may be a risk factor and requires attention. The height of each coronary ostia should be measured from the base of the virtual ring that circumscribes the nadirs of the leaflets to the ostia, keeping in mind that a long native leaflet may still present a risk despite adequate coronary height (Fig. 3-38). In most hearts, the 3 leaflets have different sizes and insertion
points along the sinus of the root.\textsuperscript{35} If there is concern, then the coronary artery may need to be prewired and an angioplasty balloon and stent placed in the left main or anterior descending artery to facilitate an intervention should one be required. Occlusions are not usually caused by the aortic valve prosthesis itself, but by the native degenerated leaflets as they are pushed up and into the coronary ostium (\textbf{Fig. 3-39}). Acute persistent hypotension is the most common early clinical indication of coronary occlusion after valve implant. Calcification of the native valve and annulus is required to anchor the prosthesis, but a large calcified nodule may cause poor apposition of the valve stent to the sinus wall and induce paravalvular leaks.\textsuperscript{36}
FIGURE 3-38 Fluoroscopy of a balloon valvuloplasty and aortic valve implant via a transapical approach. *Top left:* Heavy valvular calcification is apparent on the left coronary leaflet being pushed against a narrow sinus during balloon expansion. *Top right:* Angiogram of the aortic root during balloon expansion showing occlusion of the left main coronary artery but contrast flows down the right coronary artery. *Bottom left:* Leaflet calcification occluding the left main coronary after valve implant. An angioplasty wire and balloon were placed down the left anterior descending artery prior to valve implant in anticipation of possible compression of the left main artery. *Bottom right:* Balloon angioplasty and stent placement in the left main coronary artery.
FIGURE 3-39 Extracted prosthesis showing the deformed stent strut (arrow) due to a calcified nodule on the native leaflet (shown on computed tomography in Fig. 3-37).

Several measurements need to be made during assessment and preprocedure planning. The most important of those is a virtual ring that circumscribes the nadirs of the 3 coronary cusps (Fig. 3-40). The left ventricular outflow tract joins the aortic valve and aortic root at this level and is the annulus ring that determines the aortic valve prosthesis size. Care must be taken to measure the annulus at this level perpendicular to the 3 leaflets and during a systolic phase. The aorta changes configuration during systole from an oval to a more round shape, which conforms more to the expected prosthesis shape and becomes larger in area. Therefore, when deciding on the prosthesis size, it is more appropriate to measure the annulus during the systolic phase. A less perpendicular plane or not measuring at the virtual basal ring level may give an incorrect annular size. This is more likely with 2-dimensional (2D) imaging; 3-dimensional (3D) imaging, such as 3D TEE or multiplanar cardiac computed tomography (CT), can help avoid this error (Fig. 3-41). During angiography, the C-arm is rotated with the pigtail catheter
in the right coronary cusp until the catheter appears to be in the center of the aortic root. Adjustments are made at 10° increments until the angiogram demonstrates a coplanar view of all 3 cusps. At this angulation, the prosthesis can be centered on the annulus while observing the relative position of the aortic root and outflow tract in profile (see Fig. 3-38).\textsuperscript{38} Echocardiography may also underestimate the size of the aortic valve annulus due to measuring from the base of the commissure between 2 leaflets diagonally to the other commissure rather than to the mid-base of an opposite leaflet 180° away (Fig. 3-42). To ameliorate this, the transducer is rotated toward the left shoulder to show a more complete root and annulus and reduce foreshortening. The other important anatomic measurements include the circumference and diameter at the mid-sinus and at the sinotubular junction (STJ). The STJ is about 20% larger than the virtual basal ring.\textsuperscript{39} In cases where the STJ is smaller than the annulus, the balloon and prosthesis selected may be larger than the STJ diameter. This presents the risk of embolizing the prosthesis into the ventricle during implant or rupture of the STJ during balloon expansion. Other measurements to be done include chamber dimensions and stroke volume. Attention to the chamber size and stroke index provides insight into the etiology of the aortic gradient and identifies conditions of low-flow and low-gradient aortic stenosis as compared to pseudostenosis.

\textbf{FIGURE 3-40} \textit{Left:} The virtual basal annulus (1), mid-sinus annulus (2), and sinotubular junction diameter (3). \textit{Right:} The virtual basal ring circumscribes the nadirs of the 3 leaflets and separates the left ventricular outflow tract (LVOT) from the root of the aorta.
FIGURE 3-41 Left: On-axis annular measurement of the basal ring. Right: Off-axis measurement showing a falsely large diameter.

FIGURE 3-42 Echocardiogram (left) and cardiac computed tomography (right) of the aortic valve in the short axis. Diameter measured from the base of one commissure to the other commissure (red) yields a foreshortened width compared to the correct measurement (white) 180° opposite.

Left ventricular septal hypertrophy also presents a challenge when implanting an aortic valve prosthesis. The balloon on balloon-expandable prostheses such as the Edwards Sapien series (Edwards Lifesciences, Irvine, CA) extends distal and proximal from the valve annulus. Although a narrow STJ may embolize the valve into the ventricle, a bulging septum and hypertrophied left ventricular outflow tract may “watermelon seed” the balloon and valve proximally into the aorta during deployment (Fig. 3-43). Additionally, patients with hypertrophic cardiomyopathy are dependent on
the high afterload of the stenotic aortic valve. Relieving the obstruction and the afterload may have a catastrophic outcome in the form of severe dynamic outflow tract obstruction, which can be life threatening. Careful imaging and study of the anatomy are important before embarking on the procedure. As patients advance in age, the aorta and its root may take on a more angulated course from the left ventricular outflow tract. A horizontal aorta directs the guide wire laterally off-center toward the right of the aortic root. This may make crossing the native valve with the prosthesis difficult. To cross the valve and center the prosthesis, pulling tension on the wire lifts the device delivery catheter off the right cusp and toward the middle of the aortic root.

![FIGURE 3-43](image)

**FIGURE 3-43** Effect of left ventricular outflow tract (LVOT) septal bulge. On the left is the native aortic valve with a septal bulge prior to transcutaneous aortic valve replacement (TAVR). On the right is the outcome after prosthesis implant. The intended center of the implant was to be at the blue arrow. The septal hypertrophy displaced the valve stent toward the aorta (Ao) so that the midpoint is now at the red arrow and more aortic than intended. LA, left atrium; LV, left ventricle.

The ventricular conduction system begins in the right side of the septum and, once past the atroioventricular (AV) node, crosses the ventricular septum to emerge on the left side through the central fibrous body (CFB) connected to the tendon of Todaro in the right atrium. The CFB is a fibrous, thickened structure where the annulus of the mitral, tricuspid, and noncoronary cusps of the aortic valve meet and makes up part of the fibrous skeleton of the heart.
(see Fig. 3-33). The CFB is located along the posterior-inferior margins of the membranous ventricular septum at the nadir of the noncoronary cusp along the left ventricular outflow tract which can be imaged by either echocardiography or CT. Once the bundle of His enters the left side, it travels superficially along the edge of the septum before dividing into the anterior and posterior fascicles. An intervention that affects the left ventricular outflow tract has the potential to disrupt conduction, inducing heart block as well as causing the mechanical complications described earlier. Patients with a right bundle branch or fascicular block are at increased risk, especially with a ventricularized or long implant. This is especially a risk with prostheses that extend into the left ventricular outflow tract such as the self-expanding valves.\textsuperscript{40} In addition to the anatomic issues discussed earlier, there are specific considerations related to the approach of the aortic valve implant procedure.

**Transaortic**

The transaortic approach permits a direct and short-distance access to the aortic valve in cases where the patient may not have adequate peripheral vascular access due to severe aortoiliac disease. This approach should be avoided in patients with a brittle “porcelain” aorta, since the calcified aortic root may fracture during the procedure, making repairs difficult and potentially causing the aorta to be replaced. When deciding on the transaortic approach, the position of the aortic arch and angle between the aorta and left ventricular outflow tract need to be studied. An aorta angled behind the sternum, or to the left of it, prevents ready access to the aortic incision site and raises the risk of vascular complications. If the entry angle through the aorta to the left ventricular outflow tract is steep due to a horizontal heart, the approach will not be in a direct line and the valve may not be oriented parallel to the native valve. The access to the aorta is made from the right anterolateral side of the aorta so that the catheter is coaxial in both the coronal and axial axes. If the access is made through the anterior wall of the aorta, the catheter would be angulated posteromedially as it crosses the aortic valve (Fig. 3-44). This is more pronounced in older patients with a horizontal aorta and sharp angulation between the left ventricular outflow tract and aortic root.
FIGURE 3-44 Transaortic approach to transcutaneous aortic valve replacement. Anteroposterior (left) and lateral (right) computed tomography images of the left ventricle and aorta. The anterior approach (yellow arrow) is behind the sternum, limiting access, and directs the catheter posteriorly and behind the right cusp. A right lateral approach (white arrow) directs the catheter coaxially down the aorta and toward the center of the aortic valve.

Transapical

The transapical approach is also an option in patients with limited peripheral access. This approach has the advantage over peripheral access due to better control of the delivery catheter position, but the disadvantages of a thoracotomy and possible ventricular bleeding. Through a mini-thoracotomy, a puncture is made in the anterior-apical left ventricle, and a guide wire is advanced antegrade out the ascending aorta (see Fig. 3-38). It is necessary to angulate the needle hub posteriorly so that the tip is pointing toward the left ventricular outflow tract. If the needle is angulated posteriorly, it will preferentially direct the guide wire toward the mitral valve. Before the thoracotomy is made, a review of the coronary angiograms is useful to avoid puncturing a coronary artery or bypass graft. The goal is to puncture the apical left ventricle between the left anterior descending artery and a diagonal where there is a paucity of coronary arteries. If the left anterior descending artery does not reach the apex and the right coronary artery instead wraps
around the apex, then care should be taken to avoid the concealed coronary in the area of planned catheter introduction.

Transfemoral

Transfemoral access is the most common entry approach to the procedure. It is associated with lower morbidity and shorter hospital stays. Vascular complications still constitute the most common procedural problem in TAVR and worsen the 30-day outcomes. A thorough understanding of peripheral anatomy is required, but a brief outline is described here. The delivery system size has decreased over time, but with the early generation devices, vascular disruption was not uncommon. Accommodating the larger sheaths becomes challenging in tortuous or highly diseased vessels. Severely tortuous iliac arteries may be straightened by a stiff guide wire provided they are not rigid with calcification. Calcified nodules in the iliac arteries may produce scoring on the sheath as it is forced past the narrowed segment of the artery (Fig. 3-45).
Other concerning signs include circumferential calcification and calcification at the edges of iliac bifurcations. Circumferential calcification prevents vessel expansion and reduces the precision of CT measurements due to blooming artifact. Heavy calcification at the retroperitoneal iliac bifurcation poses a risk for tears in a region difficult to reach and repair surgically (Fig. 3-46). The internal vessel diameters are best assessed using...
imaging such as CT or magnetic resonance imaging. When using angiography, a centimeter-graduated catheter and digital subtraction should be used. Angiography is not as ideal in providing diameter measurements due to eccentric lesions and limitations on resolution. If there is concern and a lack of adequate imaging, then peripheral intravascular ultrasound may also be used to better assess arterial diameters and disease burden prior to sheath introduction. Narrowed areas of the aorta may cause the pigtail or other catheters to become trapped by the valve sheath. In these cases, the pigtail catheter would be better placed from a radial access site.

**FIGURE 3-46** Bleeding at the site of a left iliac tear with extravasation of contrast dye. Note the operator’s hands compressing the iliac artery while preparations are made to bypass the iliac rupture.
LEFT ATRIAL APPENDAGE EXCLUSION

Atrial fibrillation is the most common arrhythmia and affects 0.4% of the general population. In patients older than 80 years, the prevalence is 9%. Atrial fibrillation hospital admissions have increased by 66% over the past 2 decades due to an increase in the average age of the population, a higher prevalence of hypertension, heart disease, and better diagnosis.\textsuperscript{44}

The left atrial appendage (LAA) is a small muscular outpouching of the left atrium arising anterior and lateral to the left pulmonary veins. Embryologically, the appendage is truly part of the heart, and the main left atrium is an extension of the coalescence of the pulmonary veins into the fetal heart. This explains why the endocardium of the left atrium is thick and white, without trabeculations, and also explains why there is cardiac muscle in the pulmonary veins. Normally, blood flow into and out of the LAA is sufficiently vigorous to prevent formation of thrombus. During atrial fibrillation, the blood velocity in the appendage is chronically reduced and stasis may occur. In patients with paroxysmal atrial fibrillation, even during normal sinus rhythm, the fractional shortening of the LAA remains suppressed, and blood velocity inside the appendage is reduced dramatically.\textsuperscript{45} Although thrombi can occur in the body of the left atrium during atrial fibrillation, more than 90% of thrombi develop within the LAA due to hemostasis and the presence of interstices within the muscle fibers of the LAA.\textsuperscript{46}

Anticoagulation significantly reduces the incidence of morbidity from thromboembolism in atrial fibrillation, but at the cost of increased bleeding. Closing the LAA by surgical or transcatheter techniques is an attractive alternative to anticoagulation therapy to reduce the risk of embolic injury while avoiding the risk of potential bleeding from anticoagulation therapy. Successful transcatheter LAA occlusion requires a knowledge of the anatomy, surrounding landmarks, and morphologic variants of the LAA.

The interatrial septum is obliquely angled from the posterior right to the anterior left in relation to the long axis of the body. The left atrium is posterior to the right atrium, so pulmonary veins that enter the left atrium are located posterosuperiorly and form the dome of the left atrium (Fig. 3-47).
The walls of the left atrium are nonuniform in thickness and smooth outside the LAA. The anterior wall of the left atrium is located behind the ascending aorta and the transverse sinus and can be very thin (~1-2 mm). This presents a risk of puncture when manipulating catheters in that region. The posterior wall is the thickest (6.5 mm) part of the left atrium, but it can become thinner at the pulmonary vein orifices (Fig. 3-48). The left lateral endocardial ridge protrusion marks the junction between the mouth of the appendage and the LUPV. Thus, the major part of the left atrium, including the septal component, is smooth-walled.

**FIGURE 3-47** Left: Anterior view of the open left atrium showing the pulmonary veins and blood return from the lungs into the atrium. Right: Posterior view of the left atrium and pulmonary veins. Ao, aorta; LAA, left atrial appendage; LPV, left pulmonary vein; RPV, left pulmonary vein; SVC, superior vena cava.
The LAA junction with the left atrium is narrow and usually well-defined. The relationship between the orifice of the LAA and the LUPV is important in preprocedural planning. The LAA may be superior, inferior or, in over half of patients, at the same level as the LUPV, and care must be taken during fluoroscopy to position the catheters in the appropriate structure. To minimize the risk of cardiac perforation during LAA occlusion procedures, a low posterior transseptal puncture will direct the catheter in a more direct fashion toward the LAA orifice (see Fig. 3-18). Care must be taken to avoid angulating too superiorly and puncturing the transverse sinus or posteriorly into the pulmonary veins. A PFO, when present, will direct the catheter in a superior-posterior direction, which may sometimes make access into the LAA more difficult. A more inferior puncture is typically required even in the presence of a PFO.

The LAA is on the left border of the heart between the left ventricle and pulmonary outflow tract. It lies within the pericardium next to the superior lateral aspect of the main pulmonary artery and superior to the left ventricular free wall (Fig. 3-49). There is considerable variability in LAA shape and orientation, which influences the selection of closure device used or if the anatomy is amenable to transcatheter exclusion (Fig. 3-50). The appendage has multiple lobes in over 80% of patients, with 2 lobes in 54% and 3 lobes in 23%. The body of the LAA is composed of trabeculated pectinate muscles, greater than 1 mm in size, which may be confused with thrombus during screening echocardiography. It is important to exclude the presence of thrombus prior to the procedure, as guide wires and a pigtail catheter will be introduced into the LAA in the course of the intervention.
FIGURE 3-49 Anterior view of the heart with left atrial appendage (LAA) in relationship to pulmonary valve and aortic valve. SVC, superior vena cava.
FIGURE 3-50 Lariat suture system excluding the left atrial appendage (LAA). The intracardiac magnet is placed in the LAA via a transseptal puncture. A pericardial tap delivers the extracardiac magnet, and the 2 are approximated until they attach near the apex of the appendage (dashed lines). TEE, transesophageal echocardiography.

Morphologic variations of the LAA include metaphorical descriptions such as the chicken wing (51%), windsock (29%), cactus (15%), and cauliflower (5%) shapes (Fig. 3-51). The chicken wing variant curves in the middle of the dominant lobe. The windsock form presents as 1 dominant lobe with other lobes arising from the dominant one. These 2 forms are the most amenable to extracardiac devices such as the Lariat suture delivery system (SentreHeart, Redwood, CA). The cactus variant also has a dominant lobe with secondary lobes extending from the dominant one in all directions. The cauliflower LAA is a shorter more complex form with multiple irregular
shapes making external device attachment challenging. The closure device should be positioned to occlude all lobes of the LAA. The morphology of the LAA also appears to be associated with variations in embolic risk.

FIGURE 3-51 A. A transseptal sheath is used to inject contrast into the left atrial appendage (LAA) demonstrating a chicken wing morphology. The pericardial sheath is advanced towards the LAA apex prior to passing the Lariat magnets. B. A transseptal sheath is used to inject contrast into the LAA demonstrating a “windsock” morphology. A pericardial wire is in place prior to advancing a pericardial sheath. C. A transseptal sheath is used to inject contrast into the LAA demonstrating the “cactus” morphology. A pericardial sheath is advanced over the wire prior to passing
The Lariat magnets. D. A transseptal sheath is used to inject contrast into the LAA demonstrating the “cauliflower” morphology.

The shape of the LAA ostium is usually visualized as one of several types: oval (69%), foot-like (10%), water drop–like (8%), triangular (8%), and round (5%). The outside of the tip of the appendage is oriented anteriorly and cephalad in most patients but may also be directed inferior, posterior, or, infrequently, into the transverse pericardial sinus. Again, this will influence the approach for extracardiac device exclusion or direction of the delivery sheath for intracardiac devices. The heterogeneity of LAA morphology requires careful imaging assessment prior to attempting transcatheter closure. CT is useful to study the surrounding structures as well as to identify the LAA morphology and its suitability for transcatheter closure. TEE, however, is the most commonly used modality to evaluate the LAA and left atrium before, during, and after device implantation.

To visualize the LAA thoroughly, the TEE probe is advanced from the high esophagus to the mid esophagus. Once the pulmonary veins are visualized, the probe is rotated clockwise until the LUPV comes into view at the 2 o’clock position. The omniplane device is then rotated through 0°, 45°, 90°, and 135° to completely scan through the different aspects of the LAA. This also allows identification of the coronary artery, mitral valve annulus, and LUPV to help orient the device prior to release. Three-dimensional TEE allows for better LAA length assessment by use of reconstruction as well as en-face visualization of the ostium for device sizing. If ICE is used, initial images are obtained from the home view to position the transseptal needle (see Fig. 3-20). Once the transseptal puncture is completed, the probe can be positioned in the pulmonary artery to visualize the LAA. This is performed by unlocking and flexing the catheter, then rotating and advancing it into the right ventricular outflow tract. The LAA ostial diameter may vary depending on the loading conditions, and thus, it is best to have the left atrium pressure around 10 mm Hg when making measurements. The ostial diameter is measured from the anterior rim of the appendage adjacent to the origin of the left circumflex artery to the posterior rim approximately 1 cm below the tip of the limbus of smooth muscle that separates the LUPV from the appendage. This ridge was often mistaken for possible thrombus, resulting in initiating anticoagulation, and so it has been called the “warfarin ridge” (Fig. 3-52). The typical diameter of the ostium is 17 mm in the long axis and 11 mm in the short axis. The depth is measured from the appendage apex to the line
transecting the ostial diameter. If the depth is smaller than the ostial diameter, an Amplatzer Cardiac Plug (St. Jude Medical) may be more suitable than a WATCHMAN device (Boston Scientific, Marlborough, Massachusetts), which requires an appendage depth at least as long as the device diameter.

**FIGURE 3-52** Transesophageal echocardiography of the left atrium, left atrial appendage (LAA), left upper pulmonary vein (LUPV), and “warfarin ridge.” The color-flow Doppler demonstrates blood flow into the left atrium from the pulmonary vein (red) and blood flow into the LAA (blue).

During preliminary imaging by use of TEE or ICE, it is important to evaluate the area between the muscular trabecular wall and atrial wall, which may be quite thin and prone to perforation by the device delivery catheter. The LAA ostium is situated above the left AV groove, which contains the left circumflex artery and the great cardiac vein. The distance between the left circumflex and ostium of the LAA is variable. When the distance is narrow, special care needs to be practiced to avoid excessive pressure by an oversized closure device, which may compress the coronary artery. In patients with prior coronary bypass graft surgery or patients with pericardial adhesions, the anatomic position of venous grafts targeted to the obtuse marginal or diagonal arteries can also be close to the tip of the LAA, exposing them to injury during percutaneous epicardial approaches. The sinoatrial nodal artery can originate from the circumflex artery in 40% of patients. The sinoatrial nodal artery can course between the LAA and LUPV in 14% of patients and may also be compressed during placement of a LAA exclusion device. Other important structures that can lie in the ridge between the LUPV and LAA are
the ligament of Marshall, left phrenic nerve, and a persistent left SVC. CT imaging is the preferred modality to demonstrate the relationship of these structures to the LAA ostium and body of the left atrium. After device closure, echocardiographic evaluation is used in conjunction with fluoroscopy to better direct the catheters and improve device positioning. Three-dimensional TEE is then used to ensure adequate device sealing of the LAA including all accessory lobes, and color-flow echocardiography is used to assess flow around the device to ensure that any residual opening into the LAA is less than 5 mm.

**VENTRICULAR SEPTAL DEFECTS**

Congenital ventricular septal defects (VSDs) are the most common congenital heart defect. They are usually diagnosed in childhood, and few are seen in adults. Acquired VSDs may occur due to trauma, infection, or after a myocardial infarct, and are more often the VSDs addressed in the adult population. Surgical VSD repair remains the mainstay of treatment. The principal complications in a hemodynamically stable patient include AV and bundle branch blocks requiring a pacemaker (4%) and residual leaks (8%). In patients who are poor surgical risks, however, the option of transcatheter treatment is attractive. As with surgery, the most common complication is AV block (1%-1.9%) and bundle branch block (2.8%). Heart block is usually transient and recovers soon after or with steroid therapy.

The ventricular septum is nonlinear and interacts with both the right and left ventricular chambers of the heart. (Fig. 3-53). The more basal and posterior section of the septum is composed of membranous tissue separating the left and right ventricular outflow tracts (see Figs. 3-33 and 3-34). It lies just under and between the right and noncoronary or posterior cusp of the aortic valve. Due to the proximity of the membranous septum to the AV node, repair of a defect there runs a higher risk of heart block. If the defect extends beyond the membranous region and includes the surrounding muscular septum, it is called a perimembranous defect. This is the most common type of VSD in adults, accounting for 72%. During procedures such as TAVR, this portion of the septum may be injured by the displaced calcification, producing a membranous VSD or heart block.
A muscular VSD can be divided into 3 types: trabecular, inlet, and supracristal; however, often a VSD can have components of different types. The trabecular VSD accounts for the majority of VSDs (5%-20%). This occurs as a defect more apically between the trabeculated muscular left ventricle and the right ventricle. When muscular VSDs occur in childhood, they often close spontaneously and may be managed conservatively, especially with small, restricted shunts. The defect may be challenging to see.
by echocardiography or appear as multifenestrated due to the trabeculations. It is important to obtain detailed imaging prior to attempting transcatheter closure of this defect to assess the thickness of the trabeculations and the diameter of the defect.

An inlet septal defect occurs just below the AV valves (tricuspid and mitral). This VSD can occur in association with AV septal defects involving the endocardial cushion in cases of more complex congenital anomalies. Due to its proximity to the AV valves, a transcatheter repair is usually not possible. If this defect is suspected, additional care should be taken to assess the cardiac anatomy and look for other defects.

The supracristal defect is also called an infundibular, subarterial, subpulmonary, conal, or doubly committed VSD. It lies between the left and right ventricular outflow tracts just under the aortic and pulmonic valves and is more anterior to the membranous septum. This defect, if large enough, will present with aortic regurgitation because the right aortic cusp prolapses into the defect. With time, this can produce progressive aortic valve damage. The defects that may be managed by transcatheter techniques are the perimembranous and muscular VSDs.

A myocardial infarct due typically to occlusion of the left anterior descending coronary artery can bring about a muscular VSD usually in the trabecular region. This type of VSD presents a challenge to transcatheter closure because of the necrotic and weakened margins surrounding the area of injury as well as the thick muscular ridges. It is associated with a high mortality but may be amenable to percutaneous closure in selected patients.

Echocardiography is the principal tool to evaluate VSDs. An initial assessment should include location, size, number of defects, and other associated anomalies. The 2 initial views used to assess a VSD are the parasternal long and parasternal short-axis views. The septum is perpendicular to the ultrasound beam in those views providing the best spatial resolution. The 4-chamber view is then used to assess muscular VSDs further. Table 3-2 lists the best window used for the different defect types (Fig. 3-54).

Table 3-2  The Different Echocardiographic Views That Best Show Each Ventricular Septal Defect (VSD) Type
FIGURE 3-54 Short-axis and parasternal long-axis transesophageal echocardiography views. These are the initial orientation views to assess for the most common types of ventricular septal defects (VSDs). Color-flow Doppler is then used to assess flow. The red, blue, and green lines demonstrate where the different types of VSD are located. LV, left ventricle; MV, mitral valve; RV, right ventricle.

Using TEE, a probe is placed in the high esophagus and rotated to show the aortic valve. The omniplane is then rotated to 40° to 70° to view the aortic

<table>
<thead>
<tr>
<th>Type of VSD</th>
<th>Echocardiographic Window</th>
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<tbody>
<tr>
<td>(Base of the great vessels)</td>
<td></td>
</tr>
<tr>
<td>Membranous Supracristal</td>
<td>High parasternal short axis</td>
</tr>
<tr>
<td>Inlet Trabecular</td>
<td>Low parasternal short axis</td>
</tr>
<tr>
<td>Trabecular Supracristal</td>
<td>Parasternal long axis</td>
</tr>
<tr>
<td>Membranous (with rotation of the echo probe)</td>
<td></td>
</tr>
<tr>
<td>Muscular VSD (trabecular or inlet)</td>
<td>Apical 4-chamber view</td>
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<tr>
<td>Trabecular</td>
<td>Subcostal</td>
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valve en face. The membranous septum is then viewable in the 7 to 10 o’clock position next to the valve and just medial to the tricuspid valve. A supracristal septal defect would be observed at the 4 to 7 o’clock position. Rotating the omniplane further to show the valve in the long axis will bring into view the membranous septum just below the aortic valve; the supracristal and the muscular septum are seen further apically. Advancing the probe to the mid-esophageal position and rotating the omniplane to 0° to show the 4-chamber view will yield the inlet and trabecular muscular VSDs. Use of 3D echocardiography is helpful in reviewing all margins of the defect as well as quantifying the physiologic extent of the shunt. The hemodynamic effects of a VSD, as well as anatomic structural consequences influence the decision to intervene on the VSD. A sizing balloon can also be used to better assess the appropriate size device to be used, similar to closing an ASD. Multiplanar CT reconstruction will further help quantify the location and size of the VSD in preparation for transcatheter intervention. It is especially helpful in assessing the location of the defect in relation to the surrounding structures and valves.

Different devices are available to close the different types of defects. Due to the heterogeneity of the ventricular septum, the devices have characteristics specific to each part of the septum. Options for closure include using the Amplatzer series of VSD devices (St. Jude Medical) and the Nit-Occlud device (pfm medical ag, Köln, Germany). The Amplatzer muscular VSD occluder is a double-disk nitinol wire mesh with polyester patch designed to fit the thicker muscular septum. The muscular occluder has symmetric right and left ventricular disks 8 mm wider around the circumference than the waist (Fig. 3-55A). The postinfarct version of the device has a 10-mm-long waist to accommodate infarcted myocardial tissue at the rims (Fig. 3-55B). The membranous VSD occluder is a self-centering retrievable double-disk device with a shorter waist. The device is eccentric with a left side aortic overhang of 0.5 mm and a left side ventricular overhang of 5.5 mm. The ventricular end has a radiopaque marker to help orient the longer component of the disk toward the ventricular apex. This allows the device to be implanted without impinging on the left heart valves (Fig. 3-55C).
FIGURE 3-55 A. Amplatzer muscular ventricular septal defect (VSD) occluder. B. Amplatzer muscular VSD postinfarct occluder. This device has a wider waist to anchor to the infarcted tissue. C. Amplatzer membranous VSD occluder. The device is eccentric with a shorter disk overhang on the valve side and longer ventricular side (C). The device is sized according to the waist (A). A marker at the distal left-sided disk identifies the orientation angiographically.

After closure, further assessment by TEE is important to determine the adequacy of closure and assess for residual shunting and stability of the device. This is accomplished by use of TEE and angiography. The TEE probe or C-arm is rotated to an orthogonal plane to show the device across the
septum in profile and assess for residual flow. The goal of the procedure is to place the left ventricular disk flush with the left side of the septal wall. The rest of the device can be irregularly placed within the defect and on the right side of the septum. Should heart block develop, the patient should be monitored and possibly treated with steroids. Echocardiography also helps in viewing the nearby structures, such as valves, and looking for possible device impingement prior to release.

THE MITRAL VALVE

The mitral valve is a complex structure that permits unidirectional flow of blood between the left atrium and left ventricle. The parachute-like structure of the mitral valve is a wonder of evolutionary design. It has to withstand the full force of the left ventricular pressure during every systole for 2.2 billion heartbeats in an average lifetime. It should not be surprising that mitral regurgitation is so common in the elderly. The valve was named by Andreas Vesalius in the 1500s because it reminded him of the Pope’s hat, called a mitre. An understanding of the anatomy of the valve and relative views using different modalities is important in procedures such as the Mitraclip (Abbott Vascular, Temecula, CA), annuloplasty ring placement, coronary sinus devices, and paravalvular leak closures.

The annulus of the mitral valve is made up of fibrocollagenous tissue that creates an asymmetric valve opening of 4 to 6 cm$^2$. The annulus measures 9 to 10 cm in circumference and is reinforced by the right and left fibrous trigons, which attach to the mitral-aortic fibrous continuity anteriorly. Identification of the trigons is important because the conduction tissue lies beneath it and could be injured during surgical repair or replacement of the valve. The mitral-aortic continuity attaches to the fibrous tissue just below the interleaflet triangle between the noncoronary and left coronary cusps. This anterior segment of the annulus is more rigid and less likely to deform. The posterior segment is made up of muscular tissue and is more likely to stretch, which predisposes to functional mitral regurgitation when the left ventricle dilates.

From the short axis, the mitral valve appears to curve upward, with the trigons more apical and the middle of the valve leaflets (A2, P2) more atrial. This has been described geometrically as a hyperbolic paraboloid or saddle.
shape. The coronary sinus circumferentially parallels the mitral valve annulus, anteriorly from the great cardiac vein and posteriorly where the vein of Marshall enters and empties into the posterior right atrium at the coronary sinus ostium. The ostium is partially covered by the Thebesian valve, which makes retrograde entry into the coronary sinus difficult in 3% of patients. There may be several valves of Vieussens within the coronary sinus, which may also impede retrograde passage of catheters or pacemaker wires. The coronary sinus is 0.5 to 1 cm above (atrially displaced) the annulus of the mitral valve. Devices that are placed within the coronary sinus to “cinch” the mitral valve leaflets are actually pulling together the atrial tissue above the level of the valve, but nonetheless appear capable of approximating the mitral leaflets (Fig. 3-56). The circumflex coronary artery runs a course parallel to the annulus of the mitral valve and coronary veins. When the artery courses under the vein, there is a risk of compressing or occluding the circumflex coronary artery with devices that are placed within the coronary sinus to approximate a percutaneous annuloplasty (Fig. 3-57).
FIGURE 3-56 The relative location of the coronary sinus (CS) compared to the mitral annulus. Top: There is a displacement vertically (y) as well as laterally (x) between the CS and the mitral annulus, and this relationship changes during the cardiac cycle as well as with pathology. The CS is the opening of the GCV into the RA. Below: The CS (white arrow) as it surrounds the heart externally from different views. GCV/AIV, great cardiac vein/anterior interventricular vein; LA, left atrium; LV, left ventricle; RA, right atrium.
The broader anterior leaflet extends in a crescent shape further into the opening and attaches to the anterior fibrous annulus. The leaflet is divided into 3 sections named A1, A2, and A3, with the A1 segment positioned laterally and A3 segment positioned most medial. The attachment point of the leaflet to the annulus is called the basal zone. The center of the leaflet is named the clear zone, and the outer free edge of the leaflet where the chordae attach is named the rough zone. This is the target zone for attachment of the Mitraclip or Alfieri stitch. As described in Figure 3-48, the anterior leaflet extends further into the orifice, while the posterior leaflet involves a larger part of the mitral annulus. The posterior mitral leaflet is more narrow in width but extends over two-thirds of the circumference of the annulus. The posterior leaflet does not displace as much as the anterior leaflet into the left ventricle during diastole. The scallops of the posterior leaflet are more distinct than those of the anterior leaflet and are named P1, P2, and P3. The P1 scallop opposes the A1 scallop laterally, and the P3 scallop is more medial and apposes A3. The free edge of this leaflet also contains the rough zone where chordae attach for support.
The chordae support the valve structures and prevent the leaflets from prolapsing into the atrium during systole. The chordae act as a series of anchors to hold or tether the leaflets from moving excessively. Most chordae originate from the papillary muscles and divide into a fan shape before reaching the valve edges. There are 3 types of chordae. The primary or rough zone chordae attach to the rough free edge of each leaflet. The secondary chords attach to the body of the leaflets on the ventricular side. The tertiary or basal chordae attach only to the basal segment of the posterior leaflet and are connected directly to the ventricular wall, not the papillary muscles. The chordae tend to be closer together at the edges of the valves. The lack of basal chordae on the anterior leaflet makes passing catheters into the ventricle easier when aiming at the center of the valve away from the commissures and toward the anterior leaflet.

There are 2 papillary muscles positioned anterolaterally, and posteromedially. They can have a single or multiple projections or heads, and the chordae originate along the edge of these muscles. The chordae from each papillary muscle divide and attach to both leaflets of the valve so that during systole the valve leaflets are brought together and secured against the contracting ventricle. It is important to note the anterior papillary muscle has a dual coronary blood supply, whereas the posterior muscle is supplied only by the right coronary artery or dominant circumflex artery. A large infarct can affect the posteromedial papillary muscle more often and result in ischemic mitral regurgitation or papillary rupture. Transcatheter repair using the Mitraclip requires that the regurgitation pathology be more centralized, such as in the A2-P2 area, and with a leaflet coaptation depth less than 11 mm, flail gap less than 10 mm, flail width less than 15 mm, and mobile leaflet length greater than 10 mm. This allows the clip to properly secure the leaflets and resolve the majority of the regurgitation. There should also not be significant mitral stenosis, and the final orifice area should be greater than 4 cm². Some valves are tethered by rheumatic disease or restriction due to papillary muscle dysfunction such that the leaflets are too far apart, have a large flail gap, or already exhibit stenosis. In these cases, the likelihood of procedural success is lower, and there is a possibility of mitral stenosis if a clip is implanted.

A way to orient the operator during fluoroscopy is to consider the location of the left anterior descending artery and right coronary artery. The anterior-lateral mitral commissure is close to the ostium of the left anterior descending
artery as it leaves the left main coronary artery. In the 30° RAO projection, the anterior leaflet is seen superiorly while the posterior leaflet is inferior. The anterior-lateral commissure is anterior at the junction of the 2 leaflets. From the LAO caudal projection, the anterolateral mitral commissure is on the left, and the posteromedial commissure is on the right, with the anterior leaflet above the posterior leaflet.

CT can provide useful information in terms of structure but not function. Echocardiography remains the principal modality to best evaluate the function of the mitral valve. Multiplanar views define the aspects of the valve apparatus in several planes corresponding to fluoroscopic and echocardiographic views (Fig. 3-58). The higher spatial resolution of CT provides structural information including restriction of the leaflets, tethering of the chordae, or dilation and deformation of the annulus.
Transthoracic echocardiography is the recommended first-line modality to assess the function of the mitral valve. Three-dimensional echocardiography provides further information on structure giving a more complete picture of the valve in real time. The parasternal long and short views provide good assessment of the annulus and valve as well as possible dysfunction including inadequate tethering of the leaflets. The 2- and 4-chamber views provide information on ventricular and annular dilation as well as atrial size to produce a more complete picture of the mitral valve pathology.\textsuperscript{62}

By TEE, the valve can be visualized in the short axis from the mid-esophageal position. Starting with the omniplane at 0° to show the 4-chamber view, the probe is rotated to step through the commissures of the 2 leaflets and demonstrate all coaptation points. The interatrial septum also can be visualized to guide a transseptal puncture. The TEE probe can then be advanced to obtain transgastric views and flexed to look up toward the mitral valve in the short axis. This is especially useful to review the entire annulus. In order to position the clip in the correct orientation relative to the regurgitation jet and prolapsed segment, a TEE “bicommissural” and “LVOT” views are used to ensure the appropriate trajectory. The use of 3D echocardiography provides incremental information on the geometry of the valvular apparatus. Due to the 3D shape of the annulus and leaflets, 2D imaging may miss the extent of pathology and foreshorten important structures. Three-dimensional echocardiography provides a better guide during percutaneous interventions and improves procedural outcomes.\textsuperscript{63}

The modalities described above can all be used to gain a better understanding of the entire mitral apparatus and the cardiac chambers forming a more complete global picture. Appropriate scores such as the Wilkins or Carpentier scale can then be applied to determine the suitability of transcatheter techniques and likelihood of success or complications.

REFERENCES

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27. Naqvi T. Echocardiography in percutaneous valve therapy. *JACC*


MULTIPLE CHOICE QUESTIONS

1. During a mitral valve clip procedure, which of the following would be true when orienting the device?
   A. When crossing the septum, the device catheter should be pointed posteriorly to best cross the mitral valve.
   B. To clip medial or lateral parts of the valve, the clip may need to be rotated to be perpendicular to the coaptation plane.
   C. The location of the transseptal puncture is less important than the direction of the catheter.
   D. A patent foramen ovale can be used to cross the septum and deliver the device, avoiding the need for a transseptal puncture.

2. Which of the following is least likely to increase the risk of pacemaker implants during a transcatheter aortic valve replacement?
   A. A low implant position in the left ventricular outflow tract (LVOT).
   B. Dense LVOT calcification.
   C. A preexisting right bundle branch block.
   D. Transapical approach to the implant.
   E. Use of a self-expanding prosthesis instead of a balloon-expanding prosthesis.

3. When closing an atrial septal defect, which rim, when missing, is most likely to increase the risk of device embolization and why?
   A. Retroaortic rim due to motion of the aorta.
   B. Retroaortic rim due to tension on the device by the delivery cable.
   C. Posterior rim due to limited atrial space.
   D. Inferior vena cava rim due to tension on the device by the delivery cable.
   E. Inferior vena cava rim due to proximity to the tricuspid valve.

4. In which of the following interventions is there no risk of coronary artery
injury or occlusion?
A. Transcatheter aortic valve replacement (TAVR).
B. Coronary sinus annuloplasty.
C. Device closure of an atrial septal defect.
D. Transcatheter valve implantation in the pulmonic position.

5. Which of the following statements regarding echocardiographic imaging is true?
A. A patent foramen ovale always has right-to-left shunting by color at rest.
B. Transesophageal echocardiography is the principal tool to evaluate a ventricular septal defect.
C. Echocardiography measurement of the aortic annulus for TAVR is more accurate than computed tomography.
D. Transthoracic echocardiography is sufficient to describe the left atrial appendage anatomy for closure.
E. In intracardiac echocardiography imaging, the area at the top of the screen is the left atrium.

ANSWERS
1. B
2. D
3. D
4. C
5. B
INTRODUCTION

The advent of percutaneous therapies has revolutionized our approach to treatment of valvular heart disease. The ability to perform such interventions safely and effectively relies heavily on anatomical details. Fluoroscopic anatomy alone is inadequate to guide valvular interventions due to poor visualization of the complex 3-dimensional valve unit. More advanced imaging technology is thus required to support fluoroscopy in guiding valvular interventions. Understanding valvular anatomy and correlating it real time with presented multimodality imaging is critical for procedural success in the catheterization laboratory.

In this chapter, we describe the anatomy of the 4 cardiac valves, applying it to fluoroscopic and multimodality imaging, to guide percutaneous valvular interventions for the cardiac interventionalist.

GENERAL ORIENTATION OF THE VALVES

The heart is normally situated obliquely in the chest such that the
Interventricular and interatrial septa are approximately 45° to the anteroposterior projection (Fig. 4-1). Therefore, a 45° left anterior oblique (LAO) projection will allow distinction of the left and right structures, whereas a 45° right anterior oblique (RAO) projection will discriminate anterior and posterior structures. The planes of the mitral and tricuspid valves are virtually at right angles to the septal plane with some inferior tilt with the mitral plane situated slightly posterior to the tricuspid valve plane. In other words, LAO 45° caudal 15° may visualize the mitral and tricuspid valves en face, whereas RAO 45° caudal 15° may provide one of the side views for these valves. The inflow and outflow of the left ventricle are aligned closely with an angle of 15° to 20° in a normal heart, whereas the inflow and outflow of the right ventricle are aligned almost at 90°.
FIGURE 4-1 Anatomic structures as visualized under fluoroscopy in the right anterior oblique (A), left anterior oblique (B), anteroposterior (C), and left lateral (D)
views.

The aortic valve plane is typically tilted caudally and leftward, with the end on view being either LAO 60°C caudal 35°C or RAO 30°C cranial 45°C. Side views can be obtained with either RAO 20°C caudal 20°C or LAO 40°C cranial 30°C projections. Pulmonary valve is tilted quite posteriorly and to the right, such that the end on view is RAO 10°C caudal 50°C, and the pulmonary valve plane ranges from RAO 30°C cranial 20°C to LAO 30°C caudal 20°C. The right ventricle wraps around the outflow of the left ventricle, being mostly anterior to the left ventricle with only the inferior margin to the right of the left ventricle; the outflow tract of the right ventricle is superior and to the left of the aortic valve. The left atrium forms most of the posterior aspect of the heart as appreciated on the lateral fluoroscopic views.

**FIBROUS SKELETON OF THE HEART**

The fibrous skeleton (Fig. 4-2) formed by the valve annuli and the intervening right and left fibrous trigones defines the plane of the atrioventricular groove and houses all 4 of the cardiac valves. The aortic valve has a central location in the fibrous skeleton and is closely related to the other 3 valves. The mitral valve (posterior medial commissure) and the tricuspid valve (septal leaflet) are intimately connected to the base of the noncoronary cusp of aortic orifice by a condensed mass of fibrous tissue, the central fibrous body, also referred to as the right fibrous trigone, which continues inferiorly as the membranous interventricular septum. The left fibrous trigone is another condensed mass of fibrous tissue that connects the anterolateral commissure of the mitral valve and the base of the left coronary cusp of the aortic valve. The pulmonary valve is located anterior and to the left of the aortic valve and has a separate fibrous ring that is connected to the base of the right coronary cusp of the aortic valve by a fibrous band referred to as the conus ligament.
Away from the central body, the fibrous skeleton becomes less robust with less discrete organization. The part of the fibrous skeleton bounded by the left and right trigones connects the anterior mitral leaflet with the noncoronary cusps of the aortic valve and is commonly referred to as the aorto-mitral curtain, intervalvular fibrosa, or subaortic curtain. Calcifications of the fibrous skeleton of the mitral and aortic annuli (mitral annular calcification) are of critical importance to the outcome of transcatheter aortic valve implantation (TAVI) with respect to symmetric deployment of the valve and resultant perivalvular leak.

**AORTIC VALVE**

**Gross Anatomy**

The aortic root is a complex and dynamic ensemble of the aortic annulus, aortic valve leaflets, sinuses of Valsalva, the sinotubular junction, and the interleaflet fibrous triangles that connects the left ventricle to the ascending aorta. It is often described as resembling a crown (Fig. 4-3) that is transected
by 3 horizontal planes.\(^1\)\(^-\)\(^3\) The top of the crown, represented by an imaginary plane that transects the ring-shaped sinotubular junction in a horizontal fashion, is formed by the peripheral attachments of the aortic valve leaflets near the commissures. The base of the crown is a virtual plane formed by horizontal transection of the basal attachments of the aortic valve leaflets. Between these 2 planes exists the true anatomic aortoventricular junction marked by the area over which the fibrous wall of the arterial trunk is attached to the supporting ventricular structures, forming the third imaginary horizontal plane of the aortic root. It is important to note that these planes are not necessarily parallel to each other due to the fact that there is reflection of left and right coronary cusps over the muscular septum.

**FIGURE 4-3** The aortic annulus is defined as a virtual ring (*green line*) with 3 anatomic anchor points at the nadir (*green points*) of each of the attachments of the 3 aortic leaflets. LCC, left coronary cusp; NCC, noncoronary cusp; RCC, right coronary cusp.

**Aortic Annulus**

The term *annulus* came into vogue to express a reference plane for valve sizing and deployment during surgical aortic valve replacement. However, despite the widespread use of this term, there is no distinct anatomic or histologic circular structure that defines it. Surgically, the annulus is crown shaped and is represented by the semilunar lines of attachment of the aortic valve leaflets to the aortic root.\(^1\) Echocardiographers, however, measure the annulus along the virtual basal plane of the crown in the left ventricular outflow tract at the inferior-most aspect of the aortic valve leaflet hinge points.\(^2\)
Annular measurements are routinely performed in the parasternal long-axis view obtained on 2-dimensional (2D) transthoracic echocardiography (TTE) and rarely in the apical 5-chamber view (Fig. 4-4). The aortic annulus on transesophageal echocardiography (TEE) is measured in the 125° to 140° long-axis view of the left ventricle (see Fig. 4-4). This measurement is taken from the inner edge of the septal endocardium to the inner edge of the anterior leaflet of the mitral valve at the hinge point of the aortic valve leaflets in mid-systole. More recently, multidetector computed tomography (MDCT) has become the gold standard for annular assessment. Annular measurements using MDCT can be obtained as either a hinge-to-hinge measurement on a single oblique view as measured on TTE/TEE or can be derived from the area or the circumference of the virtual basal ring (Fig. 4-5). There are several important points about the measurement of the “annulus.” The annulus is not circular but elliptical, and therefore, different modalities that measure different planes of the annulus do not necessarily yield same results. The annular size obtained by MDCT is typically larger than when measured by 2D TTE/TEE. When the diameter of the annulus is measured solely by 2D methods (typical for TEE or TTE), special care has to be taken to get the maximal diameter because symmetric opening of the leaflets (where typically the views are obtained) does not necessarily provide the largest diameter.
FIGURE 4-4 Biplane transthoracic (top row) and transesophageal (bottom row) imaging showing the long-axis and corresponding orthogonal short-axis plane of the aortic annulus. Aortic annulus measurements performed by transthoracic and transesophageal echocardiography.
FIGURE 4-5 Aortic annular measurement on cardiac computed tomography. Hinge points of all 3 cusps are identified in both the Sagittal oblique plane (top row) and Coronal oblique plane (middle row). Reconstructed double-obliqued axial plane or transverse plane (bottom row) is then used to measure the maximal, minimal, and mean annular diameter and the annular area and perimeter.

Leaflets

The aortic valve is normally comprised of 3 semilunar leaflets or cusps of nonuniform size (Fig. 4-6). The leaflets derive their name from the associated coronary artery (right coronary cusp, left coronary cusp, and noncoronary cusp) that arises near the cusp. Each leaflet has a free margin and a margin that is attached peripherally to the aortic root in a semilunar fashion. Each leaflet also has a ventricular surface that is smooth and an arterial surface that is rougher in nature. At the center of the free margin of the leaflets is a
thickened nodule called the nodule of Arantius.\textsuperscript{7} The remainder of the free margin extending from the nodule of Arantius to the aortic attachment is called the lunule. Coaptation of the leaflets occurs at the nodule of Arantius and a thicker closing surface 1 to 2 mm below the lunule. Therefore, fenestrations, although common in the lunule, are not associated with valvular insufficiency in the normal aortic valve.\textsuperscript{7} However, if dilation of the aortic root moves the line of valve closure toward the lunule, aortic insufficiency can result from these lunular fenestrations. The lunules of adjacent leaflets are attached to each other for a very short segment at their bases to form apposition lines referred to as commissures.

\textbf{FIGURE 4-6 Anatomy of the aortic valve.}

Functionally, the leaflets separate the aorta from the left ventricle during ventricular diastole and represent the hemodynamic ventriculoarterial junction.

\textbf{Sinotubular Junction}

The sinotubular junction is a circular ridge of fibroelastic tissue at the apices of leaflet attachment to the aortic wall.\textsuperscript{2} Anatomically, the sinotubular junction marks the transition point from the aortic root to the ascending aorta. Dilation of the sinotubular junction leads to aortic insufficiency. Severe
calcification of the sinotubular junction can be problematic for balloon-expandable TAVI. If the calcification is circumferential and the sinotubular junction diameter is smaller or comparable to the diameter of the annulus, there is some risk of “watermelon seeding” of the balloon in the ventricular direction at the time of valve deployment. Precariously, this can lead to severe aortic insufficiency or even valve embolization into the left ventricle.

**Sinuses of Valsalva**

The expanded portion of the aortic root on the arterial side of the aortic valve leaflets is called the sinus of Valsalva. It is bound distally by the sinotubular ridge and proximally by the lower most attachment of the aortic valve leaflets. There are 3 sinuses, each named for the coronary artery to which it is associated (right coronary, left coronary, and noncoronary). The sinuses prevent coronary obstruction by housing the valve leaflets and generating eddy currents that further hold the leaflets away from the aortic valve during systole. The eddy currents also play a role in valve closure and stress reduction of the aortic valve leaflets during diastole.

The geometry of the aortic sinus has important implications for valve choice and size during transcatheter aortic valve replacement (TAVR). Important measurements at the aortic root include height and width of the sinus of Valsalva, take off height of the coronary ostia, and ascending aortic diameter (Fig. 4-7). These measurements are crucial to prevent coronary ostial obstruction following TAVR.
FIGURE 4-7 Measurements at the aortic root that include height and width of the sinus of Valsalva (middle row), takeoff height of the coronary ostia (top row), and ascending aortic diameter (bottom row).

A unique aspect of the noncoronary sinus is that it rests on the interatrial
septum. When doing a transseptal puncture, visualization of this sinus by contrast injection or catheter placement in the sinus is critical to avoid puncturing the aorta.

**Interleaflet Fibrous Triangle**

Semilunar attachment of the aortic leaflets creates 3 triangular areas under each commissure called the interleaflet fibrous triangles.\(^9\) They are an extension of the left ventricular outflow tract to the sinotubular junction. The triangle between the left coronary sinus and noncoronary sinus is continuous with the aorto-mitral curtain. The triangle between the noncoronary and the right cusp is in continuity with the membranous septum. The third triangle between the left and right coronary cusps attaches to the muscular septum.

**Relationships of the Aortic Root**

Familiarity with anatomic relationships of the aortic valve to the 4 cardiac chambers and to the vascular and conduction system is important to the cardiac interventionalist in the current era of transcatheter therapies for structural heart interventions.

As described earlier, the noncoronary sinus rests on the interatrial septum. Visualization of this sinus by contrast injection or catheter placement in the sinus is critical to avoid puncturing the aorta during transseptal puncture. When using fluoroscopy for transseptal puncture, the location of the fossa ovalis is “guesstimated” based on the location of the posterior boundary of the aortic root as marked by a pigtail catheter positioned in the noncoronary aortic cusp combined with bony landmarks. The classic fluoroscopic landmark for the puncture site is in the center of the spine, at the level of the aortic root.\(^12\) To avoid aortic perforation during transseptal puncture, the dilator tip should be visualized below the pigtail catheter placed in the noncoronary cusp in the 30° LAO view and posterior to the pigtail catheter in the 30° RAO view.

Coronary obstruction after TAVR is a rare but serious procedural complication that is potentially avoidable with meticulous preprocedural aortic root analysis. A low coronary ostial takeoff or, more commonly, a low takeoff in combination with a narrow aortic root and bulky valve calcification predisposes to coronary ostial obstruction by displacement of the calcified
native cusp over the coronary ostium.\textsuperscript{10,11,13} In the setting of a narrow sinus of Valsalva, the bulky calcified leaflets cannot be accommodated and invariably get pushed over the ostia of the coronary arteries and have been observed to cause coronary obstruction. A displaced calcified native leaflet is more likely to close the origin of the left main coronary artery than the right coronary artery due to a normal higher right coronary artery ostia takeoff. Furthermore, aorto-mitral continuity via the intervalvular fibrous skeleton allows complete straightening of the left coronary leaflet, placing the left coronary ostium at a higher risk. The interventricular septum, however, anchors the right coronary leaflet and limits its upward movement, an important factor that reduces the risk of right coronary artery ostial occlusion.

A sinus of Valsalva width of 27 mm (for the 26-mm CoreValve) or 28 mm (for the 29-mm CoreValve) and a coronary height of 14 mm are recommended by the manufacturer for the implantation of the CoreValve system (Medtronic, Edgewater, MD).\textsuperscript{10} There are no specific manufacturer recommendations for the Edwards valve (Edwards Lifesciences, Irvine, CA), but a cutoff of 10 mm for the coronary height is widely practiced.

Careful consideration should be given prior to stenting the left main trunk in patients intended to have a TAVI. In the absence of beveled stents, the inferior aspect of the left main stent often extrudes into the aortic lumen. It is conceivable that a percutaneously placed valve may crush the native valve leaflets against a protruding left main stent. If left main percutaneous intervention is undertaken in such patients, precise stent placement to avoid “hanging out” into the aorta is paramount. Shallow LAO or anteroposterior (AP) cranial projections (instead of the typical LAO caudal or AP caudal views) may be useful to allow conservative stent positioning.

The His bundle and the fascicles of the left bundle are closely related to the aortic root. Conduction system disturbances and permanent pacemaker requirements are thus common following TAVR. The His bundle, a continuation of the atrioventricular node, penetrates the central fibrous body, runs between the membranous septum and the muscular septum, and bifurcates at the crest of the muscular ventricular septum into the left and right bundles. At this location, the left bundle is intimately related to the base of the interleaflet triangle between the right and noncoronary cusp of the aortic valve. In autopsy specimens, the exit of the left bundle has been identified to be 6.3 ± 2.4 mm from the noncoronary cusp of the aortic valve, making it particularly vulnerable to disruption with a lower placement of a
percutaneous aortic valve. The superficial course of the left bundle as it descends along the left interventricular septum further increases its susceptibility to injury with even minor trauma. Conduction disturbances are more common after the CoreValve compared to the Edwards valve and are likely related to the frame characteristics and mechanism of implantation.

**Pathologic Anatomy**

Three basic types of aortic stenosis are recognized: (1) degenerative calcific aortic stenosis; (2) congenitally bicuspid aortic stenosis; and (3) rheumatic aortic stenosis (Fig. 4-8). Degenerative calcific aortic stenosis is present in approximately 2% to 3% of the population over the age of 65 and approximately 4% of patients over the age of 85. Nearly one-third (29%) of patients have calcific aortic sclerosis without stenosis. Degenerative calcific aortic stenosis represents the majority of patients over the age of 70 undergoing traditional aortic valve replacement. Congenitally bicuspid aortic stenosis is the most common etiology of aortic stenosis in younger patients and has been reported to occur in 1% to 2% of the population. Adjacent cusps fuse to form a single aberrant cusp, larger than its counterpart yet smaller than 2 normal cusps combined. The hemodynamic perturbations associated with the bicuspid leaflets in combination with fibrillin-1–deficient microfibrils are responsible for the premature loss of the structural integrity of the valve as well as premature degeneration of the aortic media. As such, bicuspid aortic stenosis is often associated with dilatation of the aortic root and aneurysm formation. These patients typically present in their fifth and sixth decades of life with symptomatic aortic stenosis with or without a dilated aortic root and present a unique challenge for percutaneous valve therapy. Large annular diameter, dilated aortic sinuses, and eccentric leaflet calcification often translate into suboptimal candidacy for TAVI. Even crossing the bicuspid valve can be difficult in these patients; an AL-1 catheter and a straight 0.35-inch wire can be used to accomplish this occasionally arduous task. If the left coronary leaflet is involved in the fusion (left-right or left-non), an RAO projection is often helpful in crossing these valves, whereas a traditional LAO projection is most useful for crossing valves with fusion of the right and noncoronary leaflets. Classical rheumatic aortic valve stenosis is associated with an abnormal mitral valve (diffuse leaflet fibrosis, usually stenotic) and an aortic valve characterized by commissural fusion of
at least 1 and generally 2 or 3 commissures.

FIGURE 4-8 Mechanisms of aortic stenosis and aortic regurgitation.

Three basic types of aortic regurgitation have been recognized\(^\text{17}\) (see Fig. 4-8): type I, normal leaflets with aortic root dilation or leaflet perforation; type II, leaflet prolapse or fenestration; and type III, leaflet restriction or extensive leaflet calcification. Primary aortic regurgitation with noncalcified aortic root is typically considered a contraindication for TAVR due to the risk of valve dislocation as a consequence of insufficient anchoring. However, recent advances in valve technology have expanded percutaneous catheter-based therapies to pure aortic regurgitation.\(^\text{18}\)

**Fluoroscopic Anatomy**
Pivotal to performing TAVI and other structural heart interventions is a fundamental understanding of fluoroscopic anatomy. Two basic views commonly used for fluoroscopic imaging of the aortic valve are RAO 30° and LAO 60°. In the RAO view, the right coronary cusp is the most anterior located cusp (closest to the anterior wall of the left ventricle); conversely, the noncoronary cusp is the most posterior located cusp (closest to the inferior wall of the left ventricle) (Fig. 4-9). The left coronary cusp lies between the noncoronary cusp and right coronary cusp in the RAO projection. Conversely, in the LAO projection, the left coronary cusp is well visualized (closest to the lateral wall of the ventricle), whereas the noncoronary cusp and right coronary cusp are superimposed on one another, with the noncoronary cusp lying slightly below the right coronary cusp (see Fig. 4-9). A pigtail catheter in the noncoronary cusp can be clocked to enter the right coronary cusp and counterclocked to enter the left coronary cusp.
FIGURE 4-9 Fluoroscopic image of the heart and corresponding transesophageal electrocardiography images are shown. Mitral and aortic valve details are outlined. A1, first scallop of the anterior mitral leaflet; A2, second scallop of the anterior mitral leaflet; A3, third scallop of the anterior mitral leaflet; AML, anterior mitral leaflet; AO, aorta; IAS, intra-atrial septum; LA, left atrium; LAA, left atrial appendage;
Achieving a uniform alignment of the coronary cusps for TAVI typically requires slight caudal angulation for the RAO view and slight cranial angulation for the LAO view. Kasel and colleagues\(^{20}\) have proposed a rule—“follow the right cusp”—to obtain the perpendicular implantation view on fluoroscopy. After identification of the right coronary cusp, the implantation angle can be obtained by rotating the C-arm to an RAO or LAO angulation if the right cusp is placed behind the noncoronary cusp or the left cusp, respectively, and/or rotating the C-arm cranially or caudally if the right cusp appears higher or lower than the ideal plane intercepting other cusps, respectively.

Fluoroscopy is also important for recognizing other important anatomic considerations for TAVI such as curvature of the aortic arch, aortic valve calcification, calcification of the sinotubular junction, aortoiliac calcification and diameter, and movement of equipment through the aortoiliac system.

**Computed Tomography Anatomy**

At times, echocardiographic visualization of the aortic valve is difficult, and MDCT, with its higher spatial resolution, allows for detailed evaluation and recognition of the valvular architecture. Several anatomic issues can be addressed by MDCT including anatomy of the aortic valve (eg, bicuspid), aortic valve area, severity and location of aortic root calcification, annular measurements, sinus of Valsalva measurements, and location of the coronary ostia, sinotubular junction assessment, and aortic root orientation in relation to the body axis.\(^{21}\) Anatomic assessment of the aortic root and iliofemoral arteries using MDCT has thus become a standard practice prior to TAVI.\(^{5,22}\)

Bicuspid aortic valves are present in 1% to 2% of the population and are the second most common etiology of aortic stenosis. They can be congenital or acquired. In the congenital bicuspid aortic valve, unlike the acquired variant, the cusp containing the false commissure (raphe) (conjoined cusp) is
of similar length to that of the other cusp. The bicuspid aortic valve exists in 2 major forms: a right-left (fusion of the noncoronary cusp and either the left or right cusp) and an AP (fusion of the right and left cusp) orientation of the 2 cusps. These structural changes in the bicuspid aortic valve straighten the line of lateral attachment, limiting the mobility of the valve and subjecting the valve to hemodynamic perturbations that facilitate premature degeneration and calcification of the valve. Bicuspid aortic valve is generally considered a contraindication to TAVR because of the theoretical risk of poor seating, coronary ostial obstruction, or paravalvular regurgitation from the distorted geometry of the aortic root. However, clinical experience with TAVR, although limited in this group of patients, has been promising.

Using planimetry, the aortic valve area can be measured on MDCT. Aortic valve area assessment by TTE, however, uses the continuity equation. Therefore, MDCT evaluates anatomic valve area instead of the effective area, which is evaluated by TTE. Therefore, anatomic valve area measured by MDCT is larger than that measured by TTE. Incorporation of computed tomography (CT)-derived left ventricular outflow tract measurement into the continuity equation has been shown to improve TTE aortic stenosis severity assessment.

Age-related degenerative changes in the aortic valve are those of progressive calcification and fibrosis (intrinsic and extrinsic cusp calcification). Two patterns of calcification have been described: (1) the coaptation pattern, where calcification occurs along the line of cusp coaptation; and (2) the radial pattern, where calcification occurs as spokes of a wheel, spreading from the peripheral cusp attachments toward the center. However, in advanced stages, the calcification pattern becomes unidentifiable. Aortic valve calcification can be scored both qualitatively and quantitatively by cardiac CT. Aortic valve calcification is qualitatively assessed as follows: grade 1, no calcification; grade 2, mildly calcified (small isolated spots); grade 3, moderately calcified (multiple larger spots); and grade 4, heavily calcified (extensive calcifications of all cusps) (Fig. 4-10). Extensive aortic root calcium precludes optimal valve implantation and identifies patients at risk for significant paravalvular leak after TAVR.
MDCT is regarded as the gold standard for aortic annulus measurement.\textsuperscript{30-32} In the reconstructed axial images of the aortic root, the following 3 measurements are made immediately below the most caudal attachment of the 3 aortic leaflets to measure the annulus: (1) measurement of the long and short diameters of the oval aortic annulus to calculate the mean diameter; (2) area-derived diameter (planimetry of the area of the aortic annulus and calculation of the diameter that corresponds to this area under the assumption of full circularity); and (3) perimeter-derived diameter (measurement of the circumference of the aortic annulus and calculation of the diameter that corresponds to this length again under the assumption of full circularity).

In addition to evaluation of the aortic valve and annulus, many other parameters are ascertained during the acquisition of cardiac CT that are routinely used in planning of TAVR, including aortic dimensions, coronary ostial height, sinus of Valsalva, and sinotubular junction diameters.\textsuperscript{33}

**Echocardiographic Anatomy**

Echocardiography provides excellent temporal and spatial resolution for investigating not only the anatomy but also the function of the aortic valve. Identification of various anatomic relationships in different transthoracic and transesophageal views is critical for planning and guidance of structural
interventions (Fig. 4-11). Two-dimensional Doppler TTE is the most commonly used tool for assessing the severity of aortic stenosis. This can be accomplished by estimating the valve area by planimetry or using the continuity equation, measuring the peak transvalvular velocity and the peak and mean pressure gradients across the valve. Peak pressure gradient can be calculated from the peak velocity using the Bernoulli equation ($\Delta P = 4V^2$, where $\Delta P$ = pressure gradient and $V$ = flow velocity in m/s at the site of obstruction). Aortic valve area is estimated by the continuity equation using Doppler-derived transvalvular velocities (TVIs) in conjunction with anatomic measurements of the left ventricular outflow tract (LVOT; Aortic valve area = LVOT \times LVOT VTI/aortic valve VTI).


In the presence of aortic valve regurgitation or significant left ventricular (LV) dysfunction, measuring aortic valve gradient alone is inadequate to
determine the severity of aortic stenosis. In these situations, aortic valve area should also be measured because the continuity equation is reliable even in the presence of aortic and mitral insufficiency and independent from transaortic flow.36

Many indices have been investigated for determining the severity of AS, namely, dimensionless index, jet width at the aortic valve level, valve resistance, percent LV stroke work loss, and modified ventricular-vascular coupling. However, none of these adjunctive measures have proven to more reliable than transvalvular gradient, aortic valve area, and jet velocity. As such, current guidelines define the severity of aortic stenosis based on these parameters.35

Dimensionless index is the ratio of the systolic velocity flow integral in the LVOT to the systolic velocity integral in the aortic jet and may be useful in the setting of severe LV dysfunction. Dimensionless index <0.3 is consistent with severe aortic stenosis and has a high sensitivity and specificity for diagnosis of severe aortic stenosis.37 Not surprisingly, TTE has limitations; poor acoustic windows and severe calcification of mitral and aortic annulus may lead to inaccurate measurement of LVOT diameter and aortic valve gradients translating to erroneous calculations of aortic valve area.38 Nonparallel interrogations of jet velocity may lead to underestimation of the severity of stenosis, due to the higher central velocity of aortic flow through the valve.39 In the presence of mitral regurgitation, irregular heart rhythms, or subvalvular or supravalvular stenosis, transvalvular velocities can be overestimated.40 Low cardiac output or significant LV dysfunction may lead to underestimation of aortic stenosis severity.

The enhanced resolution capability of 2D TEE can provide anatomic details not obvious on TTE (see Fig. 4-11). On TEE, the short-axis view of the aortic valve can be obtained in the mid-esophageal aortic valve short-axis view (30-60°). Aortic valve planimetry can be performed on the obtained images. Long-axis images of the aortic valve are obtained from the mid-esophageal (110-140°), transgastric (approximately 120°), or deep transgastric (0°) locations. Both of the transgastric views allow Doppler interrogation of the aortic valve due to parallel alignment of the TEE transducer to the LVOT in these views. The mid-esophageal long-axis view, on the other hand, can be used to evaluate the LVOT and aortic root dimensions. Superior aortic root analysis by TEE has been associated with
improved patient selection and success of TAVR.

Recently, there has been widespread use of cross-sectional 3-dimensional (3D) TEE (Fig. 4-12) because it has several advantages over 2D TEE imaging and provides incremental value to fluoroscopy in guiding structural heart disease interventions and in identifying complications during the procedure.\textsuperscript{41,42} Three-dimensional TEE is gaining acceptance as an accurate alternative to MDCT for aortic root analysis before TAVR.\textsuperscript{41}

\textbf{FIGURE 4-12} Aortic root morphology assessment by high-resolution 3-dimensional transesophageal echocardiography imaging.

\section*{MITRAL VALVE}

\subsection*{Gross Anatomy}

The mitral valve gets its name from the resemblance of its leaflets to a bishop’s mitre, or headdress. It is a complex functional unit composed of the
mitral annulus, anterior and posterior leaflets, subvalvular apparatus (chordae tendineae and papillary muscles), LV myocardium (attachment of the papillary muscles), and left atrial wall (Fig. 4-13). These individual structures work synchronously to open during diastole and close during systole.

FIGURE 4-13 Mitral valve complex unit and mitral annulus.

Annulus
The mitral annulus is not a distinct anatomic entity, but a saddle-shaped fibrous tissue plane at the left atrioventricular junction that serves as an insertion site for the mitral leaflets. The part of the annulus near both commissures is more ventricular, and the part supporting the middle parts of the leaflets is more atrial, giving it the saddle-shaped appearance. The annulus can be divided into anterior and posterior parts by the commissures. Anteriorly, it is continuous and extends between the left and right fibrous trigones as the aorto-mitral curtain. Posteriorly, it is discontinuous and less well developed, making it susceptible to enlargement. The annulus is strongest near the commissures at the left and right fibrous trigones. These variations allow major changes in the shape and dimensions of the annulus at different stages of the cardiac cycle. The anterior annulus is dynamic and moves toward the posterior annulus in systole (to increase LVOT size and to enhance leaflet coaptation) and toward the septum in diastole (to increase diastolic mitral valve opening). The annulus has a shorter AP extension than sidewise. The anterior annulus is related to the left ventricle, left fibrous trigone, left coronary sinus, noncoronary sinus, right fibrous trigone, and interventricular septum, from the lateral to medial direction. The posterior annulus is related to the interventricular septum and then the free wall of the left ventricle going from medial to lateral direction.

The relationship of the annulus to the coronary sinus is of particular importance due to potential devices that can modify annular shape and size. The coronary sinus opens in the right atrium just behind and to the right of the posteromedial commissure of the mitral valve. If one traces the coronary sinus more proximally, it runs on the atrial side of the mitral annulus with 0.5 to 1 cm of distance between the two. As the mitral annulus flattens in patients with severe mitral regurgitation, this distance increases. Anterolateral commissure of the mitral valve is close to where the anterior cardiac vein becomes the coronary sinus.

**Leaflets**

The aortic/anterior leaflet of the mitral valve is dome shaped with attachment to the anterior two-fifths of the annular circumference. This leaflet lies in close relation to the left and noncoronary cusps of the aortic valve in combination with which it forms the aorto-mitral curtain (Fig. 4-14). Near the tip of the leaflet on the ventricular surface, there is a deep crescentic rough
zone on the ventricular side that provides attachment to the chordae tendineae. The ridge demarcating the proximal margin of the rough zone indicates the maximal extent of the coaptation zone. The anterior leaflet does not have a basal zone as it forms the smooth boundaries for the ventricular outlet. Segmentation of the anterior leaflet is artificial, with different parts of the leaflet demarcated as A1, A2, and A3 from lateral to medial corresponding to similar segments of the posterior leaflet.

FIGURE 4-14 Mitral valve leaflets and their relationships.

The mural/posterior leaflet is quadrangular and narrow with attachment posteriorly to three-fifths of the annular circumference. It has 2 distinct indentations along the free edge that divide the leaflet into 3 lobes or “scallops”: a relatively large middle scallop (P2) and smaller anterolateral (P1) and posteromedial scallops (P3). Each scallop has a crescentic, opaque rough zone, receiving on its ventricular aspect the attachments of the chordae. This rough area, which is larger than the comparable area on the anterior leaflet, identifies the area of apposition of the leaflets. From the rough zone to within 2 to 3 mm of its annular attachment, there is a membranous clear zone devoid of chordae. Contrary to the anterior leaflet, the basal 2 to 3 mm of the
posterior leaflet are thick and vascular and receive the basal chordae.

**Chordae Tendineae**

Two types of chordae connect the leaflets to the heads of both the anterolateral and the posteromedial papillary muscles. The primary chordae connect to the free edge of the leaflet (“fan chordae”), whereas the thicker secondary chordae (“strut” chords) connect to the rough zone of the leaflets. Functional secondary chordae are critical to preserve LV geometry and contractility. A third type of chordae, the tertiary chordae, is short and connects the basal zone of the posterior leaflet to the ventricular free wall. Commissural chordae are a subtype of primary chordae that insert into the free edge of the anterolateral and posteromedial commissures. Most chordae divide into branches from a single stem soon after their origin from the apical one-third of a papillary muscle or proceed as single chordae that divide into several branches near their attachment. In the majority of hearts, the chordal density is highest in the subcommissural area. This is important to recognize because the percutaneous clip can get tangled more easily in the commissural area than in the middle of the valve. False chordae, or chordae that are not inserted into the valve leaflet, occur in about 50% of left ventricles and often cross the subaortic outflow. Their role, if any, has yet to be determined.

**Papillary Muscles**

There are 2 papillary muscles with large variation in the size, shape, and location. The anterolateral and posteromedial papillary muscles arise from the apical one-third of the lateral and inferior LV free walls, respectively. The posteromedial muscle is frequently U shaped or with multiple heads. The anterior papillary muscle usually has 1 head. Chordae tendineae arise mostly from the tip and apical one-third of each muscle, but sometimes take origin near their base. The chordae from each papillary muscle diverge and are attached to a corresponding rough zone on both leaflets. The anterolateral papillary muscle has dual blood supply from the left anterior descending and left circumflex coronary arteries, whereas the posteromedial papillary muscle is supplied commonly by only the right coronary artery, making it vulnerable to ischemic damage and rupture. The anteropapical displacement of the papillary muscle can lead to systolic anterior motion (SAM) of the mitral
valve in the absence of hypertrophic obstructive cardiomyopathy. Anterior displacement of the papillary muscle increases anterior leaflet slack and subsequently leaflet length, factors that beget SAM.\textsuperscript{44} Similarly, anomalous insertion of the papillary muscle directly into the anterior mitral leaflet can produce SAM without hypertrophic obstructive cardiomyopathy. Global LV dilatation as seen in dilated cardiomyopathy causes an imbalance between the closing (LV contractility, LV electrical synchrony, and annular contraction) and tethering (papillary muscle displacement apically, LV remodeling, and annular dilation) forces of the functional mitral unit, causing symmetric tethering of the mitral leaflets and leading to central malapposition and central mitral regurgitation (MR). On the other hand, inferior myocardial infarction exclusively displaces the posteromedial papillary muscle, leading to increased tension in the chordae arising from the posteromedial commissure and asymmetric tethering of the leaflets with subsequent posteriorly directed MR that can originate more medially, sometimes approaching the posteromedial commissure. Posterior annuloplasty may work better for this type of situation than with apical tethering. Further, clipping may be difficult if the funnel-shaped regurgitant orifice extends up to the posteromedial commissure.

**Pathologic Anatomy**

**Mitral Stenosis**

The 2 most common forms of acquired mitral stenosis are rheumatic heart disease and calcific or degenerative mitral stenosis (Fig. 4-15). The assessment of anatomy aims to distinguish between the two and identify potential contraindications to balloon mitral commissurotomy. Rheumatic process affects the tips and commissures, causing thickening and restriction of the tips. Further, there is fibrosis and shortening of the chordae. Balloon mitral valvuloplasty works well in patients with severe symmetric commissural fusion with minimal calcification and relatively well-preserved subvalvular apparatus. On the contrary, when the subvalvular fibrosis is severe with significantly shortened chordae (anterior chordae with less than 8-mm length from the tip of the mitral valve to the papillary muscle), commissural separation with balloon commissurotomy will fail to release the
leaflets for durable success. In patients with nonrheumatic degenerative mitral stenosis caused by mitral annular calcification, there is dystrophic calcification of the posterior mitral annulus, musculature of the LV base, and ventricular surface of the posterior mitral leaflet. Sparing of the anterior mitral leaflet and commissures differentiates mitral annular calcification from rheumatic mitral disease in most cases. In mitral annular calcification, balloon valvuloplasty does not work because balloon dilatation cannot mobilize the leaflets.
Mitral Regurgitation

Abnormalities of the mitral valve complex that affect valve closure during systole cause MR that can be either degenerative or primary and functional or...
secondary. Degenerative disease includes Barlow disease (myxomatous degeneration) and fibroelastic deficiency, both of which can result in mitral valve leaflet prolapse and MR. Fibroelastic deficiency is the most common etiology to present for surgical mitral valve repair, representing approximately 70% of the US surgical population. Rheumatic heart disease is an important cause of degenerative MR in other parts of the world that causes leaflet restriction with reduced motion in both systole and diastole from leaflet fusion, calcification, and apical leaflet doming. Functional MR (FMR) occurs from geometric derangement of the mitral valve functional unit subsequent to LV remodeling in the setting of regional or global LV dysfunction from any cause. Ischemic MR results from an imbalance of closing and tethering force on the mitral leaflets. Various factors can decrease the closing force, including diminished LV contractility, LV electrical dyssynchrony, and diminished annular contraction. Similarly, many factors can increase the tethering forces, such as papillary muscle displacement, LV remodeling, and annular dilation. It is becoming increasingly clear that there is tremendous interaction of ventricular, valvular, and annular factors in generation, perpetuation, and progression of FMR.

Alain Carpentier proposed a morphologic classification based on leaflet motion to describe the pathophysiologic changes that contribute to MR from either etiology (see Fig. 4-15). Carpentier class I regurgitation occurs in the presence of normal leaflet motion and is usually caused by annular dilatation or leaflet perforation. Carpentier class II is caused by exaggerated leaflet motion as a result of leaflet prolapse, which is commonly the result of chordal/papillary muscle elongation or rupture. Carpentier class III is caused by restricted leaflet motion that is subdivided into class IIIa (restricted motion in systole and diastole) seen in rheumatic heart disease from commissural fusion and/or leaflet or chordal thickening and class IIIb (restricted motion in systole only) due to posterior wall motion abnormality or papillary muscle dysfunction seen with LV dysfunction from any cause. This simplification has utility in terms of both the surgical and percutaneous approaches, as the goal of therapy is to restore normal leaflet function but not necessarily normal valve anatomy.

**Fluoroscopic Anatomy**

Orientation of the leaflets of the mitral valve is best imagined by identifying
the commissures in every projection (Fig. 4-16). The anterolateral commissure is near the left anterior descending artery ostium, and the posteromedial commissure is close to the origin of the posterior descending artery. RAO view shows the anterolateral commissure on the top and the posteromedial commissure on the bottom; both the anterior and posterior leaflets are superimposed and lie in the middle. Anterior and posterior papillary muscles are well visualized in systole during ventriculogram. In contrast, the LAO view gives appreciation of the mitral annulus and delineates the anterior and posterior leaflets. Different segments (A1, A2, A3 and P1, P2, P3) of the leaflets are also well appreciated in this view. The relation of the papillary muscle to the leaflets is also well delineated. The LVOT is well seen in this orientation, although some cranial angulation may help to eliminate foreshortening of the outflow tract. Relation of the mitral annulus to the different structures is well appreciated in this view.
FIGURE 4-16 Line diagrams of angiographic projections for assessment of the mitral valve. bs, basal septum; L, left coronary cusp; LAO, left anterior oblique; N, non coronary cusp; R, right coronary cusp; RAO, right anterior oblique.

CT Anatomy

The poor temporal resolution of MDCT limits its role in the anatomic assessment of the mitral valve. Radiation exposure is also of concern with CT. However, CT can provide useful information in special situations.
It is easier to measure annular size with MDCT because of the possibility to reconstruct the mitral annular plane from a 3D dataset. Further, one can assess the geometry of the subvalvular mitral apparatus on MDCT, which may be critical to determine the precise mechanism of FMR and in guiding interventions. MDCT also provides a unique opportunity to study the mitral annulus and its relation to the surrounding structures. The relation of the mitral annulus to the coronary sinus and the great cardiac vein, and their relationship with the left circumflex artery, can be easily recognized on MDCT. Nevertheless, due to limited temporal resolution, the relation of the mitral annulus to the coronary sinus in different phases of the cardiac cycle can be difficult to determine. There is no standard method to measure this distance; however, 2-, 3-, or 4-chamber views can be used to determine this distance. It may be important to measure the angle between the coronary sinus plane and the mitral annulus. This angle may provide some insight into the direction of pull of the device in the coronary sinus to the mitral annulus. Despite these measurements, the success of a device can still be difficult to predict from CT prior to procedure.\cite{47} Qualitative assessment to judge the calcification of the mitral annulus is also important if placement of CS devices is planned. Typically, significant calcification can be considered a relative contraindication for this approach. MDCT may be particularly helpful in accurate identification of paravalvular leaks and in procedural planning.\cite{48}

**Echocardiographic Anatomy**

Echocardiography is the preferred imaging modality for mitral valve disease. The suitability for balloon mitral valvuloplasty can be readily established from standard TTE images of the mitral valve using one of the several anatomic scores developed to predict balloon mitral valvuloplasty outcomes.\cite{49,50} The parasternal long-axis view is used to assess valve thickening, mobility, and calcification (Fig. 4-17). Modified standard views (apical 4, 2, 5, and parasternal long axis) obtained by tilting the probe medially or laterally are used to image the long axis of the papillary muscle and its attached chordae to assess subvalvular thickening, fusion, and calcification. The presence or absence of commissural calcification outperforms any of the risk scores to predict the outcome of valvuloplasty and should be assessed on the parasternal short-axis view (see Fig. 4-17).
The proximity of the mitral valve to the posteriorly positioned TEE probe in the esophagus strikingly improves anatomic assessment of the mitral valve (Fig. 4-18). This has been successfully exploited to improve patient selection and safety of percutaneous mitral valve therapies.51 For imaging of the mitral valve on TEE, 2 important planes can be visualized at 0°, one in the mid-esophagus and the other in the transgastric location. The correlation of these views to the fluoroscopic anatomy is shown in Figure 4-19. The mid-esophageal 0° view provides a 4-chamber view of the mitral and tricuspid valves (see Fig. 4-18). The relation of the interatrial septal puncture site or septal devices to the mitral valve can be best assessed in this view. When the TEE probed is advanced to the transgastric location with flexion, a short-axis view of the left ventricle at the mitral valve level can be obtained. This view
is critical for evaluating the mitral valve in short axis, which can be helpful in several mitral interventions (e.g., commissure evaluation during mitral valvuloplasty, assessing the orientation of clip in relation to valve coaptation line during MitraClip [Abbott Vascular, Temecula, CA] procedure). The orientation of different segments of mitral leaflets is shown in Figure 4-18. When the transducer is rotated at 40° to 60° with the probe at the mid-esophageal level, mitral valve commissural view can be obtained. In this view, A2 is typically located in the middle of the LV inflow, with P1 and P3 on either side. TEE is also essential to rule out clots in the left atrium prior to valvular interventions. Biplane TEE is at times helpful when devices are being advanced into the left atrium (Fig. 4-20).
FIGURE 4-19 Correlation of fluoroscopic plane to transesophageal echocardiography. AML, anterior mitral leaflet; AO, aorta; IAS, intra-atrial septum; LA, left atrium; LAA, left atrial appendage; LCC, left coronary cusp; LMT, left main trunk; LV, left ventricle; NCC, noncoronary cusp; PA, pulmonary artery; PML, posterior mitral leaflet; PV, pulmonary valve; RA, right atrium; RCC, right coronary cusp; RV, right ventricle; TV, tricuspid valve.
FIGURE 4-20 Three-dimensional transesophageal echocardiography in the MitraClip procedure. Transseptal puncture. *Left side:* Bicaval view. *Right side:* Short-axis view at the base. Introduction of the steerable guide catheter (SGC) into the left atrium (*bottom panel*).

Three-dimensional TEE has significantly improved the analytical details of the mitral valve. Its ability to visualize the valve superiorly from the left
atrium, the “en-face view” or the “surgeon’s view,” is of particular interest during treatment of mitral paravalvular leaks and edge-to-edge therapy using the MitraClip procedure (Fig. 4-21). Three-dimensional TEE provides incremental imaging information compared with 2D TEE to guide in several critical steps.\textsuperscript{52} The usefulness of real-time 3D TEE has been confirmed for safe guidance of the clip delivery system through the left atrium toward the mitral valve, precise positioning of the clip delivery system in the middle of the intercommissural line as well as at the center of the regurgitant jet, accurate alignment of the clip arms perpendicular to the intercommissural line in the left atrium as well as the left ventricle, confirmation of correct grasping location in the middle of the anterior and posterior mitral leaflets resulting in a symmetric split of the mitral orifice, and adequate positioning of a second clip relative to the first clip if required. Similar value of real-time 3D TEE for critical steps in paravalvular leak closure (see Fig. 4-21), including device deployment, has been demonstrated.\textsuperscript{53}
Tricuspid Valve

The tricuspid valve, so called because of its 3 triangular or trapezoidal leaflets, is the most apically placed cardiac valve and the one with the largest orifice (Fig. 4-22). The tricuspid valve functional unit includes the fibrous annular ring, leaflet tissue, chordae tendineae, and papillary muscles.
Similar to the mitral valve, the tricuspid annulus derives its support from the fibrous skeleton of the heart (right atrioventricular ring as opposed to the left atrioventricular ring) and has an ellipsoid and nonplanar morphology, appearing somewhat “saddle shaped” in configuration (Fig. 4-23). The highest points of the annulus are in the anteroseptal segment in close proximity to the right ventricular outflow tract and the aortic valve and the posterolateral segments. The lowest points of the annulus are in the posteroseptal segment, which is closer to the right ventricular apex and the anterolateral area. This geometry changes in patients with functional tricuspid regurgitation. As the severity of tricuspid regurgitation increases, the annulus takes on a more planar and circular configuration as the anterior-posterior distance increases disproportionately to the septal-lateral distance and the vertical axis decreases. The flattening of the tricuspid valve annulus alters the normal papillary muscle-to-leaflet and annulus relationship, causing leaflet tethering and functional regurgitation. Unlike the mitral annulus, the tricuspid annulus does not contract independently, thus making it potentially more susceptible to the function of the perianular myocardium. Additionally, the fibrous skeleton supporting the annulus is not as extensively
anchored in the periphery as the mitral annulus, which in turn allows it to be more malleable in regard to remodeling. Therefore, some degree of tricuspid regurgitation coexists with right ventricular dysfunction.

FIGURE 4-23 Tricuspid annulus and tricuspid valve leaflets. A, anterior; AVN, AV node; CSO, coronary sinus ostia; L, lateral; P, posterior; S, septal; TK, triangle of Koch; TT, tendon of Todaro.

The tricuspid annulus is closely related to the right coronary artery in its entire course around the atrioventricular groove until it gives rise to the posterior descending artery. The small cardiac vein is also related the tricuspid annulus throughout its course in the right atrioventricular groove. Both structures can be potentially injured at the time of tricuspid valve surgery with deep annular suture placement. Similarly, deep suture placement can injure the atrioventricular node due to its close proximity to the tricuspid annulus in the triangle of Koch.

**Leaflets**

As implied by the name, the tricuspid valve consists of 3 leaflets, each named in reference to their location within the right ventricle: the anterior (superior), posterior (inferior), and septal leaflets (see Fig. 4-23). Typically, the anterior leaflet is the largest, extending from the septum medially along the anterior margin of the atrioventricular groove to the acute margin of the atrioventricular groove. The anterior leaflet separates the inflow and outflow portions of the right ventricle. The attachment of the septal leaflet is to the
interventricular septum (anterior to posterior) with occasional extension to the inferior wall. It is the least mobile of the 3 leaflets of the tricuspid valve. Spanning the distance between the anterior and septal leaflets is the posterior leaflet. The septal leaflet is normally attached more apically than the anterior leaflet of the mitral valve and has chordae that attach it directly to the adjacent ventricular septum. These distinctive anatomic features are helpful in differentiating the mitral and tricuspid valves in complex congenital abnormalities. Similar to the mitral valve, the leaflets of the tricuspid valve have a rough zone, clear zone, and basal zone.

**Papillary Muscles and Chordae**

The right ventricle has a variable number of papillary muscles. Most commonly, there are 3 papillary muscles, named according to their location of origin in the right ventricle. Arising from the lateral aspect of the anterior wall of the right ventricle is the anterior papillary muscle, which is the largest and most consistent in origin. Conversely, the posterior papillary muscle arises from the posterior aspect of the right ventricle and is often bifid or trifid. The septal papillary muscle is the most inconsistent in origin and often has associated chordae that arise directly from the myocardium. A unique aspect of the right ventricle is the presence of the septomarginal trabeculae muscular ridges that connect the anterior wall of the right ventricle to the interventricular septum carrying with it the right bundle branch fibers of the conduction system (moderator band).

The tendinous chordae of the tricuspid valve arise from the upper third of the papillary muscles or directly from the ventricular wall and are classified similar to those of the mitral valve by their points of insertion into primary, secondary, and tertiary chordae.

**Pathologic Anatomy**

**Tricuspid Regurgitation**

Tricuspid regurgitation is typically referred to as functional (not related to a primary valvular pathology) or valvular. Valvular tricuspid regurgitation is less common as the etiology for tricuspid regurgitation (when it is considered
the mechanism), many etiologies exist, and the 2 broad descriptive categories are rheumatic or nonrheumatic. Nonrheumatic involves a host of disease processes that affect the tricuspid valve, including infective endocarditis, Ebstein anomaly, carcinoid syndrome, connective tissue diseases such as Marfan syndrome, papillary muscle dysfunction, valvular prolapse, and other structural problems in the valve complex that are either congenital or trauma related.

Functional tricuspid regurgitation is the most frequent etiology of tricuspid regurgitation and, although oversimplified, typically results from impaired leaflet coaptation from dilation of the right ventricle and tricuspid annulus. The clinical context in which this occurs is generally related to cardiomyopathy and mitral valve disease. Severe functional tricuspid regurgitation has a negative impact on survival and quality of life. However, surgical repair is not uniformly performed even in patients undergoing mitral valve repair or replacement. Percutaneous approaches to both repair and replace the tricuspid valve are thus gaining momentum. Strategies to treat functional tricuspid regurgitation percutaneously include the following: placement of transcatheter valves in the inferior vena cava and, rarely, in the superior vena cava to reduce regurgitant volume and pressure in the inferior vena cava; valve-in-valve therapy for degenerated tricuspid bioprosthesis; and transauricular intrapericardial tricuspid annuloplasty.

**Fluoroscopic Anatomy**

Two projections that are useful to gain a fluoroscopic understanding of the anatomy of the right-sided cardiac structures are the posterior-anterior view and a lateral view. During ventricular systole, the posterior-anterior view provides excellent visualization of the right atrium, right ventricle, tricuspid valve, and pulmonary artery. Conversely, in ventricular diastole, the lateral view nicely delineates the relationships of the superior and inferior vena cava to the right atrium and ventricle. Additionally, the lateral view also provides another vantage point of the pulmonary artery, right ventricular outflow tract, and pulmonic valve.

**CT Anatomy**

The role of cardiac CT for imaging the tricuspid valve remains to be proven.
As previously described, the tricuspid valve separates the right atrium from the morphologic right ventricle and consists of the same components as the mitral valve (leaflets/cusps, commissures, chordae tendineae, and papillary muscles). Distinguishing the morphologic left and right ventricles can be difficult in patients with complex congenital heart disease. Fortunately, there are several unique characteristics that make this possible by CT: the moderator band, a heavily trabeculated apex, well-developed infundibulum, septal papillary muscles, and the lack of fibrous continuity of the aortic valve and outflow.

Cardiac CT is also useful for evaluating leaflet morphology and thickening as well as leaflet apposition, but may not add much to TEE in this regard. Leaflet nonapposition is best determined at the end of ventricular systole in an electrocardiogram gated CT. Other indirect markers of tricuspid valve disease are the presence of contrast in the hepatic veins or inferior vena cava during the first-pass phase of CT (very sensitive marker for tricuspid regurgitation), bowing of the interventricular septum into the left ventricle during systole (indicative of elevated right-sided filling pressures), and lastly, right atrial and ventricular dilatation, which may alert one to the presence of tricuspid regurgitant disease. Constrictive pericarditis and pulmonary hypertension are important etiologies to consider when evaluating the tricuspid valve by cardiac CT. In patients with tricuspid stenosis, CT imaging is good at identifying fusion of the leaflet edges and shortening of the chordae tendineae.

**Echocardiographic Anatomy**

TTE and TEE of the tricuspid valve are more challenging than with the left-sided valves due to the tricuspid valve’s unfavorable location, behind the sternum and farther from the esophagus. The anterior and posterior leaflets can be visualized in the right ventricular inflow view, while the anterior and septal leaflets are visualized in the parasternal short-axis images and the apical 4-chamber view (Fig. 4-24). TEE has some incremental value (see Fig. 4-24). The 0° mid-esophageal 4-chamber view is often a good starting point for imaging of the tricuspid valve. Often, the etiology of the tricuspid regurgitation can be identified in this view, although supplemental views are helpful. In this view, the septal leaflet and a nonseptal leaflet (anterior or posterior) are well seen, as is the degree of tricuspid regurgitation. The
nonseptal leaflet can be either anterior or posterior depending on the positioning of the probe and degree of flexion or anteflexion. The 60° mid-esophageal right ventricular inflow-outflow view is well suited for visualization of the anterior and posterior leaflets of the tricuspid valve, as well as the right ventricular inflow and pulmonic valve. Better visualization of the chordae tendineae and papillary muscles can be accomplished with rotation of the probe to 120° for a long-axis view of the right ventricular inflow. The single best view to visualize all 3 leaflets together is the transgastric short-axis view (~30°).

**FIGURE 4-24** Tricuspid valve assessment on transthoracic and transesophageal echocardiography.
PULMONIC VALVE

The pulmonary root separates the right ventricular outflow tract from the main pulmonary artery. The components of the pulmonary root include the sinotubular junction, the sinuses of Valsalva, valvular leaflets, interleaflet triangles, and pulmonary annulus. Similar to the aortic valve, the pulmonary valve is a trileaflet valve made up of 3 semilunar cusps: anterior, left, and right. The pulmonary root similarly consists of 3 imaginary “rings” described by their anatomic relationship to the pulmonary valve. Superiorly, commissural apposition occurs at the sinotubular junction of the pulmonary trunk, signifying the location of the first ring. The ventriculoatrial junction marks the location of the second ring; the third ring is the basal-most ring occurring within the ventricle at the level of the base of the sinuses.

Pathologic Anatomy

Pulmonic Stenosis

Pulmonic stenosis (PS) produces obstruction to right ventricular outflow. Mild PS is well tolerated, but moderate to severe PS leads to progressive right ventricular hypertrophy and failure from right ventricular systolic pressure overload. Three types of PS are often described: valvular PS, supravalvular PS (stenosis of the main pulmonary artery or branch pulmonary artery stenosis), and subvalvular PS. Pulmonic valve stenosis is largely a congenital defect (Noonan syndrome, congenital rubella, tetralogy of Fallot) and is rarely the result of rheumatic fever, endocarditis, or carcinoid syndrome.

PS exists in 3 varieties. Most commonly, the pulmonic valve is a fibrotic and dome-shaped valve with preserved leaflet motility. This variety is most amenable to percutaneous balloon valvuloplasty. Conversely, the dysplastic variant (thickened leaflets with poor mobility) and the unicuspid/bicuspid variants are not particularly pliable or responsive to balloon valvuloplasty.

Balloon valvotomy of the pulmonic valve is indicated for asymptomatic patients with a mean transvalvular gradient >40 mm Hg or peak instantaneous gradient of >60 mm Hg.60 For symptomatic patients, the threshold for intervention is somewhat lower (mean gradient >30 mm Hg or
Percutaneous treatment is also recommended for focal branch and/or peripheral pulmonary artery stenosis with more than 50% stenosis and an elevated right ventricular systolic pressure greater than 50 mm Hg with or without symptoms.

Surgery is the preferred treatment for patients with severe PS and associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular PS, or supravalvular PS.

**Pulmonary Regurgitation**

Pulmonary regurgitation is principally the result of long-standing pulmonary hypertension, idiopathic pulmonary artery dilation, or connective tissue disease and remains clinically silent for many decades, although it can contribute to right-sided volume overload and dysfunction. Percutaneous therapies for pulmonary regurgitation are limited, although percutaneous pulmonary valve implantation has been successfully performed in patients with congenital heart disease and conduit dysfunction (stenosis or regurgitation).  

**Fluoroscopic Anatomy**

Right ventricular angiography is performed as a routine part of pulmonic valvuloplasty in both anterior-posterior and lateral projections to precisely locate the pulmonic valve and measure the annulus (Fig. 4-25). The lateral projection is particularly helpful in delineating the anatomy of the right ventricular outflow tract, infundibular obstruction, right ventricular function, and mobility of the pulmonic valve. Systolic doming of the valve leaflets may be appreciated on angiography. Pulmonary angiography is also useful to determine the degree of pulmonary regurgitation and evaluate for other lesions such as supravalvular or peripheral PS. With a pigtail in the right ventricle, the markers on the pigtail may be used to assess the diameter of the annulus to aid in balloon sizing. Typically, the goal balloon-to-annulus ratio is 1.2 to 1.4. A successful procedure is defined as one in which the final transvalvular gradient is <20 mm Hg.)
Complete or near-complete outflow tract obstruction by ventricular angiography should alert the operator to the likelihood of “suicide ventricle” physiology that may occur immediately after balloon valvuloplasty as the result of a sudden reduction in ventricular afterload and hypertrophic obstructive cardiomyopathy–like physiology with increased outflow tract obstruction in the setting of afterload reduction. Patients exhibiting “suicide ventricle” physiology should be treated with a β-blocker and intravenous fluids but not inotropic agents because these may exacerbate the outflow tract obstruction and hypotension. In the ensuing days to weeks, the outflow hypertrophy will regress in size and the subvalvular gradient will diminish.
CT Anatomy

Cardiac CT is useful in planning pulmonary valve procedures because these patients commonly have congenital heart disease and complex anatomy. Right ventricular outflow tract obstruction has many potential etiologies as previously outlined, and therein lies the utility of cardiac CT in planning the appropriate treatment approach. Appropriate preprocedural imaging with cardiac CT or magnetic resonance imaging may also tip off the operator to potentially poor candidates for percutaneous valvuloplasty (ie, those with bicuspid or unicuspid valves [<20% incidence] or myxomatous dysplastic valves).

Because of the ordinarily slender and delicate appearance of the pulmonic valve, it may not always be readily seen. If it is easily visible by CT, it is likely to be thickened. Like the tricuspid valve, the morphology of the pulmonic valve can be directly assessed by CT. In contradistinction to the tricuspid valve, the pulmonic leaflet apposition is best appreciated at end diastole, and the extent of leaflet excursion is better viewed in end systole. Moderate to severe PS is typically associated with poststenotic dilatation of the pulmonary artery and right ventricular hypertrophy (Fig. 4-26). Pulmonary regurgitation occurs as the result of dilatation of the pulmonic annulus, usually in the presence of pulmonary hypertension or dilatation of the pulmonary artery, either idiopathic or secondary to another disease process.
FIGURE 4-26 Sagittal computed tomography images of the right ventricular outflow tract show a dilated pulmonary root in a patient with pulmonic stenosis.

Similar to CT evaluation of the tricuspid valve, examination of the chamber size and thickness of the right heart should be performed when pulmonic valve pathology is suspected. Right atrial and ventricular dilation/hypertrophy may be present, and pulmonary trunk dimensions should also be scrutinized. Bowing of the interventricular septum into the LV cavity in systole is consistent with pressure overload; however, if septal bowing is present in both systole and diastole, this is most consistent with right-sided volume and pressure overload.

Echocardiographic Anatomy

Assessment of the pulmonic valve by TTE can be done on the parasternal short axis at the level of the aortic valve (Fig. 4-27). Severe PS is suggested by a continuous wave Doppler velocity of 4 m/s or greater across the pulmonary valve. Color-flow Doppler imaging across the pulmonary valve is used to detect pulmonary regurgitation noninvasively on echocardiography. TEE imaging of the pulmonary valve is often limited in utility. However, if TEE imaging is needed, the pulmonic valve is best visualized in 60° mid-esophageal inflow-outflow view (see Fig. 4-27). In this view, doming of the leaflets, calcification, mobility, and leaflet thickening can be assessed. Supplemental mid and upper esophageal short-axis views may also be beneficial when assessing degree of mobility, valve morphology, and procedural success.

CONCLUSION
In depth understanding of anatomy and its implications in different interventions is mandatory for the success of structural heart interventions.

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**MULTIPLE CHOICE QUESTIONS**

1. The most accurate estimate of the annular size for transcatheter aortic valve implantation is obtained from which imaging modality?
   A. Two-dimensional (2D) transthoracic echocardiography (TTE)
   B. 2D transesophageal echocardiography (TEE)
   C. Three-dimensional (3D) TEE
   D. Multidetector computed tomography (MDCT)

2. Which imaging modality is preferred for mitral valve disease?
   A. MDCT
   B. Fluoroscopy
   C. Cardiac magnetic resonance (CMR)
   D. Echocardiography

3. The anterior mitral leaflet is closely related to which of the following structures?
   A. Left and right coronary cusps of the aortic valve
   B. Left and noncoronary cusps of the aortic valve
   C. Right and noncoronary cusps of the aortic valve

4. Which is the single best view to visualize all 3 leaflets of the tricuspid valve on TEE?
   A. Midesophageal 4-chamber view
   B. The transgastric short-axis view
   C. 60° mid-esophageal right ventricular inflow-outflow view

5. Which of the following is an indication for pulmonary balloon valvotomy?
A. Asymptomatic individual with mean transvalvular gradient >40 mm Hg or peak instantaneous gradient of >60 mm Hg
B. Asymptomatic individual with mean transvalvular gradient <20 mm Hg or peak instantaneous gradient of <50 mm Hg
C. Asymptomatic individual with mean transvalvular gradient >25 mm Hg or peak instantaneous gradient of >40 mm Hg

**ANSWERS**

1. D
   Accurate measurement of the oval-shaped aortic annulus is crucial for precise valve sizing in patients undergoing transcatheter aortic valve implantation (TAVI). The “annulus” is not circular but elliptical, and therefore, different modalities that measure different planes of the annulus do not necessarily yield same results. The annular size obtained by MDCT is typically larger than when measured by 2D TTE/TEE. Aortic annulus measurement by 3D TEE, although better than with 2D TTE/TEE, is smaller than that obtained on MDCT. 3D TEE should be used for transcatheter aortic valve replacement (TAVR) sizing only when MDCT is not available or contraindicated. MDCT provides the most accurate measurement of the aortic annulus.

2. D
   Echocardiography is the preferred imaging modality for mitral valve disease. The proximity of the mitral valve to the posteriorly positioned TEE probe in the esophagus strikingly improves anatomic assessment of the mitral valve. This has been successfully exploited to improve patient selection and safety of percutaneous mitral valve therapies. The poor temporal resolution of MDCT limits its role in the anatomic assessment of the mitral valve. The anatomic information from CMR is not equivalent to that from echocardiography due to relatively thick imaging size.

3. B
   The aortic/anterior leaflet of the mitral valve is dome shaped with attachment to the anterior two-fifths of the annular circumference. This leaflet lies in close relation to the left and noncoronary cusps of the aortic valve in
combination with which it forms the aorto-mitral curtain.

4. B
The 0° mid-esophageal 4-chamber view is often a good starting point for imaging of the tricuspid valve. In this view, the septal leaflet and a nonseptal leaflet (anterior or posterior) are well seen. The nonseptal leaflet can be either anterior or posterior depending on the positioning of the probe and degree of flexion or anteflexion. The 60° mid-esophageal right ventricular inflow-outflow view is well suited for visualization of the anterior and posterior leaflets of the tricuspid valve, as well as the right ventricular inflow tract and pulmonic valve. The single best view to visualize all 3 leaflets together is the transgastric short axis (~30°).

5. A
Balloon valvotomy of the pulmonic valve is indicated for asymptomatic patients with a mean transvalvular gradient >40 mm Hg or peak instantaneous gradient of >60 mm Hg. For symptomatic patients, the threshold for intervention is somewhat lower (mean gradient >30 mm Hg or peak instantaneous gradient >50 mm Hg). Percutaneous treatment is also recommended for focal branch and/or peripheral pulmonary artery stenosis with more than a 50% stenosis and an elevated right ventricular systolic pressure greater than 50 mm Hg with or without symptoms.
Peripheral Anatomy for the Interventionalist

Joseph A. Walsh
Curtiss T. Stinis

INTRODUCTION

In contemporary practice, catheter-based interventions have become an increasingly important therapeutic modality for the treatment of nearly all areas of the peripheral arterial and venous system, including the head, neck, and great vessels, as well as the upper and lower extremities. A thorough understanding of the peripheral arterial and venous anatomy is the foundation for any successful peripheral vascular interventional procedure. This chapter describes the arterial and venous anatomy above and below the diaphragm, with emphasis on the pertinent anatomic variants and radiographic examinations in the catheterization laboratory.

AORTIC ARCH AND UPPER EXTREMITIES

The vascular anatomy of the aortic arch and upper extremities begins at the level of the sinus of Valsalva. From the sinotubular ridge, the ascending aorta travels anteriorly and superiorly, passing over the main pulmonary artery and left mainstem bronchus. At this level, the mean diameter of the ascending
thoracic aorta in the normal adult human is 3.5 cm.

The brachiocephalic or right innominate artery is the first major branch off the aortic arch. The next major vessel that arises from the aortic arch is the left carotid artery. The left subclavian artery is the last great artery that arises directly off the aortic arch. After the left subclavian artery arises, the aortic arch ends. This anatomic region, called the isthmus, is found between the last great vessel and the attachment of the ductus arteriosus, after which the descending aorta begins and continues down to the level of the iliac bifurcation.

In 30% of patients, the normal relationship described above is not seen. The most common variants are a shared ostium of the brachiocephalic artery and the left carotid artery (15%), or the so called “bovine arch,” where the left carotid artery arises from the proximal aspect of the brachiocephalic trunk (10%). Other common variants include the right subclavian arising from the arch distal to the left subclavian artery and the left vertebral artery arising directly from the aortic arch (5%) between the left carotid and left subclavian arteries.\textsuperscript{1,2} In healthy individuals, the great vessels arise from the horizontal portion of the aortic arch, but with increasing age, the vessels tend to shift counterclockwise toward the ascending aorta.

The right innominate or brachiocephalic artery gives rise to the right subclavian artery and right common carotid artery. After the bifurcation of the subclavian and carotid arteries on the right, the next vessels that arise off the right subclavian include the right vertebral artery and the right internal mammary artery. The right subclavian artery then gives rise to the thyrocervical trunk and the costocervical trunk. At this location, the subclavian artery becomes the axillary artery after it crosses the lateral margin of the first rib. On the left, the subclavian artery gives rise to the left vertebral artery and the left internal mammary artery. Anatomically, its course is similar to the right subclavian artery, giving rise to similar branches.

The axillary artery on both the left and the right gives rise to several small branches around the shoulder, including the superior thoracic, thoracoacromial, lateral thoracic, subscapular, and circumflex humeral artery. It then becomes the brachial artery at the lateral margin of the teres major muscle. The brachial artery divides into the radial and ulnar arteries in the antecubital fossa. In relationship to surface markers, the brachial artery bifurcates a few centimeters below the elbow joint. The ulnar artery then undergoes anastomosis with the median artery and forms the superficial
palmar arch in the hand. The radial artery forms the deep palmar arch. The remaining axial artery at the level of the radial–ulnar bifurcation is known as the interosseous artery. Because radial artery access has become increasingly popular for cardiac procedures, an understanding of radial artery anatomic variations is important to performing successful radial catheterization procedures. Radial artery variations are present in 9.1% of the population, with abnormal origin of the radial artery occurring in 5.2%, radioulnar loop in 1.5%, and significant tortuosity noted in 5.6%.

Arteriography of the aortic arch is carried out for diagnostic purposes and to plan interventions. Anteroposterior (AP) and 45° to 60° left anterior oblique (LAO) projections are initially used to image the arch and great vessels. Imaging the right brachiocephalic territory is best accomplished in a right anterior oblique (RAO) projection with caudal angulation. For selective shots of the left subclavian artery, an AP projection or steep LAO views are useful (Table 5-1).

**Table 5-1 Angiographic Views of the Aortic Arch and Upper Extremities**

<table>
<thead>
<tr>
<th>Vascular Territory</th>
<th>Angiographic View</th>
<th>Set Up&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right innominate artery</td>
<td>30°-60° RAO caudal</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Left subclavian artery</td>
<td>AP</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Entire aortic arch with great vessels</td>
<td>60° LAO</td>
<td>—</td>
</tr>
<tr>
<td>Carotid arteries</td>
<td>Lateral</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td></td>
<td>45° LAO, RAO</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td></td>
<td>AP cranial</td>
<td>—</td>
</tr>
<tr>
<td>Vertebral arteries</td>
<td>AP</td>
<td>Ipsilateral</td>
</tr>
</tbody>
</table>

Abbreviations: AP, anteroposterior; LAO, left anterior oblique; RAO, right anterior oblique.

<sup>a</sup>Ipsilateral or contralateral indicates the angulation for a left femoral artery is best obtained with the same-side (ipsilateral) angulation (ie, LAO projection) or, if contralateral, the opposite angulation (ie, RAO projection).
When performing diagnostic angiography of the aortic arch, it is important to determine the specific type of aortic arch (Fig. 5-1), identify any anatomic variation, and identify the presence of atherosclerotic disease, as these factors can determine both catheter selection as well as interventional technique. The three types of aortic arch are determined by the takeoff of the great vessels relative to the horizontal portion of the greater curvature and assist the clinician in determining the level of complexity and choice of catheters for selective engagement. For example, selective carotid angiography of a type I and most type II arches can be accomplished using a JR4 diagnostic catheter, whereas a type III arch would favor a Vitek or Simmons catheter.

![Aortic arch types](image)

**FIGURE 5-1** Aortic arch types.

**VENOUS CIRCULATION OF THE UPPER EXTREMITIES**

Because arteriovenous fistulas are prone to degeneration and may be suitable for percutaneous intervention, knowledge of the venous anatomy is useful. Furthermore, placement of devices, such as pacemakers and automatic implantable cardioverter-defibrillators, requires use and knowledge of upper extremity venous anatomy. The venous system of the upper extremity is predominantly superficial. The dorsal venous network of the hand empties into the basilic vein, the cephalic vein, and the antecubital veins. The cephalic vein originates dorsally and laterally, crossing the elbow joint and entering the superior aspect of the axillary vein just above the clavicle. The basilic vein, which originates on the ulnar side of the arm, continues medially to the brachial artery. It joins the brachial vein to become the axillary vein at the
The medial cubital veins are the veins that connect the basilic and cephalic veins in the antecubital fossa.

The deep veins in the upper arms and chest follow their respective arteries. The axillary and cephalic veins become the subclavian veins, which are continuations of the axillary veins. As the subclavian veins cross the sternum, they join with the internal jugular veins to form the brachiocephalic veins. The left brachiocephalic vein is longer than the right. The right and left brachiocephalic veins join behind the first anterior rib to form the superior vena cava. The azygous vein forms at the level of the second lumbar vertebra. It travels in the anterior aspect of the posterior mediastinum to the right of the midline and arches anteriorly to join the superior vena cava just above the entry into the pericardium.

Persistent left superior vena cava is an important anatomic variant that occurs in 0.5% to 2% of the general population. In this condition, the left brachiocephalic vein does not develop fully, and the left upper limb and head and neck drain into the right atrium via the coronary sinus. The variation, in isolation, is considered benign, but it is frequently associated with congenital heart defects.

**CAROTID AND VERTEBRAL ARTERIES**

The carotid and vertebral arteries are becoming increasingly important to the interventional cardiologist as endovascular therapy has become a more viable option for atherosclerotic disease of these vessels. The right common carotid artery arises in a reliable fashion from the right innominate artery and travels superiorly. It then bifurcates into the right internal and external carotid arteries. Anatomically, the left common carotid artery arises directly from the aortic arch and travels cephalad to bifurcate into the left internal and external carotids. As detailed earlier, however, the left common carotid has a more variable course in 30% of cases and may arise as a shared ostium or a direct branch of the right innominate. The common carotid arteries are paired vessels, located anteriorly within the neck. The bifurcation of the common carotid arteries into the internal and external arteries on both sides is generally at the level of cervical vertebra C3 to C4. In some patients, the
bifurcation is significantly higher and arises deep in the mandible, which would require dislocation for carotid endarterectomy. The proximal portion of the carotid bifurcation houses the carotid sinus, which regulates baroreceptor reflexes via the glossopharyngeal nerve and can cause bradycardia and hypotension during carotid intervention.

Both internal carotid arteries supply the anterior circulation of the brain as well as a portion of the skull base. The first segment of the internal carotid artery is the cervical segment, which has no branches. This is the only segment of the internal carotid artery that is extracranial and is the target for conventional endovascular intervention. The remaining three segments of the internal carotid artery are named in relation to their location in the skull: the petrous and cavernous portions, which lie within the petrous bone and cavernous sinus, respectively; and the supraclinoid segment, which runs above the level of the anterior clinoid process. The internal carotid artery runs posterolateral to the external carotid artery and then courses medially to enter the skull base through the carotid canal (Fig. 5-2). The area of the brain supplied by the anterior and middle cerebral arteries is termed the carotid territory.
The external carotid artery is a smaller artery in relation to the internal carotid artery. The distinguishing feature of the external carotid artery is its branches (Fig. 5-3): the superior thyroid, ascending pharyngeal, lingual, facial, occipital, and posterior auricular arteries. A general understanding of the branches originating from the external carotid artery is important as these branches are often wired during intervention. The external carotid artery then terminally bifurcates into the internal maxillary and superficial temporal arteries. Some patients develop temporary jaw claudication after carotid stenting if the ostium of the external carotid is compromised, but this is usually temporary and infrequently requires any intervention.
Arteriography of the carotid arteries is carried out primarily in two views: a lateral projection and an AP view with cranial angulation. The lateral view serves to separate the internal (posterior, no branches) from the external (anterior, with branches) carotids and to image the bifurcation and common carotid. Often, oblique views can also accomplish this. The AP view best characterizes the common carotid and the distal internal carotid arteries. As the internal carotid enters the cranium, it traverses the cavernous sinus and forms a siphon-like S curve. It is critical to maintain wire position below the level of the siphon because an intracranial perforation or dissection could occur if the wire or a distal protection device is allowed to enter the
intracranial carotid. It is also critical to image the intracranial carotid both before and after carotid stenting to define the key branches where complications can arise. Structures of key importance include the ophthalmic, anterior cerebral, and middle cerebral arteries, which should all be closely interrogated after the procedure for occlusion or compromise (see Fig. 5-2).

The vertebral arteries arise as the primary branches of the subclavian arteries, supplying the posterior circulation of the brain, spinal cord, and muscles of the neck. Vertebral arteries enter the foramina of the C6 vertebra and then run within the bony canals, exiting at the C2 foramina. These arteries then turn laterally to course around the C1 vertebra before returning medially to ascend through the foramen magnum to join and form the basilar artery. The most common views of the vertebral arteries are anteroposterior. The ostia of the vertebral arteries are best captured by contralateral oblique projection.

VENOUS ANATOMY OF THE HEAD AND NECK

The head is drained by the internal jugular veins and external jugular veins. The internal jugular vein is formed by the sigmoid and petrosal sinuses. These veins course inferiorly on both sides, running lateral to the carotid arteries and deep to the sternocleidomastoid muscle of the neck. They then join the subclavian vein on their respective sides. The external jugular vein drains portions of the face and the neck and runs superficial to the sternocleidomastoid muscle before joining the subclavian veins. Finally, the vertebral veins drain the occipital region of the brain and adjacent to the vertebral arteries, emptying into the innominate veins.

ANATOMY OF THE ABDOMINAL AORTA

The major arteries of interest to the interventionalist that arise from the abdominal aorta are the celiac artery, the superior mesenteric artery, the inferior mesenteric artery, and the renal arteries. The celiac artery arises
ventrally from the abdominal aorta at the vertebral level T12-L1. This artery is commonly called the *celiac trunk*, giving rise to the left gastric artery, common hepatic artery, and the splenic arteries. The left gastric artery branches off to the distal esophagus and stomach. The hepatic artery resides in the hepatoduodenal ligament and typically divides into the right, middle, and left branches. The cystic artery is most frequently a branch of the right hepatic artery. Further branches arising from the common hepatic artery are the gastroduodenal artery, the anterior and posterior superior pancreaticoduodenal arteries, and the right gastroepiploic artery. The splenic artery is particularly long and tortuous, supplying the spleen and pancreas. The main branches are the pancreatic, short gastric and left gastroepiploic arteries. The splenic artery then supplies the splenic parenchyma through numerous branches (Fig. 5-4).

![Fig. 5-4 Angiographic anatomy of the celiac trunk.](image)

The renal arteries arise from the aorta slightly inferior to the origin of the superior mesenteric artery, at the L1-L2 level. Seventy percent of the population has a single renal artery to each kidney, with the remaining 30% having multiple renal arteries, usually separate vessels to the upper and lower poles of the kidney. This could also be seen as an early bifurcation of a single renal artery, giving the appearance of 2 arteries. Usually, this variant consists of a primary renal artery and an accessory artery that can supply either the upper or the lower pole of the kidney.
It should be noted that the origins of the left and right renal arteries are in different locations as they arise from the aorta. The left renal artery orifice typically arises laterally, whereas the right renal artery is positioned anterolaterally. The renal arteries then divide into anterior and posterior segments at the renal hilus, continuing to divide into lobar arteries. The terminal branches are the arcuate arteries that supply the corticomedullary junction.

The superior mesenteric artery arises at the level of the L1 vertebral body. This artery supplies the midgut from the ligament of Treitz to the midtransverse colon. Its origin is caudal to the celiac artery but cephalad to the origin of the renal arteries. It takes a steep downward course as it travels toward the right, lower abdominal quadrant. The major branches of the superior mesenteric artery include the inferior pancreaticoduodenal artery, jejunal and ileal branches, and the middle colic artery, which supplies the transverse colon. The colic artery portion of the superior mesenteric artery is divided into the ileocolic, right colic, and middle colic arteries. The ileocolic artery provides the blood supply to the cecum and anastomotic branches to the right colic artery. The right colic artery arises between the middle and ileocolic arteries and supplies the right colon and proximal transverse colons. Of note, the arc of Riolan refers to a direct communication between the superior and inferior mesenteric arteries, via the left and middle colic branches that anastomose at the splenic flexure (Fig. 5-5).
FIGURE 5-5 Branches of the aorta below the diaphragm. Ca, celiac artery; IMa, inferior mesenteric artery; LRa, left renal artery; RRa, right renal artery; SMa, superior mesenteric artery.

The inferior mesenteric artery is the last major artery arising from the abdominal aorta. This artery typically arises at the level of the L3 vertebra and supplies the distal transverse colon, left colon, and rectum. Its origin is from the left anterolateral surface of the aorta, which gives it a very typically
arteriographic appearance. The main branches of the inferior mesenteric artery include the left colic artery, sigmoid arteries, superior rectal artery, and the marginal artery of Drummond.

Performing optimal arteriography of the major abdominal aortic arteries can be challenging. Engagement of the celiac trunk and superior mesenteric artery is often best performed in a lateral projection given that these vessels arise anteriorly from the abdominal aorta, and their origins can be more easily identified in the lateral projection (Fig. 5-6). Imaging of these vessels should include both AP and lateral projections, which will define the origin and proximal vessels as well as the distal branch territories. The renal arteries can easily be engaged and imaged in an AP projection. However, as a result of the slightly different takeoffs of these arteries, a shallow LAO projection, typically 10° to 20° LAO, is an excellent view for both engagement and selective and nonselective imaging. The inferior mesenteric artery is typically engaged and imaged in the AP projection (Table 5-2).

FIGURE 5-6 Lateral angiographic projection of the abdominal aorta.

Table 5-2 Angiographic Views of the Abdominal Aorta and Lower Extremities
<table>
<thead>
<tr>
<th>Vascular Territory</th>
<th>Angiographic View</th>
<th>Set Up¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac trunk</td>
<td>Lateral, AP</td>
<td>—</td>
</tr>
<tr>
<td>Superior mesenteric artery</td>
<td>Lateral, AP</td>
<td>—</td>
</tr>
<tr>
<td>Inferior mesenteric artery</td>
<td>Lateral, AP</td>
<td>—</td>
</tr>
<tr>
<td>Renal arteries (nonselective)</td>
<td>10º LAO</td>
<td>—</td>
</tr>
<tr>
<td>Right renal artery</td>
<td>AP, 10º-20º LAO</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Left renal artery</td>
<td>AP, 10º-20º LAO</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Distal aorta</td>
<td>AP</td>
<td>—</td>
</tr>
<tr>
<td>Common iliac arteries</td>
<td>AP</td>
<td>—</td>
</tr>
<tr>
<td>Right external and internal iliac arteries</td>
<td>10º-30º RAO</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Left external and internal iliac arteries</td>
<td>10º-30º RAO</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Right common femoral and profunda femoral arteries</td>
<td>20º-30º RAO</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Left common and profunda femoral arteries</td>
<td>20º-30º LAO</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Superficial femoral arteries</td>
<td>AP</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Popliteal artery</td>
<td>AP</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Anterior tibial artery</td>
<td>AP or steep oblique</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Peroneal artery</td>
<td>AP or steep oblique</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Posterior tibial artery</td>
<td>AP or steep oblique</td>
<td>Ipsilateral</td>
</tr>
</tbody>
</table>

Abbreviations: AP, anteroposterior; LAO, left anterior oblique; RAO, right anterior oblique.

¹ Ipsilateral or contralateral indicates the angulation for a left femoral artery is best obtained with the same-side (ipsilateral) angulation (ie, LAO projection) or, if contralateral, the opposite angulation (ie, RAO projection).
THE ILIAC ARTERIES AND LOWER EXTREMITIES

The aorta bifurcates into the common iliac arteries at the level of the L4-L5 vertebrae (Fig. 5-7). The common iliac arteries divide into the internal and external iliac arteries. The internal iliac artery is commonly referred to as the hypogastric artery. The external iliac arteries then continue, giving off the inferior epigastric and deep circumflex iliac arteries. The inferior epigastric artery anastomoses with the superior epigastric artery and runs along the anterior abdominal wall. The external iliac artery turns into the common femoral artery when the deep circumflex iliac artery arises from the external iliac. It is important to recognize that there are three structures that mark the boundary between the external iliac artery and the common femoral artery: the deep circumflex iliac artery, the interior epigastric artery, and the inguinal ligament (Fig. 5-8).
RCla = Right common iliac artery
RIIa = Right internal iliac artery
REIa = Right external iliac artery
LCla = Left common iliac artery
LIIa = Left internal iliac artery
LEIa = Left external iliac artery
The internal iliac artery divides into the posterior and anterior divisions, with the posterior division giving off the superior gluteal, iliolumbar, and lateral sacral branches. The anterior division gives rise to the obturator, inferior gluteal, and internal pudendal branches. The inferior gluteal artery supplies the gluteus muscle and branches to the sacral nerve. The internal pudendal artery gives off the inferior hemorrhoidal branch before giving rise to the penile arteries, the dorsal artery of the penis, and the cavernosal artery. There is an extensive anastomotic network between the left and right internal iliac arteries, and hence, unilateral internal iliac disease may be less likely to cause symptoms. Anastomotic connections also exist between the inferior
gluteal and perforating arteries of the femoral circulation, which explains how common iliac disease can cause claudication in the buttocks and proximal thigh.

The common femoral artery divides into the superficial femoral artery and profunda femoris artery. The profunda femoris artery courses laterally and posteriorly to the superficial femoral artery and is also known as the deep femoral artery. Major branches off the profunda femoris artery include the medial and lateral femoral circumflex arteries. One or both of these branches may occasionally (15%-20%) arise directly from the common femoral artery. The common femoral artery is a key access point for endovascular procedures, and therefore, a proper understanding of the anatomic landmarks is critical to obtaining proper femoral access and closure and reducing complications. The external iliac artery becomes the common femoral artery as it passes beneath the inguinal ligament, which is demarcated angiographically by the origin of the inferior epigastric artery (as it passes beneath the inguinal ligament) and the deep circumflex iliac artery. The inferior border of the anatomic common femoral artery is the bifurcation of the superficial femoral artery and the profunda femoris. This anatomic definition of the femoral artery, however, does not define the optimal location for femoral arterial access with respect to endovascular procedures. The optimal location for common femoral artery access is that portion of the common femoral artery that is located over the anterior pelvic bony structure known as the pubis. When a femoral sheath is removed, the gold standard for obtaining hemostasis is manual compression. This can only be effectively accomplished if the access site can be adequately compressed against an underlying bony structure (the pubis). Significant variability exists in the population with respect to the relationship of the bifurcation of the superficial femoral artery and profunda femoris artery and the pubis. Thus, it is quite possible to obtain access within the common femoral artery (as defined by the anatomic definition) yet have this site be well inferior to the pubis. Although such access is technically within the anatomic common femoral artery, it does not represent an ideal access location due to the absence of an adequate posterior bony structure against which to compress the artery for purposes of obtaining adequate hemostasis. The optimal point for common femoral artery access lies within the portion of the common femoral artery that lies over the pubis. This segment of the common femoral artery represents the “functional” common femoral artery as it relates to arterial
access for endovascular procedures (Fig. 5-9). Access sites that are inferior to the pubis are associated with a higher rate of complications such as hematoma and pseudoaneurysm formation, whereas access sites located above the pubis are associated with high rates of retroperitoneal bleeding (Fig. 5-10).

FIGURE 5-9 Anatomic versus functional common femoral artery.
FIGURE 5-10 A. Lateral diagram of common femoral artery anatomy. B. Low access
site with risk for hematoma and/or pseudoaneurysm. C. High access site with risk for retroperitoneal hemorrhage.

The superficial femoral artery courses within the medial thigh until it divides posteriorly at the level of the adductor canal. Anatomically, this region is also known as the *Hunter canal*. This area is also the anatomic boundary of the superficial femoral artery and the popliteal artery. At its origin, the popliteal artery gives off the descending genicular, superior genicular, and supreme geniculate arteries, which are a rich source of collaterals in occlusive arterial disease, as is the profunda femoris artery. The popliteal artery then divides into the anterior tibial artery and the tibioperoneal trunk below the level of the knee. The anterior tibial artery courses anteriorly to supply the interosseous muscles, continuing inferiorly to terminate as the dorsalis pedis artery in the foot. The tibioperoneal trunk gives rise to the peroneal and posterior tibial arteries. The peroneal artery follows a medial course posterior to the interosseous membrane of the tibia and fibula and terminates with the posterior communicating branch and an anterior perforating branch. The posterior tibial artery continues medially to pass posterior to the medial malleolus. Together with the branches of the dorsalis pedis branch, this artery forms the pedal arch of the foot (Fig. 5-11).
SFa = superficial femoral artery
POPa = popliteal artery
Ga = geniculate arteries (superior, inferior)
TPT = tibioperitoneal trunk
ATa = anterior tibial artery
PTa = posterior tibial artery
Pa = peritoneal artery
DPa = dorsal pedal artery
Arteriography of the iliac arteries and the lower extremities involves both ipsilateral and contralateral imaging. For the aortoiliac bifurcation and common iliac arteries, an AP view is required. To image the bifurcation of the internal and external iliac arteries, a contralateral angulated view is best. For example, an LAO view would optimize imaging for the right internal and external iliac arteries. The external iliac and common femoral arteries usually require an ipsilateral angulated view, which separates out the profunda femoris artery from the superficial femoral artery since the profunda femoris follows a lateral and posterior course. The angulation is generally between 20° and 30°. Usually, AP projections suffice for the superficial femoral arteries and the vessels of the lower extremities (see Table 5-2).6,7

ACKNOWLEDGEMENTS

The authors wish to thank Richard E. Stewart, MD, for his contributions to the previous edition of this chapter

REFERENCES

MULTIPLE CHOICE QUESTIONS

1. The most common anatomic variant in aortic arch anatomy, occurring in 15% of the population, is a common ostium of the __________ and ______________.
   A. Brachiocephalic and left common carotid arteries
   B. Left common carotid and left subclavian arteries
   C. Brachiocephalic and left subclavian arteries
   D. Brachiocephalic and left vertebral arteries

2. What is the most challenging type of aortic arch for both diagnostic imaging and therapeutic intervention?
   A. Type I
   B. Type II
   C. Type III

3. The nerve that mediates the baroreceptor reflex typically seen during carotid intervention is the __________ nerve.
   A. Trigeminal
   B. Hypoglossal
   C. Glossopharyngeal
   D. Vagus
   E. Abducens

4. During carotid intervention, it is critical to maintain wire position below the __________ to avoid intracerebral perforation or dissection.
   A. Mandible
   B. External carotid
   C. Siphon or “S” portion of the internal carotid
   D. Cavernous portion
5. What is the true anatomic landmark of the “functional” common femoral artery?
   A. Femoral head
   B. Pubis
   C. Femoral neck
   D. Anterior superior iliac spine

ANSWERS

1. A
The most common variant of the aortic arch anatomy is a shared ostium of the brachiocephalic artery and the left carotid artery, which occurs in 15% of the population.

2. C
The type III aortic arch represents the most difficult arch anatomy for both diagnostic and therapeutic interventional procedures. Because the aortic arch is highly angulated in the type III anatomy, catheter selection is key to being able to properly selectively engage the desired vessel and achieve adequate support for catheter-based intervention.

3. C
The proximal portion of the carotid bifurcation houses the carotid sinus that regulates baroreceptor reflexes via the glossopharyngeal nerve and can cause bradycardia and hypotension during carotid intervention.

4. C
It is critical to maintain wire position below the level of the siphon because an intracranial perforation or dissection could occur if the wire or a distal protection device is allowed to enter the intracranial carotid.

5. B
The optimal point for common femoral artery access lies within the portion of the common femoral artery that lies over the pubis. This segment of the
common femoral artery represents the “functional” common femoral artery as it relates to arterial access for endovascular procedures because it is the only portion of the vessel that allows the ability to adequately compress the vessel over the underlying bony structure (the pubis) when performing manual compression.
INTRODUCTION

The heart is the engine that powers life, and the coronary circulation represents the fuel pipes, providing blood with oxygen and other nutrients to keep the heart beating. Under normal physiologic circumstances, there will always be an equilibrium between oxygen demand of the myocardium and oxygen supply provided by the blood flow in the coronary arteries. There is an ingenious regulation system in the coronary circulation to maintain this equilibrium, called autoregulation. Due to the enormous reserve of the coronary circulation to provide blood to the myocardium, early stages of coronary atherosclerosis and narrowing in the coronary arteries will hardly be noticed, and if the coronary arteries become more severely narrowed, complaints will only occur in situations where the oxygen demand is increased, such as physical exercise or stress. Under those circumstances, myocardial ischemia will present itself by a characteristic pain or unpleasant sensation in the chest, arms, neck, or back, called angina pectoris. However, under resting circumstances, blood flow in the coronary circulation can be kept sufficient for a long time despite the presence of important narrowing.1

For those reasons, it is important to realize that in assessing the coronary circulation, it is not the coronary blood flow at rest that should be studied as a
measure for the severity of coronary artery disease, but the maximal achievable blood flow as can be provoked by maximum exercise or vasodilatory stimuli like adenosine. Stated in another way, the degree to which maximum blood flow in the coronary circulation is decreased determines the exercise level at which angina pectoris occurs.

Also, in case of acute coronary syndromes, fundamentally the same principles hold true. However, in those situations, a rapid and sharp decrease of coronary blood flow usually occurs due to plaque rupture and/or thrombosis, often superimposed upon preexisting lesions.

It should be realized that the severity of disease on the coronary angiogram has only a poor correlation with the degree to which coronary blood flow is decreased. In other words, it is difficult to assess the physiologic significance of a coronary artery stenosis from the coronary angiogram. Nevertheless, the angiogram is important because in performing coronary interventions, it is a road map for the interventionalist to manipulate with wires and other equipment and to place the stent(s). In this chapter, the structure of the coronary circulation is discussed, followed by the regulation of coronary blood flow. There is a brief discussion on the development of atherosclerosis and the physiologic methods to detect this in early and later stages. Some words are also spent on coronary stenoses and myocardial ischemia and the consequences of ischemia for the heart. This is followed by the paramount question why functional testing is important, leading to the concept of fractional flow reserve. Some physiologic aspects on background and features of fractional flow reserve are briefly discussed. The clinical use of fractional flow reserve is discussed later in Chapter 24. Finally, some specific manifestations of coronary artery disease and physiologic methods for how to address these are discussed.

THE CORONARY CIRCULATION

In most mammals, the coronary circulation consists of 2 blood vessels originating from the proximal aorta. In humans, these coronary arteries have a diameter of approximately 2.5 to 4.0 mm and run as a kind of corona around and across the heart. Just like all other arteries, these coronary arteries have a layered structure with an intima, media, and adventitia. It is important to realize that under normal circumstances, the resistance of the coronary
artery to blood flow is negligible, even at maximum hyperemia. From the epicardial coronary arteries, perforating branches enter the myocardium, and within the myocardium, these divide further into smaller vessels, called arterioles, with a diameter between 100 and 400 μm. Around these arterioles, smooth muscle cells are located in groups and are able to vary the resistance of the arterioles over a large domain (Fig. 6-1).

**FIGURE 6-1** Schematic representation of the coronary circulation. The coronary artery splits up into arterioles with a diameter of 100 to 400 μm, which further divide into the capillary bed. At the entrance of the arterioles, muscular sphincters are
located that can vary the resistance of the arterioles by at least 500%. Under resting conditions, the sphincters will be constricted, and if a higher blood flow is needed in response to higher oxygen demand (as in exercise), the sphincters dilate. In that way, at an equal perfusion pressure, myocardial blood flow can increase by at least 500% in healthy young individuals. In case of a moderate stenosis, an additional epicardial resistance occurs, and as a compensation, the arteriolar sphincter partially dilates even under resting conditions in order to maintain a total resistance in the bed equal to R. Consequently, during resting conditions, no noticeable effect of the epicardial stenosis is observable. However, during situations of increased demand (eg, exercise) the compensatory vasodilator reserve of the sphincters is already decreased and the maximal achievable blood flow in the coronary artery and myocardial bed is decreased accordingly. Therefore, myocardial ischemia and angina pectoris may occur during exercise. In case of a very severe stenosis in the epicardial coronary artery (lower pictograms), the epicardial stenosis can be so tight that the arteriolar sphincter needs to dilate completely to compensate the additional resistance in the coronary artery. This means that no reserve at all is left anymore. In such a case, even minimal increase in oxygen demand will result in angina pectoris. With further increase of stenosis severity, frank ischemia at rest will occur, resulting in unstable angina or an acute coronary syndrome. (From Pijls NHJ. Coronaire fysiologie en myocardischemie. In Van der Wall EE, Van de Werf F, Zijlstra F. Cardiologie. Houten, the Netherlands: Bohn Stafleu van Loghum, 2008, with permission of Springer.)

For the purpose of simplicity, these smooth muscle cells around the arterioles are indicated as a kind of sphincter. In reality, the muscle cells are more equally distributed along the arterioles. The resistance of these arterioles can vary in healthy individuals by at least 500%, which means that under normal circumstances, maximum blood flow can be at least 5 times baseline blood flow. This ratio between maximum blood flow and baseline blood flow is called coronary flow reserve (CFR), as will be discussed more extensively later. The arterioles split up into the capillaries, in analogy to any other organ in the human body. The capillary network of the heart is very dense, and every myocyte is next to a capillary. Finally, the capillaries collect into small venules and collect further into veins, which either drain directly into the heart chambers (Thebesian veins) or collect in 1 large vein, the coronary sinus, with a diameter of 5 to 10 mm and ending in the right atrium.

Coronary blood flow equals approximately 3% to 5% of total cardiac output and varies from 200 mL at rest to approximately 1 L per minute at maximum exercise in healthy young people. It is important to realize that in contrast to most other organs in the human body, oxygen extraction from the blood in the coronary circulation is very high and that oxygen saturation in
the coronary sinus is relatively low (30%-40%). This means that in the coronary circulation increase in oxygen consumption by the myocardium can only be achieved by an increase of blood flow and not by further extraction of oxygen. This issue will be discussed later in this chapter and in the other chapters.

Under baseline circumstances, the oxygen consumption of the myocardium is 0.7 to 1.3 mL O$_2$/min/g of tissue, and under maximum hyperemic circumstances, this increases to 3 to 6 mL O$_2$/min/g.

During exercise, heart rate and contractility will largely increase and lead to an increase in oxygen consumption; in addition, afterload will increase, thereby further increasing the oxygen demand and consumption of the heart. To match this tremendously increased demand, a wonderful regulation mechanism has been designed by nature, called autoregulation, which is further explained in Figure 6-1.

**Collaterals**

Collaterals are small blood vessels that can connect perfusion territories of different coronary arteries. The diameter of collaterals can vary from 10 μm to >1 mm. In the latter case, the collaterals are visible on the coronary angiogram. Collaterals can either be preexistent or develop as a response to myocardial ischemia. Repetitive ischemia is a necessary condition and the most potent stimulus to develop collaterals.

Collaterals can be either subendocardial or subepicardial. In the first case, the process underlying collateral development is often angiogenesis, and such angiogenetic collaterals only exist in a 1-layered rudimentary vessel structure. Subendocardial collaterals are often nicely observed running through the septum and connecting the septal branches of the left anterior descending artery and the posterior descending branch of the right coronary artery. In the case of subepicardial collaterals, these are often preformed (with a large variation between different individuals), have a 3-layer structure like a normal small artery, and are often very tortuous (corkscrew). This type of collaterals can often be seen across the apex connecting the distal right coronary artery and the left anterior descending artery, or running from the right ventricular branch of the right coronary artery to the left coronary artery, or even running across the atrium.
Collaterals are important because in a number of patients collaterals provide sufficient blood flow to maintain oxygen supply at rest even in case of a severe stenosis or total occlusion of the recipient coronary artery belonging to the collateral-dependent territory. The extent of collaterals and the intrinsic aptitude to develop them largely vary from one person to another and are also species dependent. In humans, in case of repetitive ischemia of the myocardium, collaterals may develop and reach a kind of maximum in most patients after approximately 3 months.

**REGULATION OF CORONARY BLOOD FLOW**

**Autoregulation**

Autoregulation is the mechanism by which oxygen supply and demand of the myocardium are matched to each other both under physiologic and pathologic circumstances (see Fig. 6-1). It is important to realize that the arteriolar sphincters can vary the resistance over a large range. If these sphincters are completely dilated, resistance in the coronary circulation decreases by roughly 500%, which means that at an equal perfusion pressure, the reserve of coronary blood flow is also 500%. Under normal circumstances, the perfusion pressure in the coronary circulation is the difference between the aortic pressure and the central venous pressure (in normal circumstances, 0-5 mm Hg). If no coronary stenosis is present, the pressure in the distal coronary artery at the entrance of the arterioles equals the aortic pressure because there is no decline of pressure in a normal coronary artery, not even during maximum hyperemia. In case of increased oxygen demand of the myocardium (exercise, stress), the arteriolar sphincters can dilate, and blood flow can increase accordingly, even if perfusion pressure remains unchanged. The mechanism by which sphincters can dilate or contract is dependent, on one hand, on mechanical factors (eg, shear stress) and, on the other hand, on humoral factors (eg, bradykinin, acetylcholine, nitric oxide). If, at exercise, arterial blood pressure further increases (and thereby also the perfusion pressure across the coronary circulation), coronary blood flow will be able to increase further and will always remain sufficient
to match the increased oxygen demand and metabolic needs of the myocardium.

The coronary autoregulation also keeps coronary flow constant despite changes in blood pressure. If, for whatever reason, blood pressure decreases, this is also accompanied by dilatation of coronary sphincters to keep coronary perfusion constant despite low blood pressure. If blood pressure increases inadvertently, contraction of sphincters prevents coronary blood flow from increasing inadvertently. In this way, coronary blood flow remains constant between mean aortic pressure from 50 to 130 mm Hg. At average blood pressures of greater than 130 mm Hg, sphincters are maximally contracted, and the further increase of blood pressure will increase coronary perfusion.

Below a mean arterial pressure of 50 mm Hg, the sphincters are maximally dilated, and a further decrease of blood pressure will lead to a pathologic decrease of coronary perfusion. As mentioned, the phenomenon whereby coronary perfusion can be maintained constant over a large range of perfusion pressures is called autoregulation of coronary blood flow.4

**Reactive Hyperemia**

Under baseline circumstances, blood flow in the left coronary artery occurs mainly during diastole. In systole, the myocardium compresses its own vasculature, and there is almost no forward blood flow in the left coronary artery. This means that blood flow in the coronary arteries is antiphasic compared to other parts of the human circulation, where blood flow mainly occurs during systole.

During maximum hyperemia of the myocardium (as present during maximum exercise but also after administration of specific vasodilatory drugs), diastolic blood flow in the coronary artery further increases, but also a systolic component in coronary blood flow occurs consisting of 15% to 25% of total coronary blood flow (Fig. 6-2).
FIGURE 6-2 A and B. Blood flow pattern in a normal left coronary artery at rest and at hyperemia. At rest, systolic blood flow is very low, and flow mainly occurs during diastole. During maximum hyperemia, a systolic component also occurs, whereas
diastolic blood flow increases even more. C. Example of reactive hyperemia after 20 seconds of occlusion of the left anterior descending artery of a dog. After relief of the occlusion, a rapid increase in blood flow occurs to 500% of resting blood flow, followed by a decrease when the oxygen debt is solved. D. Reactive hyperemia after intracoronary administration of 10 mg of papaverine in the same dog. E. Phasic and mean coronary blood flow in the left anterior descending artery of a dog after occlusions of 3, 5, 10, 20, and 30 seconds. As the time of occlusion increases, reactive hyperemia is more pronounced up to an occlusion time of approximately 20 seconds. With longer occlusions, the peak hyperemia no longer increases, but it takes longer before flow returns to baseline. (From Pijls NHJ. Coroaine fysiologie en myocardischemie. In Van der Wall EE, Van de Werf F, Zijlstra F. Cardiologie. Houten, the Netherlands: Bohn Stafleu van Loghum, 2008, with permission of Springer.22)

The blood flow pattern in the right coronary artery is more variable and more equally distributed across systole and diastole. In case of a dominant right coronary artery, it can look like a flow pattern in the left coronary artery. Normal blood flow patterns at rest and hyperemia are indicated in Figure 6-2.

If, in an experimental model (eg, a dog or a pig), the coronary artery is occluded during some time, myocardial ischemia will occur, and after release of the occlusion, a temporary increase in flow to the myocardium will occur. This is called reactive hyperemia (see Fig. 6-2). The longer the occlusion, the more pronounced and longer is the reactive hyperemia. Reactive hyperemia is maximal after occlusions of at least 20 seconds. If the occlusion lasts longer, the peak of hyperemia will not further increase but recovery of flow to baseline will take longer. Obviously, after occlusions of 20 seconds or more, the arteriolar sphincters are completely dilated. Maximum coronary hyperemia can not only be obtained by temporary occlusion of the coronary artery, but also pharmacologically by administration of specific drugs such as intracoronary papaverine or adenosine or intravenous adenosine, adenosine triphosphate, or regadenoson.5,6

Coronary Flow Reserve

The level to which coronary or myocardial blood flow can increase is indicated by CFR. The absolute CFR is defined as the ratio between hyperemic and baseline blood flow (see Fig. 6-2; Fig. 6-3).7
FIGURE 6-3 Definition and characteristics of coronary flow reserve (CFR) and fractional flow reserve (FFR). In both panels, the relationship between coronary perfusion pressure and coronary blood flow is indicated. Between an average perfusion pressure of 50 and 130 mm Hg, coronary perfusion remains constant at rest (autoregulation, horizontal lines). At maximum exercise or after administration of a vasodilatory stimulus, the arteriolar sphincters in the coronary artery are fully dilated, and a linear relation exist between perfusion pressure and blood flow (oblique lines). In case of a coronary stenosis, the slope of the oblique line will decrease. CFR is defined as maximum blood flow divided by blood flow at rest. Maximum blood flow is dependent on blood pressure, and blood flow at rest varies with heart rate and contractility. Consequently, CFR can vary over a large range for 1 specific coronary stenosis. FFR is defined as maximum blood flow in the presence of a stenosis divided by maximum blood flow in the hypothetical case where no stenosis would be present at all. This ratio is independent of changes in blood pressure, heart rate, and contractility, and under normal circumstances, FFR always has the same reference value (ie, 1.0). An FFR below 0.75 to 0.80 generally corresponds with inducible myocardial ischemia of the territory supplied by that particular coronary artery. In such cases, the stenosis is considered hemodynamically significant, and revascularization is most likely indicated.

As indicated in Figure 6-3 and as is clear from theoretical considerations, CFR correlates with blood pressure and is higher with higher blood pressure. CFR is also dependent on age and decreases with aging. In healthy young people, normal CFR is 5 to 6, but in healthy octogenarians, CFR is often hardly 1.5.

CFR is a useful theoretical parameter to understand the coronary circulation but less suitable in clinical practice to quantify the hemodynamic
significance of a coronary stenosis because of its dependency on blood pressure, age, and a number of other factors. In the practice of the interventional laboratory, apart from the lack of a normal reference value, probably the most important limitation is that to determine CFR reliably, one has to rely on resting blood flow. In the catheterization laboratory, in a patient laying on the table and undergoing an intervention, it is hard to be sure that true resting blood flow is present. As a result of these limitations of CFR in clinical studies, the threshold of CFR below which coronary ischemia is inducible varies in different studies from 1.6 to 3.3. This means that the same CFR value of, for example, 2.5 can be completely normal in one person but severely decreased in another person. Consequently, it is difficult to use CFR for decision making with respect to revascularization.

To overcome these shortcomings of CFR for clinical decision making, the concept of fractional flow reserve (FFR) has been developed. FFR is defined as maximum achievable blood flow in a stenotic coronary artery compared to maximum blood flow in that same coronary artery in the hypothetical case that the vessel would be normal. As will be explained later, FFR can be determined in the catheterization laboratory by coronary pressure measurement and is useful to characterize the hemodynamic significance of a coronary stenosis and to decide upon sense or nonsense of mechanical revascularization (stenting of bypass surgery). The concept of FFR is illustrated in Figure 6-3 and Figure 6-4 and discussed further later in this chapter.
**FIGURE 6-4** Definition of fractional flow reserve (FFR). On the left side, the epicardial coronary artery and the myocardial vascular bed are depicted. In the upper part, no stenosis is present, and normal perfusion pressure during hyperemia is 100 mm Hg. In the lower part, a stenosis is present, and distal coronary pressure at hyperemia has decreased to 70 mm Hg. Therefore, the perfusion pressure has decreased to 70 mm Hg only, whereas it should normally be 100 mm Hg. Because of the linear relationship between hyperemic perfusion pressure and hyperemic blood flow (*right part of the figure*), this means that the maximum myocardial perfusion in the presence of a stenosis has decreased to only 70% of what would be its normal value. In fact, a ratio of hyperemic blood flows is expressed as a ratio of perfusion pressures, and FFR is the hyperemic distal perfusion pressure (Pd) in the presence of the stenosis divided by the perfusion pressure in the normal case, indicated by Pa. FFR indicates the fraction of normal maximum blood flow that is still achievable in the presence of a stenosis. An FFR of 0.7 means that, as a consequence of the epicardial coronary stenosis, maximum blood flow to the supplied myocardial territory has decreased to 70% of the value it should be in a normal case. Therefore, FFR is a specific measure of the functional severity of a coronary stenosis.

**ENDOTHELIUM AND DEVELOPMENT OF ATHEROSCLEROSIS**

The early phase of atherosclerotic coronary disease is endothelial dysfunction. This is invisible by any imaging method but can be demonstrated by functional testing (*Fig. 6-5*). In reaction to a number of humoral or mechanical stimuli (eg, increased shear stress), endothelial cells produce nitric oxide (NO), leading to relaxation of underlying smooth muscle cells and vasodilation with increase of blood flow in the coronary artery. The earliest stage of (coronary) atherosclerosis is endothelial dysfunction. This can be demonstrated by intracoronary acetylcholine administration. In the presence of healthy endothelium, acetylcholine also increases NO production and, thereby, coronary blood flow. Acetylcholine also has a direct vasoconstrictive effect on the underlying smooth muscle cells, but in healthy persons, this effect is weaker than the vasodilatory NO-stimulating effect. If the endothelium is diseased, the direct vasoconstrictive effect predominates, and so-called *paradoxical vasoconstriction* occurs. This phenomenon can be used in the interventional laboratory to demonstrate endothelial dysfunction. Such a test is performed by administrating subselectively intracoronary acetylcholine under controlled conditions but is not trivial and not without
risk, and therefore, it should only be applied in specialized catheterization laboratories.

**FIGURE 6-5 Abnormal endothelial function.** The earliest stage of atherosclerosis is endothelial dysfunction, often present long before abnormalities on the angiogram can be seen. In the left panel, an apparently normal coronary angiogram is seen in a young male with many risk factors and a positive exercise test. To detect abnormal endothelial function, acetylcholine is injected into the coronary artery, resulting in severe and varying vasoconstriction in the different branches of the circumflex system. In the presence of normal endothelium, no such narrowing should be seen. In the right panel, nitroglycerin has been administered to relieve the acetylcholine effects.

The next step in the evolution of atherosclerosis is development of early plaques and often diffuse disease that is not visible on the angiogram but can be demonstrated by anatomic methods, such as intravascular ultrasound or optical coherence tomography, and by physiologic methods, such as FFR measurement. In the latter case, during hyperemia, an abnormal pressure decline will occur even in an apparently normal coronary artery.

Finally, when macroscopic, gross atherosclerosis occurs, it can be detected easily on the coronary angiogram, but physiologic measurements remain generally necessary to define the extent and physiologic significance of disease.

For the interventional cardiologist, this is important because in case of diffuse decline of coronary pressure along a coronary artery and a focal decline at 1 particular spot or a severe stenosis, stenting of the severe stenosis will not result in a restoration to normal because the diffuse gradient will persist within the artery and even increase after stenting the focal stenosis. It
is important to quantify this because, in some cases, this diffuse disease as detected by the pressure pullback recording can be responsible for residual inducible ischemia, even after successful stenting of focal spots. Similarly, by such hyperemic pressure pullback recording, patients with diffuse disease can be distinguished who cannot be treated with mechanical techniques of revascularization even though ischemia may be present. This issue will be further discussed in Chapter 24.

CORONARY STENOSIS AND MYOCARDIAL ISCHEMIA

Atherosclerosis of the coronary arteries is common in the Western world and increases with age. Approximately half of asymptomatic and apparently healthy persons between ages 50 and 65 years have visible atherosclerotic abnormalities in the coronary arteries. It is important to note that, in many of these patients, such narrowing will never cause significant problems. Therefore, the anatomic presence of a coronary stenosis does not indicate per se that revascularization is indicated. However, in case of visible atherosclerosis, preventive lifestyle management and medical treatment using aspirin, statins, angiotensin-converting enzyme inhibitors, or β-blockers might be indicated and useful.

In case of a developing stenosis in the coronary artery, an additional resistance in the coronary circulation occurs. At rest, this can be easily compensated by compensatory dilatation of the arteriolar sphincters, as can be easily understood from Figure 6-1. If at baseline, sphincter resistance is called R, minimal resistance (in this example) will be 1/5 R. A moderate stenosis in the supplying coronary artery with a resistance equaling 2/5 R can be easily compensated by a decrease of arteriolar resistance to 3/5 R.

In other words, there are now 2 resistances in series, but at rest, the total resistance remains constant assuming unchanged perfusion pressure. Therefore, coronary flow at rest will also remain constant. However, this is at the cost of CFR, which is decreased because at maximum exercise the remaining vasodilatory capacity of the sphincters has been decreased.

If the coronary narrowing becomes more severe, the situation can occur that the full vasodilatory capacity of the distal sphincters is mandatory to
compensate the increased resistance in the coronary artery and no further reserve is left. As will be clear, this is the situation with stable angina pectoris, which increases over time. With further increase of stenosis severity, even ischemia at rest may occur. Acute coronary syndromes often occur from a sudden increase of resistance in the coronary artery by plaque complication, rupture, or thrombosis. Although it is often believed that plaque rupture occurs in previously minor plaques, recent studies have indicated that the hemodynamic significance of such underlying plaques is often significant and the resultant repetitive ischemia is a potent stimulus to make a plaque vulnerable. In any case, there is a strong relationship between repetitive ischemia and vulnerability.

Whatever the relationship between vulnerability and ischemia may be, it is clear that inducible ischemia of the myocardium is the most important prognostic factor for patients with coronary artery disease. If a coronary stenosis causes no inducible ischemia, its prognosis is generally favorable, and medical treatment is the best way to continue. If a coronary stenosis is hemodynamically significant, outcome in terms of prognosis is much worse and a coronary intervention (either stenting or bypass surgery) is generally indicated. In addition, hemodynamically significant stenoses often cause complaints (angina pectoris), and mechanical intervention is the most efficient way to treat such complaints.

Consequently, one of the most important issues in interventional cardiology is to make correct decisions about which coronary stenoses should and should not be revascularized. Beyond doubt, the functional significance of a stenosis is much more important in this respect than its appearance on the angiogram. The gold standard used in the catheterization laboratory to assess the hemodynamic significance of a coronary stenosis is FFR. The physiologic background of FFR and some specific features of it will be discussed in the next section, whereas a more extensive discussion about its practicalities and clinical application will be outlined in Chapter 24.

**FRACTIONAL FLOW RESERVE**

The concept of FFR is based on 2 important principles. First, it is not resting blood flow but maximal achievable blood flow that determines the functional capacity of a patient and is decisive regarding whether myocardium will
become ischemic. Second, at maximum vasodilatation (corresponding with maximum hyperemia or maximum exercise), blood flow to the myocardium is proportional to myocardial perfusion pressure, as outlined earlier.

With those principles in mind, FFR is easy to understand from Figure 6-4. In the left upper part of the figure, a normal coronary artery and its myocardial perfusion territory are represented. If maximum vasodilation in the coronary circulation is present (all vessels and sphincters dilated), blood flow will be proportional to aortic pressure (Pa) minus central venous pressure (Pv), which is put at 0 for case of simplicity. In the left lower part of the figure, a coronary stenosis is present, resulting in a particular pressure drop at hyperemia within the coronary artery. To understand the functional significance of that stenosis for the patient, it is not the gradient across that stenosis that is important, but the degree to which the distal perfusion pressure has decreased. In our example, perfusion pressure has decreased to 70 mm Hg, whereas it should be 100 mm Hg in a normal case. Because of the proportionality between perfusion pressure and coronary blood flow at maximum hyperemia (assuming that minimal resistance is constant), maximum achievable blood flow in the diseased situation has decreased to 70% of its normal value (right part of the figure). In other words, a ratio of maximum blood flows is expressed as a ratio of perfusion pressures. In contrast to flow (which is difficult to measure directly in human coronary arteries), pressure can be measured easily by a 0.014-inch pressure wire. For that reason, FFR can be easily assessed in the practice of the catheterization laboratory by a pressure wire that measures distal coronary pressure (Pd) after administration of a maximum hyperemic stimulus and by comparing this distal coronary pressure at hyperemia to aortic pressure. Or simply stated:

$$\text{FFR} = \frac{(P_d - P_v)}{(P_a - P_v)} \approx \frac{P_d}{P_a}$$

In clinical practice, measurement of FFR is easy, as illustrated in Figure 6-6. In fact, the concept of FFR encompasses much more than only the effect of a coronary stenosis on myocardial blood flow. It is also possible to express maximum coronary artery blood flow, myocardial blood flow, and collateral blood flow quantitatively as a percentage of normal maximum myocardial blood flow. To measure the separate contributions of coronary artery and collateral blood flow to myocardial flow, however, knowledge of coronary
wedge pressure is mandatory (as can be measured during balloon occlusion). In fact, FFR gives a complete description of the coronary circulation and all components of it in terms of pressure measurement. In-depth discussion about the concept of FFR is beyond the scope of this chapter, and for that purpose, we refer the reader to the initial publication defining FFR in *Circulation* in 1993\textsuperscript{8} and a myriad of review publications.\textsuperscript{14-16}

**FIGURE 6-6**

A. Measurement of fractional flow reserve (FFR) in clinical practice in a patient with angina pectoris, a positive exercise test, and a suspected lesion in the proximal left anterior descending artery (arrow). B. A pressure wire is introduced into the coronary artery. Aortic pressure measured by the guiding catheter is indicated by the red signal, and the coronary pressure measured by the pressure sensor is indicated by the green signal. When the sensor is proximal to the suspected lesion, pressures are equal. When the pressure sensor crosses the lesion, a sudden drop in distal pressure occurs, and when inducing maximum hyperemia by IV administration of adenosine 140 μg/kg/min, distal pressure further decreases, reflecting increase of blood flow. C. At steady-state maximum hyperemia, distal coronary pressure is 52 mm Hg compared to 91 mm Hg in the aorta. FFR is easily calculated as 52/91 = 0.57. In other words, as a consequence of the visible plaque in the proximal LAD on the angiogram, maximal achievable blood flow to the anterior wall of the heart in this patient has decreased to only 57% of its normal value.

**PHYSIOLOGIC FEATURES OF FRACTIONAL FLOW RESERVE**

FFR has a number of specific advantages over other physiologic indexes that make it an easy index to assess coronary artery disease and to make decisions about the necessity of interventions. These physiologic features will be
discussed in the following section. For more practical discussion, see Chapter 24.

**Uniform Normal Value and Discrimination of Inducible Ischemia**

As discussed earlier, in a completely normal coronary artery, there is no decline of pressure, not even during maximum hyperemia. Consequently, the normal reference value of FFR is 1.0 irrespective of the patient, hemodynamic conditions, age, or any other variable. Having an uniform normal value is important, because without that, it will be impossible to define a reliable threshold value for ischemia. The threshold value of ischemia for FFR is generally taken as 0.80. In fact, it is somewhere between 0.75 and 0.80 with a small gray zone in between, as will be discussed later. In clinical practice, it is generally felt justified to revascularize a stenotic coronary artery if FFR is $\leq 0.80$ and to give medical treatment if FFR is $>0.80$.

**Relationship Between Vessel Size and Perfusion Territory**

In contrast to any anatomic method, FFR accounts for the relationship between the severity of the epicardial coronary stenosis and the size of the perfusion territory. This is especially important in assessing stenoses severity after previous myocardial infarction. Two coronary arteries might have an exactly identical stenosis with exactly identical morphologic features, but the functional severity will vary if the perfusion territory has a different extent. Such difference cannot be detected when only looking at the morphologic features of the stenotic artery. In the case of 2 identical stenoses but a larger (viable) perfusion territory distal to 1 of these lesions, the hyperemic response will be larger and the FFR consequently lower (Fig. 6-7). This explains why, after previous myocardial infarction, an apparently severe stenosis might have a rather high FFR, whereas a similar stenosis without infarction has a much lower FFR. It also explains why a moderate lesion with a large perfusion territory, including collaterally dependent myocardium, might be significant, whereas it would not be significant without the collateral perfused territory.
**FFR accounts for the extent of the perfusion area:**

![Diagram of FFR](image)

**FIGURE 6-7** Fractional flow reserve (FFR) is not only a measure of the functional severity of the coronary artery stenosis itself, but also relates stenosis severity to the extent of the perfusion territory, as indicated in this figure. In both the upper and lower parts of this figure, a similar stenosis is present, and with anatomic methods, no difference can be observed. However, because in the upper part of the figure the perfusion territory is larger, a higher hyperemic response can be provoked and FFR will be lower than in the case of a decreased perfusion territory. In fact, FFR connects coronary stenosis severity, coronary blood flow, inducible ischemia, and extent of perfusion territory with each other. See text for further explanation.

**Independency From Blood Pressure, Heart Rate, and Contractility**

In contrast to CFR, FFR is not dependent on changes in hemodynamics such as heart rate, blood pressure, and contractility. This is due to the fact that FFR is not dependent on resting blood flow, as can be understood from Figure 6-3. True resting conditions in the catheterization laboratory are difficult to obtain, and normally, during cardiac catheterization and intervention, large variations in so-called resting blood flow occur. This explains in part the large fluctuation in CFR (and other indexes relying on resting blood flow) and the wide range of CFR values in different patients with the same FFR. As illustrated in Figure 6-3, such limitation is not present for FFR. Also, in humans, studies have been performed with large variations in heart rate, blood pressure, and contractility with no effect on FFR. In the literature, it is often suggested that different values of CFR in
different patients with the same FFR is a measure of microvascular dysfunction. However, it is likely that such a range of CFRs is due to absence of one uniform normal value (eg, age, different hemodynamic circumstances) and has little to do with abnormal microvascular status.

**Collaterals**

As mentioned earlier, FFR accounts for the effects of the collateral circulation. In fact, the separate contribution of collateral and coronary artery blood flow to myocardial perfusion can be calculated by the pressure measurements, provided that wedge pressure is known.\(^8\)

In case of extensive collaterals, a stenosis might have a high FFR value, whereas in the absence of collaterals, the FFR might be low. Conversely, as mentioned earlier, a similar stenosis may have a lower FFR value if the respective artery gives collaterals to another territory.

**Issue of Maximum Hyperemia**

As discussed earlier, one of the fundamental requirements to calculate FFR is the presence of maximum coronary and myocardial hyperemia. In the catheterization laboratory, this can be achieved pharmacologically in a number of ways, as summarized in Table 6-1. When using maximum hyperemia, FFR is an extremely reliable index of ischemia and has been validated versus a true gold standard using a so-called prospective multitesting Bayesian approach.\(^{19}\)

<table>
<thead>
<tr>
<th>Table 6-1</th>
<th>Effects of Different Vasodilatory Stimuli on the Epicardial Coronary Artery and the Microvascular Bed</th>
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Although a number of ways for inducing hyperemia are available in the catheterization laboratory and not difficult with a good logistic setup, because of simplicity, it has been proposed recently to leave hyperemia out and to perform resting measurements only. Several resting indexes have been proposed, such as the Pd/Pa at rest and the so-called iFR (instantaneous wave-free ratio).\(^{20}\) Unfortunately, the physiologic basis for using resting indexes is poor and not supported by experimental studies in animals. Generally, according to Poiseuille’s law and as validated in animals and humans, a small baseline pressure gradient across the stenosis can be accompanied by a large hyperemic gradient, especially in young patients, patients with a short severe stenosis, and patients with proximal lesions or a large perfusion territory, whereas a moderate gradient with only moderate hyperemic increase can be observed in older patients, patients with distal lesions, and patients with small coronary arteries (Figs. 6-8 and 6-9).
\[ \Delta P = f \cdot Q + s \cdot Q^2 \]

FIGURE 6-8 Explanation of why resting pressure indexes are not sufficient to predict true stenosis severity. According to Poiseuille’s law, the pressure gradient across a stenosis is related to blood flow by a linear and quadratic component, representing friction \((f)\) and separation \((s)\) coefficients, respectively. In some lesions, friction is the predominant factor, which means that a moderate resting gradient will moderately increase at hyperemia. At the other end of the spectrum, where separation is predominant, a minimal resting gradient can be accompanied by a very large hyperemic gradient. The latter is especially the case in younger patients with short lesions in the proximal part of a large coronary artery with a large perfusion territory. See also Figure 6-9. LAD, left anterior descending artery.
Therefore, in clinical practice, it is generally unpredictable to what extent a baseline gradient will increase with hyperemia. Nevertheless, if a resting gradient is large and already below the ischemic threshold of FFR, just for the mere purpose of making the decision about whether or not to revascularize, no additional hyperemia will be necessary, whereas in the case of very small resting gradients, often (but not always) no inducible ischemia will be present. In addition, as mentioned earlier, it is often not possible to achieve true resting conditions in a human catheterization laboratory. When using resting indexes in the best possible way, agreement with FFR with respect to presence of ischemia is achieved in approximately 80% of cases. FFR in itself has an accuracy of approximately 95% compared to the true gold standard.\textsuperscript{19,21}

There is another reason why true hyperemia is desirable. In the current population of patients in the catheterization laboratory, who often have complex coronary artery disease, predicting whether a stenosis is causing ischemia is only 1 piece of information. The other piece is making a hyperemic pullback recording to assess abnormalities along the complete course of the coronary artery to understand the nature of the disease and to predict whether stenting will be effective. For such pullback recording, resting conditions lack sufficient spatial resolution (poor signal-to-noise ratio), and maximum hyperemia is mandatory.
A compromise between resting indexes and hyperemia might be achieved by contrast FFR (cFFR; defined as Pd/Pa after a single regular bolus of 10 mL of contrast agent). An injection of contrast agent into a coronary artery generally increases blood flow very shortly up to a level of at least 80% of maximum hyperemia. Therefore, it has been suggested to use a contrast injection to discriminate whether FFR is abnormal. Although suboptimal, cFFR is more reliable than using resting indexes only, and it is easy to obtain. In addition, lesions with a small resting gradient but large hyperemic gradient, which would be completely overlooked by resting indexes, will be easily discovered by contrast. Agreement between cFFR and true FFR is achieved in approximately 85% of patients (Fig. 6-10). Further investigation of these resting indexes and cFFR is mandatory.

**FIGURE 6-10** The pyramid of diagnostic accuracy of functional indexes to correctly predict ischemia: Accuracy of the standard angiogram, resting pressure indexes, contrast FFR and true FFR to predict coronary ischemia and to facilitate decision making with respect to revascularization. For further explanation, see text. iFR, instantaneous wave-free ratio.

**SOME SPECIFIC MANIFESTATIONS OF CORONARY ARTERY DISEASE**
**Diffuse Coronary and Microvascular Disease**

When discussing CFR and FFR, for simplicity, it is often assumed that there is 1 (or several) focal narrowing in a coronary artery. However, atherosclerosis is a diffuse disease process, and often, abnormalities will be present along the complete course of the coronary artery, as can be noticed by intravascular ultrasound or optical coherence tomography. This diffuse disease can be so severe that focal stenting or bypass surgery does not make sense. Similarly, a lot of attention is paid to microvascular disease affecting the invisible part of the coronary angiogram. It might be clear that microvascular disease will affect both CFR and FFR. Several indexes have been developed to quantify microvascular disease (eg, index of microvascular resistance and absolute coronary blood flow). The practical consequences are 2-fold; first is the understanding that sometimes angina pectoris can occur without focal epicardial disease, and second is the necessity of aggressive medical treatment in such patients. However, the importance and prevalence of microvascular disease should not be overestimated; in the majority of patients with angina pectoris, inducible ischemia, and a focal lesion, stenting or bypass surgery results in disappearance of complaints and disappearance of inducible ischemia, indicating that the epicardial disease was the predominant factor.

**Myocardial Bridging**

When performing a coronary angiogram, sometimes bridging of the left arterial descending artery is observed during systole, due to a partly intramyocardial course of the artery or to a muscle bridge across the blood vessel. Bridging increases during adrenergic stimulation and may lead to complete occlusion during systole. However, its clinical meaning is mostly minimal. It is often unclear how this bridging should be interpreted and if it can be held responsible for complaints. In the literature and in clinical practice, many confounding points of view exist.

In our view, complaints due to bridging can only be present during adrenergic stimulation. This means that complaints at rest should never be ascribed to myocardial bridging, simply because coronary blood flow at rest is predominantly diastolic. As discussed earlier in this chapter, at maximum hyperemia, the systolic component in left coronary artery blood flow equals
15% to 25% of total flow (see Fig. 6-2). If that systolic component is 20% to 25%, one can imagine that by losing 20% to 25% of flow during occlusion of the bridge at maximum exercise, a theoretical FFR value of less than 0.75 to 0.80 occurs and could be responsible for ischemia. FFR in itself is not a good method to assess bridging because, at occlusion, there is no blood flow and consequently no gradient. Therefore, in those rare cases in which bridging is suspected to be responsible for myocardial ischemia, we use a Doppler wire to measure the coronary flow pattern in the left anterior descending artery. First, we induce maximum hyperemia using adenosine and calculate the systolic component of maximum coronary blood flow. Next, we perform flow velocity registrations at dobutamine-induced hyperemia. Only if the systolic component is more that 20% of the total velocity integral with adenosine and the systolic component disappears completely during dobutamine do we believe that it is justified to hold the bridging responsible for complaints. The approach to evaluate patients with myocardial bridging, as used in the Catharina Hospital (Eindhoven, The Netherlands), is outlined in Table 6-2.

Table 6-2 Diagnostic Approach to Patients with Chest Pain and Myocardial Bridging of the Left Anterior Descending Artery in the Catharina Hospital
CONCLUSIONS AND FINAL REMARKS

The coronary circulation is designed in such a way that there is always a match between oxygen demand and supply under a wide variety of physiologic conditions. This match is maintained by an ingenious regulation system called autoregulation.

Atherosclerosis of the coronary arteries is an insidious disease interfering
with the structure and function of the coronary circulation. Disease is mostly present long before coronary artery abnormalities can be seen. In case of a visible stenosis in a coronary artery, there is only a poor relation between anatomic severity and the functional severity, and sophisticated physiologic examination may be necessary to establish whether ischemia is present and revascularization is warranted.

The gold standard for functional assessment in coronary artery disease is FFR, which is calculated during maximum coronary hyperemia by measuring distal coronary pressure using a pressure wire and comparing it to proximal pressure measured using the guiding catheter. FFR allows functional assessment in a practical and easy way and can be measured during invasive coronary angiography. The clinical use of FFR will be discussed further in Chapter 24.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. Which intracoronary parameter has been shown to be the least influenced by hemodynamic changes?
   A. Coronary flow reserve (CFR)
   B. Fractional flow reserve (FFR)
   C. Instantaneous wave-free ratio (iFR)
   D. Resting distal coronary pressure/aortic pressure (Pd/Pa)

2. In the normal heart at rest, an increase in coronary perfusion pressure of 20% will result in which of the following?
   A. An increase in myocardial blood flow by about 20%
   B. An increase in myocardial blood flow by about 40%
   C. A decrease in myocardial blood flow by about 20%
D. No change in myocardial blood flow

3. In the normal heart during maximal hyperemia, an increase in coronary perfusion pressure of 20% will result in which of the following?
   A. An increase in myocardial blood flow by about 20%
   B. An increase in myocardial blood flow by about 40%
   C. A decrease in myocardial blood flow by about 20%
   D. No change in myocardial blood flow

4. What is the accuracy of the coronary angiogram to predict whether a coronary stenosis is able to induce myocardial ischemia?
   a. 70%
   b. 80%
   c. 90%
   d. 95%

5. What is the definition of fractional flow reserve (FFR)?
   A. Pressure gradient over a stenosis during maximal hyperemia
   B. Maximum blood flow over a stenosis divided by the resting blood flow over that stenosis
   C. Maximum blood flow in the presence of a stenosis divided by the maximum blood flow in the hypothetical absence of that stenosis
   D. Minimal luminal area divided by normal luminal area in case of a stenosis

**ANSWERS**

1. B

Both animal and human studies have shown that FFR is the only parameter that is highly independent of hemodynamic variations such as heart rate, blood pressure, and contractility. The reason that FFR is fundamentally different than CFR, iFR, and resting Pd/Pa is that it is the only parameter that is not dependent on resting flow.

2. D
Coronary autoregulation keeps coronary flow constant despite changes in coronary perfusion pressure, between a mean aortic pressure of 50 and 130 mm Hg.

3. A
During maximal hyperemia (eg, induced by adenosine, severe ischemia, or a perfusion pressure out of the autoregulatory range), autoregulation is exhausted, and therefore, perfusion pressure is proportionally related to coronary flow.

4. A
The accuracy of the angiogram to predict functionally significant stenoses is rather poor—only 70%. Anatomy alone will never be sufficient to predict physiology because it does not incorporate several important determinants of maximal blood flow, including myocardial mass and microvascular function. FFR is the current gold standard in identifying hemodynamically significant stenoses and has an accuracy of about 95%.

5. C
During maximal hyperemia, autoregulation is exhausted and coronary perfusion pressure is proportional to coronary flow. In the normal vessel, the coronary pressure is the same throughout the vessel. Therefore, in a stenotic vessel, the proximal pressure is a reflection of what the distal pressure would have been in the absence of that stenosis. Consequently, by dividing distal pressure by the proximal pressure, one can determine the maximum blood flow in the presence of a stenosis divided by the maximum blood flow in the hypothetical absence of that stenosis.
INTRODUCTION

Renal artery stenosis (RAS) is the main cause of “secondary” arterial hypertension. RAS is found in 0.5% to 5% of hypertensive patients. RAS is most often atherosclerotic in nature and less frequent due to fibromuscular hyperplasia.\(^1\) The prevalence of RAS is approximately 2% in unselected patients but reaches 40% in older patients or in patients with multiple risk factors for atherosclerosis or with documented atherosclerosis in other vascular territories.\(^2,3\) Due to improvements in vascular imaging by ultrasound, magnetic resonance imaging, computed tomography, and angiography and due to the larger proportion of elderly patients undergoing coronary angiography, the finding of a RAS on angiography is a frequent occurrence. “Drive-by” renal angiograms are frequently performed during coronary angiography procedures. However, as is the case in the coronary arteries, the relationship between anatomic findings and the functional repercussion of a given stenosis is poor.\(^4\)

Thus, stenoses of the main trunk of the renal arteries are frequent and easy to identify, but their causative role in clinical manifestations is difficult to evaluate, and it is difficult to predict the effect of renal stenting.
PATHOPHYSIOLOGY OF RENAL ARTERY STENOSIS

Renal artery stenoses contribute to arterial hypertension and/or to ischemic nephropathy.

Arterial Hypertension

Much modern thinking about the physiopathology of renovascular hypertension is influenced by the classical 1-kidney-1-clip animal model (analogous to a bilateral RAS) and the 2-kidneys-1-clip model (analogous to the unilateral RAS). A simplified scheme illustrating the pathophysiology of renovascular hypertension is shown in Figure 7-1. When the perfusion pressure decreases in the renal artery, especially in the afferent renal artery, an upregulation of renin production takes place in the juxtaglomerular apparatus. The decrease in glomerular filtration pressure will be partially counteracted by a constriction of the efferent artery. The activation of the renin-angiotensin system resulting in angiotensin II–mediated vasoconstriction is a central component to this process. In contrast, the nonstenotic kidney, subjected to higher perfusion pressure, responds by an increase in the excretion of sodium (“pressure natriuresis”) that will tend to lower the pressure. This decrease in systemic pressure will in turn decrease the perfusion pressure in the stenotic kidney and further stimulate the release of renin. Elevated levels of angiotensin II induce vasoconstriction and trigger the secretion of aldosterone. The latter enhances sodium reabsorption in proximal and distal tubules. Thus, renovascular hypertension is mediated initially by elevated plasma renin, although in case of sustained hypertension, plasma renin activity will tend to decrease. Renovascular hypertension fundamentally depends on the presence and magnitude of a pressure drop due to the stenosis.
Ischemic Nephropathy

The most common cause of renal insufficiency in patients with RAS is the association of the RAS to parenchymal disease. In contrast, the occurrence of renal failure solely due to a stenosis in the trunk of the renal artery is exceptional in unilateral RAS and rare in bilateral RAS in the absence of parenchymal disease or nephrotoxic medications. In rare cases, when bilateral stenoses are critical, the perfusion pressure may become so low that the renal tissue becomes ischemic, which in turn might lead to necrosis and fibrosis. In addition, in patients with bilateral RAS or RAS in a solitary kidney, the maintenance of a sufficient glomerular filtration pressure by vasoconstriction of the efferent artery is highly dependent on angiotensin II. When angiotensin-converting enzyme inhibitors are given, the efferent arteriolar
tone is no longer maintained, and glomerular filtration rate decreases, as in patients with cardiac failure who are sodium depleted.

SIMILARITIES AND DIFFERENCES BETWEEN MYOCARDIAL AND RENAL FLOW AND PRESSURE

Like most organs, the myocardium and the renal parenchyma are perfused by large arteries opposing no or very little resistance to flow. These arteries are often the seat of atherosclerotic narrowing. Smaller arteries and arterioles penetrate the tissue, are the site of the largest resistance, and give rise to feeding vessels, the capillaries. Due to their fundamentally different functions (pump function for the myocardium and filter function for the kidney), the consequences of a narrowing on the main arteries are almost opposite of the consequences on pressure and blood flow.

The main “goal” of the myocardium is to maintain constant blood flow to allow enough oxygen and nutrients to be supplied to the contracting myofilaments. Cardiac oxygen requirements are met thanks to a high level of oxygen extraction by the myocardium. This explains the low oxygen saturation in the coronary sinus (20%). The main mechanism to increase oxygen supply is to increase absolute myocardial flow. Therefore, a gradually increasing stenosis in the epicardial arteries induces a decrease in coronary driving pressure and will be compensated by a vasodilation of the microvasculature. This mechanism, often referred to as autoregulation, maintains a constant total resistance to flow, thus allowing a normal myocardial flow ("perfusion"). This vasodilation is mainly mediated by adenosine A2\textsubscript{1} receptors. The regulation is mainly based on a local mechanism.

In contrast, renal arteries deliver more oxygenated blood to the kidney than needed for metabolic demands. Renal metabolic requirements are met with 10% of normal blood flow. This translates into a high renal venous oxygen saturation (80%). The main “goal” of the kidney is to maintain glomerular filtration constant. A decrease in the pressure in the main trunk of the renal artery, and thus in the afferent renal artery, will be compensated by
an increase in the tone of the efferent renal artery, thus maintaining glomerular filtration pressure constant. This vasoconstriction is the result of an immediate local myogenic reflex and a delayed systemic activation of the renin-angiotensin system. The vasoconstriction is largely based on the activation of adenosine A₁ receptors. The administration of adenosine in the coronary artery leads to vasodilation, whereas adenosine induces a potent vasoconstriction in the renal circulation (Fig. 7-2).

![FIGURE 7-2](image)

In this teleologic view of physiology, one might consider that the myocardium tends to preserve flow at the cost of pressure, whereas the kidney tends to maintain pressure at the cost of flow.

**INVASIVE ASSESSMENT OF RENAL ARTERY STENOSIS**

Invasive assessment of RAS mainly encompasses angiography, Doppler flow velocity, and pressure measurements.

**Renal Angiography**

Recognition of the frequent association of atherosclerosis in the coronary and renal arteries has led to an increase in “drive-by” renal angiograms performed
by cardiologists “on their way to work.” The additional contrast burden can be limited to 10 to 20 mL, the image quality is pristine, and the specificity is higher than that with duplex echocardiography or magnetic resonance angiography. As a result, the number of RASs detected in patients with arterial hypertension has increased, leaving unanswered the conundrum of the causality of these findings. Drive-by angiograms have brought more questions than answers. It is now well recognized that the relation between percent diameter stenosis and functional assessment of these lesions is poor, even for stenoses of more than 50% of diameter reduction (Fig. 7-3). Thus, invasive angiography is the most precise tool for the identification of RAS but does not give any clue about the potential renal angioplasty to reverse the hypertension or the loss of kidney function. Intravascular ultrasound–derived assessment of the luminal dimension does not seem to add to the utility of a morphologic approach (Fig. 7-4).

**FIGURE 7-3** Plot of individual values of distal coronary pressure to aortic pressure (Pd/Pa) ratio versus percent diameter stenosis. The vertical line indicates the cut-off value for hemodynamic significance based on invasive pressure gradient measurement. The horizontal line corresponds with the cut-off value based on renal angiography (50% diameter stenosis).
Doppler Flow Velocity Measurements

By noninvasive Doppler ultrasonography, it is possible to derive the renal resistance index, which is defined as follows: 

\[1 - \frac{\text{end-diastolic velocity}}{\text{peak systolic velocity}}\] \times 100.

Structural alterations in smaller renal arteries or arterioles distal to the stenosis induced by longstanding hypertension may be one possible reason for the poor response to renal angioplasty. Such hypertension may cause nephrosclerosis and glomerulosclerosis and lead to increased vascular resistance in both the stenotic and nonstenotic kidney. It was shown that when the value of the renal resistance index exceeds 80, renal angioplasty is unlikely to improve renal function or arterial hypertension. Similarly, the reactivity of the distal renal arterial bed was tested with invasive intra-arterial Doppler wires in patients with essential hypertension but no RAS. These authors showed that nitrates induced a significant dilatation of the main renal artery and an increase in blood flow velocities, resulting in a 44% increase in absolute renal blood flow. Papaverine was shown to have no effects on the main renal artery but increased renal blood flow by 60% by vasodilation of the parenchymal arteries. More importantly, there were marked interpatient differences in the response to papaverine, suggesting that in some patients with essential hypertension a functional abnormality exists in the renal microcirculation. To
the best of our knowledge, the usefulness of invasive renal flow velocity measurements has not been studied in the setting of RAS.

**Transstenotic Pressure Measurements**

The fundamental mechanism responsible for renovascular hypertension is the presence of a decrease in renal perfusion pressure related to the presence of a stenosis in the main renal artery. If there is no or hardly any gradient across an angiographically visible stenosis in the main renal artery, then angioplasty of this stenosis does not make any pathophysiologic sense.

**How to Measure the Gradient**

The pressure gradient measured by a catheter is overestimated because the presence of the catheter partially obstructs flow. The degree of overestimation is difficult to evaluate. Figure 7-5 shows an example of the overestimation provoked by the presence of a 6-Fr guide catheter through a renal stenosis. Therefore, the gradient should be measured with pressure-measuring guide wires advanced through guide catheters. The additional advantage of using pressure wires is that the aortic pressure and the distal renal pressure can be recorded simultaneously.

**FIGURE 7-5** Example of the overestimation provoked by the presence of a 6-Fr guide catheter through a renal stenosis. When the guide catheter is pulled back while leaving the pressure sensor distal to the stenosis, the true severity of renal artery stenosis becomes apparent.
Systolic Gradient, Mean Gradient, or Pd/Pa?

In contrast to the left coronary flow where the flow is mainly diastolic, the flow in the main renal artery is mainly systolic. The maximum gradient therefore occurs in mid-systole, whereas the diastolic gradient is often very modest. The mean gradient better reflects renal physiology, as it will be determined by, and thus better account for, the renal microvascular resistance (Fig. 7-6). Yet, it is important to remember that any pressure gradient depends on the level of aortic pressure. Therefore, it is more appropriate to use the ratio of distal coronary pressure to aortic pressure (Pd/Pa), which corrects the pressure distal to the RAS for the prevailing aortic pressure.

**FIGURE 7-6** Pressure difference between renal artery and coronary stenosis (distal coronary pressure [Pd], green) with equivalent Pd/Pa ratio (aortic pressure [Pa], red; expressed in mm Hg). A. Renal artery stenosis with a predominant pressure gradient during systole. B. Coronary stenosis with a predominant pressure gradient during diastole.

Resting or Hyperemic Measurements?

In the coronary arteries, the resistance reserve is large (4-6) because the myocardium aims at preserving flow rather than perfusion pressure. In contrast, in the kidney, no significant increase in flow should not be expected because the kidney aims at preserving (glomerular filtration) pressure, at the cost of flow. In a systematic study of renal vasodilatory reserve, Manoharan et al\(^ {17} \) found a maximal increase in renal blood flow by a factor 1.8. The maximal hyperemic effect was observed after intrarenal bolus administration of dopamine (50 μg/kg). This effect was significantly larger than after
papaverine. Fenoldopam, a more specific agonist of the dopamine A₁ receptors, did not produce a more potent hyperemic response. Therefore, we suggest that dopamine is the ideal renal vasodilator because it is cheaper and more widely available than fenoldopam. An example of this renal hyperemic effect is shown in Figure 7-7. It is important to realize that, even during renal hyperemia, the Pd/Pa ratio should not be called renal fractional flow reserve (FFR).[^18] FFR has been defined for the myocardium and is only valid when there is a strict proportionality between flow and driving pressure. The relationship between renal flow and pressure has not been investigated, and a strict proportionality is unlikely to occur.

**FIGURE 7-7** Example of simultaneous pressure and velocity pressure tracings before, during, and after intrarenal administration of a bolus of 50 μg/kg of dopamine (DOPA). Immediately after administration of the bolus, a marked decrease in renal artery average peak velocity is observed, followed by an almost 2-fold increase in flow velocities without changes in blood pressure or heart rate.

**What Is a Significant Pd/Pa Value?**

Because the stimulation of the renin-angiotensin system is central to the physiology of renovascular hypertension, it is reasonable to consider a stenosis as significant when severe enough to trigger the production of renin. Therefore, in patients after uncomplicated renal stenting, we induced a
unilateral, controlled, graded RAS and correlated the magnitude of the pressure gradients and of the Pd/Pa ratios to the production of renin by both kidneys. The stenosis was induced by inflation of a balloon of increasing diameters over 10 minutes. At the end of each degree of stenosis, plasma renin concentration was measured. An example of a pressure tracing is shown in Figure 7-8. For a Pd/Pa ratio >0.90, no change in renin was observed. When Pd/Pa became <0.90, a significant increase in renin concentration was observed in the vein of the stenotic kidney, finally reaching a 3- to 4-fold increase above the baseline values. In addition, a small but consistent increase in renin concentration was observed in the renal vein of the nonstenotic kidney (Fig. 7-9).

![FIGURE 7-8](image)

**FIGURE 7-8** Example of mean pressure tracings obtained simultaneously in the aorta and distal to the artificial renal stenosis induced by incremental balloon inflations. Each degree of stenosis severity was maintained for 10 minutes. The arrows indicate the timing of sampling in the aorta and in both renal veins.
FIGURE 7-9 Effects of a balloon-induced, unilateral, controlled, graded stenosis (expressed as ratio of distal coronary pressure to aortic pressure \([Pd/Pa]\)) on plasma renin concentration in the aorta (squares), in the vein of the stenotic kidney (closed circles), and in the vein of the nonstenotic kidney (open circles). BL 1, baseline before stenting; BL 2, baseline after stenting.

**Hemodynamic Predictors of Improvement After Angioplasty in RAS**

To evaluate the usefulness of renal pressure measurements to identify patients who might benefit from angioplasty in RAS, we studied 53 patients scheduled for renal angioplasty as a result of resistant arterial hypertension and the presence of a unilateral RAS. In all patients, resting and hyperemic pressure measurements were obtained, and ambulatory blood pressure
monitoring was performed before and 3 months after the intervention. The patients were considered as “responders” when a decline in systolic blood pressure ≥20 mm Hg was observed. It was shown that a hyperemic mean pressure gradient ≥20 mm Hg and a hyperemic renal Pd/Pa <0.79 were optimal criteria to predict the success of renal stenting. These data were similar to those reported by Leesar et al. 7 Both studies confirmed that hyperemic measurements perform slightly better than resting measurements and emphasize the very low predictive value of the mere angiographic criteria.

**DISCUSSION**

Two recent, large, randomized trials20,21 and a meta-analysis aggregating data from smaller trials22 all come to similar conclusions: Renal angioplasty does not improve outcome compared to medical treatment in patients with RAS. However, in none of these studies was patient selection based on a physiologic approach. As described earlier, renal artery stenoses associated with small pressure gradients and/or associated with high intraparenchymal vascular resistances cannot be improved by renal stenting regardless of the angiographic grade of severity. Randomizing such patients dilutes the potential benefit of any treatment. Further trials should only randomize patients in whom documented invasive renal hemodynamics suggests a causative relation between the stenosis and the clinical syndrome. It is likely that the latter represents only a small percentage of all angiographically documented stenoses. Drive-by angiograms might even be justified if they are associated with wire-based pressure measurements. In the meantime, it seems appropriate to suggest renal stenting in hypertensive patients, especially when they are young and presenting with flush pulmonary edema and provided they have a large pressure gradient.

**REFERENCES**

2. Schwartz CJ, White TA. Stenosis of renal artery: an unselected necropsy


**MULTIPLE CHOICE QUESTIONS**

1. The administration of adenosine:
   A. Induces vasodilatation in coronary and renal arteries
   B. Induces vasoconstriction in coronary arteries, especially in case of mild stenosis, and vasodilatation of renal arteries
   C. Induces vasodilatation in coronary arteries and vasoconstriction in renal arteries
2. What is a central component of arterial hypertension in case of renal stenosis?
   A. The activation of the renin-angiotensin system, resulting in angiotensin II–mediated vasoconstriction
   B. An increase in the excretion of sodium, namely “pressure natriuresis”
   C. The increasing levels of angiotensin II that induce vasodilatation
   D. The decrease in glomerular filtration

3. Ischemic nephropathy:
   A. Is mostly caused by the presence of renal artery stenosis (RAS)
   B. Is mostly caused by the presence the parenchymal disease
   C. Is mostly caused by the association of RAS and parenchymal disease
   D. Is independent from renal anatomic modification

4. The renal resistance index is defined as:
   a. \( (2 - \frac{\text{end-diastolic velocity}}{\text{minimal systolic velocity}}) \times 100 \)
   b. \( (1 - \frac{\text{end-diastolic velocity}}{\text{peak systolic velocity}}) \times 100 \)
   c. \( (1 - \frac{\text{systolic velocity}}{\text{maximal end diastolic velocity}}) \times 100 \)
   d. \( (1 - \frac{\text{end-diastolic velocity}}{\text{minimal systolic velocity}}) \times 100 \)

5. Concerning the recent randomized trials on renovascular hypertension, which of the following statements is correct?
   A. They confirm the effectiveness of angioplasty on the control of hypertension.
   B. They show the superiority of medical therapy over angioplasty in the treatment of patients.
   C. They show a good correlation between the angiographic appearance and the transstenotic pressure gradient.
   D. Patients were not included in the trials based on the renal transstenotic gradient.

**Answers**

1. C
Vasoconstriction is mediated by adenosine A<sub>1</sub> receptors, which are predominant in the renal arteries.

2. A

Renovascular hypertension fundamentally depends on the presence and magnitude of a pressure drop due to the stenosis. The activation of the renin-angiotensin system resulting in angiotensin II–mediated vasoconstriction is a central component to this process. This decrease in systemic pressure will in turn decrease the perfusion pressure in the stenotic kidney and further stimulate the release of renin. Elevated levels of angiotensin II induce vasoconstriction and trigger the secretion of aldosterone.

3. C

The most common cause of renal failure in patients with RAS is the association of the RAS with parenchymal disease. In contrast, the occurrence of renal failure solely due to a stenosis in the trunk of the renal artery is exceptional in unilateral RAS and rare in bilateral RAS in the absence of parenchymal disease or nephrotoxic medications.

4. B

By noninvasive Doppler ultrasonography, it is possible to derive the renal resistance-index defined as \((1 – \text{end-diastolic velocity/peak systolic velocity}) \times 100\).
The cardiac valves permit efficient forward blood flow while preventing backflow, in turn creating unidirectional forward cardiac output. Valve disease leads either to reduction in orifice area (stenosis), impeding forward flow, or to incompetence, permitting either regurgitant flow or a combination of these effects. Valve stenosis exerts a pressure overload on the ventricle behind the stenotic valve because that chamber must generate increased pressure to drive the bloodstream past the narrowed orifice. Valve incompetence exerts a volume overload on the affected ventricle, which must enlarge to compensate for the forward flow that is lost to regurgitation. The effects of these overloads on ventricular function and geometry are dealt with in subsequent chapters. This chapter focuses on the evaluation of valve lesion severity and the effects of valve disease on hemodynamics.

**VALVULAR STENOSIS**

**Mitral Stenosis**

Usually in early diastole, there is a small gradient across the mitral valve that initiates filling and then rapidly dissipates (Fig. 8-1A). Indeed, the normally opened mitral orifice is 4 to 5 cm², which creates a functionally single chamber of left atrium and left ventricle (LV) during diastole; thus, pressures in both chambers are equal. Mitral stenosis, which is usually caused by
rheumatic heart disease, reduces orifice area, in turn causing a gradient between left atrium and LV. Mitral stenosis eventually leads to pronounced hemodynamic effects, although little hemodynamic disturbance develops until orifice area is compromised to less than half its normal size. As stenosis worsens, the pressure gradient between left atrium and LV becomes larger and longer in duration (Fig. 8-1B). This gradient is added to normal left atrial pressure, causing left atrial hypertension, eventually leading to pulmonary congestion. As mitral stenosis worsens further, reduced valve aperture impairs LV filling, limiting cardiac output. Thus, despite usually normal LV muscle function, the hemodynamics are those of LV failure. Although left atrial contraction assists late atrial emptying, most transmirtal flow occurs early in diastole, and much of the propellant force creating the pressure driving blood across the valve ultimately is derived from the right ventricle. Therefore, it is this chamber that is pressure overloaded by the disease. Still further stenosis of the mitral valve causes secondary pulmonary vasoconstriction, reinforcing and worsening pulmonary hypertension and right ventricular pressure overload.

**FIGURE 8-1** A. Simultaneous normal left ventricular (LV), aortic (Ao), and pulmonary capillary wedge pressure (PCW) tracings are shown. DFP, diastolic filling period; ECG, electrocardiogram; SEP, systolic ejection period. B. Simultaneous LV and PCW tracings from a patient with mitral stenosis are shown. The shaded area

Assessing Stenosis Severity

Because transvalvular gradient is flow dependent, a measure of stenosis severity that incorporates both flow and gradient is helpful in assessing stenosis severity. Valve area has become the most widely used of these measures.\(^2\) Flow (F) is the product of orifice area (A) and stream velocity (V) \(F = A \times V\). Rearranging the terms, \(A = F/V\). When using Doppler echocardiography to assess orifice area, velocity is measured directly. In using invasive hemodynamics to assess stenosis severity, the transvalvular pressure gradient is measured and converted to velocity using the formula \(V = \sqrt{\frac{2g}{h}}\), where \(g\) is the acceleration as a result of gravity (980 m/s) and \(h\) is the mean pressure gradient. Thus, valve area equals \(\frac{F}{44.3\sqrt{h}}\). Because flow normally tends to stream through the center of an orifice, physiologic valve area is smaller than actual anatomic valve area. This property is corrected using a constant of orifice contraction, \(C_c\). Because not all of the pressure gradient is converted to flow (some energy is lost to friction), another constant, that of velocity loss (\(C_v\)), is used. In 1951, Richard Gorlin and his father\(^2\) proposed the following equation for calculation of valve area:

\[
A = \frac{F}{C_v \cdot C_c \cdot 44.3\sqrt{h}}
\]

Flow is expressed as cardiac output during the time in diastole that the mitral valve is open (diastolic filling period, dfp). Thus the final formula is

\[
MVA = \frac{CO}{HR \cdot dfp \cdot 44.3\sqrt{h}}
\]

where MVA, is mitral valve area, CO equals cardiac output in L/min, and HR is heart rate.

The Gorlins were unable to develop the constants for the equation. Instead, they compared their calculated results to actual valve areas from autopsy and surgical specimens and applied an empiric constant of 0.85 to the denominator. By doing so, the recalculated valve areas came to within 0.2
cm\(^2\) of the actual valve areas. Even as newer noninvasive methods have become available for quantifying mitral valve area, the Gorlin formula has remained a gold standard for valve area determination.

WHEN INVASIVE DETERMINATION OF MITRAL VALVE AREA IS DESIRABLE

As noted previously, several noninvasive methods have been developed for the determination of mitral valve area. The two most commonly used are the pressure–half time method and direct planimetry.\(^3,4\) In general, these methods are adequate for clinical decision making. However, in some cases, there is a discrepancy between clinical and laboratory assessment of stenosis severity; in such cases, the additional information from invasive evaluation is helpful in making a final decision regarding the severity of a given patient’s mitral stenosis and its management. The usual cause of discordance between clinical and noninvasive assessment of the severity of mitral stenosis occurs in the patient who manifests ambiguous symptoms of heart failure while valve area is calculated to be in the mild to moderate range. Here, an invasive evaluation of hemodynamics can settle the issue. Evaluation of left atrial pressure (pulmonary capillary wedge pressure [PCWP]), cardiac output, and pulmonary artery pressure at rest and during exercise is usually very illuminating. Regardless of calculated valve area, if wedge pressure and transvalvular gradient are either significantly increased at rest or more likely provoked to increase with exercise, the hemodynamics explain the patient’s symptoms and suggest that mechanical relief of obstruction will lead to clinical improvement. If exercise does not provoke significant hemodynamic abnormalities, causes other than the patient’s mitral stenosis should be sought to explain the patient’s symptoms. Unfortunately, in today’s busy interventional catheter laboratories, careful assessment of hemodynamics, especially with exercise, has become a rarity.\(^5\)

PITFALLS IN THE INVASIVE
ASSESSMENT OF MITRAL STENOSIS

Measuring the Gradient

In the absence of transseptal puncture, left atrial pressure is estimated from the PCWP. There is much debate concerning whether this is a reliable left atrial pressure surrogate. In fact, the PCWP is or is not reliable, depending on the technique used to measure it. Apart from noting that the catheter appears to be wedged and has (in sinus rhythm) typical a and v waves, it is crucial to confirm that the catheter is truly wedged by removing highly oxygen-saturated (>90%) blood from the catheter while in the wedged position. Failure to perform this confirmatory step often results in recording a pressure that is hybrid between PCWP and pulmonary artery pressure, in turn overestimating both the PCWP and the transvalvular gradient, often by as much as 5 mm Hg. In addition, the transducers measuring both the LV pressure and PCWP must be properly calibrated and zeroed. Although recording device internal standards for calibration have improved over the years, there is no substitute for mercury calibration, considering that errors of just a few mm Hg may have an impact on assessment of stenosis severity of the mitral valve, where a gradient of just 5 mm Hg is often consistent with severe disease.

Assessing Mitral Flow

The transmitral flow period used in calculating the valve area is the entire time the valve is open in diastole. This period is measured (see Fig. 8-1B) from the time the LV pressure tracing falls below PCWP in early diastole (valve opening) to where LV pressure exceeds PCWP in early systole (valve closing). However, the use of the PCWP to measure left atrial pressure causes an 80-millisecond delay from the actual pressure event in the left atrium and its recording as PCWP. Because the LV pressure is recorded directly, the 2 pressures become nonsimultaneous. This problem is corrected by tracing the PCWP recording on paper or electronically reimposing it on the LV tracing using the correct timing of the actual pressure events. Failure to make this maneuver leads to substantial overestimation of the transvalvular gradient and inaccurate measurement of the diastolic filling pressure.
Mitral regurgitation adds a second error in assessing valve area. The pressure gradient is produced by the total flow crossing the valve. The cardiac output determination measures only forward flow, thus underestimating total flow and, as a result, underestimating mitral valve area.

Finally and obviously, the cardiac output must be measured accurately. Although the gold standard for this determination is the Fick method, thermodilution is often substituted.\textsuperscript{8,9} Although this technique is usually accurate, accuracy diminishes in the presence of tricuspid regurgitation and low cardiac output, conditions commonly present in patients with mitral stenosis. In some catheterization laboratories, a “pseudo-Fick” approach is used, in which oxygen consumption is assumed from tables of normals adjusted for height and weight. Because patients with mitral stenosis are hardly normal with respect to cardiac physiology, this technique is fraught with error and should be avoided.\textsuperscript{10}

**AORTIC STENOSIS**

As with mitral stenosis, little hemodynamic disturbance occurs from aortic stenosis until the valve orifice area is reduced to less than half its normal 3.0 to 4.0 cm\textsuperscript{2}. Serious clinical consequences usually do not occur until aortic valve area is reduced to less than 1.0 cm\textsuperscript{2} when the classic symptoms of angina, syncope, and heart failure develop, presaging sudden death.\textsuperscript{11,12} As with mitral stenosis, aortic stenosis severity is usually assessed accurately noninvasively. An abundance of comparison studies show remarkable concordance between gradient measured invasively and gradient measured using Doppler echocardiography. Likewise, there is excellent concordance between invasively derived valve areas and those derived noninvasively using the continuity equation.\textsuperscript{13,14} Thus, in many catheterization laboratories, only coronary arteriography is performed prior to contemplated aortic valve replacement with stenosis severity assessed noninvasively prior to catheterization.

**Invasive Assessment of Aortic Stenosis**

Invasive assessment of aortic stenosis, like that of mitral stenosis, uses the Gorlin formula. Systolic ejection period is substituted for diastolic filling.
period (see Fig. 8-1A). However, unlike mitral stenosis, the Gorlins had no data to compare calculated to actual valve area because, at the time, it was considered malpractice to cross the aortic valve with a catheter. Thus, an empiric constant was never developed for the aortic valve area calculation. Both the invasively derived and the noninvasively derived areas for the aortic valve are flow dependent, varying directly with flow. Two explanations are usually given for this phenomenon. First, it may be that as flow through the valve is increased, the orifice truly opens wider. Second, there is speculation that the absence of knowing the discharge coefficient (or empiric constant) affects the calculation. In fact, there are data to support either point of view.

**When Invasive Determination Is Required**

The current American College of Cardiology/American Heart Association guidelines for the treatment of valvular heart disease define severe aortic stenosis as present when peak echo jet velocity is ≥4.0 m/s, when mean transvalvular gradient is ≥40 mm Hg, or when aortic valve area is ≤1.0 cm$^2$. Unfortunately, many patients show discordance among these 3 criteria and also between the clinical and objective assessment of disease severity. Invasive assessment of aortic stenosis can be helpful in resolving these discrepancies in several situations. First, invasive assessment is useful when the clinical impression of the patient’s symptoms and lesion severity does not agree with the noninvasive data; for example, in a patient with angina and a physical exam consistent with severe disease but an echocardiographic Doppler exam that shows a gradient of only 20 mm Hg, it is likely that off-axis imaging of the aortic jet velocity has caused its underestimation. Second, invasive evaluation is helpful when features of the noninvasive exam are inconsistent with one another; that is, the aortic valve opens well, yet there appears to be a large transvalvular gradient. Third, the invasive approach is often helpful in assessing the very difficult patient with low output and low gradient. Some patients in this group have impaired systolic function and reduced ejection fraction, while others have normal ejection fraction but severe concentric hypertrophy that has reduced end-diastolic volume and concomitantly reduced stroke volume. In the group with reduced ejection fraction, there is far-advanced LV dysfunction, leading to both high operative
and late mortality rates (Fig. 8-2).\textsuperscript{22,23} However, patients in this group who augment their gradient and forward output during dobutamine stress show inotropic reserve and have a relatively good outcome following aortic valve replacement, whereas patients who fail to augment their gradient and forward output during dobutamine stress have a poor prognosis (Fig. 8-3).\textsuperscript{24,25} Although dobutamine is often administered in the echo lab, administration during catheterization allows preanalysis of the coronary anatomy. This is potentially important, because patients with severe coronary disease might fail to augment during dobutamine infusion, not because they lack inotropic reserve, but because dobutamine-induced ischemia from coronary disease precludes an increase in cardiac output. In the group with low gradient and normal ejection fraction, inotropic reserve can be used to calculate gradient and valve area at a higher cardiac output, confirming that truly severe aortic stenosis is present.
FIGURE 8-2 A. Kaplan-Meier survival curve for 52 patients with aortic stenosis, decreased LV function, and low transvalvular mean gradient (MG) compared with expected survival. B. Kaplan-Meier survival curve for patients with aortic stenosis,
decreased LV function, and low MG (<30 mm Hg) compared with patients with aortic stenosis, decreased LV function, and MG ≥30 mm Hg. Operative risk was 21%.


A final vagary in managing this group of patients is a condition sometimes referred to as “pseudo-stenosis.”

In this condition, a severely stenotic orifice area is calculated at rest. However, when output is increased, gradient fails to increase very much, resulting in a much larger valve area. Presumably, in such patients, the aortic valve is only mildly or moderately stenotic but incapable of being opened by a severely diseased LV until inotropy is increased by dobutamine. Because in such cases it is primarily ventricular rather than valvular disease that is operative, it seems unlikely that such patients would improve with aortic valve replacement, although this issue has not been clearly resolved.


**Pitfalls in the Invasive Assessment of Aortic Valve Area**

**Measuring the Gradient**

The most common source of error in the invasive assessment of aortic valve area is made in measuring the transvalvular gradient. Simultaneous measurement of ventricular and aortic pressures is preferred and is necessary if the patient is in atrial fibrillation. However, a gradient measured at pullback is acceptable as long as reentering the LV is not anticipated. As with mitral stenosis, proper gradient measurement begins with 2 properly balanced and zeroed pressure transducers. Confirmation of proper transducer fidelity is made by placing both catheters side by side in the ascending aorta (fluoroscopic confirmation) or by using a double-lumen catheter and recording perfectly matched pressures. After successfully crossing the aortic valve, the ventricular catheter must be confirmed as residing in the body of the LV. This step is important because in almost all cases of aortic stenosis, there are really 2 gradients, one just beneath the valve and a second proximal to the outflow tract.\(^{28,29}\) The subvalvular gradient is not due to true subvalvular stenosis, but rather occurs as blood accelerates into the relatively (compared to the body of the LV) narrow outflow tract.

In an effort to avoid using a second arterial puncture to admit a second catheter, some laboratories use a femoral sheath to record the distal arterial pressure. This technique simply does not work.\(^ {30}\) First, there can be no simultaneous recording of LV and arterial pressure, because ventricular and femoral artery events do not occur simultaneously. Second, by the time the pressure wave reaches the femoral artery, there has been substantial pressure recovery as turbulent flow is converted back to laminar flow as velocity decreases away from the orifice narrowing. Pressure recovery can result in an extreme reduction in total gradient. Although pressure recovery is reflective of femoral hemodynamics, the same phenomenon interferes with proper measurement of the true transvalvular gradient.\(^ {31}\) Differences in pressure recording between proper and improper techniques are demonstrated in Figure 8-4.\(^ {32}\)
FIGURE 8-4 The transaortic valve gradient recorded properly with the left ventricular (LV) catheter in the body of the LV and the distal catheter in the aorta (A) is compared with the false low gradient recorded from LV outflow tract and femoral artery (B). (Reproduced with permission from Carabello BA. The timing of valve surgery. In: Colucci WS, Gotto AM, Josephson ME, Loscalzo J, Oparil S, Popma JJ, eds. Cardiovascular Therapeutics. 2nd ed. New York, NY: WB Saunders; 2002:975-993.)

VALVULAR REGURGITATION

Although both the noninvasive and invasive assessments of valvular stenosis are quite accurate using modern technology, the assessment or valvular regurgitation as commonly practiced leaves much to be desired. In both the noninvasive and invasive arenas, excellent methods for quantifying the amount of left-side regurgitation present are available but often ignored.\(^\text{20}\) The result is that the “eyeball technique” for assessing severity is often used. Here, the visual appearance of either the regurgitant jet at echocardiography or the opacification of the receiving chamber during contrast angiography is used to estimate the severity of regurgitation. Although no hard data exist,
this method probably leads to significant errors in clinical judgment about the severity of the regurgitation present in about 20% of cases. Thus, in assessing the severity of a regurgitant lesion, all aspects of the physical examination and of echocardiographic Doppler measurements should be integrated, and no one parameter should stand alone.

**Invasive Assessment of Valvular Regurgitation**

**Waveforms**

Although rarely used definitively to assess severity of valvular regurgitation, intracardiac pressures and their waveforms may give useful clues to regurgitant severity. In both mitral and aortic regurgitation, the volume overload on the left atrium (mitral regurgitation) and LV (aortic regurgitation) leads to increased pressure in those chambers. It should be noted that chamber enlargement and enhanced chamber compliance can yield normal filling pressures even in the face of severe regurgitation. However, increased filling pressure, when present, helps support the presence of severe regurgitation. Increased left atrial pressure in mitral regurgitation is often but not always accompanied by a large v wave in the left atrial (pulmonary capillary wedge) pressure tracing.\(^{33}\) In severe aortic regurgitation, a rapid rise in the LV diastolic pressure, a femoral artery systolic pressure that is ≥40 mm Hg higher than LV systolic pressure (Hill sign), and diastasis of LV and aortic pressures add evidence that the aortic regurgitation is severe (Fig. 8-5).\(^{26}\) In tricuspid regurgitation, the right atrial pressure tracing may become ventricularized; that is, as the tricuspid valve becomes progressively less competent, the right ventricular pressure is transferred progressively more to the right atrium, so that right atrial and right ventricular pressures take on similar characteristics.
Angiography

In the noninvasive assessment of valvular regurgitation, the color Doppler image observed is that of jet velocity, not of actual flow, one of the confounders in assessing regurgitant severity from jet characteristics. Contrast angiography (although still limited in assessing regurgitation) visualizes the actual flow of contrast from the initiating chamber to the receiving chamber through the regurgitant valve. This visualization, in turn, is used to estimate the amount of regurgitant flow using a semiquantitative grading scale.

Quantitative Angiography

The best way of assessing the amount of regurgitation present would be to
know actual regurgitant flow, which then could be represented as an absolute number or as a percentage of the total flow pumped by the LV (regurgitant fraction). It is generally believed that a total regurgitant flow of more than 60 mL per beat or a regurgitant fraction exceeding 0.5 represents regurgitation severe enough to cause symptoms, ventricular damage, and death.\(^\text{20}\)

\[
RF = sv_t - fsv
\]

where RF is regurgitant flow, \(sv_t\) is total LV stroke volume, and \(fsv\) is forward stroke volume. Regurgitant fraction (RFx) is

\[
RF/sv_t
\]

Total stroke volume is determined by quantitative left ventriculography as end-diastolic volume minus end-systolic volume. These volumes are determined by the area-length or Simpson rule methods. Forward stroke volume is forward cardiac output (Fick or thermodilution method) divided by heart rate.

**When Invasive Assessment of Valvular Regurgitation Should Be Employed**

In usual practice, the estimation of regurgitant severity is made noninvasively. The validity of this assessment should be challenged when the clinical impression of lesion severity is at odds with the echocardiographic assessment. The most frequent error made is failing to take the apparent amount of regurgitation into the context of the ventricular geometry present. If severe regurgitation has been present chronically and the patient is asymptomatic, adequate forward output at noncongestive filling pressure is implied. For this to occur, the LV must enlarge in order to provide enough total stroke volume to make up for that which is lost to regurgitation.\(^\text{34}\) In addition, in mitral regurgitation, the left atrium must enlarge to accommodate the regurgitant volume at normal filling pressure. If both chambers are normal in size, it implies that the regurgitation is not severe or is acute, in which case the patient should be symptomatic. Thus, when the diagnosis of severe valvular regurgitation is made in the presence of normal LV and/or left atrial volume, severity should almost always be confirmed invasively.
Pitfalls

As with the stenotic lesions, if the pressure measurements are to be useful, they must be obtained from properly calibrated and zeroed transducers. In addition, because wave contour is also a factor to be considered, proper damping of the recording system is essential. Confirmation that proper damping is present is an assessment made from experienced observers analogous to judging that an artist used the proper shade of blue in painting the sky. This art form seems to be waning as less attention is paid to proper pressure recording.

In performing contrast angiography, the most common error is the injection of too little dye into the initiating chamber. Because contrast must fill both the initiating and receiving chambers, which are enlarged to begin with, at least 60 mL of contrast should be injected. Smaller injections may lead to poor opacification of the receiving chamber, in turn causing significant underestimation of the amount of regurgitation present. In addition, in mitral regurgitation, ventricular ectopy, which by itself may cause mitral regurgitation, must be avoided, requiring careful placement of the LV angiographic catheter and a test injection free of ectopy.

SUMMARY

Current noninvasive assessment of the severity of valvular heart disease is usually quite accurate. Further knowledge is added to noninvasive assessment by the ability of the technique to help establish valve pathoanatomy. Nonetheless, noninvasive assessment and clinical assessment are at odds with each other often enough that refined invasive assessment is necessary to arrive at a clinical decision. It is especially important in this case that attention be paid to the proper hemodynamic principles that are so crucial in making the correct clinical judgment.

REFERENCES


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MULTIPLE CHOICE QUESTIONS

1. In measuring the transvalvular gradient in aortic stenosis, which of the following is unacceptable?
   A. Recording of left ventricular (LV) and aortic (Ao) pressures using a double-lumen catheter
   B. Comparison of LV and Ao pressures from a pullback tracing in a patient in sinus rhythm
   C. Matching the 2 aortic pressures before crossing the valve and after pullback
   D. Obtaining pressures from the LV and femoral artery sheath

2. Regarding the Gorlin formula, which of the following statements is false?
   A. 44.3 in the denominator of the equation is the Gorlin constant for the aortic valve.
   B. 44.3 is the empiric constant.
   C. 44.3 is the constant of orifice contraction.
   D. All are false.

3. Invasive determination of aortic valve area is appropriate in which of the following?
   A. Echocardiographic Doppler estimate of a mean gradient of 20 mm Hg and an aortic valve area (AVA) of 0.9 cm$^2$
   B. Presence of a late-peaking systolic ejection murmur and an echocardiographic Doppler AVA of 0.8 cm$^2$
   C. A patient with syncope and an echocardiographic Doppler mean gradient of 60 mm Hg
   D. An echocardiographic Doppler exam showing a heavily calcified immobile aortic valve and a mean gradient of 15 mm Hg
   E. A and D are correct

4. A 45-year-old woman complains of dyspnea on exertion. Physical exam finds a diastolic rumble, and the echocardiographic Doppler exam finds mild to moderate mitral stenosis. How can an invasive study clarify the
5. A patient complains of dyspnea on exertion. A loud holosystolic murmur is heard. Echocardiographic Doppler exam suggests mild to moderate mitral regurgitation but with discordantly large LV and left atrial (LA) volumes. How could an invasive study be helpful?
   A. By finding a normal v wave in the PCWP tracing
   B. By performing contrast ventriculography using 30 mL of contrast
   C. By recording pressures during exercise
   D. By performing contrast ventriculography using 60 mL of contrast
   E. A, B, and D are correct.

ANSWERS

1. D

The goal is to obtain the difference in the pressures between the LV and Ao. In order to be sure there is no systematic error introduced into measurement by faulty transducer calibration or catheter lumen obstruction, identical pressures must be obtained when the catheters or both lumens of a double-lumen catheter are in the same hemodynamic location of the proximal aorta. A pullback accomplishes the same goal since it is a single catheter and is not compared to a second catheter whereby an error in either could cause a false gradient to be introduced into the system. However, using the LV and femoral artery for the recording sites automatically introduces the errors of nonsimultaneous recording and pressure recovery into the system and should be avoided.
2. D

The value of 44.3 is the square root of $2 \times$ the acceleration due to gravity (980 m/s/s; i.e., 1960). The empiric constant of 0.85 was derived only for the mitral valve. The constant of orifice contraction has not been established for either valve.

3. E

In answers A and D, there is a discordance in the findings. In answer A, the valve area is in the severe range, but the gradient is not; in answer D, the valve appears severely stenotic, but there is only a small transvalvular gradient. In both cases, an invasively measured pressure gradient could resolve the issue. In answers B and C, the data are concordant and consistent with severe aortic stenosis.

4. E

A, B, D are all standards in establishing valid hemodynamics that would help clarify the patient’s presentation. C is a distractor. Oxygen consumption index varies by as much as 30% in normal patients and by more in patients with cardiac pathophysiology. Invasive measurements must be justified by being accurate. Since cardiac output is a key element in determining mitral valve area, cardiac output determined by the Fick method must use an accurate oxygen consumption determination. Exercise performed in the cath lab might clarify her status since her symptoms are occurring with exercise. Pressures should be recorded using an oxymetrically confirmed PCWP, properly aligned with the LV pressure tracing.

5. E

Exercise while recording intracardiac pressure is almost always helpful in evaluating exercise-related dyspnea. Because the LA and LV are enlarged, an amount of contrast adequate to opacify both chambers (60 mL) can be helpful in evaluating mitral regurgitation (MR) severity. A normal v wave can be found in both mild and severe MR and is of little diagnostic help, whereas a very large v wave suggests severe MR.
Arterial Disease

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Frederick G.P. Welt

ATHEROSCLEROSIS

Introduction

The complex molecular and cellular biology of the inflammatory process that promotes atherosclerosis has been elucidated through years of extensive experimental and clinical research. Vascular injury from inflammation initiates plaque formation and dictates the downstream clinical sequelae of atherosclerotic disease. It is essential that interventional cardiologists understand the natural history and pathologic processes of atherosclerosis, as well as the vascular biologic consequences of therapies employed during coronary intervention. This chapter describes (1) the pathophysiology of atherosclerosis; (2) the mechanisms responsible for an unstable plaque in acute coronary syndrome (ACS); and (3) the biology of vascular remodeling leading to restenosis, differences between balloon and stent injury, and therapies for restenosis.

A Response to Injury

Atherosclerosis is a result of risk factors and chronic arterial inflammation that promote sustained vascular injury. Several risk factors (Table 9-1) for atherosclerosis have been identified, including metabolic conditions such as
sustained exposure to low-density lipoprotein (LDL) or hyperglycemia and insulin resistance associated with diabetes mellitus or metabolic syndrome. However, additional factors, including age, family history, physical factors (eg, uncontrolled hypertension resulting in changes in shear stress), environmental factors (eg, tobacco smoke), and infectious disease, also contribute to the development of atherosclerotic plaque. Vascular injury results from an inflammatory response that involves a complex sequence of interactions between endothelial and smooth muscle cells, leukocytes, inflammatory cells (eg, macrophages) and their secreted growth factors, and cytokines, which combine with lipoproteins and components of the vascular wall to form a mature atherosclerotic plaque. Inflammation plays a central role in pathogenesis of atherosclerosis; numerous studies have demonstrated a correlation between circulating inflammatory biomarkers (eg, C-reactive protein [CRP]) and an increased risk for atherosclerosis and adverse coronary events.2-4

**Pathogenesis**

The biologic mechanisms in atherosclerotic plaque formation include intimal lipid accumulation, leukocyte recruitment, foam cell formation, neointimal growth, and vessel remodeling (Fig. 9-1).
Intimal Lipid Accumulation

A key event in the early formation of atherosclerotic lesions is the accumulation of LDL within the arterial intima, which subsequently undergoes oxidation and glycation to initiate a cascade of molecular and cellular events including growth factor and cytokine release from inflammatory, endothelial, and smooth muscle cells. It is important to recognize that dyslipidemia results in an inflammatory state and is evident in the presence of inflammatory cells within the initial lesion of atherosclerosis, the fatty streak. Foam cells are the hallmark cell of the atherosclerotic lesion and consist of macrophages that are recruited to the subintima of the vessel wall and subsequently bind and internalize oxidized lipoprotein particles via a number of scavenger receptors on the cell surface. Importantly, lipoproteins can be cytotoxic to macrophages, leading to foam cell necrosis, which, in turn, causes necrotic debris and free cholesterol esters to accumulate within the lesion to form a necrotic core. Inflammatory cells, cytokines, and proteases weaken the fibrous cap surrounding the necrotic core, which can lead to atherothrombosis in the setting of a loss of integrity of the fibrous cap barrier, allowing contact of circulating blood with the thrombotic necrotic core.

### Table 9-1 Risk factors for Vascular Injury and Atherosclerosis

<table>
<thead>
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<th>Metabolic</th>
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<td>Dyslipidemia</td>
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Leukocyte Recruitment

Leukocytes, predominantly macrophages, play a pivotal role in atherosclerosis. By releasing cytokines and growth factors, macrophages regulate atherogenesis, but also influence plaque destabilization leading to rupture and thrombosis. The process of leukocyte recruitment, attachment to the extracellular matrix, and migration into the plaque (ie, diapedesis) is a response to vascular injury. Chemokine-stimulated endothelial cells express leukocyte-specific cell adhesion molecules (CAMs), which loosely bind circulating mononuclear cells and allow rolling of the monocytes along the endothelial surface. Tight binding of monocytes to the endothelium is mediated by the integrin class of CAMs, which is the final step prior to diapedesis. Although their pathologic role is uncertain, plasma levels of CAMs (eg, E-selectin or intercellular adhesion molecule-1 [ICAM-1]) are associated with the development of coronary atherosclerosis.

Chemokines are an important group of cytokines produced by a number of
cells (eg, smooth muscle cells, endothelial cells, and leukocytes) that act as a chemoattractant for leukocytes to areas of vascular injury. Two important chemokines are monocyte chemoattractant protein-1 (MCP-1) and interleukin (IL)-8, which participate in the recruitment of monocytes and diapedesis of adherent cells.\textsuperscript{7-10}

Innate immunity and adaptive immunity have important roles in the development of atherosclerosis.\textsuperscript{11} Innate immunity is an immediate response to foreign material and relies on phagocytosis through neutrophils and monocytes. Monocytes are felt to be the first leukocytes recruited to the early atheromatous plaque and are differentiated into activated macrophages: type 1 induced by inflammatory cytokines (eg, interferon [IFN]-γ) or type 2 induced by IL-4, IL-13, and other anti-inflammatory cytokines. Type 1 macrophages produce large amounts of reactive oxygen species and inflammatory cytokines, which amplify the immune response to an atheroma. Type 2 macrophages express scavenger receptors and produce extracellular matrix proteins and remodeling stimuli.\textsuperscript{12-14} Other cells of the innate immune response have also been implicated in atherosclerosis, including neutrophils, mast cells, and natural killer cells.\textsuperscript{15} Adaptive immunity is an antigen-dependent response, and the CD4\textsuperscript{+} T lymphocyte is the primary cell present at atherosclerotic lesions. T cells actively secrete cytokines, which influence plaque progression and vulnerability.\textsuperscript{15} T lymphocytes secrete inflammatory cytokines such as IFN-γ, which can impair the extracellular matrix architecture and growth of smooth muscle cells, promote apoptosis, and cause plaque instability.\textsuperscript{16} CD4\textsuperscript{+} T cells also express the CD40 ligand to promote proteolysis through matrix metalloproteinases (MMPs) and stimulate cells to produce tissue factor to influence plaque rupture and thrombogenicity.\textsuperscript{17}

As lesions mature, leukocytes accumulate in the “shoulder” regions of plaques (ie, the border between the eccentric plaque and normal vessel architecture), which are more vulnerable to plaque rupture.\textsuperscript{18} In addition, atherosclerotic lesions develop preferentially at coronary bifurcations. Due to the disturbances in flow patterns at coronary bifurcations, altered shear stress may upregulate CAMs and increase leukocyte recruitment and plaque growth. Monocytes contribute to vascular calcification in response to cytokines such as monocyte colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κ-B (RANKL).\textsuperscript{19} Importantly, microcalcification is
associated with plaque vulnerability.\textsuperscript{20}

**Neointimal Growth**

Smooth muscle cells and their secreted products are responsible for neointimal growth and for giving structure to the mature atherosclerotic plaque, which initially is a collection of lipids and foam cells. Growth factors and chemokines (eg, platelet-derived growth factor and thrombin) initiate smooth muscle cell migration from the media into the neointima and stimulate cell proliferation. In the neointima, smooth muscle cells expand the extracellular matrix by producing its constituent proteins including collagen, proteoglycans, elastin, fibrin(ogen), fibronectin, and vitronectin. The extracellular matrix accounts for a substantial portion of plaque volume and is vital to the structural integrity of the fibrous cap. Smooth muscle cells also express bone matrix proteins, which highlight their role in vascular calcification.\textsuperscript{21-23} Mineralization of the plaque occurs through deposition of calcium and osteopontin, but calcification does not always equate to plaque stability and is associated with higher risk in some patients (eg, elderly).\textsuperscript{24}

**Plaque Angiogenesis**

Plaque angiogenesis is important to plaque growth and the pathogenesis of atherosclerotic complications.\textsuperscript{25} Angiogenic growth factors (eg, hypoxia-inducible factor [HIF] and vascular endothelial growth factor [VEGF]) stimulate the growth of vasa vasorum from the adventitia into the plaque.\textsuperscript{26} Notably, these vessels can hemorrhage, independent of plaque rupture, and extravasation of erythrocytes provides a source of cholesterol-rich red cell membrane constituents, heme, and iron, which act as stimulants for oxidative stress and vessel growth. Neovessel density is significantly higher in nonstenotic and stenotic noncalcified plaques compared with calcified lesions or vessels without plaque.\textsuperscript{27} Neoangiogenesis is driven by hypoxia, but the latter also contributes to proteolysis through MMPs. MMPs comprise a family of interstitial collagenases that weaken the fibrous cap and gellatinases that breakdown nonfibrillar collagen and the adhesions between endothelial cells, leading to plaque vulnerability.\textsuperscript{28-30} Hypoxia also promotes proinflammatory cytokine and leukotriene release, which activates
macrophages and contributes to plaque growth.\textsuperscript{29,31}

**The Mature Atherosclerotic Plaque**

The mature atherosclerotic plaque is composed of a fibrous cap consisting of smooth muscle cells and extracellular matrix overlying a necrotic lipid core consisting of free cholesterol esters, foam cells, other leukocytes (eg, T cells), and necrotic debris from dead foam cells (see Fig. 9-1). Mature plaques are typically eccentric and heterogeneous, especially in terms of the thickness of the cap and distribution of leukocytes (highest at the shoulder regions of the plaque). These features are vitally important to plaque stability and the development of ACS.

**Vascular Remodeling**

A major limitation to coronary angiography is that it only provides information on the luminal encroachment of lesions. Intravascular imaging has provided a better understanding of atherosclerotic plaque architecture not only at sites of flow-obstructing lesions but throughout the vessel. Although the interventional cardiologist may be focused on focal obstructive lesions, it is important to realize that atherosclerosis is typically present throughout the entire coronary artery. The severity of lumen narrowing is subject to the amount of plaque growth and vascular remodeling, whereby the latter involves restructuring the cellular and noncellular components of the vessel wall under a variety of stressors (eg, smooth muscle mass increasing to normalize wall stress in hypertensive patients).\textsuperscript{32} Positive remodeling is a compensatory enlargement of the vessel to preserve the luminal area and maintain coronary blood flow (Fig. 9-2). MMPs are upregulated in areas of vessel wall remodeling and play a central role in plaque rupture.\textsuperscript{33}
Clinical Sequelae of Atherosclerosis

The clinical manifestations of coronary artery disease are often described as a spectrum, from stable angina associated with exertional angina and benign outcomes, to ST-segment elevation myocardial infarction (STEMI) associated with sudden thrombotic vessel occlusion and higher rates of morbidity and mortality. Two main mechanisms are primarily responsible for the clinical manifestations of atherosclerosis: (1) luminal narrowing that leads to a mismatch between oxygen supply and demand typically resulting in symptoms of stable angina; or (2) atheromatous plaque rupture resulting in thrombus formation and coronary occlusion. Importantly, atherosclerosis can also alter the normal endothelial vasomotor function and autoregulation of blood flow (ie, endothelial dysfunction), which can cause anginal symptoms in patients with and without epicardial coronary stenoses. Nevertheless, it is critical to recognize that thrombotic complications of atherosclerosis depend on plaque morphology and vascular biologic factors, not the severity of coronary stenosis.

Progressive Lumen Encroachment and Stable Angina
Lumen encroachment occurs from the growth and expansion of atherosclerotic lesions (see Fig. 9-2). The extent of luminal narrowing depends on the size of the atherosclerotic lesion and the amount of compensatory vascular remodeling. A coronary stenosis reduces coronary blood flow to a given vascular territory. The decrease in blood flow causes the distal microcirculation to vasodilate and increase coronary blood flow, which, in turn, reduces the ability of the coronary circulation to increase blood supply in response to demand (ie, coronary flow reserve). This process typically leads to exertional angina and is relieved by rest. Importantly, luminal encroachment does not always cause symptoms and depends on many factors including the severity of the stenosis, the oxygen carrying capacity of blood, and the supply demands of the distal myocardial bed.

A general rule is that lesions typically produce symptoms when they reach a 60% to 70% diameter stenosis. However, interrogating the intracoronary hemodynamics with flow and pressure wires has revealed that lesions with the same degree of angiographic stenosis may have very different hemodynamic and ischemic consequences. Fractional flow reserve (FFR) has become the predominant method used to assess coronary hemodynamics and is defined as the ratio of the distal pressure in the coronary artery beyond the lesion divided by the aortic pressure. Based on an association with inducible ischemia on stress testing, the initial cut-off point for not performing percutaneous coronary intervention (PCI) after FFR assessment was <0.75, as established in the FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses (DEFER) study. To enhance the sensitivity and exclude ischemia using FFR, the cut-off was increased to >0.80 in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial. In FAME, routine measurement of the FFR was compared with angiography alone for guiding PCI in patients with multivessel coronary artery disease (CAD). The use of FFR significantly reduced the rate of major adverse cardiac events compared with angiography alone. Importantly, a subgroup analysis of the lesions that were assessed by FFR in FAME revealed that coronary angiography could not accurately predict the hemodynamic significance of a coronary lesion. In FAME, 35% of lesions with an angiographic stenosis of 50% to 70% (ie, intermediate) were hemodynamically significant (FFR ≤0.80), whereas 20% of lesions with an angiographic stenosis of 71% to 90% were not functionally significant by
Only when lesions had an angiographic stenosis >90% was coronary angiography able to predict hemodynamic significance, where 96% of lesions with a coronary stenosis of 91% to 99% had an FFR \( \leq 0.80 \). Furthermore, 54% of patients who were classified as having multivessel CAD did not have \( \geq 2 \) lesions with an FFR \( \leq 0.80 \). The discordance between hemodynamic significance and angiographic stenosis highlights the need to use adjunctive techniques to assess the ischemic potential of coronary stenoses.

**Plaque Rupture and Thrombosis in Acute Coronary Syndromes**

The historical view held that stable angina could convert to ACS when an atherosclerotic lesion narrowed the vessel lumen to a critical point where vasospasm or thrombosis in situ could develop and cause a myocardial infarction (MI). For years, considerable debate ensued as to whether thrombus found at autopsy was a pre- or postmortem phenomenon. This widely held view continued despite James Herrick’s landmark publication of thrombus as the predominant cause of sudden coronary obstruction in 1912. The pivotal work by DeWood et al in 1980 demonstrated angiographically that ST-segment elevation and transmural MI were associated with occlusion of an epicardial coronary vessel predominantly secondary to thrombus (Fig. 9-3). Since this discovery, autopsy studies and angioscopy have confirmed the presence of visible thrombus associated with plaque rupture (Fig. 9-4) in both unstable angina and acute MI (AMI).

FIGURE 9-4 Histologic example of a ruptured plaque with subsequent thrombosis leading to a fatal myocardial infarction. (From Constantinides P. Plaque hemorrhages, their genesis and their role in supra-plaque thrombosis and atherogenesis. In: Glagov S, Newman WP III, Schaffer SA, eds. *Pathology of the Human Atherosclerotic Plaque.* New York: Springer-Verlag; 1990:393-411, with permission of Springer.)

Early thrombolytic trials were instrumental in our current understanding of ACS. As part of these trials, patients with AMI underwent serial angiography after randomization to thrombolytics or placebo, which revealed an unexpected finding, namely that the majority of the culprit lesions had <50% in diameter stenosis (Fig. 9-5). Furthermore, in some patients, mild and moderate stenoses progressed to MI within weeks. Importantly, only 15% of AMIs arose from lesions with a coronary stenosis >60% on a prior angiogram (see Fig. 9-5). These finding focused future research efforts on determining the vascular biology of a vulnerable plaque and the mechanisms responsible for conversion from a stable plaque to a thrombotic lesion.
Noncritical lesions are significantly more abundant than critical lesions, and compensatory enlargement of the vessel often accompanies atherosclerosis. Thus, mildly stenotic lesions can have an even larger plaque burden by volume, which may portend a higher risk for plaque rupture and thrombosis.

![Graph showing diameter stenosis](image)

**FIGURE 9-5** Compiled data from 4 thrombolytic trials showing that the majority of underlying lesions responsible for acute myocardial infarction involve less than 50% diameter stenosis. (Reproduced with permission from Smith SC. Risk-reduction therapy: the challenge to change. *Circulation*. 1996;93:2205-2211.)

Plaque rupture is the proximate event leading to thrombosis, which exposes the subendothelium to circulating blood. Several histologic features have been associated with plaque vulnerability, including a thin fibrous cap, a large lipid-laden necrotic core, and an accumulation of leukocytes and inflammatory cells at the shoulder regions of the plaque (Fig. 9-6). An important natural history study of coronary atherosclerosis was recently conducted called Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). In PROSPECT, 697 patients who were stented in the setting of ACS underwent 3-vessel intravascular imaging to determine the clinical and lesion risk factors associated with future events. At 3 years, approximately 20% of patients experienced a major adverse cardiac event, in which nearly 50% of the adverse events were associated with nonculprit lesions. The majority of adverse cardiac events were in lesions that were mildly stenotic at the time of index angiography. Three lesions characteristics were strongly associated with a higher risk for
future adverse cardiac events in nonculprit lesions; these were a plaque burden \( \geq 70\% \), presence of a thin cap fibroatheroma, and a minimal lumen area \( \leq 4 \text{ mm}^2 \).\textsuperscript{45}

![Diagram of plaque types](image)

**FIGURE 9-6** Characteristics of stable versus vulnerable plaques. Vulnerable plaques have thinner fibrous caps and larger, more inflammatory cell–rich lipid cores. SMC, smooth muscle cell. (Reproduced with permission from Libby P. Molecular bases of the acute coronary syndromes. *Circulation*. 1995;91:2844-2850.)

A plaque’s structural integrity is regulated by vascular inflammation and dependent on the balance between the mass of smooth muscle cells and content of the extracellular matrix. Smooth muscle cell mass is regulated by cell migration from the media, neointimal proliferation, and cell death. The latter occurs due to cytokine release from inflammatory cells, leading to apoptosis.\textsuperscript{46} Extracellular matrix content depends on the interplay between production from smooth muscle and inflammatory cells and protease activity leading to degradation (*Fig. 9-7*). Within a plaque, activated T cells release IFN-\( \gamma \), which inhibits smooth muscle cell collagen synthesis. Inflammatory cells also produce enzymes (eg, MMPs and cathepsins) that degrade important structural components of the extracellular matrix (ie, collagens, elastin).\textsuperscript{18} This process weakens the structural integrity of a plaque by
decreasing smooth muscle cell mass and degrading the extracellular matrix.

**FIGURE 9-7** Thickness of the fibrous cap is a balance between synthesis of extracellular matrix proteins by smooth muscle cells (SMCs) and the breakdown of these products by degradative enzymes. These processes are largely under the influence of inflammatory cells. IFN, interferon; MCP-1, monocyte chemoattractant protein-1; M-CSF, monocyte colony-stimulating factor; TNF, tumor necrosis factor. (Reproduced with permission from Libby P. Molecular bases of the acute coronary syndromes. *Circulation*. 1995;91:2844-2850.)

Predicting how, why, and when a plaque will rupture is a subject of continuing study. An interesting historical observation is the diurnal variation in MI presentation, which peaks in the early morning hours. Additionally, MI rates increase during times of extreme stress (eg, earthquake). These observations suggest that variations in cortisol and adrenaline levels may impact plaque rupture through their systemic hemodynamic effects. The site of rupture coincides with the highest circumferential biomechanical force, which is located at the shoulder region of a plaque. Thus, a combination of biochemical and biophysical characteristics predispose the shoulder regions to plaque rupture, which is supported by histologic postmortem studies in patients who died from an AMI. Other processes may also be responsible for the thrombotic complications of ACS. Focal endothelial denudation can expose the internal elastic membrane to circulating blood and act as a substrate for thrombosis, which occurs more frequently in women and
diabetics. Also, mechanical injury during PCI can also disrupt plaque and lead to acute thrombosis.

Atherothrombosis is the final consequence of plaque rupture or endothelial denudation that leads to acute coronary vessel occlusion. Exposing the lipid core (ie, tissue factor associated with lipid-laden and necrotic macrophages) to circulating blood is a potent stimulus for thrombus formation. Thrombus formation following plaque rupture is regulated by the blood’s tight control over the balance between procoagulant-anticoagulant and fibrinolytic-antifibrinolytic factors. In the presence of an intact and robust fibrinolytic system, a thrombus may undergo rapid lysis and manifest clinically as unstable angina or non–ST-segment elevation MI (NSTEMI). Similarly, patients on antiplatelet therapy (eg, aspirin) may be protected from platelet activation and aggregation during subendothelial exposure to blood. Conversely, the presence of prothrombotic factors (eg, fibrinogen or plasminogen activator inhibitor-1) can accelerate the growth of a thrombus, leading to coronary occlusion. Nonocclusive thrombus can also become incorporated into a plaque during the healing process and provide a mechanism for plaque expansion and lumen encroachment and be a source for angina.

Importantly, antiplatelet and lipid-lowering therapy trials have corroborated the thrombotic paradigm of ACS and demonstrated marked reductions in the morbidity and mortality associated with an acute coronary event. Furthermore, these breakthroughs have been achieved despite a lack of change in lesion severity. Lipids have a central role in atherosclerosis and atherothrombosis as the critical initiating and sustaining inflammatory stimulus for plaque growth and rupture. The beneficial actions of statins include not only their lipid-lowering properties, but also the reduction in inflammation, which can stabilize the fibrous cap and reduce thrombogenicity of the inner lipid-laden necrotic core. Evidence supports that lipid-lowering therapy is vital to acute and chronic therapy for patients presenting with ACS.

A major goal of vascular biologists and clinical cardiologists is to develop a more complete understanding of the mechanisms of plaque rupture and the development of novel strategies to stabilize lesions. However, many different lesions of varying vulnerability may coexist throughout the coronary tree. Novel imaging techniques are being developed to identify plaques that are the most susceptible to rupture, which may allow for better prognostication and therapeutic developments.
RESTENOSIS

Introduction

Andreas Gruentzig ushered in the modern era of management of obstructive CAD with the publication of his experience with coronary balloon angioplasty in a landmark study of 5 patients in 1978.50 Yet, his first angiographic follow-up study revealed that 19% of patients undergoing successful initial angioplasty suffered restenosis.51 Since the early days of balloon angioplasty, the introduction of stenting has reduced certain limitations of balloon angioplasty. However, in-stent restenosis (ISR) still remains an important limitation of coronary stents. Bare metal stents (BMS) decreased restenosis compared to balloon angioplasty, but in selected studies, ISR remained as high as 30%.52 Drug-eluting stents (DES) further reduced the rates of ISR to as low as 5% to 20%, depending on the patient population.53-56

Our understanding of the pathophysiology of restenosis has evolved considerably. Early postmortem studies revealed a fibrocellular response at sites of prior balloon angioplasty.57 Initial animal studies revealed that endothelial denudation, medial dissection, and platelet deposition contribute to an immediate response to balloon injury, whereas late restenosis is a consequence of smooth muscle cell migration and proliferation.58,59 The initial paradigm for restenosis comprised 3 phases: (1) an inflammatory phase, (2) a granulation or cellular proliferation phase, and (3) a phase of remodeling involving extracellular matrix protein synthesis (Fig. 9-8).60 As with atherosclerosis, inflammation plays a critical role in the pathogenesis of restenosis. Coronary stenting has a profound impact on the vascular biologic response to vessel injury, especially the inflammatory response and vascular remodeling following injury. The aim of this chapter is to understand the pathogenesis of restenosis and the clinical indicators and biochemical markers associated with increased risk and to introduce the concepts of antirestenotic therapy.
FIGURE 9-8 A. A mature atherosclerotic plaque prior to intervention. B. The immediate result of stent placement with endothelial denudation and platelet/fibrinogen deposition. C and D. Leukocyte recruitment, infiltration, and smooth muscle cell (SMC) proliferation and migration in the days following injury. E. Neointimal thickening in the weeks following injury with continued SMC proliferation and monocyte recruitment. F. The long-term (weeks to months) change from a predominantly cellular to a less cellular and more extracellular matrix (ECM)-rich plaque. FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor. (Reproduced with permission from Welt FGP, Rogers C. Inflammation and
Definitions and Clinical Sequelae of Restenosis

In clinical trials, restenosis was historically defined angiographically as a binary (ie, yes or no) reduction of ≥50% of the luminal diameter compared with the reference vessel, which does not always separate clinically relevant lesions from those without any sequelae. However, restenosis can also be defined by angiographic terms that are more relevant to our understanding of the pathophysiology. Late lumen loss (LLL) is the continuous measure of angiographic luminal narrowing and is calculated by subtracting minimal lumen diameter (MLD) at the time of index revascularization from postprocedural MLD at angiographic follow-up. LLL is an important surrogate marker used to assess the effectiveness of antirestenotic therapies and different stent platforms. It is important to note that virtually all patients have some degree of restenosis. In any given population, the severity of restenosis will follow a typical Gaussian distribution (Fig. 9-9), and only a minority of patients will have severe ISR (eg, diameter stenosis >70%) and anginal symptoms. On average, LLL is 0.8 to 1.0 mm following implantation of a BMS, regardless of the reference vessel diameter, and is critically important when considering revascularization of smaller vessels. For example, a 4-mm diameter vessel would lose 44% of lumen area with an LLL of 1 mm, whereas a 2-mm vessel with the same 1-mm loss would have a 75% loss in lumen area. LLL and angiographic restenosis are related to the reference vessel diameter, and restenosis is heavily dependent on the definition used in a given clinical study. An inventory of the wide variety of angiographic and clinical definitions used to define restenosis is shown in Table 9-2.
The discordance between LLL and binary restenosis is controversial. Late loss is a useful surrogate marker for assessing the effectiveness of therapies for restenosis. However, the relationship between late loss and binary restenosis is nonlinear and a curvilinear function (Fig. 9-10), which implies that there may be a threshold of LLL that is clinically significant. The argument is that LLL below a certain level is not clinically significant and does not portend a worse clinical restenosis rate (ie, target lesion revascularization [TLR]) (see Fig. 9-10). This argument is a contentious issue in interventional cardiology. Regardless, the clinical sequelae of angiographic restenosis are not always concordant. An example of this was observed in a meta-analysis of patients with angiographic ISR from multiple stenting trials, where ISR defined as ≥50% diameter stenosis was asymptomatic in approximately 50% of patients.65 This study highlights the multifactorial nature of restenosis and discrepancy between angiographic restenosis as a binary outcome and corresponding clinical significance.
FIGURE 9-10 A. Data from the TAXUS IV trial shows the in-stent late loss for the Taxus stent (Boston Scientific) and control bare metal stent. B. Probability of target lesion revascularization (TLR) as a function of in-stent late loss revealing a curvilinear distribution. Superimposed are the mean and standard deviations for the Taxus stent late loss (red) and the control bare metal stent (blue). The distribution of the Taxus stent late loss falls along the relatively flat portion of the curve, whereas the distribution for the bare metal stent falls along the steeper portion of the curve where there is greater correlation between late loss and TLR. (Reproduced with permission from Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193-1200.)

Traditionally, restenosis has been viewed as a condition that clinically manifests as stable angina. However, there is substantial evidence to the contrary. Although the majority of patients present with stable exertional symptoms, unstable angina (26%-53%), and acute MI (3.5%-20%) are not uncommon.\textsuperscript{66,67} Restenosis following balloon angioplasty or stenting is an accelerated process compared with atherosclerosis. With balloon angioplasty, clinically significant restenosis is typically present by 6 months.\textsuperscript{68,69} Following stent implantation, the average time for ISR is approximately 5.5 months, with evidence that a shorter interval may be present in patients presenting with AMI.\textsuperscript{70} Taken together, these studies highlight that restenosis is not always a benign condition and is a distinct clinical entity from atherosclerosis.

**Risk Factors for Restenosis**

The 3 most important and historical clinical risk factors for restenosis are
In conceptualizing the risk factors for restenosis, it is helpful to classify them as biologic or mechanical, although there is considerable overlap between the 2 classifications.

**Biologic**

The risk for restenosis is high among patients with diabetes mellitus. Data from a registry involving >35,000 patients following DES (Endeavor, sirolimus-eluting stents [SES], Taxus Express, and Liberte) revealed that, at 2-year follow-up, the rates of ISR with DES implantation were significantly higher in patients with diabetes.\(^7\) Another study of 954 patients undergoing PCI revealed that TLR was also significantly higher in diabetics compared with individuals without diabetes.\(^7\) The increased risk for restenosis in diabetics is likely secondary to endothelial dysfunction, accelerated intimal hyperplasia, and increased platelet reactivity.\(^7\)

Patients may also be genetically predisposed to restenosis. For example, genetic polymorphisms associated with a higher risk for restenosis include genes for angiotensin-converting enzyme inhibitor, glycoprotein receptor IIIa PLA1/2, haptoglobin 2/2.25, and IL-8.\(^7\) Additionally, resistance to antiproliferative drugs used in DESs has been observed in patients with genetic polymorphisms to the intracellular receptor mammalian target of rapamycin (mTOR), enzymes responsible for paclitaxel or sirolimus metabolism, and mutations of proteins in the downstream signaling of mTOR.\(^7\) Thus, biologic resistance to DESs may be presents in certain individuals.

<table>
<thead>
<tr>
<th>Binary markers</th>
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<tr>
<td><strong>Quantitative coronary angiography</strong></td>
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<tr>
<td>– Stenosis increase &gt;50%</td>
</tr>
<tr>
<td>– Stenosis at follow-up &gt;70%</td>
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<tr>
<td>– Stenosis at follow-up &gt;50%</td>
</tr>
<tr>
<td>– Stenosis at follow-up within 10% of pre-PTCA</td>
</tr>
<tr>
<td>– Loss of &gt;50% of initial gain</td>
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Decrease in minimal luminal diameter >0.72 mm

**Clinical**
- Target lesion revascularization (TLR)
- Target vessel revascularization (TVR)
- Target vessel failure (includes death, myocardial infarction [MI], and TVR)
- Target lesion failure (includes death, MI, and TVR)
- Ischemia-driven TLR
- Ischemia-driven TVR
- Recurrent angina
- Positive exercise test

**Continuous markers**
- Quantitative coronary angiography
  - Late loss (mm)
  - Loss index (late loss/initial gain)
- Intravascular ultrasound
  - Neointimal area (mm$^2$)
  - Lumen size (diameter or area)

Abbreviation: PTCA, percutaneous transluminal coronary angioplasty.

Biomarkers associated with an increased risk for ISR have also been identified. Higher plasma levels of MCP-1 have been associated with a higher rate of restenosis at 6-month angiographic follow-up following balloon angioplasty.$^{79}$ CRP is considered a strong risk predictor for cardiovascular disease, but the relationship between CRP and ISR remains controversial and an area of active investigation.$^{80-84}$ Circulating MMPs have also been associated with a higher risk of developing ISR following DES implantation. MMP-2 and MMP-9 play a key role in the migration of vascular smooth muscle cells and remodeling following vascular injury. Significant elevations in MMP-2 and MMP-9 levels are strongly associated with the development of ISR following DES implantation.$^{85}$

**Mechanical**
Several mechanical factors related to stent deployment may also contribute to a higher rate of restenosis. Stent underexpansion and malapposition are associated with a higher risk of ISR, which may impact effective drug delivery in DES and cause less inhibition of neointimal hyperplasia.\(^{86,87}\) In the era of DES, geographic miss may also be responsible for restenosis. Geographic miss typically refers to an area of the treated segment that was exposed to balloon injury but not covered with a DES. Thus, this uncovered area would not receive the benefits of the antiproliferative therapy of DES. Stent fracture may also contribute to ISR in DES and lead to ineffective drug delivery.\(^{88-92}\)

**Classification of Patterns of In-Stent Restenosis**

An angiographic classification of ISR was developed and classifies restenosis according to the geographic distribution of intimal hyperplasia in reference to the implanted stent.\(^{93}\) Four classes of ISR are defined as follows (Fig. 9-11):
1. Class I: Focal ISR group
   - Lesions are ≤10 mm in length and positioned at the unscaffolded segment (ie, articulation or gap), the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR).

2. Class II: Diffuse intrastent ISR
   - Lesions are >10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s).
3. Class III: Diffuse proliferative ISR
   - Lesions are >10 mm in length and extend beyond the margin(s) of the stent(s).

4. Class IV: ISR with total occlusion
   - Lesions have a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0.

The pattern of ISR is different between BMS and DES, where BMS tends to present as focal ISR and DES presents as a diffuse pattern. Additionally, patients with AMI are likely to have diffuse ISR compared with patients presenting without MI.\textsuperscript{70,94}

**Pathogenesis of Restenosis**

The pathogenesis of restenosis is different than atherosclerosis. Restenosis is more rapid than atherosclerosis and sometimes referred to as an “accelerated arteriopathy.”

**Differences Between Balloon Angioplasty Versus In-Stent Restenosis**

In balloon angioplasty, intravascular ultrasound (IVUS) studies demonstrated that restenosis is secondary to both neointimal growth and shrinkage of the artery by acute recoil and negative remodeling. Acute elastic recoil following angioplasty is observed within a few minutes and results in vessel collapse. The amount of recoil is proportional to the extent of stretching with balloon inflation and can result in as much as 50% loss in cross-sectional area and 33% loss in lumen diameter.\textsuperscript{95} Negative remodeling is different from acute recoil. It involves contraction of the external elastic laminae and is a process that occurs over weeks to months following injury. Concurrently, neointimal proliferation is an inflammatory response to the site of injury, which leads to smooth muscle cell proliferation and excessive extracellular matrix production.\textsuperscript{96,97} In terms of their relative contribution, negative remodeling plays the largest role in restenosis following balloon injury without stent placement (Fig. 9-12).
Our understanding of the pathophysiology of restenosis relies heavily upon animal models and intravascular imaging. Initial IVUS studies determined that negative remodeling (ie, external elastic membrane area) and neointimal hyperplasia (ie, plaque plus media cross-sectional area) contributed to restenosis following vascular injury from balloon angioplasty. In an angiographic analysis of the first 2 large-scale coronary stent trials in humans, distinct differences were observed between the pattern of restenosis in balloon-injured compared with stented coronary arteries. Arteries that received a stent had a larger initial lumen gain, which was due to the rigid stent scaffolding that prevented acute elastic recoil and negative remodeling. Angiographic follow-up at 6 months revealed that the luminal area was greater (ie, lower restenosis) in stented vessels compared with balloon angioplasty. However, LLL was higher in stented arteries due to greater neointimal growth. These findings were later confirmed in IVUS
Thus, the benefit of stents for restenosis is largely attributable to the larger initial lumen gain and prevention of negative remodeling (see Fig. 9-12). The neointimal formation that occurs in ISR is similar to balloon angioplasty. Yet the response is exaggerated in stenting secondary to differences in vessel injury and inflammation. For example, one study demonstrated that the inflammatory response and volume of neointimal formation were increased when the stent struts perforated the internal and external elastic lamina. Potential contributing factors to the exaggerated inflammatory response with stenting may be related to the higher balloon pressures required for stent deployment or possibly a contact allergy to the stent metal. BMSs slowly elute metal ions and have the potential to stimulate a delayed-type hypersensitivity response within the stented vessel. One study of patients who underwent cutaneous patch testing for nickel and molybdenum hypersensitivity after stent placement found that patients with a positive test also had more ISR requiring revascularization. The data suggest that metallic hypersensitivity may account for a subset patients who presents with restenosis after stenting.

**Mechanisms of Leukocyte Recruitment and Infiltration**

Balloon expansion and/or stent placement causes vascular injury by dissection, crushing the smooth muscle cells, and de-endothelialization. Leukocytes are recruited to sites of injury and are deposited together with platelets. As part of the inflammatory response after angioplasty, the interaction between platelets and leukocytes is important. The initial loose attachment of leukocytes to surface-adherent platelets is mediated through the selectin class of adhesion molecules (eg, P-selectin), followed by firm adhesion and transplatelet migration via the integrin class of adhesion molecules (eg, β2 integrin Mac-1, also known as CD11b/CD18). In addition to promoting leukocyte recruitment, platelet binding to neutrophils amplifies the inflammatory response via proinflammatory molecules (eg, soluble CD40 ligand) by inducing neutrophil activation, amplifying the expression of CAMs, and enhancing signal transduction pathways that promote integrin activation and cytokine synthesis. Neutrophil-platelet and monocyte-platelet aggregates have been identified in patients with CAD and may be markers of disease activity and prognostic markers.
Inflammation: A Key Role in Restenosis

Restenosis is not typically secondary to accelerated atherosclerosis, but is a distinct temporal and pathophysiologic process. However, inflammation still plays a central role in both atherosclerosis and restenosis. In a study of pathologic samples of 116 stents from 87 patients more than 90 days after procedure, the severity of restenosis was associated with the extent of medial damage and inflammation. An additional study of tissue samples retrieved from direct atherectomy at the time of angioplasty demonstrated a strong positive correlation between the number of inflammatory cells and the risk of restenosis.

Inflammatory biomarkers have also provided insight into the mechanisms of restenosis. In one study, blood samples were collected from patients both proximal and distal to the site of injury following balloon dilatation, and inflammatory biomarkers of leukocyte activation (eg, neutrophil adhesion molecules L-selectin and CD11b) were upregulated after angioplasty. CD11b is upregulated on both neutrophils and monocytes in patients following angioplasty and is a prognostic marker for restenosis following angioplasty and stenting. Increased IL-1 production by monocytes isolated from blood before angioplasty was associated with LLL, whereas granulocyte activation was protective against luminal narrowing. Higher MCP-1 levels are associated with a risk for ISR following PCI. The nonspecific inflammatory marker CRP is also positively correlated with a risk for restenosis following stent placement.

Animal models have been invaluable in elucidating the basic cellular and molecular mechanisms of restenosis. CAMs are critical for leukocyte recruitment and are upregulated by an atherogenic diet, induction of diabetes, and increased shear stress in various animal models. VCAM-1, ICAM-1, and major histocompatibility complex (MHC) class II antigens are upregulated following balloon endothelial denudation. Stents induce a potent and early inflammatory response evidenced by an abundance of surface adherent leukocytes. In the days to weeks following stent implantation, macrophages invade the forming neointima and cluster around stent struts forming giant cells. Blockade of monocyte recruitment with anti-inflammatory agents results in reduced late neointimal thickening. A strong correlation exists between the number of tissue monocytes and
neointimal area, which suggests a causal role for monocytes in restenosis. Furthermore, activated macrophages influence vascular repair by production of a variety of inflammatory cytokines (e.g., IL family, tumor necrosis factor-α, MCP-1) and growth factors (e.g., platelet-derived, basic fibroblast, and heparin-binding epidermal growth factors).

Vascular injury leads to neutrophil infiltration within the arterial wall. A reduction in accumulation of neutrophils and smooth muscle proliferation by anti-inflammatory agents results in less neointimal growth. The mechanisms by which neutrophils affect vascular repair are less understood compared with monocytes or macrophages. Neutrophils may cause tissue injury through the release of reactive oxygen species, proteases, or inflammatory cytokines. Vascular smooth cell proliferation can also be stimulated by neutrophils.

**Smooth Muscle Cell Proliferation**

Vascular smooth muscle cell proliferation and migration are central to the development of restenosis and the target for antirestenosis therapies. Thus, it is important to understand two intracellular signaling pathways responsible for the regulation of smooth muscle cell proliferation: the tyrosine kinase cascade and the cyclic adenosine monophosphate (cAMP) pathway. Growth factors bind to the smooth muscle cell receptors and activate tyrosine kinase, which, via a phosphorylation cascade, activates the \( \text{ras/raf/mitogen-activated protein kinase (MAPKK)} \) signal transduction pathway, resulting in intranuclear activation of transcription factors that induce smooth muscle cell proliferation and migration. The cAMP pathway activates protein kinase A (PKA), which also activates the transcription factor cAMP responsive element binding protein (CREB). Additionally, PKA also phosphorylates \( \text{raf} \), which inhibits the other major pathway involved in the activation of smooth muscle cell proliferation. Importantly, inactivation of \( \text{ras} \) by activation of the cAMP pathway leads to a >50% reduction in neointimal formation at 14 days following balloon injury in rat carotid arteries. Similarly, inhibition of MAPKK by a dominant inhibitor mutant gene results in a decrease in neointima formation.

Downstream from these two important signal transduction pathways are other processes that regulate the progression of a smooth muscle cell through
the cell cycle. The progression from the G₀ (ie, quiescent) to G₁ phase is regulated by cyclin-dependent kinases, of which several endogenous inhibitors (eg, p21⁰⁰⁰⁰⁰⁰⁰¹, p27⁰⁰⁰⁰⁰⁰⁰¹, and INK4 families) regulate the process of a smooth muscle cell entering the G₁ phase. For example, vascular inflammation and injury decrease the level of p27⁰⁰⁰⁰⁰⁰⁰¹, which then promotes more cell division. However, cAMP activation leads to increased p27⁰⁰⁰⁰⁰⁰⁰¹ levels and can promote the proliferating cells to enter a quiescent phase.¹³³ Thus, intracellular signaling regulates the conversion of smooth muscle cells to differentiate into myofibroblasts and migration to the site of vascular injury. Histologic analysis demonstrates that these cells form a cap across the site of injury, proliferate toward the tunica media, produce the constituents of the extracellular matrix, and form the neointimal mass.¹³⁷ Importantly, the extent of neointimal formation is determined by the degree of the inflammatory response at the site of vascular injury.¹³⁸

Negative Remodeling

Remodeling is a change in vessel size following vascular injury and is responsible for luminal loss after angioplasty or stenting.⁹⁷,¹³⁹ Following balloon angioplasty, negative remodeling typically occurs within 1 to 6 months and accounts for up to 65% of luminal loss.⁹⁷,¹⁴⁰ The adventitia plays a critical role in both proliferation and concentric compression of the external elastic lamina (ie, negative remodeling).¹⁴¹ Upon injury to the vessel, inflammatory cells stimulate cell proliferation in the adventitia by converting adventitial fibroblasts to myofibroblasts, which begin to secrete components of the extracellular matrix, leading to vessel constriction and formation of a fibrotic scar within the adventitia surrounding the site of injury.¹⁴¹,¹⁴² Thus, the adventitia is not a passive player in the process of restenosis.

Biologic Differences Between Balloon and Stent Injury

Important differences exist between the vascular biologic responses to balloon versus stent injury. As an example, one study demonstrated a significantly higher expression of CD11b expression on neutrophils (ie, inflammatory response) following PCI compared with balloon angioplasty alone.¹⁴³ An increased inflammatory response may amplify neointimal
growth following stent implantation. In animal models, heparin is a well-known modulator of vascular repair and known to reduce neointimal growth following vascular injury after balloon injury or stent implantation.\textsuperscript{144-147} However, a notable difference exists between these mechanisms of vascular injury in animal models. Heparin inhibits neointimal hyperplasia in stented rabbit iliac arteries, only when given in a prolonged fashion (14 days), whereas maximal inhibition of balloon-injured arteries only requires an early and brief duration of heparin therapy (3 days).\textsuperscript{147} One explanation of this difference is suggested by immunohistologic and molecular studies, which demonstrate a distinct pattern of leukocyte infiltration that distinguishes the superficial injury from balloon-induced de-endothelialization from the deep chronic injury associated with stent implantation. In animal models, balloon injury causes early and transient infiltration of neutrophils without monocyte recruitment, whereas stenting leads to an early influx of neutrophils followed by a sustained monocyte accumulation over the ensuing weeks following implantation. These differences are mirrored by molecular studies, whereby MCP-1 and IL-8 are only transiently (ie, hours) expressed following balloon injury compared with sustained expression as late as 14 days following stenting.\textsuperscript{148}

**An Integrated View of the Pathophysiology of Restenosis**

When a balloon is inflated and a stent deployed at the site of a mature atherosclerotic plaque, a cascade of events is initiated (see Fig. 9-8). The first event is an inflammatory phase. Stent placement causes immediate de-endothelialization, crushing of the plaque with occasional dissection into the tunica media or adventitia, and stretching of the entire artery. Due to this injury, platelets and fibrin are deposited at the injured site. Activated platelets layered on the injured surface express adhesion molecules (eg, P-selectin and glycoprotein [GP] Ibα) and bind to circulating leukocytes, which initiates leukocyte rolling along the surface. Leukocytes bind tightly to the platelet receptors through the leukocyte integrin adhesion molecules (eg, Mac-1) and stop rolling after cross-linking with fibrinogen to the GP IIb/IIIa receptor. Migration of leukocytes across the platelet-fibrin layer and diapedesis into the subendothelium are amplified by cytokines released from neighboring
smooth muscle and resident cells. Following the inflammation phase, the granulation or cellular proliferation phase ensues with the release of cellular growth factors from platelets, leukocytes, and smooth muscle cells. Growth factors stimulate smooth muscle cell proliferation and migration from the media to the neointima. Thus, the resultant neointima is composed of smooth muscle cells, extracellular matrix, and macrophages that are recruited over a period of several weeks. Next, the remodeling phase is initiated over a longer period of time and involves extracellular matrix protein degradation and resynthesis and a shift from cellular accumulation to a greater production of extracellular matrix. In the balloon angioplasty era, this phase typically would result in luminal narrowing from negative remodeling. However, stented arteries are resistant to negative modeling due to the rigid scaffolding of the stent. Finally, re-endothelialization of the vessel surface occurs following balloon angioplasty or stenting.

**Neoatherosclerosis**

More recently, it has been demonstrated that some cases of ISR closely resemble atherosclerosis. This process is termed neoatherosclerosis and has been identified pathologically by clusters of foam cells and true thin capped atheromas identified within stents from patients at autopsy. Intravascular imaging techniques have identified lesions consistent with thin-capped fibroatheroma within prior placed stents. In particular, optical coherence tomography has been used, and some studies suggest a frequency of neoatherosclerosis as high as 50%, particularly in cases of DES ISR.

**Therapy for Restenosis**

Since the advent of percutaneous revascularization, therapies for restenosis have been heavily investigated. For years, numerous preclinical studies have shown efficacy against restenosis in animal models but failed in large-scale clinical trials. Finally, agents directed against smooth muscle cell proliferation delivered locally to the site of injury resulted in significant reductions in restenosis and revolutionized current clinical practice.

**Mechanical**
Several mechanical strategies have been employed to reduce the frequency of ISR including: (1) IVUS-guided high-pressure deployment to achieve larger MLD; (2) debulking therapy with rotational atherectomy; and (3) minimizing vessel injury with the avoidance of predilation by “direct” stenting. Although each strategy reduces restenosis rates in small clinical trials, large randomized controlled trials failed to support their overall efficacy. ¹⁵¹-¹⁵³

**Bare Metal Stents**

BMSs were developed as mechanical scaffolding to prevent recoil and negative remodeling for the reduction of restenosis. The rates of major adverse cardiac events and restenosis were significantly lower in patients with stable coronary disease randomized to BMS compared with balloon angioplasty. ⁵² The evidence from several early BMS trials confirmed the superiority of stenting over angioplasty alone. However, persistent high rates of ISR spurred the development of pharmacologic therapies.

**Pharmacologic Therapies**

Therapies directed toward the various pathways implicated in restenosis have been investigated including antithrombotic, anti-inflammatory, and antiproliferative agents. Given the breadth of agents that have been studied for their effect in restenosis, we limit our discussion to agents with established or emerging efficacy.

**Cilostazol**

Cilostazol is an antiplatelet agent predominantly used for the treatment of intermittent claudication. It is a selective inhibitor of phosphodiesterase-3 (PDE-3), which is abundant in platelets and vascular smooth muscle cells. Inhibition of PDE-3 increases intracellular cAMP and PKA activation to reduce platelet activation/aggregation, increase smooth muscle cell relaxation and cardiac contractility, and inhibit smooth muscle cell proliferation. ¹⁵⁴ Nonrandomized studies demonstrated that cilostazol was associated with a reduction in restenosis in patients who underwent balloon angioplasty or stenting. ¹⁵⁵ In the Cilostazol for Restenosis (CREST) trial, patients randomized to cilostazol following BMS had significantly larger MLD and reduced ISR (>50% diameter stenosis) compared with patients randomized to
A meta-analysis of 10 randomized studies supports the use of cilostazol for the reduction of ISR.\textsuperscript{157}

**Drug-Eluting Stents**

Local drug delivery has important advantages for the treatment of restenosis, namely, that drugs can be delivered at high doses locally without systemic toxicity. DESs predictably elute high doses of a therapeutic agent to reduce smooth muscle proliferation that is undetectable in the peripheral blood.\textsuperscript{158} The process of local drug delivery is complex and dependent on the dose, rate of release, tissue retention, and pharmacologic properties of the drug. Lower doses can be ineffective, whereas higher doses may result in tissue death, delayed healing, and higher rates of thrombosis.\textsuperscript{159,160} Prior studies determined that faster drug release is less effective at reducing LLL compared with slower release.\textsuperscript{161} Drugs can be directly bound to the stent. However, the majority of DESs use a polymer to store and time-release the drug. Nonerodable polymers were developed for effective drug delivery over a period of time and to not, by themselves, stimulate any additional inflammation or cell proliferation. The polymer release kinetics are critical to the prevention of ISR. In the Paclitaxel In-Stent Controlled Elution Study (PISCES), 10 or 30 μg of paclitaxel released over 10 days after DES implantation had little effect on neointimal formation, whereas 10 μg released over a 30-day period significantly reduced neointimal formation and LLL.\textsuperscript{162} Early clinical studies like PISCES supported the concept of a drug threshold with delivery over a sustained period of time to inhibit inflammation and smooth muscle cell proliferation.\textsuperscript{163} DESs are the preferred treatment for ISR. Compared with angioplasty, DESs significantly reduce the rate of restenosis and LLL in patients presenting with ISR.\textsuperscript{164} An emerging device for the treatment of ISR is the use of drug-coated balloons to deliver antirestenotic pharmacotherapy without the use of a polymer or metal scaffold.\textsuperscript{165} For the purposes of this chapter, we will introduce the pharmacologic agents used in DES and their mechanisms of action. In subsequent chapters, a review of the clinical trials related to DES and emerging technologies will be described in detail.

**Sirolimus**
Sirolimus (rapamycin) is a natural macrocyclic lactone with potent immunosuppressive and antimitotic action produced by a fungus, *Streptomyces hygroscopicus*. It binds to FK binding protein-12 (FKBP-12), forming an immunosuppressive complex that inhibits mTOR, which leads to higher levels of p27$^{kip1}$, blocking the G$_1$-S transition in the cell cycle and halting vascular smooth muscle cell proliferation.$^{166}$ Several pivotal trials conducted with sirolimus-eluting stents (SESs) led to US Food and Drug Administration (FDA) approval in April 2003. In the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent (RAVEL) trial, SES demonstrated significant reductions in LLL, neointimal hyperplasia, and ISR compared with BMS at 6-month follow-up.$^{167}$ At 1 year, SES also reduced the rate of major adverse cardiac events compared with BMS.$^{63}$ The Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial recruited patients with more complex CAD and a higher prevalence of diabetes mellitus.$^{168}$ In SIRIUS, SES reduced the rates of LLL and ISR compared with BMS, and these finding were consistent across high-risk subgroups for restenosis including small vessels, long lesions, and diabetes mellitus.$^{168,169}$

**Paclitaxel**
Paclitaxel is isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) and inhibits microtubule depolymerization, resulting in inhibition of cellular replication and cytokine-mediated smooth muscle cell proliferation and migration. The efficacy of paclitaxel-eluting stents (PES) was demonstrated in the TAXUS trials, where PES reduced ISR, TLR, and adverse cardiac events compared with BMS.$^{170-173}$ These benefits were maintained in specific subgroups, including patients with vessel diameters $<2.5$ mm, lesion lengths $>20$ mm, renal insufficiency, and diabetes mellitus.

**Everolimus**
Everolimus is a 40-O-(2-hydroxyethyl) derivative of sirolimus and shares the same mechanism. Abbott Vascular (Temecula, CA) produces several everolimus-eluting stent (EES) in the Xience family of DES, the latest of which are called Xience Expedition and Alpine. EESs are also produced by Boston Scientific (Marlborough, MA) as the Promus Element and Premier stent systems. In a pooled analysis of the SPIRIT (Clinical Evaluation of the
Xience V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) trials, EES reduced the rates of death or MI, stent thrombosis, and ischemic-driven TLR compared with PES in patients with ACS and stable CAD at 2-year follow-up.\textsuperscript{174} EES has similar clinical outcomes (ie, major adverse cardiac events and TLR) compared with SES and a lower rate of definite stent thrombosis.\textsuperscript{175}

**Zotarolimus**

Zotarolimus is an analogue of sirolimus with a similar mechanism of action that was initially designed to have a short half-life.\textsuperscript{176} The FDA approved the Endeavor zotarolimus-eluting stent (ZES) platform in 2008 after reviewing the Medtronic (Minneapolis, MN) ENDEAVOR clinical program. Importantly, the Endeavour ZES elutes >95\% of the drug within 14 days. In a combined analysis of the ENDEAVOR trials, Endeavour ZES was associated with a significantly lower rate of adverse cardiac events (death, MI, and very late stent thrombosis) compared with a pooled cohort of SES and PES patients (ie, first-generation DES).\textsuperscript{177} Endeavour ZES did have a higher rate of angiographic restenosis compared to first-generation DES, but this did not translate into a higher rate of TLR.\textsuperscript{177} The Resolute ZES was developed by Medtronic with substantially longer polymer drug release kinetics (180 days). In the RESOLUTE All-Comers trial, the clinical outcomes were comparable between Resolute ZES and EES.\textsuperscript{178}

**Biolimus**

Biolimus A9 is an analogue of rapamycin that binds to mTOR and inhibits smooth muscle cell proliferation by blocking cell cycle progression between the G\textsubscript{1} and S phases.\textsuperscript{179} Currently, 2 stents platforms, Biomatrix and Nobori, have received approval in Europe. Unique to these stent platforms is the use of a bioabsorbable polymer that is completely dissolved by 6 to 9 months following stent implantation.

**Brachytherapy**

Intracoronary brachytherapy effectively reduces neointimal proliferation and rates of ISR.\textsuperscript{180-183} Since the introduction of DES, the use of brachytherapy
for ISR is uncommon and only performed at specialized tertiary referral centers. The practical difficulty in scheduling the procedure between radiation oncologists and the catheterization lab, reduced availability at tertiary centers, and increased rates of subacute thrombosis have deterred widespread acceptance of intracoronary radiation into clinical practice for ISR of DES.\textsuperscript{184,185}

**CONCLUSION**

Over the past decades, the molecular and cellular pathophysiology of atherosclerosis has been extensively studied. Our current understanding of plaque vulnerability and the mechanisms responsible for conversion from a stable plaque to plaque rupture and atherothrombosis has shaped the landscape of pharmacotherapy and interventional cardiology for the treatment of ACS. Inflammation plays a central role in the pathogenesis of atherosclerosis and restenosis. Important molecular and biologic differences exist between atherosclerosis and restenosis. Recognition of the differences in the biologic response to vascular injury between balloon angioplasty and stenting led to the development of local drug delivery and DES for the prevention of restenosis. Improved understanding of the molecular mechanisms of atherosclerosis and restenosis, identification of plaques prone to rupture, and more effective methods to treat restenosis will continue to advance the field of interventional cardiology.

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**MULTIPLE CHOICE QUESTIONS**
1. Sectioning of atherosclerotic lesions at postmortem can reveal the architecture of atherosclerotic plaques. Which of the following would typically be present in plaques at low risk of rupture?
   A. Thin fibrous cap
   B. Abundant expression of collagen fibrils
   C. Abundant free cholesterol esters
   D. Abundant inflammatory cells
   E. High concentration of matrix metalloproteinases

2. Immune cells can be divided into those involved in the adaptive response and the innate response to antigens. Which of the following cell types belongs to the innate response?
   A. Macrophages
   B. Platelets
   C. Dendritic cells
   D. T lymphocytes
   E. Mast cells

3. A 55-year-old man presents with increasing angina despite best medical therapy. A high-grade lesion is identified in the proximal left anterior descending artery (LAD) with a minimal lumen diameter of 0.5 mm. After stent placement, the diameter is increased to 3.5 mm. The patient returns at 6 months with recurrent angina, and an angiogram shows a minimal lumen diameter of 1.5 mm. What is the loss index?
   A. 0.1
   B. 0.25
   C. 0.33
   D. 0.5
   E. 0.66

4. You are performing catheterization on a 65-year-old man who is 1 year out from bare metal stent placement in the LAD in the setting of an acute anterior myocardial infarction (MI). He now presents with stable angina on a maximal medical regimen, and a recent exercise tolerance test combined with a sestamibi scan revealed ischemia in the left circumflex coronary artery (LCX) territory. Catheterization reveals 50% in-stent restenosis in the prior placed LAD stent and a new long 80% lesion in a
2.5-mm LCX artery. What is the most appropriate strategy?
A. Treat the LCX lesion with a drug-eluting stent (DES). Defer therapy of the LAD.
B. Treat the LCX lesion with DES. Treat the LAD lesion with DES as well, given the evidence of restenosis.
C. Treat the LCX lesion with DES. Treat the LAD lesion with plain balloon angioplasty (POBA) and brachytherapy, given evidence of restenosis.
D. Recommend urgent coronary artery bypass grafting (CABG) given restenosis in the LAD, marking the patient as a poor candidate for percutaneous coronary intervention (PCI).

5. The pathogenesis of atherosclerosis has many similar features to the development of restenosis. Which of the following features would help differentiate a restenotic lesion from a primary atherosclerotic lesion?
   A. Time course
   B. Inflammatory cell involvement
   C. Smooth muscle cell proliferation
   D. Adhesion molecule expression

**ANSWERS**

1. B
Vulnerable plaques are characterized by thin fibrous caps, which are relatively poor in smooth muscle cells (SMCs) and extracellular matrix proteins (such as collagens), and large lipid-rich necrotic cores, which are abundant in inflammatory cells.

2. D
The immune response can be divided into the innate immune response, which is an immediate response to foreign antigens and injury and is largely based on phagocytic cells and preformed mediators, and the adaptive response, which is a learned response to specific antigens and involves cell-mediated and humoral immune responses. The innate immune response has traditionally been thought of as the major player in atherosclerosis, with
macrophages being the predominant cell type. However, there is mounting evidence for an important role for the adaptive response as well, as evidenced by the presence of T cells within atherosclerotic plaques.

3. E

Loss index is equal to the late loss divided by acute gain. The acute gain in this example is 3 mm and the late loss is 2 mm. Therefore, the loss index is 2/3 or 0.66.

4. A

The lesion in the LCX is long and in a small-caliber vessel, marking it as high risk for restenosis when treated with either POBA or bare metal stent. Treatment with DES is appropriate. Data would suggest that most cases of restenosis will occur within the first 6 to 12 months. There is no reason to suspect that the LAD restenosis will proceed to a clinical significant degree, and there is no evidence of ischemia in that territory. Neither PCI nor CABG to address the LAD is warranted. Conservative management of this lesion is most appropriate.

5. A

As with atherosclerosis, the mechanisms of restenosis involve an inflammatory response to injury involving leukocyte recruitment amplified by the release of cytokines and growth, which eventually lead to smooth muscle cell proliferation and migration. However, in contrast to atherosclerotic plaques, restenosis is termed an accelerated arteriopathy with a time course that is measured in months as opposed to decades.
The catheterization laboratory continues to evolve with time, initially concentrating on hemodynamic assessment of the heart and, in particular, valvular heart disease, before becoming very “coronary-centric” with the advent of balloon angioplasty and the heightened prevalence of coronary artery disease. As we enter the next phase of evolution, the catheter-based treatments of structural heart disease are bringing back some of the early lessons of the importance of ventricular performance and its evaluation. Complicating the transition is the need to synthesize information across multiple noninvasive and invasive modalities of cardiac assessment to determine clinical decision making for individual patients.

Left ventricular dysfunction may occur in the setting of impairment of systolic performance, diastolic performance, and/or abnormal hemodynamic loading conditions. Although, an in-depth understanding of left ventricular mechanics does not directly translate into improved day-to-day clinical practice for the interventional cardiologist, a general understanding of the factors impacting left ventricular performance remains imperative to appropriate therapeutic decisions.

INVASIVE ASSESSMENT OF GLOBAL LEFT VENTRICULAR FUNCTION: THE LEFT VENTRICULOGRAM
In the cardiac catheterization lab, ventricular pathophysiology is most frequently recognized by the performance of left ventricular (LV) wall motion seen on the left ventriculogram. The left ventriculogram visually portrays the relationship between stroke volume and the end-diastolic volume, and either quantitatively or qualitatively, an ejection fraction is determined. Universally, ejection fraction has been accepted as an estimate of the global LV contractile state. Furthermore, an assessment of regional LV function by wall motion on ventriculography has become an essential part of every cardiac catheterization.¹

Qualitative assessment of LV function rests on the visual appreciation between stroke volume and end-diastolic volume. An increase in end-diastolic volume (ie, dilated LV chamber size) is commonly seen in patients with volume overload states (eg, aortic insufficiency). However, stroke volume (ie, the difference between end-diastolic and end-systolic volumes, also known as ejection fraction) is dependent on the myocardial contractile state and, in part, loading conditions. A reduction in the ventricular contractile state may be secondary to intrinsic myocardial disease (ie, nonischemic cardiomyopathy) or may be secondary to coronary artery disease and its associated regional wall motion abnormalities.

Depressed regional wall motion, defined as hypokinesis, reflects a decrease in the contractile state of a particular region of the left ventricle. Noncontraction of a region (akinesis) or outward contraction of a segment during systole (dyskinesis) may reflect the occurrence of a prior myocardial infarction.² Commonly, the left ventricle is imaged in a right anterior oblique projection, giving good assessment of the anterior-basilar, anterolateral, apical, diaphragmatic, and posterior-basilar segments (Fig. 10-1). In select cases involving the lateral LV wall, the left anterior oblique projection is used to estimate the lateral, posterior, and septal walls. Assessment of regional wall motion is critical to risk stratification and management of patients with coronary artery disease.
Several methods are available to quantify the measurement of ejection fraction from the angiographic image by online software. One method is the so-called area-length method. This method assumes an ellipsoid shape to the ventricle. Calculations of ventricular volume are made from the end-systolic frames and end-diastolic frame using the dimensional measurements of the ventricle. Regression equations correct for the overestimation of the calculated volume to the true volume. A second method, the center line method, has also been used because of its ability to quantify both regional wall motion as well as ejection fraction. This method does not assume a geometric configuration of the ventricle and measures the shortening fractions of 100 chords, which are constructed perpendicular to a centerline.
that is drawn midway between the end-diastolic and end-systolic contours.

Despite the wealth of information obtained during the performance of ventriculography, practice patterns are highly variable with respect to its current performance. In a recent evaluation of practices across Veterans Affairs (VA) catheterization labs over the years 2000 to 2010, more than 450,000 catheterizations were performed, and only 58% of those procedures involved left ventriculography. In fact, when looking at the trend of performance over that decade, there was a significant drop over time (Fig. 10-2). Furthermore, there was marked variation among VA facilities in the frequency of performance of ventriculography that could not be explained by patient or clinical factors. Thus, the operator preferences seemed to predominate regarding obtaining ventriculography.


**NONINVASIVE ASSESSMENT OF LEFT VENTRICULAR FUNCTION**

In current practice, there are multiple options available to the operator in assessing LV function, and often, patients present to the catheterization lab
with prior noninvasive testing. In an evaluation of a health maintenance organization population, more than 90,000 catheterization procedures performed over the course of a year were administratively evaluated. Almost 82% of these patients had concomitant performance of left ventriculography, despite the fact that 41% of these same patients had already had noninvasive assessment within the preceding 30 days. Although this does not in itself allow conclusions to be drawn on an individual case-by-case basis, operators must be versed in the value of the noninvasive imaging testing performed prior to catheterization.

Transthoracic echocardiography has become a standard tool for the assessment of LV function. As with cardiac ventriculography, echocardiography allows the assessment of global LV function as well as regional wall motion in the 3-dimensional chamber. Furthermore, it has the ability to better assess coexistent valvular disease (whereas ventriculography essentially only evaluates for mitral regurgitation), especially for aortic and mitral pathology. In addition, assessment of the tricuspid regurgitation jet permits an estimate of right ventricular pressure and systolic function, which can alert the clinician to impaired hemodynamics that may require further evaluation. Furthermore, analysis of mitral inflow patterns and tissue Doppler signals gives great insight into ventricular mechanics, including diastolic dysfunction and restrictive physiology. Radionuclide ventricular imaging also possesses the ability to measure LV volume, ejection fraction, and regional wall motion by the adaptation of gated image acquisition techniques. By the same token, recent advances in contrast computed tomography and magnetic resonance imaging technologies have provided these noninvasive imaging techniques with the ability to evaluate LV size and function.

A large number of clinical trials have been performed to show the reliability of ejection fraction assessed by both radionuclide imaging and echocardiography. In a clinical practice, single-center cohort of unselected patients, there was a close correlation between measurements by these modalities and invasive ventriculography. There tended to be an overestimate of ejection fraction by echocardiography in the lower range of the measurements compared with ventriculography. Furthermore, nuclear imaging tended to overestimate ejection fraction compared with ventriculography at the lowest values and underestimate it at the higher values. Although all 3 modalities have some variability and are not interchangeable in a 1-to-1 fashion, the absolute variability between
measurements was not found to affect clinical decision making.

INVASIVE HEMODYNAMIC ASSESSMENT OF THE LEFT VENTRICLE

Pressure-Volume Relationships

A great deal of work has been done in evaluating the interdependence of the multiple factors affecting overall LV performance. The earliest means to understanding LV pump function was the assessment of the LV pressure-volume loop (Fig. 10-3).9,10 The lower portion of this loop (from left to right in Fig. 10-3) illustrates ventricular filling from the opening of the mitral valve (D) to end diastole (A). A steep increase in pressure occurs from end diastole to the opening of the aortic valve (B), and this is represented on the right side of the loop. The top of the loop begins at aortic valve opening (right to left) and ends at aortic valve closing (C), representing the stroke volume. The left side of the loop represents isovolemic relaxation between the closure of the aortic valve and the opening of the mitral valve.

FIGURE 10-3 A representation of a left ventricular pressure (on y-axis)—volume (on
x-axis) loop. End diastole is seen at point A and end systole at point C. Diastole occurs between points D and A, whereas systole occurs between points B and C. The total of the loop is representative of left ventricular stroke work.

The area of the pressure-volume loop represents LV stroke work, which remains a good surrogate for LV systolic function under the loading conditions present when the pressure-volume curve was obtained. One of the main drawbacks in using stroke work as an estimate for LV function is that loading conditions do not remain constant outside the experimental lab. Furthermore, stroke work represents a global estimate of LV performance and, as such, does not take into account regional differences in function that are frequently present in patients with established coronary artery disease.

The end-systolic pressure-volume relationship (ESPVR) has also been established as a marker of the overall contractile state of the ventricle. This relationship is constructed by producing multiple pressure-volume loops over varying loading conditions. A line can be drawn that connects the upper left portion of each loop (Fig. 10-4), and the slope of this line represents the ESPVR. In general, a shift in the ESPVR to the left with an increased slope is associated with an increase in contractility, whereas a decrease in slope with a rightward shift to the line is associated with decreased contractility.

**FIGURE 10-4** Multiple pressure-volume loops from the same ventricle under varying loading conditions or inotropic states can be drawn. The line that intersects all end-systolic points (Ees) is the end-systolic pressure-volume relationship (ESPVR). The
greater the slope of the line, the greater is the contractility of the ventricle. Ed, end diastole; LV, left ventricular. (Reproduced with permission from Chen CH, Nakayama M, Nevo E, et al. Coupled systolic–ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. J Am Coll Cardiol. 1998;32:1225.)

LV diastolic function can also be readily appreciated by looking at the lower portion of the pressure-volume loop (see Fig. 10-3).\textsuperscript{15,16} With an increase in LV stiffness, the curve shifts upward, and with an increase in ventricular compliance, the curve moves downward along the y-axis.

**Ventricular Loading Conditions**

LV systolic function is intimately tied to loading conditions. Preload represents the load that stretches the ventricular myofibrils during diastole, and it has been quantified in the patient as the LV end-diastolic pressure. Increasing preload tends to increase the LV diameter, whereas its effects on overall function depend on the ventricle’s ability to accommodate this stretch. This ability to distend can be estimated by evaluating the ventricular diameter and extrapolating the concepts derived from the Frank-Starling curve (Fig. 10-5).
Afterload represents the force that resists the systolic contraction of the ventricle. The calculation of systolic wall stress by the Laplace law \[ \text{stress} = \frac{\text{pressure} \times \text{chamber radius}}{\text{wall thickness}} \] is generally thought to represent ventricular afterload. One caveat that applies is that this wall stress varies during systole.\(^{17,18}\) Therefore, the end-systolic wall stress remains as the best representative of afterload. Increasing afterload, in general, tends to decrease the stroke volume.

The intrinsic property of the myocardium to forcefully eject blood and do work is represented by the term \textit{contractility}. Classically, contractility is independent of preload and afterload. However, from a practical standpoint, it
is difficult to evaluate these parameters independently. Contractility, also described as inotropy, is affected by circulating catecholamines or pharmacologic agents (eg, dobutamine, β-blockers). The maximal rate of rise in LV systolic pressure per unit time (dP/dt) remains the best estimate of contractility. Increases in dP/dt are seen with exercise, norepinephrine, and isoproterenol. Although dP/dt remains as an excellent marker of ventricular contractility, its measurement in the catheterization lab requires a micromanometer catheter capable of high-frequency signal differentiation, an impractical situation in the clinical lab where fluid-filled catheters coupled to electrical strain gauges are in daily use. Thus, dP/dt is not routinely assessed.

**Left Ventricular End-Diastolic Pressure**

Proper evaluation and interpretation of LV end-diastolic pressure (LVEDP) can give the operator a strong indication of the hemodynamic health of the left ventricle without performance of ventriculography or the more complex assessment of pressure-volume relationships. First, evaluation of the trend across the diastolic portion of the LV pressure curve provides assessment of ventricular relaxation. Abnormal relaxation of diastolic dysfunction can then be exhibited by a low overall LVEDP with a decline in the diastolic pressure tracing over the diastolic phase (Fig. 10-6). Conditions such as concentric hypertrophy due to valvular stenosis, restrictive or infiltrative cardiomyopathy, or other diseases of the ventricular muscle will produce a stiffer chamber and an overall elevated LVEDP. Thus, recognition of abnormalities in the LVEDP can lead to dramatically different treatments for a given patient—from preload reduction to a ventricular assist device.
FIGURE 10-6 A. Schematic representation of the normal left ventricular (LV) diastolic pressure tracing depicting a nadir and end systole with a gradual upslope throughout the diastolic period culminating in a reflected “a” wave corresponding to atrial contraction. EKG, electrocardiogram. (Reproduced from Applegate RJ, Rankin KM, Powers JC, Little WC. Evaluation of diastolic function. Catheter Cardiovasc Interv. 2001;53:85-93.) B. Example of abnormal diastolic function as assessed by left ventricular pressure. Note the low overall left ventricular end-diastolic pressure (LVEDP) and the declining nature of this pressure during the diastolic phase. C. Left ventricular pressure tracing demonstrating marked elevation in overall LVEDP.

CORONARY ARTERY DISEASE AND LEFT VENTRICULAR DYSFUNCTION

Coronary artery disease remains the most prevalent diagnosis among patients requiring cardiac catheterization. As previously discussed, coronary artery disease usually manifests itself in regional ventricular wall motion abnormalities. In an acute setting, the wall motion abnormality may give early clues to the coronary artery involved as well as the location of the offending lesion. Severe degrees of LV dysfunction may represent the etiology of cardiogenic shock, in which the heart is unable to maintain enough forward perfusing pressure to supply blood.

Mechanical complications of acute myocardial infarction or acute coronary syndromes that compromise LV function can be detected by left ventriculography, including most notably, the occurrence of mitral regurgitation secondary to papillary muscle dysfunction and/or papillary muscle rupture, ventricular pseudoaneurysm formation, ventricular free wall rupture, and ventricular septal defects. Although the incidence of these complications is rare, it is important to recognize their existence. Early surgical intervention will decrease the morbidity and mortality associated with these conditions. Although left ventriculography per se may not routinely be performed in all patients presenting with acute myocardial infarction and/or acute coronary syndromes, the assessment of LV function remains one of the strongest predictors of short- and long-term survival in patients. Therefore, it is of critical importance to obtain either an angiographic or an echocardiographic assessment of global and regional LV function in all patients under these conditions. Furthermore, with the complex nature of myocardial necrosis with myocardial stunning, follow-up
assessment of regional and global LV function also becomes paramount in
the estimate of overall survival after primary reperfusion strategies (Fig. 10-
7).^{25}

![Graph showing the striking relationship between overall left
ventricular function (ejection fraction) and cardiac mortality in patients following an
acute myocardial infarction.](image)

FIGURE 10-7 Graph showing the striking relationship between overall left
ventricular function (ejection fraction) and cardiac mortality in patients following an
acute myocardial infarction. (Reproduced with permission from Gottlieb S, Moss AJ,
McDermott M, et al. Interrelation of left ventricular ejection fraction, pulmonary

The patient presenting with angina-like symptoms and/or an abnormal
stress test represents the most common presentation to the cardiac
catheterization laboratory. Assessing the patient’s coronary anatomy with the
goal of improving myocardial perfusion either by coronary artery bypass
grafting or percutaneous coronary intervention remains the principal initiative
in these cases. Ventricular performance weighs heavily in the decision-
making process of revascularization techniques (Fig. 10-8).^{26-28}
Systolic LV function (ie, LV ejection fraction) has been well established as a strong independent predictor of outcomes in all cardiac patients. It is especially evident in patients with coronary artery disease in whom LV dysfunction is manifest in congestive heart failure symptomatology. The Coronary Artery Surgery Study registry firmly established that benefits of coronary artery bypass surgery were more pronounced in most patients with moderate-to-severe depression of global ejection fractions (Fig. 10-9). In fact, in this patient population, upwards of 40% of the patients will have significant improvements in their ejection fraction over time following coronary vascularization presumably secondary to the presence of hibernating but viable myocardium. Given these findings, all patients with coronary artery disease and severe LV dysfunction are evaluated for possible revascularization.
When combining data from noninvasive assessment of LV function with invasive angiography, Gimelli et al\textsuperscript{8} compared the predictive ability of this assessment by echocardiography, ventriculography, and nuclear perfusion imaging. Within their study population, clinical factors such as age, sex, history of angina, and previous infarction were shown to have a good prediction of patient survival ($\chi^2 = 35.7$). Ejection fractions as assessed by echocardiography ($\chi^2 = 38.8$) or ventriculography ($\chi^2 = 39.9$) were also highly predictive of survival, but not dramatically different than by using the clinical features alone. However, the investigators found that nuclear perfusion imaging–derived ejection fraction predicted survival the best ($\chi^2 = 40.6$, $P = .039$ vs other models using likelihood ratio test). Thus, operators
must take into account clinical variables, as well as ejection fraction if available from noninvasive imaging or from ventriculography, in assessing clinical treatment options in patients with coronary artery disease.

As suggested by the Bypass Angioplasty Revascularization Investigation (BARI) study, diabetic patients with LV dysfunction associated with 2- or 3-vessel coronary artery disease remain best treated by coronary artery bypass surgery compared to percutaneous coronary intervention (Fig. 10-10). Furthermore, decreased LV function has been proven to be an independent negative risk predictor for patients undergoing percutaneous revascularization or coronary artery bypass grafting.

### FIGURE 10-10
Seven-year follow-up data from the Bypass Angioplasty Revascularization Investigation (BARI) trial showing better outcomes associated with coronary artery bypass surgery (CABG) in patients with impaired left ventricular (LV) function. PTCA, percutaneous transluminal coronary angioplasty; TDM, treated diabetes mellitus. (Reproduced with permission from The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol.* 2000;35:1122.)

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11 Operational Radiation Management for Patients and Staff
12 Computed Tomography of the Coronary Arteries
13 Intracardiac Echocardiography in the Catheterization Laboratory
14 Cardiac Catheterization Laboratory Physiologic Recorders
INTRODUCTION

Fluoroscopic radiation is a carcinogen that can also cause severe injury (“radiation burns”) in patients and practitioners. Figures 11-1 through 11-4 illustrate the severe effects of radiation. All effects pictured were caused by radiation associated with fluoroscopy. Note the characteristic demarcation of injuries with sharp borders, a feature usually but not always associated with severe radiation effects from fluoroscopy.
**FIGURE 11-1** Breast cancer and skin injuries induced by fluoroscopically guided intervention for pulmonary tuberculosis. (Adapted with permission from MacKenzie I. Breast cancer following multiple fluoroscopies. *Br J Cancer*. 1965;19:1-8.)

Figure 11-1 is a breast cancer caused by fluoroscopically guided interventional procedures performed to cure pulmonary tuberculosis in the mid-20th century. Chronic radiation dermatitis is also readily apparent in this picture, taken in the 1960s approximately 10 to 15 years after exposure to the radiation.

Figure 11-2 shows a deep necrotic wound following 2 ablation procedures 6 and 10 months previously. The ribs underlying the wound necrosed at about 4 years after the procedure. Advances in cardiac mapping during electrophysiologic procedures have mitigated the need for long-duration fluoroscopy and have reduced the likelihood of such effects in these patients.
FIGURE 11-2 Deep skin wound following 2 ablation procedures separated by 4 months and having occurred 6 and 10 months previously. Wound progressed into deep tissue necrosis and osteoradionecrosis of the ribs, shown approximately 4 years after procedures. (Copyright retained by patient and figure reproduced with permission.)

Figures 11-3 and 11-4 are skin injuries in patients who underwent fluoroscopically guided invasive cardiologic procedures. The patient in Figure 11-3 underwent coronary angioplasty and stent placement involving 63 minutes of fluoroscopy and about 5000 frames of cine fluorography. The affected skin area required a full-thickness graft. The patient in Figure 11-4 underwent a prolonged procedure for coronary artery intervention. Both cases involved x-ray irradiation with the x-ray beams oriented in a fixed trajectory for long periods of time, resulting in very high doses to the affected areas.

FIGURE 11-3 Injury following percutaneous transluminal coronary angioplasty (PTCA) and stent placement involving 63 minutes of fluoroscopy and nearly 5000 frames of cine. This left anterior oblique (LAO) view with cranial tilt resulted in a large entrance dose build-up in the lower right back. The injury required grafting. (Adapted with permission from Wagner LK. Radiation dose management in interventional radiology. In: Balter S, Chan R, Shope T, eds. Interventional Brachytherapy—Fluoroscopically Guided Interventions (American Association of Physicists in Medicine Monograph #28). Madison, WI: Medical Physics Publishing; 2002;195-218.)
The first radiation injury related to interventional cardiology occurred in 1990. By September 1994, the US Food and Drug Administration (FDA) had issued a warning to physicians and healthcare providers about occasional but severe radiation injuries in patients undergoing certain fluoroscopically guided interventional procedures. The warning described the nature of these injuries and provided numerous recommendations on how to avoid them. Many, but not all, of those recommendations are addressed in this chapter.

The FDA has since retired this warning, but their recommendations to physicians and facilities regarding the need to pursue a high level of quality radiation management for medical procedures remains and is available on their website (http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/Rays/ucm115354.htm#imagingteam). In the years since the FDA warning, hundreds of serious radiation-induced injuries have occurred. Many have been reported in the medical literature.2,3,5-15

Many medical practitioners of the 20th century accumulated considerable
radiation doses during their medical practice and developed radiation-induced cancer, cataracts, or skin injury. The modern interventional radiation environment creates conditions conducive to the accumulation of high doses in personnel. Attention to rigorous radiation abatement measures is therefore warranted and required.

When fluoroscopy is well managed, the likelihood that these severe effects could occur is extremely low. However, when it is not well managed, the carcinogenic risk to both personnel and patient is higher than necessary, and the risk for injury to the patient increases. The goal of this chapter is to discuss factors involved in the careful management of fluoroscopic and fluorographic radiation.

**QUANTIFICATION OF RADIATION LEVELS**

No discussion of radiation management is meaningful without a clear understanding of the quantities used to measure or describe radiation levels. In particular, a well-honed understanding and use of the concepts of air kerma, absorbed dose, equivalent dose, effective dose, and dose area product are essential. Table 11-1 summarizes the relevant quantities.

| **Table 11-1** Relevant Radiation Quantities |
Air kerma relates to how much radiation is present at a specific location. The presence of x-rays at any location can be measured by analyzing the ionization they produce in air at that location. Because energy must be transferred to create ions in air, air kerma is defined as the concentration of energy released by the x-rays in air. The special unit of air kerma is the gray (Gy) or milligray (mGy). One gray of air kerma is the same as 1 joule of energy released in 1 kilogram of air. One manufacturer sometimes reports air kerma in units of microgray (μGy). Air kerma is used to monitor and manage

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units of Measurement</th>
<th>What It Is</th>
<th>What It Measures</th>
<th>Why It Is Useful</th>
<th>Conversion Between Old and New Units</th>
</tr>
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<tbody>
<tr>
<td>Absorbed dose</td>
<td>Gray (Gy) or milligray (mGy) (rad or millirad [mrad])</td>
<td>The amount of energy locally deposited in tissue per unit mass of tissue</td>
<td>Measures concentration of energy deposition in tissue</td>
<td>Assesses the potential biologic risk to that specific tissue</td>
<td>100 mrad = 1 mGy 1 rad = 10 mGy</td>
</tr>
<tr>
<td>Effective dose</td>
<td>Sievert (Sv) or millisievert (mSv) (rem or millirem [mrem])</td>
<td>An attributed whole-body dose that produces the same whole-person stochastic risk as an absorbed dose to a limited portion of the body</td>
<td>Converts any localized absorbed or equivalent dose to a whole-body risk factor</td>
<td>Permits comparison of risks among several exposed individuals, even though the doses might be delivered to different sets of organs in these individuals</td>
<td>100 mrem = 1 mSv 1 rem = 10 mSv</td>
</tr>
<tr>
<td>Air kerma(^a)</td>
<td>Gray (Gy) or milligray (mGy) (rad or millirad [mrad])</td>
<td>The sum of initial kinetic energies of all charged particles liberated by the x-rays per mass of air</td>
<td>Measures the amount of radiation at a point in space</td>
<td>Assesses the level of hazard at the specified location(^b)</td>
<td>100 mrad = 1 mGy 1 rad = 10 mGy</td>
</tr>
<tr>
<td>Equivalent dose(^c)</td>
<td>Sievert (Sv) or millisievert (mSv) (rem or millirem [mrem])</td>
<td>A dose quantity that factors in the relative biologic damage caused by different types of radiation</td>
<td>Provides a relative dose that accounts for increased biologic damage from some types of radiations</td>
<td>The most common unit used to measure radiation risk to specific tissues for radiation protection of personnel(^d)</td>
<td>100 mrem = 1 mSv 1 rem = 10 mSv</td>
</tr>
</tbody>
</table>

\(^a\)The physician should be aware that air kerma can be presented in two separate ways. Incident air kerma is the kerma to air from an incident x-ray beam measured on the central beam axis at the position of the patient and excludes backscattered radiation. Entrance surface air kerma is the kerma to air from an incident x-ray beam measured on the central beam axis at the position of the patient with backscattered radiation included. The two may differ from each other by as much as 40%.

\(^b\)Exposure and air kerma are both used for the same purpose. Exposure used to be the most common measure, but with the switch to international units, air kerma is the preferred unit.

\(^c\)For x-rays, gamma rays, and electrons, there is no difference between absorbed dose and equivalent dose (ie, 1 mGy = 1 mSv). This is not the case for neutrons and alpha particles, but these radiation types are not relevant to x-ray exposure. The important issue is that cardiologists recognize that for their interests, there is no practical difference between a measurement of mGy and that of mSv.

\(^d\)Adapted from Hirshfield JW, Balter S, Brinker JA, et al. ACCF/AHA/HRS/SCAI clinical competencies statement on optimizing patient safety and image quality in fluoroscopically guided vascular interventions: A report of the American College of Cardiology/American Heart Association/American College of Physicians Task Force on Clinical Competence (ACCF/AHA/HRS/SCAI Writing Committee to Develop a Clinical Competence Statement on Fluoroscopy). J Am Coll Cardiol. 2004;44:2259. Copyright © 2004 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.
radiation delivery to patients, as discussed later.

Instantaneous air kerma and cumulative air kerma differ only in the temporal interval or sequence over which all air kerma is delivered. When air kerma is measured at some reference position in space, the air kerma is said to be instantaneous if it is measured over a short interval of time, usually on the order of seconds or less. When multiple short radiation exposures occur or when several long exposures occur, the cumulative air kerma is the summation of all air kerma measurements over the entire procedure time.

**Absorbed Dose**

Absorbed dose is used to assess the potential risk for stochastic and deterministic effects in specific tissues. *Absorbed dose* is the concentration of radiation energy transferred to and absorbed by a particular tissue. Specifically, as x-rays pass through tissues, they interact with the biologic matter, and this transfers energy that causes molecular changes. These changes can potentially lead to biologic effects. Assessing the concentration of energy deposited in the specific tissue provides a measure of the amount of biochemical disruption, and thus a measure of risk for biologic effects. The special unit of absorbed dose is the gray, and 1 Gy is the same as 1 J of energy concentrated in 1 kg of tissue.

Absorbed dose and air kerma are measured in the same units of gray, but they are not the same thing. There is no fixed relationship between the two, but there are some rules of thumb. For instance, the absorbed dose to the skin of a patient is about 40% greater than the air kerma at the location of the skin when the air kerma is measured under the same radiation output conditions but without the patient present.

**Equivalent Dose**

*Equivalent dose* is an estimate of the biologic potency that a particular radiation might have for an absorbed radiation dose delivered by that radiation. Equivalent dose is the quantity usually quoted in radiation safety reports for doses to the hands or to the eyes of personnel. For radiations other than x-rays, equivalent dose can be quantitatively greater than the absorbed dose and is specified in units of sievert (Sv) or millisievert (mSv). Because cardiologists do not apply other types of radiation during interventional work,
this quantity is used solely to communicate radiation safety doses. For our purposes in interventional cardiology, 1 Sv of equivalent dose is the same as 1 Gy of absorbed dose. (It should be remembered that this is not true for other specialties, like radiation therapy, where neutron radiation might be used.) Thus, *equivalent dose* is a radiation safety term that, for our purposes, carries the same risk as the absorbed dose in gray.

Many radiation safety reports for personnel exposures still use outdated units of *millirem*. To convert the dosimetry to units of millisievert, just divide the value in millirem by 100. That is, 100 millirem are equal to 1 millisievert.

**Effective Dose**

*Effective dose* is used to relate the potential for stochastic risk to an individual from an exposure to radiation, regardless of the spatial nonuniformities of the exposure. For example, interventionalists wear lead aprons to protect themselves. When an interventionalist is exposed in the laboratory, the arms, legs, and head are not as well protected from radiation as are the internal organs under the apron. Therefore, the spatial distribution of the radiation throughout the interventionalist’s body is very nonuniform. This is permitted because the exposed limbs and head are not as radiosensitive as thoracic and abdominal organs. The risk associated with such an exposure is not well specified by absorbed dose because low-sensitivity limbs receive a much higher dose than sensitive organs in the thorax and abdomen.

Effective dose attempts to remove this complexity in risk assessment. Effective dose is a hypothetical dose that would have to be delivered uniformly to an interventionalist’s entire body to yield the same numerical risk for stochastic effects as the nonuniform dose actually delivered. Thus, as a hypothetical uniform whole-body dose, effective dose is a risk descriptor that permits us to compare the risk associated with any type of nonuniform exposure to that of any other nonuniform exposure.

Derivation of effective dose from the nonuniform exposure is complex and not within the scope of this chapter. (For a more complete description, see the International Commission on Radiological Protection Report No. 103 entitled “The 2007 Recommendations of the International Commission on Radiological Protection.”[22]) The important thing to know is that effective dose allows assessment of stochastic risks from nonuniform dose deliveries. The special unit of effective dose is the sievert or millisievert. In cardiology,
any effective dose measured in units of millisievert may be considered to be the same as a hypothetical uniform whole-body absorbed dose of x-rays assigned the same numerical value but quoted in units of milligray. That is, an effective dose of 1 mSv in cardiology is the same as a uniform whole-body absorbed dose of 1 mGy.

**Air Kerma Area Product (or Dose Area Product)**

Air kerma area product (KAP) and dose area product (DAP) are the same thing because air kerma from cardiologic-type x-rays and the absorbed dose to air (as opposed to the absorbed dose to tissue) are the same thing. This quantity is used to assess the total stochastic risk to patients from x-rays. It is the multiplicative product of the beam area at entrance to the patient and the free-in-air air kerma located at the entrance surface of the patient. “Free-in-air” means the measurement is made as if the patient were not present. This means that the measurement is not enhanced by radiation scattered back into the area by the presence of a patient. KAP, therefore, is an indirect measure of the total number of x-rays that entered the patient. This makes it an indicator of stochastic risk to the patient.

DAP has no relevance for radiation exposure to personnel.

**Rates and Accumulation of Radiation**

All of the previous dose and kerma descriptors can be assessed as an instantaneously delivered amount or as an amount accumulated over time. The rate at which radiation is delivered can also be of importance, as, for example, air kerma rate, which is measured in units of milligray per minute (mGy/min). These concepts should be clear in the context of any discussion on dose or air kerma.

**MONITORING DOSE**

Dose delivery is monitored for both patients and personnel.

**Monitoring Doses to Personnel**
Personal radiation monitors are used to assess the cumulative amount of radiation to which an individual is exposed during the course of their work. Measurements of cumulative radiation exposure are made over intervals of months. Typically, the primary personal radiation monitor should be worn at the collar outside the lead apron. Some states might require that 2 monitors be worn, one outside and the other under the lead apron. All personal radiation exposures are reported in terms of equivalent dose or effective dose. The unit primarily used in the United States is the millirem, where 1 mrem is the same as 0.01 mSv.

Personal radiation monitoring is a serious business. It is an essential tool in assuring healthy working habits around radiation. A rule of guidance is that the annual effective dose to interventionalists from exposure to stray fluoroscopic or angiographic radiation should not exceed 20 mSv and, by regulation, must not exceed 50 mSv. If your monitor suggests you are exceeding the 20-mSv effective dose per year, then remedial action should be taken to try to reduce this dose accumulation.

Doses to extremities can also be monitored using extremity monitors that come in a variety of forms. Monitors attached to rings can be worn on a finger. These ring monitors can be sterilized using a hydrogen peroxide vapor technique. Ring badges are an important monitoring device if the hands get close to the radiation field. This might be the case, for example, for physicians assisting in transcatheter aortic valve replacement procedures.

**Monitoring Doses to Patients**

All modern cardioangiographic units have built-in monitors to help assess dose delivered to the patient. Since 2006, the air kerma and air kerma rate at a reference point must be displayed for the physician to see.

Monitoring radiation delivery to patients has many advantages. It provides useful information about radiation risks to your patients; it provides highly effective quality improvement data; and it can be applicable during a prolonged procedure, when dose buildup can be substantial and dose abatement steps may be necessary.

There are several types of monitors, including monitors that measure cumulative air kerma at a standard point located at a fixed distance from the x-ray source, cumulative KAP monitors (also known as *DAP meters*), and dose mapping monitors.
Cumulative Air Kerma at the Intervventional Reference Point

The interventional reference point (IRP) is located 15 cm from isocenter along a line between the x-ray source and the isocenter of the C-arm (Fig. 11-5). (The isocenter is the point in space about which the imaging system rotates, and an object at that point remains in the center of the image regardless of beam rotation.) The IRP roughly approximates the position of the skin where the beam enters the patient. Figure 11-5 demonstrates the location of this reference point. The measure of cumulated air kerma at this position in space is highly useful as a quality control device and as a guide to manage procedures. Almost all modern machines measure and record this quantity.
FIGURE 11-5 Location of the interventional reference point (IRP; indicated by the dark rectangle marked IRP). This point is located along a line from the x-ray source to the image receptor and 15 cm from the isocenter (dot in figure) of the C-arm in a direction toward the x-ray tube. As the C-arm is rotated, the IRP rotates with it. Although the IRP is representative of the entrance skin site, for some beam orientations and patient positions, it is located a distance from the actual skin site. Thus, the cumulative dose at the IRP might over- or underestimate the true cumulative skin dose. This dose reference must therefore be used only as a guide for patient care and not as an absolute measure of risk to the skin. (Adapted with permission from Hirshfeld JW, Balter S, Brinker JA, et al. ACCF/AHA/HRS/SCAI clinical competence statement on optimizing patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures: a report of the American College of Cardiology/American Heart Association/American College of Physicians Task Force on
Because the cumulative air kerma is measured at a point fixed relative to the source, 3 things must be kept in mind when using it. First, as an accumulation monitor, it adds up all the radiation produced by the source, regardless of beam orientation. This fact means that radiation dose to a single skin site might be overestimated. Second, at any one skin site, the actual skin dose is about 40% greater than the cumulated entrance air kerma; thus, the cumulated air kerma might render an underestimated impression of the true skin dose. Third, the reference point is only an approximation of the position of the skin, and the true entry site might be closer to or further away from the x-ray tube, rendering an over- or underestimation of the true skin dose. Thus, the cumulative air kerma is not an exact measure of skin-absorbed dose and can only be used as a rough guide to assess the risk to skin when procedures are prolonged and doses are high. Regardless of these difficulties, dose at the IRP is a highly useful tool to assist the physician in management of the patient’s skin dose.

For example, guidelines might be established to assist the physician during a procedure. It might be useful, for example, to establish a 2-4-6-8 rule for management. If the reference accumulation air kerma reaches 2 Gy, then the physician is advised that dose is building and that this is an “FYI” so that the physician knows the pace of radiation buildup. The threshold for transient erythema (Table 11-2) may have been breached, but transient erythema is not a significant health concern. At 4-Gy air kerma, the physician is advised again and now knows that the threshold of skin erythema (as opposed to transient erythema; see Table 11-2) might have been reached if the beam was not reoriented and if the IRP is inside the skin surface. At 6-Gy air kerma, the potential for skin erythema is higher, and actions to abate the risk might be an important consideration. At 8-Gy air kerma, the risk of skin injury is an important possibility, especially if there was no beam reorientation earlier and the same skin site is being dosed. The purpose of this is to assist the physician in making the appropriate benefit-risk decisions for the patient and in managing the patient after the procedure. Other recommendations by national organizations are available.23

Table 11-2 Tissue Reactions from Single-Delivery Radiation Absorbed Dose to Skin of Neck, Torso, Pelvis, Buttocks, or Arms
Kerma Area Product and Dose Area Product Meters

A full discussion of use of a KAP meter to monitor patient absorbed skin dose is beyond the scope of this chapter. Recall that KAP is the product of the air kerma at a position in space and the area of the beam at that position. With distance from the source, beam area naturally increases and air kerma naturally decreases in identically compensating manners. The product of these two entities is, therefore, theoretically the same at all positions along the unobstructed accessible beam. It is primarily a quality control tool and is not a very useful monitor of dose to the skin of a patient, although that task is possible. A medical physicist is usually employed in any attempts to use such

<table>
<thead>
<tr>
<th>Band</th>
<th>Single-Site Acute Skin-Dose Range (Gy)</th>
<th>NCI Skin Reaction Grade</th>
<th>Approximate Time of Onset of Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0–2</td>
<td>NA</td>
<td>Prompt: No observable effects expected; Early: No observable effects expected; Midterm: No observable effects expected; Long Term: No observable effects expected</td>
</tr>
<tr>
<td>A2</td>
<td>2–5</td>
<td>1</td>
<td>Prompt: Transient erythema; Early: Epilation; Midterm: Recovery from hair loss; Long Term: No observable effects expected</td>
</tr>
<tr>
<td>B</td>
<td>5–10</td>
<td>1–2</td>
<td>Prompt: Transient erythema; Early: Erythema, epilation; Midterm: Recovery; Long Term: Recovery; at higher doses, prolonged erythema, permanent partial epilation</td>
</tr>
<tr>
<td>C</td>
<td>10–15</td>
<td>2–3</td>
<td>Prompt: Transient erythema; Early: Erythema, epilation; possible dry or moist desquamation; recovery from desquamation; Midterm: Prolonged erythema; permanent epilation; Long Term: Telangiectasia; dermal atrophy or induration; skin likely to be weak</td>
</tr>
<tr>
<td>D</td>
<td>&gt;15</td>
<td>3–4</td>
<td>Prompt: Transient erythema; after very high doses, edema and acute ulceration; long-term surgical intervention likely to be required; Early: Erythema, epilation; moist desquamation; Midterm: Dermal atrophy; secondary ulceration due to failure of moist desquamation to heal; surgical intervention likely to be required; at higher doses, dermal necrosis, surgical intervention likely to be required; Long Term: Telangiectasia; dermal atrophy or induration; possible late skin breakdown; wound might be persistent and progress into a deeper lesion; surgical intervention likely to be required</td>
</tr>
</tbody>
</table>

Note—Applicable to normal range of patient radiosensitivities in absence of mitigating or aggravating physical or clinical factors. Data do not apply to the skin of the scalp. Dose and time bands are not rigid boundaries. Signs and symptoms are expected to appear earlier as skin dose increases. Prompt is ≤2 weeks; early, 2–8 weeks; midterm, 6–52 weeks; long-term, >40 weeks.

*Skin dose refers to actual skin dose (including backscatter). This quantity is not the reference point air kerma described by Food and Drug Administration (21 CFR § 1020.32 [2008]) or International Electrotechnical Commission (57). Skin dosimetry is unlikely to be more accurate than ± 50%. NA = not applicable.

†NCI = National Cancer Institute

§Refers to radiation-induced telangiectasia. Telangiectasia associated with area of initial moist desquamation or healing of ulceration may be present earlier.

a device for management of skin doses to patients. The National Council on Radiation Protection and Measurements also provides recommendations on how to use KAP as a skin dose monitor.\textsuperscript{23}

**Skin Dose Mapping**

Skin dose mapping (Fig. 11-6) provides explicit diagrams showing the accumulation of dose to specific skin sites of a patient. This dose monitor takes the guesswork out of accumulation of skin dose during procedures. It accounts for a wide variety of factors that are not accounted for by the previously discussed dose monitors. These factors include beam orientation, scattered radiation, location of the entrance skin site from the x-ray source, table attenuation of radiation, and other factors. It is the preferred method for monitoring dose to a patient because it is the best assessment of skin dose in real time. This monitoring is visually enhanced by a patient contour map showing how dose is distributed around the patient as the beam is rotated (see Fig. 11-6).
FIGURE 11-6 Example of a skin dose map displaying different levels of irradiation at various skin sites on patient’s back. (Image courtesy of and reproduced with permission from Dan Bednarek, PhD, University of Buffalo, New York.)

RADIATION EFFECTS

Health effects of radiation are commonly separated into 2 categories: stochastic and deterministic.

Stochastic Effects

Stochastic effects involve alterations in single cells that render them adversely functional. Alterations of important macromolecules can conceivably result from a single interaction with radiation. Therefore, these effects probably occur at any radiation dose level, although they are extremely unlikely to occur at very minimal levels. The two prominent
stochastic effects are radiation-induced neoplasm and heritable changes in reproductive cells. The likelihood of their occurring increases as dose increases, and induced cancer becomes measurable in exposed adult populations at doses in excess of about 100 mSv.\textsuperscript{24} In children and in the fetus, lower doses have been implicated as carcinogenic.\textsuperscript{25} Although genetic effects heritable by progeny have been observed at high doses in animal studies, bona fide genetically heritable effects have never been observed in humans.

**Deterministic Effects**

Deterministic effects are the result of damage to many cells. Examples are skin erythema, depilation, and vision-impairing cataract. Because the effect results from changes in multiple cells, a certain minimal level of radiation damage is necessary before the effect can occur. This is referred to as the threshold dose. As dose increases beyond the threshold, the severity of the effect increases. The most familiar examples of this are effects in the skin. Table 11-2\textsuperscript{26} lists various effects of large doses to the skin. Note how the severity increases as dose increases. Variations on sensitivities occur for different skin sites, and there are also variations among individuals due to differences in health of the skin, medications that the patient is taking, and other factors.\textsuperscript{23,26}

The threshold for radiation-induced cataract is now known to be lower than previously believed.\textsuperscript{27} Radiation may have subtle or progressively worsening effects on vision, and only careful attention to radiation management can avoid them or reduce their severity.

**Temporal Patterns of Radiation Effects**

For both stochastic effects and deterministic effects, there is a delay between irradiation and the detection of a change. For neoplasms, delays may be as short as two years or as long as many decades. For deterministic effects in the skin, the delay is typically many days to weeks before erythema develops and is likely to be weeks to months before inflammation or necrosis develops. The delays provided in Table 11-2 are relevant to effects occurring following acute threshold doses. Delays vary depending on skin sensitivity, dose level,
and rate of accumulation of dose. The transient form of erythema can occur within 24 hours, but this does not always occur and usually goes unnoticed. It may sometimes be confused with erythema resulting from electrosurgical pads.

An important fact is that a fluoroscopy-related “burn” is markedly unlike that of a thermal burn. Thermal insults are readily recognized by conscious individuals, and immediate measures can be taken by them to defend against further injury. With medical radiation, there is no sensation that forewarns of an injury; the first signs that an injury has been induced usually do not occur until the procedure has been long over. Therefore, physicians cannot rely on any signal from the patient that a burn is occurring. In contrast to an injury from fluoroscopy, the progression of a thermal burn occurs within a short time after the injury (days), and the extent of medical care necessary for treatment can be readily determined soon afterward. For a fluoroscopic radiation injury, the progression of the injury is slow (months), and early interventions often fail because of residual injury that has yet to manifest itself. Prevention of these painful and slowly developing injuries is clearly an important goal. Proper radiation management with fluoroscopic equipment requires a knowledgeable application of the effective and careful use of radiation to keep risk of skin injury at bay. The strategic use of radiation monitoring devices is a valuable resource in achieving this goal.

DESIGN STRATEGIES TO LIMIT EXPOSURE TO RADIATION

Room Design

The primary feature of room design is space. Large rooms (~60 m² with ~15 m² control room) are preferred for many reasons, one of which is radiation management for personnel. Only a large room is conducive to maximal effective use of distance and shielding. Satisfactory space is required at ceiling level for suspended shields and other equipment. At floor level, space is required for mobile shields that are often used to protect in-room personnel who remain positioned at a single station during the procedure. Because dose decreases rapidly with distance, a large room provides the opportunity for
personnel to attend to their duties at a healthy distance from the source of radiation, which is primarily the patient, while remaining readily available to attend the patient when necessary.

**Equipment Design**

Cardioangiographic equipment is some of the most sophisticated and complex equipment used in medicine. To effectively perform procedures, at least 3 essential factors must be in place: (1) the equipment must be properly designed for the procedures; (2) the equipment must be well maintained; and (3) the users must be well trained in the use of their specific equipment. Training is related both to the technical aspects for the efficient and effective completion of a procedure and to the proper deployment of available dose-management features. These features differ from machine to machine, and important differences can exist, even for two machines that appear to be identical. Although we review general principles of operation of equipment, understanding and effectively using specific features are the responsibility of the operator.

**Fundamental Aspects of Image Production**

Fluoroscopy systems produce images by generating a beam of x-rays, transmitting the beam through the patient, and capturing the residual transmitted beam at the other side of the patient to render an image. The x-rays emanate from a point of origin inside the x-ray tube and fan out in all directions from the source. The housing of the x-ray tube is designed to permit only those that travel toward the patient to escape their enclosure (Fig. 11-7).\(^{28}\) (A small number of x-rays do escape the housing, but by regulation, this is less than 1 mGy/h at 1 m when operated at maximum continuous output. The actual leakage is typically less than this.)
X-rays are produced in all directions, but shielded housing stops most of the x-rays from penetrating the encasement. Only the beam that is directed toward the patient is permitted to escape at imaging intensities.

**FIGURE 11-7** X-ray production. X-ray photons are produced from a very small area (~1 mm$^2$) inside the x-ray housing. The housing is shielded to keep radiation levels below limits set by regulation. The beam that emerges from the imaging port is made up of x-rays that fan out in a diverging pattern, resulting in a beam that increasingly widens with distance and correspondingly decreases in intensity. (Adapted with permission from Louis K. Wagner, PhD.)

X-ray radiations are individual particles of pure energy called *photons*. They travel at the speed of light, and their path is a straight line, unless they interact with something in their way. Interaction is critical to the imaging process. **Figure 11-8** shows that a beam of evenly distributed x-rays enters the patient. There is no effective pattern to the x-ray beam at this point. As the beam passes through the patient, many of the x-rays interact with atoms and molecules of the tissues. This interaction either removes them or redirects them away from their place in the beam. Interactions of other photons continue until there emerges from the patient a residual beam of undisturbed x-rays. At this point, because of the interactions that previously took place, the beam is now very nonuniform, and this nonuniformity is the x-ray image. Only a small percentage (~1%-3%) of the original beam makes it through to exit the typical adult patient.
FIGURE 11-8 Image production. Demonstrated is how the uniform x-ray beam is transformed into an x-ray image as the beam passes through the patient. A diagram of a cross-sectional image of the patient is shown at top. A uniform beam of x-rays enters the patient. Due to anatomical structures in the paths of x-rays, many x-rays are eliminated from the beam as they pass through the patient. The residual nonuniform beam at exit from the patient is the image. A similar cross-section of the chest depicted at top is highlighted in the chest image below. (Adapted with permission from Louis K. Wagner, PhD.)

Controlling Beam Energy (kV and Filters)

Not all x rays are the same; and in fact, the x-ray beam is initially composed of a mix of useful and useless x-rays. The energy of an x-ray determines its usefulness because the energy determines the likelihood for interaction processes that create the image. Only a small portion of the x-rays that are produced are appropriate for cardiologic procedures. The two major factors that control the energy characteristics of the x-ray beam are kV and filtration. The kV is the electric potential that determines the energies of the x-rays. The kV can vary from about 60 kV to about 120 kV, sometimes up to 140 kV. This is necessary to control beam penetration and image quality for various sizes of patients and imaging tasks. The filtration is comprised of thin sheets of materials like aluminum or copper that selectively removes unnecessary x-rays from the beam. These metal filters are placed at the x-ray tube portal so that they stop the unnecessary x-rays before they escape the tube housing to expose the patient. Although some useful x-rays are also removed by the filters, the net result is an x-ray beam with a better mix of x-ray energies. Filtration is often adjustable for the same reasons that kV is adjustable. The goal is to produce an x-ray beam that results in an excellent compromise between appropriate image quality and acceptably low radiation dose to the patient. Some equipment does this better than others.

While removing unnecessary x-rays from the beam, the filtration process also reduces the useful beam intensity. To compensate for the reduced intensity, the x-ray tube must operate at higher production rates. This results in generation of a considerable amount of heat that stresses the tube. Manufacturers therefore put a great deal of consideration into tube design so that tubes can withstand or circumvent the stress of well-filtered x-ray production. Some x-ray tubes are better engineered than others; and inevitably, good engineering adds to cost.
In addition to permanent filtration that is typically equivalent to about 5 mm of aluminum, all angiocardiologic equipment should use x-ray tubes with heavily filtered x-ray sources. An option of filters should be available, typically in tenths of millimeters of copper (eg, 0.1, 0.2, or 0.3 mm). How the filters are used may differ among different machines and manufacturers. Many manufacturers incorporate filters into different dose-management schemes. The particular filter incorporated into a procedure is often decided by the dose-management option selected by the user and is also based on the mass of tissue that the beam must penetrate. Typically, thicker filters are reserved for small patients, whereas the thinnest filters are used on the largest patients. During cine fluorography (also known as cineangiocardiography, or “cine” for short), thin filters are often used because the beam intensity must be high during the acquisition. Although the user selects a dose-management scheme that influences how filters are deployed, the machine assumes control over selection of filters during the procedure.

**Variable Pulsed Fluoroscopy**

The reproduction of motion is controlled by the dynamics of fluoroscopic and cine imaging. The perception of motion is achieved by displaying in rapid succession a sequence of distinct still images, each of which represents the same scene at a progressively different moment in time. Each static image is separated from the previous image by a very short moment. The fidelity of the motion improves with shorter time intervals between images. This principle applies to fluoroscopy as well as to cine.

Most people perceive continuous motion when about 30 images per second are displayed. This rate has been a standard in the United States for the entertainment industry. However, in cardiology, the goal is not to entertain, but to use the imaging system as a tool to assist in the advancement of a catheter along a lumen. To accomplish different tasks, the necessary number of distinct images captured per second is variable. This is true for fluoroscopy as well as for serial imaging such as digital angiographic runs or cine. Choosing an adequately low image capture rate is one of the most effective user-selectable ways to limit utilization of radiation.

In fluoroscopy, the image capture rate is often called the **pulse rate**. For recorded dynamic imaging, it is often called the **frame rate**. In all modern cardiology units, each fluoroscopic image is captured using a very short pulse
of radiation (~3-15 ms). The use of short pulses is necessary to stop the action in each image. Longer pulses result in significant motion blur. Each pulse of x-rays results in one image, and the pulse rate is therefore identical to the image capture rate. Between pulses, no radiation is produced. If 30 images are captured per second, fluidity in motion is perceived, but the radiation utilization might be excessive for the task. If the pulse rate is reduced to 15 images per second, the motion might no longer appear completely fluid, but it is likely adequate for the task, and the radiation utilization is potentially reduced by 50%. For interventional procedures, a reduction in dose by 50% is substantial and could mean the difference between a severe skin reaction and no skin reaction for long procedures in large patients. For this reason, cardiologists should use the lowest pulse rate option for fluoroscopy and the lowest frame rate option for any fluorography (serial imaging such as digital angiography or cine) that is adequate for the efficient and effective completion of a procedure. (A word of caution: Not all machines or modes of operation are set up for dose-reduction options when changing the pulse rates in fluoroscopy. Users must understand what occurs when different fluoroscopic pulse rate options are used for their specific equipment.)

**Dose-Rate Control**

The challenge in all radiologic imaging tasks is to reach the best compromise in radiation dose delivery and image quality. Dose-rate control is achieved in many ways as, for example, by adjusting pulse frequency, pulse width, tube current (mA), x-ray beam energy (kV), and filtration, only some of which are under the operator’s control. Selecting a lower pulse rate, as described earlier, is a method of operator-based dose-rate control. However, that method affects the temporal image display and has only an indirect effect on the appearance of noise due to dynamics of human vision, a concept that is beyond the scope of this chapter. The effects of noise are demonstrated in Figure 11-9. Pulse width, tube current (mA), x-ray beam energy (kV), and filtration have a more direct effect on the quality characteristics of each image because they affect the radiation level that produces the image.
Angiocardiographic machines are designed to operate in different dose-rate modes that affect image quality. The temptation might be to use the dose-rate mode that produces the best image quality, but this is inevitably the mode that results in the highest dose rate. The challenge to the cardiologist is to select the dose-rate mode that draws the most appropriate compromise between dose to the patient and adequate, but not excessive, image quality. Monitoring dose rate for each mode will be a topic of later discussion.

There are frequently at least 2 types of dose-rate controls for the fluoroscopic aspects of the procedure. The first type provides a selection of dose rates, none of which allow the unit to exceed standard limits on fluoroscopy output. The other type is an option that allows the unit to operate at up to twice the standard limit. These are explained next.

**Standard Limit on Dose-Rate Options**
The FDA places legal restrictions on the manufacture of fluoroscopes. For example, for angiographic equipment, the maximum output of the radiation...
in the standard fluoroscopic mode is restricted to less than 87.6 mGy air kerma per minute when tested at 30 cm from the image receptor. Standard dose-rate options for fluoroscopy that are selectable by the user all operate under this limit. However, each option has different operating characteristics to control image quality and dose rate to the patient.

Cardiologists can determine how different modes change output rates by observing the dose-rate indicator that is available on all machines manufactured after 2006. The cardiologist or an assistant can watch that indicator during fluoroscopy to see how it changes as different modes are selected during a procedure.

Physicians should familiarize themselves with these options and understand the consequences of each selection with regard to changes in dose rate as well as image quality. Select the option that provides the best balance between imaging needs and radiation use. Regardless of which level is selected, the output should not exceed the standard maximum.

**High-Level Fluoroscopy**
The FDA allows machines to be manufactured with a high dose-rate option for fluoroscopy. Units manufactured since 1995 may have a high-level option that restricts output to less than twice the standard maximum rate for fluoroscopy. This option can result in fluoroscopic entrance-skin dose rates in excess of 0.4 Gy per minute under some configurations of use. This is a particularly important option to understand because it is a special mode that enhances image quality by amplifying radiation dose rates to patients. For this option, a special means of selection must be available and a special sound must warn the operator that the high-level mode is engaged. Sometimes this sound is barely audible to the user. Therefore, users must be aware of this mode and know when it is engaged. The dose-rate monitor on the video screen will indicate this amplified dose rate.

High-level control should be used infrequently and only when special imaging detail is momentarily necessary.

**A Word About Governmental Regulation and Radiation Output**
One of the most common errors of logic is to assume that regulatory restrictions on radiation output render fluoroscopes safe for virtually unrestricted use. This most certainly is not true. The regulations apply only to fluoroscopy and only to a standard testing configuration that places the
entrance skin surface at 30 cm from the face of the image receptor for angiographic devices. It also excludes the effects of scattered radiation in elevating the actual rates. In addition, no restrictions on output exist for serial imaging modes such as cine.

Under normal cardioangiographic beam orientations, the skin of the patient where the beam enters is frequently much further away from the image intensifier than 30 cm, placing the patient closer to the source than what is assumed during compliance testing. This frequently means that the entrance air kerma at the true skin position can be in excess of 40% greater than that at the compliance testing position. The effects of scatter boost the actual skin-dose rate by another 30% to 40%. The combined results of these two factors mean that the actual dose rates to the skin during fluoroscopy can be a factor of two or more higher than the regulatory air kerma limit, which means more than 175 mGy per minute in the standard mode of operation. At maximum standard rate, a necrosing skin injury can occur in 100 minutes of fluoroscopy on-time, and this does not take into account the additional dose from cine. If we assume for the sake of discussion that half the dose to the patient is from fluoroscopy and half is from cine, then a necrosing skin injury can occur after about 50 minutes of standard fluoroscopy in large patients. This often surprises many physicians.

Maximum cine air kerma rates can exceed 1000 mGy per minute at the compliance point. The actual dose rate to the skin of the patient can be well in excess of 2000 mGy per minute. For 20 6-second cine runs, the skin dose from cine alone could be 4 Gy (4000 mGy). Under these circumstances, a procedure involving 80 minutes of fluoroscopy and 20 6-second cine runs focused over the same area could result in a skin necrosis. This is exactly what has occurred in many cases for which necrotic skin injury has been reported (eg, see Fig. 11-3). The actual skin dose rate depends on many factors, one of the most important of which is the amount of tissue mass that must be penetrated to produce an image.

PHYSICIAN-OPERATOR STRATEGIES TO LIMIT RADIATION RISK TO THE PATIENT
The important question now becomes, “What can be done to limit radiation risk?” There are many options for the physician to limit radiation risk. Most essential is that the physician be properly trained and experienced enough for the procedure and for dose management. Inexperienced personnel typically use more radiation to complete a procedure than do veterans. The expeditious completion of a procedure is a primary factor in the conservative use of radiation.

Radiation management for the patient has three phases: before, during, and after the procedure.

**Before the Procedure**

The first phase of patient management involves an assessment of the radiation risk for the patient. Small adult patients are at low risk for skin injury because of their size. Many factors work in their favor: image quality is usually high, radiation output rates are at their lowest, and good geometry is usually easier to achieve. Large patients with difficult lesions that require highly oblique beam orientations are at greatest risk for the opposite reasons.

Facilities should assess their procedures and decide under which conditions patient counseling on radiation risk should take place. This depends on the type of procedure, the size of the patient, the number of lesions, and perhaps the anticipated difficulty in treating the lesions.

A history of a previous interventional procedure should prompt a brief physical examination of the patient’s skin, particularly the back, to determine if there might be some residual evidence of radiation effects. A previous procedure might result in a weakened skin structure that could elevate the risk of serious skin effects from additional irradiation. If residual effects are noted, the cardiologist can try to avoid the injured site, and should advise the patient of this increased risk. In addition, patients with certain diseases, patients taking medications, or patients receiving treatments for other problems may be at elevated risk for adverse and perhaps severe skin reactions. It is thought, for instance, that patients with connective tissue disease, such as discoid lupus erythematosus, scleroderma, mixed connective tissue disease, or even rheumatoid arthritis, can be at elevated risk depending on factors related to their disease at the time of the radiation exposure. Patients with diabetes mellitus are also suspected to be at higher risk. Patients homozygous for ataxia telangiectasia and patients with Fanconi anemia,
among other conditions, are known to be at high risk.

The following is an example of counseling: “Your procedure uses x-rays, and in some cases, exposure can be prolonged. Although the vast majority of procedures do not demonstrate any adverse consequences associated with the radiation, there is a small risk that an adverse response could occur. There may be a slight elevation in cancer risk associated with this exposure. In addition, there is a risk that a skin rash may result from the radiation exposure. In rare cases, severe skin effects may occur, resulting in blistering, ulceration, and sores. These extremely rare events may require surgical correction.”

**During the Procedure**

Besides using equipment-related factors minimizing fluoroscopy time, minimizing intensity, and limiting the number and rate of serial imaging frames, other highly effective strategies can be used. These include considerations regarding beam orientation and patient setup, monitoring of dose, and a more subtle factor of avoiding the presence of unnecessary body parts in the beam.

**The Importance of Positioning**

Figures 11-10 and 11-11 demonstrate how dose rate to the patient can change with simple changes in the position of the patient relative to the image receptor and the x-ray tube. This occurs because the x-ray source originates in a diverging pattern from a small spot inside the x-ray tube and the beam intensity at the skin depends in a complex way on distances between that source and the patient’s skin as well as between the source and the image receptor and the patient and the image receptor.
FIGURE 11-10 Dose rate and position of the image receptor. A. The physician performs the procedure with the image receptor well above the patient. Dose rate to the patient is highest for this configuration. B. The physician performs the procedure with the image receptor closer to the patient than in A. This reduces dose rate from that of A. C. The physician moves the image receptor to as safe a proximity to the patient as is reasonable. This reduces dose rate to its lowest level due to the reduced x-ray output that is automatically adjusted by the machine as a result of the closer proximity of the image receptor to the source. Dose rate savings of 20% to 40% are very substantial and can result in a savings on the order of several grays of absorbed dose to a patient’s skin. (Adapted with permission from Wagner LK, Archer BR. Minimizing Risks from Fluoroscopic X-Rays. 5th ed. The Woodlands, TX: Partners in Radiation Management; 2014.)
FIGURE 11-11 Dose rate and position of the patient relative to the x-ray tube and the image receptor. A. The physician performs the procedure with the patient table elevated and the image intensifier close to the patient. B. The physician uses a lower table setting. Due to the closer proximity of the patient to the source, dose rate to skin of patient increases by about 40%. C. The physician uses an even lower table height. The skin dose to the patient is now approximately 60% higher than that to the patient in A. (Adapted with permission from Wagner LK, Archer BR. Minimizing Risks from Fluoroscopic X-Rays. 5th ed. The Woodlands, TX: Partners in Radiation Management; 2014.)

Distance of Image Receptor From Patient

Dose rate to the patient’s skin decreases as the image receptor (image intensifier or flat panel detector) is moved closer to the patient (see Fig. 11-10). This is because the machine controls output rate by monitoring the input rates to the image receptor. The machine tries to keep exposure rate to the imaging device relatively constant. As the image receptor moves closer to the patient, the machine senses that the input rate to the receptor increases due to the closer proximity of the receptor to the source. The machine therefore reduces output rate of the x-ray source to nullify this change and, because the patient did not move relative to the source, the entrance skin dose rate also decreases. Thus, a very important rule for dose management is to keep the image receptor as reasonably close to the patient as is safe for the procedure.
Position of Patient Between X-Ray Source and Image Receptor

A second rule, regarding the position of the patient’s skin relative to the x-ray source, might also apply. This rule is to keep the entrance site of the patient’s skin at a maximum practicable distance from the x-ray source. This rule has two components; one component regards the position of the table, and the other component regards the angular orientation of the imaging arm. We will address table height in this section and angular orientation in the next section.

When isocentric geometry is employed for cardiac imaging, the position of the table relative to the x-ray source is essentially predetermined. The isocenter is typically at a fixed distance from the x-ray source, and the table must be raised to the level where the heart is positioned at the isocenter. This applies only to machines for which the x-ray source is at a fixed position on the C-arm and has no independent capability for linear movement, as is true for the vast majority of machines.

However, when isocentric geometry is not used, the rule is to raise the table to a height that keeps the table at a distance as reasonably far from the source as is comfortable for the safe completion of the procedure. This rule is sometimes confusing because the output rate indicator on the monitor will increase as table height increases because the image receptor must also be moved further away from the source. However, as the table height increases, the entrance skin surface of the patient also moves further away from the source. Thus, there are two competing factors at play, and the net effect is that skin dose rate decreases as distance from the source to the skin increases. So, even though output rate increases as the patient and image receptor are moved further from the source, the dose rate to the entrance skin surface actually decreases. We explain this in further detail in Figure 11-11 and Figure 11-12.

Figure 11-11 illustrates the effects of different positions of the patient relative to the image receptor and x-ray source. The dose rate at the skin of the patient in Figure 11-11B is about 40% greater than that in Figure 11-11A, and dose rate at the skin of the patient in Figure 11-11C is about 60% greater than that in Figure 11-11A. This is all due to the diverging nature of the beam. The radiation output does not change by much as a result of these table height adjustments. As the skin gets closer to the source, all x-rays have to enter the patient in a smaller and smaller area. These percentage differences in dose rate translate into very large dose differences when procedures are prolonged. The changes in dose rates are less if the image receptor is moved...
closer to the patient, as shown in Figures 11-12B and 11-12C. However, due to closer proximity of the patient to the source, the dose rate to the skin is still greater than that in Figure 11-12A.

![Figure 11-12](image_url)

**FIGURE 11-12** Dose rate and position of the x-ray tube and image receptor. A. The physician performs the procedure with the patient table elevated and the image intensifier close to the patient. B. The physician uses a lower table setting but also moves the image receptor to a distance close to the patient. Due to the closer proximity of the patient to the source and due to the machine-adjusted output rate, dose rate to skin of patient increases by about 10%. C. The physician uses an even lower table height but continues to lower the image receptor to just above the patient. The skin dose to the patient is now approximately 20% higher than that to the patient in A. While the dose rate monitor will indicate lower output rates for B and C, the actual dose rate to the skin of the patient increases due to closer proximity of the patient to the source. (Adapted with permission from Wagner LK, Archer BR. *Minimizing Risks from Fluoroscopic X-Rays.* 5th ed. The Woodlands, TX: Partners in Radiation Management; 2014.)

**Patient Size and Beam Orientation**

Large patients are inevitably the patients at greatest risk for skin injury. Their size generates a large amount of image-degrading scatter that reduces contrast. Because of their size, a high-energy beam must be used to penetrate the body mass adequately, reducing contrast even further. Beam pulse time
might increase, which leads to motion blur. These imaging difficulties are obstacles that lead to an increase in procedure time. Also, large size alone means that radiation output is markedly increased over that of a thin patient. When lesions prove difficult to treat, doses can be extremely high.

X-rays are a poorly penetrating radiation. As previously noted, only a few percent or less of the x-rays entering an average-sized patient (~23-cm thick mediastinum) actually emerge from the patient to make an image. For large patients (~30-cm thick mediastinum), this percentage is even less. To compensate for this reduced penetration, large patients require entrance dose rates considerably greater than average or thin patients. Dose rates to the patient generally double for every 4 to 5 cm of additional tissue that must be penetrated to produce the image.

The patient-related factor most influential in determining how much radiation must be used to render a proper image is the mass of tissue that must be penetrated between the positions where the beam enters to where it emerges from the patient. Oblique and cranially or caudally tilted beam orientations result in the thickest tissue mass and require markedly higher outputs than do simple posteroanterior orientations (Fig. 11-13). Not only must the machine generate radiation at a higher rate to penetrate the mass, but also the geometry of the situation inevitably places the skin of the patient closer to the x-ray source. In addition, the image receptor is often moved further away from the source to avoid collision with the patient. The combined effects of these factors greatly increase dose rate to the skin, as is demonstrated in Figure 11-3. A necrotic injury resulted from 63 minutes of fluoroscopy and more than 5000 frames of cine in this gentleman, who has an unusually large chest. The thick body mass of the chest coupled with the oblique and cranially tilted beam resulted in high radiation dose rates to the skin and the rectangular skin injury. When doses are high and procedures prolonged, the physician can consider rotating the beam to a different location so that a different skin area is irradiated.
FIGURE 11-13 Dose rates at steep beam angles. Dose rates to the entrance skin surface are highest for oblique and cranially or caudally tilted beams, especially in large patients. The primary factor increasing dose rate is the increased thickness of tissue that must be penetrated. However, there are additional factors. Steep angles also force the skin of the patient to be in closer proximity to the x-ray source, where the beam is more intense. In addition, the source to image receptor distance often increases in order to avoid collisions with the patient. This additionally causes the machine to increase output. All these factors contribute to increased dose rates to the entrance skin site of the patient. The injury shown in Figure 11-3 occurred in the case of a steep beam angle through a large-chested man. The cumulative dose resulted in necrosis and involved 63 minutes of fluoroscopy and nearly 5000 frames of cine. (Adapted with permission from Wagner LK, Archer BR. Minimizing Risks from Fluoroscopic X-Rays. 5th ed. The Woodlands, TX: Partners in Radiation Management; 2014.)

Rotating the beam to a new skin site has merit if the dose to a particular site is already at a high risk for causing injury. However, rotation has consequences. If a steeper beam angle is employed, the dose rate to the new entrance skin site will be significantly greater than before. If rotation is insufficient to eliminate overlap of x-ray fields between the old and new site, dose buildup in the overlapped area will increase. Typically beam rotations of more than 12° and up to 40° might be required to eliminate overlap, depending on many factors. If beam rotation is to a less steep angle, dose rates generally decrease.

Extraneous Body Parts

We have just seen that thick patients are more difficult to manage for good reasons. Sometimes, extraneous body parts like the breasts and arms intercept
the beam. This should be avoided because they increase the amount of tissue mass that the beam must penetrate. This drives up dose rates, reduces image quality, and places those tissues at elevated risks.

The young female breast (≤40 years of age) is known to be at substantively elevated risk for induced breast cancer; with older women, there is less risk. Working diligently to keep the breasts out of the direct x-ray beam, and especially out of the entrance x-ray beam, is a worthwhile task and has 2 potential advantages. By keeping extra tissue away from the beam, dose rates are lower, and by keeping breasts away from the direct beam, the dose to the glandular tissue is maintained at markedly lower levels. This is especially important for the breast in closest proximity to the x-ray source. For this breast, dose accumulations can be very substantive.

Arms in the direct beam are a known hazard. Figure 11-14 demonstrates the geometry of this procedure. Efforts must be made to manage arms in a manner that is comfortable to the patient (maintaining good circulation) and that keeps the arms away from the direct path of the beam. This applies to both arms. Although the arm that is on the exit side of the beam receives only an exit dose, its presence adds tissue mass to the radiation path, thus increasing output and dose rate to the entrance skin site. The arm on the x-ray tube side is at greatest risk because it not only drives up output, but also experiences the more intense beam because of its proximity to the diverging x-ray source.

FIGURE 11-14 Demonstration of arm intercepting the x-ray beam close the x-ray source. The diagram depicts a biplane fluoroscopic configuration illustrating how arms inadvertently placed in the x-ray beam can be seriously injured. The erythemas on the back healed with scarring. The injury to the arm required surgery. (Image at
After the Procedure

Counseling the Patient

After a prolonged procedure in which the skin dose may have been high, the patient should be counseled about the complexity of the procedure and that a skin reaction could develop within the next few weeks. The patient should be told the approximate location where this might occur and to report any skin reaction to the physician’s office. This information has many advantages. The first is that the patient is not surprised if it occurs. The second is that you now have feedback that your procedure did result in a reaction, and you can assess how frequently this occurs. You can use this knowledge to take any appropriate action to reduce this. The final advantage is that you can recommend that the patient see a dermatologist and the physician can call the dermatologist to let him or her know that the skin reaction might be due to x-ray radiation from the patient’s previous angiocardiographic procedure. The dermatologist can then determine if the location is correct and will not be puzzled by the rare event or by its delayed progression should it get worse. This will also render a biopsy unnecessary, and a biopsy should be discouraged because this may compromise healing. A principal course of action will be to build a shield around the affected area and provide medication to reduce skin irritation in the hope that the wound will not endure any abrasion and remain closed. This will give the wound a chance to heal and avoid ulceration and infection as long as the dose did not surpass the threshold for necrotic development.

Recording Dose

Dose utilization as a result of all fluoroscopy procedures should be recorded in the patient’s record. Since 1994, the FDA has recommended that patient dose be recorded. Recording of radiation output and the location of the principally exposed area in the patient’s record has several benefits. The first
is that dose can be reviewed when additional procedures are required. It could also become important if the patient requires radiation treatment at a later date. Maintaining records for quality control of radiation utilization is highly valuable. It can be effective at discovering ways to modify working habits to reduce radiation use, and it can be helpful in discovering which machines use radiation better. It might also be useful for administrative purposes when justifying expenditures for equipment replacement.

The Pregnant Patient

Periodically, a woman who is pregnant might require a cardiologic procedure. Pregnancy should not be considered an absolute contraindication for any needed cardiologic study. Dose to a baby from a cardiologic procedure can usually be well managed so as to avoid any radiation levels that would significantly place the conceptus at risk. For example, direct irradiation of the pelvis results in the most direct dose to an early pregnancy. In many cases, irradiation of the pelvis can either be completely avoided or be kept to a very short interval. The only radiation reaching the conceptus from fluoroscopy of the thorax is scattered radiation that must penetrate many centimeters of the patient’s abdomen before reaching the conceptus. This is much reduced in intensity from that of the primary beam. To minimize scattered radiation to the pelvis when examining anatomy in the chest, the area of the beam should be collimated to the area of interest. For a conceptus more than 10 cm from the primary beam, dose to the conceptus is typically much less than 2% of the entrance skin dose. A cumulative entrance skin dose of more, and usually much more, than 2.5 Gy would have to be delivered before dose to the conceptus would approach 50 mGy. At doses under 50 mGy, the only suspected risk to the child is a possibility of induced neoplasia. The risk for a 10-mGy dose to the conceptus is thought to be about 1 mortality in 1000 cases and, overall, less than 4 cases of induced neoplasia.29 The threshold dose for malformation is estimated at 100 mGy, but the magnitude and the likelihood depend on gestation age. Between 50 and 100 mGy, some subtle effects on the developing central nervous system might occur if development is between 8 and 15 weeks postconception. A complete discussion of these risks is beyond the scope of this chapter, and the reader is referred to other texts for a complete discussion.29 Therefore, in evaluating a pregnant patient for a procedure, a benefit-risk decision is
necessary. Well-executed dose-management practices can in select cases result in an acceptable benefit/risk for the patient.

**PERSONNEL SAFETY**

One adage of good radiation management is, “What’s good for the patient is usually very good for personnel.” Patients are infrequently exposed to radiation, but their doses during one intervention can be large. Personnel, however, are frequently exposed to radiation, but at low levels. Economic use of radiation in the patient helps circumvent unnecessary long-term buildup of high radiation doses to personnel. Therefore, practicing good radiation management for the patient has the added benefit of a safer working environment for personnel.

*Time*

Previously, we noted the importance of limiting beam-on time for the patient. This has the added benefit of also limiting exposure time for personnel. To further reduce exposure time to personnel, only those who must be in the room with the patient should be there, and only when their services are needed. Otherwise, personnel should limit their time of exposure to radiation by leaving the procedure room or by remaining behind a fixed radiation barrier.

*Intensity*

This safety measure relates to the management of the intensity of radiation delivered to the patient as previously described for both fluoroscopy and fluorography (cine and digital acquisitions).

Another aspect relates to a savvy understanding of how radiation is distributed in the room. Figure 11-15 demonstrates how radiation is distributed in an interventional environment when the C-arm is in a left anterior oblique (LAO) orientation. Scattered radiation (also called stray radiation) results from interactions of x-rays with matter. From this, it follows that stray radiation is most intense closest to sites where the most interactions occur, which is always the site where the x-ray beam enters the
patient. Generally speaking, stray radiation emanates in all directions from the site of interaction, but because of the patient’s body, the scatter distribution around the patient is very lopsided, as shown in Figure 11-15. At the exit surface of the patient, the beam is markedly reduced in intensity (by about a factor of about 30-100 in most adult patients), and thus, stray radiation from this site is much lower than that from the entrance site. Thus, personnel positioned near the entry site of the patient (near the x-ray tube) experience the most intense exposure to stray radiation, whereas those on the correspondingly opposite side experience the least. This is why the x-ray systems are usually oriented with the x-ray tube under the patient and the image receptor over the patient. In this orientation, the intense scatter off the posterior aspect of a supine patient is directed primarily at the floor. The scatter emanating from the anterior surface of an adult is much less, saving considerable radiation exposure to the face and hands. With the C-arm oriented in an LAO position with cranial tilt, the intense scatter field is directed at the feet and legs of personnel standing to the right of the supine patient. Thus, the legs and feet of cardiologists are at considerable risk to accumulate very large doses of radiation after years of work.
**FIGURE 11-15** Depiction of stray radiation intensities from a patient in an interventional environment for a left anterior oblique beam orientation. These patterns apply only to this beam orientation. In other orientations, an analogous pattern is produced, with the greatest intensity emanating from the skin area where the beam enters. A person standing at a position near where the beam enters the patient receives about three times more radiation than a person at the opposing position near the exit beam side of the patient.

Figure 11-15 applies only to the LAO orientation. The distribution of stray radiation changes with different orientations. What workers must remember is that stray radiation is most intense on the side where the beam enters the patient and least intense on the opposite side where it exits the patient.

**A Note on Equipment Design**

There is a perceptually misleading circumstance for the worker who is on the exit side of the beam when the beam is oriented in a lateral manner. The individual near the image receptor can see the port of the x-ray tube and the collimator housing. Logically, the concern is that they are standing in the direct path of the x-ray beam. This should not be the case, and some simple tests, as listed next, can be applied to make sure that no direct beam is exposing them.

1. The FDA requires that the x-ray beam that emerges from the x-ray port be directed at and confined to the area of the image receptor, regardless of any operating configuration. This should be verified by a medical physicist when the quality control survey is performed.
2. It is easy to verify that the beam is confined to the image receptor during a procedure. Simply observe the image for the presence of collimator blades. If the collimator blades are visible in the image, the beam is confined to that area and must be inside the area of the image receptor.
3. By federal regulation, the image receptor is housed in a shielded container to block stray radiation generated inside the image receptor. The small amount of radiation penetrating the shield is very low. This can be verified by a medical physicist.
4. The x-ray tube and collimator housings are also well-shielded and well-regulated devices. Their shielding can be tested by a medical physicist.
**Distance**

The use of distance to reduce radiation exposure is extremely effective. Commonly referred to as the *inverse square law*, radiation levels decrease rapidly with increasing distance from the source. Specifically, with each doubling of distance from the patient, scatter decreases by about a factor of 4. So, if you are standing at about 1 m from the patient, taking a 1-m step backward decreases the unshielded intensity by about a factor of 4. The working rule of thumb that “One should work at a practicable maximum distance from the irradiated area of the patient while in the room” is one that serves everyone well.

**Shielding**

Shielding materials are abundantly available. Generally speaking, shielding is any material that absorbs or deflects a substantial portion of the x-rays that strike it. Many forms of shielding are available and include protective aprons, protective eyewear, thyroid shields, ceiling-suspended shields to protect the upper body, floor shields or table-side shields to protect the legs, stand-up mobile barriers to protect the entire body, and flexible shields that are draped on the patient to stop scatter at its source. There is further shielding in the walls to protect people outside the room. Sometimes, due to modern construction techniques that use thin concrete slabs between floors, extra shielding in floors and ceilings may also exist. Regarding radiation shields, the following are some guidelines:

1. Verify that there is sufficient shielding in the walls, floor, and ceiling to protect people who are outside the room. In one full year, no secretary, clerk, or other member of the public should receive more than 1 mSv effective dose from man-made radiation that penetrates these barriers.
2. Radiation levels behind the barrier of a control booth should not exceed 5 mSv per year.
3. Barriers suspended from the ceiling, the table, or standing on the floor should be a minimum of 0.5 mm of lead equivalent (ie, equivalent to the same protection provided by 0.5 mm of lead). Some shields are equivalent to 1.0 mm of lead or more.
4. Barriers suspended from the ceiling must be readily accessible and should
be designed so as to block radiation from the patient. This can be achieved with a drape or by purchasing a specially contoured hard shield that fits snugly against the patient’s body. Flexible shields that lie over the patient may be alternatively used.

5. Protective eyewear is optional in most cases. Eyewear should be equivalent to about 0.5 mm of lead and should fully cover the eyes, wrapping around the sides to cover the entire eye. Goggles that also provide splash protection should be considered. Standard glasses are not satisfactory for this purpose.

6. Thyroid shields are an option. They should be comfortable to wear. (The adult thyroid of the average person is not a highly radiosensitive organ, but protection is always recommended as a precaution.)

7. Protective aprons must be comfortable. Many states require by regulation that they be 0.5-mm lead equivalent in the front. This blocks about 95% of the radiation. Protection should wrap around the sides. Aprons that are 0.35-mm lead equivalent should be adequate and are much lighter. Rear torso protection of at least 0.15 mm is also recommended for personnel working in close proximity to the patient and for personnel who might have to work with their backs sometimes toward the patient. Support belts that distribute the weight between the shoulders and hips are recommended, and a 2-piece vest-plus-skirt design is preferred by some.

8. Radiation monitors must be worn at all times during procedures to measure the amount of radiation incident on personnel. Some regulatory bodies require that the monitor be worn under the lead apron, whereas others require that it be outside the lead apron, and some require that 2 monitors be worn, 1 under the apron and 1 outside. These varying points of view often confuse workers and are the result of a conflict between the need to monitor for safety versus the need to monitor as a matter of regulatory mandate. For safety purposes, I recommend that one monitor be worn outside the lead apron near the collar on the side of the body that is closest to the x-ray source. This adequately monitors the exposure to the unprotected areas of the head and neck and provides sufficient information to assure adequate safety measures can be taken when necessary. The dose under a 0.5-mm lead equivalent apron is roughly 5% of that dose. My goal for heavy users of radiation is that the annual readings at the collar outside the lead apron not exceed 50 mSv. I never recommend that only 1 under-
the-apron monitor be worn because this renders a false sense of security and ignores potentially high doses to important unprotected body parts.

9. Cardiologists should consider monitoring, periodically at least for several months, the doses to their legs and hands. This is achieved by attaching a monitor to the pant leg and a ring badge to the dominantly exposed finger. This provides important information on the adequacy or inadequacy of protection for these areas. Extra shielding or better attention to using shields should be considered if doses to these sites exceed 50 mSv in 1 year.

THE PREGNANT EMPLOYEE

Radiation exposure to an employee who is or might become pregnant must be managed so as to adequately protect the conceptus while not interfering with the individual’s ability to execute her duties. To do this, I recommend that preparations for pregnancy be taken before any employee becomes pregnant and that certain actions be taken once her pregnancy becomes known.

Preferably, before or at the commencement of employment, the worker should be advised of policies regarding radiation and pregnancy. This should be conducted for both men and women so that all employees are familiar with the policies. It must be made clear that extra protective measures cannot be initiated until the radiation safety staff is apprised of a pregnancy. Therefore, it is incumbent on the employee to advise the radiation safety officer (RSO), preferably in writing, when she first becomes aware of her pregnancy. Her options regarding safe practices can then be reviewed and extra precautions initiated.

I recommend that all female employees of childbearing potential who are required to have a whole-body dosimeter also be provided a specially marked “abdominal badge” dosimeter. The special marking helps ensure that the badges are easily distinguished. Although the whole-body badge should be worn at the collar outside the lead apron, the abdominal badge should be worn under all protective devices at the level of the belt. The readings of these badges should be reviewed by the RSO to assure that they do not exceed 0.25 mGy per month. This limit assures that any would-be conceptus would receive less than half that of the maximum recommended by professional agencies (recommended maximum dose to the conceptus is 0.5
mGy per month). If the readings do exceed 0.25 mGy, action should be taken to determine the cause, and corrective measures should be initiated.

Once an employee advises the RSO that she is pregnant, the following should be considered:

1. Review the abdominal badge history. This should demonstrate that current practices are sufficient to protect the baby. If not, corrective actions are necessary.
2. Provide the employee with the option of wearing an additional pelvic shield. This could be as simple as a small lap apron that can be 0.25 or 0.5 mm of lead equivalent material. This further reduces any potential exposure to the child.
3. Continue to provide the abdominal badge and switch it to monthly readouts if the present exchange is less frequent. In some cases, employees might also want to wear a real-time dose monitor under their protective apron. This provides daily feedback about the radiation exposure under the apron, rather than having to wait for the badge report at monthly intervals.
4. Provide the employee with duties involving less exposure to radiation, if necessary.

CONCLUSION

Radiation can be both friend and foe. To remain a friend, it must be treated with respect. Developing respectful habits that appropriately protect patients and personnel is the goal of all radiation management training.

ACKNOWLEDGEMENT

The author extends his sincere thanks to Dr. Stephanie Leon for her astute remarks in providing a critical review of this chapter.

REFERENCES

1. Mackenzie I. Breast cancer following multiple fluoroscopies. Br J


13. Frazier TH, Richardson JB, Fabré VC, Callen JP. Fluoroscopy-induced


MULTIPLE CHOICE QUESTIONS

1. For a fluoroscopy procedure, cumulative air kerma at a reference point is best described as:
   A. The total absorbed dose to the patient
   B. The amount of radiation accumulated at a specified point
   C. The total effective dose to the patient accumulated over time
   D. The total probability of inducing a cancer in a patient

2. For doses delivered from high-dose fluoroscopically guided interventions in nonpregnant patients, stochastic effects differ from radiation-induced tissue reactions (deterministic effects) in that tissue reactions:
   A. Increase in severity as dose increases past the threshold
   B. Can occur in tissues remote from the irradiated site
   C. Become evident while the radiation is applied
D. Are independent of the patient’s specific health status

3. Why are medical staff required to wear a personal radiation monitor during fluoroscopic procedures?
   A. To assure government regulators that the machine is operating safely
   B. To assure government regulators that safe practices are being exercised
   C. To protect the staff by absorbing ambient radiation in the environment
   D. To assess their exposure over time to see if increased protection is warranted

4. Which of the following actions is most likely to result in an increase in entrance absorbed dose rate to the skin of the patient?
   A. Decrease magnification (use larger field of view)
   B. Decrease distance of image receptor from the patient
   C. Employ high-level fluoroscopy
   D. Use a lower pulse rate for fluoroscopy

5. Which beam orientation is most likely to result in the highest entrance absorbed dose rate to the skin of the patient?
   A. 10° left anterior oblique (LAO), 0° cranial
   B. 20° LAO, 0° cranial
   C. 10° LAO, 15° cranial
   D. 20° LAO, 15° cranial

**ANSWERS**

1. B
2. A
3. D
4. C
5. D
Computed tomography (CT) was developed in the early 1970s. The first computed axial tomography (CAT) scanners developed by Sir Geoffrey Hounsfield and colleagues required long acquisition and reconstruction times and were only suited for (small) stationary body parts like the head. However, within the same decade, scanners dedicated to cardiac imaging were developed that were able to acquire images in 100 milliseconds or less, which was sufficient to virtually freeze cardiac motion. Contrary to mechanical CT scanners, these electron-beam CT systems lacked mechanically rotating parts. Instead of a rotating tube-detector unit, a beam of electrons was electromagnetically swept along a stationary tungsten target ring around the patient. As the electrons hit the tungsten ring, a roentgen fan beam was created. On the opposite side of the gantry, attenuated roentgen rays were collected by a stationary ring of roentgen detectors. For over 2 decades, these scanners were in operation, primarily to image coronary calcium, but also to image the coronary lumen after intravenous contrast injection. Technical and other practical challenges to electron-beam contrast CT, such as difficulties expanding the number of simultaneously acquired slices and expanding the longitudinal scan range, stalled further exploitation.
FIGURE 12-1 Early computed tomography scanner (EMI, 1971) for brain imaging, on display at the Museum of Science, London, United Kingdom.

In the 1990s, the introduction of slip-ring technology for cableless exchange of energy between the rotating and stationary scanner components of mechanical CT scanners allowed for faster, uninterrupted scanner rotation and the development of spiral CT imaging techniques. Spiral or helical scan protocols, through continuous table movement and data acquisition, allow for faster longitudinal coverage and propelled the possibilities for contrast-
enhanced CT applications, including coronary imaging. Just before the turn of the millennium, the first 4-slice spiral CTs with electrocardiogram (ECG) synchronization for cardiac imaging were introduced.\textsuperscript{4,5} Over the next decade, the technical capabilities of cardiac CT improved rapidly, with faster rotating scanners and increasing numbers of detector rows for better and easier coronary imaging (Fig. 12-2). However, concerns about the increasing radiation burden associated with cardiac CT emerged, which motivated technical innovations to reduce the radiation dose while maintaining sufficient diagnostic accuracy.

\textbf{FIGURE 12-2} Computed tomography angiography of a patient with a single coronary artery. The right coronary artery (RCA) arises from the middle portion of the left anterior descending coronary artery (LAD) and then transverses in front of the pulmonary artery to the right atrioventricular groove.

In addition to noninvasive assessment of coronary stenosis, coronary CT
also allows for assessment of the atherosclerotic changes in the vessel wall. Endeavors to noninvasive identify vulnerable plaques are ongoing. As the technologic accuracy of coronary CT angiography (CTA) matured and the radiation exposure reached acceptable levels, scientific attention shifted toward the clinical validation of the technique to define its most effective role in cardiovascular medicine. Several trials, both small and large, have been performed to assess the value of coronary CT (eg, in patients with stable angina or acute chest pain). Over the past decade, practicing physicians have become increasingly aware of the importance of functional stenosis assessment in the management of coronary artery disease. Although coronary CTA is an excellent means to exclude coronary disease, imaging of anatomy does not allow direct interpretation of the hemodynamic relevance. Several functional CT applications, such as coronary attenuation patterns, virtual fractional flow simulations, and stress myocardial perfusion imaging, are currently being investigated as options to complement CTA to provide a comprehensive assessment of patients and guide therapy.

**PRINCIPLES AND TECHNIQUES**

*Computed Tomography*

CT is an imaging technique based on the roentgen attenuation characteristics of tissues. While the emitting roentgen tube and opposing detectors rotate around the patient, a large number of roentgen projection profiles are collected. From these projection profiles that represent the cumulative attenuation under varying angular degrees, the regional attenuation contribution, which depends on atomic composition and density, can be calculated using sophisticated reconstruction algorithms. The resulting image is the spatial distribution of the attenuation properties throughout a cross-section, relative to the attenuation properties of water, expressed in Hounsfield units (HU). By definition, the attenuation value of water is 0. Fat tissue has attenuation values just below 0, while in the relative absence of matter (air), attenuation values are very low (conventionally represented by dark shades of gray). Most (nonenhanced) soft tissues have positive attenuation values just above water, whereas tissues containing heavier atoms (eg, calcium, iodine, metals) have substantially higher attenuation values.
(bright shades).

**Contrast Enhancement**

Because the attenuation values of blood and the vessel wall are similar, the lumen cannot be imaged without the use of a contrast medium. Iodine-containing contrast media are usually injected through a peripheral vein. Arterial imaging is best during the first passage of contrast medium, and the required duration of the enhancement plateau depends on the scan duration. While with 4-slice scanners a cardiac scan took 30 to 40 seconds, current 64- to 320-detector technology requires only a few seconds, which allows for a smaller contrast bolus and more comfortable breath hold. Optimal timing of the scan relative to the arrival of contrast medium can be achieved by first performing a test bolus injection or by a bolus tracking technique, in which case the data acquisition is automatically started as soon as aortic enhancement is detected on a monitoring scan.

**Temporal Resolution**

The main challenge for coronary imaging by CT lies in the continuous movement of the coronary arteries. The temporal resolution of CT is relatively modest, at least in comparison to some other cardiac imaging techniques, which increases vulnerability to artifacts caused by coronary displacement. The temporal resolution of cardiac CT is determined by the time necessary to acquire the minimal number of projections for image reconstruction. Partial scan reconstruction algorithms can reconstruct images based on an approximately 180° gantry rotation. Consequently, for single-source scanners with a rotation time of 250 to 350 milliseconds, the fundamental temporal resolution is around 125 to 175 milliseconds. The temporal resolution can be improved in several ways. By combining 2 tube-detector systems at an angular off-set of 90°, dual-source CT scanners collect all projections over a 90° rotation, improving the temporal resolution by a factor of 2 (down to 65 milliseconds). Alternatively, phase-consistent data of the same section that were acquired over 2 or more heart cycles can be combined for image reconstruction, which improves the effective temporal resolution, albeit in a less predictable manner and at the expense of a higher radiation dose. Finally, the effective temporal resolution can also be
improved by slowing the heart rate using β-blockers or other medication.

**ECG Synchronization**

Despite efforts to improve the temporal resolution, the maximum achievable temporal resolution of CT does not allow for motion-free imaging of the coronary arteries throughout the cardiac cycle. Coronary displacement is less during mid-diastole and at the end of systole. Because most scanners cannot cover the heart in a single beat, multiple stacks of data are acquired over a number of heart cycles. To assure reconstruction of images during the optimal motion-sparse phases within the heart cycle, consistently over several heart cycles, some form of ECG synchronization is required. When coronary imaging using mechanical 4-slice CT emerged at the beginning of the 21st century, a spiral CT scan mode was applied for continuous, temporally overlapping data acquisition, after which images were reconstructed for the desired cardiac phases based on a recorded ECG trace. This robust technique allows for correction for rhythm irregularities. Often, it was necessary to reconstruct many phases to find a dataset with minimal motion artifacts, given the slower scanner rotation at the time. Although retrospectively ECG-gated spiral-mode cardiac CT is still available and applied in patients with arrhythmia or when full-cycle data are needed, for routine coronary imaging, this scan mode has been largely replaced by more dose-considerate techniques. The current default scan technique for coronary CTA is the prospectively ECG-triggered axial scan mode, also referred to as the prospective scan mode, or step-and-shoot mode (Fig. 12-3). Contrary to the spiral scan mode, using prospectively ECG-triggered axial imaging, each consecutive stack of data is acquired by roentgen exposure limited to the desired cardiac phase, based on the preceding heart rhythm, while the table remains in a stationary position. Contemporary axial scan protocols include arrhythmia recognition algorithms, which interrupt and/or repeat scans in case of a rhythm disturbance, as well as the option to extend the exposure window for reconstruction of different cardiac phases. Although spiral scan protocols have also been modified with the objective to lower dose, axial scan protocols generally achieve the lowest exposure. Second- and third-generation dual-source CT scanners can perform an ECG-triggered spiral imaging at very fast table advancement to cover the entire heart in a single heart cycle. Scanners with very wide detector arrays that completely cover
the heart require no table advancement during the scan.

**FIGURE 12-3** Cardiac computed tomography (CT) scan techniques. The spiral scan mode can be performed by continuous exposure (green) or with electrocardiogram (ECG)-triggered tube modulation and nominal exposure limited to the phase(s) of interest. Depending on the selected table speed and heart rate, a degree of overlap will be created between the consecutive acquisitions per heart cycle. Axial scan protocols minimize the exposure to the phase of interest but can be extended to allow for reconstruction of more phases (padding), with minimal longitudinal overlap between acquisitions. Second and third dual-source CT systems can perform high-pitch spiral scans, in which case all data are acquired (over a longer interval) within a single heart cycle. The purple bar superimposed over the ECG represents the minimal exposure duration for reconstruction of a single dataset/phase.

**Image Reconstruction Techniques**

Until recently, limitations in computer performance necessitated the use of filtered back-projection techniques for the reconstruction of CT images. As a
result of accelerated computer processing power, computationally more demanding iterative reconstruction algorithms can now be applied to CT data at acceptable reconstruction times. The advantage of iterative reconstruction algorithms is the improved image quality. In addition to axial scan protocols, more dose-aware operating techniques, and more efficient tube settings, iterative reconstruction algorithms have contributed to the lower radiation exposure of contemporary coronary CTA by reducing noise levels at lower tube output settings.\(^6\)\(^7\) Reported dose values peaked at around 15 mSv with the first 64-slice scanners\(^8\) but, since then, have gradually dropped to well below 5 mSv using standard CT technology and even below 1 mSv using state-of-the-art technology in selected populations.\(^9\)

CORONARY CT ANGIOGRAPHY

*Image Interpretation*

A cardiac CT scan is essentially a large stack of overlapping axial slices. Each image slice consists of 512 × 512 image elements, whereas the dimensions of each 3-dimensional image element, called a voxel, are approximately 0.3 × 0.3 × 0.4 mm. The images can be assessed slice by slice or with the use of secondary postprocessing techniques to visualize longer sections of the coronary arteries and facilitate interpretation of obstructive disease. These secondary reconstruction techniques include double-oblique cuts, curved cross-sections along the axis of the vessel, and 3-dimensional volume-rendered reconstructions. Often a combination of techniques is used for interpretation. Guidelines recommend classification of the stenosis severity into categories rather than exact percentages of lumen narrowing (Table 12-1).\(^{10}\) Standardized coronary classification systems may be used to specify the location of disease. The recently published Coronary Artery Disease Reporting and Data System (CAD-RADS) criteria can be used to classify coronary CTA findings.\(^{11}\)

| Table 12-1 | Society of Cardiovascular Computed Tomography Recommended Stenosis Grading and Qualitative Interpretation of Flow Limitation |\(^{10}\) |
Diagnostic Performance

Over the past 2 decades, noninvasive coronary CTA has gradually evolved into a reliable technique for the assessment of obstructive coronary artery disease (Fig. 12-4). Many single-center studies, as well as a number of multicenter trials, have been performed to test the technical accuracy of coronary CTA against invasive coronary angiography (Table 12-2).\textsuperscript{12-17} The sensitivity of CTA is high (93%-100%) on a per-patient level, and the probability of coronary disease is very small in case of a normal CT angiogram because the per-patient negative predictive value approaches 100%. The specificity of CTA is slightly lower (78%-96%), which means that the angiographic disease severity is overestimated in comparison to invasive angiography. There are several contributory factors to this. The spatial resolution of CTA prevents visualization of small vessels, but also increases the apparent size of calcifications and other high-attenuating material in combination with filtering effects. The appearance of obstruction may be created by artifacts, including motion blurring and misalignment between data stacks. The propensity toward overcalling stenosis severity may also be the indirect result of the visualization of atherosclerotic plaque. Similar to intravascular ultrasound the perceived stenosis severity on CTA may increase in the presence of large plaques and outward vessel remodeling (Fig. 12-5). Naturally, the performance of CTA will improve with better image quality. Nonmodifiable technical and patient characteristics, such as

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<tr>
<td>0</td>
<td>Normal</td>
<td>Absent plaque and no lumen narrowing</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
<td>Plaque with &lt;25% narrowing</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>25%-49% narrowing; probably not flow limiting</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>50%-69% narrowing; possibly flow limiting</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>70%-99% narrowing; probably flow limiting</td>
</tr>
<tr>
<td>5</td>
<td>Occluded</td>
<td>100% occluded</td>
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</table>
temporal resolution and longitudinal coverage or the heart rhythm and size of the patient, need to be factored into the expectations for the examination. A high calcium burden decreases the diagnostic performance of CTA, and patients with a very high calcium score may benefit more for another type of testing than CTA. Aspects amenable to optimization include patient cooperation and heart rate. Adequate patient instructions and practice can avoid breathing and other patient movement during the scan. β-Blockers are recommended for all patients with a heart rate over 65 to 70 bpm to reduce motion artifacts and allow for more dose-efficient scan protocols. A fast-acting β-blocker may be administrated orally or intravenously. Alternatively, calcium antagonists or sinus node inhibitors may be used to slow the heart rate. Nitroglycerin is administrated sublingually for coronary vasodilation and improves image quality.

**FIGURE 12-4** Computed tomography angiography (A and C) and invasive angiography (B and D) demonstrate diffuse, partially calcified atherosclerosis and a severe stenosis (arrow) of the left anterior descending coronary artery.
Table 12-2 Performance of Coronary Computed Tomography Angiography

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segments</td>
<td>91% (86%-95%)</td>
<td>96% (94%-97%)</td>
<td>22 (15-31)</td>
<td>0.09 (0.06-0.15)</td>
</tr>
<tr>
<td>Vessels</td>
<td>97% (95%-98%)</td>
<td>93% (89%-96%)</td>
<td>14 (9-22)</td>
<td>0.03 (0.02-0.05)</td>
</tr>
<tr>
<td>Patients</td>
<td>100% (98%-100%)</td>
<td>89% (85%-92%)</td>
<td>9 (7-13)</td>
<td>0.00 (0.00-0.02)</td>
</tr>
</tbody>
</table>

Note: Meta-analysis based on the pooled results from 13 studies using low-dose coronary computed tomography angiography, including 789 patients, 2622 vessels, and 11,518 vessel segments.10
FIGURE 12-5 Invasive angiography (A and C) and computed tomography angiography (CTA) (B and D). In the proximal left anterior descending coronary artery (LAD), a noncalcified lesion (arrow) can be observed on CTA, corresponding with a similarly severe lesion on invasive angiography. CTA also shows a large calcified plaque in the distal left main (arrowhead). Stenosis appears more severe on computed tomography compared to invasive angiography due to a combination of outward vessel remodeling and blooming effect of the highly attenuating calcium. D1, first diagonal branch; LCX, left circumflex coronary artery.
Coronary Anomalies

Cardiac CT is regarded as the clinical reference for the in vivo anatomic depiction of coronary anomalies (see Fig. 12-2). Without the need for selective catheter intubation, aberrant branches will opacify regardless of whether the origin of the vessel is known. The exact course, the relation with other structures, and the termination of fistulas can be visualized unambiguously. Mechanical effects like intra-arterial compression may be displayed using dynamic cardiac CT reconstructions. Myocardial bridging is frequently observed on CT angiograms.

PLAQUE IMAGING

Nonenhanced Calcium Imaging

Without injection of contrast medium, ECG-synchronized CT can be used to image and quantify calcium deposits in the coronary artery wall. Although there are many ways to quantify the coronary calcium burden, the semi-quantitative Agatston score remains the most widely used method (Fig. 12-6). Population studies have demonstrated an age-, sex-, and race/ethnicity-dependent distribution and progression of coronary calcium. The calcium score is associated with the risk of adverse cardiac events, adds (substantial) prognostic value to conventional risk predictors, and appears to outperform other secondary risk predictors such as C-reactive protein, N-terminal pro-B-type natriuretic peptide, or carotid intima-media thickness. The calcium score can correctly reclassify the risk of asymptomatic individuals and appears most effective in those at intermediate risk by conventional factors.
FIGURE 12-6 A. Coronary calcium imaging. Nonenhanced cardiac computed tomography (CT) shows calcified disease in the aortic root and the coronary arteries (3-dimensional [3D] rendered reconstruction). B. Automatically highlighted tissues with an attenuation value above 130 HU and belonging to the coronary arteries can be manually selected, after which an Agatston score is calculated based on the calcified lesion areas and maximum attenuation value per lesion. C. 3D-rendered CT angiogram of the same patients showing the extensive calcification in relation to the coronary anatomy. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

Contrast-Enhanced Plaque Imaging

In addition to the calcified components, CTA also has the ability to show noncalcified plaque tissue (see Figs. 12-4 and 12-5). The global angiographic disease burden is associated with clinical outcome. In addition to the stenotic disease burden, the presence of nonobstructive plaque also predicts adverse events. When coronary disease is absent on CTA, the probability of an adverse cardiac event is extremely low over the subsequent 6 years. Because differentiation from the perivascular tissues is more difficult, the sensitivity for the detection of noncalcified plaque is lower than for calcified
plaque, and absolute quantification remains only moderately reproducible between different software packages. Based on measured attenuation values, the differentiation of lipid-rich (lower attenuation values) and fibrous-rich plaques (higher attenuation values) has been demonstrated in several studies. However, absolute values depend on contrast enhancement and scan conditions; within studies, overlap between plaque types is considerable, and between studies, the reported thresholds vary substantially. Various plaque characteristics associated with plaque rupture can be reproduced by CTA, including plaque size, large low-attenuating plaque, outward vessel remodeling, and calcified nodules. Identification of large lipid cores on CTA has been reported by a number of investigators. While it is not possible to image several other parameters of plaque instability, such as cap thickness, macrophages, or intraplaque hemorrhage, prospective studies suggest that the aforementioned CT characteristics, in addition to plaque progression, predict the occurrence of adverse cardiovascular events.

**CLINICAL ROLE OF CT ANGIOGRAPHY**

*Evaluation of Coronary Artery Disease in Patients with Angina Pectoris*

Based on the diagnostic performance of CTA, in particular the high negative predictive value in comparison to invasive angiography, the technique is thought to be most effective in patients with a low to intermediate probability of coronary disease. The 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for stable ischemic heart disease included several recommendations on the use of coronary CTA (Table 12-3). Coronary CTA angiography was considered a reasonable first-line option in patients with an intermediate probability of coronary artery disease (CAD), in particular for patients with contraindications to stress testing. Coronary CTA may also be considered for patients with a nonconclusive stress test result. Coronary CTA should only be considered if adequate CT scanner technology and expertise are available and patient
characteristics suggest that diagnostic image quality can be achieved. Since publication of the American and European guidelines, the results of several randomized controlled trials on the clinical effectiveness of coronary CTA compared with current standard diagnostic management were published. The largest of these, the National Institutes of Health–sponsored PROMISE trial, randomized over 10,000 patients between coronary CTA and standard care (mostly stress imaging). Both strategies performed equally well in terms of hard end points, which occurred at a lower rate than originally anticipated. The use of CTA was associated with a higher rate of catheterizations and revascularizations, but a lower rate of normal invasive angiograms. The Scottish SCOT-HEART trial tested whether the addition of cardiac CT to standard care (including exercise ECG) improved diagnostic confidence. In addition to an increased certainty about the diagnosis, secondary analysis demonstrated a lower event rate in patients in whom CTA was added. The CRESCENT trial randomized 350 patients between a tiered cardiac CT protocol and standard care (mostly exercise ECG). In this study, CTA was only performed in patients with a positive calcium scan or high pretest probability, which reduced radiation exposure and cost, without a negative effect on outcome. Meta-analyses of these trails suggest an overall increase in subsequent catheterization and revascularization rates after CTA, but also suggest a lower myocardial infarction rate.

Table 12-3 Coronary Computed Tomography Recommendations
**Acute Chest Pain**

The triage of patients with acute chest pain but no evident myocardial ischemia or necrosis remains a diagnostic challenge that physicians confront on a daily basis. While a small proportion of patients will suffer from a (potentially) life-threatening condition, the vast majority of patients presenting at the emergency department will have a more benign cause. The diagnostic algorithm for triage of these patients requires sufficient sensitivity to identify conditions that benefit from immediate intervention, while avoiding excessive use of resources for the entire group. While currently

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class (Level of Evidence)</th>
</tr>
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<tbody>
<tr>
<td><strong>2012 ACC/AHA: Stable Ischemic Heart Disease</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Patients with suspected stable IHD who require noninvasive testing</td>
<td></td>
</tr>
<tr>
<td>CCTA is reasonable for patients with an intermediate pretest probability of IHD who:</td>
<td>Iia (C)</td>
</tr>
<tr>
<td>a) have continued symptoms with prior normal test findings, or</td>
<td></td>
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<tr>
<td>b) have inconclusive results from prior exercise or pharmacologic stress testing, or</td>
<td></td>
</tr>
<tr>
<td>c) are unable to undergo stress with nuclear myocardial perfusion imaging or echocardiography</td>
<td></td>
</tr>
<tr>
<td>CCTA might be reasonable for patients with an intermediate pretest probability of IHD who have at least moderate physical functioning or no disabling comorbidity.</td>
<td>IIb (B)</td>
</tr>
<tr>
<td>For patients with a low to intermediate pretest probability of obstructive IHD, noncontrast cardiac CT to determine the CAC score may be considered.</td>
<td>IIb (C)</td>
</tr>
<tr>
<td><strong>Patients with known stable IHD who require noninvasive testing for risk assessment</strong></td>
<td></td>
</tr>
<tr>
<td>CCTA can be useful as a first-line test for risk assessment in patients with stable IHD who are unable to exercise to an adequate workload regardless of interpretability of ECG.</td>
<td>Iia (C)</td>
</tr>
<tr>
<td>CCTA can be useful for risk assessment in patients with stable IHD who have an indeterminate result from functional testing.</td>
<td>Iia (C)</td>
</tr>
<tr>
<td>CCTA may be reasonable for risk assessment in patients with stable IHD who are able to exercise to an adequate workload but have an uninterpretable ECG.</td>
<td>IIb (B)</td>
</tr>
<tr>
<td>CCTA might be considered for risk assessment in patients with stable IHD unable to undergo stress imaging or as an alternative to invasive coronary angiography when functional testing indicates a moderate- to high-risk result and knowledge of angiographic coronary anatomy is unknown.</td>
<td>IIb (C)</td>
</tr>
<tr>
<td>Pharmacologic stress imaging (nuclear MPI, echocardiography, or CMR) or CCTA is not recommended for risk assessment in patients with stable IHD who are able to exercise to an adequate workload and have an interpretable ECG.</td>
<td>III (C)</td>
</tr>
<tr>
<td><strong>2014 ACC/AHA Non-ST-Segment Elevation Myocardial Infarction</strong>&lt;sup&gt;22&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy.</td>
<td>Iia (A)</td>
</tr>
<tr>
<td><strong>2013 ACC/AHA Assessment of Cardiovascular Risk</strong>&lt;sup&gt;23&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following may be considered to inform treatment decision making: family history, hs-CRP, CAC score, or ABI.</td>
<td>IIb (B)</td>
</tr>
</tbody>
</table>

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Abbreviations: ABI, ankle-brachial index; ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance imaging; hs-CRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; MPI, myocardial perfusion imaging.
confident rule-out of an acute coronary syndrome often requires prolonged observation, serial sampling of myocardial biomarkers, and noninvasive or invasive investigations, cardiac CT has been introduced as a means to expedite the clinical triage of acute chest pain.

According to several observational trials, the absence of atherosclerotic plaque on coronary CTA virtually rules out an acute coronary syndrome. However, the absence of calcium (on a nonenhanced calcium scan) or the absence of >50% coronary stenosis lowers the probability of an acute coronary syndrome considerably but does not provide the same certainty as the absence of any plaque. In addition to severe coronary obstruction, cardiac CT can detect several other life-threatening conditions, such as aortic dissection or pulmonary embolism.

Based on these observations, several randomized controlled trials have been performed to study the value of cardiac CT in comparison with standard care in low (or intermediate)-risk patients with acute chest pain. The CT-STAT trial compared coronary CTA with single-photon emission CT myocardial perfusion imaging in 700 patients and demonstrated that CTA resulted in a shorter time until diagnosis and reduced expenses at the emergency department. The ACRIN-PA trial demonstrated in 1370 low-risk patients with chest pain, randomized 2:1 between CTA and standard care, that triage by CT is safe and allows for earlier discharge of patients. ROMICAT II compared coronary CTA and standard care in nearly 1000 patients and also found that cardiac CT was associated with a shorter length of stay and higher early discharge rate. Despite these advantages, cardiac CT was also associated with higher rates of invasive angiography and revascularization procedures. The BEACON trial compared coronary CTA with standard care in a European setting after the introduction of high-sensitivity troponin assays. While the use of cardiac CT was found to be safe and reduced the need for further downstream testing, previously observed logistic advantages were not reproduced in this trial. Shorter lengths of stay and high early discharge rates were observed in both arms, likely facilitated by the use of high-sensitivity troponins. The 2014 ACC/AHA guideline for the management of non–ST-segment elevation acute coronary syndromes concludes that CTA can result in a more rapid, more cost-effective diagnosis than stress myocardial perfusion imaging and considers cardiac CT a reasonable option in patients with a possible acute coronary
syndrome, normal ECG, normal cardiac troponins, and no history of CAD (Class IIa, Level of Evidence A; see Table 12-3).\textsuperscript{52}

**Early Detection of Subclinical Coronary Disease**

Semi-quantification of the coronary calcium burden on a nonenhanced cardiac CT scan has incremental prognostic value over conventional risk factors. It allows for better risk stratification compared to other secondary prognosticators and appears particularly effective in individuals at intermediate risk. Contrary to the European guidelines, the 2013 ACC/AHA guidelines do not provide strong recommendation of the use of calcium imaging for risk stratification (see Table 12-3).\textsuperscript{53,54} Although, contrast-enhanced CTA allows for more in-depth interpretation of the total atherosclerotic burden, as well as the presence of subclinical stenosis, there is currently insufficient evidence for CTA screening of asymptomatic individuals.\textsuperscript{55,56} Based on registry data, CTA seems to have incremental prognostic value over calcium imaging in high-risk populations, such as diabetic patients or patients with hypercholesterolemia.\textsuperscript{56,57} Since their diabetic status generally qualifies them for intensive risk factor management already, it is unclear whether additional testing provides outcome benefit.\textsuperscript{58}

**CT Guidance for Coronary Interventions**

CTA can provide additional information to invasive angiography that may be of value for interventional procedures. Whereas invasive angiography provides 2-dimensional projections of selectively enhanced coronary arteries, CTA visualizes the coronary arteries in 3-dimensional space without vessel overlap or foreshortening. Vessel segment length and angles between branches may be more reliable on CT (Fig. 12-7). CTA also visualizes less intensely opacified structures and can provide information about plaque location, size, and composition, potentially relevant to the intervention procedure. For recanalization of coronary occlusions, CTA can provide information about the occluded section, such as occlusion length and course, the presence of side branches, and the presence, location, and extent of calcifications, all of which are relevant before and during the revascularization procedure. Independent CT-derived predictors of complicated lesion crossing include the extent of the calcifications, long
occlusion length, multiple occlusions, negative vessel remodeling, blunt stump, and bending of the occlusion.\textsuperscript{59-62} While CT may not be performed routinely, it should be considered for second-attempt procedures. CT images have been used for magnetic navigation in the treatment of complex CAD.\textsuperscript{63}

\textbf{Avoiding Invasive Angiography}

Overall, coronary CTA can reduce the proportion of invasive angiograms without obstructive coronary disease. There are specific situations where an invasive procedure is particularly undesirable. Aortic valve endocarditis or aortic dissections add challenges and risks to catheterization procedures, while the yield of invasive angiography tends to be low in these situations (Fig. 12-8). Prior to noncoronary cardiac surgery or solid organ transplantation, invasive angiography is often part of the routine workup, although the proportion of abnormal examinations is relatively low. In the
majority of these patients, noninvasive coronary angiography by CT provides sufficient reassurance to avoid another invasive procedure. In addition, in patients with (assumed to be) nonischemic heart failure, CTA can be offered as a means to exclude CAD.

**FIGURE 12-8** A and B. Patient with endocarditis involving the aortic and mitral valves (*arrows*). C and D. Coronary computed tomography angiography was performed to rule out coronary artery disease prior to surgery. Nonobstructive, partially calcified coronary disease was found in the left anterior descending coronary artery (LAD; *arrow*, D). LCX, left circumflex coronary artery.

**FUNCTIONAL INTERPRETATION OF**
CORONARY LESIONS

The negative predictive value of CTA is excellent, and CAD can be ruled out reliably. However, for previously described reasons, CTA overestimates the angiographic severity of coronary disease. In addition, angiographic techniques generally overestimate the functional severity, at least when conservative stenosis thresholds are applied (50% diameter narrowing). In most cases, the finding of a stenotic lesion on CTA is not sufficient for revascularization decisions. There are various invasive and noninvasive techniques to establish the functional importance of angiographic lesions, as discussed elsewhere. Instead of performing a second examination, there is also substantial interest in secondary CTA parameters that inform us about the functional relevance of angiographic obstructions.

Coronary Attenuation Patterns

In case of a severe stenosis, one can imagine that blood flow to the distal vessel will be delayed. Therefore, similar to the invasive Thrombolysis in Myocardial Infarction (TIMI) score, it may be possible to demonstrate slow flow by differences in lumen opacification. Chow et al\(^6^4\) compared attenuation values proximal and distal to coronary stenoses, normalized for attenuation values in the left ventricle, and found that larger opacification differences were associated with low TIMI flow on invasive angiography. By extensive sampling of the intracoronary attenuation throughout the coronary artery, the transcoronary attenuation gradient (TAG) can be calculated. While initial experiences showed promising correlation between the TAG and the functional stenosis severity by invasive fractional flow reserve (FFR), subsequent studies reported lower diagnostic performance.\(^6^5-6^7\) These contradicting results may be explained by differences in CT technology (incomplete vs complete heart coverage) and CTA techniques (late scanning using contrast bolus tracking).

CTA-Derived Fractional Flow Reserve

The CTA-derived FFR is a relatively new technique to calculate the hemodynamic significance of CAD on CT angiograms (Fig. 12-9). By
applying computational fluid dynamics onto a CT angiogram, it is possible to model the blood flow through the coronary arteries and estimate intracoronary pressures at rest and during simulated hyperemia.\textsuperscript{68} By comparing the calculated blood pressure in the coronary arteries during hyperemia with the pressure in the aorta, FFR measures can be calculated throughout the coronary arteries. Computational CTA-FFR does not require additional scans or injection of vasodilators, but can be performed on any CT angiogram of sufficient image quality. The CTA-FFR application developed by HeartFlow Inc. (Redwood City, CA) has been tested against invasive FFR in a series of multicenter studies. The technique correlates well with invasive FFR and shows better specificity and accuracy in comparison to CTA (50% stenosis threshold).\textsuperscript{69,70} CTA combined with CTA-FFR can avoid normal invasive angiograms in patients referred for catheterization, which can reduce costs.\textsuperscript{71,72} HeartFlow CTA-FFR is commercially available, and performance of the simulations on dedicated computers requires transfer of the CT data. Alternative CTA-FFR applications are under development, of which some can be performed locally on regular workstations by applying less complex computational fluid dynamic solutions.\textsuperscript{73-76} Initial results with these new CTA-FFR applications are promising, but none is yet commercially available. Thus far, CTA-FFR has only been validated in fairly standard populations, without other abnormalities or prior revascularization procedures.

\textbf{FIGURE 12-9} Computed tomography angiography (CTA)–derived fractional flow
reserve (FFR) after percutaneous coronary intervention with a bioresorbable scaffold. Curved multiplanar reformation of a dominant left circumflex coronary artery (LCX) with the remains of a bioresorbable scaffold (arrowheads) in the distal segment (A). CTA-derived FFR with color-coded FFR display. Blue to green shades represent CTA-FFR values above 0.80, ruling out hemodynamically significant stenosis (B). RCA, right coronary artery.

**Stress Myocardial Perfusion Imaging**

In a manner similar to other stress imaging modalities, CT can be used for stress myocardial perfusion imaging. Infusion of a vasodilator causes myocardial hyperemia but less flow increment for myocardium supplied by obstructed coronary arteries. These variations in hyperemic blood flow are reflected by differences in myocardial contrast enhancement. For cardiac CT, there are 2 myocardial perfusion imaging methods. Either a single high-resolution CT scan is performed after contrast injection to capture instantaneous qualitative differences in myocardial enhancement (static perfusion imaging), or a sequence of low-resolution CT images is acquired to depict the time-resolved changes in myocardial enhancement for quantitative myocardial perfusion measures (dynamic perfusion imaging). Static perfusion imaging can be performed on most clinically used CT scanners and is associated with a lower radiation dose (equal to or lower than a standard CTA on the same system), whereas the dynamic perfusion imaging approach requires wide detector coverage and dedicated reconstruction software and results in a higher radiation dose (Fig. 12-10). In both single-center and multicenter studies, static perfusion imaging has been shown to correlate well with other stress imaging techniques and improves the specificity of CTA alone.\(^{77-80}\) In largely single-center studies, dynamic myocardial perfusion shows at least equal diagnostic performance.\(^{81-84}\) While there are many options to assess the hemodynamic severity of CAD, the combination of CTA and CT myocardial perfusion imaging may have practical advantages and provide a complete comprehensive assessment in a single session.
FIGURE 12-10 Severe angiographic obstruction (arrows) of the left circumflex coronary artery by computed tomography (CT) angiography (A) and invasive angiography (C). Dynamic CT myocardial perfusion imaging shows a discrete area (between arrows) of decreased myocardial perfusion in the lateral wall of the left ventricle (short-axis, myocardial blood flow map, B).

CARDIAC CT AFTER CORONARY REVASCULARIZATION

After Coronary Stenting
Conventional stents are made of highly attenuating metal alloys. The combination of strong attenuation and image filtering causes blooming artifacts (ie, the stent struts appear much larger than they are in reality). Beam hardening occurs when heterochromatic roentgen passes through a high-density structure. Disproportionate attenuation of low-energy roentgen and low attenuation of the remaining high-energy roentgen behind the high-density structure cause shadowing. Consequently, stented coronary segments are more difficult to interpret. The severity of the artifacts and the ability to interpret the lumen within the device depend on the type of alloy, the metal density, and the diameter size of the stent.\textsuperscript{85,86} Artifacts are aggravated by inferior image quality, particularly the presence of residual motion. Most studies that validated CTA against invasive angiography in (selected) patients with a history of coronary stenting report that a substantial proportion of devices cannot be interpreted and diagnostic accuracy is lower compared with nonstented vessels (sensitivity 86% and specificity 93%).\textsuperscript{87} While complete occlusion or patency can often be concluded with reasonable certainty, stenoses of intermediate severity are more difficult to assess (Fig. 12-11). Cardiac CT is most reliable in larger stents, in the proximal coronary arteries, and in grafts, provided that sufficient image quality can be achieved. Iterative reconstruction and dedicated filters can improve the interpretation of stents (Fig. 12-12). Stents without a metal backbone can be imaged better. Biodegradable scaffolds made of polylactic acid are invisible on CT, except for the small platinum markers at the edges of the device (Fig. 12-9 and Fig. 12-13).\textsuperscript{88} Cardiac CT has been used for mid- and long-term angiographic follow-up in the ABSORB trials.\textsuperscript{89} Whether the scaffold is still present shortly after implantation, or fully resorbed, CTA can be performed unhindered.
FIGURE 12-11 Three-vessel percutaneous coronary intervention and computed tomography angiography follow-up. Two stents of different make (arrows) in the left anterior descending coronary artery (A). The first stent appears incompletely deployed. Occluded stent in the proximal left circumflex coronary artery, as well as severe obstruction proximal to the stent, and collateral opacification of the distal vessel (B). Multiple stents in the right coronary artery with diffuse in-stent hyperplasia (insert) of uncertain obstructive severity (C).

After Bypass Graft Surgery
Because of the large diameter and less displacement during cardiac contraction, bypass grafts can be imaged well by CT. A number of technical validation studies have been performed that showed that CTA is a reliable technique to assess graft patency (accuracy approaching 100%) and detect graft restenosis (accuracy >95%) (Fig. 12-14).\textsuperscript{90-92} Surgical material in the form of vascular clips, sternal wires, and indicators at the proximal anastomosis site may obscure parts of the graft. Clips at the level of the distal anastomosis of arterial grafts may prevent reliable interpretation, particularly when residual motion is present. In patients who underwent bypass graft surgery, the native coronary arteries, distal run-off branches, and nongrafted vessels are more difficult to assess due to frequent diffuse atherosclerotic disease. Interpretation of angiographic findings often requires some form of functional testing, particularly in case of multiple lesions, prior myocardial infarction, or collateral coronary development. Cardiac CT may have incremental value over invasive angiography in certain situations. Because selective catheter engagement is not required, knowledge of the surgical anatomy is less important to image the grafts. In case of re-thoracotomy, CTA better visualizes the intrathoracic relations, the proximity of patent grafts to the sternum, adhesions, and so on.
FIGURE 12-12 Reconstruction of a stent in the left main and left anterior descending coronary arteries, using 0.8-mm slices and a smooth kernel (A), 0.8-mm slices and a sharper kernel (B), and 0.5-mm slices and a sharper kernel (C), which shows better stent definition, but also increases image noise.
FIGURE 12-13 Follow-up after treatment with bioresorbable scaffolds. Platinum markers at borders of the device remain present after absorption (arrowheads). Patent proximal right coronary artery (A); patent proximal marginal branch with visible plaque and overlap with conventional metal stent (B); severely calcified left anterior descending coronary artery (C); and proximal left anterior descending coronary artery with severe stenosis of the previously treated vessel (D).
FIGURE 12-14 Computed tomography angiography after bypass graft surgery. Right internal mammary artery (RIMA) with distal anastomosis to a diagonal branch (DB) and the left anterior descending coronary artery (LAD). Left internal mammary artery (LIMA) with distal anastomosis to a marginal branch (MB). The right coronary artery (RCA) is occluded.

ACKNOWLEDGMENT

Dr. Nieman reports institutional research support from Siemens, GE, Bayer, and HeartFlow and speaker fees from Siemens.

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**MULTIPLE CHOICE QUESTIONS**

1. Interpretation of the in-stent coronary lumen by computed tomography angiography is improved by which of the following?
   - A. High heart rates
   - B. High metal strut density
   - C. Larger stent diameter
   - D. Absence of drug coating

2. In case of *moderate* coronary stenosis on computed tomography (CT), hemodynamic significance is thought to be:
   - A. Impossible
   - B. Unlikely
   - C. Possible
   - D. Likely

3. Which statement about plaque characterization by CT is true?
   - A. Fibrous plaques are expected to have lower attenuation values than lipid-rich plaques.
B. Metabolic activity on CT angiography predicts plaque rupture.
C. The border between vessel lumen and plaque is more difficult to delineate than the outer plaque border.
D. Contrast medium affects the measured attenuation values in the plaque.

4. Which statement regarding CT angiography (CTA)–derived fractional flow reserve is true?
   A. It requires dedicated CT equipment.
   B. It requires administration of an intravenous vasodilator.
   C. It requires detailed segmentation of the coronary arteries.
   D. It requires purchase of a supercomputer.

5. Which statement regarding coronary CTA for the assessment of coronary stenosis is true?
   A. The negative predictive value of CTA is higher than the positive predictive value.
   B. The sensitivity of CTA is lower than the specificity.
   C. CTA underestimates angiographic stenosis severity.
   D. CTA underestimates functional stenosis severity compared to fractional flow reserve.

**ANSWERS**

1. C

   The size of the artifacts depends on the strut size and the quality of the scanner and is fairly constant regardless of the stent diameter. Therefore, the proportion of artifact-free, interpretable, lumen increases disproportionally with increased vessel size. High heart rates and denser metal create more artifacts, whereas nonmetal drug coatings have no effect.

2. C

   Moderate stenosis means a 50% to 70% lumen narrowing, which may or may not cause hemodynamic obstruction.
3. D
Due to image filtering, motion, and perhaps microvascular enhancement, the attenuation values measured in plaques increase when the adjacent lumen contains more contrast. If anything, fat should result in lower attenuation values than soft tissues. Metabolic activity cannot be assessed by CT angiography. Due to the vasa vasorum and small attenuation differences with the epicardial tissue, the delineation of the outer plaque borders is more difficult.

4. C
Segmentation of the coronary arteries is necessary for the computational fluid dynamics model. It can be performed on regular scanners without injection of a vasodilator. It is performed on a regular workstation on site, or the CT scan is transferred to a remote high-performance computer.

5. A
Compared with invasive angiography, CTA has the tendency to overestimate stenosis severity. Therefore, sensitivity and negative predictive value are high, whereas specificity and positive predictive value are lower. Angiographic techniques generally overestimate the functional severity (using conservative stenosis thresholds).
Intracardiac echocardiography (ICE) is an intravascular ultrasound (IVUS) modality that provides diagnostic imaging of cardiac structures from within the heart and has become widely used for guiding noncoronary interventions in the catheterization and electrophysiology laboratories. The first IVUS catheters used high-frequency transducers (20-40 MHz) containing a single ultrasound crystal that rapidly rotated at the end of the catheter, producing a radial 2-dimensional image.\(^1\) This type of high-frequency IVUS transducer provides excellent spatial resolution in the near field, making it uniquely suited for imaging the coronary arteries and other small vessels. The main limitation of IVUS in this frequency domain, however, is the short imaging depth (several millimeters).\(^1\)\(^-\)\(^2\) To accomplish ICE imaging from atria to apex, lower frequency transducers (5-12 MHz) have been miniaturized and mounted onto catheters capable of percutaneous insertion and manipulation within the heart.\(^1\)\(^,\)\(^3\)\(^-\)\(^7\) These lower frequency transducers are capable of greater tissue penetration and imaging depth, permitting high-resolution two-dimensional imaging of the whole heart.\(^2\)\(^,\)\(^8\)\(^-\)\(^11\) The earliest experiences with such low-frequency ICE catheters were described in the late 1970s and early 1980s.\(^3\)\(^,\)\(^4\) More recently, with the introduction of the newest phased array transducers, full Doppler flow data can be obtained.
Two different types of ICE catheters are currently available for clinical use. A mechanical transducer, similar to that used with IVUS, has a rotating ultrasound transducer driven by a motor unit at the opposite end of the drive shaft, which results in a 360° “radial” view perpendicular to the axis of the catheter. The second type is a fixed or phased array catheter-mounted transducer that uses electronically controlled transducers mounted on one side of the catheter shaft, which results in a wedge-shaped 90° image sector similar to that of transthoracic or transesophageal echo probes.

Both types of catheters provide high-resolution, real-time images of cardiac morphology and devices or catheters in the heart. Current ultrasound catheters, with a diameter size between 6- and 10-Fr, are typically introduced via a sheath in the femoral vein. Phased array catheters offer a large depth of field and add Doppler imaging capabilities, whereas mechanical catheters offer superior near-field resolution.

**BENEFITS OF INTRACARDIAC ECHOCARDIOGRAPHY**

ICE offers imaging that is comparable or, in some cases, superior in quality to transesophageal echocardiography (TEE). ICE adds substantial anatomic information to x-ray fluoroscopy for electrophysiologic ablation procedures and transcatheter atrial septal defect closure. ICE has been shown to provide procedural benefits in the context of radiofrequency ablation procedures for atrial fibrillation and transcatheter atrial septal closure procedures, and as such, ICE has become the “reference standard” for imaging during these procedures. The major advantage over TEE is that no general anesthesia is needed for ICE. Patients who have contraindications to TEE, eg, those with significant esophageal disease, can also avoid TEE while maintaining adequate imaging using ICE. In addition, if sufficiently skilled and knowledgeable, the operator performing the percutaneous closure can also manipulate the ICE catheter and interpret the images. In this setting, ICE has been shown to improve patient comfort and shorten procedure and fluoroscopy time, at comparable cost, compared to TEE-guided interventions under general anesthesia. ICE is currently used as the primary imaging modality during percutaneous transcatheter closure (PTC) without need for
supplemental transthoracic echocardiography (TTE) or TEE. ICE has also been shown to provide incremental diagnostic benefit over TTE and TEE. In a series of 94 patients undergoing PTC,\textsuperscript{28} ICE revealed additional diagnoses in 32\% of patients, despite preprocedural performance of TTE and TEE in the vast majority of patients. These diagnoses included additional atrial septal defects, atrial septal aneurysms, atrial septum redundancy, anomalous pulmonary venous return, pulmonary arteriovenous malformations, and pulmonary vein stenoses.

Additional interventional applications of ICE include guidance of transseptal catheterization, left atrial appendage occlusion, placement of ventricular assist device cannulas, percutaneous mitral balloon valvuloplasty, and many others (Table 13-1).\textsuperscript{29-43} Intracardiac imaging may serve as a diagnostic alternative in patients with contraindications for TEE (eg, esophageal pathology) or to assess anatomic regions that are inadequately visualized by TEE (eg, tracheal shadowing of the aorta).\textsuperscript{44-46} Similarly, ICE can readily evaluate native and prosthetic valves that are not invariably well visualized by TEE.

Table 13-1 Current and Potential Uses of ICE

<table>
<thead>
<tr>
<th>Interventional</th>
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<tr>
<td>• Percutaneous PFO and ASD closure</td>
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<tr>
<td>• Guidance of transseptal procedures</td>
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<tr>
<td>• Placement of left atrial appendage occlusion device</td>
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<tr>
<td>• Percutaneous ventricular septal defect closure</td>
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<tr>
<td>• Percutaneous left ventricular assist device cannula placement</td>
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<tr>
<td>• Pulmonary vein percutaneous transluminal venoplasty and stenting (after atrial fibrillation ablation)</td>
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<tr>
<td>• Percutaneous mitral repair (MitraClip, coronary sinus device)</td>
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<tr>
<td>• Mitral and aortic balloon valvuloplasty</td>
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<tr>
<td>• Hypertrophic cardiomyopathy alcohol septal ablation</td>
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<td>• Guidance of myocardial biopsy</td>
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<tr>
<th>Electrophysiologic</th>
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<tr>
<td>• Pulmonary vein isolation (atrial fibrillation ablation)</td>
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<td>• Sinus node modification</td>
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• Aortic cusp ablation
• Right and left ventricular ventricular tachycardia ablation
• Extraction of pacer and defibrillator leads

**Diagnostic intracardiac imaging**
• Alternative to TEE in those with contraindication
• Aortic evaluation including arch (“TEE blind spot”)
• Tricuspid and pulmonic prosthetic valve evaluation

Abbreviations: ASD, atrial septal defect; ICE, intracardiac echocardiography; PFO, patent foramen ovale; TEE, transesophageal echocardiography.

In the electrophysiology laboratory, ICE provides guidance for pulmonary vein isolation in patients with atrial fibrillation, sinus node modification, ablation procedures for idiopathic ventricular tachycardia (right ventricular outflow tract and aortic sinus locations), ablation procedures in the left ventricle, and extraction of pacemaker or ICD leads.\(^{13,47-50}\) In the electrophysiology laboratory, shorter procedure times, reduced arrhythmia recurrence, and reduced pulmonary vein stenosis occurrence have all been attributed to ICE guidance.\(^{13-16,18,19,51}\)

**ICE SYSTEMS**

Currently there are 3 commercially available ICE systems, each with unique features and advantages.\(^ {52}\) The Boston Scientific UltraICE Plus system uses a mechanical radial ICE imaging transducer, is not steerable, and does not provide Doppler-derived information. This 8.5-Fr system requires a short amount of time for catheter preparation: the housing must be flushed with saline and then physically spun prior to use. The transducer rotates at 1800 rpm and has a fixed frequency of 9 MHz. Both Siemens AcuNav and the St. Jude (formerly EP Medsystems) ViewFlex Xtra use phased array transducers. These transducers are steerable and deflectable. They provide 2-dimensional sector imaging with color and spectral Doppler capabilities. The ViewFlex Xtra and AcuNav systems have 4 directions of steering (anterior, posterior, right, and left). All 3 systems use a single-use ICE imaging catheter, require 8- to 11-Fr venous access, and are relatively expensive, with an approximate price range of $800 to $2800. The 8-Fr transducer catheters provide
somewhat less depth of imaging when compared to larger French systems.

Phased array ICE systems are generally bulkier than rotational ICE, with a handle and 2 dials to aid in maneuvering the catheter to a desired image while providing a 90° field of imaging. They also provide color Doppler and do not require flushing prior to use. Real-time 3-dimensional imaging is under investigation in the United States for both phased array systems. A housed rotational ICE system provides single 360° planar imaging but does not provide color Doppler. It is also less bulky and less maneuverable. No 3-dimensional imaging is currently available with rotational ICE.

**Table 13-2** Risks of Intracardiac Echocardiography

<table>
<thead>
<tr>
<th>Risk</th>
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<tr>
<td>Vascular trauma at groin site</td>
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<tr>
<td>Superficial cutaneous nerve palsy</td>
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<tr>
<td>Vascular bleeding and access site hematoma</td>
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<tr>
<td>Retroperitoneal hematoma</td>
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<tr>
<td>Perforation of venous structures</td>
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<tr>
<td>Pericardial effusion</td>
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<tr>
<td>Cardiac tamponade</td>
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<tr>
<td>Atrial arrhythmia</td>
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<td>Thromboembolism</td>
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</table>

**Limitations of ICE**

Current limitations of ICE include the relatively high cost of the single-use catheters and their large shaft diameters (less of an issue with the release of 8-Fr catheters). They provide only single-plane imaging with a relatively narrow field of view. Complications from the use of ICE are rare, but include all of the traditional vascular access–related complications, as well as perforation of the caval vein or cardiac chambers, which could result in cardiac tamponade *(Table 13-2)*.

**Principles of Imaging**

Images acquired with the newer phased-array steerable transducers such as the AcuNav catheter produce images that are similar to TEE images, except
that they originate from within the heart and accordingly require that the interpreter become familiar with a different set of image orientations. The AcuNav transducer has lockable steering controls, so that a particular imaging plane may be set and held in a stable position. Typically, AcuNav images are 90° sector images originating from the transducer location within a cardiac cavity. The AcuNav catheter is usually inserted via a femoral vein. Advancing and withdrawing the catheter shifts the images sideways (in-plane) on screen. A small marker placed outside the imaging sector indicates the proximal boundaries of the image (“operator end”). By emerging convention the image is displayed with the (marked) proximal end of the cross-section on the left side of the screen. Similar to the handling of a TEE probe, subtle rotation of the catheter will result in different angular cross-sections. While the transducer is typically positioned in the right atrium, images can be obtained from any cardiac and vascular structure into which the transducer tip of the catheter can be maneuvered. By systemic venous vascular access, the right atrium, the venae cavae, and the right ventricle can be reached, as well as the left atrium through the atrial septum. In contrast, with radial ICE imaging, the catheter is typically placed in the right atrium or venae cavae, with a more limited range of motion, as these catheters are neither steerable nor deflectable.

**RIGHT ATRIAL IMAGING VIEWS**

The imaging sequence with AcuNav usually begins from the right atrium, with the catheter in a neutral position and the locking mechanism disengaged. In the default position, the ultrasound array is sagittally oriented, parallel to the catheter, and upward in correspondence with the indicator line on the handle. All subsequent maneuvers are described relative to this starting position. The catheter is gently rotated approximately 15° to 30° clockwise from the default position to image the “home view” (Fig. 13-1). This view provides excellent imaging of the mid-right atrium, tricuspid valve, and right ventricle, and typically provides an oblique or short-axis view of the aortic valve.
Further clockwise rotation up to approximately 30° will display the right ventricular outflow tract and pulmonic valve. The aortic valve appears in a near short-axis view (Fig. 13-2). With clockwise rotation up to approximately 45°, the left ventricle can be seen in an oblique long-axis view with the apex toward the outer edge of the imaging sector. Also the left ventricular outflow tract and aortic valve will be visible (Fig. 13-3). Color-flow Doppler interrogation in this orientation may reveal aortic regurgitation (Fig. 13-4).
FIGURE 13-2 Echocardiographic image of the “right ventricular outflow tract view.” AV, aortic valve; PV, pulmonic valve; RA, right atrium; RV, right ventricle.

FIGURE 13-3 Echocardiographic image of the “left ventricular outflow tract view.” AV, aortic valve; LV, left ventricle; RA, right atrium; RVOT, right ventricular outflow tract.
FIGURE 13-4 Echocardiographic image of the “left ventricular outflow tract view” demonstrating mild aortic regurgitation (AR) by color-flow Doppler. RA, right atrium.

Further clockwise rotation to approximately 60° will provide a long-axis view of the left ventricle (LV) and the mitral valve (Fig. 13-5). Minimal anterior tilting toward the septum may improve visualization of the LV. At 70° to 80° clockwise rotation, the interatrial septum (IAS) is visualized, with the left atrial appendage in the far field (Fig. 13-6). At 90° to 100° clockwise rotation and with the ICE transducer positioned along the IAS, the left inferior and left superior pulmonary veins in the far field are seen (Fig. 13-7). Color-flow Doppler and pulse-wave Doppler flow patterns help differentiate the left atrial appendage (LAA) from the left pulmonary veins. From this position, the beam is aligned parallel to the pulmonary vein flow direction for optimal Doppler interrogation.
FIGURE 13-5 Echocardiographic image of the “left ventricular long-axis view.” IAS, interatrial septum; LA, left atrium; LAA, left atrial appendage; MV, mitral valve.

FIGURE 13-6 Echocardiographic image of the “interatrial septal view” in a patient with a PFO. AV, aortic valve; DAo, descending thoracic aorta; LA, left atrium; PFO, patent foramen ovale; RA, right atrium.
At 150° to 180° clockwise rotation, the right-sided pulmonary veins can be visualized, as well as the right atrial appendage (Figs. 13-8 and 13-9) with continued rotation. These views can also be reached by up to 30° counterclockwise rotation if these structures are the primary imaging targets (ie, crista ablation, pulmonary vein isolation for atrial fibrillation). To image the superior vena cava (SVC) entry into the right atrium (RA), the catheter is rotated approximately 210° to 240° from the starting position, with posterior tilting of the catheter to image upward (Fig. 13-10).
FIGURE 13-8 Echocardiographic image of the “right pulmonary veins view.” RIPV, right inferior pulmonary vein; RPA, right pulmonary artery; RSPV, right superior pulmonary vein; TS, transverse sinus.

FIGURE 13-9 Echocardiographic image of the “right atrial appendage view.” CT, crista terminalis; RAA, right atrial appendage.
ALTERNATIVE IMAGING VIEWS

Imaging with the transducer in the left atrium is achieved by passing the catheter through an atrial septal defect (ASD), a patent foramen ovale (PFO), or potentially other structures. Imaging from the left atrium (LA) provides excellent images of the LAA, as well as of the mitral valve (Figs. 13-11 and 13-12). Imaging from the SVC demonstrates the ascending aorta and arch (Fig. 13-13). Imaging from the RV through the intraventricular septum (IVS) provides near long-axis views of the LV and the mitral valve (MV) (Fig. 13-14), as well as of the right ventricular outflow tract (RVOT) and pulmonic valve. Imaging from the aorta has also been performed and used to guide endovascular interventions and biopsy procedures.
FIGURE 13-11 Echocardiographic image of the left atrium, left ventricle, and mitral valve after the catheter has been passed through an atrial septal defect. AL, anterior mitral valve leaflet; CS, coronary sinus; LA, left atrium; LV, left ventricle; PL, posterior mitral valve leaflet.
FIGURE 13-12 Echocardiographic image of the left atrial appendage from the left atrium after the catheter has been passed through an atrial septal defect. LA, left atrium; LV, left ventricle; LAA, left atrial appendage.

FIGURE 13-13 Echocardiographic image from the superior vena cava of the aortic arch (Ao Arch) and great vessels.
FIGURE 13-14 Imaging from the right ventricle through the IVS provides near long-axis views of the LV and mitral valve. IVS, interventricular septum; LA, left atrium; LV, left ventricle; PE, pericardial effusion.

ICE GUIDANCE FOR PERCUTANEOUS SEPTAL CLOSURE PROCEDURES

PTC of ASDs and PFOs serves as a model for the use of ICE in the catheterization laboratory. Using steerable and deflectable catheters, images are obtained with the transducer in the right atrium. Using posterior and rightward tilting of the transducer away from the IAS, excellent imaging of the septum and surrounding structures can be achieved. Posterior tilting increases the distance between the IAS and the ICE probe and improves spatial resolution for structures in the near field. This is particularly helpful in imaging the septum in the presence of an atrial septal aneurysm. From this position, radial sweeping to obtain the desired imaging plane may be accomplished either by gentle catheter rotation or by moving the right and left control wheel.
The preprocedural assessment of the IAS by ICE includes a complete evaluation of the entire IAS and its surrounding structures. A *patent foramen ovale (PFO)* is defined as a right-to-left communication through the fossa ovalis, in the anatomic region where septum primum overlaps the septum secundum (*Fig. 13-15*). Right-to-left shunting can be demonstrated by intravenous injection of agitated saline at rest or by applying shunt provoking maneuvers such as Valsalva, coughing, or sniffing (Mueller maneuver) (*Fig. 13-16*). It is important to image the passage of contrast through the foramen itself, as opposed to merely evaluating for the appearance of echo-contrast on the left side of the heart. Intrapulmonary shunting from pulmonary arteriovenous malformations or other right-to-left shunts may also cause contrast opacification of the left side of the heart and may be misinterpreted as a PFO. When right atrial pressure exceeds left atrial pressure, resting or intermittent right-to-left Doppler color flow may be seen, although this finding is not invariably present in all patients with PFO. An *atrial septal aneurysm* is usually defined as greater than 15 mm of total movement of a 15-mm length of atrial septal tissue. This can be demonstrated by M-mode echocardiography (*Fig. 13-17*) and measurement of the total peak-to-trough excursion. A *stretched PFO* is defined as an interatrial communication at the fossa ovalis in the anatomic region where the septum primum overlaps with the septum secundum, accompanied by a resting or intermittent left-to-right flow by color-flow Doppler imaging (*Fig. 13-18*). A stretched PFO is often the result of elevated left atrial pressure.
FIGURE 13-15 Imaging from the mid-right atrium (RA) demonstrating a patent foramen ovale (PFO); note the opening of the PFO tunnel with color Doppler demonstrating right-to-left flow. LA, left atrium.
FIGURE 13-16 Imaging from the mid-right atrium during saline contrast (bubble) with Valsalva maneuver demonstrating passage of right-to-left contrast consistent with patent foramen ovale. A. Initial opacification of the right atrium (RA) and the foramen with saline microbubble contrast (arrow). B. Initial contrast passage into the fossa (arrow) and left atrium (LA). C. Continued passage of saline microbubbles into the left atrium. AV, aortic valve; DAo, descending aorta.
FIGURE 13-17 M-mode demonstration of characteristic hypermobility of the interatrial septum seen with atrial septal aneurysm.

FIGURE 13-18 Imaging from the mid-right atrium (RA) demonstrating a stretched patent foramen ovale with left-to-right color-flow Doppler. DAo, descending aorta; LA, left atrium.
Associated abnormalities of the pulmonary veins, IVC, SVC, coronary sinus, and atrioventricular valves should be excluded. Careful evaluation of the pulmonary veins should be performed to exclude anomalous drainage that could require surgical correction. Measurement of the largest static diameter of the atrial septal defect is performed using 2-dimensional imaging (Fig. 13-19). Assessment of the rim of tissue around the defect is important in anticipation of PTC. Generally, a rim of 5 mm is considered adequate for percutaneous closure (Fig. 13-20). The inferior and superior rims may be particularly important. However, successful PTC has been reported in small series with deficient rims.

**FIGURE 13-19** Imaging from the mid-right atrium (RA) demonstrating a prominent atrial septal aneurysm with a large ostium secundum atrial septal defect. DAo, descending aorta; LA, left atrium.
Sizing of the ASD using balloons can be achieved by 1 of 2 methods. For the “pulling technique,” a sizing balloon is inflated in the left atrium to a size larger than the ASD and then pulled to occlude the defect, which is documented by lack of flow on color Doppler imaging. The balloon is then gradually deflated until it passes through the ASD to the right atrium. By measuring the remaining fluid in the passing balloon and comparing it with a size reference chart, the diameter size of the ASD can be determined. The simpler and more commonly used “stationary balloon” or “stop-flow” technique involves inflation of a soft, low-pressure balloon across the ASD monitored by ICE as well as fluoroscopy. When the defect is completely occluded, flow will no longer be observed by color-flow Doppler imaging, and a “waist” may appear in the balloon contour. The balloon waist diameter measured by echocardiography and fluoroscopy corresponds to the stretched diameter of the ASD (Fig. 13-21).
FIGURE 13-21 Imaging during balloon stretch sizing of an ostium secundum atrial septal defect. The arrows represent the “waist” of the balloon, corresponding to an average diameter of the defect. LA, left atrium; RA, right atrium.

The balloon is then removed with the guide wire left in place (Fig. 13-22). A device delivery sheath of appropriate size is then passed over the wire into the left atrium under ICE guidance (Fig. 13-23). The closure device is delivered through the sheath into the left atrium. Various devices and insertion techniques are currently in use, but typically it involves opening the disc or arms of the device on the left side and pulling it back to the interatrial septum (Fig. 13-24). Once the left atrial aspect of the device is in position, the right-sided aspect is employed, thereby “sandwiching” the septum. Because the arms of the device rest on atrial tissue around the defect, it is more difficult to achieve a stable position of the device when the ASD lacks adequate rims. For specific devices (eg, Amplatzer Septal Occluder), stable device positioning is confirmed by moving the connecting cable with the attached device back and forth (Fig. 13-25).
FIGURE 13-22 Image demonstrating the guide wire passing from right atrium (RA) to left atrium (LA) through the atrial septal defect.
FIGURE 13-23 Image demonstrating the device delivery sheath passing from right atrium (RA) to left atrium (LA) through an ostium secundum atrial septal defect. GS, Guide Sheath.
FIGURE 13-24 Image demonstrating the Amplatzer ASO disc opening in the left atrium (LA). RA, right atrium.
FIGURE 13-25 Image demonstrating the push–pull maneuver (“Minnesota wiggle”) to ensure stability of the Amplatzer device. LA, left atrium; RA, right atrium.

After confirmation of satisfactory placement, and before the device is finally released, the surrounding structures need to be evaluated. Large ASD or PFO closure devices may obstruct the right pulmonary veins, venae cavae, and coronary sinus, and occasionally may interfere with the function of the tricuspid and mitral valves. After final release of the device, echocardiography is repeated to assess for immediate ASD or PFO closure, as well as changes in device position, which often occur as traction from the connecting cable is released (Fig. 13-26). In PFO closure, a bubble contrast study is typically performed with and without Valsalva to document the immediate postprocedural adequacy of closure.
ICE GUIDANCE FOR OTHER PROCEDURES

As noted above, electrophysiology procedures may also benefit from ICE. ICE is typically used to aid in transseptal punctures and to aid in delineation of other structures within the left atrium, such as the left atrial appendage, pulmonary veins, and mitral valve, as well as to help localize ablation catheters along the RV outflow tract. These electrophysiology ICE procedures are often used with other mapping and imaging devices, such as CARTO, and may allow the use of zero or near-zero fluoroscopy for routine ablation.\textsuperscript{53-56} The significant reduction in radiation exposure to both the patient and the operator, without loss of efficacy and safety, may lead to wider adoption of this technique.
Another use of ICE is to obtain biopsy specimen of intracardiac masses.\(^{57}\) In this procedure, ICE is deployed from the right internal jugular vein through a large venous sheath. The biopsy equipment is delivered via a long sheath from the femoral vein into the right heart, and ICE is used to direct the biopsy needle to its intended target. An incision is made in the long femoral sheath, after estimating the distance from the right femoral vein access site to the level of the planned biopsy. A wire is then directed into the right heart, and the smaller sheath from the internal jugular vein is used to house a snare to pull the wire externally and overlap the 2 sheaths above the site of the planned biopsy needle exit to help stabilize the system. The ICE is deployed from the internal jugular vein near the level of the planned biopsy to guide the fixed curve biopsy needle through the slit into position and obtain the necessary samples.

An alternative to this method is to simply deploy ICE in the vicinity of the mass and guide a bioptome to the mass while monitoring bioptome contact and the removal of sample tissue\(^{59}\); this technique generally involves the use of bilateral femoral venous access, although there are other case reports of the ICE from the groin and the bioptome from the internal jugular vein.

**FUTURE DIRECTIONS**

Further refinement and miniaturization of ICE transducers, through continued technologic progress, will facilitate primary operator–controlled, integrated ultrasound–guided interventional devices. Smaller catheters under development may extend the range of catheter rotation, as well as reduce the risk of vascular complications. Online, real-time, 3-dimensional ICE, which offers additional advantages in the guidance of percutaneous noncoronary interventions, is currently being developed.\(^{59-61}\) These modalities offer the advantage of being able to delineate the complex relationships among intracardiac anatomy, physiology, and device function, although they have not been evaluated systematically in these settings.

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Cardiac Catheterization Laboratory
Physiologic Recorders

John W. Hirshfeld, Jr.

HISTORICAL BACKGROUND

Today’s clinical cardiac catheterization laboratory evolved from facilities that were originally human hemodynamic research laboratories. In the 1940s and 1950s, these facilities worked out much of our current understanding of human cardiovascular physiology and pathophysiology with a principal focus on cardiac valve disease.

Catheterization laboratory physiologic recorders were developed to meet 2 needs of these endeavors:

1. The need to monitor a patient’s condition during invasive procedures
2. The need to make permanent analog recordings of physiologic signals from patients

The catheterization laboratory physiologic recorder evolved from multichannel oscillographic physiologic recorders that had been developed for animal physiologic research in the first half of the 20th century. The original physiologic recorders were ink-writing multichannel oscillographs.

The importance of displaying and recording multiple superimposed channels of physiologic signals was rapidly recognized. Thus, the first major development was the move from ink-writing oscillographs to multichannel oscillographic recorders. These instruments could display multiple channels of
physiologic signals in real time on an oscilloscopic screen. The physician operator could view the screen in order to monitor in real time both the data being obtained and the patient’s condition. These instruments also added an important adjunct—the ability to superimpose multiple analog signals in a time-based display. This capability enhanced signal interpretation by displaying the nuances of relationships between different signals. (eg, superimposing pressure signals from adjacent cardiac chambers facilitates the recognition and measurement of pressure gradients.) This capability required incorporating photo-optical recorders that could record the individual superimposed oscilloscopic beams on light-sensitive paper, enabling permanent recordings of the physiologic signals.

These early instruments made the development of cardiac catheterization possible. However, they also had many shortcomings. They did not have the ability to record the events of a procedure in their entirety. The photo-optical recordings were fragile and easily degraded. It was difficult to make recordings available for remote review or to make illustrations for teaching and publication.

During the past 25 years, progress in electronic instrumentation, computer capability, and networking and improvements in display technology have fostered an evolution of the cardiac catheterization laboratory recorder, refining its functionality and enabling it to incorporate additional information management and reporting capabilities.

Currently available catheterization lab recorders are the core component of a comprehensive information system that, through hospital information system networking, has become an integral part of an overall cardiovascular information system and a health care institution’s electronic medical record.

In addition to serving their original function, current systems also serve as front ends for patient flow management, clinical database management, hospital information system data, clinical report generation, laboratory inventory management, and quality assurance analysis. Although these functionalities provide enhanced capabilities, they also require more detailed planning when selecting and configuring a system in order to optimize configurations and connectivities.

**Original Purposes**

The purpose of the original catheterization laboratory recorders was to
receive, condition, and display various types of patient physiologic signals that were of value for monitoring the patient and for assessing the patient’s pathophysiology. In addition to displaying signals in real time, they also had the capability to record signals for subsequent analysis.

Cardiovascular physiologic signals fall into 3 basic types:

1. Pressure signals from pressure transducers
2. Electrocardiogram (ECG) signals
3. Direct current (DC) voltage signals representing either voltages recorded from the patient or signals from other instruments such as flow meters, respiration and pulse oximetry probes, and other instruments

The early recorders had the capability to display these processed signals with appropriate gain in a variety of superimposition formats in order to present a comprehensive picture of the patient’s condition and the relationships between the phenomena represented by the different signals. In addition, the early recorders could produce a hard copy output to preserve selected signal recordings for archiving and analysis.

EVOLUTION TO CURRENT UNITS

Several developments have refined and extended the capabilities of physiologic recorders, yielding the highly capable units that are in current use. These include the following:

1. The development of stable, reliable, solid-state electronics and computer technology
2. The refinement of displays to high-resolution multicolor flat panel monitor units
3. The application of computer technology to system control, signal display, signal archiving, data analysis, and hard copy output generation
4. The evolution of cardiovascular and hospital information systems leading to the interface of catheterization laboratory recorders with hospital information systems and cardiovascular databases

The principal development in the evolution of the catheterization laboratory physiologic recorder was the incorporation of a computer for operational control. This transformed recorder design to fundamentally a
computer-run device. The physical recorder itself is now an assembly of generic computer hardware, input devices, output devices, display devices, and network connections. Because computer hardware is now mostly generic, system capabilities and the distinction between different systems are determined by the operating software. Thus, in the final analysis, a cardiac catheterization laboratory recording system is essentially a software product. The software generates the system’s human interface and operates the system’s components.

**CAPABILITIES OF AND PERFORMANCE CRITERIA FOR CURRENT UNITS**

**Capabilities**

A current fully functional catheterization laboratory physiologic recorder should have the following capabilities and features:

1. Accept, condition, and display a minimum of 8 physiologic signals from patient. These should include intravascular pressure from pressure transducers, 12-lead ECG, DC signals from other portable equipment such as flow meters and other transducers that produce a DC output signal, pulse oximetry, noninvasive blood pressure, and respiration.
2. Display the analog signals and their derived numeric values on a color monitor available for the operating physician to view in order to monitor the patient during the procedure.
3. Record the physiologic signals both as a hard copy and as a digital archive that can be exported as a Digital Imaging and Communications in Medicine (DICOM) object to a laboratory archiving system. The recorder should record and archive and be able to retrieve a complete record of the procedure from beginning to end (full disclosure).
4. Perform physiologic calculations such as valve orifice areas and conduct image analysis such as quantitative ventriculography and coronary arteriography.
5. Interface with the catheterization laboratory x-ray system to link the x-ray
images to the physiologic recordings from the procedure and incorporate the 2 outputs into a single record.

6. Maintain a time-stamped narrative procedure log of the procedure’s events including patient vital signs for the purposes of conscious sedation monitoring.

7. Interface with the hospital information system in order to read admissions/discharge/transfer (ADT) demographic data from the hospital information system as well as to export procedure utilization data back to it.

8. Record supplies used during the procedure for inventory management and billing purposes.

9. Generate a final catheterization report, ideally integrated with the x-ray system so that it can incorporate angiographic images.

10. Archive the report on the laboratory archive as a DICOM object.

11. Export the report to the hospital information system to facilitate clinical information transfer.

Performance Criteria

There are 9 performance criteria that should be assessed when judging a cardiac catheterization laboratory physiologic recorder.

1. **Stability and reliability:** This is the core performance criterion for any cardiac catheterization laboratory system and is a major component of the US Food and Drug Administration (FDA) certification criteria. These systems are computer applications that run on top of any one of several commercially available operating systems. The introduction of the computer into the cardiac catheterization laboratory recording system creates a new issue not previously present in earlier non–computer-based units—the computer crash. This is particularly important because a computer crash could potentially render the system inoperable until the computer is successfully restarted and reinitialized. Current systems, although based on very fast computers, are also based on complex operating systems, and the applications that they run are complex. Consequently, the “boot” or initialization time for a system to either start up after being shut off or reinitialize after a crash can be tiresomenly long. Therefore, it is important that these systems have very robust code that is
relatively crash-proof. Ideally, these systems should be isolated from the Internet so that they are at less risk of virus infection. Successful isolation may be challenging to achieve because the system must interact with the hospital information system and also needs to be accessed from outside for servicing and upgrade installation. Because systems are networked to data archives for deep storage of images and data, they should be capable of functioning autonomously in the event that the network connection is disrupted. Finally, it is essential that systems have a “limp home” mode that permits them to continue to perform basic monitoring functions even if the main computer system has crashed or is in the process of being restarted. This capability will ensure patient safety by continuing to provide patient monitoring during a restart if necessary.

2. **User interface:** This must be intuitive and easy to use. During a procedure, the recorder operator has multiple responsibilities in addition to actually operating the recorder. These include monitoring the patient and maintaining communication outside of the laboratory. These systems now have many features and functions that are accessed through a graphical user interface. As they have become more complex and have acquired additional capabilities, interface design has become increasingly demanding. The organization of that interface, including the menus, the design and placement of icons, and the overall screen layout, presents a major challenge to the interface designer. A good interface has menus that contain functions organized logically according to typical catheterization laboratory workflow. This facilitates the performance of the “routine” procedure. In addition, however, it should be easy and straightforward to configure the recorder for an unusual circumstance.

3. **X-ray system interface:** The system must interface with the laboratory’s x-ray system, which may be furnished by a different vendor. The system should read and record x-ray exposure data from the x-ray system for incorporation into the overall procedure record. In addition, the system should transmit patient demographic information to the x-ray system in order to enable linking of the x-ray images to the rest of the procedure information. When more than 1 vendor is involved, issues of proprietary protocols may interfere with some of this important functionality.

4. **Portable equipment interface:** A variety of portable equipment is used in cardiac catheterization laboratories. This includes various ultrasound machines, blood analysis meters, thermal dilution cardiac output
computers, oxygen consumption instruments, pressure wires, and more. The system should be able to accept signals from these devices and incorporate them into the overall procedure record and into the final procedure report.

5. **Hemodynamic measurements and calculations:** Although many cardiac catheterization procedures are principally angiographic procedures with only basic hemodynamic measurements, laboratories also need to evaluate valve disease, which may be complex, and, on occasion, complex congenital heart disease. The system must perform hemodynamic calculations including valve areas, vascular resistance, shunt calculations, and fractional flow reserve according to valid algorithms. It is important that the system display the component data employed in a hemodynamic calculation so that the validity of the calculation may be easily verified.

6. **Hospital information system interface:** Whereas earlier recorders were stand-alone systems, current systems are tightly linked to the hospital information system, the x-ray system, and the catheterization laboratory’s database and DICOM archive. Although considerable progress has been made to systematize data structures and communications protocols, building communication interfaces across different vendors has the potential to be problematic because of proprietary coding within individual systems. It is important to verify prior to installation that a selected system is also compatible with the other systems with which it must interface.

7. **Report generation:** The system must generate a properly organized report that is constructed in a manner that effectively communicates the procedure’s findings and, in particular, effectively reports any unusual circumstances or findings. Particular care must be taken in the report design to allow adaptation to the exigencies of particular procedures so that the reports do not all come out with a generic quality to them. Some systems may incorporate the report-generating function into the system. Other systems may export structured reporting data elements to a third-party report generator.

8. **National registry interface:** Most laboratories participate in national registries such as the American College of Cardiology National Cardiovascular Data Registry (NCDR). These registries receive a dictionary of defined data elements and store them for statistical analysis.
A well-designed system can automatically extract the core data elements stored by the registry and transmit them automatically to the registry’s data archives.

9. **Electronic medical record interface:** The completed catheterization procedure report should be exported to the hospital electronic medical record system and be distributed either electronically or as hard copy to constituent health providers. If the system generates the report internally, the completed report can be transmitted as a document to the electronic medical record. Alternatively, the electronic medical record may be configured to archive the data elements as data in addition to archiving the clinical report.

**CONCLUSION**

Current cardiac catheterization lab physiologic recorders are complex units that have many valuable capabilities made possible by the sophisticated application of computer technology to the task of monitoring a patient and recording, analyzing, storing, and reporting physiologic and imaging data obtained during cardiac catheterization procedures. Such systems have the potential to streamline cardiac catheterization laboratory operations and, through enhanced access to information and systematizing, can substantially improve overall quality of cardiac catheterization laboratory operations. However, given these systems’ complexity, careful advance planning for system design and configuration is necessary to create an optimally functioning system. Such advance planning will be rewarded by a system that operates efficiently and effectively.
Part III Pharmacology

15 Antithrombin Therapies

16 Antiplatelet Therapies in Contemporary Percutaneous Coronary Intervention

17 Thrombolytic Therapy

18 Radiographic Contrast Media

19 Renal Complications of Contrast Media

20 Contemporary Patient Sedation and Anesthesia in the Cardiovascular Catheterization Laboratory
INTRODUCTION

Acute coronary artery occlusion is a dynamic process that involves three essential processes: compromise of vascular integrity, platelet activation and aggregation, and acceleration of the coagulation cascade with fibrin formation. Although the role of thrombin (factor IIa) is well documented in blood coagulation, fibrin formation, and thrombus stabilization, it is also central to interplay among these processes. Angiographic, intravascular ultrasound (IVUS), and pathologic studies during acute coronary syndromes (ACS) have helped delineate the pathophysiology of coronary artery occlusion: atherosclerotic plaque rupture leads to release of tissue factor (TF), which has broad impact to stimulate platelets and generate thrombin. TF activates factor VII, which activates the common pathway via the extrinsic pathway, and also activates factor IX, activating the intrinsic pathway (Fig. 15-1). Subsequent generation of factor Xa leads to thrombin activation.
Inhibition of thrombin, along with the other serine proteases, is crucial in breaking this cycle and allowing either endogenous or exogenous fibrinolysis to occur. Thrombin is a well-suited target for therapeutics given its central role in arterial thrombosis. Current clinically available anticoagulants work via direct inhibition of either thrombin or an immediate upstream target, largely factor Xa.
HEPARIN

Mechanisms of Action

Heparin was first studied in ACS in 1988 and has been a mainstay for acute ischemic heart disease therapy since then. Heparins represent a heterogeneous group of negatively charged, heavily sulfated glycosaminoglycans. Heparins have a heterogeneous effect on the coagulation cascade, although most of the effect is mediated through binding with antithrombin, causing a conformational change leading to inactivation of multiple enzymes in the coagulation cascade. While factors IXa, Xla, and XIIa are targets as well, thrombin (factor IIa) and factor Xa are the most clinically relevant. As mentioned, thrombin inhibition leads to inhibition of fibrin formation and factors needed for its cross-linking and stabilization. Heparins also have an impact on arterial and venous thrombosis by increasing vessel wall permeability and binding to von Willebrand factor, leading to some inhibition in platelet activation. Unfractionated heparin (UFH) represents a heterogeneous compound with some important limitations:

- Propensity to bind to plasma proteins
- Inability to inhibit clot-bound thrombin
- Does not inhibit thrombin’s activation of platelets via protease-activated receptor-1 (PAR-1)
- Can induce an immune-mediated response, leading to heparin-induced thrombocytopenia

Low-molecular-weight heparins (LMWHs) are modified derivatives of UFH created by depolymerizing the larger heparin molecules. LMWH exert most of their anticoagulant effect via antithrombin-mediated inhibition of coagulation factors. Factor Xa is more affected than factor IIa in a ratio of 2:1 to 3:1. LMWHs have a benefit biochemically over heparin in that they have less of a propensity to bind to plasma proteins and cells, leading to a more predictable anticoagulant response and requiring less monitoring. However, LMWHs can cause heparin-induced thrombocytopenia, cannot inhibit clot bound thrombin, and do not inhibit thrombin’s activation of platelets.
Pharmacology and Dosing

Unfractionated Heparin

One of the major challenges in predicting the pharmacologic response to UFH is the significant heterogeneity in the product delivered. Appropriate levels of anticoagulation can be monitored by either activated partial thromboplastin time (aPTT) levels or activated clotting time (ACT) levels, with the latter being used in many catheterization labs. Although the following discussion is based on current guidelines and represents current practice, it is important to note recent data that show less correlation between ACT levels and hard clinical outcomes. With concurrent glycoprotein (GP) IIb/IIIa inhibition, the intravenous (IV) loading dose of UFH is 50 to 70 U/kg to achieve a therapeutic ACT of 200 to 250 seconds. Without concurrent GP IIb/IIIa inhibition, the IV loading dose of UFH is 70 to 100 IU/kg to achieve a therapeutic ACT of 250 to 300 seconds (HemoTec device; HemoTec Medical, Munich, Germany) or 300 to 350 seconds (Hemochron device; Accriva, Piscataway Township, NJ). These are listed as a Class I, Level of Evidence (LOE) C in the most recent American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) ST-segment elevation myocardial infarction (STEMI) guidelines. ACTs may be checked as soon as 5 minutes after bolus is given. If therapeutic ACT has not been achieved, additional bolus doses of 2000 to 5000 IU can be given to achieve target ACT. Continuation of heparin after percutaneous coronary intervention (PCI) has not been shown to be beneficial, but rather increases bleeding complications.

Low-Molecular-Weight Heparin

An intrinsic benefit to LMWH use is the predictability of its anticoagulant effect. Enoxaparin is the most widely studied and clinically used LMWH. The plasma half-life of enoxaparin is approximately 4 to 6 hours with peak effect seen within 3 to 5 hours after subcutaneous injection and a duration of action of up to 12 hours in normal renal function. Enoxaparin is hepatically metabolized and renally cleared (40% of actual dose and 10% of its active metabolites). There is little binding to plasma proteins and a more uniform molecular structure, leading to its more predictable effect. Routine
monitoring is not necessary. Anti–factor Xa activity is the monitoring test of choice, with a suggested therapeutic range of 0.8 to 1.8 IU/mL.

Maintenance enoxaparin dosing is dependent on age, renal function, and clinical scenario. Standard dosing is 1 mg/kg administered subcutaneously every 12 hours provided age <75 years and creatinine clearance (CrCl) >30 mL/min. In patients with age >75 years, a lower dose of 0.75 mg/kg per dose has been associated with lower bleeding complications. In patients with CrCl >15 mL/min but less than 30 mL/min, 1 mg/kg subcutaneously every 24 hours is recommended. In patients with CrCl <15 mL/min, enoxaparin is contraindicated. While no specific recommendations are noted in the guideline for concurrent GP IIb/IIIa use, some experts feel 0.75 mg/kg per dose may be more appropriate than a full dose. For ACS patients undergoing PCI, therapeutic anti–factor Xa levels were observed in 98% of those who received subcutaneous enoxaparin between 2 and 8 hours prior.\textsuperscript{3,4} For patients who received subcutaneous enoxaparin more than 8 hours prior to PCI, an IV enoxaparin dose of 0.3 mg/kg resulted in therapeutic anti–factor Xa levels in nearly all patients.\textsuperscript{4} Table 15-1 summarizes key concepts in pharmacology and dosing of UFH, LMWH, and fondaparinux.

| Table 15-1 Comparison of Key Characteristics of Unfractionated Heparin, Low-Molecular-Weight Heparin, and Fondaparinux |
Clinical Trials

Unfractionated Heparin

Over the past 2 decades, UFH has been a cornerstone therapy for ACS. A meta-analysis of 6 small trials showed that combination of heparin and aspirin conferred a 33% relative risk reduction in myocardial infarctions compared to aspirin alone. Subsequent ACS studies included UFH in the control arm. In a meta-analysis of trials testing LMWH, the UFH arm had an average rate of death and reinfarction of 11.0% in non–ST-segment elevation (NSTE) ACS and 11.8% in STEMI. The cumulative rates of major bleeding for UFH in these studies were 1.8% among STEMI patients and 5.4% among NSTE-ACS patients.

Some initial studies showed the rates of ischemic events to be related to degree of antithrombotic activity. A meta-analysis of six randomized controlled trials compared UFH to different regimens of antithrombotic and
antiplatelet therapies to assess whether level of antithrombotic activity as measured by ACT had an effect on 7-day ischemic event rates. A total of 5216 patients were included in the ischemic event rate analysis with only 15% of patients receiving stents and initially no patients receiving dual antiplatelet therapy. Of note, the vast majority of these patients had their ACT measured via the Hemochron device, and the ACT levels were divided into 25-second intervals for analysis, starting at 275 seconds. Ischemic end points followed a U-shaped distribution with relation to minimum ACT levels, with the lowest event rate at 7 days being 6.6% among patients with minimum ACT between 350 and 375 seconds. This optimal range was consistent among different subgroups, including diabetics, those presenting with ACS, and those receiving stents. Of note, minimum ACT levels above 375 seconds showed an increase in ischemic event rate, supporting the hypothesis of heparin-induced platelet activation at higher levels.

In the same analysis, rates of major and minor bleeding indexed for maximum ACT levels showed a similar U-shaped distribution. The lowest rate of major and minor bleeding was 8.6% and was seen among patients with maximum ACT levels between 325 and 350 seconds. There was a steady increase in bleeding rates with higher ACT levels, with a substantial increase between 350 and 375 seconds (12.4%) and ACT levels beyond that.

Based on these data, the STEMI guidelines have included target ACT levels to help guide dosing for antithrombotics. However, more recent data suggest less correlation between ACT levels and ischemic and bleeding event rates after ACS and PCI. This is likely due to multiple advances in medical therapy (eg, newer thienopyridines, earlier initiation of antiplatelet therapies, lower antithrombotic dosages) as well as changes in procedural technique (eg, radial access, smaller sheaths, changes in stent design).

Subsequent analysis of those receiving abciximab showed that concurrent GP IIb/IIIa inhibition has lower optimal ACT ranges with a plateau of ischemic events from 275 to 375 seconds, but a steady increase in bleeding risk with ACT levels from 275 to 375 seconds. The analysis of the different devices used was consistent with the 28% lower readings with the HemoTec device compared to the Hemochron device.

**Low-Molecular-Weight Heparin**

Multiple early clinical trials were conducted showing the efficacy of
enoxaparin in different clinical scenarios. A meta-analysis done in 2007 looked at 6 randomized controlled trials comparing enoxaparin with UFH in NSTE-ACS patients and 6 randomized controlled trials comparing enoxaparin with UFH in STEMI patients.\textsuperscript{6} In the NSTE-ACS cohort, there were 21,945 patients, with a consistent enoxaparin dose of 1 mg/kg twice a day versus varying dosages of UFH. There was a modest reduction in the combined ischemic end point of death and nonfatal myocardial infarction (MI) in the group receiving enoxaparin compared to UFH (10.0% vs 11.0%; odds ratio, 0.90 [95% confidence interval [CI], 0.81-0.996]; \(P = .043\)). This was driven by a reduction in nonfatal MI (8.0% vs 9.1%; OR, 0.87 [95% CI, 0.79-0.96]; \(P = .005\)), and there was no reduction in death (3.0% each; OR, 0.99 [95% CI, 0.83-1.18]; \(P = .890\)) (Fig. 15-2). However, there was also a non–statistically significant increase in major bleeding in the enoxaparin group (6.3% vs 5.4%; OR, 1.13 [95% CI, 0.84-1.54]; \(P = .419\)) (Fig. 15-3). The net effect of death, nonfatal MI, and nonfatal bleeding was not different between enoxaparin and UFH (14.1% vs 14.3%; OR, 0.97 [95% CI, 0.86-1.09]; \(P = .607\)).

**FIGURE 15-2** Enoxaparin (Enox) versus unfractionated heparin (UFH) in the comparison of death or nonfatal myocardial infarction (MI), using a random effects model. Black squares represent odds ratios (ORs), the size of which reflects the statistical weight of a trial in calculation of the OR. The horizontal lines represent
95% confidence intervals (CIs). There was evidence of heterogeneity between ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndromes (NSTEACS) \((P = .005)\). (Reproduced with permission from Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28(17):2077-2086.)

![Figure 15-3 Enoxaparin (Enox) versus unfractionated heparin (UFH) in the comparison of major bleed, displayed using a random effects model. Black squares represent odds ratios (ORs), the size of which reflects the statistical weight of a trial in calculation of the OR. The horizontal lines represent 95% confidence intervals (CIs). NSTEACS, non–ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction. (Reproduced with permission from Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28(17):2077-2086.)](image)

In the pooled STEMI cohort, there were 27,131 patients, with the ExTRACT-TIMI 25 trial providing the majority of patients \((n = 20,479)\). The enoxaparin dose was 1 mg/kg twice daily in most of the trials. In ExTRACT-TIMI 25, the dose of enoxaparin was reduced to 0.75 mg/kg twice daily for patients over the age of 75. The dose of UFH was most often 60 units/kg as a bolus with a continuous infusion of 12 units/kg/h. The combined ischemic end point was lower in the enoxaparin group than UFH group \((9.6\% \text{ vs} \)
Similar to the NSTE-ACS cohort, this combined end point was driven mainly by nonfatal MI (3.4% vs 5.1%; OR, 0.64 [95% CI, 0.52-0.78]; \( P < .001 \)) with no difference in mortality (6.6% vs 7.1%; OR, 0.92 [95% CI, 0.84-1.01]; \( P = .097 \)) (see Fig. 15-2). The rates of major bleeding were also higher with LMWH in the STEMI cohort (2.6% vs 1.8%; OR, 1.45 [95% CI, 1.23-1.72]; \( P < .001 \)) (see Fig. 15-3). The net effect of death, nonfatal MI, and nonfatal bleeding was lower in the enoxaparin group (11.1% vs 12.9%; OR, 0.84 [95% CI, 0.73-0.97]; \( P = .018 \)). One of the challenges in the clinical application of earlier trials is the lack of contemporary use of PCI. Three major clinical scenarios specifically warrant comment: elective PCI, PCI in NSTE-ACS, and PCI in STEMI, with a brief discussion on rescue PCI after fibrinolysis.

The Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients and International Randomized Evaluation (STEEPLE) study compared 2 doses of IV enoxaparin versus UFH in elective PCI. This was an open-label randomized trial where 3528 patients were randomized to 1 of 3 arms (0.5 mg/kg IV enoxaparin vs 0.75 mg/kg IV enoxaparin vs UFH) with a primary outcome of major or minor bleeding not related to coronary artery bypass grafting (CABG). Approximately 94% of patients received a stent (>50% drug-eluting stent [DES]). The trial was deemed to be underpowered to assess for differences in ischemic end points. The occurrence of major or minor bleeding within the first 48 hours was lower in the 0.5 mg/kg enoxaparin arm compared to UFH (5.9% vs 8.5%; \( P = .01 \)). The occurrence of major or minor bleeding within the first 48 hours was also lower in the 0.75 mg/kg enoxaparin arm (6.5% vs 8.5%; \( P = .05 \)). Importantly, major bleeding was significantly lower in both LMWH groups (1.2% vs 2.8% in the UFH arm; \( P = .004 \) for the 0.5 mg/kg enoxaparin arm and \( P = .007 \) for the 0.75 mg/kg enoxaparin arm). Conclusions from this trial were that lower dose enoxaparin (0.05 mg/kg) was deemed superior to UFH in elective PCI in decreasing rates of major or minor non–CABG-related bleeding, driven predominantly by decreased rates of major bleeding. It is important to note that the trial was underpowered to detect differences in ischemic end points that might have offset the reduction in bleeding.

In the Enoxaparin Versus Unfractionated Heparin in High-Risk Patients With Non-ST Segment Elevation Acute Coronary Syndromes Managed With an Intended Early Invasive Strategy (SYNERGY) trial, 9978 patients were analyzed after randomization to either enoxaparin or UFH. Of these patients,
over 47% received PCI and 19% underwent CABG. This trial was included in the meta-analysis discussed earlier. In the overall analysis, there was no difference in the combined ischemic end point of death and nonfatal MI (14.0% vs 14.5%; hazard ratio [HR], 0.96 [95% CI, 0.86-1.06]). Specifically, in patients undergoing PCI, there was no difference in ischemic complications, with similar rates of abrupt closure (1.3% vs 1.7%), threatened abrupt closure (1.1% vs 1.0%), unsuccessful PCI (3.6% vs 3.4%), or emergency CABG (0.3% each). However, there was an increase in Thrombolysis in Myocardial Infarction (TIMI) major bleeding (9.1% vs 7.6%; \( P = .008 \)), but not in Global Use of Strategies to Open Occluded Arteries (GUSTO) severe bleeding (2.7% vs 2.2%; \( P = .08 \)) or transfusions (17.0% vs 16.0%; \( P = .16 \)). Compared to previous NSTE-ACS trials, the patients in SYNERGY were older, and a more aggressive antiplatelet strategy was used. Conclusions from this trial were that enoxaparin was noninferior to UFH in terms of preventing ischemic end points both in the overall cohort and the PCI subgroup, despite the short duration of antithrombotic use prior to PCI (<48 hours) compared to those undergoing medical therapy. However, there was an increase in overall bleeding, but not in life-threatening bleeding or bleeding requiring transfusions.

As compared to ExTRACT-TIMI 25, which was a fibrinolysis study, the ATOLL trial enrolled patients undergoing primary PCI. The ATOLL trial randomized 910 patients to either enoxaparin 0.5 mg/kg IV or UFH in an open-label fashion.\(^\text{10}\) Stents were implanted in 95% of patients (18% DES). Roughly three-fourths of patients in both arms received GP IIb/IIIa inhibitors. This trial did not meet its primary composite end point of net clinical benefit of death, complication of MI, procedure failure, or major bleeding (28% in the enoxaparin arm vs 24% in UFH arm; risk ratio [RR], 0.83 [95% CI, 0.68-1.01]; \( P = .063 \)). However, there was a net reduction in its main secondary end point, which was a combined ischemic end point of death, nonfatal MI or ACS, or urgent revascularization (7% vs 11%; RR, 0.59 [95% CI, 0.38-0.91]; \( P = .015 \)), and no difference in procedural failure, defined as definite stent thrombosis, bailout use of GP IIb/IIIa inhibitor, non-TIMI 3 flow after procedure, or <50% reduction in ST elevation after procedure (26% vs 28%; RR, 0.94 [95% CI, 0.75-1.19]; \( P = .61 \)). In addition, there was also no difference in rates of major or minor bleeding (11% vs 12%; RR, 0.92 [95% CI, 0.64-1.32]; \( P = .65 \)) or rates of blood transfusions (2% each; RR, 0.81 [95% CI, 0.32-2.04]; \( P = .65 \)). Conclusions from this trial were that although
enoxaparin led to fewer combined ischemic events compared to UFH with no increase in procedural failure or clinically significant bleeding in patients with STEMI undergoing a primary PCI strategy, enoxaparin was not superior to UFH in net clinical benefit.

Rescue PCI has become more of a historical clinical scenario, but with STEMI networks often encompassing large geographical areas, it is still occasionally encountered. ExTRACT-TIMI 25 was discussed previously as a part of the large meta-analysis comparing LMWH to UFH. One notable subgroup analysis from this landmark trial was evaluation of rescue PCI within 30 days of initial event. While noting limitations in any post hoc analysis, this was a relatively robust analysis, with 2272 patients in the enoxaparin group undergoing PCI within 30 days and 2404 patients in the UFH group undergoing PCI within 30 days. The only pre-PCI variable that differed between the 2 groups was concomitant use of a GP IIb/IIIa inhibitor, which was higher in the UFH group (15.4% vs 19.2%; \( P = .001 \)). Among patients undergoing PCI, enoxaparin use was associated with a decreased incidence of the combined ischemic end point of death or nonfatal MI at 30 days (10.7% vs 13.8%; RR, 0.77 [95% CI, 0.66-0.90]; \( P = .001 \)), which was driven by a decrease in nonfatal MI (8.2% vs 11.3%; RR, 0.73 [95% CI 0.61-0.87]; \( P < .001 \)). There was also no difference in TIMI major or minor bleeding (4.6% vs 4.0%; RR, 1.15 [95% CI, 0.88-1.51]; \( P = .310 \)).

Conclusions from this trial were that enoxaparin is superior to UFH in rescue PCI after fibrinolysis in preventing the combined end point of death and nonfatal MI without an increased risk in major or minor bleeding.

**Summary and Guidelines**

**Medical Management and Fibrinolysis**

UFH provides the background upon which subsequent anticoagulants have been tested. Meta-analysis of UFH shows continued efficacy and a broader application given contraindications for other agents. In the most recent 2012 focused update from the ACC/AHA on unstable angina (UA)/non–ST-segment elevation MI (NSTEMI) patients undergoing an initial medical management strategy, enoxaparin and UFH carried a Class I recommendation with LOE A given the numerous randomized clinical trials comparing these
two therapies. The decreased ischemic event rates at the expense of slightly increased incidence of major bleeding shapes the Class IIa indication that for patients undergoing initial medical management, enoxaparin may be preferable to UFH. Duration of anticoagulation therapy in medically managed patients should be 48 hours for UFH and for the duration of hospitalization, up to 8 days, for enoxaparin.

Based on the 2013 focused update from the ACC/AHA on STEMI, both UFH (LOE C) and enoxaparin (LOE A) are Class I indications for adjunctive anticoagulation with fibrinolysis. The current guidelines do not recommend a particular agent, despite the findings of ExTRACT-TIMI 25.

**Percutaneous Coronary Intervention**

In UA/NSTEMI patients undergoing an early invasive strategy, both enoxaparin and UFH have a Class I, LOE A recommendation for initiation as soon as possible. In those undergoing PCI, anticoagulation should be discontinued as soon as PCI is completed, provided PCI was uncomplicated. Of note, in the STEMI guidelines, enoxaparin is not recommended due to the lack of supporting evidence, as the ATOLL trial failed to meet its primary composite end point of net clinical benefit of death, complication of MI, procedure failure, or major bleeding.

In patients undergoing PCI after fibrinolysis, UFH (LOE C) or enoxaparin (LOE B) may be continued through PCI. Additional boluses of UFH may be needed to achieve target ACT, depending on whether concurrent GP IIb/IIIa inhibitors are used. If subcutaneous enoxaparin was last given >8 hours prior to PCI, a single dose of 0.3 mg/kg of IV enoxaparin should be given.

**PENTASACCHARIDES**

*Mechanism of Action*

Pentasaccharides derive their name from the pentasaccharide sequence of heparin (Fig. 15-4). The only available pentasaccharide is fondaparinux. Fondaparinux works through a high affinity toward antithrombin (AT), leading to a conformational change in AT. This conformational change leads
to markedly increased affinity for factor Xa with little effect on its AT activity. The effect of fondaparinux is dependent on AT levels, and once plasma AT is depleted, the antithrombotic effect plateaus. The binding of fondaparinux to AT is reversible; however, the binding of AT to factor Xa is irreversible and requires subsequent clearance from plasma. The effect on thrombin is indirect via decreased thrombin generation from decreased factor Xa levels.


Thrombocytopenia is often seen with fondaparinux with reported rates of moderate and severe thrombocytopenia of 2.9% and 0.2%, respectively, in clinical trials. In addition, although fondaparinux does not cross-react with the serum of patients with heparin-induced thrombocytopenia, it can induce the production of anti-PF4 antibodies, leading to a low risk of heparin-induced thrombocytopenia. This association is controversial. Similar to heparin and LMWH, fondaparinux cannot inhibit factor Xa bound to prothrombinase complex.

**Pharmacology and Dosing**

Fondaparinux has 100% bioavailability after subcutaneous administration, reaching maximum serum concentrations in less than 2 hours. The antithrombotic effect is thought to be linear in most healthy patients with doses between 2 and 8 mg. The plasma half-life is slightly longer in elderly patients (21 hours) as compared to younger patients (17 hours). Based on this plasma half-life, the drug reaches steady-state levels after 3 to 4 days. Most of the drug is excreted unmodified in the urine, and moderate to severe renal insufficiency decreases clearance by 40% to 55% (see *Table 15-1*). There is some evidence to suggest that fondaparinux may be dialyzable.
Clinical trials assessing fondaparinux in deep vein thrombosis (DVT) prophylaxis and ACS have used doses of 2.5 mg subcutaneously once daily. Some DVT and pulmonary embolism trials have used larger dosages (up to 7.5 mg daily), but these doses are not recommended for ACS patients. Currently, there is no antidote, and protamine is not effective in reversing the effects of fondaparinux. Nonspecific agents, such as recombinant factor VIIa (rFVIIa), rapidly restored thrombin generation time and normalized mildly elevated aPTT in patients who received a single large dose of 10 mg of subcutaneous fondaparinux. Despite this biochemical relationship, the clinical efficacy of reducing bleeding with rFVIIa has not been tested.

aPTT and international normalized ratio (INR) are not effective monitoring tools for fondaparinux activity. Although aPTT and prothrombin time experience an average mild increase with fondaparinux, the increase is mild at best, and it is unclear whether it is dose dependent. There is minimal interference with INR, making fondaparinux an ideal tool for monitoring oral anticoagulation with warfarin. The most effective monitoring tool is anti–factor Xa activity, which closely reflects anticoagulation with fondaparinux.

**Clinical Trials**

There have been two major clinical trials looking at the role of fondaparinux across the ACS spectrum. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial was a randomized, double-blind, double-dummy trial to assess whether patients who presented with NSTE-ACS had lower rates of ischemia and bleeding with fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg twice daily for a mean of 6 days). A total of 20,078 patients were randomized, and there was no difference in the primary outcome of death, MI, or refractory ischemia at 9 days (5.8% vs 5.7%; HR, 1.01 [95% CI, 0.90-1.13]; \( P = .007 \) for noninferiority). This effect persisted at 30 days (8.0% vs 8.6%; HR, 0.93 [95% CI, 0.84-1.02]; \( P = .13 \)) and 180 days (12.3% vs 13.2%; HR, 0.93 [95% CI, 0.86-1.00]; \( P = .06 \)). A decrease in mortality was noted in the fondaparinux group at both 30 days (2.9% vs 3.5%; HR, 0.83 [95% CI, 0.71-0.97]; \( P = .02 \)) and at 180 days (5.8% vs 6.5%; HR, 0.89 [95% CI, 0.80-1.00]; \( P = .05 \)). The primary safety outcome was incidence of major bleeding, which was lower in the fondaparinux group compared to the enoxaparinux group at 9 days (2.2% vs 4.1%; HR, 0.52 [95% CI, 0.44-0.61]; \( P < .001 \)), 30 days (3.1% vs 5.0%; HR, 0.62 [95% CI, 0.54-
The net clinical benefit of death, MI, refractory ischemia, and major bleeding consistently favored fondaparinux over enoxaparin at 9 days (7.3% vs 9.0%; HR, 0.81 [95% CI, 0.73-0.89]; \( P < .001 \)), and this persisted over 30 days (10.2% vs 12.4%; HR, 0.82 [95% CI, 0.75-0.89]; \( P < .001 \)) and 180 days (15.0% vs 17.1%; HR, 0.86 [95% CI, 0.81-0.93]; \( P < .001 \)). An interesting finding was noted in the 39.5% of patients who underwent PCI. Although rates of overall procedural complications were not different between the 2 groups, there was a higher rate of catheter-associated thrombi in patients who received fondaparinux (0.9% vs 0.4%; HR, 3.59 [95% CI, 1.64-7.84]; \( P = .001 \)). Conclusions from this trial were that fondaparinux had similar rates of combined ischemic end point and lower incidence of major bleeding compared to enoxaparin up to 180 days from initial randomization in patients who presented with NSTE-ACS, but higher rates of catheter-associated thrombi in those undergoing PCI.

OASIS-6 was conducted to assess the effect on ischemic events and bleeding rates in 12,092 patients who presented with STEMI when randomized to fondaparinux or heparin.\(^\text{15}\) OASIS-6 was a randomized, double-blind trial and stratified patients based on whether they had an indication for UFH. Patients in stratum 2 were further stratified based on whether they were proceeding to PCI. Approximately 36.8% of patients had PCI during their index hospitalization, with an additional 3.4% having PCI after discharge. More than 44% of patients in both arms underwent thrombolytic therapy during their index hospitalization. Analysis of the primary end point showed no difference between fondaparinux and either placebo or UFH with regard to death or reinfarction at 9 days (7.4% vs 8.9%; HR, 0.83 [95% CI, 0.73-0.84]; \( P = .003 \)), and this persisted at 30 days (9.7% vs 11.2%; HR, 0.86 [95% CI, 0.77-0.96]; \( P = .008 \)) and at study end, which was 3 to 6 months (13.4% vs 14.8%; HR, 0.88 [95% CI, 0.79-0.97]; \( P = .008 \)). Of note, there was a reduction in death and reinfarction rates at each of these time points. The rate of severe bleeding in the overall analysis was not different in the fondaparinux group compared to placebo or UFH at 9 days (1.0% vs 1.3%; HR, 0.77 [95% CI, 0.55-1.08]; \( P = .13 \)). The prespecified subgroup analysis showed no improvement in death or reinfarction rates in the PCI group at 9 days (4.2% vs 4.1%; HR, 1.01 [95% CI, 0.74-1.38]; \( P = .96 \)), 30 days (6.1% vs 5.1%; HR, 1.20 [95% CI, 0.91-1.57]; \( P = .19 \)), or at the end of the study (8.5% vs 8.2%; HR, 1.06 [95% CI, 0.84-1.33]; \( P = .61 \)).
The patients undergoing no reperfusion strategy saw a reduction in ischemic events at 30 days (12.2% vs 15.1%; HR, 0.80 [95% CI, 0.65-0.98]; \( P = .003 \)), as did those who received a fibrinolytic agent (10.9% vs 13.6%; HR, 0.79 [95% CI, 0.68-0.92]; \( P = .003 \)). This was clearly not observed in the primary PCI group. Conclusions from this trial were that in STEMI patients not pursuing a primary PCI strategy, fondaparinux as compared to placebo or UFH significantly reduced mortality and reinfarction without increasing bleeding risk.

Summary and Guidelines

Medical Management and Fibrinolysis

The role of fondaparinux is firmly rooted in medical management and as an adjunctive antithrombotic agent to fibrinolysis. The current UA/NSTEMI guidelines have a Class I indication for fondaparinux in either an early invasive strategy (LOE B) or an initial conservative strategy (LOE B).\(^ {13} \) There is also a Class IIa indication recommending fondaparinux over UFH in those pursuing an initial conservative strategy (LOE B). In those patients, fondaparinux is recommended for the duration of the hospitalization up to 8 days. This is a reflection of the clinical efficacy and safety seen in OASIS-5.

As adjunctive therapy to fibrinolysis, fondaparinux has a Class I indication (LOE B) as long as CrCl is greater than 30 mL/min, based on the significant reduction in mortality and reinfarction rates in OASIS-6 among patients who received fibrinolysis.\(^ {2} \)

PCI

Fondaparinux has a limited role in support for either primary PCI or for rescue PCI after fibrinolysis due to the increased risk of catheter thrombosis seen in both OASIS-5 and OASIS-6, as well as the lack of clinical efficacy seen in OASIS-6. Currently, sole use of fondaparinux has a Class III indication for both primary PCI (LOE B) and rescue PCI after fibrinolysis (LOE C).\(^ {2} \) Current guidelines recommend an agent with activity against factor IIa, although optimal dosing and agents have not been clearly defined.
DIRECT THROMBIN INHIBITORS

Mechanism of Action

Direct thrombin inhibitors (DTIs) have become ubiquitous in their use over the last decade. In addition to thrombin’s effect on platelets, one of the principle mechanisms of activated thrombin is to cleave soluble fibrinogen into insoluble fibrin. This occurs at the active, or catalytic site, where fibrinogen is cleaved via serine protease activity. There are also 2 exosites, with exosite 1 being the binding site for fibrinogen and exosite 2 being the principle binding site of heparins (Fig. 15-5). DTIs are divided into bivalent inhibitors, which bind at both the active site and exosite 1, and univalent inhibitors, which primarily bind to the active site. As can be expected, bivalent inhibitors, such as hirudin and bivalirudin, are more selective than univalent inhibitors, such as argatroban. This is particularly important since the active site of thrombin is structurally similar to other serine proteases, and there can be significant unintended effects. This is appreciated clinically in the form of increased heterogeneity in clinical outcomes among different DTIs.
Overall, DTIs offer some potential benefits over heparins:

- They do not induce an immune-mediated response.
- They can inactivate clot bound thrombus.
- They do not bind to plasma proteins.

Currently, there are 4 parenteral DTIs available in the United States, with only bivalirudin and argatroban carrying indications for use in ACS patients. The single US Food and Drug Administration (FDA)–approved oral DTI, dabigatran, is only indicated at this time for nonvalvular atrial fibrillation and
is beyond the scope of this discussion.

The first 2 available DTIs were recombinant hirudin (rhirudin)—lepirudin and desirudin. Hirudin was originally isolated from the saliva of a medicinal leech, *Hirudo medicinalis*, and was subsequently produced synthetically using recombinant DNA technology in *Saccharomyces cerevisiae*. Lepirudin is an IV rhirudin and differs from the original 65-amino acid polypeptide by 2 amino acids. Desirudin is a subcutaneous rhirudin. Both bind irreversibly to thrombin at both the active site and exosite 1, with a strong affinity and no available antidote. Although the rhirudins are 10 times less potent in their binding with thrombin compared to hirudin, they still form irreversible 1:1 complexes with thrombin. This led clinically to increased bleeding events compared to heparin in ACS patients.

As a result, bivalirudin was developed. Bivalirudin is a synthetic analog of hirudin. This synthetic polypeptide is composed of 20 amino acids, and the active site is cleaved by thrombin, leaving only binding at exosite 1. This forms a significantly weaker bond with thrombin at both the active site and exosite 1 (approximately 800 times weaker than hirudin), allowing for potential competitive displacement of bivalirudin. Clinically, this was manifest as decreased bleeding rates compared to hirudin.

Argatroban is the only FDA-approved univalent DTI and binds reversibly to the active site. Unlike other univalent inhibitors, there is less cross-reactivity with other serine proteases, leading to a more consistent degree of anticoagulation.

**Pharmacology and Dosing**

Table 15-2 summarizes the key pharmacologic characteristics of the 4 FDA-approved DTIs. Because only bivalirudin and argatroban are currently indicated in ACS patients, the rest of the discussion will focus on these 2 agents.

Table 15-2 *Comparison of Different Direct Thrombin Inhibitors*
Bivalirudin has a plasma half-life of approximately 25 minutes in patients with normal renal function. Most of the drug metabolism occurs via proteolytic cleavage in the bloodstream and hepatic metabolism; however, approximately 20% is excreted via the kidney. In patients with moderate renal impairment (glomerular filtration rate [GFR] between 30 and 59 mL/min), the plasma half-life is 34 minutes, and in patients with severe renal impairment (GFR between 10 and 29 mL/min), the plasma half-life is 57 minutes. In patients on renal replacement therapy, the plasma half-life is 210 minutes. Therefore, in patients with a CrCl of 15 to 60 mL/min, a dose reduction is recommended, and bivalirudin is contraindicated in patients with a CrCl of <15 mL/min.

Monitoring for bivalirudin is most often clinically achieved via ACT, although aPTT can also be used. INR can also be prolonged during infusion, although it is not a reliable marker clinically. In patients with normal renal function, anticoagulant effects return to baseline within 2 hours (4 half-lives). In renal failure patients, large amounts of the drug can be cleared via
plasmapheresis or hemofiltration with large-size pores.

The onset of action for bivalirudin is immediately following IV injection, with a linear dose-response relationship. With a bolus infusion, therapeutic ACTs are achieved usually within 5 minutes, making it an ideal antithrombin for the catheterization lab. Target ACT levels vary clinically depending on many factors, including GP IIb/IIIa use, oral anticoagulation status, bleeding risk, and hypercoagulable states. Bivalirudin is also used in heparin-induced thrombocytopenia patients undergoing PCI.

Argatroban is hepatically metabolized and eliminated, and in patients with normal hepatic function, the plasma half-life is approximately 45 minutes. Steady-state plasma concentrations take longer to achieve regardless of bolus dosing. Therefore, argatroban is started without bolus dosing, followed by 2 μg/kg/h. In patients with hepatic dysfunction, dose adjustments are often necessary, and argatroban is contraindicated in severe liver failure. Monitoring is achieved with either aPTT or ACT. Target aPTT is 1.5 to 3 times that of baseline. INR will also be prolonged, and argatroban attenuates INR prolongation of warfarin.

**Clinical Trials**

The story of DTIs in ACS is a continuously evolving one, with recent data adding to our understanding of their effect. Initial clinical trials of DTIs in ACS were heterogeneous in their choice of DTI as well as their use of PCI. This led to heterogeneity of results as well as concerns of applicability in the current era of early invasive approach in ACS patients.

The Direct Thrombin Inhibitor Trialists Collaborative Group conducted a meta-analysis published in 2002 that assessed several DTIs in the larger ACS trials conducted up to that point. There were 11 total ACS trials comprising of 35,790 patients, with only 2 of the 11 trials being PCI trials. In the pooled efficacy analysis, patients treated with DTIs compared to UFH experienced a decrease in the cumulative end point of death and MI at the end of treatment (4.3% vs 5.1%; OR, 0.85 [95% CI, 0.77-0.94]; \( P = .001 \)) and at 30 days (7.4% vs 8.2%; OR, 0.91 [95% CI, 0.84-0.99]; \( P = .02 \)). However, this was driven primarily by a decrease in MI (2.8% vs 3.5%; OR, 0.80 [95% CI, 0.51-0.90]; \( P < .001 \)), and there was not an observed reduction in death rates (Fig. 15-6). These results were observed at 180 days as well. In patients undergoing PCI, there was no difference in the combined end point of death
and MI between DTIs and UFH, although over 75% of the patients came from 1 trial (Bivalirudin Angioplasty Trial). Analysis of the different DTIs showed a decrease in the cumulative end point of death and MI for the bivalent inhibitors (hirudin and bivalirudin) but not the univalent inhibitors (inogatran and argatroban).

FIGURE 15-6 Efficacy and safety of direct thrombin inhibitors (DTIs) versus heparins. Black squares represent odds ratios (OR), the size of which reflects the statistical weight of a trial in calculation of the OR. The horizontal lines represent 95% confidence intervals (CIs). There was evidence of heterogeneity among the DTIs \((P < .0001)\). (Reprinted from Direct Thrombin Inhibitor Trialists’ Collaborative Group.)

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<thead>
<tr>
<th>Death or myocardial infarction</th>
<th>Direct thrombin inhibitor (n = 18786)</th>
<th>Heparin (n = 17184)</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of treatment</strong></td>
<td>855 (4.3%)</td>
<td>883 (5.1%)</td>
<td>0.85</td>
<td>(0.77–0.94)</td>
</tr>
<tr>
<td><strong>7 days</strong></td>
<td>947 (5.0%)</td>
<td>990 (5.8%)</td>
<td>0.88</td>
<td>(0.80–0.96)</td>
</tr>
<tr>
<td><strong>30 days</strong></td>
<td>1399 (7.4%)</td>
<td>1409 (8.2%)</td>
<td>0.91</td>
<td>(0.84–0.99)</td>
</tr>
</tbody>
</table>

| Death | | | |
|-------| | | |
| **End of treatment**          | 355 (1.9%)                          | 346 (2.0%)      | 0.97 | (0.83–1.13) |
| **7 days**                    | 422 (2.2%)                          | 395 (2.3%)      | 1.00 | (0.87–1.16) |
| **30 days**                   | 685 (3.6%)                          | 642 (3.7%)      | 1.01 | (0.90–1.12) |

| Myocardial infarction         | | | |
|-------------------------------| | | |
| **End of treatment**          | 522 (2.8%)                          | 596 (3.5%)      | 0.80 | (0.71–0.90) |
| **7 days**                    | 601 (3.2%)                          | 672 (3.9%)      | 0.81 | (0.72–0.91) |
| **30 days**                   | 876 (4.7%)                          | 917 (5.3%)      | 0.87 | (0.79–0.95) |

| Stroke | | | |
|--------| | | |
| **End of treatment**          | 62 (0.33%)                          | 60 (0.35%)      | 0.95 | (0.66–1.35) |
| **7 days**                     | 72 (0.38%)                          | 70 (0.41%)      | 0.94 | (0.68–1.31) |
| **30 days**                    | 120 (0.64%)                         | 110 (0.64%)     | 0.01 | (0.78–1.31) |

| Major bleeding during treatment* | | | |
|-------------------------------| | | |
| **Intracranial bleeding during treatment** | 21 (0.11%) | 28 (0.16%) | 0.72 | (0.42–1.23) |

*Heterogeneity \(p<0.0001\)
In the safety analysis of the pooled data, there was a decrease in the DTI group of major bleeding, with no difference in the rates of intracranial hemorrhage. However, there was significant heterogeneity between the different DTIs, specifically an increased rate of major bleeding with hirudin (1.7% vs 1.3%; OR, 1.28 [95% CI, 1.06-1.55]) and a decreased rate of major bleeding with bivalirudin (4.2% vs 9.0%; OR, 0.44 [95% CI, 0.34-0.56]). Subgroup analysis showed higher rates of major bleeding in patients with no ST elevation (1.0% vs 0.5%; OR, 1.79 [95% CI, 1.29-2.50]); however, there was no significant difference in major bleeding when used in conjunction with thrombolytics or PCI. However, heterogeneity between the different DTIs was observed in each of these subgroups.

Based on the paucity of data in PCI patients as well as the emerging evidence on the benefit of early invasive strategies in ACS patients, subsequent trials looked at the role of DTIs in patients undergoing PCI. Given the lack of efficacy of univalent inhibitors and the increased rates of major bleeding with hirudin, subsequent trials used bivalirudin as the DTI of choice. However, most of the subsequent trials were compared to UFH and routine use of GP IIb/IIIa inhibitors.

The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial was a randomized, double-blind trial with 6010 patients who underwent elective or urgent PCI to assess whether bivalirudin with provisional GP IIb/IIIa inhibition (used in approximately 7% of patients randomized to this arm) reduced clinical events compared to UFH with planned GP IIb/IIIa inhibition. All patients received dual antiplatelet therapy, and 85% of patients received stents. There was no difference between bivalirudin and UFH with GP IIb/IIIa inhibition in the cumulative ischemic end point of death, MI, and severe myocardial ischemia requiring urgent revascularization (7.6% vs 7.1%; OR, 1.09 [95% CI, 0.90-1.32]; P = .40). Major bleeding rates were decreased in the bivalirudin group versus the heparin plus GP IIb/IIIa inhibition group (2.4% vs 4.1%; P < .001).

Conclusions from this trial of relatively low-risk patients, specifically including elective PCI patients, are that bivalirudin is noninferior in terms of clinical efficacy but has decreased rates of major bleeding when compared to
UFH plus GP IIb/IIIa inhibition.

Long-term follow-up of these patients showed no difference in mortality, nonfatal MI, or repeat revascularization at 6 months or 1 year between bivalirudin and UFH plus GP IIb/IIIa, suggesting comparable long-term efficacy.\(^{19}\)

Given the intrinsically low-risk group studied in REPLACE-2, the question still remained as to whether high-risk ACS patients would also derive this benefit. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial included 13,819 patients who presented with high-risk UA or NSTEMI and assessed whether bivalirudin either with or without GP IIb/IIIa inhibition reduced ischemic event rates compared to heparin plus GP IIb/IIIa inhibition.\(^{20}\) Patients were randomized to 1 of 3 arms: bivalirudin alone, bivalirudin plus GP IIb/IIIa inhibition or UFH, or enoxaparin plus GP IIb/IIIa; patients underwent PCI within 72 hours. The combined ischemic end point was similar to that in REPLACE-2 and included death, MI, and myocardial ischemia requiring revascularization within 30 days. Not surprisingly, there was no difference in the combined ischemic end point between bivalirudin plus GP IIb/IIIa inhibition and heparin plus GP IIb/IIIa inhibition (7.7% vs 7.3%; RR, 1.07 [95% CI, 0.92-1.23]; \(P = .39\)). Bivalirudin monotherapy was also found to be noninferior compared to heparin plus GP IIb/IIIa inhibition (7.8% vs 7.3%; RR, 1.08 [95% CI, 0.93-1.24]; \(P = .32\)). There was a significant reduction in major bleeding in the bivalirudin monotherapy group compared to both bivalirudin plus GP IIb/IIIa inhibition and heparin plus GP IIb/IIIa inhibition (3.0% vs 5.3% and 5.7%, respectively; RR, 0.53 [95% CI, 0.43-0.65]; \(P < .001\) for bivalirudin monotherapy vs heparin plus GP IIb/IIIa inhibition). Similar to REPLACE-2, conclusions from this trial were that bivalirudin monotherapy is noninferior in preventing ischemic events but significantly reduces major bleeding rates compared to either bivalirudin or heparin plus GP IIb/IIIa inhibition. Of note, the only prespecified subgroup that showed higher rates of the composite ischemic event in the bivalirudin monotherapy group compared with the heparin plus GP IIb/IIIa group were patients who did not receive upstream thienopyridine (ischemic event rates of 9.1% vs 7.1%; RR, 1.29 [95% CI, 1.03-1.63]; \(P = .054\)).

Long-term follow-up of these patients showed no difference in all-cause mortality or composite ischemic events at 1 year, suggesting once again noninferiority in preventing ischemic events with bivalirudin monotherapy.
compared to UFH plus GP IIb/IIIa inhibition.\textsuperscript{21,22}

Although these studies investigated the role of bivalirudin in non–ST-segment elevation ACS and stable angina, there still were questions regarding role of DTIs in STEMI. Initial trials looked at concurrent use of DTIs in fibrinolysis, with GUSTO-IIb and TIMI 9b showing similar rates of the composite ischemic end points of death and reinfarction at 30 days, but with a potentially higher rate of nonintracranial major bleeding seen in TIMI 9b when comparing hirudin versus UFH in conjunction with thrombolytic therapy. In HERO-2, patients were randomized to bivalirudin versus UFH in conjunction with streptokinase. At 30 days, there were similar rates of death and major bleeding but more minor and moderate bleeding in the bivalirudin group. Of note, there were fewer reinfarction rates in the bivalirudin group at 96 hours.\textsuperscript{23}

The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study attempted to address the role of bivalirudin in primary PCI for STEMI.\textsuperscript{24} STEMI patients (n = 3602) were randomized to receive either bivalirudin or heparin plus GP IIb/IIIa. All patients were preloaded with thienopyridine (>99% with clopidogrel), and over 95% of patients received a stent. Of note, more than 91% of patients were Killip class I, and 7.2% of patients in the bivalirudin group received GP IIb/IIIa inhibition, noted by the authors to be due to suboptimal results of the PCI. In the combined ischemic end point of death, reinfarction, revascularization for ischemia, and stroke, there was no difference between bivalirudin and UFH with GP IIb/IIIa inhibition (5.4% vs 5.5%; RR, 0.99 [95% CI, 0.76-1.30]; \(P = .95\)). Similar to NSTE-ACS trials, there was a reduction in major bleeding with bivalirudin (4.0% vs 8.3%; RR, 0.60 [95% CI, 0.46-0.77]; \(P < .001\)). The conclusions from this trial, similar to the NSTE-ACS trials, were that bivalirudin is associated with similar rates of ischemic events but a significantly decreased rate of major bleeding, conferring a net clinical benefit compared to UFH with GP IIb/IIIa inhibition. There was a reduction in cardiovascular mortality (2.1% vs 3.8%; HR, 0.57 [95% CI, 0.38-0.84]; \(P = .005\)) and all-cause mortality (3.5% vs 4.8%; HR, 0.71 [95% CI, 0.51-0.98]; \(P = .037\)) out to 1 year with bivalirudin.\textsuperscript{25}

However, this mortality benefit was not seen in the longer term follow-up from REPLACE-2 or ACUITY (Fig. 15-7).\textsuperscript{26}
Since these trials, there has been a shift in procedural practice, with routine use of GP IIb/IIIa inhibition being supplanted by early initiation of potent oral antiplatelet agents. Also, the vast majority of PCIs were done via femoral access, and with routine use of radial access virtually eliminating access site bleeding, it is speculated whether the reduction in bleeding with bivalirudin would still be seen in a more contemporary trial. In addition, there is limited evidence on bivalirudin versus UFH without routine use of GP IIb/IIIa inhibition. Both the EUROMAX and HEAT-PPCI studies attempted to address these gaps in the evidence.

The European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) study was an international, open-label, randomized controlled trial that randomized patients being transported with STEMI to early bivalirudin or UFH with optional use of GP IIB/IIIa inhibition in both arms. A total of 2198 patients were randomized (1089 in the bivalirudin arm and 1109 in the UFH arm), with acetylsalicylic acid (ASA; aspirin) and P2Y$_{12}$ inhibitor loading in 98% of patients. Radial access was used in approximately 47% of patients, and a stent was implanted in approximately 92% of patients. Of note, there was a significant difference in both arms in the total use of GP IIB/IIIa inhibition (11.5% in the bivalirudin arm and 69.1% in the UFH arm), as well as the routine use of GP IIB/IIIa inhibition (3.9% in the bivalirudin arm and 58.5% in the UFH arm). The primary outcome was the composite of death and non-CABG major bleeding and was significantly lower in the bivalirudin arm (5.1% vs 8.5%; RR, 0.60 [95% CI, 0.43-0.82]; $P = .001$). The principle secondary outcome, which was a composite of death, reinfarction, or non–CABG-related major bleeding, was also lower in the bivalirudin arm (6.6% vs 9.2%; RR, 0.72 [95% CI, 0.54-0.96]; $P = .02$). There was no difference in mortality between the 2 groups (2.9% vs 3.1%; RR, 0.96 [95% CI, 0.60-1.54]; $P = .86$), and the primary end point was driven by non-CABG major bleeding (2.6% vs 6.0%; RR, 0.43 [95% CI, 0.28-0.66]; $P < .001$).
addition, there was an increase in acute stent thrombosis (defined as <24 hours) in the bivalirudin arm (1.1% vs 0.2%; RR, 6.11 [95% CI, 1.37-27.24]; \( P = .007 \)). Conclusions from this trial were that early initiation of bivalirudin on transport to a PCI-capable hospital for STEMI had decreased rates of the composite of death and non-CABG major bleeding as compared to UFH but higher rates of stent thrombosis. The net clinical benefit, as defined by the principle secondary outcome, favored the routine use of bivalirudin. Although the use of GP IIb/IIIa inhibition was optional, there was still significantly higher use in the UFH arm, similar to previous trials.

The Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention (HEAT-PPCI) study was an open-label, single-center randomized control trial that randomized patients presenting to a high-volume, tertiary care center with STEMI to either bivalirudin or UFH with provisional use of GP IIb/IIIa inhibition in both arms. A total of 1812 patients were randomized (905 in the bivalirudin arm and 907 in the UFH arm), with ASA and P2Y_{12} inhibitor loading occurring in 99% of patients. In addition, radial access was used in approximately 80% of patients, and PCI was attempted in 82% of patients, with a >97% successful intervention rate in each arm (stent implanted in 90% of patients). GP IIb/IIIa inhibition was not significantly different in the 2 arms (13% in bivalirudin arm and 15% in UFH arm). The primary efficacy end point was the composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target vessel revascularization at 28 days and was higher in the bivalirudin arm (8.7% vs 5.7%; RR, 1.52 [95% CI, 1.09-2.13]; \( P = .01 \)). Specifically, there was a higher rate of definite or probable stent thrombosis in the bivalirudin arm (3.4% vs 0.9%; RR, 3.91 [95% CI, 1.61-9.52]; \( P = .001 \)) and a higher rate of acute in-stent thrombosis (2.9% vs 0.9%; RR, 3.26 [95% CI, 1.32-8.07]; \( P = .007 \)). The primary safety end point was major bleeding (Bleeding Academic Research Consortium type 3-5) and was not different between the 2 arms (3.5% vs 3.1%; RR, 1.15 [95% CI, 0.70-1.89]; \( P = .59 \)). Conclusions from this trial were that there was an increase in major adverse cardiovascular event rates among STEMI patients treated with bivalirudin compared to UFH with no difference in rates of all bleeding or major bleeding. This increase in major adverse cardiovascular events was driven by acute stent thrombosis and was consistent with the bivalirudin arms of the HORIZONS-AMI and EUROMAX trials.

HEAT-PPCI was met with significant controversy, specifically regarding
its controversial consent process as well as the discrepant results from previous trials. Given that it is a single-center experience, validation of these findings are important, but the trial likely represents a more contemporary experience than the landmark trials. This also raises the question as to the effect of provisional versus planned GP IIb/IIIa inhibitor use on the bleeding risk in the landmark trials.

A recent meta-analysis attempted to look at the composite bivalirudin experience in patients undergoing PCI. Data from 16 trials involving almost 34,000 patients across the spectrum of stable angina and ACS were included. There was an increase in major adverse cardiovascular events with bivalirudin-based regimens compared to UFH-based regimens (RR, 1.09 [95% CI, 1.01-1.17]; \( P = .02 \)) driven primarily by increase in MI (RR, 1.12 [95% CI, 1.03-1.2]). This likely is due to an increase in acute stent thrombosis, which was pronounced in the 3 most recent randomized controlled trials (RR, 4.27 [95% CI, 2.28-8]; \( P < .0001 \)). Major bleeding rates were lower in the bivalirudin group (RR, 0.62 [95% CI, 0.49-0.78]; \( P < .0001 \)); however, this effect was heterogeneous depending on use of GP IIb/IIIa inhibition. The provisional use of GP IIb/IIIa in both arms (RR, 0.78 [95% CI, 0.51-1.19]; \( P = .25 \)) and the planned use of GP IIb/IIIa in both arms (RR, 1.07 [95% CI, 0.87-1.31]; \( P = .53 \)) showed no difference in rates of major bleeding. Conclusions from this analysis suggest an increase in acute stent thrombosis with bivalirudin-based regimens, which is consistent with the 3 most recent randomized controlled trials (Fig. 15-8).

<table>
<thead>
<tr>
<th>Acute stent thrombosis</th>
<th>Bivalirudin</th>
<th>Heparin</th>
<th>Stent thrombosis risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HORIZONS-AMI²</td>
<td>21/1571 (1%)</td>
<td>4/1553 (&lt;1%)</td>
<td>5.19 (1.79–15.08)</td>
</tr>
<tr>
<td>EUROMAX</td>
<td>12/1089 (1%)</td>
<td>2/109 (&lt;1%)</td>
<td>6.11 (1.37–27.74)</td>
</tr>
<tr>
<td>HEAT PPC²</td>
<td>20/697 (3%)</td>
<td>6/682 (1%)</td>
<td>3.26 (1.32–8.07)</td>
</tr>
<tr>
<td>Overall</td>
<td>53/3357 (2%)</td>
<td>12/3344 (&lt;1%)</td>
<td>4.27 (2.28–8.00)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subacute stent thrombosis</th>
<th>Bivalirudin</th>
<th>Heparin</th>
<th>Stent thrombosis risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HORIZONS-AMI²</td>
<td>19/1571 (1%)</td>
<td>26/1553 (2%)</td>
<td>0.72 (0.40–1.30)</td>
</tr>
<tr>
<td>EUROMAX</td>
<td>5/1089 (&lt;1%)</td>
<td>4/109 (&lt;1%)</td>
<td>1.27 (0.34–4.73)</td>
</tr>
<tr>
<td>HEAT PPC²</td>
<td>4/697 (1%)</td>
<td>0/682 (0%)</td>
<td>8.81 (0.48–163.26)</td>
</tr>
<tr>
<td>Overall</td>
<td>28/3357 (1%)</td>
<td>30/3344 (1%)</td>
<td>1.06 (0.43–2.61)</td>
</tr>
</tbody>
</table>

**FIGURE 15-8** Acute stent thrombosis rates between bivalirudin- and unfractionated

One proposed reason for the increase in stent thrombosis with bivalirudin is the relatively short duration of action, and different protocols for bivalirudin may offset the increased risk of acute stent thrombosis. As an optimal protocol is identified, the risk of acute stent thrombosis will likely need to be reassessed.

The extent of the decrease in bleeding with bivalirudin has been brought into question, and may be due, at least in part, to the use of GP IIb/IIIa inhibitors in the major trials (Fig. 15-9). The most contemporary trials have been split on the risk of bleeding with bivalirudin, and further investigation in a multicenter randomized controlled trial will be needed.
**Summary and Guidelines**

Univalent inhibitors have been shown to be ineffective compared to heparin in ACS patients and, therefore, are limited to use in patients who cannot receive heparin due to absolute contraindications, such as heparin-induced thrombocytopenia. Recombinant hirudins are also limited in clinical use to non-ACS indications due to the increased bleeding risk in ACS trials.
Bivalirudin is the only clinically relevant DTI, with its major clinical application in patients undergoing PCI. Based on recent randomized clinical trials, there appears to be an increased risk of acute stent thrombosis with bivalirudin-based regimens. The majority of clinical trials show a reduction in bleeding risk with bivalirudin versus UFH; however, the impact of GP IIb/IIIa inhibition on this bleeding risk is under investigation.

**Medical Management and Fibrinolysis**

Current ACC/AHA guidelines for NSTE-ACS have a very limited scope for the use of bivalirudin for medical management, predominantly due to the lack of data in this patient population. In patients undergoing an initial conservative strategy, bivalirudin is not currently indicated. In patients who undergo diagnostic angiography after which a conservative strategy is pursued, bivalirudin can either be discontinued immediately or continued at 0.25 mg/kg/h for up to 72 hours per the physician’s discretion. For patients undergoing CABG, bivalirudin should be stopped 3 hours prior to surgery.

Use of bivalirudin in patients undergoing fibrinolysis is limited to patients who have presumed or documented heparin-induced thrombocytopenia, due to increased bleeding risk seen in fibrinolysis trials.

**Percutaneous Coronary Intervention**

Bivalirudin’s largest contribution to ACS management has been in patients undergoing PCI. The guidelines are driven by the data that showed similar ischemic event rates with decreased incidence of major bleeding compared to UFH with GP IIb/IIIa inhibition. Bivalirudin use in patients undergoing an initial invasive strategy carries a Class I indication (LOE B) in the most recent ACC/AHA UA/NSTEMI guidelines. It is important to note, however, that the rate of acute stent thrombosis is higher, even in studies that had thienopyridine loading prior to PCI.

**SPECIFIC CLINICAL SCENARIOS**

**Oral Anticoagulant Use**
There has been a substantial increase in the clinical availability and use of oral anticoagulants, both DTIs and anti–factor Xa agents. All clinical trials have looked at oral agents in the setting of recent ACS. The anti–factor Xa agents apixaban and darexaban were shown to have increased rates of major bleeding compared to placebo, limiting their use in this clinical scenario. Rivaroxaban has been studied more extensively in the stable post-ACS patient. In a phase II clinical trial of rivaroxaban, ATLAS ACS-TIMI 46, there was no net clinical benefit seen in patients undergoing revascularization; however, in medically managed patients, there was a decrease in ischemic end points with a concomitant increase in major bleeding. This led to a phase III clinical trial, ATLAS ACS-TIMI 51. In ATLAS ACS-TIMI 51, rivaroxaban at a lower dose (2.5 mg twice a day) was associated with a decrease in the primary end point of cardiovascular death, nonfatal MI, or nonfatal stroke compared with placebo (9.1% vs 10.7%; HR, 0.84 [95% CI, 0.72-0.97]; P = .02), with a decrease in both cardiovascular death and all-cause mortality.\textsuperscript{31} There was also an increase in both TIMI major bleeding and intracranial hemorrhage, but not fatal bleeding. The phase II RE-DEEM study compared multiple dosages of the oral DTI dabigatran versus placebo in patients with recent ACS, showing increased rates of bleeding with dabigatran compared to placebo. The study was not powered to assess for ischemic end points. This has led to a potential role, albeit a limited one, for oral anticoagulants in the post-ACS patient.

A more salient question is what to do about antithrombotic use in patients already on oral anticoagulants. Over 5% of patients referred for PCI are on oral anticoagulants chronically. Unfortunately, there are limited available data to guide therapy and currently no prospective data. A retrospective, multicenter analysis showed an increase in rates of major bleeding and vascular site complications in patients who had their warfarin interrupted, which was hypothesized to be due to increased use of parenteral anticoagulants and GP IIb/IIIa inhibition.\textsuperscript{32} Multiple retrospective analyses support the performing of PCI on therapeutic warfarin if the INR is between 2 and 3. However, there is an increase in femoral access complications with therapeutic warfarin, especially if additional heparin is given periprocedurally, and radial access is recommended. Interrupting or bridging systemic anticoagulants has not been shown in the limited data available to decrease either ischemic or bleeding complications and leads to prolonged hospitalization and more time with subtherapeutic anticoagulation.\textsuperscript{33} Given
warfarin’s predictable effect on ACT, some propose using a parenteral antithrombotic (preferably UFH) as needed to maintain therapeutic ACTs during the PCI. Newer oral anticoagulants have even less data, and any current recommendations are made based on anecdotal evidence.\textsuperscript{34} Table 15-3 summarizes the proposed management for patients on oral anticoagulants proceeding to PCI.

Table 15-3 Proposed Management for Patients on Oral Anticoagulants Proceeding to PCI

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>STEMI</th>
<th>NSTEMI/UA</th>
<th>Elective PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC management</td>
<td>Continue VKA and NOAC</td>
<td>Continue VKA</td>
<td>Hold VKA and NOAC if possible</td>
</tr>
<tr>
<td>PCI considerations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access</td>
<td>Radial if possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Reduced dose UFH; follow ACT levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choice of stent</td>
<td>BMS, second-generation DES or later</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAP therapy</td>
<td>The optimal antiplatelet and antithrombotic therapy should be determined after discussion weighing risk of stent thrombosis versus bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric protection</td>
<td>Can consider</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACT, activated clotting times; BMS, bare metal stent; DAP, dual antiplatelet therapy; DES, drug-eluting stent; NOAC, new oral anticoagulant; NSTEMI, non-ST-segment elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; UFH, unfractionated heparin; VKA, vitamin K antagonist.

**Heparin-Induced Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT), while rare, is especially problematic in ACS patients given the proven benefit of AT therapies. The incidence of HIT is variable based on series studied and confirmatory test used, but can be as high as 5% of patients exposed to heparins for longer than 4 days. It is an immune-mediated condition with antibodies to the complex of heparin and platelet factor 4 (PF4). This leads to platelet activation and a prothrombotic state. These bound platelets are then cleaved from circulation, leading to an observed thrombocytopenia. Clinical scoring systems help to identify patients at high risk for HIT. Anti-PF4 antibodies are extremely sensitive but lack specificity to diagnose HIT. Anti-PF4 antibodies are the first-line test for any patient at low or intermediate pretest probability for HIT. The gold standard test is the serotonin release assay (sensitivity of 100% and specificity of 97%), but other confirmatory tests are available to aid in the diagnosis, including heparin-induced platelet aggregation assays.
(sensitivity of 80% and specificity of >90%) and solid phase immunoassay (sensitivity of >90% but low specificity).

Given the risk of thrombosis in HIT, any patient suspected of having HIT should be on AT therapy. UFH and LMWH are absolutely contraindicated. Given case reports of HIT with fondaparinux, this is often avoided as well, although this relationship is controversial. DTIs have a very specific role across the clinical spectrum of HIT. rHirudins, such as lepirudin and desirudin, are not indicated in ACS patients due to increased incidence of major bleeding. Current STEMI guidelines recommend bivalirudin as first-line therapy in patients undergoing revascularization either with fibrinolysis or PCI. Argatroban may also be used for ACS patients with HIT. Current guidelines do not specifically recommend an agent for medical management of ACS patients.

**Cardiac Surgery**

The decision to proceed with cardiac surgery is often made after an initial ACS presentation. Although some smaller studies suggest bivalirudin is safe and effective during CABG, UFH remains the cornerstone of therapy. Current guidelines recommend discontinuation of enoxaparin 12 to 24 hours prior to CABG, fondaparinux 24 hours prior to CABG, and bivalirudin 3 hours prior to CABG, with patients being maintained on UFH per institutional protocol (Class I, LOE B recommendations).13

**CONCLUSION**

AT therapies have evolved significantly to mirror clinical need. Although UFH has remained an important therapeutic option, multiple additional agents, including LMWH, fondaparinux, and DTIs, have been added to the armamentarium of the clinician to help individualize therapy for ACS patients, especially those proceeding to revascularization. With further developments in antiplatelet therapy, stent design and deployment, and postacute care management, more data will help guide combination therapies to further decrease both ischemic and bleeding complications of ACS. This will help further direct our use of AT therapies.
REFERENCES


19. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of


MULTIPLE CHOICE QUESTIONS

1. A 64-year-old woman presents to the emergency department with substernal chest pressure that started approximately 3 hours ago. She had an electrocardiogram (ECG) done within 10 minutes, which showed ST-segment elevation in the inferior leads with reciprocal changes noted anteriorly. The catheterization laboratory is activated, and as the team prepares the lab, you are asked about procedural anticoagulation since the patient had a recent serious heparin allergy. Laboratory results, other than troponin, are within normal limits. Which of the following antithrombotic regimens would be most appropriate?

A. Enoxaparin 0.3 mg/kg intravenously (IV) × 1 followed by 1 mg/kg subcutaneously (SC) at 12 hours
B. Fondaparinux 7.5 mg SC × 1 with subsequent dosing based on activated clotting time (ACT) levels
C. Unfractionated heparin 60 units/kg × 1 with subsequent dosing based on ACT levels
D. Argatroban 350 μg/kg × 1 with subsequent dosing based on ACT levels
2. A 73-year-old woman with a past medical history notable for coronary artery disease (CAD), multiple PCI procedures, and remote cerebrovascular accident (CVA) presents to the emergency department with intermittent chest pressure with exertion over the last 2 to 3 days. The pain was occurring with less exertion until this morning, when she started having rest pain. In the emergency department, she is noted to have 1-mm ST-segment depression with T-wave inversion in the anterolateral leads with the chest pain, and the first troponin is elevated. The patient’s pain persists despite medical therapy, and the decision is made to activate the catheterization laboratory. She has had significant procedural bleeding in the past including a large retroperitoneal hematoma. Which of the following strategies can reduce the risk of major bleeding in this patient?
   A. Radial approach
   B. Upstream glycoprotein (GP) IIb/IIIa use
   C. Aspirin plus prasugrel instead of aspirin plus clopidogrel
   D. Planned intra-aortic balloon pump (IABP) due to concern for an anterolateral infarction

3. A 57-year-old man with a past medical history notable for diabetes, hypertension, and hyperlipidemia presents to your clinic with recurrent exertional chest pain for the past 3 to 6 months and lower extremity edema and orthopnea for the past 2 to 3 weeks. He states that the chest pain is stable, but the new orthopnea and edema are concerning. Echocardiography shows left ventricular dysfunction with an ejection fraction of 25% to 30% with anterior and anteroseptal akinesis and diffuse hypokinesis. Coronary angiography reveals multivessel coronary artery disease with good bypass targets, and you plan to recommend urgent surgical revascularization. Of the strategies presented, which would be the most appropriate preoperatively?
   A. Enoxaparin SC with final dose given just prior to sending the patient to the operating room (OR)
   B. Fondaparinux SC with final dose within 12 hours of going to the OR
   C. Bivalirudin IV with infusion stopped 3 hours before going to the OR
   D. Bivalirudin IV with infusion continuing en route to the OR

4. A 65-year-old man presents for follow-up after primary PCI to the right
coronary artery. He is doing well on optimal medical therapy and has just
started cardiac rehabilitation. He remembers being told in the hospital that
his heart attack was due to a “clot” in his artery, and he asks about
whether he should be on a “blood thinner” as well as his antiplatelet
agents. Which of the following statements is the most accurate regarding
maintenance antithrombin agents after an acute coronary syndrome
(ACS) event?
A. They reduce clinical event rates with a reduction in bleeding
complications.
B. They reduce clinical event rates with an increase in bleeding
complications.
C. They result in no change in clinical event rates with a reduction in
bleeding complications.
D. They result in no change in clinical event rates with an increase in
bleeding complications.

5. All of the following are advantages of bivalirudin over heparin products
except:
   A. Does not induce an immune response
   B. Can inactivate clot bound thrombus
   C.Reduces acute stent thrombosis risk
   D. Does not bind to plasma proteins

ANSWERS

1. D

In the setting of confirmed or suspected severe heparin allergy or heparin-
induced thrombocytopenia, unfractionated heparin and enoxaparin are
contraindicated due to risk of recurrent adverse events. Fondaparinux does
not have this same risk of complications; however, it should not be used as
monotherapy in primary percutaneous coronary interventions (PCIs) due to
the risk of catheter thrombosis. Another therapy with better activity against
factor II (thrombin) would need to be added to fondaparinux to minimize the
risk of catheter thrombosis. In these settings, any direct thrombin inhibitor
would be appropriate and is the only indication for argatroban in the most
recent STEMI guidelines. In contemporary practice, bivalirudin is the most commonly used direct thrombin inhibitor.

2. A

The question centers on strategies to reduce major bleeding risk in an elderly woman with a previous history of a CVA. Radial approach has been shown to reduce the risk of access site bleeding, particularly in experienced laboratories, and despite the slightly higher risk of nonaccess site bleeding, the overall risk of major bleeding is reduced. Prasugrel is contraindicated in this patient given an increased risk of intracranial hemorrhage and is generally associated with more bleeding than clopidogrel. The other two options are associated with an increase in the risk of major bleeding.

3. C

The decision to proceed with cardiac surgery is not uncommonly made after an acute coronary syndrome presentation. Current guidelines recommend discontinuation of enoxaparin 12 to 24 hours prior to coronary artery bypass grafting (CABG), fondaparinux 24 hours prior to CABG, and bivalirudin 3 hours prior to CABG, with patients being maintained on unfractionated heparin per institutional protocol (Class I, Level of Evidence B recommendations).

4. B

In ATLAS ACS-TIMI 51, rivaroxaban at a lower dose (2.5 mg twice a day) was associated with a decrease in the primary end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared to placebo (9.1% vs 10.7%; hazard ratio, 0.84 [95% CI, 0.72-0.97]; \( P = .02 \)), with a decrease in both cardiovascular death and all-cause mortality. There was also an increase in both Thrombolysis in Myocardial Infarction (TIMI) major bleeding and intracerebral hemorrhage, but not fatal bleeding. The phase II RE-DEEM study compared multiple dosages of the oral direct thrombin inhibitor dabigatran versus placebo in patients with recent ACS, showing increased rates of bleeding compared to placebo. The study was not powered to assess for ischemic end points.
5. C

Several major studies comparing bivalirudin to heparin in the setting of an ACS have shown either similar stent thrombosis risk or higher stent thrombosis risk with bivalirudin. A recent meta-analysis showed higher acute stent thrombosis risk with bivalirudin, but this risk may be mitigated by a postprocedural infusion of bivalirudin.
INTRODUCTION

In 1979, Andreas Gruentzig reported his experience with the first 50 coronary angioplasty procedures. In those first 50 patients, antiplatelet therapy was empiric and consisted of 1.0 g of aspirin (approximately 65 mg) for 3 days and dextran during the procedure. In the 36 years since that publication, the scientific understanding of arterial thrombus formation in response to arterial injury and clinical experience with pharmacologic means to mitigate this process have grown by immeasurable proportions. Specifically, the understanding of surface receptors and ligands necessary for the transformation of platelets to their active state, as well as the surface proteins responsible for adherence to fibrin, leukocytes, and other platelets, has facilitated the development of therapies targeted to specific steps in the activation sequence. Clinical investigation and experience continually refine the circumstances under which specific therapies are best applied in order to maximize benefit and minimize risk. In contemporary coronary angioplasty, the interplay between arterial wall, platelets, plaque components, clinical presentation, stent design, stent components, and concomitant medications
HISTORICAL PERSPECTIVE

From the initial angioplasty procedure in 1977 through the introduction of coronary stents in the early 1990s, thrombosis at the site of angioplasty was recognized as a primary mediator of acute vessel closure during and immediately after the procedure. Heparin was empirically used successfully during and in the immediate periprocedural period, but only aspirin was administered at patient discharge. In the earliest experience with intracoronary stents in the early 1990s, stent thrombosis rates approached 20% and became a focus of postprocedure care. The empiric approach of universal oral anticoagulation with warfarin following stent implantation reduced the incidence of stent thrombosis to 3% to 5%, but at a significant cost of access site–related and non–access site–related bleeding complications. Some operators even suggested that the thrombotic risk of stents was too excessive to justify routine use.

In 1995, a landmark study changed stent practice and shifted pharmacologic strategy from antithrombotic to antiplatelet following percutaneous coronary intervention (PCI). After initial observations that 80% of stents were inadequately expanded when examined by intravascular ultrasound (IVUS), Colombo and colleagues elegantly demonstrated that full stent expansion with apposition to the artery wall was both necessary and sufficient for patients to be safely treated with 2 antiplatelet medications (aspirin and ticlopidine) rather than warfarin. The calculus again changed substantially with the introduction of drug-eluting stents. Although the benefits of a durable revascularization result have been well documented, the combination of delayed healing and polymer hypersensitivity made these stents more susceptible to late thrombosis and lengthened the duration of antiplatelet therapy after PCI.

Twenty years of clinical studies of coronary stent procedures have resulted in the following principles of contemporary PCI with regard to antiplatelet therapy: (1) stent thrombosis is platelet mediated and carries a high morbidity and mortality; (2) adequate platelet inhibition before, during, and after the procedure is associated with optimal clinical outcome; (3) bleeding avoidance
is as important as preventing ischemic complications; and (4) both patient and procedural factors (including stent design) determine relative risk of stent thrombosis and the intensity and duration of platelet inhibition required for the lowest rates of both ischemic and bleeding complications. In this chapter, we outline the evidence for current antiplatelet therapies during and after PCI, as well as strategies for management of antiplatelet therapies in the setting of other medications and complicating clinical circumstances.

CYCLOOXYGENASE-1 INHIBITORS: ASPIRIN

Pharmacokinetics of Aspirin

Aspirin is rapidly absorbed in the stomach and upper intestine when administered in a chewable formula or oral liquid to reach peak plasma levels in 30 to 40 minutes. In patients unable to take medication by mouth, rectal administration also results in rapid absorption. Aspirin is hydrolyzed to salicylic acid, which irreversibly inhibits the cyclooxygenase-1 (COX-1) activity of platelets within the portal circulation, and platelet inhibition is evident within 1 hour.

The half-life of aspirin is short at 15 to 20 minutes. However, the circulating platelets are irreversibly inhibited for the duration of their lifespan, which is approximately 10 days. Approximately 10% of platelets are replaced each day; hence, almost 50% of platelets continue to be inhibited at 5 to 6 days after a single loading dose.¹

Optimal Dosing of Aspirin in PCI

Aspirin has been used empirically in all angioplasty since Gruentzig’s initial report. There is a single reported angioplasty study that randomized patients to an arm that did not include aspirin treatment. Although not designed to assess the necessity of aspirin (but rather restenosis rates), the study is often quoted as being the basis for the universal use of aspirin in contemporary practice. In this study, the periprocedural events included a Q-wave myocardial infarction (MI) rate of 6.8% in the placebo arm, compared to
1.3% in the aspirin arm. Performed in the balloon angioplasty era with a small number of patients, the applicability to current practice is questionable, yet this study remains an important influence regarding the primacy of aspirin as a pharmacologic adjunct to angioplasty.

The minimum effective dose prior to PCI in patients presenting with acute coronary syndrome has not be studied prospectively. Considering available data, the current guidelines for treatment of ST-segment elevation myocardial infarction (STEMI) recommend 162 to 325 mg of non–enteric-coated aspirin given as early as possible prior to primary PCI as a Class I recommendation.² In elective PCI, guidelines suggest a loading dose of 325 mg prior to PCI in aspirin-naïve patients and 81 to 325 mg in patients on chronic aspirin therapy.³

Aspirin sensitivity/allergy is an important consideration prior to PCI because as many as 3% to 5% of patients being considered for PCI report a history of respiratory or cutaneous symptoms or reactions after aspirin ingestion. A number of aspirin desensitization protocols are available, using sequential administration of escalating doses of oral aspirin. Patients with true anaphylaxis to aspirin can be desensitized, although at increased risk. In our practice, we generally desensitize those patients with sensitivity, but in cases of true anaphylaxis or where the patient does not consent to desensitization, we have proceeded successfully with thienopyridine monotherapy.

Many well-designed randomized trials have shown that a maintenance dose of aspirin less than 100 mg is effective as secondary prevention in patients with coronary atherosclerosis.⁴,⁵ These studies, which did not include patients who underwent PCI, are insufficient to confirm that low-dose aspirin would suffice to prevent stent thrombosis. However, in the PCI-CURE trial,⁶ a post hoc analysis of the PCI cohort of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial,⁷ 2658 patients with acute coronary syndromes undergoing PCI were stratified into 3 aspirin dose groups and followed up to 1 year. The high-dose group received more than 200 mg, and the low-dose group received less than 100 mg, with the moderate-dose group receiving doses in between. The moderate- and high-dose groups had similar rates of cardiovascular death, MI, or stroke compared to the low-dose group. From a safety standpoint, major bleeding was increased with high-dose aspirin with net adverse clinical events (death, MI, stroke, and major
bleeding) favoring low-dose aspirin over high-dose aspirin. Therefore, in this observational analysis of patients undergoing PCI, low-dose aspirin appeared to be as effective as higher doses in preventing ischemic events but was also associated with a lower rate of major bleeding and an improved net efficacy-to-safety balance.

In the CURRENT-OASIS\textsuperscript{8} study, 25,086 patients with an acute coronary syndrome who were referred for an invasive strategy were randomized to higher dose aspirin (300-325 mg daily) or lower dose aspirin (75-100 mg daily). The primary outcome was cardiovascular death, MI, or stroke at 30 days. There was no significant difference between higher dose and lower dose aspirin with regard to the primary outcome. From a safety standpoint there was no increase in major bleeding (2.3% vs 2.3%; hazard ratio [HR], 0.99 [95% confidence interval (CI), 0.84-1.17]; \( P = .9 \)) between the groups. However, the rate of minor bleeding was increased (5.0% vs 4.4%; HR, 1.13 [95% CI, 1.00-1.27]; \( P = .04 \)) and major gastrointestinal bleeding was more frequent (0.4% vs 0.2%; \( P = .04 \)) with higher dose aspirin.

Most recently, the ADAPT-DES registry\textsuperscript{9} followed 8582 patients after PCI with stent implantation who were treated with low-dose aspirin and clopidogrel and had platelet functional testing performed to detect both clopidogrel and aspirin nonresponsiveness prior to discharge. In this study, aspirin nonresponsiveness did not predict stent thrombosis events, MI, or death. However, aspirin responsiveness was associated with a higher likelihood of clinically evident bleeding. Small case series have also described successful PCI with stent placement using P2Y\textsubscript{12} inhibitors alone in patients unable to take aspirin. Finally, although thienopyridine discontinuation is frequently identified as a clinical factor strongly associated with stent thrombosis, aspirin discontinuation is less predictive. Discontinuation of aspirin in clinical trials has been reported to be as high as 18%. Taken together, these data suggest that aspirin may not be as important as previously thought in the prevention of post-PCI ischemic complications, a hypothesis that certainly deserves further study, particularly in cases of aspirin allergy or the need for oral anticoagulation.

In summary, currently available data indicate that a loading dose of 325 mg before PCI followed by low-dose aspirin after PCI (100 mg or less) is a reasonable standard. However, there is some evidence to suggest that the necessity of aspirin should be formally reexamined.
P2Y$_{12}$ RECEPTOR ANTAGONISTS: TICLOPIDINE, CLOPIDOGREL, PRASUGREL, TICAGRELOR, AND CANGRELOR

Upon arterial injury, circulating platelets are exposed to subendothelial proteins such as von Willebrand factor, vitronectin, and collagen. Platelet collagen receptors mediate more firm attachment of platelets and result in the release of platelet-dense granules, which contain, among other vasoactive components, the extracellular signaling purine nucleotide adenosine diphosphate (ADP). ADP acts locally to attract and activate other platelets and amplify the local response to injury. The primary receptor for ADP on the platelet is the P2Y$_{12}$ receptor, which is a member of a large family of purine and pyrimidine nucleotide receptors.

Thienopyridines are a group of compounds that have antithrombotic activity mediated through irreversible binding and inactivation of the P2Y$_{12}$ receptor. The first thienopyridine, tinoridine, was isolated in 1970 and has anti-inflammatory and analgesic properties; it is currently marketed in a number of countries worldwide as a nonsteroidal anti-inflammatory. Ticlopidine is a tinoridine derivative that exhibited antithrombotic properties, and was first marketed in Europe in 1978 for prevention of clotting in hemodialysis and cardiopulmonary bypass. It subsequently proved effective in patients with other clinical manifestations of atherosclerosis, such as in transient ischemic attacks (TIAs), stroke, and peripheral vascular disease, and became available in the United States in 1991. In 1995, Colombo and colleagues demonstrated that P2Y$_{12}$ inhibition with ticlopidine was an important strategy to avoid stent thrombosis, and ticlopidine became a standard of care. With wider use, hematologic dyscrasias from ticlopidine helped to accelerate the development of other, less toxic thienopyridines. Although the P2Y$_{12}$ receptor was not cloned until 2001, its existence was inferred from the effects of thienopyridines on platelet function. Due to the success of thienopyridines, nonthienopyridine P2Y$_{12}$ receptor antagonists have been developed, including those that do not irreversibly inactivate the
receptor.

There are now 4 P2Y$_{12}$ inhibitors that have clinical utility in the treatment of atherosclerotic cardiovascular disease and, in particular, have clinical data supporting their use during and after PCI.

**Clopidogrel (Plavix)**

**Pharmacokinetics of Clopidogrel**

Clopidogrel is a prodrug that is rapidly absorbed in the intestine following oral administration. However, 85% of the dose is eliminated as an inactive metabolite. Following intestinal absorption, clopidogrel is activated in the liver by 2 sequential oxidative steps. The first step results in the formation of 2-oxo-clopidogrel, which is then further metabolized by cytochrome P450 isoforms including CYP3A4/5 and CYP2C19 to generate the active metabolite. Variability in the efficiency of this second step is mediated through differences in CYP2C19 alleles, resulting in different degrees of platelet inhibition depending on genotype. The active metabolite irreversibly binds to the P2Y$_{12}$ receptor, inhibiting ADP binding of the platelet. Once clopidogrel binds to the P2Y$_{12}$ receptor, platelet function is inhibited for the lifespan of the platelet, generally 7 to 10 days.

**Dosing of Clopidogrel in PCI**

While the practice of using thienopyridines to prevent stent thrombosis after PCI was introduced by Colombo’s observations in 1995, it was not until 5 years later that PCI-CURE established the principal of thienopyridine pretreatment. Randomizing 2658 subjects with non–ST-segment elevation myocardial infarction (NSTEMI) to clopidogrel or placebo for 6 days before PCI, clopidogrel was associated with a relative risk of 0.7 compared to placebo for a composite end point of death, MI, or urgent revascularization at 30 days. ISAR-REACT showed that clopidogrel had a similar magnitude of effect as glycoprotein IIb/IIIa inhibitors in elective PCI.

The timing and dose of clopidogrel loading prior to PCI, in both elective cases and acute coronary syndromes, have been extensively studied. Muller et al$^{10}$ compared the effect of a high clopidogrel loading dose (600 mg)
versus a loading dose of 300 mg on platelet aggregation in response to ADP in patients undergoing PCI. Faster and more profound suppression of platelets was achieved following a 600-mg loading dose.\textsuperscript{10}

In the CREDO trial,\textsuperscript{11} there was no reduction in events (death, MI, or stroke), compared with placebo, when 300 mg of clopidogrel was given 3 hours prior to the procedure. However, in a prespecified subgroup analysis, patients who received 300 mg of clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6\% (95\% CI, –1.6\%-62.9\%; \(P = .051\)) at 28 days.

Following a load of 600 mg of clopidogrel, peak suppression of platelet activity is seen by 2 hours after administration. In 428 patients undergoing PCI, the 30-day composite rate of major adverse cardiac events was not significantly different in patients undergoing PCI within 2 hours after a loading dose of 600 mg or at a later time point.\textsuperscript{12}

The ARMYDA-2 trial was the first randomized trial to evaluate the impact of a 600-mg loading dose in comparison to the 300-mg conventional loading dose in patients undergoing PCI. Three hundred twenty-nine patients with typical exertional angina and a positive stress test or non-ST-segment elevation acute coronary syndrome (ACS) were randomized to either 300 or 600 mg of clopidogrel between 4 and 8 hours prior to PCI. The composite end point (death, MI, or target vessel revascularization) was significantly higher in patients treated with the conventional dose of clopidogrel than in patients treated with the high loading dose (12\% vs 4\%; \(P = .041\)). The incidence of MI was significantly higher in patients treated with the conventional dose (5\% vs 15\%). Bleeding complications were similar, and the difference in frequency of entry site hematoma was not statistically significant (7.1\% vs 4.7\%; \(P = .56\)). Furthermore, significantly more patients in the conventional-dose arm had elevations of cardiac biomarkers following the procedure (creatine kinase [CK]-MB, \(P = .038\); troponin I, \(P = .021\); myoglobin, \(P = .002\)). In this study, the event-free survival at 30 days significantly favored the high loading dose (\(P = .017\)). Multivariate analysis identified pretreatment with the 600-mg dose of clopidogrel and statin therapy as independent predictors of decreased risk of periprocedural MI (\(P = .044\) and \(P = .020\), respectively). Additional benefit was noted in high-dose patients who were on statin therapy before the intervention (\(P = .017\)).\textsuperscript{13} A loading dose of 900 mg was studied, but no additional benefit beyond that of
600 mg was seen.

To obtain maximum clinical benefit in clopidogrel-naïve patients, the data suggest that it is reasonable to treat patients with a 600-mg loading dose if administered at least 2 hours prior to PCI to ensure full antiplatelet activity. Benefit from a 300-mg loading dose is not expected unless administered at least 6 hours prior to PCI.

Administering a loading dose of clopidogrel routinely to patients prior to diagnostic coronary angiography may be problematic should coronary artery bypass grafting (CABG) be necessary, as there is an increased risk of bleeding and reoperation in patients undergoing bypass surgery while on clopidogrel. Current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for CABG surgery recommend clopidogrel and ticagrelor be discontinued for at least 5 days prior to elective CABG surgery and 24 hours prior to urgent CABG surgery.\textsuperscript{14}

It is not infrequent that patients on chronic clopidogrel therapy are referred for PCI. Two studies have examined the impact of reloading of clopidogrel. The Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-4 RELOAD) trial was conducted to evaluate safety and effectiveness of clopidogrel reloading in patients on chronic clopidogrel therapy undergoing PCI. Five hundred three patients on chronic clopidogrel therapy for greater than 10 days presenting with stable angina and ACS were randomized to receive either 600 mg of clopidogrel loading 4 to 8 hours before PCI or placebo. The primary end point of 30-day incidence of death, MI, or target vessel revascularization (TVR; major adverse cardiac events [MACEs]) was not significantly different between the reload and placebo arms (6.7\% vs 8.8\%, respectively; odds ratio [OR], 0.75 [95\% CI, 0.37-1.52]; \( P = .50 \)). In patients with stable angina, 1-month MACEs were not significantly different (\( P = .36 \)), whereas ACS patients had significant clinical benefit with reloading (\( P = .033 \)). There was no excess bleeding in the reload arm.\textsuperscript{15}

The ARMYDA-8 RELOAD-ACS study evaluated the benefit of administering a 600-mg dose of clopidogrel compared with placebo in patients with NSTEMI on chronic clopidogrel therapy for more than 10 days. The primary end point of 30-day incidence of death, MI, and TVR occurred in 4.1\% of patients in the reload arm versus 14.1\% of patients in the placebo arm (OR, 0.26 [95\% CI, 0.10-0.73]; \( P = .013 \)). The benefit in the reload arm
was driven mainly by reduction of periprocedural MI in the reload arm. There was no difference in bleeding outcomes between the 2 groups.\textsuperscript{16} Taken together, the ARMYDA-4 and ARMYDA-8 studies indicate that patients presenting with ACS while on chronic clopidogrel therapy would benefit from reloading using a 600-mg dose of clopidogrel.

Genetic variability in the metabolism of clopidogrel leads to variability in the antiplatelet effect as measured by in vitro testing and in the clinical effectiveness of clopidogrel after PCI with stenting. The GRAVITAS trial measured the degree of routine platelet inhibition in 2214 subjects and randomized half of the patients to receive high-dose clopidogrel (150 mg/d). Although the higher dose of clopidogrel did not improve outcomes, individuals with better responsiveness as measured by VerifyNow P2Y\textsubscript{12} platelet functional testing (Accriva Diagnostics, San Diego, CA) had the lowest risk of adverse events. An on-treatment VerifyNow measurement (12-24 hours after PCI) of less than 208 P2Y\textsubscript{12} reaction units was associated with a 60-day HR of 0.28 for cardiovascular death, MI, and stent thrombosis.

Similarly, Thrombolysis in Myocardial Infarction (TIMI)-38 showed that clopidogrel was associated with less severe bleeding but more evidence of post-PCI ischemic events (cardiovascular death, nonfatal MI, nonfatal stroke), including a 50\% increase in stent thrombosis, compared to prasugrel. Both of those observations are consistent with variations of genes that result in reduced conversion of clopidogrel to the active metabolite. All evidence for safety and efficacy of clopidogrel must be interpreted in the context of the individual variation in clopidogrel responsiveness.

**Prasugrel (Effient)**

**Pharmacokinetics of Prasugrel**

Prasugrel, the third thienopyridine to become available after ticlopidine and clopidogrel, is a more rapid, potent, and consistent antiplatelet agent. Prasugrel is a prodrug that is absorbed in the intestine and rapidly hydrolyzed by esterases to a thiolactone metabolite, which is then oxidized in a single cytochrome P450 (CYP)-dependent step to the active metabolite. CYP3A4/5 and CYP2B6 play a major role in this conversion, whereas CYP2C19 and CYP2C9 are less important; clinically, there is universal responsiveness to
the drug. As with clopidogrel, the active metabolite irreversibly binds to the platelet P2Y$_{12}$ receptor, thus inhibiting ADP-activated platelet activation and aggregation for the life of the platelet.

The active metabolite of prasugrel reaches peak plasma levels within 30 minutes. A dose-proportionate concentration is noted between doses of 5 and 60 mg. Prasugrel does not interact to any clinically significant extent with other drugs, including those also metabolized by the hepatic CYP isoenzymes CYP3A4, CYP2C9, CYP2C19, and CYP2B6, which are responsible for prasugrel metabolism. Therefore, prasugrel has a pharmacokinetic and pharmacodynamic profile that compares favorably with those of existing antiplatelet agents.

**Dosing of Prasugrel in PCI**

Prasugrel is more potent than clopidogrel on several fronts. In a randomized, double-blind, crossover study in patients undergoing cardiac catheterization with planned PCI, loading with 60 mg of prasugrel resulted in greater platelet inhibition than a 600-mg clopidogrel loading dose. Maintenance therapy with prasugrel 10 mg/d resulted in a greater antiplatelet effect than 150 mg/d of clopidogrel.$^{17}$ Antiplatelet effects of prasugrel have not been found to change with moderate liver disease, end-stage renal disease, diabetes, or smoking. However, in a population pharmacokinetic analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), patients older than 75 years had 19% higher exposure to the active metabolite of prasugrel compared with patients less than 75 years old and 25% higher exposure compared with patients less than 60 years old. In addition, patients <60 kg had 30% higher exposure than patients ≥60 kg and 42% higher exposure than patients ≥85 kg.$^{18}$

The pivotal trial of the safety and efficacy of prasugrel was TRITON-TIMI 38, published in 2007.$^{19}$ In this trial, 13,608 patients with moderate- to high-risk ACS (including unstable angina, NSTEMI, and STEMI) with planned PCI and who were naïve to thienopyridine therapy were randomized to receive either a 300-mg loading dose of clopidogrel followed by 75 mg daily or a 60-mg loading dose of prasugrel followed by 10 mg daily. Patients with unstable angina/NSTEMI or STEMI treated initially with medical
therapy were randomized and treated only after the coronary anatomy was known to be suitable for PCI; patients with STEMI and planned primary PCI were randomized and treated on first contact. The primary efficacy end point was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The key safety end point was major bleeding, and patients at high risk for bleeding were excluded. Over a median duration of therapy of 14.5 months, the primary composite end point occurred in 12.1% of the patients receiving clopidogrel and 9.9% of patients receiving prasugrel (\(P < .001\)). The primary efficacy end point was driven by a 24% reduction in MI (including both fatal and nonfatal MI). There was no significant difference between the 2 treatment groups in the rate of stroke or death from cardiovascular causes not preceded by recurrent MI. The beneficial effect of prasugrel was seen across the board in patients presenting with STEMI (HR, 0.79 [95% CI, 0.65-0.97]; \(P = .02\)) and non–ST-segment elevation ACSs (HR, 0.82 [95% CI, 0.73-0.93]; \(P = .002\)). An important finding from TRITON–TIMI 38 was a significant reduction in stent thrombosis among patients receiving prasugrel. Overall, for the duration of the trial, Academic Research Consortium (ARC)-defined definite or probable stent thrombosis was reduced by 52% (1.1% vs 2.4%; HR, 0.48 [95% CI, 0.36-0.64]; \(P < .001\)), and definite (angiographic or autopsy proven) stent thrombosis was reduced by 58% (0.9% vs 2.0%; HR, 0.42 [95% CI, 0.31-0.59]; \(P < .001\)) in patients in the prasugrel arm. These findings were similar among patients receiving bare metal stents or drug-eluting stents. The reduction in stent thrombosis was also noted before and after 30 days of PCI (\(P < .0001\) and \(P = .03\), respectively).

Conversely, the increased potency of prasugrel resulted in higher rates of bleeding. The main safety end point of non–CABG-related TIMI major bleeding was observed more frequently with prasugrel than clopidogrel (2.4% vs 1.8%; HR, 1.32 [95% CI, 1.03-1.68]; \(P = .03\)); there was also an increase in non–CABG-related TIMI major or minor bleeding (5.0% vs 3.8%; HR, 1.31 [95% CI, 1.11-1.56]; \(P = .002\)) and bleeding requiring transfusion (4.0% vs 3.0%; HR, 1.34 [95% CI, 1.11-1.63]; \(P < .001\)).

Regarding non–CABG-related bleeding, the increased rate was driven predominantly by an increase in spontaneous bleeding (1.6% vs 1.1%; HR, 1.51 [95% CI, 1.09-2.08]; \(P = .01\)), commonly gastrointestinal bleeding, with no difference in intracranial bleeding. The rate of major bleeding was not significantly different between the 2 groups within the first 30 days. However, after 30 days, a significant increase in TIMI major bleeding was
observed (1.42% vs 0.97%; HR, 1.48 [95% CI, 1.04-2.09]; \( P = .03 \)). Still, the prespecified net end point of all-cause death, MI, stroke, and non-CABG TIMI major bleeding was evaluated and significantly favored the prasugrel group over the clopidogrel group (12.2% vs 13.9%; HR, 0.87 [95% CI, 0.79-0.95]; \( P = .004 \)).

Prespecified landmark analyses for efficacy were performed from randomization to day 3 and from day 3 to the end of the trial to examine individually the effects of the loading dose and the maintenance dose in patients enrolled in TRITON-TIMI 38. Significant reductions in ischemic events, including MI, stent thrombosis, and urgent TVR, were observed with the use of prasugrel, both during the first 3 days and from 3 days to the end of the trial. TIMI major non-CABG bleeding was similar to that of clopidogrel during the first 3 days but was significantly greater with the use of prasugrel from 3 days to the end of the study. Net clinical benefit significantly favored prasugrel both early and late in this trial. One criticism of TRITON-TIMI 38 was the choice of a 300-mg loading dose of clopidogrel, rather than the more effective dose of 600 mg.

A post hoc analysis of TRITON-TIMI 38 identified 3 patient groups who did not experience a net benefit from prasugrel: patients \( \geq 75 \) years old, patients weighing <60 kg, and patients with a prior history of stroke or TIA. Any 1 of these 3 factors was associated with increased bleeding, and in patients with prior stroke or TIA, there was no benefit compared to clopidogrel, but a strong trend toward increased major bleeding, including intracranial bleeding. Importantly, these findings led to prasugrel labeling instructions in the United States to indicate that the drug should not be used in these specific subgroups.

**Ticagrelor (Brilinta)**

Ticagrelor is a potent P2Y\(_{12}\) receptor antagonist that is not a thienopyridine. This drug belongs to the cyclopentyltriazolopyrimidine class. In contrast to thienopyridine agents, ticagrelor reversibly binds to the P2Y\(_{12}\) receptor and does not require metabolic activation.

**Pharmacokinetics of Ticagrelor**
Although the parent compound does not require activation for platelet inhibition, ticagrelor is metabolized primarily by the CYP3A isoenzyme into an active metabolite (AR-C124910XX). This metabolite exerts similar potency in inhibiting the P2Y\textsubscript{12} receptor and is present at about 40% of the parent concentration.

Ticagrelor is rapidly absorbed, with maximum levels achieved in 90 to 120 minutes. However, significant platelet inhibition is noted within 30 minutes of administration of a loading dose of 180 mg of ticagrelor.

Compared with clopidogrel, ticagrelor achieved 1.6 times greater platelet inhibition 1 to 2 hours after a 180-mg loading dose than that seen 8 hours after administration of a 600-mg clopidogrel loading dose. Platelet inhibition by ticagrelor continued to be significantly higher than clopidogrel at the end of 6 weeks of treatment ($P < .0001$).\textsuperscript{22} The degree of platelet inhibition is similar at 24 hours after discontinuation of clopidogrel and ticagrelor, and the antiplatelet effect seen on day 3 after the last dose of ticagrelor was similar to that seen on day 5 after clopidogrel (Fig. 16-1).\textsuperscript{22} Although there may be benefit to the rapid offset (as in patients in need of coronary artery bypass surgery), ticagrelor would be a less attractive choice in patients with poor compliance, because discontinued treatment would result in a reduction of platelet inhibition within a shorter time period, potentially increasing risk of cardiovascular events and stent thrombosis.

Excretion of ticagrelor and its active metabolite occurs through the hepatobiliary system. Severe hepatic impairment is a contraindication to use of ticagrelor, with no restriction in mild liver disease. CYP3A inhibitors, including diltiazem and ketoconazole, increase the plasma concentration of ticagrelor. Ticagrelor increases the levels of simvastatin, as it is a CYP3A substrate. Therefore caution should be used in patients on high doses of simvastatin. Similar to prasugrel, there is no alteration in efficacy of ticagrelor with any specific CYP2C19 genotype.

**Dosing of Ticagrelor in PCI**
The Dose Confirmation Study Assessing Antiplatelet Effects of AZD6140 Versus Clopidogrel in Non–ST-Segment Elevation Myocardial Infarction-2 (DISPERSE-2) trial was performed to compare the safety and initial efficacy of ticagrelor versus clopidogrel in patients with non–ST-segment elevation ACSs. Nine hundred ninety patients who were treated with standard therapy for ACS, including aspirin, were randomized in a double-blind fashion to receive ticagrelor 90 mg twice daily, ticagrelor 180 mg twice daily, or clopidogrel 300-mg loading dose plus 75 mg once daily for up to 12 weeks. Patients randomized to receive ticagrelor were also subrandomized to either a 180- or 270-mg loading dose of ticagrelor. There was no difference in the primary outcome of major and minor bleeding at 4 weeks between the ticagrelor groups and the clopidogrel group ($P = .43$ and $P = .96$, respectively). The use of a loading dose of ticagrelor did not significantly affect bleeding rates. There was no difference in any of the secondary clinical end points (all-cause death, cardiovascular death, MI, stroke, or recurrent ischemia) between the ticagrelor 90 mg and clopidogrel groups. However, there was a dose-dependent increase in the rate of reported dyspnea and asymptomatic ventricular pauses with ticagrelor.$^{24}$

The Study of Platelet Inhibition and Patient Outcomes (PLATO) was the pivotal trial evaluating the efficacy and safety of ticagrelor.$^{25}$ This multicenter, double-blind, randomized trial enrolled 18,624 patients from 43 countries with ACS with or without ST-segment elevation, who were randomized to receive either ticagrelor as a 180-mg loading dose followed by 90 mg twice daily or clopidogrel as a 300- to 600-mg loading dose followed by 75 mg daily thereafter. In contrast to TRITON-TIMI 38, which excluded patients receiving thienopyridines within 5 days and delayed study drug administration until coronary angiography was performed, the PLATO investigators administered the study drugs as early as possible within 24 hours of chest pain and included patients already treated with clopidogrel. The primary efficacy end point was a composite of death from cardiovascular causes, MI, or stroke. The major safety end point was major bleeding, which was a more inclusive than TIMI-defined major bleeding used in TRITON-TIMI 38.$^{19}$ In PLATO, major bleeding was defined as a decrease of 3.0 g/dL in the hemoglobin, transfusion of 2 units of packed red blood cells, or bleeding that led to a significant clinical disability.

The results of the study demonstrated a significant reduction in the primary composite end point in patients treated with ticagrelor compared to
clopidogrel (9.8% vs. 11.7%; HR, 0.84 [95% CI, 0.77-0.92]; \( P < .001 \)). This benefit was replicated in the 13,408 patients treated with a planned invasive strategy.

Despite the higher potency and efficacy of ticagrelor as an antiplatelet agent, no significant difference in the rates of major bleeding, as defined by the trial, was found between the ticagrelor and clopidogrel groups (11.6% vs 11.2%, respectively; \( P = .43 \)). The rate of fatal intracerebral hemorrhage was significantly greater with ticagrelor therapy, but this was offset by a higher rate of nonintracranial fatal bleeding with clopidogrel, resulting in an overall similar rate of fatal bleeding with the 2 therapies. Although there was no difference in CABG-related bleeding, non–CABG-related TIMI major bleeding was significantly more frequent with ticagrelor (HR, 1.25 [95% CI, 1.03-1.53]; \( P = .03 \)).

As noted in DISPERSE-2, dyspnea occurred more frequently in the ticagrelor group than the clopidogrel group, and Holter monitoring revealed a higher incidence of ventricular pauses in the first week in the PLATO study. The proposed mechanism of both dyspnea and ventricular pauses is ticagrelor’s interference with the normal clearance of adenosine. The ventricular pauses were rarely symptomatic, with no increased requirement of pacemaker implantation. The levels of creatinine and uric acid increased slightly more during the treatment period with ticagrelor than with clopidogrel. The exact pharmacologic mechanisms leading to these effects are unclear at the present time.

A main criticism of the PLATO trial was the lack of reduction in the primary end point seen among 1814 patients enrolled in the United States and Canada.\(^{26}\) Although no clear explanation is available, a maintenance dose of 300 mg of aspirin was used in these sites, and aspirin dose has been a referenced explanation for the regional differences. Therefore, the US Food and Drug Administration (FDA) issued a warming directing the use of less than 100 mg of aspirin as a maintenance dose when used concurrently with ticagrelor.\(^{27}\) Table 16-1 shows a comparison of oral antiplatelet agents.

| Table 16-1 Comparison of Oral Antiplatelet Agents |
Cangrelor

Pharmacokinetics of Cangrelor

Cangrelor is an adenosine triphosphate analog that, when given intravenously, is a direct-acting platelet P2Y12 inhibitor that is rapidly reversible. The antiplatelet effect of a bolus dose of cangrelor is rapid, with >95% platelet inhibition within 15 minutes of administration. The plasma half-life is approximately 3 to 5 minutes, and antiplatelet effects are maintained by a continuous infusion. Normalization of platelet aggregation occurs 60 minutes after discontinuation of the infusion.

The clinical efficacy of cangrelor was evaluated in the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION)-PCI28 and CHAMPION-PLATFORM29 trials, which were phase III, randomized, clinical trials comparing cangrelor with clopidogrel administered before and after PCI, respectively. Both trials were stopped prematurely by the Data and Safety Monitoring Committee after an interim review showed that neither study would show a benefit, although the trials had enrolled 93.6% and 83.8% of planned patients, respectively. The results of these parallel studies were simultaneously published in The New England Journal of Medicine in 2009.

Dosing of Cangrelor in PCI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>NSAID</td>
<td>Thienopyridine prodrug</td>
<td>Thienopyridine prodrug</td>
<td>Nonthienopyridine</td>
</tr>
<tr>
<td>Mechanism of platelet inhibition</td>
<td>Irreversible COX-1 inhibitor</td>
<td>Irreversible P2Y12 inhibitor</td>
<td>Irreversible P2Y12 inhibitor</td>
<td>Reversible modification of P2Y12 receptor</td>
</tr>
<tr>
<td>Loading dose</td>
<td>325 mg</td>
<td>300 mg; 600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>81 mg/d</td>
<td>75 mg/d</td>
<td>10 mg/d</td>
<td>90 mg twice a day</td>
</tr>
<tr>
<td>Antiplatelet effect after loading dose</td>
<td>60-180 min</td>
<td>120 min after 600 mg</td>
<td>60 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Time to offset</td>
<td>7 days</td>
<td>7 days</td>
<td>7 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Major trials in PCI</td>
<td>PCI-CURE, CURRENT-OASIS, ADAPT-DES</td>
<td>PCI-CURE, ISAR-REACT, ARMYDA-2, ARMYDA-4 RELOAD</td>
<td>TRITON-TIMI 38</td>
<td>PLATO, DISPERSE-2</td>
</tr>
</tbody>
</table>

Abbreviations: COX, cyclo-oxygenase; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention.
The CHAMPION-PCI\textsuperscript{28} study randomized 8877 patients to receive either cangrelor 30 minutes before and for 2 hours after PCI in a loading dose of 30 μg/kg body weight followed by a 4 μg/kg/min infusion, or an oral loading dose of 600 mg of clopidogrel administered 30 minutes before PCI. Cangrelor was not superior to 600 mg of clopidogrel with respect to the primary composite end point of death from any cause, MI, or ischemia-driven revascularization at 48 hours (OR, 1.05 [95% CI, 0.88-1.24]; \( P = .59 \)) or 30 days.

The CHAMPION-PLATFORM\textsuperscript{29} trial included 5362 stented patients randomized to receive either placebo or cangrelor during PCI, followed by 600 mg of clopidogrel at the end of the procedure. Results of the trial showed that the primary end point occurred in 185 (7%) of 2654 patients receiving cangrelor versus 210 (8%) of 2641 patients receiving placebo (OR, 0.87 [95% CI, 0.71-1.07]; \( P = .17 \)). Two prespecified secondary end points that were significantly reduced at 48 hours in the cangrelor group were the rate of stent thrombosis (from 0.6% to 0.2%; \( P = .02 \)) and the mortality rate from any cause (from 0.7% to 0.2%; \( P = .02 \)).

Because the initial CHAMPION trials evaluating cangrelor did not show an increased efficacy in comparison to clopidogrel, the CHAMPION-PHOENIX trial\textsuperscript{30} was designed as a double-blind, placebo-controlled trial in which the primary efficacy end point was a composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization and the primary safety end point was severe bleeding at 48 hours. In contrast to the prior trials, stent thrombosis was included in the primary end point, and the definition of periprocedural MI was modified.

A total of 11,145 patients who were undergoing either urgent or elective PCI were randomized after diagnostic angiography to receive either a bolus and infusion of cangrelor or a 300- or 600-mg loading dose of clopidogrel, with the dose decided at the discretion of the provider. Cangrelor infusion was continued for at least 2 hours or the duration of the procedure. At the completion, patients who received cangrelor received 600 mg of clopidogrel.

A significant efficacy benefit was seen with the use of cangrelor in this study, with the primary efficacy end point reached in 4.7% of patients in the cangrelor group, compared to 5.9% of patients in the clopidogrel group (adjusted OR with cangrelor, 0.78 [95% CI, 0.66-0.93]; \( P = .005 \)). The rate of the primary safety end point was similar between cangrelor and clopidogrel.
However, the FDA rejected the approval of cangrelor in February of 2014, citing 2 previous negative studies and trial design difficulties of CHAMPION-PHOENIX.

In summary, although there are an increasing number of P2Y_12 inhibitors available, clopidogrel remains the most widely used. Clinical trials of dual antiplatelet therapy (DAPT) continue to focus primarily on clopidogrel, perhaps related to considerations of cost and safety profile, as well as once-a-day dosing. In clinical situations where rapidity of onset is of primary importance (such as primary PCI), prasugrel or ticagrelor may be more appropriate.

**PROTEASE-ACTIVATED RECEPTOR-1: VORAPAXAR**

Local generation of thrombin at the site of arterial injury serves to convert soluble fibrinogen into insoluble fibrin, contributing to the formation of clot. However, thrombin also acts on a variety of other targets, including the protease-activated receptor-1 (PAR-1) on platelets. In 2014, the FDA approved a selective PAR-1 antagonist, vorapaxar, as the first antiplatelet agent in this class for use in patients with coronary artery disease (CAD).

Two large phase III randomized clinical trials examined the efficacy and safety of vorapaxar—the TRACER study in patients with ACS, and TRA 2P TIMI-50 for secondary prevention in patients with stable CAD. TRACER examined whether the addition of vorapaxar to standard therapy (aspirin and clopidogrel) could reduce ischemic events in patients with non–ST-segment elevation ACS, compared with placebo, in 12,944 patients. In this study, 57.4% of patients receiving placebo and 58.1% of patients receiving vorapaxar underwent PCI. Follow-up in the study was terminated early due to an excess of bleeding events, including a significant increase in intracranial hemorrhage (0.2% with placebo vs 1.1% with vorapaxar; \( P < .001 \)), without a benefit in the primary end point. In patients undergoing PCI, there was no difference in definite/probable stent thrombosis during the follow-up period.

In patients with stable CAD, the TRA 2P TIMI-50 trial did demonstrate a reduction in the primary composite end point of cardiovascular death, MI, or
stroke at 3 years. However, came at a cost of increased Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) moderate or severe bleeding; the increase in intracranial hemorrhage in this study did not reach significance.

Although these studies raise interesting questions, for now, there appears to be no role for this medication in patients undergoing PCI.

GLYCOPROTEIN IIB/IIIA INHIBITORS

The platelet integrin receptor αIIbβ₃ (glycoprotein [GP] IIb/IIIa) plays a critical role in coagulation by mediating interactions between platelets and several other ligands, primarily fibrinogen. This receptor consists of 2 separate subunits, αIIb (GP IIb) and α₃ (GP IIIa). Following platelet activation, the IIb/IIIa receptor undergoes conformational changes, and several binding sites for fibrinogen and other ligands are exposed. In competing with fibrinogen and von Willebrand factor for GP IIb/IIIa binding, GP IIb/IIIa inhibitors (GPIs) interfere with platelet cross-linking and platelet-derived thrombus formation. Because fibrinogen binding to the activated receptor GP IIb/IIIa constitutes the final common pathway of platelet aggregation, GPIs are very effective platelet inhibitors, independent of the type of platelet agonist.

Three intravenous GP IIb/IIIa antagonists are approved for use at the current time: abciximab, eptifibatide, and tirofiban. Abciximab (ReoPro) is a large monoclonal antibody with a high binding affinity that results in a prolonged antiplatelet effect. The drug is a Fab (fragment antigen binding) fragment of a monoclonal antibody that targets the GP IIb/IIIa receptor on the platelet membrane. In contrast to the small molecular GPIs eptifibatide and tirofiban, abciximab is a noncompetitive inhibitor. Following a bolus administration, the plasma concentration of abciximab decreases rapidly with an initial half-life of less than 10 minutes and a second-phase half-life of approximately 30 minutes. However, due to the increased affinity to the GP IIb/IIIa receptor, the biologic half-life remains between 12 and 24 hours. Abciximab remains detectable in the circulation for almost 15 days. The recommended loading dose of abciximab is 0.25 mg/kg followed by an infusion of 0.125 mcg/kg/min for 12 hours with no renal dose adjustment.

Eptifibatide (Integrilin), a cyclic heptapeptide GPI, is a small-molecule
antagonist with rapid onset of action and short half-life of 2 to 2.5 hours. It reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive ligands to GP IIb/IIIa. Platelet aggregation inhibition is reversible following completion of the eptifibatide infusion, likely from dissociation of eptifibatide from the platelet. Recovery of platelet function occurs within 4 hours of cessation of eptifibatide.

Administration of a single 180 mcg/kg bolus combined with an infusion at 2 mcg/kg/min produces an early peak level, followed by a small decline prior to attaining steady state within 6 hours. Dose confirmation studies show that this decline is prevented, and the steady state reached faster, with a second bolus of 180 mcg/kg administered 10 minutes after the first. In patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min), the clearance of eptifibatide is reduced by approximately 50%. Hence, the recommended maintenance dose in these patients is 1 mcg/kg/min, whereas the bolus doses are unchanged.

Tirofiban (Aggrastat) is a tyrosine-derived, nonpeptide inhibitor and is a highly specific, competitive agonist for the GP IIb/IIIa receptor. It is associated with a rapid onset and a short duration of action, with a half-life of approximately 2 hours. Platelet recovery with tirofiban occurs in 4 to 8 hours of completion of infusion. Tirofiban is not approved in the United States for use during PCI but is widely used in other parts of the world. Considering that prior suboptimal results with tirofiban use in PCI were likely due to low doses (bolus of 10 mcg/kg followed by infusion of 0.15 mcg/kg/min for 18-24 hours), a high bolus dose (25 mcg/kg) is currently under study in the SAVI-PCI study. Because 75% of tirofiban clearance is renal, dose adjustment is required in renal failure.

The benefits of adding GPIs to heparin in PCI have been widely studied. However, GPIs were developed and brought to clinical use before stents were widely available. Hence, studies evaluating the efficacy of GPIs could be divided into “predominantly angioplasty studies” and “mostly stent-related studies,” with the latter being more applicable to current practice.

**Angioplasty Studies**

The first studies of GPIs were the EPIC and EPILOG studies, where addition of abciximab to heparin led to a 35% to 50% reduction in major
adverse cardiovascular events at 30 days, predominantly driven by a reduction in periprocedural MI. However, this benefit was at the cost of increased bleeding, with TIMI major bleeding being 50% higher in the GPI arm in the EPIC study. In EPILOG, bleeding was mitigated through a weight-based reduced-dose heparin strategy. Similar benefits were seen in studies examining tirofiban\(^{35}\) (18.5% vs 22.3%; \(P = .03\)) and epitifibatide\(^{36}\) (14.2% vs 15.7%; \(P = .04\)), with a significant reduction in death and nonfatal MI occurring up to 30 days after the index event. However, the issue of increased bleeding was also seen with these agents.\(^{35,36}\)

**Use of GPIs in Contemporary Practice**

**GPI Use in PCI With Stents Without Thienopyridine Preloading**

Early trials of GPIs enrolled patients not pretreated with a thienopyridine. The ESPIRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin)\(^{37}\) and EPISTENT (Effect of Abciximab on Angiographic Complications During Percutaneous Coronary Stenting in the Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial)\(^{38}\) trials each randomized over 2000 patients to eptifibatide versus placebo or abciximab versus placebo, respectively. Results of the ESPIRIT study demonstrated a 37% relative risk reduction (from 10.5% to 6.6%; \(P = .0015\)) in the primary composite end point of death, MI, and need for urgent TVR. There was a small but significant increase in bleeding from 0.4% to 1.3% with eptifibatide (\(P = .027\)). In EPISTENT, there was a 51% relative risk reduction of the composite primary end point of death, MI, and need for urgent revascularization in the first 30 days with abciximab in addition to heparin. Major bleeding was higher with abciximab but did not reach statistical significance. This beneficial effect persisted at 6 and 12 months.\(^{39}\)

Together, the ESPIRIT and EPISTENT trials indicate that in patients undergoing PCI without prior thienopyridine loading, GPIs reduce ischemic complications at a possible cost of increased rate of bleeding.

**GPI Use in Patients With Clopidogrel Preloading and**
Coronary Stenting

More contemporary studies performed with routine stenting and P2Y$_{12}$ therapy have been valuable in identifying the specific group of patients that would benefit from GPIs in current practice. The ISAR-REACT$^{40}$ (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial studied 2159 low-risk patients preloaded with 600 mg of clopidogrel at least 2 hours prior to PCI; in this low-risk elective population, the addition of abciximab to heparin did not reduce ischemic complications. At 30 days, the incidence of death, MI, and urgent TVR did not differ between the groups (4.0% vs 4.0%; $P = .82$). There was no difference in bleeding in the treatment groups. Similar results were obtained in diabetic patients undergoing elective angioplasty, when compared to routine pretreatment with clopidogrel.$^{41}$

In contrast to the initial studies evaluating low-risk patients, an analysis of the CAPTURE, PURSUIT, and PRISM-PLUS data indicated a more important role for GPIs in patients with ACS. This was confirmed in the ISAR-REACT-2 study, which randomized 2022 high-risk patients with non–ST-segment elevation ACS undergoing PCI to receive either abciximab or placebo with heparin in addition to aspirin and a 600-mg loading dose of clopidogrel administered at least 2 hours prior to the procedure. Among patients with elevated troponin levels, the incidence of the primary end point of the study, which was the composite of death, MI, or urgent TVR at 30 days, was significantly reduced in the abciximab group (relative risk, 0.71 [95% CI, 0.54-0.95]; $P = .02$), with no increase in major or minor bleeding between the 2 groups.$^{42}$ The benefit seen in these high-risk patients was maintained at 1 year, with a 20% reduction in death, MI, or TVR and a 25% reduction in death or MI among patients randomized to receive abciximab.$^{43}$ The ISAR-REACT-2 study was critical in establishing the benefit of GPIs for patients receiving routine thienopyridine treatment and coronary stents, particularly in patients with ACS with high-risk features.

GPIs in Primary PCI

The use of a powerful and rapid-acting antiplatelet agent is an appealing choice in patients with STEMI, considering the large thrombus burden and highly activated platelets; additionally, the time dependency of
revascularization means that pretreatment with P2Y$_{12}$ inhibitors may not be possible. Not surprisingly, there is a large body of literature regarding the efficacy and safety of the use of GPIs in primary PCI.

The ADMIRAL trial randomized 300 patients with STEMI to either heparin or heparin plus abciximab and showed a significant reduction in a composite 30-day end point of ischemia-related events (death, reinfarction, or urgent TVR); there were too few major bleeding events to make a comparison. The CADILLAC trial randomized 2018 patients in a 2×2 factorial design to percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary angioplasty plus abciximab, bare metal stent, or bare metal stent plus abciximab. The primary end point (death, reinfarction, stroke, or ischemia-driven TVR) was lowest in the stent/abciximab arm. Abciximab also reduced the rates of subacute thrombosis and urgent, ischemia-driven TVR in the first several weeks after the index procedure. BRAVE-3 randomized 800 patients to abciximab or placebo in STEMI, but detected no difference in the primary end point of infarct size; similarly, a composite secondary end point of death, reinfarction, stroke, or urgent revascularization was not different at 30 days or 1 year.

These 3 studies are a small sample of the published trials, but they highlight the difficulties with the available data, which include relatively small trials (mostly with abciximab), variable use of clopidogrel, and divergent results. Meta-analyses of a larger group of available studies have suggested that although there is no clear benefit to universal application of GPI in STEMI, there may be certain subgroups of high-risk patients who receive a mortality benefit. These studies have also consistently shown a persistent increase in bleeding with GPI use. These aggregate data are the basis of the Class IIa recommendation for GPI use in STEMI in the most recent ACCF/AHA and Society for Cardiovascular Angiography and Interventions PCI practice guidelines.

**GPI and Bivalirudin**

Although heparin and platelet inhibition with GPIs have established efficacy in preventing periprocedural ischemia, excess bleeding events remain a barrier to more routine use. Bivalirudin is a specific inhibitor of thrombin with predictable bioavailability and anticoagulant effects and has been an effective alternative to heparin in PCI since the balloon angioplasty era.
Several important studies have examined bivalirudin in the current PCI era, comparing bivalirudin to the combination of heparin and GPI. Although designed to evaluate bivalirudin, these studies have added significantly to our understanding of the current role of GPI.

The REPLACE-2 trial randomized 6000 patients undergoing elective PCI to bivalirudin and provisional GPI or heparin and planned GPI. In this study, only 7% of patients in the bivalirudin arm received GPI, and there were equivalent 30-day ischemic events in both groups. Importantly, there were significantly fewer bleeding events in the bivalirudin arm.

The ACUITY trial randomized 13,819 patients with intermediate- to high-risk non–ST-segment elevation ACS to 1 of 3 strategies: bivalirudin monotherapy, bivalirudin plus GPI, or heparin plus GPI. In this trial, only 60% of patients received a thienopyridine prior to going to the catheterization lab. The results at 30 days and 1 year showed equivalent ischemic events with bivalirudin monotherapy but significantly lower bleeding when compared to either of the arms using GPIs. ISAR-REACT-4 evaluated abciximab plus unfractionated heparin versus bivalirudin alone in 1721 patients with NSTEMI (all pretreated with clopidogrel) with similar results: no difference in ischemic end points, but increased bleeding with abciximab at 30 days. The comparable outcomes between the 2 arms persisted at 1 year.

HORIZONS-AMI repeated these comparisons in patients with STEMI. In this trial, 3602 patients (all pretreated with either 300 or 600 mg of clopidogrel) were randomized to receive heparin plus GPI or bivalirudin alone. The trial had 2 primary end points: major bleeding and net adverse clinical events (a combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, TVR for ischemia, and stroke within 30 days). There was a significant reduction in the 30-day rate of net adverse clinical events in the bivalirudin group (9.2% vs 12.1%; \( P = .005 \)), mainly due to a lower rate of major bleeding (4.9% vs 8.3%; \( P < .001 \)). Treatment with bivalirudin alone, as compared with heparin plus GPIs, resulted in significantly lower 30-day rates of death from cardiac causes (1.8% vs 2.9%; \( P = .03 \)) and death from all causes (2.1% vs 3.1%; \( P = .047 \)). These benefits were preserved at 1 and 3 years. A 600-mg loading dose of
clopidogrel was an independent predictor of lower rates of ischemic events at 30 days.

The weight of evidence from the bivalirudin studies has resulted in a reduced role for GPIs in even the highest risk PCI. However, there are 2 important caveats to keep in mind before dismissing GPIs from the antiplatelet armamentarium. First, radial artery access was used in a small minority of the patients, which may result in an overstated bleeding reduction benefit of bivalirudin (because a substantial proportion of bleeding events were access site related). Second, in both ACUITY and HORIZONS, there was an increased incidence of early MACE (in the first 10 days) including definite stent thrombosis in the first 24 hours (although stent thrombosis at 30 days was similar). This tendency toward increased early stent thrombosis was also observed in the EUROMAX trial, a more contemporary study that included a majority of patients receiving either prasugrel or ticagrelor (rather than clopidogrel) and almost 48% radial access (2218 randomized to either bivalirudin monotherapy or heparin with GPI).

Finally, the most contemporary trial clinical trial of PCI for STEMI, HEAT-PPCI, summarizes the current state of GPI utilization. Enrolling 1829 patients in 2012 and 2013, the investigators used radial access in 80% of patients and rapidly acting, potent thienopyridines (prasugrel and ticagrelor) in 90% of patients. Under these circumstances with experienced operators in a tertiary center, bailout GPI use was only 13% with bivalirudin and 15% with heparin, resulting in a 30-day MACE rate of 8.7% in the bivalirudin arm and 5.7% in the heparin arm. Although there are many valid criticisms of this trial, it does provide a glimpse of the result of strictly bailout GPI. It would appear that although GPIs have a role in current PCI, they are reserved for a minority of even the most acute cases.

In our practice, we favor radial access for STEMI, with unfractionated heparin as the anticoagulant. In cases where the patient has not had adequate thienopyridine pretreatment (6 hours for clopidogrel or 1 hour for prasugrel/ticagrelor), a bolus and short-duration infusion of a GPI, such as eptifibatide, can ensure platelet inhibition until thienopyridine loading is effective. Eptifibatide is also used in patients with a large thrombus burden, with evidence for distal embolization, or in whom there is less than TIMI grade 3 flow at the conclusion of the intervention. In femoral access cases, we favor bivalirudin; similarly, a bolus with or without a short infusion of eptifibatide is used in patients that have not been pretreated with a
thienopyridine or in whom the results are suboptimal.

**DUAL ANTIPLATELET THERAPY: DURATION OF THERAPY**

Historically, the primary indication for DAPT after PCI is the avoidance of stent thrombosis. In contemporary practice, stent thrombosis rates are low; registry data from 21,009 patients receiving 31,065 stents (63.8% bare metal) between 2004 and 2007 reported a stent thrombosis rate of 2.1% at a median follow-up of 30.9 months. Interestingly, 73% of stent thromboses occurred within the first 30 days, and 88% of these patients were still taking DAPT. Although cessation of antiplatelet therapy (specifically thienopyridine therapy) remains a predictor of early stent thrombosis, clearly there are patient- and procedure-related factors that are also important.

With bare metal stents, the duration of antiplatelet therapy can be brief. In the STARS trial, 4 weeks of aspirin and ticlopidine resulted in a stent thrombosis rate of 0.5%, presumably related to adequate stent endothelialization. A low rate of subsequent stent thrombosis persists for bare metal stents, even at 3 years. The STARS data remain the basis for current guideline recommendations regarding bare metal stents.

In drug-eluting stents, the information regarding duration of antiplatelet therapy continues to evolve rapidly. In the initial SIRIUS trial evaluating the sirolimus-eluting Cypher stent (Cordis, Fremont, CA), aspirin and clopidogrel were administered for a total of 8 weeks based on animal model estimates of time to full reendothelialization. In this study of 238 patients (120 received the drug-eluting stent), there were no reported stent thrombosis events at the 6-month primary end point. By the time of FDA approval, labeling recommendations for the duration of DAPT were 3 months for the Cypher and 6 months for the Taxus stents (Boston Scientific, Marlborough, MA). Despite these prolonged treatment times, early signals appeared of higher than expected late stent thrombosis events, with associated high morbidity and mortality. Within the first year of their approval, the FDA issued a public health notification to remind physicians that off-label use of drug-eluting stents and early discontinuation of antiplatelet therapy may contribute to increased stent thrombosis rates. Within 3 years, continued
reports of stent thrombosis, as well as studies indicating that longer duration of antiplatelet therapy might reduce stent thrombosis rates, prompted the FDA to convene an advisory panel to review the data. The conclusions of this panel in early 2007 included a recommendation to extend the duration of antiplatelet therapy to 12 months for all drug-eluting stents. Although this recommendation was endorsed in the ACC/AHA practice guidelines, it was made in the absence of any supporting randomized data.

Since 2007, 3 factors have substantially altered our understanding of the need for prolonged DAPT: (1) evolution of stent design, including drug and polymer; (2) the availability of clinical tests of platelet function to assess the effects of antiplatelet medication in an individual patient; and (3) an increased appreciation that avoidance of bleeding is equal to ischemia/stent thrombosis as a measure of clinical success and long-term mortality.

Since the sirolimus-eluting and paclitaxel-eluting “first-generation” stents, stent design has changed with respect to the stent metal composition, polymer composition, and drug. A full discussion of the details of these changes is beyond the scope of this chapter, but almost all the changes have been associated with a steady reduction in stent thrombosis rates. Recent meta-analyses have indicated that second-generation drug-eluting stents are superior to first-generation DESs with regard to definite or definite/probable ARC-defined stent thrombosis, including both early and late stent thrombosis events. Thin strut stent platforms have been associated with extremely low stent thrombosis rates. In the HOST-ASSURE trial, cobalt chromium zotarolimus-eluting stents had a 1-year definite/probable stent thrombosis rate of 0.67%, and platinum chromium everolimus-eluting stents had a stent thrombosis rate of 0.36%. Further reduction in stent thrombosis rates may be possible with biodegradable polymers and/or biodegradable struts, and this is being examined in ongoing clinical trials of the newest stent designs. Interestingly, stent thrombosis events in these studies are so low that detecting differences has become exceedingly difficult. One-year follow-up of the Nobori bioabsorbable stent (Terumo, Elkton, MD) versus the everolimus-eluting stent showed noninferiority in the primary end point in almost 3000 patients, but the stent thrombosis rate was less than 1% at 1 year. Finally, continued evolution of PCI techniques and adjunctive drug therapy may also make clinical differences in stent design difficult to detect; in the recently published PROTECT study, there was no difference between a first-generation stent (sirolimus) and a second-generation stent (everolimus)
at 3 years, although there were more very late stent thrombosis events in sirolimus-eluting stents (after discontinuation of antiplatelet therapy). This study is notable for the fact that it is the only stent study to use stent thrombosis as the primary end point and that both of these stents are no longer commercially available.

As noted previously, available P2Y\textsubscript{12} inhibitors have variable metabolism and efficacy in platelet inhibition, which are largely mediated through genetic differences in metabolic enzymes. Wholesale change to those agents with more reliable platelet inhibition has been limited primarily by cost, as well as concerns for increased neurologic and bleeding complications. Both genetic differences and degree of platelet inhibition can now be detected by rapid clinical tests in individual patients. Although there was great initial enthusiasm for routine use of platelet functional testing and/or genetic testing to identify individuals with inadequate platelet inhibition, clinical trials have failed to show differences in patient outcomes with routine testing. This is best illustrated in the ADAPT-DES study,\textsuperscript{9} a registry of over 8500 patients undergoing PCI. Routine platelet functional testing after PCI and treatment with clopidogrel confirmed that inadequate platelet inhibition is strongly associated with stent thrombosis; however, adequate platelet inhibition was also strongly associated with bleeding episodes. Because both stent thrombosis and bleeding impact mortality, neither adequate nor inadequate platelet inhibition was associated with improved overall long-term outcome. Interestingly, aspirin responsiveness was only associated with bleeding; better aspirin effect was not correlated with less stent thrombosis. The important implication of platelet functional studies in terms of length of treatment is that better inhibition of platelets is associated with bleeding over time, and duration of treatment needs to balance these dual goals of avoidance of stent thrombosis and bleeding events.

Bleeding episodes at the time of PCI are powerful predictors of long-term mortality, even when the initial bleeding event is not catastrophic. Strategies for bleeding avoidance at the time of the procedure, such as use of bivalirudin or radial access, may be associated with improved long-term survival. Similarly, late bleeding episodes are also associated with increased mortality, and late bleeding is related to DAPT. The PRODIGY trial enrolled 2013 patients to be randomized to 6 or 24 months of DAPT and found no difference in ischemic outcomes (including ARC-defined stent thrombosis) but a significant increase in bleeding events, including life-threatening
bleeding, in the 24-month DAPT group.

Two large randomized studies will soon bring new data into the duration of therapy debate. The ISAR-SAFE trial is enrolling up to 6000 patients to be randomized between 6 and 12 months of clopidogrel and aspirin, with a primary composite end point (death, MI, stent thrombosis, stroke, and TIMI major bleeding) to be assessed at 15 months after the index procedure. The recently reported DAPT trial randomized 9961 patients who received either DESs or bare metal stents to 12 or 30 months of DAPT. The coprimary efficacy end points were the cumulative incidence of definite/probable stent thrombosis and a composite of death, MI, and stroke in months 12 to 30 (randomization period). The primary safety end point was GUSTO-defined moderate or severe bleeding. Importantly, a specific thienopyridine was not mandated, nor was a specific stent type.

The end points in DAPT strongly favored the longer duration of treatment. First, prolonged antiplatelet therapy was associated with a lower rate of stent thrombosis (0.4% in 24-month group vs 1.4% in 12-month group). Second, the risk of MACE (death, MI, and stroke) was also lower in the prolonged therapy group (4.3% vs 5.9%), driven primarily by a reduction in MI (2.1% vs 4.1%). A reduction in non–stent-related MI accounted for 55% of the treatment effect in this end point. Not unexpectedly, moderate to severe bleeding occurred more often in the prolonged therapy group (2.5% vs 1.6%). Although all-cause mortality was higher with prolonged therapy (2.0% vs 1.5%; HR, 1.36; \( P = .05 \)), deaths related to bleeding (11 deaths in 24-month therapy group and 3 in 12-month therapy group) did not achieve statistical significance (\( P = .06 \)). Finally, the incidence of MI and stent thrombosis increased in the first 3 months after cessation of therapy in both groups, leaving the question of duration of treatment still unanswered. However, a consideration of the DAPT conclusions must keep in mind 2 important details of the study. First, by design only, patients who made it through 12 months of therapy without a major cardiovascular or bleeding event were randomized, which was a minority of those enrolled (9961 of 25,682, or 38.7%), suggesting the final study population was skewed toward a lower risk profile. Second, 38% of randomized patients received first-generation sirolimus-eluting (Cypher) or thin strut paclitaxel-eluting (Taxus Liberte) stents, which may have higher stent thrombosis rates than current-generation everolimus and zotarolimus stents. Still, the finding that prolonged therapy with thienopyridines prevents MI, not just stent thrombosis, is important and must
be part of the discussion about the most appropriate medications for secondary prevention. The DAPT and PEGASUS-TIMI 54 trials are indicative of a growing understanding that the benefits of antiplatelet therapy after PCI extend beyond the increasingly rare issue of stent thrombosis. One of the most exciting ideas to emerge is that of antiplatelet treatment durations of less than 6 months. In 2012, the Xience everolimus-eluting stent (Abbott Vascular, Santa Clara, CA) received approval in Europe for use for only 3 months of DAPT, based on postmarketing registry data from over 10,000 patients. In 2013, the results of OPTIMIZE became available, where 3119 patients were randomized to either 3 months or 12 months of aspirin and clopidogrel after receiving a zotarolimus DES. The primary end point was a net benefit composite of both ischemic and bleeding events, and after 1 year, there was no difference between the 2 DAPT strategies. Similar results were seen in the RESET trial, which used the Endeavor zotarolimus-eluting stent (Medtronic, Edgwater, MD). Although encouraging, this stent is no longer available, having been replaced by the Resolute Integrity zotarolimus stent (Medtronic) with a more prolonged drug elution profile that more closely imitates competing stent elution profiles. The change in rate of drug elution significantly decreased the degree of intimal hyperplasia in the new stent and, as a result, may have altered thrombosis risk. There are currently several proposed or actively enrolling studies that are designed to evaluate 3 versus 6 months of treatment using current generation stent designs.

**Bioabsorbable Polymer and Scaffold**

Concerns regarding the long-term thrombogenicity of the polymer matrix, either through hypersensitivity reactions or other direct mechanisms, has led to the development of bioabsorbable polymer stent. Three studies (LEADERS, ISAR-TEST 3 and ISAR-TEST 4) have compared first-generation DESs to absorbable matrix stents in a total of 4062 patients. At 4 years, the total number of stent thrombosis events was lower in the bioabsorbable platforms, particularly with respect to very late stent thrombosis events (between 1 and 4 years). Although this seems to lend validity to the hypothesis that elimination of polymer will improve vessel healing and long-term safety, these differences may not persist when compared to second-generation DESs. Long-term results of the COMPARE 2 study (Nobori bioabsorbable stent vs everolimus DES) and EVOLVE II
(Boston Scientific Synergy stent vs everolimus-eluting stent) will hopefully give insight into this category of stent but will not specifically address the issue of length of treatment. The largest study of bioabsorbable polymer to date, LEADERS, mandated 12 months of dual therapy.

A number of concepts in totally resorbable stent platforms have reached the level of entering early clinical investigation. The device farthest along this path is the bioreabsorbable vascular everolimus-eluting scaffold; a trial is currently enrolling patients in a comparison of this device against a metal, permanent polymer everolimus-eluting stent. All trials continue to mandate 12 months of DAPT, but the potential exists for this to be tailored after the initial experience is available. To date, stent thrombosis events have been low in an overall low-risk population.

**SPECIAL CIRCUMSTANCES**

**DAPT and Anticoagulation**

In patients prescribed oral anticoagulants, the need for PCI and stent placement often presents the clinician with the obligation to consider continuing oral anticoagulation concomitantly with DAPT (triple therapy). In patients treated with warfarin, the evidence is clear that there is a substantially increased risk of severe bleeding when aspirin and clopidogrel are added after PCI. By 6 months, the relative risk of any bleeding is as high as 3.12 compared to DAPT, whereas the relative risk of major bleeding is 2.87. The recognition of this relationship may lead to relative underuse and/or decreased intensity of anticoagulation, with a resultant increase in both bleeding episodes and number of strokes while on triple therapy. A single, relatively small (573 patients) study has examined the strategy of clopidogrel alone with warfarin after PCI. When compared to triple therapy, clopidogrel was associated with a significantly lower rate of bleeding (12.0% vs 2.2%) and blood transfusion (9.5% vs 3.9%) without an increase in stroke or stent thrombosis. In patients on warfarin undergoing PCI, a clear examination of thrombosis risk with interruption of warfarin needs to be balanced against the need for a DES, and consideration must be given to shortened duration of DAPT.
In patients receiving newer, nonwarfarin oral anticoagulants, the data are scant but do suggest similar increased bleeding events when DAPT is added. Two meta-analyses have suggested a 2- to 3-fold increase in bleeding episodes, similar to warfarin.\textsuperscript{58,59} Importantly, no study has examined the effect of duration of DAPT while on new oral anticoagulants. Finally, there are no data for new oral anticoagulants when combined with P2Y\textsubscript{12} inhibitors other than clopidogrel, but one must assume bleeding rates would be even higher given the more uniform platelet inhibition with these agents and the documented increase in bleeding episodes even in the absence of oral anticoagulants.

**DAPT and Noncardiac Surgery**

As many as 23\% of patients undergoing PCI with stent placement will have noncardiac surgery within 48 months of their stent procedure. Current guidelines (last revised in 2007) recommend delaying surgery until after 12 months of DAPT have been completed or, if necessary, until the year following PCI, continuing DAPT through the perioperative period. These recommendations (Class IIa, Level of Evidence C) are based on the observation of high stent thrombosis rates when surgery is performed early after the stent procedure and the assumption that complete reendothelialization of the stented segment will be associated with the lowest probability of stent thrombosis and cardiac events at the time of surgery.

The largest observational study provides evidence from 28,029 patients who had noncardiac surgery within 24 months of coronary stenting (52.4\% bare metal).\textsuperscript{60} This study did not specifically examine stent thrombosis, but rather repeat revascularization and MI without death, repeat revascularization/MI with death, and death. The overall MACE rate was 4.7\%, but was 5.1\% before the publication of the 2007 guidelines and 3.5\% for operations performed after 2007. Interestingly DESs were slightly less associated with MACE (OR of 0.91 compared to bare metal stent), although obviously, only bare metal stents were available in the earliest part of the study, when event rates were highest. There appeared to be no association between the occurrence of MACE and antiplatelet therapy cessation. Interestingly, clinical variables such as emergency surgery, recent MI, and a high revised cardiac risk index score were among the most powerful predictors of MACE. With regard to stent-specific variables, a shorter period
of time between the stent procedure and surgical procedure was predictive of MACE. These findings are largely similar to other, smaller registries and would suggest a reevaluation of the 2007 guidelines.

CONCLUSION

Antiplatelet therapy in patients undergoing PCI is a therapeutic challenge that is continuously, and rapidly, evolving. Recognition of factors that place patients at greatest risk for ischemic complications, rapid progress in stent design, and availability of new antiplatelet therapies have pushed stent thrombosis rates to all-time lows. Long-respected cornerstones of therapy, such as universal use of aspirin, may be less relevant. Recognition of the short- and long-term consequences of peri-PCI bleeding episodes has raised bleeding avoidance to equal ischemia prevention as dual therapeutic objectives of therapy following stent placement. The rapid refinement of therapy in the first 10 years of DESs gives great hope that our antiplatelet therapy can be tailored, using shortened duration and more rapidly acting, consistently effective medications to further reduce bleeding events and eliminate stent thrombosis.

REFERENCES


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**MULTIPLE CHOICE QUESTIONS**

1. Ticlopidine was the first P2Y$_{12}$ inhibitor to be used clinically for dual antiplatelet therapy after stent placement. Ticlopidine was quickly replaced by clopidogrel, however, because of which of the following disadvantages or side effects?
   A. Twice-daily dosing
   B. High incidence of gastrointestinal upset
   C. Neutropenia/thrombocytopenia
   D. All of the above

2. The TRITON-TIMI 38 trial compared prasugrel to clopidogrel in patients with acute coronary syndrome (ACS) receiving drug-eluting stents. Which of the following subgroups was identified in a post hoc analysis as patients who did **not** benefit from prasugrel because of an excess of bleeding complications?
   A. Patients over the age of 75
   B. Patients over 80 kg in weight
   C. Patients with a prior transient ischemic attack (TIA)
   D. A and C
   E. B and C
   F. A, B, and C

3. Which of the following antiplatelet medications achieves its therapeutic effect by interfering with the functioning of the P2Y$_{12}$ receptor on
platelets?
A. Vorapaxar
B. Aspirin
C. Ticagrelor
D. Cangrelor
E. Abciximab
F. C and D
G. A, C, and E

4. The results of the HORIZONS-AMI trial compared bivalirudin monotherapy to heparin and glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI). The results of this study indicated which of the following?
A. That glycoprotein IIb/IIIa inhibitors maintain a strong advantage in this patient group
B. That drug-eluting stents should not be used in primary PCI
C. That bivalirudin reduced bleeding events compared to heparin and glycoprotein IIb/IIIa inhibitor
D. That femoral access is the best means of arterial access in STEMI
E. C and D

5. Which factor(s) impacts any calculation of the duration of dual antiplatelet therapy after drug-eluting stent placement?
A. Stent design
B. Stent polymer
C. Stent diameter and length
D. Risk of bleeding for a specific patient, including other medications
E. All of the above

ANSWERS

1. D

Ticlopidine 250 mg twice a day (along with aspirin) was the antiplatelet therapy used in the first clinical study to prove that antiplatelet therapy was superior to anticoagulation (ie, warfarin) in patients who received stents.
However, there were a significant proportion (8%-10%) of patients who suffered nausea and diarrhea while taking ticlopidine. More serious bone marrow suppression was less frequent. Clopidogrel was better tolerated, did not cause bone marrow suppression, and was dosed once daily—all significant advantages.

2. D

Patients in the TRITON-TIMI 38 trial benefitted from more reliable protection from ischemic events provided by prasugrel compared to clopidogrel, although at a cost of more frequent serious bleeding events. For the majority of patients in the trial, the net effect was still benefit, even when considering bleeding. Post hoc analysis identified 3 groups in whom the bleeding was equal to ischemia prevention, and so there was no benefit: patients older than 75, patients with body weight less than or equal to 60 kg, and patients with a prior TIA or stroke. These findings led to labeling instructions that indicate that use of this medication should be restricted in patients who meet these criteria.

3. F

Platelets may be activated through a number of surface receptors: the thrombin receptor (PAR-1), adenosine diphosphate (ADP) receptors (including P2Y\(_{12}\)), the thromboxane A\(_2\) (TP) receptor, and collagen receptors. Interference with the receptors and/or receptor agonists of the activation sequence is the primary mechanism of antiplatelet therapy. Vorapaxar is an antagonist of the thrombin receptor; aspirin inhibits formation of thromboxane A\(_2\); and clopidogrel, cangrelor, prasugrel, and ticagrelor are P2Y\(_{12}\) antagonists. Abciximab, eptifibatide, and tirofiban exert their effect by blocking the ability of activated platelets to bind to fibrinogen, thus preventing platelets from adhering to clots and other platelets.

4. C

HORIZONS-AMI randomized patients to 1 of 2 anticoagulation strategies for primary PCI: either the direct thrombin inhibitor bivalirudin or heparin combined with a glycoprotein IIb/IIIa inhibitor. The results of the study indicated that there was a lower overall mortality, a lower cardiac mortality,
and a lower reinfarction rate at 3 years in the bivalirudin arm. These results may have been mediated, at least in part, by a lower rate of major bleeding in patients receiving bivalirudin.

A second randomization within HORIZONS-AMI compared bare metal stents to paclitaxel-eluting stents; in this analysis, the drug-eluting stent was associated with lower rates of target vessel revascularization without any safety concerns.

The vast majority of patients in HORIZONS had their procedure by femoral access; there was no meaningful comparison between access methods in the trial design or in post hoc analysis.

5. E

The duration of antiplatelet therapy is a treatment parameter that is difficult to generalize because there are so many factors that can be important for any individual patient. First-generation drug-eluting stents were initially plagued by late and very late stent thrombosis, which in turn favored a very long duration of antiplatelet therapy. Changes in stent design and polymer composition have made the stents less prone to thrombosis, and duration of antiplatelet therapy has shortened accordingly. In addition to stent factors, procedural factors, including stent size and length or bifurcation stenting, raise the risk for stent thrombosis and may favor longer dual antiplatelet therapy duration. Patient factors, such as the need for anticoagulation or prior major gastrointestinal bleeding, renal disease, or liver disease, raise the bleeding risk and may favor shorter dual antiplatelet therapy duration. In any individual patient, the clinician must balance ischemic risk and bleeding risk when deciding how long to continue antiplatelet therapy after stent placement.
INTRODUCTION

The recognition of the proximate role of coronary thrombosis secondary to plaque rupture or erosion as the underlining cause of ST-segment elevation acute myocardial infarction (AMI) opened the door to the development of pharmacologic and mechanical interventions that have saved countless lives from a disease process that previously had few options and carried a high mortality rate. Thrombolytic agents were the first to provide substantial and sustained improvements in the morbidity and mortality of AMI. Summarized in this chapter are the key trials of thrombolytic agents and adjuncts to fibrinolysis along with recommendations for their application in AMI.

BACKGROUND

The discovery that hemolytic streptococci produce a thrombolytic substance is attributed to a 1933 report by Dr. William Smith Tillett. However, it would be another 50 years before streptokinase was systemically evaluated in the treatment of AMI. Although sporadic use of streptokinase in AMI was reported during that interval, concerns regarding antigenicity, hemodynamic effects, efficacy, dosing, timing, and even method of delivery restricted acceptance. In 1986, the landmark Gruppo Italiano per la Sperimentazione
della Streptochinasi nell’ Infarto Miocardico (GISSI) study was published demonstrating a marked improvement in AMI survival with treatment. The GISSI study evaluated 11,806 patients presenting with an AMI within 12 hours of symptom onset. Patients were randomized to treatment with streptokinase or placebo, with both groups otherwise receiving standard of care. There was a significant reduction in 30-day and 1-year mortality compared with placebo (10.7% vs 13.0% and 17.2% vs 19.0%, respectively). It was observed that the more rapidly a patient received streptokinase from symptom onset, the greater the mortality benefit. The results were confirmed by the Second International Study of Infarct Survival Collaborative Group (ISIS-2) trial (see below), resulting in the acceptance of streptokinase as first-line treatment of AMI.

THROMBOLYTIC AGENTS

With the therapeutic benefits of streptokinase well established, pharmaceutical research and development turned to identifying agents with greater specificity for fibrin and with fewer side effects. There are currently four US Food and Drug Administration (FDA)-approved thrombolytic agents for the use in the United States: streptokinase, alteplase, reteplase, and tenecteplase (Table 17-1). The three fibrin-specific agents are discussed in the following sections.

Table 17-1 Comparison of the Available Thrombolytics
Alteplase (tPA) is a recombinant tissue plasminogen activator. It promotes fibrinolysis by converting plasminogen to plasmin. The efficacy and safety of tPA were evaluated and compared with streptokinase in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trial published in 1993. The investigators randomized 41,021 patients presenting with an AMI into 1 of 4 treatment regimens: (1) streptokinase 1.5 million units over a 60-minute period, with subcutaneous heparin at 12,500 units twice daily, beginning 4 hours after the start of thrombolytic therapy; (2) streptokinase 1.5 million units over a 60-minute period, with an intravenous heparin bolus dose of 5000 units and infusion of 1000 units per hour adjusted for an activated partial thromboplastin time between 60 and 85 seconds; (3) accelerated tPA in a bolus dose of 15 mg, followed by a 0.75 mg/kg of body weight infusion over 30 minutes (not to exceed 50 mg), followed by 0.5 mg/kg over the subsequent 60 minutes (not to exceed 35 mg), with the same intravenous bolus.
heparin regimen as arm 2; and (4) the combination of intravenous tPA as a 1.0 mg/kg infusion over 60 minutes (not to exceed 90 mg, with 10% given in a bolus dose) and streptokinase (1.0 million units over 60 minutes) given simultaneously but through separate intravenous catheters, along with intravenous heparin. The results demonstrated a statistically significant reduction in mortality at 24 hours and at 30 days with accelerated tPA and intravenous heparin compared with streptokinase (10 lives saved per 1000 patients treated). However, there was an increased risk of hemorrhagic stroke in the accelerated tPA arm compared with streptokinase (2 hemorrhagic strokes per 1000 patients treated). Despite the increased risk of intracranial bleeding, tPA was easier to use, lacked the antigenicity of streptokinase, and had an overall mortality benefit. As a result, tPA rapidly became the preferred agent for the treatment of AMI.

**Reteplase**

Reteplase (rPA) is a deletion mutant of recombinant plasminogen activator. The key differences are that it lacks the kringle-1, finger, and growth factor portions of wild-type tPA. These differences result in the same specificity for fibrin but decreased affinity, with a longer half-life, making it suitable for bolus administration. The pilot evaluations of rPA compared with tPA were the Reteplase Angiographic Phase II Interventional Dose-Finding Study (RAPID)-I and RAPID-II. These studies demonstrated a slight increase in the rate of artery patency by coronary angiography at 90 minutes without an increase in the risk of bleeding. However, the key registration trial, GUSTO-III, demonstrated essentially no differences in mortality or bleeding between rPA and tPA. The primary advantage of rPA is thus easier administration (as a double bolus) compared with the bolus plus infusion regimen of tPA.

**Tenecteplase**

Tenecteplase (TNK) is a genetically altered variant of tPA with three amino acid substitutions. The result is a more fibrin-specific lytic, with a longer half-life and greater resistance to plasminogen activator inhibitor 1 (PAI-1). This allows TNK to be administered as a single bolus. The key registration trial of TNK was the Assessment of the Safety and Efficacy of a New Thrombolytic Study (ASSENT)-2 head-to-head comparison with tPA. As
with GUSTO-III, the results of the study demonstrated no difference in 30-day mortality or intracranial hemorrhage. Of note, there were statistically significantly fewer nonintracranial bleeding events and a lower need for transfusions; these observations were attributed to the increased fibrin specificity of TNK. Given the ease of administration, equivalent efficacy, and slightly improved bleeding profile, TNK now enjoys the largest share of the thrombolytic market for AMI in the United States.

**ADJUNCTIVE THERAPY**

While the seminal trials of fibrinolysis in AMI incorporated heparin anticoagulation, there still remained a significant risk of reinfarction and subsequent angina, heart failure, or death attributable to vessel reclosure within 30 days of randomization. As a result, investigators have evaluated a series of adjunct therapies to the thrombolytic agents to reduce the incidence of coronary artery rethrombosis and its consequences.

**Low-Molecular-Weight Heparin**

Low-molecular-weight heparin (LMWH) is an attractive alternative to unfractionated heparin (UFH) for several reasons. The action of LMWH is to inhibit the coagulation cascade at an earlier point in the cascade than heparin. LMWH also proportionally inhibits the activity of factor Xa versus factor IIa to a greater extent than UFH. Theoretically, this reduces thrombin generation and provides for a more even and reliable anticoagulant effect. Additionally, in the absence of renal dysfunction, there is little need for monitoring. In the Enoxaparin Versus Unfractionated Heparin With Fibrinolysis for ST-Elevation Myocardial Infarction–Thrombolysis in Myocardial Infarction (ExTRACT TIMI)-25 trial, the investigators compared enoxaparin and UFH as adjunctive therapy for fibrinolysis in AMI. The choice of thrombolytic agent (streptokinase, tPA, rPA, or TNK) was left to the discretion of the treating physician. In the trial, 20,506 patients were randomized in a 1:1 fashion to either LMWH or UFH based on the thrombolytic they received. The results demonstrated a significant reduction in the primary end point of death or nonfatal myocardial infarction with LMWH compared with UFH (9.9% vs 12.0%; \( P < .001 \)). Additionally, there was a significant reduction in
the secondary end point of death, nonfatal reinfarction, or need for urgent revascularization (11.7% vs 14.5%; \( P < .0001 \)). The benefits came at a cost of increased risk of major bleeding (2.1% vs 1.4%; \( P < .001 \)) at 30 days. Of note, enoxaparin was continued to the end of the index hospitalization, whereas UFH was continued for 48 hours, suggesting a possible explanation for the observation of increased bleeding.

**Fondaparinux**

Fondaparinux is an anti-Xa inhibitor with a half-life of 16 to 24 hours. The seminal trial of fondaparinux in ST-segment elevation myocardial infarction was the Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST Elevation Myocardial Infarction–Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-6 trial. In OASIS-6, 12,092 patients presenting with an AMI were randomized to receive fondaparinux 2.5 mg daily for up to 8 days versus usual care (placebo or UFH). Of these patients, 2692 received thrombolytic therapy and fondaparinux, whereas 2744 received thrombolytic therapy with usual care.\(^{12}\) Rate of death or reinfarction at 30 days was lower in those treated with fondaparinux versus UFH/placebo (9.7% vs 11.2%; \( P < .008 \)), with a trend toward lower bleeding events. Of note, fondaparinux alone as an anticoagulant is not recommended in patients undergoing percutaneous coronary intervention (PCI) secondary to the observation of guide catheter thrombosis in OASIS-6.

**Bivalirudin**

Bivalirudin is a short-acting (half-life ~25 minutes) direct thrombin inhibitor that acts on both clot-bound and unbound thrombin.\(^{13}\) It is highly specific and does not result in platelet activation. It also partially inhibits platelets via blocking the binding of thrombin to the platelet protease activated receptor (PAR)-1. As an adjunct to thrombolytic therapy, bivalirudin was studied in the Hirulog Early Reperfusion Occlusion (HERO)-2 trial, which enrolled 17,073 patients presenting with an AMI to receive bivalirudin or UFH with standard-dose streptokinase.\(^{14}\) The trial demonstrated no significant difference in mortality at 30 days (10.8% vs 10.9%, respectively; \( P = .85 \)). There was a statistically significant increase in mild to moderate bleeding but
not severe or intracranial bleeding with bivalirudin treatment. Given the lack of mortality benefit and increased bleeding profile, bivalirudin is not recommended for routine use in the initial treatment of AMI after thrombolysis except in patients with a history of heparin-induced thrombocytopenia.

**Platelet Glycoprotein IIb/IIIa Inhibitors**

The platelet glycoprotein IIb/IIIa receptor inhibitors are a potent group of medications whose effect is directed at blocking platelet aggregation. The final common pathway of platelet activity is a conformational change in the glycoprotein IIb/IIIa receptor allowing for cross-linkage with other platelets via dimeric adhesion molecules. This process stabilizes thrombus and contributes to resistance to fibrinolysis and to artery reocclusion. A series of studies have been performed evaluating the efficacy of glycoprotein IIb/IIIa receptor blockade with thrombolytic therapy. Small dose-finding studies such as the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis–Acute Myocardial Infarction (IMPACT-AMI) trial of eptifibatide with tPA demonstrated improved patency rates when compared with placebo, prompting several large phase III studies. Among these, the GUSTO-V trial was a large multicenter, randomized, open-label trial that randomized 16,588 patients to standard-dose rPA or half-dose rPA plus full-dose abciximab. Both treatment arms also received UFH and aspirin. The study failed to produce a significant difference in the primary end point or mortality at 30 days. Although secondary end points including reinfarction, recurrent ischemia, and the need for “bailout” revascularization were significantly reduced, this was offset by an approximate doubling in nonintracranial bleeding and other measures of bleeding. Given the lack of mortality benefit and the increase in bleeding complications, routine use of glycoprotein IIb/IIIa inhibitors in combination with thrombolytic therapy is not recommended.

**Aspirin**

Aspirin is a reversible cyclooxygenase-2 (COX-2) inhibitor with well-documented cardiovascular benefits. It was first studied in a large randomized fashion in the setting of AMI in the ISIS-2 study published in
In ISIS-2, 17,187 patients with suspected AMI were randomized to receive one of the following regimens: aspirin alone, streptokinase alone, both aspirin and streptokinase, or placebo. With respect to aspirin, the observed mortality with aspirin alone (10.7% at 5 weeks) approached the benefit observed with streptokinase alone (10.4%). In addition, the combination of aspirin and streptokinase had a significant additive benefit (an additional 2.4% absolute risk reduction in mortality on top of the benefit seen with streptokinase). As a result, aspirin is a recommended adjunct in all patients who receive thrombolytic therapy.

**Clopidogrel**

Clopidogrel is an oral agent that blocks the adenosine diphosphate P2Y$_{12}$ receptor, resulting in inhibition of platelet activation. It is an irreversible prodrug that requires metabolism by the CYP2C19 enzyme for activation. Two large trials have evaluated the efficacy and safety of clopidogrel as an adjunct to thrombolytic therapy. The Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY TIMI)-28 trial, published in 2005, evaluated the efficacy of a 300-mg loading dose followed by 75 mg daily of clopidogrel compared with placebo in 3491 patients presenting with an AMI and receiving thrombolytic therapy. The choice of thrombolytic agent was at the discretion of the treating physician, and aspirin and heparin were also administered. The primary efficacy end point was a composite of an occluded infarct-related artery (defined as Thrombolysis in Myocardial Infarction [TIMI] flow grade 0 or 1) at angiography, death, or recurrent myocardial infarction before angiography. The results demonstrated a statistically significant reduction in the primary end point at initial angiography and at 30 days (14.1% vs 11.6%; $P = .03$). There was no significant difference between the clopidogrel arm and placebo in TIMI major or minor bleeding. These results were reinforced by the COMMIT study (Addition of Clopidogrel to Aspirin in 45,852 Patients With Acute Myocardial Infarction: Randomized Placebo-Controlled Trial, part of the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study). In this study, 45,852 patients in China were randomized to clopidogrel versus matching placebo. The results demonstrated a significant reduction in the primary end point of death, reinfarction, or stroke (9.2% vs 10.1%; $P = .002$) with use of clopidogrel versus placebo without a significant
increase in bleeding.\textsuperscript{17}

**SUMMARY OF CURRENT GUIDELINES**

Current AMI management guidelines were published in 2013.\textsuperscript{18} The use of thrombolytic therapy has gradually decreased over the past decade, being supplanted by primary PCI. Nonetheless, thrombolytic therapy is still the treatment of choice in perhaps 20% of AMI patients. A clear understanding of indications for thrombolytic therapy versus transfer for immediate PCI is critical. In the AMI guidelines, the decision to administer thrombolytic therapy (in the absence of a contraindication; \textit{Table 17-2}) is framed by 2 considerations: (1) time from the onset of symptoms to first medical contact (FMC), and (2) time from FMC to anticipated time of PCI. The greatest benefit of reperfusion occurs within 1 to 3 hours from symptom onset. As the time from symptom onset to the administration of thrombolytic therapy increases, there is a concomitant decrease in benefit with an associated increase in risk (\textit{Fig. 17-1}). In the current guidelines, it is a Class I recommendation, with Level of Evidence A, to administer thrombolytic therapy to patients when there is an anticipated delay to primary PCI of greater than 120 minutes. In other words, if the anticipated time from FMC to first balloon is anticipated to be greater than 120 minutes, then thrombolytic therapy should be given. If thrombolytic therapy is decided upon, then the goal is to administer the thrombolytic agent (the door-to-needle time) in less than 30 minutes. Given these time frames, when the difference in anticipated time between the 2 reperfusion strategies is less than 90 minutes, the preferred strategy is to transfer to a PCI center.
FIGURE 17-1 Projected reduction in mortality with reperfusion in acute ST-segment elevation myocardial infarction (curve), with recommendations for reperfusion strategy by time from onset of symptoms. The efficacy of fibrinolytic therapy declines rapidly over the first few hours following vessel occlusion. Nonetheless, when a delay to primary percutaneous coronary intervention (PCI) of >120 minutes is anticipated, fibrinolytic therapy should be given (absent contraindication). *Primary PCI (but not fibrinolytic therapy) is recommended when there is evidence for ongoing ischemia and a large area of myocardium at risk or hemodynamic instability, even when >12 hours has elapsed since the onset of symptoms. (Concepts adapted from Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? JAMA. 2005;293:979-986.)

Table 17-2 Absolute and Relative Contraindications for Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any prior intracranial hemorrhage</td>
</tr>
<tr>
<td>2. Known cerebral vascular lesion or intracranial neoplasm</td>
</tr>
<tr>
<td>3. Ischemic stroke within 3 months except if within 4.5 hours</td>
</tr>
<tr>
<td>4. Suspected aortic dissection</td>
</tr>
<tr>
<td>5. Active bleeding or bleeding diathesis (excluding menses)</td>
</tr>
<tr>
<td>6. Significant closed-head or facial trauma within 3 months</td>
</tr>
<tr>
<td>7. Intracranial or spinal surgery within 2 months</td>
</tr>
<tr>
<td>8. Severe uncontrolled hypertension that is unresponsive to emergency treatment</td>
</tr>
</tbody>
</table>
9. If using streptokinase, previous administration within 6 months

**Relative Contraindications**

1. History or chronic, severe, or poorly controlled hypertension
2. Significant hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
3. History of prior ischemic stroke >3 months
4. Dementia
5. Known intracranial pathology that is not an absolute contraindication
6. Traumatic or prolonged (>10 minutes) cardiopulmonary resuscitation
7. Major surgery less than 3 weeks
8. Noncompressible vascular punctures
9. Pregnancy
10. Active peptic ulcer
11. Oral anticoagulant therapy

In patients whose time of onset to FMC is greater than 12 hours, the diminished efficacy coupled with the risks of fibrinolysis preclude treatment with thrombolytic agents, and thrombolytic therapy is generally not recommended. However, in symptomatic patients with persistent ST-segment elevations who are hemodynamically unstable and where PCI is unavailable, thrombolytic therapy should be considered. The current guidelines give this group of patients who present in the 12- to 24-hour time frame and have a large area of myocardium at risk a Class IIa, Level of Evidence C recommendation.

**Adjunctive Therapy**

It is a class I recommendation that both anticoagulant and antiplatelet therapies be administered in conjunction with thrombolytic agents in AMI (Tables 17-3 and 17-4). Absent contraindication, both aspirin and clopidogrel (dual antiplatelet therapy) are recommended. Only 1 anticoagulant is to be administered, with the choice of agent depending on local practice and expected time to referral to the catheterization laboratory for definitive revascularization. In general, anticoagulation is to be discontinued at the time of revascularization to reduce bleeding following intervention.
Table 17-3 Antiplatelet Therapy in Conjunction With Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>162 mg to 325 mg loading dose</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>81 mg to 325 mg maintenance dose</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>81 mg daily preferred maintenance dose</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><em>P2Y₁₂ Receptor Inhibitors</em> Clopidogrel</td>
<td>Class of Recommendation</td>
<td>Level of Evidence</td>
</tr>
<tr>
<td>Age &lt; 75: 300 mg loading dose</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Followed by 14 daily for at least 14 days and up to 1 year</td>
<td>I</td>
<td>A (14 days)</td>
</tr>
<tr>
<td>Age &gt; 75: no loading dose</td>
<td>I</td>
<td>C (1 yr)</td>
</tr>
<tr>
<td>Followed by 14 daily for at least 14 days and up to 1 year</td>
<td>I</td>
<td>A (14 days)</td>
</tr>
</tbody>
</table>


Table 17-4 Anticoagulant Therapy in Conjunction with Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV bolus of 60 units/kg (max of 4000 units) followed by an infusion of 12 units/kg/h (max of 1000 units). Adjust to maintain an aPTT of 1.5 to 2 times normal (50-70 seconds)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Duration: 48 h or until revascularized</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enoxaparin</th>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;75: 30 mg IV bolus followed in 15 min by 1 mg/kg SC every 12 h (max of 100 mg for the first 2 doses)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Age &gt;75: no bolus, 0.75 mg/kg SC every 12 h (max of 75 mg for the first 2 doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;30 mL/min: 1 mg/kg SC every 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration: for the index hospitalization up to 8 days or until revascularized</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fondaparinux</th>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV bolus of 2.5 mg, followed by 2.5 mg SC every 24 h</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CrCl &lt;30 mL/min: contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration: for the index hospitalization up to 8 days or until revascularized</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; IV, intravenous; SC, subcutaneous; UFH, unfractionated heparin.


REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. Which of the following most strongly suggests the failure of fibrinolytic therapy to achieve reperfusion?
   - A. >50% residual ST-segment elevation
   - B. Occurrence of ventricular tachycardia or ventricular fibrillation
   - C. Cardiogenic shock
   - D. Lack of complete relief of chest discomfort

2. Which of the following approaches is associated with the greatest
reduction in mortality in the patient <75 years of age who fails to reperfuse within 90 to 120 minutes following fibrinolytic therapy?
A. Administration of a second dose of fibrinolytic therapy  
B. Administration of a platelet glycoprotein IIb/IIIa inhibitor  
C. Transfer of the patient to a percutaneous coronary intervention (PCI)-capable hospital for rescue PCI  
D. Administration of enoxaparin by intravenous (IV) bolus and subcutaneous injection

3. The time window of benefit of primary PCI in patients with cardiogenic shock extends to what duration?
A. 24 hours from symptom onset  
B. 48 hours from symptom onset  
C. 24 hours from the onset of shock  
D. 48 hours from the onset of shock

4. Compared with implantation of a bare metal stent (BMS) during primary PCI for STEMI, the rate of which of the following is reduced with implantation of a drug-eluting stent (DES)?
A. Death  
B. Myocardial infarction  
C. Bleeding  
D. Target vessel revascularization

5. In the patient receiving a BMS during primary PCI for STEMI, what is the recommended duration of dual antiplatelet therapy (absent contraindication)?
A. 1 month  
B. 3 months  
C. 6 months  
D. 1 year

6. Based on clinical trials including INFUSE-AMI, TASTE, and TOTAL, what is the recommendation for the use of aspiration thrombectomy in primary PCI during acute STEMI?
A. Aspiration thrombectomy should never be used.  
B. Aspiration thrombectomy should be evaluated on a case-by-case
C. Aspiration thrombectomy should be used only when there is a large thrombus.
D. Aspiration thrombectomy should be performed only when the infarct lesion is in the left main, proximal left anterior descending, proximal left circumflex, or proximal right coronary artery.

ANSWERS

1. A
A number of factors have been identified as being predictive of successful coronary reperfusion with fibrinolytic therapy, including the reduction and/or relief of chest pain, resolution of ST-segment elevation, and the presence of reperfusion arrhythmias. Conversely, >50% residual ST-segment elevation, ongoing chest discomfort, and the absence of reperfusion arrhythmias are indicative of reperfusion failure. The presence of cardiogenic shock is correlated with the amount of myocardium at jeopardy. Complete relief of chest discomfort does not always occur with coronary reperfusion.

2. C
The REACT study demonstrated the superiority of a strategy of immediate transfer of the patient for primary PCI compared with repeat fibrinolysis or conservative therapy. Several studies, including the GUSTO-V and FINESSE trials, evaluated glycoprotein IIb/IIIa therapy in conjunction with fibrinolysis in ST-segment elevation myocardial infarction (STEMI), but not as rescue therapy. Furthermore, these trials were negative. Enoxaparin, including dose adjustment based on age, proved superior to heparin as an adjunct to fibrinolytic therapy in the ExTRACT-TIMI 25 study when given in conjunction with the fibrinolytic agent, not in the context of reperfusion failure.

3. B
Patients with shock complicating acute STEMI are a very-high-risk subgroup, with in-hospital mortality of 40% to 80% in reported series. In the SHOCK trial, the benefit of emergency revascularization was apparent across
a very wide time window, extending up to 54 hours after the onset of symptoms and 18 hours after shock onset.

4. D
The benefit of DES compared with BMS in STEMI patients is mainly in reducing restenosis (in-stent restenosis, target lesion revascularization, and target vessel revascularization, along with the need for repeat revascularization), while not affecting rates of recurrent myocardial infarction or death. Critically, stent thrombosis does not appear to be increased with DES compared with BMS in trials of second-generation stents. Bleeding is actually increased in patients receiving a DES due late bleeding associated with prolonged dual antiplatelet therapy.

5. D
The duration of P2Y$_{12}$ treatment following stent implantation during primary PCI for STEMI is determined by the presenting syndrome (acute STEMI) rather than the type of stent (BMS vs DES). Current guidelines recommend 1 year of treatment.

6. B
The current recommendation is that aspiration thrombectomy should be evaluated on a case-by-case basis, rather than being considered as a universally applicable strategy. Importantly, subgroup analyses of aspiration thrombectomy in patients with a large thrombus burden did not show an advantage. There was also no specific advantage in the INFUSE-AMI study, which selectively enrolled patients with a large anterior myocardial infarction.
Despite the prolific increase in new technology in interventional cardiology, x-ray imaging combined with radiographic contrast media continues to be the mainstay in imaging technology. Visualization of vascular structures using x-rays requires the use of a radiographic contrast medium in order to distinguish them from surrounding tissues, which aside from bones, absorb x-rays poorly. Iodinated radiographic contrast agents have been used for this purpose since the 1950s. Since then, just as digitalization and evolution of imaging equipment technology have made significant strides in improving image quality and reducing exposure to ionizing radiation, refinements in the design of and judicious use of iodinated contrast has improved patient safety and reduced adverse outcomes.

**PHARMACOLOGY**

The iodine atom, with its relatively high atomic weight, attenuates x-rays and is used in most intravascular contrast agents today. Iodine’s K shell binding energy of 33.2 keV is ideal for x-ray photon absorption. Covalent bonding of 3 iodine atoms to a benzene ring at the 2, 4, and 6 position—the basic structure of all iodinated contrast agents (Fig. 18-1)—allows iodine to be delivered intravascularly, free of the side effects of free iodine, and also increases the effective molecular concentration of iodine, improving the ability to attenuate x-rays.\(^1\) An iodine concentration of 320 to 370 mg/mL is
optimal for angiographic studies. Although all iodinated contrast agents use this basic benzene ring structure, the number of rings per molecule (monomers or dimers) and the side chains at the 1, 3, and 5 positions give each of them unique chemical properties.²

![Chemical structures of contrast agents](image_url)

**FIGURE 18-1** Schematic of iodinated benzene monomers and dimers used in radiographic contrast media.

Contrast agents are classified based on whether they are monomers or dimers, ionic or nonionic, and high, low, or iso-osmolar (Table 18-1). Ionic
agents have 2 osmotically active particles per molecule, whereas nonionic agents have 1 osmotically active particle per molecule. High-osmolar agents are generally 4 to 6 times the osmolarity of blood, low-osmolar agents are 1.5 to 3 times the osmolarity of blood, and iso-osmolar agents are usually the same osmolarity of blood.

Table 18-1 Iodinated Intravascular Contrast Media
These iodinated contrast agents are generally hydrophilic and quickly
distribute throughout the extravascular space but do not cross lipid membranes and, therefore, remain extracellular. There is minimal protein binding. The circulatory half-life is approximately 1 to 2 hours with primarily renal excretion via glomerular filtration. Ionic, high-osmolar contrast agents have calcium-chelating properties as they are preserved in ethylene diamine tetra-acetic acid (EDTA), which contributes to their hemodynamic and electrophysiologic side effects such as bradyarrhythmias and ventricular fibrillation. Therefore, calcium was added to contrast formulations to reduce these adverse effects.

**ADMINISTRATION**

During interventional cardiology procedures, contrast is generally injected directly into the vascular structures of interest using catheters during fluoroscopy, allowing x-ray visualization of the lumen of the vessel. Administration rates are determined by the flow rates of the vascular structure being visualized (generally ranging from 1-30 mL/s). The intravascular injections are usually performed through 4- to 8-Fr (1.3-2.6 mm) diameter catheters, ranging from 10 to 120 mm in length. Viscosity of the different contrast agents varies and can limit the maximum delivery rate through these relatively narrow, long tubes, with increasing viscosity in the low- and iso-osmolar agents. Warming high-viscosity contrast agents, particularly iso-osmolar agents (iodixanol), to body temperature lowers viscosity and optimizes their injectability.

**Optimal Contrast Use**

In recent years, interventionalists have become conscious of contrast volume use to prevent contrast nephropathy. Minimizing contrast volume while maintaining good imaging is the key and includes the following measures:

1. Estimation of contrast volume to be used
2. Small manifold syringes
3. 50:50 diluted contrast
4. Small diagnostic catheters (4 and 5 Fr)
5. Small-caliber guiding catheters (5 and 6 Fr)
6. Biplane imaging  
7. Zooming for image magnification  
8. Ultrasound imaging with intravascular ultrasound (IVUS) in optimizing percutaneous coronary intervention (PCI) procedures  
9. Marker wires for lesion length and device position  
10. Markers on IVUS catheters  
11. Mechanized contrast injectors delivering prefixed contrast amount

**Contrast Volume Estimation**

The maximal acceptable contrast dose (MACD) minimizes the chance of contrast nephropathy is calculated as follows\(^4-6\):

\[
5 \text{ mL} \times \text{Body weight (in kg)/Serum creatinine (mg/dL)}
\]

Ratios of contrast volume used: MACD > 1 predict acute kidney injury. Complex coronary interventions, such as the opening of chronic total occlusions, require large contrast volumes, often approaching the MACD. The importance of these volume estimations have now extended to complex structural heart disease intervention, including transcatheter aortic valve replacement, perivalvular leaks plugging, complex congenital abnormality treatment, and endografts for abdominal and thoracic aneurysms, where large volumes of contrast are often used.

**PHYSIOLOGIC EFFECTS**

Hemodynamic effects of intraventricular contrast administration include a mild and transient decrease in ventricular function and increase in ventricular filling pressures, effects that are greater with high-osmolar than with low- or iso-osmolar agents. Contrast administration also increases intravascular volume, again more profoundly with high-osmolar than low- or iso-osmolar agents. These effects may be important in patients with heart failure, and contrast ventriculograms, in particular, should be performed with caution. Another hemodynamic effect of intra-arterial contrast administration is transient arteriolar vasodilation, resulting in decreased vascular resistance, increased blood flow, and potentially decreased systemic pressure.\(^1,2\)

Electrophysiologic effects of intracoronary contrast administration include
transient changes on the surface electrocardiogram such as QRS prolongation, axis shift, ST-segment depression, PR prolongation, and QT prolongation. Bradyarrhythmias, such as sinus bradycardia and asystole, may also occur. These arrhythmias are more common following injection of the right coronary artery and may reflect a vagal response as well as a direct effect on the sinoatrial node. Such bradyarrhythmias are often transient but, when necessary, generally respond to coughing or to intravenous (IV) atropine. Contrast also lowers the myocardial ventricular fibrillation threshold. All of these electrophysiologic effects are more common with the high-osmolar agents than the low- or iso-osmolar agents. Furthermore, the bradycardia and ventricular fibrillation potential are exacerbated by concomitant ischemia. For example, during an acute inferior ST-segment elevation myocardial infarction, reflow following restoration of coronary flow can cause asystole and heart block, and repetitive contrast injection can worsen the arrhythmia.1,2,7

Bench testing demonstrated that ionic agents were less likely to cause thrombosis than nonionic agents because these agents bind to the anion binding site of thrombin. There was also less platelet degranulation and aggregation and less thrombus formation.8-12 Finally, there was more thrombus deposition on guide wires and guiding catheters by electron microscopy with nonionic iopamidol versus ionic ioxaglate.13 Initial clinical studies also suggested less thrombotic effects with ionic agents. In acute coronary syndromes (ACSs), there was less urgent recatheterization procedures following PCI performed with ionic ioxaglate (17.8% vs 8.1%).14 Nonrandomized studies, such as the Evaluation of c7E3 Fab in the Prevention of Ischemic Complications (EPIC) trial, demonstrated greater abrupt closure and Q-wave myocardial infarction with nonionic agents.15 In the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIB trial,16 there was less refractory ischemia with ionic agents, and fewer ischemic events were noted in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) study with ionic agents.17 There was a reduction in stent thrombosis and 12-month major adverse cardiac events (MACE) with ionic ioxaglate with early-generation stents as reported by Scheller et al.18

However, later clinical trials have not uniformly supported reduced thrombotic events with ionic contrast agents. In the randomized, controlled
Contrast Media Utilization in High-Risk Percutaneous Transluminal Coronary Angioplasty (COURT) trial,\textsuperscript{19} in-hospital MACE occurred less with nonionic, iso-osmolar iodixanol versus ionic, low-osmolar ioxaglate (5.4\% vs 9.5\%, respectively; \( P = .027 \)). No difference between ionic and nonionic agents was observed in a primary PCI study after adjustment for baseline characteristic differences.\textsuperscript{20} No difference in MACE was also noted in the Visipaque in Percutaneous Coronary Angioplasty (VIP) randomized controlled trial comparing nonionic iodixanol and ionic ioxaglate.\textsuperscript{21} Finally, in the randomized Visipaque Versus Isovue in Cardiac Catheterization (VICC) trial comparing iopamidol versus iodixanol, in patients primarily undergoing PCI, there was no significant difference in the occurrence of myocardial infarction between 2 and 30 days after PCI.\textsuperscript{22}

Currently, there is insufficient evidence to support a clinical advantage of nonionic agents such as iodixanol over ionic agents such as ioxaglate. Thrombotic complications during contrast angiography, regardless of the agent used, are generally avoided by:

- Frequent catheter flushing with heparinized saline
- Avoiding contrast stasis with blood in manifold syringes or tubing\textsuperscript{23}
- Avoiding prolonged coronary engagement with catheters without frequent flushing or anticoagulating the patient
- Additive use of heparin or other anticoagulant (other than fondaparinux\textsuperscript{24}) if procedure is prolonged and/or involves intracoronary devices

### ADVERSE REACTIONS

Adverse reactions due to radiographic contrast media are generally due to their cardiovascular physiologic effects, other chemotoxic effects, or immune-mediated hypersensitivity. However, clinically, it is also practical to classify contrast reactions based on the time of occurrence, with \textit{immediate reactions} occurring within 1 hour of administration and \textit{delayed reactions} occurring greater than 1 hour after administration (Table 18-2).

**Table 18-2 Most Common and Significant Adverse Contrast Reactions**
Immediate Reactions

Immediate reactions that are due to radiographic contrast media’s physiologic and chemotoxic effects are generally dependent on dose and infusion rate. Symptoms include warmth, flushing, nausea, emesis, burning, and/or pain. These reactions are usually transient and self-limited. Sometimes a vagal syndrome may occur, including lightheadedness, hypotension, and bradycardia, and will reverse with IV fluid administration and atropine. Overall, randomized trials and large registry surveys show that the incidence of such mild to moderate immediate adverse reactions is significantly reduced with the use of nonionic and low- or iso-osmolar contrast media as compared to high-osmolarity agents (9%-14% vs 29%-40%).25-27

Immediate hypersensitivity reactions (IHRs) are generally independent of dose and infusion rate. Seventy percent of these reactions occur within 5 minutes of contrast media administration, and 96% occur within 20 minutes.27-30 Clinical manifestations can include pruritus, urticaria, angioedema, abdominal pain, diarrhea, bronchospasm, wheezing, laryngeal edema, stridor, and hypotension. The syndrome can appear identical to a type 1 hypersensitivity anaphylactic reaction. Mild IHRs (pruritus, urticaria) have
been estimated to occur in 0.7% to 3.1% of patients receiving nonionic radiographic contrast media, whereas severe reactions (respiratory failure, hypotension) have been reported in 0.02% to 0.04% of patients, with fatalities occurring in 1 to 3 per 100,000. Large registry studies show that high-osmolar radiographic contrast media are associated with a higher rate of IHRs (mild, 5%-13%; severe, 0.04%-0.22%).

The mechanism of IHRs is not completely understood but appears to involve complement activation and bradykinin formation, resulting in mast cell and basophil activation with histamine and tryptase release. Evidence of immunoglobulin E (IgE) mediation has not been identified in most patients, and reactions often occur without any prior exposure, suggesting a non–IgE-related mechanism. Direct compliment activation and/or a direct membrane effect of the contrast media due to its osmolarity or chemical structure are therefore likely causes of IHRs. However, in some patients with severe IHRs, positive skin tests and basophil activations tests have been found, suggesting a possible IgE-mediated reaction may also play a role. Testing has shown that iodine is rarely, if ever, the cause of IHRs.

Diagnosis of IHRs is usually made based on the clinical presentation. In diagnostically difficult situations, the occurrence of an IHR may be confirmed by blood samples for histamine and tryptase analysis drawn as soon as possible after the reaction as well as during convalescence for comparison. The utility of allergy skin testing after recovery is controversial.

Risk factors for IHRs include a prior IHR as well as asthma and atopy. Shellfish or seafood allergies are not independent risk factors for IHRs, nor is contact dermatitis to povidone-iodine skin disinfectant. Prevention of recurrent IHRs is of paramount importance. In patients with a history of prior reaction, the recurrence rate without prophylaxis is in the range of 16% to 44%. Prevention starts with the use of a low- or iso-osmolar contrast. Using a different agent in patients with a prior reaction may be beneficial, although cross-reactivity between agents does occur. In addition, adequate pretreatment of patients with prior reactions using steroids and antihistamines reduces the recurrence rate substantially. A regimen of 50 mg of prednisone administered 13 hours, 7 hours, and 1 hour before the procedure, as well as 50 mg of diphenhydramine administered 1 hour before the procedure, reduced the risk of recurrent anaphylactoid reaction to
A regimen of prednisolone 32 mg given 6 to 24 hours and 2 hours prior to contrast administration also reduced the risk of anaphylactoid reaction. However, a single dose of prednisolone 32 mg 2 hours before contrast administration was not effective at lowering the risk of anaphylactoid reactions. Because H₂ receptors have a significant role in the vasodilatory response to histamine release and H₂ blockers have been shown to be effective in the treatment of refractory IgE-mediated anaphylaxis, administration of H₂ blockers (eg, cimetidine) should also be considered. There are minimal data on the “pretreatment” of patients with prior contrast reactions undergoing emergency PCI. One group has suggested that IV steroids (eg, 80-125 mg of methylprednisolone, 100 mg of hydrocortisone sodium succinate), as well as oral or IV diphenhydramine and IV cimetidine, may be useful in preventing reactions. Because severe reactions may still develop despite prophylaxis, the potential benefits of any procedure using contrast media must be carefully weighed against the residual risk of IHR. Pretreatment of unselected patients without risk factors for IHRs has not been shown to be beneficial. Pretreatment of unselected patients without risk factors for IHRs has not been shown to be beneficial.

Treatment of severe IHRs, such as those associated with hypotension and respiratory failure, should be similar to that of anaphylaxis and include maintenance of the airway and breathing and circulatory support. Epinephrine (0.1 mg IV with repeated doses as needed), oxygen, IV fluids, and antihistamines (diphenhydramine 25-50 mg IV) are essential in patients with hypotension and/or airway compromise. Prochlorperazine or ondansetron may be given for nausea and vomiting. Glucocorticoids administered during emergency management are not known to impact acute symptoms, but may be beneficial in preventing or reducing the severity of delayed symptoms. Intubation may be required, with supportive medications potentially necessary for up to 72 hours. Treatment of mild IHRs (urticaria only) should include antihistamines with or without steroids, as well as consideration of immediate interruption of the administration of the contrast. After treatment, the affected patient should be closely observed for symptom progression or recurrence.

**Delayed Reactions**

Delayed reactions include nephrotoxicity, hyperthyroidism, and delayed
hypersensitivity reactions (DHRs). For an extensive discussion of contrast-induced nephrotoxicity, see Chapter 19.

DHRs manifest primarily as skin exanthemas, usually macular or maculopapular. Less common delayed skin manifestations include urticaria, angioedema, symmetrical drug-related intertriginous and flexural exanthema, drug-related eosinophilia with systemic symptoms, erythema multiform minor, fixed drug eruption, and rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, graft-versus-host reaction, and vasculitis. These reactions usually start within 3 days of contrast exposure but may present after up to 10 days.\(^3\)\(^0\) They are estimated to occur in 1% to 3% of patients.\(^4\)\(^9\) The mechanisms of most DHRs are believed to be T-cell–mediated type 4 hypersensitivity reactions.\(^4\)\(^9\) Evidence supporting this mechanism includes the fact that the maculopapular exanthemas resemble other drug-induced T-cell–mediated hypersensitivity reactions; the onset is 2 to 10 days after first exposure and 1 to 2 days after reexposure (consistent with a sensitization phase), and the histopathology reveals perivascular infiltrates of CD4\(^+\) and CD8\(^+\) T cells plus eosinophils.\(^5\)\(^0\),\(^5\)\(^1\) This pathogenesis likely explains why patients treated with interleukin-2, a potent T-cell stimulator, are at higher risk.\(^5\)\(^2\) As with IHRs, iodine is rarely, if ever, the eliciting agent.\(^3\)\(^6\)

Diagnosis of DHRs is usually based on the clinical features and scenario. The maculopapular rashes often include erythema, swelling, and pruritus (Fig. 18-2). Differential diagnosis often includes reactions to other recently newly introduced medications, such as thienopyridine antiplatelet agents. If the differential diagnosis extends beyond a drug reaction, a skin biopsy may be useful.\(^3\)\(^0\) Hematology and clinical chemistry need only be considered in the case of more severe exanthemas to exclude systemic involvement.\(^2\)\(^9\)

Skin testing can be considered 2 to 6 months after the reaction, particularly if there is a question of the offending drug or consideration of repeat contrast administration. While skin testing may have a high specificity, it only has a moderate sensitivity.38,53

The main risk factor for DHRs is a prior DHR, but patients with a strong history of atopy may also be susceptible.30,53 Some, but not all, studies have suggested that nonionic, iso-osmolar contrast agents (eg, iodixanol) more commonly cause these reactions than other contrast agents (by 3- to 4-fold).54 Sun exposure following contrast exposure may exacerbate the development of DHRs.55 Prevention should consist of avoiding the culprit contrast medium. If other contrast media are identified by skin testing, they should also be avoided. Skin testing does have a negative predictive value but does not guarantee tolerance.30 Steroid prophylaxis can be given to prevent delayed reactions with some, but not complete, success.56,57

The most common maculopapular rashes are generally transient and self-limited, resolving within 3 to 7 days after onset. Treatment of these is usually based on symptoms and may include antihistamines (diphenhydramine 25-50 mg every 6 hours by mouth) as well as consideration of topical
corticosteroids and antipruritics. More severe reactions require consultation with a dermatologist.

Hyperthyroidism

The use of iodinated contrast has been linked with thyroid dysfunction, both hyperthyroidism and, to a lesser degree, hypothyroidism. The incidence has not been well defined, but has been reported in the 0.05% to 5% range. The mechanism is likely related to the exposure to a large supraphysiologic bolus of iodine, which serves as substrate for thyroxine production or, alternatively, triggers a pathologic thyroid inhibitory effect. Patients with diagnosed or subclinical hyperthyroid conditions (eg, Graves disease, nontoxic diffuse or multinodular goiter), particularly when age is >65 years or when patients are from iodine-deficient areas, are predisposed to iodinated contrast–induced hyperthyroidism. Likewise, hypothyroidism may occur, particularly in patients with prior thyroiditis, with thyroid ablation, or on chronic dialysis. Contrast-induced hyperthyroidism can be difficult to manage and should trigger referral to an endocrinologist, whereas contrast-induced hypothyroidism is usually self-limited and can be treated with temporary levothyroxine replacement therapy. Although some have recommended prophylaxis against iodinated contrast–induced thyroid dysfunction in high-risk patients using perchlorate and thiamazole, these drugs may have significant side effects, and this practice has not been widely adopted.

CARDIOGENIC SHOCK

Cardiogenic shock and associated hypotension can result in multiorgan failure and acute kidney injury (AKI). The additive effect of contrast use exacerbates AKI. In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) trial, AKI developed in 24% of patients with initial medical therapy versus 13% in the early revascularization arm. AKI exacerbates the bleeding complications of PCI, prolongs hospitalization, and is associated with increased hospital mortality. Although contrast use is a bystander in the complex syndrome associated with shock, judicious contrast use and early revascularization contribute to
improved survival.

**GLUCOPHAGE**

Diabetes causes endothelial dysfunction and decreased production of nitric oxide. Contrast-induced vasoconstriction and lack of a vasodilatory response result in decreased renal blood flow. Glucophage or metformin is excreted unchanged in the kidneys. With renal insufficiency, which may be exacerbated by contrast use, glucophage accumulates in tissues and can cause lactic acidosis. Contrast-induced lactic acidosis is rare at 3 per 100,000 patient-years, with a mortality of 1.5 per 100,000 patient-years.

**General Guidelines**

- In a patient with serum creatinine >2.0 mg/dL, glucophage should be discontinued permanently.
- With normal renal function, contrast studies can be performed without holding glucophage before the procedure. Glucophage can be resumed in 48 hours if serum creatinine levels are in the normal range.

With emergent procedures, contrast studies need not be delayed; hydration should be continued and serial creatinine levels obtained.

**NONIODINATED CONTRAST AGENTS**

**Gadolinium**

Gadolinium, a rare, natural, heavy metal, is used extensively in magnetic resonance imaging (MRI). It is used in radiographic imaging in patients with severe iodine allergy. In the recommended concentration of 0.4 mmol/kg body weight, only small doses can be injected in the coronary circulation, and image quality is inferior to iodinated contrast, but is still diagnostic. The viscosity of the agent can cause cardiac arrhythmias, in particular ventricular fibrillation. This adverse effect is enhanced by catheter dampening of the coronary artery. Repeat injections are not recommended, and hence, there is a
lack of usefulness in coronary intervention procedures. Gadolinium does not prevent contrast-induced nephropathy. It is well tolerated in patients with serum creatinine levels of <2.0 mg/dL but can worsen renal function in patients with creatinine levels >2.0 mg/dL. In patients with renal insufficiency (estimated glomerular filtration rate <30 mL/min) and end-stage renal disease, the heavy metal accumulates in body tissues, causing nephrogenic systemic fibrosis.

**Carbon Dioxide**

Carbon dioxide, given via an injector, in the vasculature is absorbed over a 2-minute period by the blood, where it is converted into sodium bicarbonate and excreted by the lungs as carbon dioxide. It produces radiologic contrast and neither causes an allergic reaction nor nephrotoxicity. The image quality is less than iodinated contrast and requires enhancement by digital subtraction angiography.

Carbon dioxide imaging is used in below-the-diaphragm visceral, renal, and lower extremity angiography, renal stent placement, and endovascular aortic repair for abdominal aortic aneurysms. Delivery of carbon dioxide is through special injectors and connecting tubes, free of air contamination. Generally, 20 to 40 mL of carbon dioxide is injected through 3- to 4-Fr catheters. It is not used in coronary or pulmonary angiography because it produces a “vapor lock” that resolves over a 2-minute period of absorption of the gas, and in the coronary circulation, this may cause myocardial ischemia similar to coronary air embolism. In the pulmonary circulation, this vapor lock is similar to pulmonary air embolism, resulting in hypotension.67-70

**CONCLUSION**

Iodinated radiographic contrast media are essential for the angiography necessary to guide the practice of interventional cardiology today. Low- and iso-osmolar agents are very well tolerated in measured doses in most patients. The interventional cardiologist’s awareness of the physiologic effects and adverse reactions occasionally caused by these agents, including their prevention and treatment, helps to protect vulnerable patients.
REFERENCES


36. Scherer K, Harr T, Bach S, Bircher AJ. The role of iodine in


MULTIPLE CHOICE QUESTIONS

1. Cardiovascular physiologic effects of radiographic contrast media include which of the following?
   A. Arteriolar vasodilation
   B. Electrocardiogram (ECG) QRS prolongation
   C. Ventricular hypercontractility
   D. A, B, and C
   E. A and B

2. Dose- and/or infusion rate–dependent adverse reactions that occur immediately after radiographic contrast media administration include all the following except:
   A. Nausea and emesis
   B. Burning and/or pain
   C. Pruritus
   D. Flushing
   E. Warmth

3. Risk factors for immediate hypersensitivity reactions (IHRs) include which of the following?
   A. Shellfish reaction
   B. Contact dermatitis to povidone-iodine
   C. Asthma
   D. Seafood allergy

4. Delayed hypersensitivity reactions can manifest as all the following except:
   A. Macular skin exanthemas
   B. Angioedema
   C. Urticaria
   D. Hematuria
   E. Erythema multiform minor

5. Interventions that may prevent hypersensitivity reactions include which of the following?
A. Minimizing contrast media dose
B. Prednisone
C. Aminophylline
D. Intravenous epinephrine

ANSWERS

1. E
Hemodynamic effects of intraventricular contrast administration include a mild and transient decrease in ventricular function and increase in ventricular filling pressures. Another hemodynamic effect of intra-arterial contrast administration is transient arteriolar vasodilation, resulting in decreased vascular resistance, increased blood flow, and potentially decreased systemic pressure. Electrophysiologic effects of intracoronary contrast administration include transient changes on the surface electrocardiogram such as QRS prolongation, axis shift, ST-segment depression, P-R prolongation, and QT prolongation. Bradyarrhythmias, such as sinus bradycardia and asystole, may also occur. All these electrophysiologic effects are more common with the high-osmolar agents than the low- or iso-osmolar agents.

2. C
Immediate reactions that are due to radiographic contrast media’s physiologic and chemotoxic effects are generally dependent on dose and infusion rate. Symptoms include warmth, flushing, nausea, emesis, burning, and/or pain. These reactions are usually transient and self-limited. However, immediate hypersensitivity reactions are generally independent of dose and infusion rate. Seventy percent of these reactions occur within 5 minutes of contrast media administration, and 96% occur within 20 minutes. Clinical manifestations can include pruritus, urticaria, angioedema, abdominal pain, diarrhea, bronchospasm, wheezing, laryngeal edema, stridor, and hypotension.

3. C
Risk factors for IHRs include a prior IHR as well as asthma and atopy. Shellfish or seafood allergies are not independent risk factors for IHRs, nor is
prior contact dermatitis to povidone-iodine skin disinfectant.

4. D

Delayed hypersensitivity reactions manifest primarily as skin exanthemas, usually macular or maculopapular. Less common delayed skin manifestations include urticaria, angioedema, symmetrical drug-related intertriginous and flexural exanthema, drug-related eosinophilia with systemic symptoms, erythema multiform minor, fixed drug eruption, and rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, graft-versus-host reaction, and vasculitis. These reactions usually start within 3 days of contrast exposure but may present after up to 10 days. They are estimated to occur in 1% to 3% of patients.

5. B

Prevention starts with the use of a low- or iso-osmolar contrast. Using a different agent in patients with a prior reaction may be beneficial, although cross-reactivity between agents does occur. In addition, adequate pretreatment of patients with prior reactions using steroids and antihistamines reduces the recurrence rate substantially. A regimen of 50 mg of prednisone administered 13 hours, 7 hours, and 1 hour before the procedure, as well as 50 mg of diphenhydramine administered 1 hour before the procedure, reduced the risk of recurrent anaphylactoid reaction to around 0.5%. A regimen of prednisolone 32 mg given 6 to 24 hours and 2 hours prior to contrast administration also reduced the risk of anaphylactoid reaction. However, a single dose of prednisolone 32 mg 2 hours before contrast administration was not effective at lowering the risk of anaphylactoid reactions. Because H₂ receptors have a significant role in the vasodilatory response to histamine release and H₂ blockers have been shown to be effective in the treatment of refractory IgE-mediated anaphylaxis, administration of H₂ blockers (eg, cimetidine) should also be considered. Aminophylline would not be anticipated to prevent immediate hypersensitivity reactions. IV epinephrine may be used to treat immediate hypersensitivity reactions after they occur. Hypersensitivity reactions are not dose or infusion rate dependent.
Renal Complications of Contrast Media

Anand Prasad
Peter A. McCullough

HISTORICAL PERSPECTIVE

Radiocontrast was first described to cause nephrotoxicity in the 1960s.\textsuperscript{1,2} Contrast-induced nephropathy (CIN), now termed \textit{contrast-induced acute kidney injury} (CI-AKI), is likely to increase in frequency over the next 10 to 15 years. This rise is largely due to increasing use of radiocontrast studies in patients who are older, sicker, or have attendant comorbidities such as diabetes mellitus, renal failure, cardiac failure, and volume depletion.\textsuperscript{3} CI-AKI is currently described as the third most common cause of hospital acquired renal failure, accounting for approximately 11\% of cases.\textsuperscript{4} The incidence of CI-AKI reported in the literature has ranged between 1\% and 45\%, largely depending on the comorbidities of the study population, the clinical scenario in which the contrast is given, and the parameters used to define CI-AKI.\textsuperscript{5} With more than a million radiocontrast procedures performed annually in the United States, the incidence of CI-AKI is approximately 150,000 cases per year. At least 1\% of these episodes require dialysis therapy (in half of patients, it will be permanent) with prolongation of hospital stay to an average of 17 days, with an additional cost of approximately $32 million annually. For episodes that do not require dialysis, the average prolongation of the hospital stay is 2 days (at $500 per day), and
this translates to an added cost of $148 million annually.\textsuperscript{6,7} The incidence and costs are higher in critically ill patients, who have associated comorbidities such as hypotension, hypovolemia, diabetes, and congestive heart failure.

This chapter will first examine the important renal complications of contrast media. This will be followed by an evaluation of laboratory investigations that provide insights into the pathogenesis of this disorder. The last section deals with 2 important clinical issues: (1) the use of low-osmolality radiocontrast agents specifically to reduce the incidence of CI-AKI and (2) adjunctive methods currently used to prevent the development of CI-AKI.

**THE CARDIORENAL INTERSECTION**

The obesity pandemic is a central driver of the dysmetabolic syndrome, hypertension, and diabetes. It is thus anticipated that there will soon occur a secondary epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD).\textsuperscript{8} Among patients with diabetes for 25 years or more, the prevalence of diabetic nephropathy in type 1 and type 2 diabetes is 57\% and 48\%, respectively. Approximately half of all cases of end-stage renal disease (ESRD) are due to diabetic nephropathy, with most of these cases driven by obesity-related type 2 diabetes and hypertension.\textsuperscript{9} With the graying of America and cardiovascular care shifting toward the elderly, the imperative thus exists to understand the relationship between decreasing levels of renal function as a major adverse prognostic factor in cardiac patients. AKI after contrast exposure as the most proximal renal event is predictable and highlights an opportunity for preventive measures outlined later in this chapter.

**SMALL RISES IN CREATININE ARE LINKED TO POOR LONG-TERM OUTCOMES**

The overall prevalence of CI-AKI, defined as a transient rise in serum creatinine (Cr) $\geq$0.3 mg/dL above the baseline, occurs in approximately 7\%
of patients undergoing percutaneous coronary intervention (PCI) (Fig. 19-1).\textsuperscript{10} Fortunately, rates of CI-AKI leading to dialysis are quite low (0.5%-2.0%). However, the occurrence of CI-AKI is associated with catastrophic outcomes, including a 36% in-hospital mortality rate and a 2-year survival of only 19%.\textsuperscript{10} Transient rises in Cr are directly related to longer intensive care unit and hospital ward stays (3 and 4 additional days, respectively) after cardiac bypass surgery.\textsuperscript{11} Recently, it has been shown that even transient elevations in Cr translate to differences in adjusted long-term outcomes including mortality, ESRD, and all-cause hospitalization after diagnostic catheterization or PCI (Fig. 19-2).\textsuperscript{12,13} In addition to a heavy degree of confounding by older age, diabetes, and other factors, a secondary explanation is that when renal function declines, the associated abnormal vascular pathobiology accelerates, and hence, the progression of other diseases, including CVD, accelerates.

\textbf{FIGURE 19-1} Incidence of contrast-induced acute kidney injury from the American College of Cardiology National Cardiovascular Data Registry, as defined by the Acute Kidney Injury Network (AKIN) definitions (analogous to Kidney Disease Improving Global Outcomes criteria): stage 1, ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in serum creatinine (Cr); stage 2, >2- to 3-fold increase in serum Cr; and stage 3, >3-fold increase in serum Cr or serum Cr >4.0 mg/dL with an acute increase of >0.5 mg/dL. Dialysis was an in-hospital outcome identified using a predefined National Cardiovascular Data Registry data element for acute or worsening renal failure, necessitating new renal dialysis. (Reprinted from Tsai TT, Patel UD, Chang TI, et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients...

![Diagram](image)

**FIGURE 19-2** Rates of (A) mortality, (B) long-term end-stage renal disease, or (C) all-cause hospitalization according to acute kidney injury (AKI) stage after contrast exposure in the catheterization laboratory. (Reproduced with permission from James MT, Ghali WA, Knudtson ML, et al. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. *Circulation*. 2011;123(4):409-416.)

The limitations of our understanding of the epidemiology of CI-AKI should be emphasized. The literature has been impacted by inconsistent definitions of AKI based on temporal changes in the serum Cr level. This variation makes comparison of different populations and studies challenging. Earlier studies, including some that established risk prediction models for AKI in the context of cardiac procedures, used an increase in serum Cr of >0.5 mg/dL or a relative 1.5- to 3-fold increase (coupled with assessment of urine output) as the definition of CI-AKI. These criteria established in 2004 by the Acute Dialysis Quality Initiative are referred to as the RIFLE criteria (risk, injury, failure, loss, ESRD).

The RIFLE definition correlates with progression to CKD and mortality. In 2007, these definitions were further modified by the Acute Kidney Injury Network (AKIN). The AKIN criteria included a more sensitive definition of acute Cr change, using a relative increase of >0.3 mg/dL. Although this latter definition may identify more cases of AKI, the differential impact on outcome prediction versus the RIFLE criteria remains modest at best. Lastly, the Kidney Disease Improving
Global Outcomes (KDIGO) criteria combined elements of both RIFLE and AKIN but kept the 0.3 mg/dL cutoff for AKI.\(^\text{17}\)

More problematic for the study of CI-AKI is the reliance on the serum Cr as the biomarker of renal damage. Increases in serum Cr, regardless of the definitions used, require serial measures and are temporally delayed from the acute injury. Serum Cr also provides no information as to the anatomic location or mechanism of injury. In this regard, novel biomarkers of glomerular and tubular injury offer promise as more sensitive and specific measures of AKI. Most relevant in the context of contrast administration are serum cystatin C, which provides a sensitive approximation of glomerular function, and urinary tubular markers such as neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (LFABP), and kidney injury molecule-1 (KIM-1). Beyond the scope of this discussion are additional numerous molecules and signaling markers that are actively being investigated as alternatives to the serum Cr for the detection of CI-AKI.\(^\text{18}\)

### RISK FACTORS FOR CONTRAST-INDUCED ACUTE KIDNEY INJURY

Mild, transient decreases in glomerular filtration rate (GFR) occur after contrast administration in almost all patients and are usually subclinical.\(^\text{19}\)

There is a brief increase in renal blood flow followed by prolonged vasoconstriction within the kidneys after contrast exposure. The development of clinically significant CI-AKI can be predicted based on the presence or absence of specific risk factors (Table 19-1). A multivariable analysis of prospective trials has shown that baseline renal impairment, diabetes mellitus, congestive heart failure, and higher doses of contrast media increase the risk of CI-AKI.\(^\text{20,21}\)

Other risk factors include reduced effective arterial volume (eg, due to dehydration, nephrosis, cirrhosis) or concurrent use of potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory agents and aminoglycosides. Multiple myeloma has been suggested as a potential risk factor for CI-AKI, but a large retrospective study failed to demonstrate an increased risk in these patients.\(^\text{22}\)

Of all these risk factors, preexisting renal impairment appears to be the single most important; patients with diabetes mellitus and renal impairment, however, have a substantially higher risk of
CI-AKI than patients with renal impairment alone.\textsuperscript{23,24}

A growing population of individuals at risk for CI-AKI are those with symptomatic peripheral arterial disease (PAD). PAD impacts 8 to 12 million Americans and is a rising epidemic, driven by the aging of the population and increasing rates of diabetes. Management of symptomatic PAD, spanning the spectrum from claudication to critical limb ischemia, has evolved in the past decade to an endovascular first approach. Within the context of peripheral angiography, the specific risk factors for CI-AKI remain poorly defined. Extrapolating from the coronary experience, concerns related to total contrast volume, atheroembolism, and volume status remain key components of risk assessment and prevention. Pooled data would suggest the incidence of CI-AKI is approximately 10% to 15%.\textsuperscript{25}

Table 19-1 Risk Factors for the Development of Contrast-Induced Nephropathy

<table>
<thead>
<tr>
<th>Risk Factors for the Development of Contrast-Induced Nephropathy</th>
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<tbody>
<tr>
<td>• eGFR $\leq$ 60 mL/min/1.73 m\textsuperscript{2}</td>
</tr>
<tr>
<td>• Diabetes</td>
</tr>
<tr>
<td>• Urine ACR $&gt; 30$</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• History of structural kidney disease or damage</td>
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<tr>
<td>• Congestive heart failure</td>
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<tr>
<td>• Preprocedural volume depletion</td>
</tr>
<tr>
<td>• Intraprocedural hypotension</td>
</tr>
<tr>
<td>• Intra-aortic counterpulsation</td>
</tr>
<tr>
<td>• Cholesterol emboli syndrome</td>
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<tr>
<td>• Use of large volume of contrast</td>
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</tbody>
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ACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate. Reprinted with permission of MedReviews\textsuperscript{®}, LLC. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. Rev Cardiovasc Med. 2003; 4(suppl 5):S3-S9. All rights reserved.

CLINICAL FEATURES
The vast majority of patients who develop CI-AKI are asymptomatic, contributing to the lack of universal awareness of this complication. CI-AKI manifests usually as a decrease in GFR without hematuria and is typically nonoliguric. Nonoliguric AKI is generally more common in patients initially having a lower serum Cr prior to receiving contrast. In oliguric AKI, the time course of the oliguria and the rise in serum Cr depend on the preprocedure baseline serum Cr. Patients with normal renal function or mild renal functional impairment prior to receiving radiocontrast agents usually have oliguria lasting 2 to 5 days, with recovery to baseline renal function by day 7. Dialysis is infrequently required.\textsuperscript{24,26} Some degree of residual renal impairment has been reported in as many as 30\% of those affected by CI-AKI.\textsuperscript{24} Other comorbidities such as sustained hypotension, hypovolemia, atheroembolism, and the concurrent use of nephrotoxic medications can also contribute to CI-AKI after coronary angiography and intervention. The occurrence of CI-AKI usually prolongs the hospital stay.\textsuperscript{27} Finally, mortality is increased in patients who develop CI-AKI. In a retrospective study, Levy et al.\textsuperscript{28} compared the outcomes of hospitalized patients with CI-AKI to a control group of patients matched for age, baseline serum Cr, and type of diagnostic procedure who did not develop CI-AKI. The mortality in the CI-AKI group was 34\% compared with 7\% in the control group ($P < .001$; odds ratio, 5.5), even after controlling for baseline factors and in-hospital comorbidities.\textsuperscript{28}

The antidiabetic agent metformin may lead to the development of lactic acidosis in the setting of CI-AKI. This complication is rare and occurs only if the contrast administration results in significant renal failure and the patient continues to take metformin. In a recent review of this subject, no conclusive evidence was found to indicate that the use of contrast precipitated metformin-induced lactic acidosis in patients with serum Cr <1.5 mg/dL or 130 μmol/L at baseline. The complication was almost always observed in non–insulin-dependent diabetic patients with decreased renal function before injection of contrast media. Thus, while there is no justification to discontinue metformin before the day of the contrast-requiring procedure, it is recommended that patients not take this drug for 48 hours or so after contrast administration and resume taking the drug only if there are no signs of nephrotoxicity. This is especially true for patients in high-risk subgroups, described earlier.\textsuperscript{29}
DIAGNOSIS OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

CI-AKI usually develops within 24 to 72 hours following a radiocontrast study. In 2012, the KDIGO guidelines defined CI-AKI as a rise in serum Cr of ≥0.3 mg/dL within 48 hours of contrast exposure or a rise in serum Cr ≥1.5 times the baseline within a week of exposure or urine volume <0.5 mL/kg/h for a 6-hour period after contrast administration. Because the urine output is commonly influenced by intravenous fluids and diuretics, most patients are diagnosed with CI-AKI based on the serum Cr. One interesting feature of oliguric CI-AKI is the presence of a low fractional excretion of sodium during the initial stages, despite the absence of clinical evidence of volume depletion. The urinalysis microscopic exam demonstrates renal tubular epithelial cell casts or coarsely granular brown casts, but may occasionally be negative. Even in the absence of a rise in serum Cr, radiocontrast agents may still alter the urinary sediment, showing epithelial cells, epithelial cell casts, granular or muddy brown coarsely granular casts, and occasional crystals. Hence, routine urinalysis is not particularly specific and is not recommended after contrast procedures.

A persistent nephrogram 24 to 48 hours after the contrast study has been reported to be a sensitive indicator of the presence of renal failure (83% of patients with renal failure had a positive nephrogram) with high specificity (93% of patients without renal failure lacked the persistent nephrogram). The persistent nephrogram has been related to an abnormal and persistent intrarenal vasoconstriction after contrast exposure.

PATHOPHYSIOLOGY

There are 3 core elements that are intertwined in the pathophysiology of CI-AKI: (1) direct toxicity of iodinated contrast to nephrons; (2) micro-showers of atheroemboli to the kidneys; and (3) contrast- and atheroemboli-induced intrarenal vasoconstriction. Direct toxicity to nephrons with iodinated contrast has been demonstrated and appears to be related to the osmolality of the contrast. Hence, low ionic or nonionic and low-osmolar or iso-osmolar contrast agents have been shown to be less nephrotoxic in vitro. Micro-
showers of cholesterol emboli are thought to occur in up to 50% of percutaneous interventions where a guiding catheter is passed through the aorta. Most of these showers are clinically silent. However, in approximately 1% of high-risk cases, an acute cholesterol emboli syndrome can develop manifested by AKI, mesenteric ischemia, decreased microcirculation to the extremities, and in some cases, embolic stroke. Because AKI occurs after coronary artery bypass surgery with nearly the same risk predictors as in patients undergoing contrast procedures, it is thought that atheroembolism may be a common pathogenic feature of both causes of renal failure. Finally, intrarenal vasoconstriction as a pathologic vascular response to contrast media and (perhaps) to cholesterol emboli is a third mechanism leading to hypoxic/ischemic injury to the kidney. Hypoxia triggers activation of the renal sympathetic nervous system and results in a reduction in renal blood flow, especially in the outer medulla (Fig. 19-3). It is important to note that animal studies do not demonstrate agreement regarding the direct vasoconstrictive and/or vasodilatory effects of contrast on the kidney. In humans with vascular disease, endothelial dysfunction, and glomerular injury, it is believed that contrast and the multifactorial insult of renal hypoxia provokes a vasoconstrictive response and, hence, mediates in part an ischemic injury. The most important predictor of CI-AKI is underlying renal dysfunction. The “remnant nephron” theory postulates that after sufficient chronic kidney damage has occurred and the estimated GFR (eGFR) is reduced to <60 mL/min/1.73 m², the remaining nephrons must pick up the remaining filtration load, have increased oxygen demands, and are thus more susceptible to ischemic and oxidative injury.
Pathophysiology of contrast-induced nephropathy (CIN) involves acute ischemia to the outer medulla, the most vulnerable part of the kidney, due to direct cellular toxicity and sustained intrarenal vasoconstriction and reduction in renal blood flow. This process is worsened by multiple factors including hypoxia, anemia, and systemic hypoperfusion. (Adapted from Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. *N Engl J Med*. 1995;332(10):647-655. Copyright © 1995 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

It is important to distinguish CI-AKI from cholesterol emboli syndrome (CES) or atheroembolic renal disease. The incidence of CES following coronary angiography has been reported to be 1.4% in a recent study. Scolari et al. retrospectively reported that 15 of 16,223 vascular procedures were complicated with CES, which had an incidence of 0.09%. In contrast, an autopsy study reported that the overall prevalence of CES was 25% to 30% of patients after cardiac catheterization. Ramirez et al. noted cholesterol emboli at autopsy in 30% of patients who died within 6 months after undergoing aortography and 25.5% of patients who died within 6 months after undergoing coronary angiography. In contrast, the incidence of cholesterol embolism was 4.3% in age-matched controls who had not
undergone a previous invasive vascular procedure. The cholesterol emboli in the control group may have resulted from spontaneous erosion of atheromatous plaques or from previous anticoagulant or thrombolytic therapy. In patients with CES occurring after angiographic and vascular surgical procedures, the interval from the inciting event to the onset of renal symptoms may vary greatly. Some patients have immediate clinical features, but in others, the onset can be more insidious, with a delay of weeks or months between the precipitating event and clinical features. In 17 patients who developed atheroembolization after an arteriographic procedure, Frock et al found the mean interval between the inciting event and diagnosis of atheroembolic renal disease to be 5.3 weeks. Contrast media–associated nephrotoxicity immediately follows the radiographic study. There is an increase in Cr level a few days after the procedure (usually within 72 hours); peak Cr level elevation occurs approximately 1 week after exposure and returns to baseline within 10 to 14 days. Conversely, atheroembolic renal damage frequently has a delayed onset (days to weeks) and a protracted course; the outcome is often poor, resulting in progressive renal failure requiring dialysis. When a fulminant disease develops rapidly after angiography, the concomitant cutaneous, neurologic, and gastrointestinal complications usually accompany renal atheroembolic disease. The recent development of transcatheter aortic valve replacement, which is performed in patients with high levels of comorbidities including CKD, has brought interest to the combination of embolic and chemotoxic injury with this procedure. During predilation of the aortic valve or balloon aortic valvuloplasty, it is possible that showers of cholesterol, calcium hydroxyapatite, and fibrotic material are received into the renal arterial bed. This, in addition to higher contrast volumes than in diagnostic angiography or PCI, is believed to be part of the explanation for the high rates of more severe cases of CI-AKI. A systematic review found 13 studies with more than 1900 patients reporting rates of CI-AKI defined by the Valve Academic Research Consortium (VARC) criteria, which correspond to the KDIGO definition presented previously, that ranged from 8.3% to 57% of the patients. The following factors were associated with CI-AKI: blood transfusion; transapical access; higher preoperative Cr concentration; peripheral vascular disease; hypertension; and procedural bleeding events. Not unexpectedly, the 30-day mortality rate in patients with CI-AKI ranged from 13.3% to 44.4% and was
2-6-fold higher than in patients without CI-AKI. Interestingly, the amount of contrast agent used (typically >200 mL) was not associated with the occurrence of CI-AKI in most, but not all, studies.

RENAL PROTECTION FOR PATIENTS UNDERGOING CONTRAST PROCEDURES

Renal protection for CKD patients at risk (eGFR <60 mL/min/1.73 m²) can be thought of in 3 separate spheres: (1) long-term cardiorenal protection, (2) removal of renal toxins, and (3) prevention measures carried out before contrast exposure. Long-term cardiorenal protection involves 2 important concepts. The first concept is blood pressure control in CKD to a target of approximately 125/75 mm Hg. The second concept is to use an agent that blocks the renin-angiotensin system, such as an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), but not both used together. Of note, either agent will cause a chronic rise in Cr >25% above the baseline in approximately 10% of cardiovascular patients. Even with an increase in Cr, the benefits of ACEI/ARB agents with respect to a reduction in new cases of ESRD, CHF, or cardiovascular death appear compelling. It has been sufficiently shown that these benefits extend to nondiabetics and to African Americans with CKD.

Removal of toxins largely refers to the discontinuation of nonsteroidal anti-inflammatory agents, aminoglycosides, and cyclosporin. These agents all complicate contrast procedures and increase the risk of CI-AKI. Prevention measures done prior to contrast exposure include volume expansion, approaches to reduce the direct cellular toxicity of the contrast, and measures to reduce the intrarenal vasoconstriction, which occurs uniquely in CKD patients when exposed to iodinated contrast.

PREDICTION OF CONTRAST-INDUCED ACUTE KIDNEY INJURY
CKD is defined through a range of eGFR values, and the class of CKD at baseline is strongly associated with the frequency of CI-AKI and the risk of dialysis, as shown Figure 19-4. Most studies of cardiovascular outcomes have associated the development of CI-AKI, restenosis, recurrent myocardial infarction, diastolic/systolic heart failure, and cardiovascular death with an eGFR below 60 mL/min/1.73 m², which roughly corresponds to a serum Cr of >1.5 mg/dL in the general population. Because Cr is a crude indicator of renal function and often underestimates renal dysfunction in women and the elderly, calculated measures of eGFR or Cr clearance (CrCl) by the Cockcroft-Gault equation or by the Modification of Diet in Renal Disease (MDRD) equations, now available on the Web, personal digital assistants, and hand-held plastic estimators are the preferred methods of estimating renal function. The 4-variable MDRD equation for CrCl is the preferred method because it does not rely on body weight. This equation is given below:

\[
\text{CrCl} = \frac{141 \times \text{eGFR} \times \text{body weight (kg)}}{72.5 \times \text{serum Cr (mg/dL)}}
\]

186.3*(serum Cr^{-1.154})*(age^{-0.203}); calculated values are multiplied by 0.742 for women and by 1.21 for African Americans

In addition, microalbuminuria (defined as random urine albumin/Cr ratio of 30-300 mg/g) at any level of eGFR is considered to represent CKD and has been thought to occur as the result of endothelial dysfunction in the glomeruli. It is critical to understand that the risk of CI-AKI is related in a curvilinear fashion to the eGFR, as shown in Figure 19-4. Multivariate prediction scoring schemes have been developed and indicate that patients with multiple risk factors can have a very high, if not certain, expectation for the development of CI-AKI after contrast exposure during coronary angiography or PCI (Fig. 19-5). For example, a hypotensive, critically ill patient with heart failure, anemia, diabetes, and an eGFR <60 mL/min/1.73 m² faces an estimated 57.3% risk of CI-AKI and a 12.6% risk of needing dialysis with a contrast procedure (derived from Fig. 19-5).
FIGURE 19-5 Risk prediction scheme for the development of contrast-induced acute kidney injury and for serious renal failure requiring dialysis after coronary angiography or percutaneous coronary intervention. Anemia, baseline hematocrit value <39% for men and <36% for women; CHF, congestive heart failure functional class III/IV and/or history of pulmonary edema; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; hypotension, systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24 hours periprocedurally. (Reproduced with permission from Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004;44(7):1393-1399. Copyright © 2004, with permission from American College of Cardiology Foundation.)

PREVENTIVE STRATEGIES

For patients with significant CKD, that is, a baseline eGFR <60 mL/min/1.73 m² or other evidence of renal disease such as proteinuria, a CI-AKI prevention strategy should be employed. In general, at an eGFR of 30 mL/min/1.73 m², the expected rate of CI-AKI is 30% to 40%, and the rate of AKI requiring dialysis is approximately 2% to 8%; with transcatheter aortic valve replacement, the rates could be doubled. These rates may be even higher and can be accurately predicted from multiple risk factors, as shown in Figure 19-5, in the setting of the cardiac catheterization laboratory. There are 4 basic concepts in CI-AKI prevention: (1) intravascular volume expansion; (2) choice and quantity of contrast; (3) pre-, intra-, and postprocedural end-organ protection with pharmacotherapy; and (4) postprocedural monitoring and expectant care.

Volume supplementation with intravenous (IV) normal saline or isotonic sodium bicarbonate solution remains key, starting 3 to 12 hours prior to the procedure at a rate of 1 to 2 mL/kg/h. A simple IV rate to remember from clinical trials of IV volume expansion is 100 to 150 mL/h. In those at risk, at least 300 to 500 mL of IV fluid should be received before contrast is administered. If there are any concerns regarding volume overload or heart failure, a right heart catheterization may be considered for management during and after the case. A urine output of 150 mL/h should be the target infusion rate after the procedure. Importantly, if patients have diuresis of more than 150 mL/h, they should have replacement of extra losses with more
IV fluid. In general, this strategy calls for IV fluid orders of 150 mL/h for at least 6 hours after the procedure. When adequate urine flow rates were achieved in a clinical trial setting, there was a 50% reduction in the rate of CI-AKI observed.\(^{68}\)

A small but growing line of data point to the benefits of a hemodynamically tailored volume expansion protocol approach. The Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial randomized 396 patients to volume expansion guided by the left ventricular end-diastolic pressure (LVEDP) or by conventional weight-based isotonic saline volume expansion.\(^{69}\) The results demonstrated a significant reduction in CI-AKI in the LVEDP-guided group (6.7% vs 16.3%; \(P = .005\)). Similar in concept, Qian et al\(^{70}\) examined the role of central venous pressure (CVP)-guided volume expansion versus conventional IV fluid orders in patients with heart failure and CKD undergoing invasive angiography. The findings demonstrated a lower incidence of AKI in the CVP-guided group (15.9% vs 29.5%; \(P = .006\)). In the latter 2 trials, tailored volume expansion was not associated with the development pulmonary edema. Thus, it appears that CI-AKI is responsive to volume expansion, and via the mechanism of enhanced renal tubular transit of contrast, this clinical maneuver is associated with lower rates of CI-AKI.

Using lower osmolality contrast agents and limiting the amount of contrast administered are associated with lower rates of CI-AKI. This has now been confirmed in 2 large-scale, double-blind, randomized controlled trials. In the Iohexol Cooperative Study (n = 1196), iohexol (Omnipaque) was found to be superior to high-osmolality contrast (diatrizoate meglumine [Hypaque-76]) in patients with diabetes and baseline CKD.\(^{24}\) In the recently completed Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study (NEPHRIC), iodixanol (Visipaque), a nonionic, iso-osmolar contrast agent was proven to be superior to iohexol with lower rates of CI-AKI observed.\(^{71}\) A meta-analysis of head-to-head randomized trials has found that iso-osmolar iodixanol is associated with lower rates of prespecified CI-AKI than low-osmolar agents (Fig. 19-6); however, these differences are limited to the intra-arterial administration of iodinated contrast and not IV injections.\(^{72}\)
FIGURE 19-6 Forest plot of clinical trials with contrast-induced acute kidney injury (CI-AKI) as a prespecified outcome that compared iso-osmolar iodixanol (IOCM) versus low-osmolar contrast agents (LOCM). This plot demonstrates a 53.8% relative risk (RR) reduction in CI-AKI with iodixanol. CI-AKI is defined as ≥0.5 mg/dL increase in serum creatinine from baseline. CI, confidence interval. (Reproduced with permission from McCullough PA, Brown JR. Effects of intra-arterial and intravenous iso-osmolar contrast medium (iodixanol) on the risk of contrast-induced acute kidney injury: a meta-analysis. Cardiorenal Med. 2011;1(4): 220-234. Copyright © 2011 Karger Publishers, Basel, Switzerland.)

Although it is logically desirable to limit the amount of contrast to the smallest volume possible, there is disagreement as to whether there is a “safe” contrast limit.\textsuperscript{73} This is mainly due to the fact that the lower the eGFR, the smaller is the amount of contrast needed to cause CI-AKI. In general, it is desirable to limit contrast to <100 mL for any procedure or no more than 2 times the eGFR in contrast volume.\textsuperscript{10,59} If staged procedures are planned, it is desirable to have >10 days between the first and second contrast exposure if CI-AKI has occurred on the first contrast exposure.\textsuperscript{74}

There have been over 40 randomized trials testing various strategies in the prevention of CI-AKI. The majority of trials have been small and underpowered and did not find the preventive strategy to be better than placebo. A few lessons have been learned from these trials: (1) diuretics in the form of loop diuretics or mannitol can actually worsen CI-AKI if there is inadequate volume replacement for the diuresis that follows; (2) low-dose or
“renal dose” dopamine and fenoldopam did not provide renal protection, presumably because of counterbalancing forces of intrarenal vasodilatation via the dopamine-1 receptor versus the vasoconstrictive effects on the dopamine-2, α, and β receptors; and (3) nephrotoxic agents including nonsteroidal anti-inflammatory agents, aminoglycosides, and cyclosporine should not be administered in the periprocedural period.

Although there are currently no approved agents for the prevention of CI-AKI, smaller studies of oral or IV N-acetylcysteine (NAC), a cytoprotective agent against oxidative injury, have not been validated in larger scale trials, which have found neutral results compared to placebo. If NAC is going to be used for emergent or urgent procedures involving radiocontrast, a dose of 1 g orally 1 hour before and 4 hours after radiocontrast exposure may be given. In one trial of NAC, patients with mild to moderate CKD undergoing PCI were randomized to receive NAC plus IV fluid or IV fluid alone. An NAC infusion (150 mg/kg) was given IV before contrast exposure and was continued (50 mg/kg) over the following 4 hours. Thus, in a 70-kg patient, the cumulative NAC dose was 14,000 mg—a significantly higher dosage than that used in previous studies (~2400 mg). In the 2 groups, the contrast volumes were 238 mL and 222 mL, and CI-AKI occurred in 5% and 21% of cases, respectively (P = .045). The Veterans Administration Clinical Trials Investigators will be conducting a very large (n = ~9000), randomized, placebo-controlled trial of NAC in a factorial with IV volume expansion with saline or bicarbonate with the primary outcome being CI-AKI. The outcomes from the trial are needed to firmly make a recommendation for the routine use of NAC.

As indicated earlier, there have been many small trials of other strategies including aminophylline, endothelin receptor antagonists, ascorbic acid, dopamine, fenoldopam, and a variety of other agents, all of which have been either neutral or of equivocal benefit. There have been 8 clinical trials involving the use of aminophylline or theophylline in the prevention of CI-AKI, of which 2 studies did not show any protective effect and 6 showed a positive effect in prevention of CI-AKI. A recent meta-analysis of studies employing theophylline or aminophylline for prevention of CI-AKI identified a statistically significant favorable effect on the decline in kidney function. However, the authors note the translation of this effect to clinically meaningful benefit (reduced need for dialysis or in-hospital mortality)
remains to be proven.\textsuperscript{87} Because endogenous adenosine activates intrarenal adenosine receptors causing vasoconstriction, the adenosine antagonism provided by aminophylline may have a favorable effect on renal blood flow. Therefore, aminophylline is considered optional as a preventive strategy and certainly can be continued in pulmonary patients who are already taking the drug.

Prophylactic continuous hemofiltration has been proposed as an interventional strategy to prevent CI-AKI in advanced CKD patients.\textsuperscript{88} Hemofiltration works to (1) guarantee preprocedure IV fluid infusion, (2) provide hemodynamic stability before and after procedure, and (3) provide a blood milieu lower in uremic toxins, thus allowing remnant nephrons to work more efficiently. A recent trial of hemofiltration before and after contrast exposure in patients with advanced CKD (mean Cr, 3.0 mg/dL) resulted in lower CI-AKI rates compared to a control group (5\% vs 50\%; \(P \lt .001\)) (Fig. 19-7). Temporary hemodialysis was required in 25\% of the control patients and in 3\% of the patients in the hemofiltration group.\textsuperscript{88} This trial needs replication. However, at the time of this writing, for patients with severe CKD, prophylactic hemofiltration as done in the trial in an intensive care unit setting 4 to 6 hours before the coronary procedure and for 18 to 24 hours after the procedure is a reasonable option. The hemofiltration circuit requires a Y-shaped 12-Fr double-lumen catheter placed in a femoral vein. Blood is driven through the circuit at a rate of 100 mL/min. The flow of isotonic replacement fluid is set at a rate of 1000 mL/h and is exactly matched with the rate of ultrafiltrate production so that no net fluid loss results. A heparin bolus of 5000 IU is required before hemofiltration, and heparin is continued at a rate of 500 to 1000 IU per hour through the inflow side of the circuit. In most centers, this process will be managed by nephrologists and their dialysis staff.
FIGURE 19-7 The lines represent changes in creatinine (Cr), blood urea nitrogen (BUN), and urine output in 114 patients randomized to prophylactic hemofiltration versus control. Changes from baseline in the Cr and BUN concentrations were significant ($P < .01$) before the procedure and on days 1, 2, and 3 in the hemofiltration group and at day 2, day 3, and discharge in the control group; the difference between the 2 groups was significant beginning on day 1. Control urine output rates differed

It is important to realize that treatment before the procedure is critical and that preemptive dialysis after contrast exposure has not been shown to prevent CI-AKI. Vogt et al. evaluated prophylactic hemodialysis started soon after the administration of the contrast agent and continued for an average of 3 hours. The rationale for the study was to remove the contrast agent efficiently by hemodialysis, thus reducing the concentration of contrast agent to which the kidneys would be exposed. However, this strategy did not show any beneficial effect as compared with saline treatment alone, and patients who were treated with hemodialysis were more likely to have a decline in renal function and to require additional hemodialysis treatment.

A possible explanation for the difference in results with postprocedure hemodialysis compared with periprocedural continuous hemofiltration is that hemodialysis may induce hypovolemia and consequently may worsen renal ischemic injury, delay recovery of renal function, and result in a need for prolonged treatment. On the other hand, hemofiltration is associated with hemodynamic stability and, by preserving the volume of circulating blood, safeguards against renal hypoperfusion. This effect is particularly useful when coronary procedures are performed in patients with critical conditions such as myocardial infarction or acute cardiovascular events such as pulmonary edema or severe left ventricular dysfunction. In addition to hemodynamic stability, hemofiltration provides controlled high-volume hydration and removal of contrast agent from the circulation, with a resultant reduction in the kidneys’ exposure to the agent. It can also be speculated that in addition to high-volume controlled hydration, the removal of mediators of contrast media–induced toxicity by convective filtration and adsorption to the filter membrane may play a significant role.

Once CI-AKI has been recognized, there is no specific treatment, and management involves supportive treatment of AKI, including dialysis treatment as needed. Most operators believe that, given the seriousness of CI-AKI as a complication, the relative safety of the strategies used, and the evolution of clinical trials shaping our practice, the combination of intensive
IV fluid administration (saline or possibly sodium bicarbonate) and use of iodixanol in as low a volume as reasonable is a prudent approach to minimize CI-AKI and the risk of AKI requiring dialysis.

Postprocedural monitoring is an issue in the modern era of short stays and outpatient procedures. In general, high-risk patients in the hospital should have IV volume expansion started 3 to 13 hours before the procedure and continued for at least 6 hours afterward (Fig. 19-8). A serum Cr should be measured 24 hours after the procedure. For outpatients, particularly those with eGFR <60 mL/h, either an overnight stay or discharge to home with 24- to 48-hour follow-up and Cr measurement is advised. It has been demonstrated that individuals who develop severe CI-AKI have a rise in Cr >0.5 mg/dL in the first 24 to 48 hours after the procedure. Hence, for those who have not had this degree of Cr elevation, and otherwise have had uneventful courses, discharge to home may be considered.

**FIGURE 19-8** Suggested algorithm for patients undergoing coronary angiography and intervention. All patients should have the estimated glomerular filtration rate (eGFR) calculated and have an assessment for contrast-induced acute kidney injury (CI-AKI) risk based on validated multivariate scoring schemes. ACS, acute coronary syndrome; AKI, acute kidney injury; Cr, creatinine; CrCl, creatinine clearance; DM,
diabetes mellitus; NSAIDs, nonsteroidal anti-inflammatory drugs; TAVR, transcatheter aortic valve replacement.

In summary, for CI-AKI risk assessment and prevention, the action items as shown in Figure 19-8 are advised. It is important that in the consent process CI-AKI risks are discussed. For patients with eGFR <30 mL/min/1.73 m$^2$, the possibility of dialysis should be mentioned. Finally, in patients with eGFR <20 mL/min/1.73 m$^2$, nephrology consultation is advised with possible planning for dialysis after the procedure.

CONCLUSION

CIN is an important cause of AKI and death in critically ill patients. The presence of multiple risk factors can anticipate up to an approximate 50% probability of CI-AKI in specific patients. Risk prediction and preventive measures are mandatory. Once AKI occurs, even with dialysis and expectant management, high rates of in-hospital and long-term mortality can be expected.

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**MULTIPLE CHOICE QUESTIONS**

1. Which of the following statements is true about contrast-induced acute kidney injury (CI-AKI)?
   A. It is the most common cause of hospital-acquired renal failure.  
   B. The incidence of CI-AKI is well defined in the literature and is
approximately 20%.
C. One percent of episodes of CI-AKI require dialysis.
D. Episodes of CI-AKI not requiring dialysis add, on average, 7 days to the hospitalization.

2. Which of the following statements is true about transient rises in serum creatinine following contrast administration?
   A. Changes >0.1 mg/dL are considered significant.
   B. A rise of >0.3 mg/dL in serum creatinine occurs in approximately 7% of patients undergoing percutaneous coronary intervention (PCI).
   C. Transient rises in serum creatinine have not been associated with adverse long-term outcomes.
   D. Definitions of CI-AKI have had consistent criteria with respect to acute changes in serum creatinine.

3. Which of the following statements is true about biomarkers for CI-AKI?
   A. Tubular markers for AKI, including liver-type fatty acid binding protein, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin, have improved sensitivity for renal injury as compared to serum creatinine.
   B. Serum creatinine changes provide rapid detection of renal injury following contrast administration.
   C. Cystatin C is a tubular marker that is upregulated during AKI.
   D. Changes in urine creatinine levels are more reliable than serum creatinine for AKI.

4. Which of the following occurs after contrast administration?
   A. Prolonged renal vascular vasodilation
   B. A brief increase in renal blood flow followed by prolonged vasoconstriction
   C. No acute changes in renal perfusion
   D. An acute decline in renal vein renin levels

5. Which of the following statements is true about management and prevention of CI-AKI?
   A. Metformin-induced lactic acidosis is most common in non–insulin-dependent diabetics with underlying renal dysfunction.
B. Volume expansion is important only prior to contrast administration.
C. Use of N-acetylcysteine has been definitively shown to prevent CI-AKI in most patients.
D. The use of fenoldopam has been reliably shown to reduce the incidence of CI-AKI.

**ANSWERS**

1. C
2. B
3. A
4. B
5. A
Contemporary Patient Sedation and Anesthesia in the Cardiovascular Catheterization Laboratory

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Sedation for patients undergoing procedures in the cardiac catheterization laboratory (CCL) can be managed by the primary physician with nursing staff or by a dedicated anesthesiology team. The choice of sedation and/or anesthetic techniques is dependent on institutional policies, patient and physician preference, and the type of procedure being performed. This discussion will focus on interventional procedures in the CCL and not hybrid operating room procedures that add an additional layer of complexity and more often than not will be staffed with an anesthesia team.

CCL sedation offers patient comfort (analgesia and anxiolysis) during invasive procedures requiring patients to hold still, potentially for long periods, without resorting to general anesthesia. In pediatric populations and uncooperative adults, either deep sedation or general anesthesia, provided by an anesthesiology care provider, is typically warranted. General anesthesia may also be warranted for patients who cannot lie flat due to cardiac or pulmonary pathology or joint pain. General anesthesia is also frequently used for patients requiring transesophageal echocardiography as part of their procedure.
At times, these sedation practices may result in cardiac or respiratory depression; these must be rapidly recognized and appropriately managed to avoid the risk of hypoxic brain damage, cardiac arrest, or death. Conversely, inadequate sedation/analgesia may result in undue discomfort, patient injury due to lack of cooperation, or adverse physiologic or psychological response to stress.¹

In general, patients managed with moderate sedation will have a shorter recovery period prior to return to their hospital room or discharge home. There may also be a shorter room turnover time for patients managed with sedation versus general anesthesia. Patients receiving general anesthesia must be recovered in a unit staffed with nurses trained in recovery of postanesthesia patients. If this unit is distant from the interventional area, room turnover will be delayed during transport of patients and transfer of care to the recovery team. Moderate sedation administered by a nurse under the supervision of the cardiologist may decrease the resource utilization and total institutional cost for the procedure by avoiding usage of these additional resources.

DEFINITION OF SEDATION

Sedation (minimal, moderate, or deep) and general anesthesia are defined points on an otherwise continuous scale of sedation defined by anesthesiologists (Table 20-1). At the origin of this scale, the individual is fully awake and conscious; at the opposite end, he or she is unarousable, apneic, and possibly hemodynamically unstable.

Table 20-1 Levels of Sedation and Anesthesia and Accompanying Physiologic Parameters²
- Minimal sedation (anxiolysis): A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

- Moderate sedation/analgesia (conscious sedation): A drug-induced depression of consciousness during which patients respond purposefully (reflex withdrawal from a painful stimulus does not constitute a purposeful response) to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

- Deep sedation/analgesia: A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully (again, reflex withdrawal from a painful stimulus does not constitute a purposeful response) following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

- General anesthesia: A drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required due to depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.
Because sedation is a continuum, it is not always possible to predict how an individual patient will respond to a given sedation strategy. Consequently, practitioners intending to produce a given level of sedation should be able to care for and rescue the patient whose level of sedation becomes deeper than initially intended. Individuals administering moderate sedation/analgesia (conscious sedation) should be able to rescue patients who enter the state of deep sedation/analgesia; those administering deep sedation/analgesia should be able to manage the situation where the patient enters the state of general anesthesia.

Each hospital is normally accredited by the specific credentialing body regarding the types of practitioners who can provide sedation outside of the operating room, as well as which levels of sedation are allowed. These policies are not universal across institutions but will provide both guidance and limitations of the sedation practice and establish minimum standards of care. Additionally, there may be provisions regarding provider recertification, equipment use, and other elements particular to a given hospital.

**PREOPERATIVE ASSESSMENT**

A thorough history and physical examination are the first steps in selecting the proper sedation technique for the specific patient and the procedure. Special emphasis should be given to the history of previous anesthetic problems, medication and contrast dye allergies, and tolerance to alcohol and recreational drugs, as these may alter the sedation approach. It is also advisable to inquire about rare but potentially critical complications such as family history of malignant hyperthermia, use of medications with potential for serious adverse reactions such as long-term amiodarone, cancer chemotherapy with bleomycin or doxorubicin, and severe or debilitating illness.¹

Physical examination should address, at a minimum, pulmonary and cardiovascular status as well as assessment of the airway. The most common airway assessment tool is the Mallampati³ score, which assigns grades I to IV based on soft palate and uvula visualization with the patient’s mouth opened (Fig. 20-1). Patients with scores of III and IV, as well as those with receding mandibles (defined as having <3 fingerbreadths distance between the chin and the hyoid bone), obese patients, or patients with full beards, may be more
difficult to ventilate and may present a challenge should endotracheal intubation become necessary. Finally, a review of past anesthetic records may clarify the degree of difficulty in managing the patient’s airway when the physical exam is nonreassuring or if the patient has a history of airway surgery.

**FIGURE 20-1 The Mallampati score for airway assessment.** (Reproduced from Mallampati et al. A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anesth Soc J.* 1985;32.4:429-434, with permission of Springer.)
Based on the results of the history and physical examination, a given patient can be classified as 1 of the 6 American Society of Anesthesiologists (ASA) classes (Table 20-2). The ASA classification stratifies the complexity of the patient’s comorbidities in order to develop the sedation management strategy, predict outcome expectations, and assist with resource management. Additionally, the ASA status is often included in the research data as an overall means of intraoperative complication risk assessment.¹ For patients receiving sedation, a minimum 6-hour fasting period is recommended, with the exception of clear fluids, which can be continued to within 3 hours of the procedure. The fasting time should be increased in patients with known delayed gastric emptying to mitigate aspiration risk.¹ ⁴

Table 20-2 American Society of Anesthesiologists (ASA) Classification of Patients

<table>
<thead>
<tr>
<th>ASA Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>A healthy patient</td>
</tr>
<tr>
<td>Class II</td>
<td>A patient with mild systemic disease</td>
</tr>
<tr>
<td>Class III</td>
<td>A patient with severe systemic disease</td>
</tr>
<tr>
<td>Class IV</td>
<td>A patient with severe systemic disease that is a constant threat to life</td>
</tr>
<tr>
<td>Class V</td>
<td>A moribund patient not expected to survive without the procedure</td>
</tr>
<tr>
<td>Class VI</td>
<td>A brain-dead patient whose organs are being donated</td>
</tr>
<tr>
<td>E</td>
<td>An add-on modifier to ASA class to indicate emergency surgery</td>
</tr>
</tbody>
</table>

Treatment with metoclopramide or a nonparticulate antacid may benefit some patients with delayed gastric emptying or increased gastric acid secretion, but indiscriminate use in all patients is not recommended.⁴

PERSONNEL AND EQUIPMENT

The ASA taskforce recommends that a designated individual, other than the
practitioner performing the procedure, should be present to monitor the patient throughout a procedure that is performed with sedation/analgesia; during deep sedation, this individual should have no other responsibilities. However, during moderate sedation, this person may assist with minor, interruptible tasks once the patient’s level of sedation/analgesia and vital signs have stabilized, provided that adequate monitoring for the patient’s level of sedation is maintained.

Individuals responsible for patients receiving sedation/analgesia should understand the pharmacology of the administered agents, as well as the role of pharmacologic antagonists for opioids and benzodiazepines. Individuals monitoring patients receiving sedation/analgesia should be trained to recognize the associated complications. At least 1 individual capable of establishing an advanced airway and positive-pressure ventilation as well as means for summoning additional assistance should be available whenever sedation/analgesia is administered. It is recommended that an individual with advanced life support skills be immediately available (within 5 minutes) for moderate sedation and within the procedure room for deep sedation.

Pharmacologic antagonists and appropriately sized equipment for establishing an advanced airway and providing positive-pressure ventilation with supplemental oxygen should be present whenever sedation/analgesia is administered. Suction, advanced airway equipment, and resuscitation medications should be immediately available and in good working order (Table 20-3). A functional defibrillator should be immediately available when deep sedation is administered or when moderate sedation is administered to the patient with cardiovascular disease.1

Table 20-3 Emergency Equipment for Sedation and Analgesia

<table>
<thead>
<tr>
<th>Appropriate emergency equipment should be available whenever sedative or analgesic drugs capable of causing cardiorespiratory depression are administered. The lists below should be used as a guide, which should be modified depending on the individual practice circumstances. Items in brackets are recommended when infants or children are sedated.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous equipment</strong></td>
</tr>
<tr>
<td>• Gloves</td>
</tr>
<tr>
<td>• Tourniquets</td>
</tr>
<tr>
<td>• Alcohol wipes</td>
</tr>
</tbody>
</table>
• Sterile gauze pads
• Intravenous catheters [24-22 gauge]
• Intravenous tubing [pediatric “microdrip” (60 drops/mL)]
• Intravenous fluid
• Assorted needles for drug aspiration, intramuscular injection
  • [Intraosseous bone marrow needle]
• Appropriately sized syringes [1-mL syringes]
• Tape

Basic airway management equipment
• Source of compressed oxygen (tank with regulator or pipeline supply with flowmeter)
• Source of suction
• Suction catheters [pediatric suction catheters]
• Yankauer-type suction
• Face masks [infant/child]
• Self-inflating breathing bag-valve set [pediatric]
• Oral and nasal airways [infant/child-sized]
• Lubricant

Advanced airway management equipment (for practitioners with intubation skills)
• Laryngeal mask airways [pediatric]
• Laryngoscope handles (tested)
• Laryngoscope blades [pediatric]
• Endotracheal tubes
  • Cuffed 6.0, 7.0, 8.0 mm internal diameter (ID)
  • [Uncuffed 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 mm ID]
• Stylet (appropriately sized for endotracheal tubes)

Pharmacologic antagonists
• Naloxone
• Flumazenil

Emergency medications
• Epinephrine
• Ephedrine
• Vasopressin
• Atropine
• Nitroglycerin (tablets or spray)
• Amiodarone
• Lidocaine
• Glucose 50% [10% or 25%]
• Diphenhydramine
• Hydrocortisone, methylprednisolone, or dexamethasone
• Diazepam or midazolam

Supplemental oxygen should be considered for moderate sedation and should be administered during deep sedation unless specifically contraindicated for a particular patient or procedure. Supplemental oxygen should be administered if hypoxemia is anticipated or is encountered during sedation/analgesia.

PATIENT MONITORING

The standards for intraoperative monitoring of patients undergoing procedures under general anesthesia are, for the most part, applicable to the sedation setting.

Oxygenation monitoring is accomplished by pulse oximetry, which is rapid, quantitative, and reliable. It uses a minimum of 2 wavelengths of light to detect concentrations of oxyhemoglobin and deoxyhemoglobin and displays an empirically derived numeric value of percent hemoglobin saturation. When coupled with a variable pitch audio output, this monitor provides a continuous background of information about both the patient’s heart rate and blood oxygenation, and it is one of the essential monitors recommended by ASA during general anesthesia and deep sedation.¹,⁵

Ventilation monitoring is dramatically different between the sedation in the CCL and an in the operating room equipped with the anesthesia machine. Usually the CCL environment lacks the mechanical ventilation devices that monitor tidal volumes, circuit integrity, and airway pressures and analyze inhaled and exhaled gas continuously. However, most modern patient monitors have the capacity for capnogram capture; the use of capnography is recommended by the ASA for all cases where sedation is used, unless precluded or invalidated by the nature of the patient, procedure, or
equipment. The capnography unit can be programmed to alert the practitioner in the event that patient’s respiratory rate is too low, indicating the potential for hypoventilation, as well as in case of the total absence of carbon dioxide, which can be caused by apnea, oxygen delivery/sampling line disconnection from the patient, or cardiovascular collapse.

It is a common misconception that pulse oximetry provides enough data to not require capnography; this assumption is quite dangerous because the patient may maintain a normal pulse oximetry profile while being totally apneic for a significant amount of time. Once the hypoxia ensues, sometimes minutes after the cessation of ventilation, the patient will require a much more involved resuscitation and may possibly require positive-pressure ventilation to restore homeostasis. However, if an appropriate intervention, such as airway repositioning, patient stimulation to breathe, or administration of sedative antagonist, is performed at the time of capnography tracing loss, the procedure can usually continue with minimal interruption.

Patients with depressed, but not totally suppressed, ventilation may also display normal pulse oximetry reading but can develop severe hypercarbia and respiratory acidosis, producing symptoms of somnolence, restlessness, or cardiovascular disturbances. If one suspects inadequate ventilation, an arterial blood gas may be necessary to rule out hypoventilation and respiratory acidosis.

*Circulation monitoring* is accomplished with several modalities; continuous electrocardiography monitoring is recommended for the duration of the procedure because it is reliable, simple, and noninvasive. When used appropriately, it allows a reliable monitoring of cardiac ischemia and will alert to cardiac rhythm disturbances quicker than other monitoring modalities. The most commonly monitored leads are II and V₅, which together provide 80% sensitivity for myocardial ischemia. Modern telemetry machines are capable of monitoring 5 or more leads, automatically alerting the provider if ST-segment morphology change is detected.

It is also recommended by the ASA that a blood pressure assessment be performed at least every 5 minutes when using an automated blood pressure cuff or a sphygmomanometer and a stethoscope. For patients with an arterial line in place for blood pressure monitoring or the arterial access for the procedure, it is still recommended to place a noninvasive blood pressure cuff because these require no calibration and thus are not subject to calibration errors. Additionally, arterial lines may fail due to thrombosis or malposition.
Meanwhile, arterial sheath pressure transducers may have to be disconnected in the course of the procedure for the transit of catheters or devices; usually, these events are the ones that require more thorough blood pressure monitoring. The blood pressure cuff should fit snugly around the patient’s limb and must be sized appropriately so that the inflatable part covers at least 80% of the limb’s circumference.5

The ASA also made the following statement pertaining to patients undergoing general anesthesia: “[A] secondary circulatory function assessment [should be performed] by at least one of the following: palpation of a pulse, auscultation of heart sounds, monitoring of a tracing of intra-arterial pressure, ultrasound peripheral pulse monitoring, or pulse plethysmography or oximetry for an additional layer of safety.” This may be applicable to deep sedation cases, and this requirement is easily satisfied because CCL patients will commonly have the pulse oximetry data.

Temperature monitoring is applicable in general anesthetic cases where the patient’s control of homeostatic functions, such as vasoconstriction and shivering, is impaired. It is reasonable to consider monitoring patient’s body temperature during procedures that are prolonged or require levels of sedation that preclude the patient from alerting the provider that he or she is getting cold. Prevention of hypothermia with forced air heating blankets and minimization of the patient’s exposure should be a part of the procedure plan if there is a potential for hypothermia due to exposure of the large areas of patient’s body for prolonged periods of time of if there is an anticipated infusion of a large volume of intravenous fluids.

SEDATION PROCEDURE OVERVIEW

After confirming the patient’s identity and the type of procedure, as well as confirming informed consent, the patient may be premedicated if it is indicated and is a part of the sedation plan. Usually the premedication is an anxiolytic, unless the patient has underlying pain that needs to be treated. An intravenous line may be established prior to premedication, or afterward if nonintravenous premedication is chosen. Often premedication may be omitted, and the patient may arrive to the CCL fully conscious if he or she is not anxious or uncooperative.1

The choice of intravenous line gauge lies with the sedation provider, but
these flexible catheters often range between 18 and 22 gauge and are 1 to 2 inches in length, unless an indication for larger-bore access exists.

After application of selected monitors, described earlier, a combination of sedative and analgesic agents may be administered as appropriate for the procedure being performed and the condition of the patient. Ideally, each component should be administered individually to achieve the desired effect (eg, additional analgesic medication to relieve pain or additional sedative medication to decrease awareness or anxiety). The propensity for sedative and analgesic agents to synergistically cause respiratory depression and airway obstruction emphasizes the need to appropriately reduce the dose of each component as well as the importance of continuous monitoring of the respiratory function. Intravenous sedative/analgesic medications should be given in small, incremental doses that are titrated to the desired effect of analgesia and sedation. Sufficient time must be allowed between doses to assess the effect of the preceding dose prior to the subsequent drug administration. This time interval becomes more critical when the medications are administered by nonintravenous routes (eg, oral, rectal, intramuscular, transmucosal), since medication absorption by routes other than intravenous may be unpredictable. The administration of repeat doses of oral medications to supplement sedation/analgesia is not recommended.1,6

SEDATIVES

Benzodiazepines

Benzodiazepines enhance the effect of the neurotransmitter γ-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic, anxiolytic, euphoric, anticonvulsant, and muscle-relaxing properties, as well as an amnestic effect.

Benzodiazepines are the most commonly used sedative agents due to their anxiolytic properties, with midazolam being the most frequent choice. Midazolam has a quick onset (1-2 minutes) and short duration of action (typically 15-30 minutes), and it provides better amnesia than other benzodiazepines. Of all the intravenous sedatives, midazolam produces the least amount of discomfort on injection, a property not shared by other
Diazepam (onset 1-5 minutes; terminal half-life \( t_{1/2} \) 30-60 hours) and lorazepam (onset 15-20 minutes; \( t_{1/2} \) 14 hours) can also be used if a longer acting sedative is required. Diazepam is painful on injection and may cause phlebitis; it also has an active metabolite, desmethyldiazepam, with a half-life of 30 to 100 hours. Both diazepam and lorazepam may result in longer recovery and delayed dismissal. Benzodiazepines should be avoided in pregnancy, especially in the first trimester, because of known risk of birth defects. Elderly individuals have an increased risk for delirium and confusion with benzodiazepine administration, and these should be used sparingly. Small initial doses of midazolam for frail or elderly individuals who do not receive benzodiazepines routinely should be used, with incremental subsequent doses repeated until the appropriate levels of anxiolysis and sedation are achieved. Benzodiazepines can be largely avoided by the use of topical anesthetic, low-dose analgesics, and reassurance by the treatment team in a select group of patients during short, minimally uncomfortable procedures. Many institutions also have dosage limits above which consultation with an anesthesia provider is indicated regardless of the intended sedation level.

Benzodiazepines can produce paradoxical excitation in less than 1% of the population. Patients with psychiatric disorders and those taking other psychoactive substances both medically and recreationally should be monitored more closely, and the risk of administration of benzodiazepines should be carefully weighed.

Overdose of benzodiazepines generally results in excessive somnolence, inability to maintain the airway, and depressed ventilation. Supportive measures and cessation of the offending agent administration are often sufficient for the patient to recover.

Flumazenil is a specific competitive benzodiazepine receptor antagonist that can be used to reverse sedative effects of all benzodiazepines. Flumazenil doses of approximately 0.1 to 0.2 mg produce partial antagonism, whereas higher doses of 0.4 to 1 mg usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. These small incremental doses can be administered every minute until a desired reversal effect is attained. The use of flumazenil may be complicated by its short duration of action (distribution half-life of 4-11 min, \( t_{1/2} \) of 40-80 minutes), leading to the patient slipping back into an overly sedated state when the
effect of flumazenil diminishes; repeat doses may be required.

Chronic benzodiazepine administration is a relative contraindication to flumazenil as these patients may experience seizures due to rapid withdrawal of GABA stimulation. Patients with heavy alcohol use also fall in the relative contraindication category due to potential risk of precipitating delirium tremens.

**Opioids**

Opioids are frequently used as adjuncts to benzodiazepines to provide analgesia for the uncomfortable portions of the procedure, such as establishment of vascular access, use of electrocautery, or defibrillation. Opioids and benzodiazepines are synergistic in their respiratory depressant effects, and caution is warranted when administering them simultaneously.

Fentanyl is the most commonly used opioid due to almost instantaneous onset of action, short duration of action (intravenous, 30-60 minutes; intramuscular, 1-2 hours), and more favorable hemodynamic profile than morphine or meperidine due to minimal histamine release. Fentanyl is estimated to be 50 to 100 times more potent that morphine at equal doses. The typical intravenous bolus dose for an adult ranges from 25 to 100 μg and may be repeated until a desired effect is achieved.

Fentanyl, like other opioids, will cause respiratory depression, and this effect may last beyond the duration of analgesia, necessitating careful postprocedure monitoring and patient counseling before discharge. Opioids increase the incidence of nausea, and their use must be weighed against potentially longer recovery to discharge.

Administration of large doses or rapid administration of fentanyl may cause chest wall rigidity, which can transiently make ventilation of the patient nearly impossible. This can be confused with bronchospasm or laryngospasm, but the temporal proximity of fentanyl injection to the appearance of symptoms should help the practitioner to decipher the etiology. A larger dose than is used in sedation practice is usually the culprit, but doses as low as 50 to 100 μg were implicated in several case reports. Treatment may consist of opioid reversal with naloxone, and in extreme cases, an induction of general anesthesia, administration of a muscle relaxant, and tracheal intubation may be required.
The symptoms of opioid overdose that warrant opioid reversal are generally excessive sedation and/or respiratory depression. Classically, the patient with relative opioid excess will take breaths on command but will have blunted response to respiratory acidosis and hypercarbia. Withdrawing the offending agent and allowing for the patient to recover are often all that is necessary. A specific opioid antagonist, naloxone, can be used in extreme overdose incidents.

Naloxone is a competitive antagonist at the μ-opioid receptor with a rapid onset (usually less than a minute if administered intravenously) and an approximate duration of action of 45 minutes. Similarly to flumazenil, the short duration of action can result in recurrence of overdose symptoms when a longer acting opioid was used.

Naloxone will cause immediate withdrawal symptoms in patients who are chronically treated with opioids, and it must be used with caution, if at all, in the opioid-dependent patients. The usual naloxone dose for total opioid reversal is 0.2 to 2 mg; it can be administered intravenously, intramuscularly, via endotracheal tube, or even intranasally, although the onset by intravenous route is the fastest. The starting dose of naloxone for partial opioid reversal should be 0.05 to 0.4 mg intravenously repeated every minute until respiratory rate is >12 breaths per minute.

Side effects of naloxone may include hypertension, tachycardia, flash pulmonary edema, nausea, vomiting, diaphoresis, and withdrawal symptoms. An extended period of patient monitoring is recommended if the reversal agent was used.8

Propofol

Propofol is an intravenous sedative-hypnotic that is not typically used by nonanesthesia personnel in spontaneously ventilated patients due to high risk of apnea associated with dose titration and the subsequent need for airway management. Many states have laws preventing the administration of propofol by nonanesthesiologists, unless the patient is intubated and mechanically ventilated. The advantage of propofol for the purpose of sedation, despite its higher cost, is the rapid sedation onset and recovery, with fewer lingering sedation-related side effects and no increase in cardiopulmonary complications compared with the benzodiazepine-narcotic combination. Propofol is also least likely to cause nausea and has antiemetic
properties when given in small doses to a postoperative patient, a practice that is considered off-label. Anticipated propofol use in the catheterization lab requires coordinated scheduling with the anesthesiology services, thus increasing scheduling complexity.

Propofol is a nonbarbiturate sedative with minimal analgesic effect, rapid (40 seconds) onset, and short duration of action, lasting between 2 and 5 minutes after a 2-mg/kg intravenous bolus. Propofol’s action is produced at the GABA$_A$ receptor, where it increases the duration of channel opening, similarly to the mechanism of action of barbiturates and benzodiazepines. It is rapidly redistributed from the central nervous system, which accounts for its short duration of action despite the half-life of 1 to 3 hours. Sedation with propofol for a prolonged period of time increases the half-life to several days due to saturation of propofol redistribution sites. This phenomenon is known as context-sensitive half-life and is not unique to propofol, as many other drugs rely on redistribution as the primary means of terminating their effect.\(^8\)

Propofol is contraindicated in individuals who have allergies to egg or soy products and glycerol, as the formulation contains 10% soybean oil, 1.2% egg phospholipid emulsion, and 2.25% glycerol. This formulation causes pain on injection, especially if injected rapidly and into a small vessel. A new aqueous-based formulation of the prodrug, fospropofol, is being investigated because it may be less painful during injection.

Propofol dosing for sedation is ideally accomplished with a 0.1 to 0.5 mg/kg initial bolus to rapidly achieve the drug concentration in the bloodstream immediately prior to the stimulating part of the procedure such as procedural vascular access, as well as the infusion of 25 to 75 μg/kg/min for the maintenance of sedating effect. Elderly and severely debilitated patients or those receiving additional sedatives or hypnotics should receive a lower initial dose, and the infusion should commence at 5 to 10 μg/kg/min and be titrated carefully.

There is no specific antidote for propofol overdose; the treatment consists of supportive measures, intubation, mechanical ventilation, cardiovascular support with inotropes and vasopressors, and allowing patient’s metabolism to resolve the overdose.

Various studies comparing cost-effectiveness of propofol-based sedation to the conventional strategies demonstrated increased, decreased, or equivalent cost. Evaluation of the utility and cost-effectiveness of propofol-
based sedation in the given setting is necessary to determine whether the increase in cost and the need for the anesthesiologist’s or anesthetist’s involvement are offset by the potentially faster recovery and dismissal and increased patient satisfaction scores.\textsuperscript{10,11}

**Ketamine**

Ketamine is a phencyclidine derivative analgesic and a dissociative anesthetic, better known for its use in the emergency department for procedural sedation. The profound analgesic effect of ketamine is employed during short but painful procedures without the need for a general anesthetic; it is also widely used in veterinary medicine.

Ketamine acts on the $N$-methyl-$D$-aspartate receptor in the central nervous system causing a dissociative state in which the patient’s respiration and cardiovascular status remain unchanged but the memory and pain perception are impaired.

The initial dose of ketamine for sedation is 1 to 2 mg/kg intravenous bolus. There appears to be a minimum dose threshold for the dissociative effect, and sedation is not increased with additional dosing. A single intravenous dose of ketamine will maintain analgesia and sedation for 5 to 10 minutes, and the patient may typically be dismissed within 1 to 2 hours of the administration. During ketamine sedation, the response to painful stimuli may be absent, which would be consistent with general anesthesia (see Table 20-1), yet ventilation will be maintained at a level comparable to minimal or moderate sedation. This threshold nature of ketamine, with all-or-none effect, may result in difficulty when estimating the depth of sedation.\textsuperscript{8,12}

A unique niche for ketamine is in patients with pericardial tamponade, where spontaneous ventilation, avoidance of further cardiac chamber compression, and maintenance of the cardiovascular tone are preferred while the pericardiocentesis is performed. Given the potential for complications during open pericardiocentesis, it may be prudent for a cardiac anesthesiologist to lead the sedation efforts. After prepping and draping the patient and having the sterile field ready for the procedure, a small premedication dose of midazolam (0.5-2 mg) followed by an induction dose of ketamine (2-4 mg/kg intravenous) will render the patient sufficiently sedated for the procedure. Repeat doses of ketamine at 0.5 to 1 mg/kg may be necessary to maintain the sedation while the procedure is under way.
Ketamine may cause hallucinations, vivid dreams, and out-of-body experiences, some of which may be quite unpleasant. An amnestic dose of benzodiazepine as a premedication prior to ketamine administration may diminish these objectionable recollections. A transient increase in intracerebral and intraocular pressure after induction is common; nausea and vomiting occur with incidence of approximately 8%, limiting ketamine utility in routine cases.

Another side effect of ketamine is hypersalivation, which may play an important role if the advanced airway management is required; this can be mitigated with administration of an anticholinergic medication such as glycopyrrolate 0.2 mg intravenously.

Absolute contraindications to ketamine are central nervous system mass lesions leading to deterioration with increasing intracerebral pressure, glaucoma or a ruptured eye globe, and hyperthyroidism or pheochromocytoma/paraganglioma, which are exacerbated by ketamine’s sympathomimetic effect.12

**Etomidate**

Etomidate is an intravenous anesthetic with an imidazole molecular structure. It possesses amnestic and anesthetic, but not analgesic, properties and is traditionally used as a general anesthesia induction agent, as well as for short procedural sedation. Etomidate acts on the GABA$_A$ receptor, similarly to benzodiazepines, barbiturates, and propofol.

A typical general anesthesia induction dose is 0.2 to 0.6 mg/kg intravenously with 30- to 60-second onset and 5- to 10-minute duration. Etomidate terminates its action via redistribution from the target tissue, and its elimination half-life is approximately 75 minutes. With the administration of etomidate, the patient’s cardiovascular status is usually maintained, and the intracerebral pressure is lowered, resulting in increased cerebral perfusion pressure; this feature is unique to etomidate and is not shared by other intravenous agents. Ventilation is maintained with sedative doses of etomidate but may become impaired once general anesthesia level is achieved.8

Etomidate is one of the drugs of choice for inducing a general anesthesia in patients with impaired cardiac function, such as critical mitral or aortic
stenosis, or severely depressed ejection fraction, because any decrease in cardiac contractility or vascular tone may be poorly tolerated. Similarly to ketamine, etomidate can be useful in patients with cardiac tamponade for similar reasons.

Etomidate causes pain during injection, a property shared with propofol, and amnestic premedication may lessen or eliminate the patient’s recollection of the burning at the intravenous site on induction. Additionally, etomidate reversibly inhibits 11-β-hydroxylase, an enzyme responsible for cortisol production.

Etomidate-induced adrenal suppression may last up to 72 hours, thus making the drug unsuitable for repeated or continuous sedation. In a recent analysis of over 2600 patients receiving etomidate or propofol during noncardiac surgery, there was an observation of increased mortality (odds ratio, 2.5), cardiac morbidity (odds ratio, 1.5), and length of hospital stay. These findings are based on a retrospective study, and thus, an argument can be made that patients receiving etomidate were more unstable, therefore prompting the use of etomidate. Nonetheless, etomidate should probably be reserved for patients with a clear indication for its hemodynamic-preserving properties and not used for routine sedation.

**Dexmedetomidine (Precedex)**

Dexmedetomidine is a fairly novel (approved for use in 1999) sedative with an unusual target receptor. It is an α₂-agonist in the central nervous system. Elimination half-life is biphasic, with a 6-minute redistribution half-time and 2-hour t₁/₂. Both liver and kidneys are involved in its elimination.

Dexmedetomidine has anxiolytic and hypnotic effects and is used for intensive care unit sedation as well as procedural sedation. It also decreases sympathetic tone, which may be beneficial to counteract the increased sympathetic activation caused by an uncomfortable procedure. The slow onset of drug action necessitates the use of a loading dose (0.5-1 μg/kg over 5-10 minutes) with subsequent maintenance infusion of 0.5 to 1.4 μg/kg/h. There is minimal to no respiratory depression when the drug is used as prescribed, and the patient may be awoken from the sedation by verbal or tactile stimulation, indicative of the moderate sedation. Ideally, dexmedetomidine infusion is started in advance of the uncomfortable parts of
the procedure, so that a plane of sedation can be attained. This baseline anxiolysis and anesthesia is then supplemented by small boluses of rapid and short-acting analgesic as needed.

Another use for dexmedetomidine is a sedative for a fast-track extubation of a patient who needs a more gradual wean from ventilatory support following a procedure under general anesthesia. This is accomplished by titrating down the infusion rate to 0.2 to 0.5 μg/kg/h and waiting for patient emergence, at which point the patient may be weaned off the ventilator support while experiencing the benefit of mild anxiolysis through the low-dose infusion.

It is worth noting that peripheral α2 receptor activation may produce hypotension and bradycardia as a result of the presynaptic inhibition of the sympathetic nervous system. The responses to activation of the receptors in other areas include decreased salivation, decreased bowel motility, contraction of vascular and other smooth muscle, inhibition of renin release, increased glomerular filtration, increased secretion of sodium and water by kidneys, decreased intraocular pressure, and decreased insulin release from the pancreas, all of which are of less importance in the CCL.14

SPECIAL CONSIDERATIONS FOR MANAGEMENT OF SEDATION IN THE CARDIAC CATHETERIZATION LABORATORY

The CCL has been the primary location for percutaneous therapy of coronary and peripheral arterial disease. Percutaneous therapies for patients with structural, congenital, and valvular heart disease have significantly increased over the last decade and can also be performed in the CCL. Transfemoral transcatheter aortic valve replacement (TAVR) has only recently transitioned from the hybrid operating room (OR) with general anesthesia to the CCL, using nurse-driven moderate sedation and hemodynamic support. Currently, the TAVR procedure in the CCL requires 4 team members fulfilling specific roles. A registered nurse (RN) is solely devoted to handling respiratory management, hemodynamic support, and patient comfort. A registered
cardiovascular interventional specialist (RCIS) or RN is required to monitor and co-circulate. A certified RCIS or RN is required to scrub for valve preparation.

The TAVR patient population has unique needs related specifically to their age, comorbidities, and concurrent procedure. Thus, pharmaceutical and associated care must be individualized. Timely administration of medication at key points during the procedure (eg, femoral access, artery dilation, valve manipulation and valve placement, and/or closure) is important to maintain patient comfort while also reducing the total amount of medications needed to evoke a moderate sedative state. Patients typically receive supplemental oxygen via nasal cannula at 2 to 4 L/min. Due to the high percentage of frail patients with arthritic complications, patient comfort measures are made to facilitate a positive experience and circumvent any procedural delay due to positional complaints. To reduce pain secondary to prolonged positioning, support is placed under knees and ankles. Normothermia is accomplished by an external convective warming system, an under body blanket, and minimization of patient exposure during procedure preparation.

Maintaining adequate patient comfort and minimizing sedation result in stable hemodynamics and the ability to assess the patient for acute neurologic events. The circulating nurse is also in charge of administrating intravenous fluids and hemodynamic agents during the TAVR procedure. If the pre-TAVR left ventricular end-diastolic pressure is <15 mm Hg, a fluid bolus of balanced salt solution (250-500 mL) should be given to prevent fluctuations in blood pressure during the subsequent procedure. Immediately after valve deployment, patients with hypertrophic ventricles may require 250- to 1000-mL fluid boluses to maintain adequate preload and blood pressure. Small doses of background sympathomimetics may be required to support patient hemodynamics, particularly prior to balloon aortic valvuloplasty and during valve placement. Patients with low systolic blood pressure (<100 mm Hg) who are euvolemic should be treated with vasoactive agents (eg, norepinephrine at 0.025-0.1 μg/kg/min; Table 20-4) prior to rapid pacing. These background agents facilitate smoother recovery of hemodynamic status while at the same time reducing the total amount of agents required to recover the patient. As the procedure progresses with further manipulation of the stenotic aortic valve, vasopressor support can be titrated to effect. Adequate systolic blood pressure is mandatory to maintain sufficient coronary perfusion and prevent subendocardial ischemia. After the
deployment of the valve, vasopressors should be weaned gradually as the patient’s hemodynamics return to normal.

Table 20-4 Different Inotropes and Vasopressors Used During Transcatheter Aortic Valve Replacement in the Cardiac Catheterization Laboratory

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bolus</th>
<th>Solution/Concentration/Dosage</th>
</tr>
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| Norepinephrine (Levophed) | No bolus | 4 mg in 250 mL D5W or NS  
Concentration is 16 μg/mL  
Maintenance is 0.01-1 μg/kg/min, titrated to effect |
| Phenylephrine (Neo-Synephrine) | 50-100 μg | 25 mg in 250 mL NS or D5W  
Concentration is 100 μg/mL  
Maintenance/ICU is 0.1-5 μg/kg/min, titrated to effect |
| Epinephrine (Adrenalin) | No bolus | 4 mg in 250 mL in D5W or NS  
Concentration is 16 μg/mL  
Maintenance is 0.01-1 μg/kg/min, titrated to effect |
| Dopamine (Intropin)    | No bolus | 400 mg in 250 mL D5W  
Concentration is 1600 μg/mL  
Maintenance is 2-20 μg/kg/min, titrated to effect |

Abbreviations: D5W, 5% dextrose in water; ICU, intensive care unit; NS, normal saline.

Not all patients are candidates for TAVR with conscious sedation. Patients requiring alternative access points (eg, transapical, transaortic, transcarotid, femoral cut down, retroperitoneal access for vascular conduit, transcaval) should have general anesthesia and a hybrid OR environment. Individuals with high tolerance for opioids or benzodiazepines, inability to lie flat for the duration of the procedure, severe obstructive sleep apnea, severe dementia with inability to cooperate, or poor acoustic windows for TTE should be considered for general anesthesia.

Patients undergoing general anesthesia will require longer recovery periods than those with moderate sedation; however, many patients can be extubated immediately after the conclusion of the TAVR procedure. The use of general anesthesia does not preclude patients from leaving the procedure room spontaneously ventilating, with transfer to a floor bed after a standard recovery period. Patients undergoing transapical/transaortic procedures or with severe sleep apnea are typically recovered in an intensive care setting with gradual weaning of mechanical ventilation.

By offering moderate sedation procedures in the CCL and general anesthetic in the hybrid OR, we are able to provide excellent outcomes at both locations while serving a greater number of TAVR patients overall. This hybrid practice should be considered in any center where hybrid room
availability or anesthesia staffing is at a premium.

Transfemoral TAVR can be successfully performed with moderate sedation in the CCL or with general anesthesia in the OR. Successful management of these patients requires additional equipment and personnel, whether a specially trained nurse is administering the sedation with midazolam and fentanyl, or an anesthesia team is providing deep sedation or general anesthesia with propofol, dexmedetomidine, volatile anesthetic, or a combination thereof. As of September 2014, our center has performed >250 TAVR procedures with moderate conscious sedation, and 95% of our patients with transfemoral access undergo the procedure awake in the CCL. Our initial experience comparing 140 patients with different levels of sedation demonstrated equivalent safety, a shorter length of stay, decreased resource utilization, and lower cost when using moderate sedation in the CCL.¹⁵

REFERENCES

5. American Society of Anesthesiologists. Standards for basic anesthetic monitoring. ASA Standards and Practice Parameters. Available at:


MULTIPLE CHOICE QUESTIONS

1. What sedation plane is described by responsiveness to verbal command accompanied by tactile stimulation, unaffected respirations, and cardiovascular stimulation?
   A. Minimal sedation/anxiolysis
   B. Moderate sedation
   C. Deep sedation
   D. General anesthesia
   E. Awake state

2. During a preoperative examination, a patient’s mouth was examined, and only a small part of the uvula and soft palate were visible. Which Mallampati score should be assigned?
   A. I
   B. II
   C. III
   D. IV

3. Which benzodiazepine has the shortest half-life and is the most practical in the setting of short procedural sedation?
   A. Midazolam
   B. Diazepam
   C. Lorazepam
   D. Flumazenil

4. Which sedating agent has as its target site a central α-receptor?
   A. Propofol
   B. Ketamine
   C. Dexmedetomidine
   D. Etomidate
   E. Midazolam

5. A patient with which of the following conditions is most appropriate for transcatheter aortic valve replacement (TAVR) under moderate sedation?
   A. Hypertension, obesity with body mass index of 53, heart failure,
orthopnea, obstructive sleep apnea
B. Diabetes, hypertension, dyslipidemia, esophageal stricture due to lye ingestion
C. Chronic obstructive pulmonary disease, aortoiliac occlusive disease
D. History of chronic back pain, claustrophobia, and panic attacks

ANSWERS

1. B

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. Moderate sedation/analgesia (conscious sedation) is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Deep sedation/analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required due to depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

2. C

Mallampati score is one of the tools that allow screening for potentially challenging airways.
- Class I: Soft palate, uvula, fauces, pillars visible
- Class II: Soft palate, uvula, fauces visible
- Class III: Soft palate, base of uvula visible
- Class IV: Only hard palate visible

3. A

The elimination half-life of midazolam is estimated to be approximately 3 hours, much shorter than the diazepam half-life of 30 to 60 hours and lorazepam half-life of 14 hours. That, coupled with rapid distribution of midazolam from the action site, accounts for rapid onset and offset of sedation. Flumazenil is a benzodiazepine antagonist that is not used for sedation routinely. Its half-life is short (4- to 11-minute redistribution and 40- to 80-minute elimination), which explains the occasional need to repeat reversal treatment, especially for overdose of a long-acting benzodiazepine.

4. C

Benzodiazepines, propofol, and etomidate all produce their sedating effect via the γ-aminobutyric acid receptor. Ketamine acts via an N-methyl-D-
aspartate receptor. Dexmedetomidine is a selective $\alpha_2$-agonist in the central nervous system, similarly to clonidine.

5. B

Patient B has a contraindication to transesophageal echocardiography probe placement and no indicated contraindication to sedation in the abbreviated medical history. The procedure can be done in the cath lab with sedation and transthoracic echocardiography. Patient A may have poor transthoracic echocardiography windows and inability to lay flat for prolonged periods of time, making TAVR under sedation potentially challenging. Patient C may require alternative access (transapical, transaortic, transcaval) to place her transcatheter valve, given her peripheral vascular disease. Patients in whom femoral cut down is required are also suboptimal candidates for TAVR under moderate sedation. Patient D will most likely be unable to tolerate prolonged sedation and immobility. While there is no clear-cut guideline about a patient’s psychosocial dysfunction impacting sedation, this patient would be better served with either deep sedation or general anesthesia in a hybrid operating room and under the care of an anesthesiologist.
Part IV  Procedures

21  Coronary and Left Ventriculographic Procedures: Special Considerations

22  Radial Approach to Coronary Angiography

23  Peripheral Angiography

24  Adjunctive Diagnostic Techniques: Fractional Flow Reserve

25  Adjunctive Diagnostic Techniques: Intravascular Ultrasound, Optical Coherence Tomography, and Spectroscopy

26  Emerging Clinical Applications of Physiologic and Intravascular Imaging Tools

27  Coronary Guidewire Manipulation

28  Coronary Balloon Angioplasty

29  Basic Stent Deployment Techniques

30  Drug-Eluting Coronary Stents

31  Special Stents: Bioresorbable Coronary Scaffolds
Drug-Coated Balloon Technologies: Technical Features and Clinical Applications

In-Stent Restenosis

Coronary Atherectomy: Concepts and Practice

Percutaneous Coronary Intervention in Chronic Total Occlusion

Intervention in Venous and Arterial Grafts

Special Considerations: ST-Segment Elevation Myocardial Infarction

Complex Lesion Intervention: Bifurcation, Left Main Coronary Artery, and Ostial Lesions

Special Considerations: Small Vessel and Diffuse Disease

Special Patient Subset: Diabetes Mellitus

Inoue-Balloon Mitral Valvuloplasty

Aortic Valvuloplasty

Patient Selection, Procedural Techniques and Complications of Balloon-Expandable Transcatheter Aortic Valve Replacement

Balloon-Expandable Transcatheter Aortic Valve Replacement

Clinical Outcomes With Self-Expanding Transcatheter Aortic Valve Bioprostheses

Pulmonary Balloon Valvuloplasty and Percutaneous Pulmonary Valve Implantation
Prior to Gruentzig’s seminal development of balloon angioplasty, coronary arteriograms were largely used to discriminate patients with and without coronary artery disease and to select those who should be referred for coronary bypass surgery. In the modern era, the cardiac interventionalist must be supremely competent in performing, interpreting, and understanding the studies that define the coronary anatomy and cardiac function. The unique demands of decision making for interventional cardiology require a new understanding of the principles and procedures that enable percutaneous coronary revascularization to be performed. To this end, acquiring high-quality diagnostic cardiac angiographic studies is critical. This chapter will review special considerations of coronary and left ventricular angiography.

INDICATIONS FOR CORONARY ARTERIOGRAPHY

In the 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines,¹
the indications for coronary arteriography are summarized as below:

1. Patients with stable angina or asymptomatic individuals with high-risk criteria on noninvasive testing.
2. Patients resuscitated from sudden cardiac death or having threatening ventricular arrhythmias.
3. Patients with unstable coronary syndromes of all varieties, including acute myocardial infarction as a preamble to primary angioplasty and those who developed complications of acute infarction.
4. Patients with ischemia at low levels of exercise in the recovery phase of myocardial infarction.
5. Patients with suspected or known coronary artery disease undergoing preoperative evaluation.
6. Patients undergoing heart valve replacement or in those patients in whom there is a need to establish the etiology of congestive heart failure. Table 21-1 lists indications and contraindications for cardiac catheterization and coronary angiography.

**Table 21-1A Indications for Coronary Angiography**
<table>
<thead>
<tr>
<th>Indications</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suspected or known coronary artery disease</td>
<td>LV, COR</td>
</tr>
<tr>
<td>a. New-onset angina</td>
<td>Lv, COR</td>
</tr>
<tr>
<td>b. Unstable angina</td>
<td>Lv, COR</td>
</tr>
<tr>
<td>c. Evaluation before a major surgical procedure</td>
<td>Lv, COR</td>
</tr>
<tr>
<td>d. Silent ischemia</td>
<td>LV, COR, ERGO</td>
</tr>
<tr>
<td>e. Positive exercise tolerance test</td>
<td>LV, COR, ERGO</td>
</tr>
<tr>
<td>f. Atypical chest pain or coronary spasm</td>
<td>LV, COR, ERGO</td>
</tr>
<tr>
<td>2. Myocardial infarction</td>
<td>LV, COR</td>
</tr>
<tr>
<td>a. Unstable angina post infarction</td>
<td>LV, COR</td>
</tr>
<tr>
<td>b. Failed thrombolysis</td>
<td>LV, COR, RH</td>
</tr>
<tr>
<td>c. Shock</td>
<td>LV, COR, RH</td>
</tr>
<tr>
<td>d. Mechanical complications (ventricular septal defect, rupture of wall or papillary muscle)</td>
<td>LV, COR, L+R</td>
</tr>
<tr>
<td>3. Sudden cardiovascular death</td>
<td>LV, COR, R + L</td>
</tr>
<tr>
<td>4. Valvular heart disease</td>
<td>LV, COR, R + L, AO</td>
</tr>
<tr>
<td>5. Congenital heart disease (before anticipated corrective surgery or ASD/PFO closure)</td>
<td>LV, COR, R + L, AO</td>
</tr>
<tr>
<td>6. Aortic dissection</td>
<td>AO, COR</td>
</tr>
<tr>
<td>7. Pericardial constriction or tamponade</td>
<td>LV, COR, R + L</td>
</tr>
<tr>
<td>8. Cardiomyopathy</td>
<td>LV, COR, R + L, BX</td>
</tr>
<tr>
<td>9. Initial and follow-up assessment for heart transplant</td>
<td>LV, COR, R + L, BX</td>
</tr>
</tbody>
</table>

Abbreviations: AO, aortography; BX, endomyocardial biopsy; COR, coronary angiography; ERGO, ergonovine provocation of coronary spasm; LV, left ventriculography; RH, right heart oxygen saturations and hemodynamics (eg, placement of Swan-Ganz catheter); R + L, right and left heart hemodynamics; ± = optional.
### Table 21-1B Contraindications to Cardiac Catheterization

- **Absolute Contraindications**
  - Inadequate equipment or catheterization facility
- **Relative Contraindications**
  - Acute gastrointestinal bleeding or anemia
  - Anticoagulation (or known, uncontrolled bleeding diathesis)
  - Electrolyte imbalance
  - Infection and fever
  - Medication intoxication (eg, digitalis, phenothiazine)
  - Pregnancy
  - Recent cerebrovascular accident (<1 month)
  - Renal failure
  - Uncontrolled congestive heart failure, high blood pressure, arrhythmias
  - Uncooperative patient


### CLINICAL ASSESSMENT PRIOR TO CORONARY ANGIOGRAPHY

The physician should not proceed to coronary angiography without the proper workup. The subtle clinical presentations of myocardial ischemia require diligent interpretation of the patient’s complaints. The judgment of a well-trained and knowledgeable physician skilled at taking an accurate history is critical to appropriate diagnosis and treatment. A superficial history identifying chest pain of any type is not a license to perform coronary arteriography. To establish the indications for coronary arteriography, results of the medical history, the electrocardiogram, and various other indices of myocardial ischemia are needed. Understanding the relationship of increased metabolic demands on fixed lesions and understanding the pathophysiology of acute coronary syndromes is fundamental to the practice of treating patients with ischemic heart disease. Depending on the clinical findings,
stress testing during exercise or at-rest (pharmacologic) stress testing with nuclear perfusion studies or echocardiographic imaging may be needed. Interventionsal cardiologists should not let their skills in interpreting these studies lapse and should not simply read the reports. The location and extent of ischemic defects, as well as the level of exercise performed, are important in determining the relative benefit of revascularization.

Noninvasive diagnostic imaging of the coronary arteries with electron beam computed tomography or multi-slice computed tomography can identify the presence of coronary artery disease. The detection of a large amount of calcium in the coronary arteries in young individuals heralds the presence of atherosclerosis, but does not confirm obstructive disease. Multi-slice computed tomography is accurate in identifying calcification in coronary arteries, the course of vessels, and a degree of coronary obstruction. In the future, such technology may supplant diagnostic coronary arteriography; however, at this time, coronary arteriography remains the standard for selecting patients for coronary interventions and for the planning and performance of the interventional procedure.

COMPONENT PROCEDURES OF CORONARY ANGIOGRAPHY

Coronary angiography and ventriculography is accomplished by a series of linked procedures beginning with vascular access and moving to angiographic catheter passage and engagement of coronary arteries and image acquisition through appropriate imaging angulations to display the critical features of the diseased artery. With the basic information of the angiograms, the interventional procedure can proceed as detailed elsewhere. Following the intervention, vascular hemostasis is performed for the particular method through a number of vascular closure devices.

Vascular Access

Vascular access for coronary angiography is performed from either the femoral or the radial artery. In the United States, the most popular approach has been femoral access, while the radial approach is favored outside the
United States. (The brachial artery should be reserved as access of last resort when the other arteries cannot be cannulated.) The radial approach has gained acceptance in the United States of late because of the increased safety associated with reduced access site bleeding. Any debate about which vascular access is better can be summarized in one sentence: Femoral access is quicker and easier, but with more complications, while radial access is more difficult and takes more skill and time, but has fewer complications. It should be noted that neither femoral nor radial access technique can be used exclusively, due to complicated anatomy and patient-specific factors. Hence, operators are required to learn and employ both access methods. We currently recommend radial access as the default approach. The new generation of cath lab operators should be able to do procedures from both approaches with the same facility and safety.

**Radial Artery Catheterization**

Compared to the femoral artery, the superficial location of the radial artery permits easy access, is not located near significant veins or nerves, and enables secure control of bleeding. In patients with a normal Allen’s test confirming a patent dual blood supply to the hand, concerns about radial artery occlusion are negligible. Importantly, patient satisfaction is enhanced by the ability to sit up and walk immediately after the procedure.

**Patient Selection and Use of the Allen’s Test**

The Allen’s test is used to demonstrate patency of both the ulnar and radial circulation through an intact palmar arch. Most operators require a normal or near-normal test before proceeding. The Allen’s test is performed as follows: After the patient makes a fist, both the radial and ulnar arteries are occluded simultaneously. When the hand is opened, it appears blanched. Release of the ulnar artery should result in return of pink hand color within 8 to 10 seconds. Satisfactory ulnar flow can also be documented by using the pulse oximeter. The pulse wave is displayed with both arteries open. The radial artery is then compressed and the pulse wave of ulnar flow observed. The results of the oximetric Allen’s test are divided into 3 grades of wave forms during radial artery occlusion: type A, no change in pulse wave; type B, a damped but distinct pulse wave; type C, loss of phasic pulse waveform. Radial artery cannulation can proceed with either type A or B and is not recommended for
type C or D (Fig. 21-1).

**FIGURE 21-1** Top, pulse oximeter displays radial pulse as transmitted to the thumb. Compression of the radial artery may result in 1 of the 4 patterns shown at right. Modified Allen’s test to assess patency of the palmar arterial arches. Barbeau Classification. The presence of an arterial waveform (even if delayed or with reduced amplitude) and a hemoglobin oxygen saturation >90% (Barbeau grades A, B, and C) confirms the adequacy of a collateral vascular supply to the hand. An arm with an abnormal modified Allen’s test result (Barbeau grade D) should be avoided.


In addition to type C Allen’s test, we also avoid patients who have forearm dialysis A-V fistulae or in whom the radial artery may be used for coronary artery bypass graft (CABG) surgery. In patients with CABG including a left internal mammary artery (LIMA) graft, the left radial approach is usually successful.
Use of the left radial artery approach provides easier manipulation of the Judkins shapes with minimal effort. The left arm should be brought over the abdomen so that the operator can work from his or her usual position on the right of the patient. In patients of small stature (under 5’5” in height) or those with CABG with LIMA, the left radial approach is preferred.

**Technique of Radial Artery Access and Catheter Selection**

The patient should be well sedated and comfortably positioned with a movable arm board allowing the arm to be positioned at the patient’s hip after radial sheath placement. The radial pulse is palpated, and lidocaine is given. Using a 0.018-in micropuncture needle, the artery is entered at 30° to 45° angulation.

Both arterial and venous access for either the femoral or radial approaches may be facilitated with ultrasonic direct visualization transducers (Fig. 21-2). Ultrasound access may be particularly valuable in patients who have altered anatomy, obesity, or scarring caused by prior surgical procedures (eg, peripheral vascular surgery, multiple prior catheterizations, or prior intraaortic balloon pumps [IABP] or support cannulas), where standard access technique may be unsuccessful.

![Figure 21-2](image-url)

**FIGURE 21-2** Technique of Ultrasound-Guided Radial Access. A. Axial position of draped ultrasound probe over the right radial artery. The needle is inserted just below the center of the probe when the artery is in the center of the image plane. B. Visualization of radial artery and veins. C. Compression causes closure of radial veins and reveals pulsatility of artery. D. Visualization of the needle tip (arrow) compressing and puncturing the artery. E. Confirmation of wire position (arrow) in

After introducing the guide wire and sheath, a vasodilator cocktail of verapamil or other calcium channel blockers can be given, followed by heparin or bivalirudin intravenously. The arm can now be moved to patient’s side for catheter introduction.

The most common catheters selected for the radial approach are the numerous specialized ‘universal’ shapes like the Jacky, TIG or multipurpose catheter (Fig. 21-3). A decrease in catheter exchanges has been shown to decrease the incidence of upper extremity vasospasm. The standard preformed diagnostic Judkins or Amplatzer catheter shapes may also be used, but require more manipulation. For selective engagement of the left coronary ostium, a Judkins left 3.5 catheter instead of the 4.0 size is typically used.
Femoral Artery Access and Catheter Selection

The femoral artery is palpated at the inguinal (groin) ligament which is often, but not always, denoted by the skin crease. Because of the uncertainty of external landmarks, a metal clamp can be laid over the proposed entry site visualizing the tip of the clamp over the medial edge of the middle of the head of the femur. The common femoral artery, between the lower edge of the inferior epigastric artery and above the bifurcation of the superficial and profunda branches, is the optimal location for introduction of the interventional sheaths and support devices (Fig. 21-4).

The importance of correct femoral puncture to avoid bleeding complications after interventional procedures in patients who are often intensely anticoagulated cannot be underestimated. The correct puncture site above the femoral bifurcation is a requirement for utilization of various arterial closure devices. A puncture site that is above the common femoral artery engenders the high risk of retroperitoneal bleeding and, in some elective procedures, may necessitate postponement of the interventional
portion of the procedure to another time when better access can be achieved. The steps to introduce a femoral artery sheath are similar to those for the radial artery sheath, and are described in detail elsewhere.\(^5\)

For the femoral procedure, the Judkins left (JL) catheter 4.0 size is the most commonly used for diagnostic studies (Fig. 21-5). In small aortic roots, a JL 3.5 catheter may be preferred, and, in very large aortic roots, it may be necessary to move to a JL 5.0 catheter. Right coronary artery cannulation is usually accomplished with the right Judkins catheter, but in cases of high origin or anomalous takeoff from the aorta, the Amplatz right catheter may be helpful. The Amplatz curve catheters are sometimes required for entry into an ectopically placed left coronary ostium and some very large aortic roots. The Amplatz left coronary catheter is helpful in intubating high and anteriorly placed right coronary ostia. Other catheters, such as the hockey stick curve, the multipurpose catheter and the Amplatz right catheter, as well as the internal mammary catheter, can sometimes be helpful in intubating right coronary arteries. Of particular help in the anteriorly placed ostium of the right coronary artery is the out-of-plane right coronary catheter (Williams catheter).

**FIGURE 21-5 Judkins catheters and pigtail ventriculography catheter.**

Operators should familiarize themselves with several of the unique catheters available for cases of difficult coronary arteriography. For example, there is a specially designed internal mammary artery catheter, left and right coronary bypass graft catheters, and the unique Amplatz curved catheters. The Amplatz left (AL) 2 catheter is used predominantly for the left coronary
artery and the AL 1 catheter most commonly for difficult right coronary intubation.

It is uncommon to perform coronary interventions with catheter sizes smaller than 6-French (Fr). For diagnostic studies, the most commonly used catheter sizes are 6-Fr, with some operators utilizing 5-Fr and, rarely, 4-Fr catheters. The advantage of 6-Fr diagnostic catheters over the 5-Fr and 4-Fr catheters is that their shape retention and torque control is optimal. While use of smaller size catheters may reduce femoral complications, most interventions require size 6-Fr to accommodate multiple stents or non-stent devices. While it is true that femoral vascular closure devices have reduced bleeding following the interventional procedures, their particular failure mode presents a source of continued concern in some patients.

**ANGIOGRAPHIC IMAGING ANGULATIONS FOR CORONARY INTERVENTIONS**

Before PCI, the angiographer should use experience and multiple angiographic projections to do the following:

1. Establish the relationship of the coronary ostium to the aorta for guide catheter selection.
2. Verify target vessel, pathway, and angle of entry.
3. Separate associated side branches and degree of ostial atherosclerosis.
4. Visualize distribution of collateral supply.
5. Determine the true (maximally vasodilated) diameter of the coronary artery at the target site. Angiography for coronary interventions requires establishing the lesion morphology, lesion length, degree of calcification, presence of thrombus and the associated involvement of side branches, and the extent of coronary artery disease which may lead to branch closure.

The routine coronary angiographic views used for diagnostic studies are normally incorporated into the interventionalist’s training and form the basic image set used for most interventions (Table 21-2). Individualized angiography projections may be needed to visualize the origin and course of
both the major and branch vessels in at least two different projections to eliminate branch overlap. Because of the wide variation in coronary anatomy, one should expect to use several modified views. The optimal projections for viewing various segments of the coronary tree are illustrated in Figures 21-6 through 21-9.

Table 21-2 Optimal Angiographic Views for Specific Coronary Artery Segments
<table>
<thead>
<tr>
<th>Coronary Segment</th>
<th>Origin/ Bifurcation</th>
<th>Course/Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main</td>
<td>AP</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>LAO cranial</td>
<td>LAO cranial</td>
</tr>
<tr>
<td></td>
<td>LAO caudal</td>
<td>LAO caudal</td>
</tr>
<tr>
<td>Proximal LAD</td>
<td>LAO cranial</td>
<td>LAO cranial</td>
</tr>
<tr>
<td></td>
<td>RAO caudal</td>
<td>RAO caudal</td>
</tr>
<tr>
<td>Mid-LAD</td>
<td>LAO cranial</td>
<td>RAO caudal</td>
</tr>
<tr>
<td></td>
<td>RAO cranial</td>
<td>RAO cranial, caudal, or straight</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>Lateral</td>
</tr>
<tr>
<td>Distal LAD</td>
<td>AP</td>
<td>RAO cranial</td>
</tr>
<tr>
<td></td>
<td>RAO cranial</td>
<td>RAO cranial</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>RAO cranial</td>
</tr>
<tr>
<td>Diagonal</td>
<td>LAO cranial</td>
<td>LAO cranial, caudal, or straight</td>
</tr>
<tr>
<td></td>
<td>RAO cranial</td>
<td>RAO cranial</td>
</tr>
<tr>
<td>Proximal circumflex</td>
<td>RAO caudal</td>
<td>LAO cranial</td>
</tr>
<tr>
<td></td>
<td>LAO caudal</td>
<td>LAO cranial</td>
</tr>
<tr>
<td>Intermediate</td>
<td>RAO caudal</td>
<td>RAO caudal</td>
</tr>
<tr>
<td></td>
<td>LAO caudal</td>
<td>RAO caudal</td>
</tr>
<tr>
<td>Obtuse marginal</td>
<td>RAO caudal</td>
<td>RAO caudal</td>
</tr>
<tr>
<td></td>
<td>LAO caudal</td>
<td>RAO caudal</td>
</tr>
<tr>
<td></td>
<td>RAO cranial</td>
<td>RAO cranial (distal marginals)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal RCA</td>
<td>LAO</td>
<td>LAO</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>LAO</td>
</tr>
<tr>
<td>Mid-RCA</td>
<td>LAO</td>
<td>LAO</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>RAO</td>
<td>RAO</td>
</tr>
<tr>
<td>Distal RCA</td>
<td>LAO cranial</td>
<td>LAO cranial</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>LAO cranial</td>
</tr>
<tr>
<td></td>
<td>RAO</td>
<td>RAO</td>
</tr>
<tr>
<td>PDA</td>
<td>LAO cranial</td>
<td>RAO</td>
</tr>
<tr>
<td>Posterolateral</td>
<td>LAD cranial</td>
<td>RAO</td>
</tr>
<tr>
<td></td>
<td>RAO cranial</td>
<td>RAO cranial</td>
</tr>
</tbody>
</table>

Abbreviations: AP, anteroposterior; LAD, left anterior descending artery; LAO, left anterior oblique; PDA, posterior descending artery (from RCA); RAO, right anterior oblique; RCA, right coronary artery.

*Horizontal hearts.
FIGURE 21-6 Commonly used angulations for coronary angiography. Top from left to right: right anterior oblique (RAO), anterior posterior (AP), left anterior oblique (LAO). Middle: AP projection; Bottom left: cranial angulation, caudal angulation.

FIGURE 21-7  A. Left panel: Diagrammatic representation of the left anterior oblique (LAO) left coronary arteriogram. The image intensifier is above the patient in the LAO position, and the x-ray beam travels in a posterior-to-anterior direction. The value of this view depends in large part on the orientation of the long axis of the heart. When the heart is relatively horizontal, the left anterior descending (LAD) coronary artery and diagonal branches are seen end-on throughout much of their course. In this illustration, the heart is in an intermediate position, and there is moderate foreshortening of the LAD and diagonal branches in their proximal portions. The left anterior oblique (LAO) projection is frequently inadequate to visualize the proximal LAD and its branches; the left main branch, which is directed toward the image tube and therefore foreshortened; and the proximal circumflex coronary artery, which may be obscured by overlapping vessels as in this illustration. The LAO projection is frequently used to visualize the proximal circumflex artery when there is not overlap, the distal LAD and its branches, the mid circumflex coronary artery in the atrioventricular groove, and the distal right coronary artery when it is filling via collaterals from the left coronary artery. (D1, D2, D3 = first, second, third diagonal; OM = obtuse marginal; SP = septal perforator.) (Reproduced from King SB III, Douglas JS Jr, Morris DC. New angiographic views for coronary arteriography. In: Hurst JW, ed. Update IV: The Heart. New York, NY: McGraw-Hill; 1981.)  

Right panel: Diagrammatic illustration of the left coronary arteriogram in the 45° left anterior oblique (LAO) view with 30° cranial angulation. The image intensifier is on the patient’s left and the direction of the x-ray beam is posterior to anterior. This is the most valuable view of the left coronary artery in most patients. Foreshortening of the left main and proximal LAD arteries and diagonal branches, which occurs in the LAO view, is usually overcome by cranial angulation of the intensifier. The proximal...
left coronary artery segments are usually visualized at an angle almost perpendicular to their long axis. The ostium of the left main coronary artery, the proximal portion of the LAD, and the origin of the diagonal branches are usually well visualized without overlap. Some overlap may occur with branches of the proximal circumflex coronary artery, and this may be overcome by using a 60° LAO with 30° cranial angulation. The value of the LAO cranial view is considerably less when the proximal left coronary artery has a cephalad direction, in which case caudal angulation of the image intensifier is frequently helpful. (D1, D2, D3 = first, second, third diagonal; OM = obtuse marginal; SP = septal perforator.) (Reproduced from King SB III, Douglas JS Jr, Morris DC. New angiographic views for coronary arteriography. In: Hurst JW, ed. Update IV: The Heart. New York, NY: McGraw-Hill; 1981.) B. Cineangiographic frames of left coronary artery in the LAO. Left: Cranial projection. Right: Caudal projection.
FIGURE 21-8  A. Left: Diagrammatic illustration of the left coronary arteriogram in
the 15° right anterior oblique (RAO) view with 30° cranial angulation. This view is particularly helpful in analyzing the mid–left anterior descending (LAD) coronary artery and the origin of diagonal arteries and septal perforating arteries. Overlap with diagonal branches is usually avoided. The origin of the circumflex artery may be well seen, as in this illustration. (D1, D2, D3 = first, second, third diagonal; OM = obtuse marginal; SP = septal perforator.) (Reproduced from King SB III, Douglas JS Jr, Morris DC. New angiographic views for coronary arteriography. In: Hurst JW, ed. Update IV: The Heart. New York, NY: McGraw-Hill; 1981.) Right: Diagrammatic illustration of the left coronary arteriogram in the 30° right anterior oblique (RAO) view with 15°caudal angulation of the image intensifier. The image intensifier is positioned over the patient’s liver and the direction of the x-ray beam is posterior to anterior. This view is helpful to unravel overlapping diagonal branches to better visualize the proximal portion of the circumflex coronary artery, whose long axis was parallel to the x-ray beam in the routine RAO view, and to better visualize the mid–lateral anterior descending (LAD) artery, which overlaps diagonal branches in the standard RAO views. In this illustration, the mid-LAD is well visualized, as is a portion of the first diagonal not well visualized in the RAO view. There is slight unfolding of the proximal circumflex artery as well. (D1, D2, D3 = first, second, third diagonal; OM = obtuse marginal; SP = septal perforator.) (Reproduced from King SB III, Douglas JS Jr, Morris DC. New angiographic views for coronary arteriography. In: Hurst JW, ed. Update IV: The Heart. New York, NY: McGraw-Hill; 1981.) B. Cineangiographic frames of left coronary artery in the RAO. Left: Cranial projection. Right: Caudal projection.
**FIGURE 21-9** A. Diagrammatic illustration of the right coronary artery in the 45° left anterior oblique (LAO) projection. The image intensifier is positioned on the patient’s left and the x-ray beam travels in a posterior-to-anterior direction. This view is excellent for visualizing the proximal, mid, and distal right coronary artery in the
atrioventricular groove, because the direction of the x-ray beam is perpendicular to these arterial segments. Ostial lesions of the right coronary artery are not well visualized if the proximal right coronary artery takes an anterior direction from the aorta and therefore travels in a direction parallel to the x-ray beam. This can usually be overcome by turning to a steeper LAO projection. The posterior descending (PD) and left ventricular (LV) branches of the right coronary artery, which pass down the posterior aspect of the heart toward the apex, may be severely foreshortened, because the long axis of these vessels is in the same direction as the x-ray beam. The proximal portion of the posterior descending branches can be visualized by cranial angulation of the overhead intensifier or using a right anterior oblique view with cranial angulation. (Reproduced from King SB III, Douglas JS Jr, Morris DC. New angiographic views for coronary arteriography. In: Hurst JW, ed. Update IV: The Heart. New York, NY: McGraw-Hill; 1981.) B. Cineangiographic frames of right coronary artery in the LAO. Left: Cranial projection. Right: RAO projection.

OVERCOMING PITFALLS IN THE INTERPRETATION OF CORONARY ANGIOGRAMS

Foreshortening

To estimate the length of target lesions, the coronary artery segment containing the lesion should be viewed en face. The x-ray beam should be perpendicular to the artery segment in question to demonstrate that the segment achieves its maximum length.

Vessel Size

Estimation of vessel size usually is performed by comparison with the angiographic catheter shaft. Larger angiographic catheters, such as 6-Fr and 7-Fr, provide easier calibration than smaller catheters. For best vessel size estimation, the operator must obtain views in which the catheter tip and the segment in question are at the same level relative to the x-ray tube and the image intensifier. Out-of-plane magnification errors will result if the catheter tip and arterial segment are different distances from the image intensifier. An example of such an error would be judging the size of the mid–anter
descending artery in the left anterior oblique cranial view. In this view, the anterior descending artery is foreshortened and closer to the image intensifier than the catheter tip seated in the aorto-ostium further away. This perspective would cause the image of the catheter to be magnified while decreasing magnification of the anterior descending artery, making it appear smaller than its actual size.

**Lesion Length**

Measurement of the length of the lesion should be accomplished using views in which foreshortening has been minimized. The most accurate measures of the lesion length are accomplished with guidewires having calibration marks or with balloon catheters utilizing the known distance between markers. Estimates of lesion length can be made from the diagnostic angiogram, however, by calibrating the guide catheter and then performing quantitative angiographic assessment of the lesion length. Although experienced interventionalists can often estimate lesion length from diagnostic angiograms within a reasonable margin of error, final assessment of lesion length should be obtained at the time of the interventional procedure. The assessments of edges of the lesion are often subjective due to the limited resolution of the angiogram. For the most precise determination of lesion length, intravascular ultrasound may be required.

**Bifurcations**

Bifurcations are best visualized from a perspective without branch overlap. Accurate visualization of a bifurcation lesion is critical in planning for the best interventional approach to assess the lesion severity, and to avoid plaque shifting and loss of side branches. Common views for left anterior descending diagonal bifurcations are left anterior oblique cranial views and occasionally anteroposterior cranial views; for the circumflex marginal branches, the right anterior oblique caudal views; and for the right coronary artery posterior descending bifurcation, the shallow left anterior oblique cranial view.

**Poor Contrast Opacification**
Contrast streaming or poor filling of the vessel may lead to a false impression of lesion severity or presence of a thrombus. Inadequate contrast opacification may appear as a luminal irregularity. Enhanced contrast delivery can be achieved by obtaining better coaxial engagement of the guiding catheter, using a larger bore catheter, injecting during phase 3 of the Valsalva maneuver, or using a power injector.

**Catheter-Induced Spasm**

Catheter-induced spasm may appear as a fixed atherosclerotic stenotic lesion. Catheter spasm usually occurs near the tip of the catheter and has been observed in both right and left (and left main) coronary arteries. Vasospastic areas may be single and proximal or may be multiple and located some distance from the coronary ostium. Nitroglycerin should be administered in every case of an ostial lesion not previously evaluated prior to initiating intervention. Repositioning of the catheter and administration of nitroglycerin (100-200 mcg through the catheter) may resolve the dilemma.

**Left Main Artery Angiography**

The left main aorto-ostial and mid-body lesions can be easily demonstrated in standard orthogonal views, but the distal left main coronary artery (LM) with left anterior descending/circumflex (LAD/CFX) ostial narrowings may be more difficult to delineate (Fig. 21-10). As in cases of any bifurcation angiography, branch overlap must be minimized. Optimal views to identify the LM remain the same as for those during diagnostic studies, with a shallow right anterior oblique (RAO) with cranial or caudal angulation often providing an excellent view. In addition, complementary LAO caudal view (spider view) will display the LM in an orthogonal projection. An additional problem is the appreciation of the hemodynamic significance of the left main stenoses especially when the angiographic narrowing is of questionable severity. For this situation, fractional flow reserve measurement (FFR) can provide the hemodynamic lesion severity. LM FFR (>0.80) has a low 5-year major adverse cardiac event rate comparable to that of CABG for FFR (<0.80).
Anomalous Coronary Artery Angiography

The most common coronary anomaly is origin of the circumflex artery arising from the right coronary cusp (Fig. 21-11). The vessel may come from the right coronary artery itself or separately just anterior to the right coronary ostium. Commonly, it arises in a caudal direction, and the multipurpose catheter is frequently helpful in selective cannulation of this vessel.
When the right coronary artery arises from the left coronary cusp, it is anterior to the left coronary ostium and sometimes can be cannulated with a left Judkins catheter or a long-tipped multipurpose catheter. The Amplatz L2 catheter is usually successful in engaging the ectopic origin of the right coronary artery from the left cusp. A discussion of the angiography of anomalous coronary arteries is provided in more detail elsewhere. PCI for these arteries is performed in a routine fashion once stable guide catheter position is achieved.

**Angiographic Lesion Severity**

The severity of a coronary stenosis is usually expressed as percent diameter and cross-sectional area reduction relative to the adjacent normal distal angiographic segment. Intravascular ultrasound imaging studies have shown that angiographic ‘normal’ segments are frequently not normal and therefore the reference vessel size may be underestimated. Adaptive (either positive or negative) arterial remodeling in response to atherosclerotic plaque...
accumulation further complicates assessment of lesion severity. Regardless of
the limitations, the minimal lumen diameter, percent diameter, or area
reduction, compared with the ‘normal’ reference segment, remain the
standards. Figure 21-12 shows the classic relationship of lesion severity to
flow reduction as identified in the experiments of Gould. In defining
angiographic lesion severity, experimental animal studies showed that
increasing coronary stenosis severity was associated with a predictable
decine in coronary flow reserve (CFR). CFR begins to decline at about a
60% artery diameter narrowing and, hence, it was thought that such
narrowings carried physiologic importance. This is a truth in the animal but
not the human experiment models, because CFR in humans is the sum of the
epicardial flow and the microvasculature. Thus, an abnormal CFR may
accompany a vessel with only a minimal degree of narrowing and, hence, the
correlation between angiographic lesion severity and CFR is poor. At
diameter stenoses >80% to 90%, all available coronary reserve has been
exhausted and resting flow begins to decline. Although on-line quantitative
assessment is available in many laboratories, it is seldom used in the
decision-making process. Although some form of quantitative angiography is
helpful for reproducibility, the functional significance of any lesion,
especially those in the intermediate range, should be determined by direct
measurements such as FFR. The degree of an angiographic narrowing
(stenosis) is reported as the estimated percentage lumen reduction of the most
severely narrowed segment compared to the adjacent angiographically
normal vessel segment, seen in the worst x-ray projection (Fig. 21-13).
Because the operator uses visual estimations, an exact evaluation is
impossible with a ± 20% variation even among experienced angiographers.
Stenosis severity alone should not always be assumed to be associated with
abnormal physiology (flow) and ischemia. Moreover, coronary artery disease
is a diffuse process and thus minimal luminal irregularities over a long
segment of the artery may produce abnormal flow despite appearing as non-
obstructive CAD. Area stenosis is always greater than diameter stenosis and
assumes the lumen is circular, whereas the lumen is usually eccentric. In
general, 4 categories of lesion diameter severity can be assigned:
FIGURE 21-12 The relation of resting mean blood flow (dotted line) and hyperemic flows (solid line) to percentage of arterial diameter reduction. Flows are expressed as ratios to control resting mean values at the beginning of the experiment. The shaded area represents the range of values measured in individual dogs: $r$ = correlation coefficient; $\text{SQ DEV} =$ mean square of deviations. (Reprinted from Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. *Am J Cardiol*. 1974;33(1):87-94, Copyright © 1974, with permission from American College of Cardiology Foundation.)
1. Minimal or mild CAD, with narrowings <50%
2. Moderate CAD, with stenosis between 50% and 75%
3. Severe CAD, with stenosis between 75% and 95%
4. Total occlusion

**Ischemia and Angiographic Lesion Severity**

Stenosis severity is an anatomic variable and may not always represent abnormal physiology (or ischemia), especially for lesions 40% to 70% narrowed. Anatomic factors producing resistance to coronary flow include morphologic lesion characteristics such as entrance angle, length of disease, length of stenosis, minimal lumen diameter, minimal lumen area, eccentricity of lumen, area of reference vessel segment, and viscosity (Fig. 21-14). To determine hemodynamic lesion severity and propensity to be associated with ischemia, translesion pressure ratios at maximal coronary flow, called the fraction flow reserve (FFR), is an in-lab standard prior to proceeding to intervention in the absence of other objective evidence of ischemia.\(^8\)\(^9\)

**Coronary Stenosis Morphology**

The morphology of the lesion can help guide the interventional approach.
The presence of angiographic calcifications may require the use of intravascular ultrasound to determine whether rotary ablation should be employed before stenting. The presence of angiographic lumen filling defects may prompt use of mechanical thrombectomy. Ulcerations and irregularities within lesions may identify them as culprit lesions in the acute coronary syndrome patient.

There are a number of general descriptive characteristics of the stenoses which aid the interventionalist in assessing the risk and outcome of the procedure. These characteristics include: tortuosity; arterial calcification; sequential or tandem lesions; length; eccentricity; ostial location (either aorto-ostial or branch ostium); bifurcation or side branch involvement; smooth, irregular, or ulcerated lumen contour; or thrombus. Intravascular ultrasound or optical coherence tomography (OCT) imaging of stenosis defines lumen and plaque characteristics better than angiography (Fig. 21-15).
FIGURE 21-15 Top panel shows ultrasound cross-sectional images of atherosclerotic vessel narrowing. Plaque characteristics, lumen and reference vessel area are more accurately quantitated with intravascular ultrasound than with angiography. Lower panels show optical coherence tomographic images of coronary plaque erosion (A), rupture (B), and thrombus (C).

Determination of Coronary Flow by Angiography

In the setting of acute myocardial infarction interventions, angiographic coronary flow rates predict short- and long-term outcomes. The relative flow in coronary arteries has been classified according to the TIMI (thrombolysis in myocardial infarction) flow scale, as follows:

- TIMI 0 (no flow).
- TIMI 1 (opacification of the distal vessel without runoff).
- TIMI 2 (reduced flow compared with non-obstructed arteries).
- TIMI 3 flow (flow in the affected artery that is equal to other unobstructed arteries).

To quantitate TIMI flow rates, the number of angiographic frames required for contrast media to traverse the coronary artery is reported.\(^\text{10}\) The number of frames from the initial appearance of the dye in the coronary artery to a distal predetermined landmark is calculated. Gibson has proposed a correction of this frame count called the corrected TIMI frame count, which uses the frame count from the ostial opacification to pre-specified distal targets in the left anterior descending artery such as the apical LAD bifurcation; the distal target in the circumflex artery is the distal bifurcation of the terminal segments, and for the right coronary artery as the first branch of the posterolateral artery.\(^\text{10}\) Because the anterior descending artery is longer than the other vessels, the normal TIMI frame count for the left anterior descending artery is 36; for the circumflex artery, 21; and for the right coronary artery, 22. The corrected TIMI frame count divides the anterior descending count by 1.7 to equate the three vessels. TIMI frame counts have been found to be of value in judging clinical response after reperfusion therapy in the setting of acute syndromes.

**CHRONIC TOTAL OCCLUSIONS**

Percutaneous coronary intervention (PCI) of a chronic total occlusion (CTO), defined as a total occlusion (with TIMI grade 0 flow) of >3 months’ duration, is one of the most technically challenging lesions with significantly lower success rates of crossing the lesions with the usual guide wires. PCI success rates for CTOs are reported in the 50% to 80% range (compared to >80%-90% for occlusions <3 months old). Recent developments and dedicated operators using both antegrade and retrograde approaches to CTO are increasing the success rates of recanalization. Newer techniques with specialized guide wires, retrograde access, and subintimal reentry methods increase the success rate to nearly 90%.\(^\text{11,12}\)

Numerous features have been identified that predict the ability to cross chronic total occlusions, including whether there is a tapering into the
occlusion or “a beak.” This angiographic appearance sometimes signals the presence of small recanalized channels within a total occlusion and correlates with an increased success rate from interventions. Conversely, there is a lower chance of success in patients with total occlusions that are abruptly occluded.

The least favorable appearance is the total occlusion that terminates in a side branch at the exit of the total occlusion; this scenario can cause wires to migrate into that side branch, minimizing the ability to cross the total occlusion. Other characteristics that influence success include the curvature of the artery at the site of the total occlusion and beyond it, and, especially, the length of the total occlusion. CTO PCI mortality rate is reported to be 0% to 2% and emergency coronary artery bypass surgery <1% to 2%. Abrupt vessel closure following CTO PCI may occur in up to 5% to 10% of patients, but is often clinically silent, depending on the collateral supply.

**Collateral Vessel Angiography**

Visualization of collateral circulation from contralateral or ipsilateral injections can identify the length of the total occlusion and thereby influence the chance for success from interventional procedures. Such an assessment of total occlusions is very important in selecting patients for attempted intervention versus continued medical therapy or bypass surgery.

The observation of collateral flow is used to estimate whether ischemia will be improved by revascularization. It is unusual to have no collateral filling into segments of viable myocardium in the chronic phase of CAD. Collateral flow is a sign that viable myocardium potentially exists in those zones. Examination of the left ventriculogram in combination with the collateral filling to discrete myocardial zones can help predict which patients will benefit symptomatically from reperfusion therapy.

The opacification of a vessel beyond a totally occluded segment from antegrade or retrograde contrast is defined as collateral filling. The collateral circulation is graded angiographically as follows:

**Grade Collateral Appearance**

0  No collateral circulation
1  Very weak (ghostlike) opacification
2. Opacified segment, less dense than the feeding vessel and filling slowly
3. Opacified segment as dense as the feeding vessel and filling rapidly

Important features for making decisions about which vessels might be protected or lost during the intervention include whether the collateral supply is ipsilateral (eg, same-side filling, proximal RCA to distal RCA collateral supply) or contralateral (eg, opposite-side filling, LAD artery to distal RCA collateral supply) or whether collateral filling forward (anterograde) or backward (retrograde).

**Left Ventriculography**

The left ventriculogram provides information about overall and regional myocardial function. Abnormal wall motion indicates the presence of coronary ischemia, infarction, aneurysm, or hypertrophy. Left ventriculography also provides quantitative information, such as the ventricular volumes, the ejection fraction, presence of hyperdynamic contraction, and valvular regurgitation. Left ventricular ejection fraction predicts the long-term outcome of patients with CAD.

Ventriculography may be performed before or after coronary angiography. Because ventricular function can be obtained through noninvasive methods, most accurately with echocardiography, ventriculography can be deferred in some patients with renal insufficiency, severe left main coronary stenosis, or aortic stenosis. Low-volume, nonionic, low-osmolar contrast ventriculograms can be performed with little or no complications related to myocardial depression, hypotension, or arrhythmias. The indications, contraindications, and complications for ventriculography are shown in Table 21-3.

**Table 21-3 Indications and Complications of Left Ventriculography**

<table>
<thead>
<tr>
<th>Indications:</th>
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<tbody>
<tr>
<td>1. Identification of LV function for patients with coronary artery disease, myopathy, or valvular heart disease</td>
</tr>
<tr>
<td>2. Identification of ventricular septal defect</td>
</tr>
<tr>
<td>3. Quantitation of the degree of mitral regurgitation</td>
</tr>
<tr>
<td>4. Quantitation of the mass of myocardium for regression of hypertrophy or other similar research studies</td>
</tr>
</tbody>
</table>
Indications for right ventriculography are as follows:

1. Documentation of tricuspid regurgitation
2. Assessment of RV dysplasia for arrhythmias
3. Assessment of pulmonary stenosis
4. Assessment of abnormalities of pulmonary outflow tract
5. Assessment of right-to-left ventricular shunts

Complications:

1. Cardiac arrhythmias, especially non-sustained, brief VT, do not require treatment. Sustained VT and ventricular fibrillation require immediate cardioversion. *Note:* Arrhythmias and staining (see below) are more common with the use of end-hole catheters than with pigtail catheters
2. Intramyocardial contrast media staining during power injection (generally transient and of no clinical importance unless it is deep or perforating producing tamponade)
3. Embolism (thrombi or air)
4. Contrast-media related complications
5. Transient hypotension (<15-30 seconds) is common with ionic high osmolar contrast media

There are 3 specialized catheters—the pigtail, Halo, and multipurpose (MP)—used for ventriculography. The pigtail catheter is the safest and most commonly used. The preshaped circular tip has an end hole and 6 to 12 side holes on the catheter shaft above the curve. The method of catheter passage into the LV is described elsewhere. Once inside the ventricle, the catheter can be placed in front of the mitral valve with the loop directed toward the apex, away from the valve (in the RAO position). An angled (145°) pigtail catheter may be helpful for this purpose, especially for horizontally oriented hearts.

Abbreviations: LV, left ventricular; RV, right ventricular; VT, ventricular tachycardia.

A Halo catheter is a novel 5-Fr catheter with a perpendicular helical tip with inward-and-upwardly directed tip. The side holes are located on the helix (not the shaft) and produce ventriculograms without ectopy since the contrast jets are directly inwardly and not to the myocardium. Because there are no side holes on the shaft, it is ideal to measure distal left ventricular chamber pressure in patients with presumed hypertrophic obstructive
cardiomyopathy.

The multipurpose (MP) and other end-hole type catheters should not be used for ventriculography because of the increased risk of ventricular tachycardia, contrast injection in the myocardial tissue (contrast staining), or ventricular perforation.

In patients with CAD, left ventriculography may show asynchronous myocardial contractility relating to long term prognosis. Each of 5 myocardial segments may be graded as being either normal in contraction, hypokinetic, akinetic (no motion), or dyskinetic with paradoxical systolic expansion (Fig. 21-16 and Fig. 21-17). In the poorly contracting ventricle, myocardial viability is suggested by the thickness and movement of the impaired LV segment. Whereas akinetic and dyskinetic segments are often judged to have a low chance of recovery, more recent magnetic resonance assessments of viability have shown that even quite thin arterial segments can undergo significant recovery after revascularization.

Complications of Coronary and Ventricular Angiography

For diagnostic catheterization, analysis of the complications in more than 200,000 patients indicated the incidence of risks as follows: death, less than 0.2%; myocardial infarction, less than 0.05%; stroke, less than 0.07%; serious ventricular arrhythmia, less than 0.5%; and major vascular complications (thrombosis, bleeding requiring transfusion, or pseudoaneurysm), less than 1% (Table 21-4). Vascular complications occurred more frequently when the brachial approach was used and least when the radial approach was used. Risks are increased in well-described subgroups (Table 21-5).

Table 21-4 Complications of Cardiac Catheterization

<table>
<thead>
<tr>
<th>Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>
Myocardial infarction
Ventricular tachycardia, fibrillation, or serious arrhythmia

**Other Complications**

Aortic or coronary dissection
Cardiac perforation, tamponade
Congestive heart failure
Contrast reaction, anaphylaxis, nephrotoxicity
Heart block, asystole
Hemorrhage (local, retroperitoneal, pelvic)
Infection
Protamine reaction
Supraventricular tachyarrhythmia, atrial fibrillation
Thrombosis, embolus, air embolus
Vascular injury, pseudoaneurysm
Vasovagal reaction


**Table 21-5 Conditions of Patients at Higher Risk for Complications of Catheterization**

Acute myocardial infarction
Advanced age (>75 years)
Aortic aneurysm
Aortic stenosis
Congestive heart failure
Diabetes
Extensive three-vessel coronary artery disease
Left ventricular dysfunction (left ventricular ejection fraction <35%)
Obesity
Prior cerebrovascular accident
Renal insufficiency
Suspected or known left main coronary stenosis
Uncontrolled hypertension
Unstable angina


The most potentially lethal condition leading to complications of diagnostic coronary arteriography is the presence of severe left main coronary artery stenosis, particularly ostial involvement. Placement of the diagnostic catheter into the coronary ostium, especially if it causes disruption of plaque, may lead to immediate hemodynamic instability and a downward spiral. All physicians performing angiography should be prepared to administer vasopressor agents immediately should blood pressure fall in the setting of left main artery stenosis. Increasing the filling pressure as quickly as possible is critical if one is to avoid the spiral of decreased coronary flow leading to decreased contractility and further decreases in arterial pressure. In centers equipped with interventional cardiology equipment, an early decision for urgent angioplasty and stenting as a bail-out technique for left main artery occlusion should always be added to the armamentarium. Lesser degrees of emergency can be dealt with using vasopressor agents, followed by catheter-based LV hemodynamic support (eg, IAPB or Impella) to stabilize the situation, and then definitive surgery; however, it is sometimes impossible to stabilize the patient quickly enough using these measures, and the emergency placement of left main artery stents has, in some cases, been lifesaving.

**Contrast-Induced Nephropathy (CIN)**

The most common contrast media for PCI is nonionic or low-osmolar contrast agents because of safety, patient tolerance, and cost.\(^{15,16}\) Any iodine-based intravascular contrast media may cause acute renal failure following PCI, called contrast-induced nephropathy (CIN). CIN is typically defined as a relative increase in serum creatinine of >25% or an absolute increase >0.5 mg/dL. While it is not uncommon to develop transient increases in serum
creatinine, it is rare to need temporary dialysis and even rarer to need permanent dialysis following CIN. The time course of CIN demonstrates an increase in creatinine starting in 12 to 24 hours for most patients, but it may take as long as 48 to 96 hours to peak. Mehran, et al developed a validated risk scoring system in order to predict the likelihood of developing CIN.\(^\text{17}\)

In high risk patients, CIN prevention consists of preprocedure hydration and limitation of the contrast volume administered. No specific pharmacologic regimen has been demonstrated to reduce CIN. Limiting the volume of contrast media is an important goal for both the diagnostic and interventional aspects of the procedure, since many procedures are combined. If prior coronary arteriograms have been obtained, it may be possible to avoid repeating unnecessary views and, if there has been no clinical change, it may also be possible to avoid ventriculography.

In patients at high risk for CIN, left ventriculography may be deferred in favor of echocardiography. Optimal views should be obtained, preferably in biplane imaging if available (Figure 21-18). Unnecessary additional views should be avoided. Rotational angiography (ie, rotating the x-ray tube or image tube gantry throughout an arc during coronary injection, thereby obtaining multiple views of the arteries with a single coronary injection) may be another method to reduce contrast volume in CIN-prone patients.
FIGURE 21-18 The cardiac cath lab with biplane cineangiographic imaging C-arms in place.

SUMMARY

Percutaneous coronary interventions must be based on accurate information supplied by the coronary arteriogram and left ventricular functional measurements. Inaccurate or poorly performed coronary angiography can lead to an erroneous decision for both the selection of appropriate candidates and for the performance of the interventional procedure.

As interventional procedures continue to evolve into more intricate and novel device applications including new bioabsorbable and second generation drug-eluting stents, debulking techniques and physiologic lesion assessment (eg, FFR), intravascular ultrasound and optical coherence imaging, the interventionalist must not forget the more “mundane” activity of coronary arteriography. The successful procedure must start with the proper clinical assessment and accurate diagnostic testing, including basic coronary angiography and ventriculography, to deliver the highest quality outcomes of coronary interventions.

REFERENCES


MULTIPLE CHOICE QUESTIONS

1. A 59-year-old man is admitted to the emergency department with chest pain that has mostly resolved. The ECG shows nonspecific ST-T changes. Of the following, what is an indication for urgent coronary angiography?
   A. Frequent PVCs
   B. Elevated troponin
   C. Decreased ejection fraction on echocardiography
   D. Hypotension corrected by IV fluids

2. During coronary angiography, the operator notes a very long ‘left main’ segment. Which is the most common coronary anomaly associated with this finding?
   A. Right coronary artery (RCA) originating from the Left coronary sinus
   B. Left main originating from the right coronary sinus
   C. High take-off of the RCA
   D. Circumflex artery originating from the right coronary artery
   E. Single coronary originating the non-coronary cusp

3. The operator has finished the diagnostic portion of the angiography and is
preparing to perform percutaneous coronary intervention (PCI) when a cardiology fellow suggests that the 60% narrowing of the left anterior descending (LAD) artery is occurring in an area opposite that identified on the stress test. What is the best way to determine if this lesion is appropriate for revascularization?
A. Quantitative analysis of the angiogram
B. Intravascular ultrasound imaging
C. Optical coherence tomography
D. Defer the PCI and repeat the stress test
E. Fractional flow reserve measurement (FFR)

4. A 72-year-old man undergoes a stress exercise test and develops chest pain and new ST-segment elevation in anterior leads and AVR. All ST changes resolve on recovery, but there is persistent ST elevation in AVR. The patient is pain free and after an overnight stay in the critical care unit (CCU), undergoes cardiac catheterization and angiography. Which of the following most likely explains the clinical scenario?
A. Exercise-induced vasospasm
B. Congestive heart failure with sudden decompensation
C. Left main stenosis
D. Takasubo cardiomyopathy
E. Proximal left anterior descending (LAD) artery stenosis

5. An 81-year-old woman with diabetes mellitus, hypertension, peripheral vascular disease, and creatinine of 1.5 mg/dL is scheduled to undergo cardiac catheterization and angiography. Which of the following is the best prevention to reduce the chances of contrast-induced nephropathy (CIN)?
A. Lasix (furosemide) before the procedure
B. 500 to 1000 mL of normal saline before the procedure
C. Nifedipine 10 mg orally, 3 days before the procedure
D. Mannitol, intravenously, on the day of the procedure
E. N-Acetylcysteine (Mucomyst), orally, 3 days before the procedure

ANSWERS
1. B

This patient has a non-ST segment elevation myocardial infarction (NSTEMI) and the timing of catheterization will be related to his event risks. Other indications for catheterization as noted in the 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for coronary arteriography are summarized below:

1. Patients with stable angina or asymptomatic individuals with high-risk criteria on noninvasive testing.
2. Patients resuscitated from sudden cardiac death or having threatening ventricular arrhythmias.
3. Patients with unstable coronary syndromes of all varieties, including acute myocardial infarction as a preamble to primary angioplasty and those who developed complications of acute infarction.
4. Patients with ischemia at low levels of exercise in the recovery phase of myocardial infarction.
5. Patients with suspected or known coronary artery disease undergoing preoperative evaluation.

2. D

The most common coronary anomaly is origin of the circumflex artery arising from the right coronary cusp (See Fig. 21-11). The vessel may come from the right coronary artery itself or separately just anterior to the right coronary ostium. Commonly, it arises in a caudal direction, and the multipurpose catheter is frequently helpful in selective cannulation of this vessel.

When the right coronary artery arises from the left coronary cusp, it is anterior to the left coronary ostium and sometimes can be cannulated with a left Judkins catheter or a long-tipped multipurpose catheter. The Amplatz L2 catheter is usually successful in engaging the ectopic origin of the right coronary artery from the left cusp. Percutaneous coronary intervention (PCI) for these arteries is performed in a routine fashion once stable guide catheter position is achieved.
Stenosis severity is an anatomic variable and may not always represent abnormal physiology (or ischemia), especially for lesions 40% to 70% narrowed. Anatomic factors producing resistance to coronary flow include morphologic lesion characteristics such as entrance angle, length of disease, length of stenosis, minimal lumen diameter, minimal lumen area, eccentricity of lumen, area of reference vessel segment and viscosity (See Fig. 21-14). To determine hemodynamic lesion severity and propensity to be associated with ischemia, translesion pressure ratios at maximal coronary flow, called the fraction flow reserve (FFR) is an in-lab standard prior to proceeding to intervention in the absence of other objective evidence of ischemia.

**FIGURE 21-14** Morphologic characteristics of a stenotic lesion. 1. entrance angle; 2. lesion length; 3. minimal lumen diameter length; 4,5,6 lumen area, eccentricity, diameter; 7. normal reference vessel area.

ST elevation during an exercise tolerance test is often associated with left main coronary artery (LM) stenosis or 3V coronary artery disease. High-risk features of stress testing may also be demonstrated including persistent chest pain, drop in blood pressure with exercise, marked ST segment depression or new elevation, or short duration of exercise with onset of symptoms.
It should be noted that the most potentially lethal condition leading to complications of diagnostic coronary arteriography is the presence of severe LM stenosis, particularly ostial involvement. Placement of the diagnostic catheter into the coronary ostium, especially if it causes disruption of plaque, may lead to immediate hemodynamic instability and a downward spiral. All physicians performing angiography should be prepared to administer vasopressor agents immediately should blood pressure fall in the setting of left main artery stenosis. In centers equipped with interventional cardiology equipment, an early decision for urgent angioplasty and stenting as a bail-out technique for left main artery occlusion should always be added to the armamentarium. Lesser degrees of emergency can be dealt with using vasopressor agents, followed by catheter-based left ventricle (LV) hemodynamic support [eg, intraaortic balloon pump (IABP) or Impella] to stabilize the situation, and then definitive surgery; however, it is sometimes impossible to stabilize the patient quickly enough using these measures, and the emergency placement of left main artery stents has, in some cases, been lifesaving.

5. B
Contrast-induced nephropathy (CIN) is typically defined as a relative increase in serum creatinine of >25% or an absolute increase >0.5 mg/dL. No single factor or agent has been shown to reduce the risk of CIN better than hydration with normal saline in even the most high-risk patient.

The most common contrast media for angiography are nonionic or low-osmolar contrast agents because of safety, patient tolerance, and cost. Any iodine-based intravascular contrast media may cause acute renal failure following percutaneous coronary intervention (PCI). While it is not uncommon to develop transient increases in serum creatinine, it is rare to need temporary dialysis and even rarer to need permanent dialysis following CIN. The time course of CIN demonstrates an increase in creatinine starting in 12 to 24 hours for most patients, but it may take as long as 48 to 96 hours to peak. Mehran et al developed a validated risk scoring system in order to predict the likelihood of developing CIN.

In high risk patients, CIN prevention consists of pre-procedure hydration and limitation of the contrast volume administered. No specific pharmacologic regimen has been demonstrated to reduce CIN. Limiting the volume of contrast media is an important goal for both the diagnostic and
interventional aspects of the procedure since many procedures are combined. If prior coronary arteriograms have been obtained, it may be possible to avoid repeating unnecessary views and if there has been no clinical change, it may also be possible to avoid ventriculography.
Radial Approach to Coronary Angiography

Jennifer A. Tremmel

**HISTORY**

The first known attempt at radial artery access for angiography was made in March 1947 by Dr. Stig Radner in Lund, Sweden. He reported on his new technique a year later, describing a radial artery cutdown in the upper third of the forearm, after which a 7-Fr to 9-Fr catheter was advanced in a retrograde fashion to perform a thoracic aortogram.\(^1\) It was not until over 4 decades later that the radial artery started to be accessed percutaneously, rather than through a cutdown, and for the purpose of cannulating the coronary arteries. In 1989, emboldened by the safety of the radial arterial line for critically ill patients, Dr. Lucien Campeau from Montreal Heart Institute described his experience of accessing the left radial artery for coronary angiography in 100 patients (90 men and 10 women).\(^2\) Primarily using a 5-Fr system, he was successful in cannulating the radial artery in 90% of patients, and reported only 2 complications, including a brachial artery dissection and a radial artery occlusion, neither of which were symptomatic. Three years later, in 1992, the first coronary stents were placed in 3 men via the right radial artery by Dr. Ferdinand Kiemeneij in Amsterdam.\(^3\) He attributed his ability to do this to “miniaturization” of coronary guiding catheters to 6-Fr and adequate crimping of a Palmaz-Schatz stent on a balloon to allow it to pass without becoming dislodged within the small guide.
Following these successes, the use of radial access spread worldwide. However, the enthusiasm was short-lived in some countries, including the United States, where there was a rise and fall of radial procedures during the 1990s. United States operators quickly grew frustrated by the difficulty in performing a radial procedure compared to the ease of a femoral procedure, in which there were not issues of spasm, tortuous anatomy, or limitations in guide size. By the late 2000s, 50% of percutaneous coronary interventions (PCI) were performed radially in Europe and Canada, and 60% in Japan, but only 1.7% in the United States, putting it on par with the Middle East and Africa.\textsuperscript{4,5} Around the same time, though, concerns regarding the morbidity and mortality associated with bleeding and vascular complications, the emergence of new radial-specific equipment, and the enthusiasm of young operators who had no memory of the struggles of their predecessors, began to take hold. Within a 6-year period, radial PCI in the United States grew to over 30%, and has not shown signs of stopping (Fig. 22-1). Few interventional fellows in the country now graduate without being proficient in both radial and femoral procedures, and a new paradigm is seen within cardiac catheterization laboratories across the country where patients can ambulate right after their procedure and go home that same day.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure22-1.png}
\caption{Percentages of radial percutaneous coronary interventions in the United States by calendar year.}
\end{figure}
United States from 2007 to 2015.

**BENEFITS OF THE RADIAL APPROACH**

*Reduction in Bleeding and Vascular Complications*

Bleeding is the most common complication after PCI. It is independently associated with a 3-fold increase in mortality and major adverse cardiovascular events (MACE)\(^6\) and contributes to 12.1% of all in-hospital mortalities after PCI.\(^7\) In addition, 2.3% of patients receive a blood transfusion post-PCI, which has also been independently associated with an increased risk of mortality and MACE.\(^8\) Although non-access site bleeding has been associated with a worse prognosis than access site bleeding, access site bleeding still carries a 1.7-fold increased risk of mortality compared with no bleeding.\(^9\) While femoral access site bleeding and vascular complications have decreased over the past decade, they still occur in ~2% of all PCIs, and women have a >2-fold increased risk compared to men.\(^10,11\) Moreover, patients with a particularly high bleeding risk, such as those presenting with ST-segment elevation myocardial infarction (STEMI), have femoral bleeding rates of 5% or more.\(^12,13\)

Observational studies and randomized controlled trials (RCTs) have consistently demonstrated a reduction in bleeding and vascular complications with radial versus femoral access.\(^5,14-17\) In addition, this reduction increases as a patient’s bleeding risk increases, and those with the highest baseline bleeding risk benefit most from a radial approach.\(^18\) Similarly, as the baseline bleeding risk increases, there is an increased risk of mortality, and the impact of strategies that reduce bleeding, such as the radial approach, begin to reduce mortality. It has been demonstrated in larger RCTs of STEMI patients that those who have a higher risk of baseline bleeding and mortality do benefit from radial versus femoral access, whereas this has not necessarily been the case in lower-risk cohorts.\(^13,15,16,19\)

*Decreased Cost*
In 2013, there were several studies published evaluating the cost benefit of radial procedures, and all showed very similar results.\textsuperscript{20-22} They all examined both the periprocedural and postprocedural costs associated with radial versus femoral access. There was no periprocedural cost benefit with radial PCI versus femoral PCI, and, in fact, in the case of a diagnostic catheterization, the cost of radial PCI was slightly higher (likely due to the radial-specific equipment) compared to femoral PCI, when vascular closure devices were rarely used (~10%).\textsuperscript{21} On the other hand, radial PCI produced a cost savings postprocedurally of $571 to $705 per case. This savings was primarily due to a decreased length of stay rather than bleeding, which accounted for <20% of the savings. The shortened stay was not due to same-day discharge, which was occurring in <5% of the cases. Instead, presumably from early ambulation and recovery, radial patients were able to leave the hospital approximately one third of a day sooner than femoral patients, saving money on bed space and nursing staff. While the amount of money saved per patient seems small, the effect on the health care system is quite large when translated across the country, totaling $50 million or more.\textsuperscript{20} It is also noteworthy that the largest cost savings from radial PCI comes when employed in patients who were at the highest risk of bleeding ($642 in low risk patients and $1621 in high risk patients). This mirrors the data seen with bleeding and mortality—the higher-risk the patient, the more benefit is gained from a radial procedure.

**Higher Patient Satisfaction**

The data regarding patient satisfaction with radial procedures is limited, but for anyone who does radial procedures, the testimonials given by patients are convincing enough. Still, in an old, but often-cited article, Cooper et al. reported that 80% of patients who had undergone both techniques strongly preferred the radial approach, whereas only 2% preferred the femoral approach.\textsuperscript{23} Likewise, patients in both RIVAL (Radial Versus Femoral Access for Coronary Intervention) and SAFE-PCI (Study of Access Site for Enhancement of PCI for Women) significantly preferred radial access over femoral access if they were to need to have their procedure again.\textsuperscript{15,24}


**DOWNSIDES OF THE RADIAL APPROACH**

*The Learning Curve*

One of the biggest challenges of doing radial procedures is getting through the learning curve. It must be remembered that the wrist is not a small groin, and that there are new skills to learn, even for the most adept femoral operator. Becoming proficient at radial procedures is about case volume, not operator status. Therefore, when learning radial approaches, everyone is starting at ground zero, which can be frustrating, particularly for long-standing femoral operators, as well as their staff. Investigations into the initial learning curve have suggested that it takes approximately 50 cases to master the basics. However, as with learning any skill, technical proficiency continues to improve well beyond the initial learning curve, so the more cases one does, the better one gets.  

In a study evaluating the learning curve for diagnostic cases, radial experts (defined as experienced femoral angiographers who had received formal training in radial techniques with >100 previous radial procedures) were compared with radial non-experts (defined as experienced femoral angiographers with basic or no radial experience) at baseline, and then over the course of 12 months as both groups performed radial procedures. At baseline, the radial experts had significantly shorter procedural and fluoroscopic times compared with the radial non-experts. By ~36 cases, there was no significant difference in procedural times between the experts and non-experts, but still a difference in fluoroscopic times. By ~63 cases, the procedural and fluoroscopic times between the radial expert and non-expert were no longer appreciably different. Similarly, in operators newly performing radial PCI, the odds of failure decline substantially up to 50 cases, while further decline in failures after 100 cases is small. A large analysis tracking new radial operators in the United States also concluded that the threshold to overcome the learning curve is approximately 30 to 50 PCIs. In addition, median fluoroscopy times and contrast use decreased significantly with increasing radial volume, and despite operators doing more complex radial procedures, as their experience grew, procedure success
remained consistently high.

There are several ways to approach one’s learning curve. To begin with, operators can start on their own, or the entire cardiac catheterization laboratory can change together. The latter may be more logistically difficult in the beginning, but likely results in more efficiency in the end. Operators can also choose to start with easy cases, gradually increasing to more complex cases as their comfort and skill level grows, or they can take a “radial-first” approach from the start. A rapid transition to a radial-first approach is likely best. Many operators get stuck in their learning curve, tending to favor the radial approach in stable male patients, whereas the patients most likely to benefit, due to higher risk of bleeding and vascular complications, are older, female, and unstable patients, particularly those with STEMI. This avoidance of the radial approach in potentially more challenging cases has created a risk–treatment paradox in the United States, whereby the patients who are most expected to benefit from a radial procedure are the least likely to receive it. Consequently, it is encouraged that operators complete their learning curve, pushing themselves to do more radial procedures and to get comfortable with all types of patients. It has been shown that as radial PCI volume increases, more females, more patients with New York Heart Association class IV heart failure, and more patients with higher bleeding risk are selected to undergo radial PCI. Operators also perform more multi-vessel PCIs and technically complex PCIs as they gain experience with radial interventions. The last frontier of the learning curve is generally the STEMI patient, who will be discussed in more detail later in this chapter.

**Excess Radiation Exposure**

Data regarding radiation exposure with radial versus femoral procedures have been mixed. Overall, it appears that operators and patients get higher radiation exposure with radial procedures compared with femoral procedures, but this improves as operators advance through their learning curve. In fact, one of the biggest factors of radiation exposure for either a radial or femoral operator is procedural volume. In a radiation substudy of the RIVAL trial, there was a nominal overall increase in radiation dose with radial versus femoral access, but this difference was observed only in lower-volume centers and operators. Medium- and high-volume centers showed no
significant difference, and high-volume centers had the lowest radiation dose irrespective of which access site they used.

All operators should do what they can to minimize radiation exposure. In addition to the usual steps such as using standard shielding, maintaining distance, and lowering the frame rate, certain radial-specific devices, including a radial radiation protection board, a radiation shield over the radial sheath insertion site, and draping the patient’s pelvis with a lead shield, should be strongly considered.

**Radial-Specific Vascular Complications**

While bleeding and vascular complications with the radial approach are rare, they can occur. Hematoma of the forearm is generally easily controlled with a brief course of manual compression. Wrapping the forearm with an Ace bandage or a self-adherent elastic wrap for 15 to 30 minutes following manual compression can prevent recurrence, but close attention needs to be paid to make sure that the hematoma is not expanding, in which case manual compression needs to be resumed. A blood pressure cuff may also be utilized, inflated to systolic pressure and then gradually released over time. In all cases where there is circumferential pressure around the arm, venous stasis can occur. A brief hiatus to allow perfusion before continued compression may be necessary. Compartment syndrome is a poorly managed hematoma that leads to hand ischemia. If radial patients are being closely tended to in recovery, compartment syndrome should never occur.

Both pseudoaneurysms and arteriovenous fistulas can occur in the radial artery, but are rare. A pseudoaneurysm is usually easily treated by having patients wear a hemostatic device over the radial artery for up to an hour. If unsuccessful, a longer duration may be necessary or a thrombin injection could be considered. Other complications, including spasm, vessel dissection or perforation, and radial artery occlusion will be specifically addressed below.

**THE RADIAL TECHNIQUE**

**Patient Preparation and Setup**
The entire cardiac catheterization laboratory needs to be educated about the radial approach so that procedures run smoothly and safely from the time of the patient’s arrival to his or her departure. In the pre-procedural area, intravenous (IV) tubes should not be placed near the wrist, and an antecubital IV should be placed if a right heart catheterization (RHC) is anticipated (see below). Groins will often be prepped, particularly earlier in the learning curve.

Most patients are suitable candidates for radial access. Some relative contraindications to consider are the presence of severe Raynaud’s phenomenon, presence of a dialysis arteriovenous fistula, and history of a left internal mammary artery (LIMA) bypass graft where the left radial artery has also been used as a bypass conduit. In this situation, the LIMA will have to be accessed from the right radial artery, which is challenging, though not impossible. Whether to also forgo the radial approach on patients who have an abnormal modified Allen’s or Barbeau test is controversial. There are no data demonstrating that performing a modified Allen’s or Barbeau test to evaluate the patency of the ulnopalmar arch predicts hand ischemia, but many operators, particularly in the United States, still prefer to do it. Compared to the modified Allen’s test, the Barbeau test has been found to be more sensitive and is also typically used in a reverse fashion when assessing for patent hemostasis (see below).

Once in the procedural room, either the right or left arm will be prepared for access. The right arm is generally more convenient, but there are advantages to the left arm. The left subclavian artery is often less tortuous than the right subclavian/innominate, particularly in patients who are older than 75 years of age and shorter than 165 cm. In addition, the curves taken by the catheter more closely mimic those seen when coming from the groin. As a consequence, operators may find the procedures easier and the learning curve shorter when using the left arm. There are also data to suggest that radiation exposure is less from the left arm. Regardless of the preferred side, becoming facile at left arm setup is a must for any lab. The left arm will be needed for coronary artery bypass grafting (CABG) cases and crossover if access or engagement from the right radial artery fails.

For left arm procedures, the left radial artery is typically accessed from the left side of the patient. Then the operator returns to the right side of the patient, where she or he is accustomed to standing and driving the table. The
left arm is brought up on the patient’s body and secured in place. Various methods have been employed for securing the arm, but a high arm board and some blankets usually suffice. The wrist then sits at about the level of the left groin.

For radial access preparation, the arm is placed on a board that will allow the arm to be brought to the patient’s side during the procedure, or up on the body in case of left wrist access. The wrist is slightly hyperextended, either with a rolled towel or specialized wrist splint (Fig. 22-2). For new radial operators, the groin should be prepped and ready for access, so that crossover does not add to the burden of learning a new skill. However, as proficiency grows and crossover decreases, consideration should be given to discontinuation of groin prep, which is rarely needed and only adds to staff preparation time. For right arm procedures, there should be a board distal to the arm that extends from the table and provides a working surface, as it is often not feasible to work on the patient’s body, as is usually done from the femoral approach. Finally, the patient can be draped with a specialized radial drape, or a neck drape can be used to cover the arm in addition to the usual femoral drape (Fig. 22-3).

**FIGURE 22-2** The wrist is slightly hyperextended.
FIGURE 22-3 Patient prepped for radial access.

Access

Prior to starting the case, take a moment to make sure that the patient is
comfortable and reasonably sedated. Anxious patients are more prone to spasm, and the key to avoiding spasm is prevention. The optimal site for radial access is approximately 2 cm proximal to the radial styloid process (Fig. 22-4). There is a tendency for new operators to creep distally, but while the radial pulse may be stronger at the level of the styloid process, the radial artery is more likely to turn or give off branches in this area, making access more difficult. Once the proper location is identified, a small amount of lidocaine should be administered. Only about 1-2 mL is needed (Fig. 22-5), and too much may obscure the pulse.

FIGURE 22-4 The optimal site for radial access is approximately 2 cm proximal to the styloid process.
There are 2 techniques for accessing the radial artery. The first is the modified Seldinger technique, which uses a short micropuncture needle, and the second is the Seldinger technique, which uses an angiocath needle. The modified Seldinger technique involves making an anterior wall stick and, once in the vessel, slightly adjusting the needle’s position for the best blood return possible prior to advancing the wire. The Seldinger technique involves puncturing the anterior wall, which results in blood return, and then continuing the puncture through the posterior wall until the blood return stops (Fig. 22-6). This ensures that the needle catheter is deep enough when the needle is removed. After removal of the needle, the catheter is pulled back at a superficial angle until there is blood return, at which point the wire is advanced (Fig. 22-7). With this latter technique, there are no other adjustments of the needle catheter—once it is in, it is in. While either technique is safe and effective, the Seldinger technique may be easier, particularly for new operators.45

FIGURE 22-6 The Seldinger technique involves puncturing through the anterior and posterior walls.
For access, the needle is held at a 30° angle, and once the pulse is identified, the needle should be advanced gently, but definitively. If the artery is missed, prior to pulling back on the needle, determine if the pulse is more medial or lateral. Then, withdraw the needle just to the surface of the skin and redirect, preferably without making a new puncture in the skin. Rather than manual palpation, another option is ultrasound. Some operators like to use it when they are having difficulty hitting the artery or the pulse is weak, whereas others use it routinely. When used routinely, ultrasound has been shown to decrease the number of attempts and time to access. Another trick to use if the pulse is weak is to have someone occlude the ulnar artery or the radial artery distal to the access site to increase the force of the pulse.

The hydrophilic sheath is one of the advances in radial artery equipment that has improved the procedure since the 1990s. Hydrophilic sheaths have been shown to reduce spasm, but the length of them has not. Since the sheath has the largest outer diameter of anything being put in the artery, minimizing its length whenever possible seems prudent. Because of its hydrophilicity, a skin nick is rarely needed. Instead, the sheath is advanced directly through the skin while being rotated side to side (Fig. 22-8). If the skin is tough, a small nick can be made. However, the sheath can slide easily in and out of the skin, so the nick should be kept to a minimum. Once the sheath is in place, some operators like to secure it with a Tegaderm dressing to keep it from slipping out. There should not be any significant pain or resistance.
when advancing the sheath. If there is, investigate before advancing further. Perhaps the artery is too small for the sheath, or there is spasm or heavy calcification.

![Image](image_url)

**FIGURE 22-8** The hydrophilic sheath is advanced directly through the skin—no nick is generally required.

Sheath size should be kept to a minimum. Larger sheaths, particularly in relation to the size of the radial artery, have been implemented as one of the causes of radial artery occlusion.\(^ {47}\) For diagnostic cases, a 5-Fr system is generally sufficient and some operators use 4-Fr. Newer thin-walled sheaths allow for passage of 6-Fr equipment while maintaining a 5-Fr outer diameter, or 5-Fr equipment while maintaining a 4-Fr outer diameter. Another advantage to the thin-walled sheath is that it can minimize sheath exchanges. Prior to their advent, an operator would start with a 4-Fr or 5-Fr sheath for the diagnostic angiogram, but if the case needed to go to PCI, the operator either had to do a 5-Fr PCI, which had equipment limitations, or upsize to a 6-Fr sheath. Now, a 6-Fr thin-walled sheath can be used for the entire case. Most PCIs can be done with a 6-Fr system. In rare circumstances, an operator might want to upsize to a 7-Fr or 8-Fr. Few patients, especially women, can safely accommodate that size sheath in their radial artery. As an alternative, there is a now a 7-Fr thin-walled sheath (with a 6-Fr outer diameter) or there are sheathless systems. Sheathless systems eliminate the sheath and drop the French size down to the outer diameter of the guide, which is ∼2-Fr smaller than the outer diameter of the traditional sheath. The sheathless system,
however, requires a smooth transition at the tip of the guide so that it can be advanced from the skin into the artery with minimal trauma. There are limited dedicated sheathless guides or one can be made by putting a smaller introducer within the guiding catheter.\textsuperscript{48}

Once the sheath is in place, a radial artery cocktail is given to reduce spasm. This can be varied based on operator preference, but a good rule of thumb is 2.5 mg of verapamil and 100 to 200 μg of nitroglycerin. These drugs are generally well tolerated except by patients who have severe aortic stenosis, in which case they should be avoided or given with caution. The cocktail may also contain heparin, which is important for reducing radial artery occlusion. If given via the radial artery, it is often diluted with blood because it tends to burn. It is also fine to give the heparin via a peripheral IV. Some operators like to wait to give heparin until after they have successfully navigated up the arm in case they have to cross over to the groin. The recommended dose is 50 units/kg. Bivalirudin has also been shown to be effective in reducing radial artery occlusion, and is an acceptable alternative. However, warfarin (Coumadin) is not. Patients with a therapeutic International Normalized Ratio (INR) from warfarin still need to be given the usual dose of heparin.

**Navigating Up the Arm**

In the majority of cases, a J-tipped guidewire (either 3 mm or 1.5 mm) will slide up the arm without difficulties. Using such a wire provides safety and minimizes the need for fluoroscopy. If any resistance is met with the J-tipped wire, fluoroscopy can be used to see where the wire is impeded. At that point, switching to a straight hydrophilic wire and maneuvering it under fluoroscopy is generally enough to successfully navigate the arm. However, if there are still issues, an angiogram of the arm should then be performed to ascertain the necessary path. A notable obstacle that may be seen is the radial loop (Fig. 22-9). The radial loop varies in terms of complexity and can often be navigated without much difficulty. In such cases, the hydrophilic wire may easily go through and straighten the loop itself, or the guide can be manipulated around the loop and then gently pulled back and torqued to straighten the loop. Other times, a coronary wire and smaller catheters are needed, and the patient may find it painful. In such situations, operators have to decide if they want to continue their efforts or switch to the contralateral
wrist. A radial loop on one side does not necessarily predict a radial loop on the other side.

Another, more common, encounter when going up the arm is a high-takeoff of the radial artery, where the origin of the radial artery is proximal in the brachial artery or even in the subclavian artery. If the radial artery is reasonably sized, this anomaly generally goes unnoticed. However, it is often detected when the wire passes smoothly, but the catheter meets resistance. A similar situation can occur if one has gone into an accessory radial artery. Caution needs to be taken in these smaller radial vessels, which are more
prone to spasm and dissection or perforation. An angiogram of the arm should indicate if there is an alternate path into the brachial artery that was missed, in which case the wire should be redirected, or if one has only the small radial to use. If the latter is the case, the operator needs to decide if she or he can safely advance the catheter, or if she or he needs to use an alternate access site. Downsizing the catheter may be helpful. Another useful technique for navigating small or tortuous vessels is balloon-assisted tracking. This involves inflating a coronary balloon at the end of the catheter to make an atraumatic tip, which is then advanced over a coronary wire.

If a dissection, a perforation, or both occur in the arm, a new operator’s instinct is often to abort the procedure. However, this is the wrong inclination. On the contrary, trying to safely advance a wire and catheter through the traumatized area is the key to treating it. This may require a coronary wire, a smaller catheter, and balloon-assisted tracking. Still, once the catheter is across the dissection/perforation, the vessel will tamponade and seal itself. This can be confirmed with an angiogram at the end of the case (Fig. 22-10).

Once up the arm, the catheter has to be advanced into the ascending aorta.
The subclavian/innominate arteries can be tortuous, but with practice, these curves become less cumbersome. Having the patient take a deep breath will often straighten out the path. In addition, pointing the catheter in the direction one needs to go will aid wire passage. The use of a hydrophilic wire can also be helpful. The most challenging type of curve in the aortic arch is due to arteria lusoria. Arteria Lusoria is the most common aortic arch anomaly, in which the right subclavian artery arises as the most distal branch off the aortic arch, and then travels between the esophagus and trachea to supply the right arm. This can be negotiated, but sometimes requires great effort and may be an instance in which to consider crossing over to another access site.

Tortuosity in the subclavian/innominate and aortic arch also leads to difficulties in engaging catheters even once one makes it into the ascending aorta. Again, having the patient hold a deep breath while torquing can be helpful, as can leaving the guidewire in the catheter/guide while torquing. These 2 maneuvers become increasingly necessary as the amount of torque increases. A novel complication with radial procedures is the catheter loop and kink, which is the result of excessive torque. Not only is there a kink in the catheter, which is seen with excessive torquing from the femoral artery, but there is also a loop, which simply spins around and cannot be undone without traction on the distal catheter (Fig. 22-11). The best approach is to have a high index of suspicion for this complication when aggressively torquing a catheter and to stop immediately if pressure dampening is noted or the distal end of the catheter does not seem to be responding to proximal movements. If the kink has not gotten too bad, it can often be undone with a counter-torque while advancing the guidewire. On the other hand, if a loop and kink occur, and no wire can be advanced, distal traction needs to be placed on the catheter, either externally or internally. External traction can include manually trying to compress the catheter through the arm or application of a blood pressure cuff. Internal traction is generally done with a snare. Once the distal catheter is fixed, the proximal end can be counter-torqued to get rid of the loop and kink. Another option is to try advancing a longer sheath or a larger catheter over the existing catheter. This involves cutting the end of the existing catheter, removing the sheath, and then sliding the longer sheath or larger catheter over the existing catheter up to the location of the loop/kink. Then, the existing catheter is counter-torqued and pulled into the larger lumen.
A final problem encountered in the arm is spasm. As previously mentioned, the key to avoiding spasm is prevention. In addition, as radial operators become more experienced, their rates of spasm decrease. The use of adequate sedation, a hydrophilic sheath, and a spasmolytic cocktail have already been discussed. In addition, minimizing catheter manipulations and exchanges is important. There are early signs of impending spasm including more friction on the catheter and complaints of pain by the patient. These warnings should result in immediate cessation of catheter manipulation, at which time the patient should be given more sedation. Consideration should also be given to downsizing the catheter. If the catheter is exchanged for a smaller size, an additional spasmolytic cocktail can be administered. A warm blanket can also be placed on the arm. If early warning signs are ignored and frank spasm occurs, additional sedation should be given and the catheter should be left alone. Continuing to pull on it only exacerbates the spasm and an overly forceful pull could result in radial artery evulsion. Another trick is to inflate a blood pressure cuff for 5 minutes on the arm and then release it.
The resultant flow-mediated dilation may allow release of the catheter. If after 10 to 20 minutes of rest, adequate sedation, and readministration of vasodilators, the catheter is still stuck, an anesthesiologist needs to be called. She or he can administer propofol, which is generally successful in getting the radial artery to relax. If not, general anesthesia may be required.

**Catheters/Guides**

Each operator must find his or her own workhorse catheters and guides. For diagnostic cases, some operators like a universal catheter (used for both the left and right coronary arteries), while others prefer to stick with a Judkins left 4 and Judkins right 4. The advantage to a universal catheter is that it minimizes catheter exchanges. The disadvantage is that it is a new catheter for most operators and takes some getting used to. Still, with practice, the universal catheters can be mastered fairly easily. Similarly, for interventional cases, there are radial-specific guides, some universal, as well as all of the standard femoral guides that operators are familiar with. For most PCIs, standard femoral guides work very well. Because support is more commonly an issue from the wrist than the groin, one may want to start with a more supportive guide, such as an extra back-up guide for the left coronary artery and an Amplatz for the right coronary artery. For STEMI cases, starting with a universal guide can decrease time by eliminating catheter exchanges.

For diagnostic cases in a coronary artery bypass graft (CABG) patient, the left radial artery will generally be accessed, and any of the diagnostic catheters used for the femoral approach can also be used from the radial approach. If the angle into the LIMA is less than 90°, a no-torque right catheter may be able to better make the hook than the internal mammary artery catheter. For PCI of a saphenous vein graft (SVG), an Amplatz guide is usually needed. An exception is the vertically oriented SVG to the right coronary artery, in which case a multipurpose guide can be deep-seated and will offer the best support.

All catheter/guide exchanges need to be made over a wire. This keeps catheters and guides from catching on the great vessels and maintains positioning in the ascending aorta. This becomes especially important if it was hard to get into the ascending aorta to begin with. In addition, it is common when approaching from the right radial artery that catheters/guides will need to be downsized a half French size for the left coronary artery and
upsized a half French size for the right compared to what is usually used from the femoral approach.

Because having adequate support is more of an issue from the radial approach, in addition to using supportive guides, operators need to become adept at using tools and techniques that will provide them with increased support when necessary. A simple buddy wire will often suffice. More often, a guide extension catheter will be needed. If neither of those options is enough, use of an anchor balloon provides the most support. In this situation, a second coronary wire is advanced into a less important branch, generally a marginal on the right or a septal branch on the left. Next, a semi-compliant balloon sized to the branch is gently inflated in the branch. This anchors the guide in place and the equipment for the target lesion can now be advanced into the artery (Fig. 22-12).
branch to anchor the guide.

**Right Heart Catheterization**

The need for a right heart catheterization (RHC) should not be a reason to forgo the radial approach. Instead, the right brachial vein can be used. In fact, any superficial vein will go to the deep veins, so all that is needed is an IV placed in the antecubital fossa. This can be done preprocedurally by a nurse and then the area can be prepped and draped by the staff in the room. It is preferable if a more medial vein is chosen, which is more likely to drain in a relatively straight course into the basilic vein that then joins with the brachial vein to form the axillary vein and, ultimately, the subclavian vein. When advancing up by this approach, little to no fluoroscopic guidance may be required. More lateral veins, on the other hand, may drain into the cephalic vein, which enters the axillary vein at a “T-junction.” This intersection results in a right angle turn that can be more difficult to negotiate. If the nurses are unable to place an antecubital IV, the brachial vein can be accessed directly by the operator using ultrasound and a micropuncture kit.

In a sterile fashion, the existing IV is threaded with an 0.018-in wire. Once the IV is removed, a small amount of lidocaine is administered at the site. Next, a 5-Fr hydrophilic sheath is advanced over the wire and gently pushed right through the skin into the vein. No nick is needed. The wire can be left in place and used as a track to advance the 5-Fr balloon-tipped pulmonary artery (PA) catheter, or the PA catheter can be advanced without the wire. It must be recognized, however, that the PA catheter will sometimes get hung up on valves or have a hard time making a turn, in which case the wire may be needed after all. Force should never be applied as veins are more fragile than arteries and can tear or perforate if aggressively handled. If a wire or catheter is not progressing, a limited venogram can be helpful. For routine diagnostic right heart catheterization, the commercially available 5-Fr balloon-tipped catheters and thermodilution catheters are generally best, although larger systems can be used if needed.

**Hemostasis**

Once the case has ended, a hemostatic device is placed on the wrist. While some operators simply use a rolled piece of gauze and an Ace bandage, it is
strongly recommended that a device with a mechanism for fine-tuning the amount of pressure on the radial artery be used. This is because the goal is not to simply have hemostasis, but to have patent hemostasis, meaning that the artery is not only not bleeding, but is still perfusing. Patent hemostasis, along with adequate anticoagulation and minimizing the sheath size, are the 3 key components to minimizing radial artery occlusion.\textsuperscript{50,51} The reported incidence of radial artery occlusion is quite variable, but is probably somewhere around 10%. However, when these 3 particular evidence-based steps are taken to reduce radial artery occlusion, the incidence drops to <1%, so they should be routine goals in every cath lab.

To achieve patent hemostasis, a pulse oximeter with plethysmography is placed on the index finger, and the hemostatic device is applied with the least amount of air or pressure possible. Next, the operator occludes the ulnar artery and evaluates the plethysmograph to confirm patency of the radial artery (reverse Barbeau test). Simply feeling the radial pulse once the hemostatic device is in place is insufficient because the pulse may actually be arising from the ulnar artery and going around the palmar arch rather than coming from the radial artery. Ideally, one will achieve a reverse Barbeau A, B, or C waveform on the plethysmograph (Fig. 22-13). If the plethysmograph shows a flat line (reverse Barbeau D), an attempt should be made to decrease the amount of air/pressure in the device. If further air/pressure cannot be removed without bleeding, then the band is left as is with the expectation that it will be tended to in recovery. Upon arrival to recovery, it should be standard protocol that the reverse Barbeau test be repeated. If the patient still has a reverse Barbeau D, another attempt should be made to decrease the amount of air/pressure while maintaining hemostasis. Generally, patent hemostasis can be achieved upon arrival to recovery if it was not achieved in the cath lab. If patent hemostasis still has not been achieved upon arrival to recovery, attempts should be repeated every 15 minutes until they are successful. Once patent, it is also important to have periodic checks to confirm that the radial artery remains patent. In the very rare situation that the radial artery is not patent by discharge, the hemostatic device can be reversed, occluding the ulnar artery for up to 1 hour to get the radial artery open.\textsuperscript{52} Low-molecular-weight heparin can also be given for several days post discharge if the radial artery remains occluded, although there are limited data regarding this technique. Early occlusion (≤24 hours) is associated with late occlusion (≥30 days), whereas early patency nearly guarantees late
patency (99.1%), so every effort should be made to keep the artery open throughout recovery.

FIGURE 22-13 Reverse Barbeau oximetry waveform categories. (Adapted by James Bonnett from Barbeau, 2004 (40).)

The duration of use of the hemostatic band will vary depending on the type of procedure. Generally, for a simple diagnostic case, the band will stay on for 1-2 hours. Some operators will start gradually decreasing the air/pressure prior to removal, whereas others do not. For interventional cases, the band will generally stay on for 2-4 hours. Nursing protocols need to be adapted to each institution’s practice. Notably, for prevention of radial artery occlusion, the duration of the hemostatic device is less important than the maintenance of patent hemostasis. Since some patients will be cared for on an inpatient unit, unit nurses also have to be trained on how to use the hemostatic device and how to maintain patent hemostasis. While it may seem obvious, recovery staff should be reminded that radial patients (whether diagnostic or PCI) are to be ambulatory during recovery as soon as their hemodynamic stability has been confirmed. Keeping radial patients in cardiac chairs rather than on hospital beds and letting them get dressed can also facilitate their recovery and discharge.

INCORPORATING STEMI INTO A RADIAL PROGRAM
As mentioned, it is important to complete one’s learning curve, being able to tackle the most challenging cases radially, in order to provide the most benefit to patients from this approach. The pinnacle of the learning curve is primary PCI. Doing STEMI patients requires not only a certain level of mastery of the radial approach, but also a confidence in one’s ability. It requires that the cath lab staff be skilled and comfortable with the approach as well.

Once one has decided to start doing STEMIs radially, it is advisable to begin with some straightforward cases, such as good-sized men who are hemodynamically stable. As confidence grows, more and more challenging cases can be taken on until the radial approach is the default strategy for all STEMI cases. Even if one no longer preps the groin for elective radial cases, the groin should always be prepped for STEMI radial cases. The good possibility of the need for an intra-aortic balloon pump (IABP) and/or left ventricular assist device (LVAD) makes easy femoral access a necessity. In addition, operators new to radial STEMI naturally feel more comfortable knowing a bailout strategy is close by. Rough guidelines as to when a radial operator may want to cross over to the groin during a STEMI include when radial access is taking >3 minutes, when the time from sheath placement to engaging the infarct-related artery with the guide catheter is taking >10 minutes (including the time to inject the non-infarct artery), or when the total time from radial artery access to crossing the infarct lesion is taking >20 minutes.

Patients with cardiogenic shock can be the most challenging. The radial pulse can be hard to feel due to poor perfusion and the radial artery may be constricted from vasopressors. Moreover, giving a spasmolytic cocktail may be unsafe. An operator ultimately has to do what she or he thinks is in the best interest of the patient. Still, small studies have shown that a radial approach is safe and feasible in at least one half of cardiogenic shock patients. The use of ultrasound for access can facilitate radial artery cannulation when the pulse is weak. Likewise, up-front placement of an IABP, LVAD, and/or pacer may be helpful, as the patient’s hemodynamic status may improve. There is less chance of a bleeding or vascular complication with 1 stick to the groin rather than 2, so having accessed 1 femoral artery is not a good reason for accessing a second if the radial approach is an option.

One of the biggest concerns for operators in transitioning to a radial
STEMI program is that it will adversely affect their door-to-balloon (D2B) times. In fact, the impact is negligible. An interesting study modeling the mortality benefit of the radial approach against the mortality benefit of minutes to reperfusion found that a delay of 83 minutes in D2B time would be needed to fully offset the mortality benefit gained by the radial approach. When beginning a radial STEMI program, it is reasonable to track D2B times, and if any significant deviations are noted, it should be decided if they were secondary to the access site. If so, further radial training or stricter guidelines for crossover may be needed.

**SAME-DAY PCI**

One of the advantages to the radial approach is the ability to comfortably send patients home the same day. This adds to patient satisfaction and lower costs, and is the result of fewer bleeding and vascular complications. While most of the data regarding same-day PCI are based on femoral patients, most operators do not send their femoral cases home same-day because the concern for a femoral complication is simply too high. There are several studies demonstrating that same-day discharge for patients undergoing radial PCI is safe and effective. In fact, if any complications are going to occur after a radial procedure, they either occur in the first 6 hours or after 24 hours, with no unheralded complications occurring between 6 to 24 hours.

In the femoral era, most patients undergoing an uncomplicated PCI typically stayed in the medical facility overnight (considered an outpatient or 23-hour observation stay with same-day PCI, the patient returns home or to a nonmedical facility (ie, a hotel) the same day. Currently, the reimbursement for a same-day PCI is the same as for a 23-hour observation stay. That means that the hospital gets paid the same amount, but with same-day discharge there are fewer nursing costs, as well as an open bed that can be used for someone else.

Sending patients home with same-day discharge requires a protocol. Based on current data, patients should be kept 6 hours after their procedure, but less time before discharge may be possible. Regardless, doing PCIs earlier in the day to allow for same-day discharge is recommended. Certain patients will not be eligible for same-day procedures, such as those with an unstable residual dissection, loss of a major side-branch, or ongoing evidence of
ischemia. Likewise, certain social situations may preclude same-day discharge, such as having no driver or living too far from a medical facility. All patients should have a designated responsible adult who can be available for assistance if necessary. If a patient is already an inpatient, same-day discharge may also not make financial sense (since inpatients are reimbursed at a higher rate than outpatients) or may not be feasible because of the time needed for discharge planning. Some discharge planning is required even for patients who are simply being discharged from the recovery unit. By discharging patients the same day rather than the next morning, operators are eliminating morning rounds, which is where there is often an important discussion regarding the procedure, the need for dual antiplatelet therapy, and the plans for followup. This all has to be done prior to discharge on the same day. These details can be hard for patients to remember, especially after sedation, so having another adult present can be helpful. In addition, there must be a planned call the following morning by a nurse to review the above details and to see if the patient had any concerns overnight or has any questions. The attending physician should be contacted if there are any outstanding issues. If the patient cannot be reached, the responsible adult should be contacted.

SUMMARY

Within the past several years, the radial approach has gained traction and is changing the paradigm of interventional cardiology in the United States. Transitioning from a femoral to radial lab takes a patient and cooperative effort from all members of the cardiac catheterization team, but is routinely being done with great effect. The benefits are clear, with significant reductions in bleeding and vascular complication rates, improved patient satisfaction, and decreased cost. The more high-risk the patient, the more pronounced the benefits. Increasingly, PCI is being seen as a same-day procedure, and the radial approach is making that possible. All because of where we stick a patient, interventional cardiology will never look the same again.

REFERENCES


51. Pancholy SB, Patel TM. Effect of duration of hemostatic compression on


**MULTIPLE CHOICE QUESTIONS**

1. Which patient would benefit most from a radial procedure?
   A. 67-year-old man with a body mass index (BMI) of 32 and unstable angina
   B. 83-year-old woman with a BMI of 19 and ST-segment elevation myocardial infarction (STEMI)
   C. 54-year-old man with a BMI of 28 and STEMI
   D. 64-year-old woman with BMI of 33 and unstable angina
   E. 85-year-old man with BMI of 23 and stable angina

2. What is the primary driver of decreased cost with radial procedures?
   A. Less expensive equipment
B. Fewer complications
C. Shorter lengths of stay
D. Higher reimbursement
E. Faster procedure times

3. What is the advantage of right radial access compared with left radial access?
   A. Convenience
   B. Less radiation exposure
   C. Shorter learning curve
   D. Easier in post-coronary artery bypass graft (CABG) patients
   E. Less tortuosity

4. Which of the following is most important in reducing radial artery occlusion?
   A. Minimizing sheath size
   B. Minimizing sheath duration
   C. Achieving patent hemostasis
   D. Giving intravenous or intra-arterial heparin
   E. Giving intra-radial nitroglycerin before pulling the sheath

5. Which of the following is true regarding ST-segment elevation myocardial infarction (STEMI) procedures from the radial artery compared with the femoral artery?
   A. Door-to-balloon times are significantly slower
   B. Mortality is significantly lower
   C. Cardiogenic shock is an absolute contraindication
   D. Stroke rates are significantly higher
   E. Most operators doing radial procedures do their STEMIs radially

ANSWERS

1. B

Bleeding risk is higher in those who are older, female, and presenting with a more severe coronary syndrome. In addition, bleeding risk is highest in those
with the lowest body mass index (BMI) (<22.5). Excess BMI does not start to increase bleeding risk until it reaches 40 (morbid obesity), and those with a BMI of 25 to 35 have the lowest risk. Therefore, “little old ladies” are at the highest risk of bleeding, especially when presenting with an ST-segment elevation myocardial infarction (STEMI), and will most benefit from a radial approach. However, these are the patients who are least likely to get a radial procedure. Operators tend to use radial access in younger, average-sized male patients with stable angina (risk–treatment paradox) because these patients are typically easier—larger vessels, less tortuosity, less urgency. In order to reap the bleeding and mortality benefits, operators need to master radial procedures in all patient subsets.

2. C

While fewer complications contribute to the decreased cost of radial procedures compared with femoral procedures, the primary economic benefit comes from shorter lengths of stay. For any observational patient post-percutaneous coronary intervention (PCI) (radial or femoral), regardless of how long they stay during that observational period, the reimbursement is the same. As a consequence, the sooner a patient goes home, the less money is used on resources, especially nursing, and the sooner that bed can be filled with another revenue-generating patient.

3. A

The main advantage of right radial access is convenience. Left radial procedures require that the operator either go around or reach across the table for access, and then the left arm has to be positioned and secured on the patient’s torso, so that the operator can work from the right side of the table, which they are most familiar with, without leaning over. While less convenient, being able to do procedures from the left radial is still a must. This is primarily for post-coronary artery bypass graft (CABG) patients who have a left internal mammary (LIMA) bypass graft, because engaging the LIMA from the right radial approach can be challenging. Left radial access may also be needed for patients who do not have an accessible right radial artery or whose procedure cannot be completed from the right because of technical difficulties. In addition, it has been shown that there is a shorter learning curve and less radiation exposure with the left radial approach.
compared to the right. The left radial approach may also be easier in those who are shorter and older, as these patients tend to have more right subclavian/innominate artery tortuosity.

4. C

All of the choices have been shown to reduce radial artery occlusion, but achieving patent hemostasis appears to be the most important. In comparing sheath size, sheath duration, and patent hemostasis, only patent hemostasis was a predictor of radial artery occlusion. More recent data also suggest that heparin use may not be as important if radial artery patency is actively maintained during hemostasis.

5. B

Radial access for STEMI has been shown to significantly reduce bleeding, major adverse cardiovascular events (MACE), and mortality compared with femoral access. The impact on door-to-balloon time is negligible, adding ~1 to 4 minutes. As operators improve, this time lessens, and some investigators have even reported faster door-to-balloon times with the radial approach compared with the femoral approach. There is no difference in stroke rate with the radial vs the femoral approach. Cardiogenic shock makes radial access more challenging because the pulse may be weak and spasmolytic agents may be unsafe. In addition, if vasopressors are used, radial lumen size can be reduced. Still, at least half of patients with STEMI and cardiogenic shock can be done via the radial artery. While STEMI patients have the most significant reductions in bleeding, as well as a mortality benefit with the radial approach, a minority of STEMI cases are performed radially, even by operators who frequently use the radial artery for their non-emergent cases. Completion of the learning curve by performing emergent cases radially will ultimately be necessary to maximize the positive impact of the radial approach on patient outcomes.
Peripheral Angiography

Jose A. Silva

INTRODUCTION

Atherosclerosis is a systemic vascular disease that often affects multiple vascular territories and leads to peripheral artery disease (PAD). The age-adjusted prevalence of peripheral atherosclerotic disease is approximately 12%. However, patients with established risk factors for this condition, such as diabetes mellitus, or patients with known coronary artery disease (CAD), have a much higher prevalence of peripheral athero-occlusive disease.

Peripheral atherosclerotic disease remains poorly recognized, as recently demonstrated by the PARTNERS (Peripheral Arterial Disease Awareness, Risk and Treatment: New Resources for Survival) Investigators, a US national survey of almost 7000 patients seen in 320 primary care clinics. The survey showed that only 45% of the patients with peripheral vascular disease had been diagnosed with this condition prior to the PARTNERS Program.

Consequently, clinicians must have a high grade of suspicion for detecting PAD in patients with known risk factors or with established CAD, and these patients must undergo a detailed history and physical examination as well as non-invasive tests such as ankle-brachial index and/or arterial duplex ultrasound to rule out the presence of peripheral vascular disease. In those with significant symptoms, assessment of the peripheral vascular anatomy is necessary if intervention is being considered.

Despite major advances in noninvasive imaging techniques such as duplex ultrasonography, angiographic computerized tomography (CTA) (Fig. 23-1),
and magnetic resonance angiography (MRA) (Fig. 23-2), contrast angiography remains the gold standard method for diagnosing peripheral arterial vascular disease, because it provides the anatomic details necessary to plan percutaneous or surgical revascularization. In the present chapter, we will address the basic anatomy and angiographic procedures for the vascular territories that more commonly undergo percutaneous or surgical intervention.

**FIGURE 23-1** Digital subtraction angiography of a severely diseased superficial artery (right) compared with angiographic computerized tomography (CTA) (left).
FIGURE 23-2 Magnetic resonance angiography (MRA) of the aortic bifurcation, iliac, femoral, popliteal and infrapopliteal arteries.

GENERAL CONSIDERATIONS

The operator must be familiar with the techniques and equipment for different arterial vascular access sites (ie, common femoral artery [CFA], brachial artery, and radial artery). To obtain high quality angiographic images, it is essential to have a radiographic gantry with angulation capability in both the axial and sagittal planes as well as a large-field (14-16-in or 36-41-cm) image intensifier capable of capturing the larger regions of interest, such as the entire aortic arch, entire pelvic vasculature, and both legs.\(^5\)

Digital angiography allows immediate monitor display of the acquired image, as well as electronic processing to enhance contrast, reduce noise, and subtract bony and soft-tissue density. Digital subtraction angiography (DSA) significantly enhances the angiographic anatomical detail and allows less contrast to be used, which shortens procedure time. A preliminary image
(mask) is recorded immediately prior to the contrast injection, so that any background densities—such as bone, calcification, radiopaque objects, soft tissue, and air densities—can be subtracted from subsequent images (Fig. 23-3). Quantitative online angiographic analysis is available and often helps to provide an objective method of measurement.\textsuperscript{5} We have presented the most common angiographic views for performing peripheral angiography in Table 23-1.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Digital subtraction angiography of an aortic arch showing a subtotal occlusion of the left subclavian artery.}
\end{figure}

\begin{table}[h]
\centering
\caption{Most Useful Angiographic Views for Different Vascular Territories}
\end{table}
The use of low or iso-osmolar contrast agents is preferred to the use of high osmolar agents. These new agents are better tolerated since they produce fewer undesirable side effects such as nausea, vomiting, lightheadedness, or pain. In addition, low/iso-osmolar agents carry a lower osmotic load. This results in less fluid retention, which is desirable in patients with impaired left ventricular and/or renal function.

Alternatives to iodinated contrast, including carbon dioxide (CO₂) and gadolinium (eg, gadopentetate dimeglumine), are available to patients with severely impaired renal function and/or a history of life-threatening contrast allergy; however, these agents can also cause complications in a small
percentage of patients, including distal embolization and stroke if used above the diaphragm (occurring with CO\textsubscript{2}), or nephrogenic systemic fibrosis (occurring with gadolinium).\textsuperscript{7-10}

A wide variety of diagnostic catheters and guidewires are available for vascular angiography. Standard guidewires vary in diameter from 0.012 to 0.052 inch, but the most commonly used sizes are 0.035 and 0.038 inch. The length of most standard guidewires is between 100 and 180 cm, and the longer exchange guidewires measure between 260 and 300 cm. Tip configurations include straight or angled tip and “J” shape. Shafts may have varying degrees of stiffness. Devices with stiff, rigid shafts allow advancement through tortuous vessels, and low-friction, hydrophilic-coated wires allow passage in tortuous or difficult-to-cross lesions.

**AORTIC ARCH AND THORACIC AORTA**

The aortic arch and thoracic aorta include the ascending, transverse, and descending aorta to the diaphragm. The ascending aorta begins just distal to the sinus of Valsalva and courses from anterior to posterior in the chest. The transverse portion begins as the aorta crosses the main pulmonary artery and the left mainstem bronchus, and stretches to the ligamentum arteriosum (the remnant of the fetal ductus arteriosum). The descending portion begins distal to the ligamentum arteriosum and continues to the diaphragm.\textsuperscript{11} The normal aortic diameter ranges from 2.2 to 3.8 cm.\textsuperscript{12}

The transverse portion of the thoracic aorta courses posteriorly and gives rise to the brachiocephalic trunk proximally, the left common carotid artery in the mid portion, and the left subclavian artery in its distal portion. In 10% to 20% of patients, the left common carotid artery may originate from a common ostium with the brachiocephalic trunk or from the brachiocephalic trunk itself, an anatomic variation also known as a “bovine arch” (Fig. 23-4).\textsuperscript{13} Other less common anatomic variations also occur, including origination of the left vertebral artery directly from the aortic arch between the left common carotid artery and the left subclavian artery, and the origination of the right subclavian artery from the aortic arch distal to the origin of the left subclavian artery.\textsuperscript{13} The descending aorta courses anterior to
the spine and gives origin to nine pairs of intercostal arteries (T3 to T11).

**FIGURE 23-4** Bovine aortic arch showing the left common carotid artery arising from the brachiocephalic trunk.

**Thoracic Aortography**

Thoracic aortography is usually performed for the diagnosis of vascular diseases such as aneurysms, aortic dissection, coarctation of the aorta, patent ductus arteriosus, or vascular rings, as well as for the evaluation of vascular injuries such as blunt or penetrating chest trauma and stenoses in the origin of the great vessels. It is also useful prior to planning cerebrovascular intervention, to determine whether a brachial or femoral access site would be most beneficial. However, most of this pathology may also be diagnosed with high accuracy using non-invasive tests such as CT scan, magnetic resonance imaging, ultrasonography, and transesophageal echocardiography.14
The common femoral arterial access is the most frequently used vascular access, although the brachial or radial approaches are also useful for performing thoracic aortography. A 4- to 6-French (Fr) pigtail catheter is advanced into the ascending aorta and positioned just above of the sinus of Valsalva. Using a power injector, a total of 40 to 60 mL of contrast material is injected at 20 to 30 mL/sec. For cine imaging, 15 to 30 frames/sec is commonly used. The left anterior oblique (LAO) projection (30°-60°) best separates the ascending from the descending aorta and allows visualization of the origin of the great vessels. The anteroposterior (AP) and right anterior oblique (RAO) views may be helpful to assess the cervical branching vessels (vertebral, subclavian, common carotid).

The anatomy of the aortic arch has recently been classified into three types based on the relationship between the origin of the great vessels and a transverse line drawn at the level of the apex of the aortic arch. The Type I aortic arch is characterized by origin of all three great vessels in the same horizontal plane as the outer curvature of the aortic arch. In the Type II aortic arch, the innominate artery originates between the horizontal planes of the outer and inner curvatures of the aortic arch. In the Type III aortic arch, the innominate artery originates below the horizontal plane of the inner curvature of the aortic arch. (Fig. 23-5).\(^{15}\) This classification has practical clinical applications since the degree of difficulty and complication rates for performing selective cervical and cerebrovascular angiography and intervention are related to the aortic arch type (III > II > I).
Cervical Vessels

Three arteries originate in the transverse portion of the thoracic aorta, the brachiocephalic trunk, the left common carotid, and the subclavian artery. The brachiocephalic trunk or “innominate artery” bifurcates into the right common carotid artery and the right subclavian artery. Although the left common carotid most commonly arises separately from the aortic arch, in 10 to 20% the left common carotid artery may originate from a common ostium or from the proximal portion of the innominate artery and is termed a “bovine arch.”

The common carotid arteries run lateral to the cervical vertebral bodies in the AP view and bifurcate into the external and the internal carotid arteries at the level of C4 vertebrae. The internal carotid artery does not give origin to branches in its extracranial portion. It then enters the skull through the petrous portion of the temporal bone, after which it becomes very tortuous in a portion known as the carotid siphon, which courses within the cavernous sinus and the supraclinoid segment. Thereafter, it terminates into the anterior cerebral artery (ACA) and middle cerebral artery (MCA).

The most important branches of the subclavian artery are the internal mammary and the vertebral arteries, which arise at the inferior and the
superior aspects of this vessel, respectively, opposite each other. The vertebral artery is the first, and usually the largest, branch of the subclavian artery, arising from the upper and posterior surface of the vessel. It angles backward to the transverse process of the C_6 vertebra and courses cephalad through the foramina of the transverse processes of the upper five cervical vertebrae, where it enters the skull. After penetrating the foramen of the atlas, it turns medially and posteriorly to enter the skull through the foramen magnum. It then gives origin to the posterior inferior cerebellar artery (PICA), and subsequently joins the contralateral vertebral artery to form the basilar artery.

The vertebral artery is divided into four segments, identified as V_1 to V_4 (Fig. 23-6). This division is of clinical importance because atherosclerotic disease is commonly located in the most proximal 2-cm segment, sometimes called V_0, and within the first 2 segments of the vertebral artery (V_1 and V_2). V_1 begins after the ostial (V_0) portion and continues to the vertebral artery’s entrance into the foramen of the 6th transverse process (in 88% of cases). V_2 courses cephalad through the foramina of the transverse processes until it reaches the transverse process of the axis. V_3 continues to its entrance into the spinal canal, and it courses laterally and posteriorly to pass through the transverse foramen of the atlas, approaching the midline and then cephalad to perforate the posterior atlanto-occipital membrane to enter the vertebral canal. V_4 perforates the dura mater and passes through the foramen magnum, then joins the contralateral vertebral artery to form the basilar artery.
FIGURE 23-6 Diagrammatic representation of the 4 segments of a vertebral artery.
Angiography of the Brachiocephalic and Cervical Arteries

Vascular access may be obtained at the common femoral artery, the brachial artery, or the radial artery. An aortic arch aortogram (30°-60° LAO) is performed prior to selective angiography. This nonselective angiogram allows the operator to identify ostial disease, significant tortuosity, or anatomic variations in any of the brachiocephalic vessels.

Carotid Angiography

Carotid angiography remains the gold standard diagnostic technique for estimation and quantitation of stenoses of the carotid arteries, despite major advances in non-invasive diagnostic modalities such as duplex ultrasonography, MRA, and CTA in recent years. Selective carotid angiography is performed after obtaining an aortic arch aortogram in the LAO (30°-60°) view, which allows the operator to visualize the level at which the brachiocephalic trunk and left common carotid artery originate from the aortic arch. Using the same LAO angle, the brachiocephalic trunk may be easily engaged from the femoral access with a variety of shaped catheters: 4- or 6-Fr angled catheters such as right Judkins-4, internal mammary, and Berenstein; or shepherd’s crook shapes, such as Vitek, Headhunter, and Simmons Types I, II, and III. From the arm access, selective angiography may be performed with the shepherd’s crook shapes, particularly the Simmons catheters.

For selective angiography, after the ostium of the primary branch vessel has been cannulated, a 0.035-in “J” tip or soft-tip guidewire (Wholey wire, Covidien/Medtronic, Dublin, Ireland) is steered into the proximal portion of the common carotid artery and the catheter advanced over the guidewire, positioning it at the origin of the common carotid artery. The catheter is then aspirated and cleared to minimize the risk of embolization. Injections of contrast by hand are preferred to power injections for selective angiography (Fig. 23-7 and Fig. 23-8). When using small catheters and DSA, iodinated contrast may be diluted with saline 1:1 or 1:2 to enable better filling of the vessels.
FIGURE 23-7 Digital subtraction angiography of a left internal carotid artery stenosis affecting the ostium of the internal carotid artery in an oblique view.
FIGURE 23-8 Intracranial angiography of the left internal carotid artery and its bifurcation into the left anterior and middle cerebral arteries. It can also be appreciated with the right anterior and middle cerebral arteries (arrow), filling through the anterior communicating artery in the AP view. This particular patient had a chronic total occlusion of the right internal carotid artery.

Subclavian and Vertebral Angiography
The right or left subclavian arteries can be selectively engaged using the same technique, catheters, and guidewires previously described for selective carotid angiography. The AP view with or without shallow oblique views usually will demonstrate the area (or areas) of stenosis. In patients with a tortuous proximal left subclavian artery (the left subclavian artery is affected with PAD 3-4 times more frequently than the right\textsuperscript{20}) a steep caudal or RAO view with steep caudal views are very useful for showing the proximal vessel, which may not be obvious in the AP view. When the stenosis is suspected in the ostium of the right subclavian artery, the AP view may not
show the stenosis due to overlapping of the origin of the right common carotid artery (Fig. 23-9). A steep RAO caudal (40°-60° RAO with 10°-20° caudal), or RAO cranial view may be necessary to separate the origin of the right subclavian artery from the right common carotid artery (Fig. 23-10).

**FIGURE 23-9** Angiography in the AP view of the innominate artery and its bifurcation into the right subclavian and common carotid artery. The AP view overlaps the origin of the right subclavian artery and the right common carotid artery and may obscure a significant stenosis in the proximal portion of the subclavian artery.
FIGURE 23-10 The same patient as Figure 23-9 shown in the RAO caudal view, which separates the view of these two vessels and allows visualization of a mild plaque in the proximal right subclavian.

Vertebral artery angiography is usually performed with a non-selective injection of contrast in the subclavian artery close to the origin of vertebral artery, since the ostium is the most commonly affected area of stenosis. The vertebral artery usually arises from the superior aspect of the subclavian artery; however, not infrequently, the vertebral artery may arise posteriorly. A shallow cranial oblique (RAO or LAO with cranial angulation 10°-30°) is often needed to demonstrate the ostial stenosis (Fig. 23-11).
FIGURE 23-11 Non-selective digital subtraction angiography of the right vertebral artery in the AP view. The ostium in the V₁ portion of the vessel may not be well appreciated in this view. An AP cranial view is often necessary for better visualization of these segments.

When necessary, selective engagement of the vertebral artery can be performed with angled tip catheters (4-6-Fr internal mammary catheter, Berenstein catheter, or right Judkins-4 diagnostic catheter).

ABDOMINAL AORTA

The abdominal aorta begins at the level of the diaphragm at the 12⁰ thoracic vertebra. At this level, the aorta is anterior and leftward of the spine before its bifurcation into the common iliac arteries at the fourth lumbar vertebra.¹¹ The normal diameter of the abdominal aorta ranges between 1.5 cm and 2.15 cm.²² There are 3 main branches originating from the anterior aspect of the abdominal aorta: The first is the celiac trunk or celiac artery which arises at
the level of T₁₂ to L₁. Next, the superior mesenteric artery (SMA) originates above the renal arteries, between L₁ and L₂. The final branch, the inferior mesenteric artery (IMA), takes off in a left anterolateral direction at the level of L₃ to L₄. The renal arteries originate from the lateral aspect of the abdominal aorta at the level of L₁ to L₂ taking a lateral and posterior direction. Below the main renal arteries, four pairs of lumbar arteries arise in a posterolateral direction.¹¹

**Abdominal Aortogram**

Vascular access may be obtained from the arm or leg. A 4-Fr to 6-Fr pigtail catheter is positioned in the abdominal aorta so that the side holes are directly adjacent to the ostia of renal arteries. With a breath hold and subtraction angiogram, a power injection of contrast at 15 to 20 mL/sec, for a total of 30 to 40 mL of contrast, is usually adequate for good quality angiograms. It is important that the upper, lower, and lateral margins of both kidneys are visualized. This usually requires an image intensifier of 12 inches or larger. Two views should be obtained: the AP view allows good visualization of the renal arteries, and the lateral view enables assessment of the origin of the celiac and mesenteric arteries (Fig. 23-12 and Fig. 23-13). It is important to obtain images through the venous phase to visualize any late-filling collaterals. Of particular importance are pelvic collaterals that may be filling the mesenteric vessels.
FIGURE 23-12 Abdominal aortogram in the AP view showing significant ectasia and stenosis of the abdominal aorta.
Renal Arteries

The renal arteries arise from the lateral aspect of the abdominal aorta, usually between L₁ and L₂. They course laterally and posteriorly, and may take a caudal, horizontal, or cranial orientation. In about one quarter of the normal population an accessory renal artery will be present, which may originate anywhere from the suprarenal aorta down to the iliac arteries. Identifying these accessory branches is a major reason to perform an abdominal aortogram first, rather than proceeding immediately to selective renal angiography.

Renal Angiography

After an abdominal aortogram has identified the origin of the renal arteries,
selective renal angiography may be indicated if the aortogram demonstrates a renal artery stenosis of questionable hemodynamic significance, detailed images are required, or there is a need for pressure gradient measurement. Selective renal angiography is indicated if intrarenal vascular disease is suspected, as in fibromuscular dysplasia (FMD), vasculitis, or aneurysmal disease.

The renal arteries can be selectively engaged with 4-Fr to 6-Fr angled diagnostic catheters, although shepherd’s crook shapes (Sos Omni or Simmons) may be helpful in some cases. Selective renal angiography is performed with hand injection of contrast in a shallow LAO angulation (5°-10°) for both renal arteries (Fig. 23-14). The shallow LAO view has been shown to be the best view for the assessment of the ostium and proximal portions of both the right and the left renal arteries. Occasionally, some caudal or cranial angulation (15°-20°) may be helpful for tortuous vessels.

![Non-selective subtracted abdominal aortograms in the AP view of normal renal arteries (left) and bilateral renal artery stenoses (right).](image)

**FIGURE 23-14** Non-selective subtracted abdominal aortograms in the AP view of normal renal arteries (left) and bilateral renal artery stenoses (right).

**Mesenteric Arteries**

The celiac artery, superior mesenteric artery (SMA), and the inferior
mesenteric artery (IMA) constitute the mesenteric or splanchnic circulation. The celiac artery arises at the level of T₁₂ to L₁ and supplies blood to the stomach and half of the duodenum (foregut). The SMA originates at the level of L₁ to L₂ and provides blood flow to the lower half of the duodenum, ileum, cecum-appendix, ascending colon, and proximal two-thirds of the transverse colon (midgut). The IMA takes off in a left anterolateral direction at the level of L₃ to L₄ and supplies blood to the distal third of the transverse colon, descending colon, sigmoid colon, rectum, and the upper part of the anal canal (hindgut).²⁴

**Mesenteric Angiography**

Angiography of the mesenteric arteries is the gold standard to assess the anatomy of this vascular system. As is the case for the renal arteries, before selective angiography is performed, an abdominal aortogram should be obtained in the AP and lateral projections (Fig. 23-15). After the origin of the mesenteric vessels has been identified, selective angiography, if indicated, may be performed in the lateral view using angled diagnostic catheters (Fig. 23-16). The IMA often arises in a very acute inferior angle on the anterior portion of the abdominal aorta, for which a Simmons-1 or Sos Omni catheter is very useful for engagement.
FIGURE 23-15 Subtracted abdominal aortogram in the lateral view to assess the ostium and proximal portion of the celiac trunk and the superior mesenteric arteries.
Selective engagement of the mesenteric arteries allows measurement of translesional pressure gradients, since, as is the case for the renal arteries, the majority of stenoses in these vessels are located in their ostium or their very proximal portion. Using hand injections, selective angiography is performed in the lateral and oblique views.

**Pelvic and Lower Extremity Arterial Circulation**

The abdominal aorta bifurcates into the common iliac arteries (CIA) at the level of L₄ to L₅. The CIA bifurcates into the internal iliac artery (IIA) or hypogastric artery and external iliac artery (EIA) at the level of the lumbosacral junction. At the level of the inguinal ligament, two small branches originate from the EIA: the inferior epigastric artery, which follows...
a medial and superior direction, and the deep iliac circumflex artery, which takes a lateral and superior direction. These vessels are important to visualize as they may be the source of post-procedure access site bleeding.

Once the EIA crosses the inguinal ligament, it becomes the common femoral artery (CFA), which courses medially over the femoral head. When it reaches the lower edge of the femoral head, the CFA divides into the superficial femoral artery (SFA) and profunda femoris artery (PFA), also known as the deep femoral artery. The PFA runs posterior and lateral along the internal aspect of the femur. A few centimeters after its origin, the PFA gives origin to two small branches—the lateral femoral circumflex and the medial femoral circumflex arteries—and, subsequently, to several small perforating arteries. The SFA continues down the anteromedial thigh, and in its distal portion runs deeper to cross the abductor (eg, Hunter’s) canal where it becomes the popliteal artery. The popliteal artery crosses the knee and gives origin to small muscular branches, 2 sural branches, and 3 geniculate arteries (superior, medial, and inferior).27

Below the knee, the popliteal artery gives rise to the anterior tibial (AT) artery and continues as the tibioperoneal trunk (TPT). The AT artery runs laterally and anterior to the tibia to the foot, and as it passes over the ankle onto the dorsum of the foot, and becomes the dorsalis pedis (DP) artery. The TPT, bifurcates into the posterior tibial (PT) and the peroneal arteries. The PT courses posteromedially in the calf, while the peroneal runs near the fibula between the AT and PT arteries. The peroneal artery then rejoin the PT above the ankle via the posterior division, and the anterior tibial through the anterior division. On the dorsum of the foot, the DP artery has lateral and medial tarsal branches. After the PT artery passes behind the medial malleus, it divides into medial and lateral plantar arteries. The lateral plantar and distal DP arteries join to form the plantar arch.27

**Angiography for the Pelvis and Lower Extremity**

Vascular access is equally effective from the arm or femoral arteries for diagnostic angiography. If the CFA is chosen, the less symptomatic extremity is preferred. A 4-Fr to 6-Fr pigtail catheter is positioned in the terminal aorta, below the IMA and above the aortic bifurcation at L₄ or L₅. A power injection of 8 mL to mL/sec for a total 80 to 100 mL is needed to image both legs (from the CIA to the feet) using a stepping table and DSA.
Selective angiograms in different angulations of a particular artery or arterial segments are useful when the non-selective angiogram shows possible stenoses or when further anatomic clarification is needed. If access has been obtained from the CFA and the arterial segment in question is located in the contralateral extremity, a diagnostic internal mammary catheter is positioned at the origin of the contralateral CIA. A Simmons Type I or II catheter can also be used in case of significant acute angulation between the origin of both CIA. A soft-tip straight steerable 0.035-in guidewire such as a Wholey wire, or an angled Glidewire (Terumo Interventional Systems, Somerset, NJ) is advanced to the CFA. The angiographic catheter is advanced over the guidewire to the area of interest, and angiography is obtained.

There are specific angiographic views which help to improve anatomical detail. In the AP view, there is significant overlapping of the origin of the EIA and the IIA, and ostial lesions in either vessel may be missed. In order to “separate” these 2 segments, the contralateral oblique 20° with 20° caudal view is very useful (Fig. 23-17 and Fig. 23-18). The proximal portions of SFA and the PFA are overlapping in the AP view. They are separated best with a 30° lateral angulation (Fig. 23-19). Finally, it is desirable to avoid overlapping of the SFA, popliteal, or infrapopliteal arteries with the dense cortical leg bones. Lateral oblique angulation (30°), with digital subtraction images offer an excellent separation of the vessels (Fig. 23-20 to Fig. 23-22).
FIGURE 23-17 Digital subtraction angiography of the left common iliac artery and its bifurcation in AP view, showing significant overlapping of the origin of the internal and external iliac arteries.
FIGURE 23-18 The same patient as Figure 23-17. Digital subtraction angiography of the left common iliac artery and its bifurcation shown in the right anterior oblique caudal view reveals a significant stenosis in the ostium of the left internal iliac artery not visualized in the AP view.
FIGURE 23-19 Angiography of the right common femoral artery (CFA) bifurcation in the AP view (left). A stenosis at the ostium of the profunda femoris artery (PFA) is noted in the ipsilateral oblique (20° right anterior oblique) view which was missed in the AP view (right).
FIGURE 23-20 Digital subtraction angiography of the right anterior tibial artery, tibioperoneal trunk, peroneal and posterior tibial artery.
FIGURE 23-21 Digital subtraction angiography of the right popliteal artery showing occlusion of the anterior tibial (AT) artery and the tibio-peroneal trunk (TPT), before (A) and after (B) stent placement of the TPT and peroneal arteries and angioplasty of the posterior tibial artery.
FIGURE 23-22 Occlusion of the left dorsalis pedal artery (white arrow).

COMPLICATIONS OF PERIPHERAL VASCULAR ANGIOGRAPHY

Complications leading to significant morbidity or mortality, although unusual, do occur, and the operator must remain vigilant during and after angiography in order to minimize them.

The registry of the Society for Cardiac Angiography and Interventions (SCAI) found an incidence of vascular complications for diagnostic angiography of 0.5% to 0.6%. When CFA access is used, the most common vascular complication is hematoma, which usually resolves within a few weeks after the procedure. If the hematoma remains in continuity with the arterial lumen due to inadequate sealing of the puncture site, a pseudoaneurysm may develop. This is usually manifested as a painful
pulsatile mass with an audible bruit. The diagnosis is easily confirmed with
duplex ultrasound. When the femoral arterial puncture (front or back wall) is
above the inguinal ligament, a hematoma may extend into the retroperitoneal
space, with bleeding not evident from the surface examination.

Retroperitoneal bleeding must be strongly suspected when a patient
becomes hypotensive after angiography from common femoral arterial
access, with or without flank pain. Aggressive volume replacement with
normal saline is indicated. If the patient remains hemodynamically unstable,
he must be taken for angiography of the vascular access to identify and stop
the bleeding with balloon inflation. Although the majority of retroperitoneal
hematomas resolve spontaneously, some require treatment. Percutaneous,
catheter-based modalities, may be effective for treating retroperitoneal
bleeding in selected patients. Other less frequent vascular complications
include arterial laceration, which requires a covered stent or surgical repair,
and symptomatic arteriovenous fistulas, which usually require surgical
treatment.

Stroke may occur as a rare but potentially devastating complication after
catheter placement in the aortic arch. The SCAI registry found a 0.07%
incidence of stroke during cardiac catheterization. The incidence of
neurologic events during carotid angiography is substantially higher,
identified as 0.78% to 1% in prospective studies. In general,
asymptomatic patients have a lower risk, whereas patients who undergo
angiography in the setting of transient ischemic events have a slightly higher
complication rate. The neurologic complication rate for patients with
severe bilateral carotid stenoses is 12.5%. In a review of cerebral
angiography performed by cardiologists, the risk of angiography was 0.05%.

Allergic and anaphylactoid reactions have substantially decreased with the
use of low/iso-osmolar contrast agents. Their reported incidence is less than
1%. The risk of developing CIN is highest in patients with baseline chronic
renal insufficiency (creatinine >2.1 mg/dL), diabetes mellitus, multiple
myeloma, and those who are receiving other nephrotoxic drugs such as
aminoglycosides, nonsteroidal anti-inflammatory drugs, and angiotensin-
converting enzyme inhibitors. Patients at higher risk for CIN must be
well hydrated before and after the procedure, and the volume of contrast
administered must be minimized. There is inconsistent and conflicting
data regarding the efficacy of the dopamine-1 receptor antagonist, fenoldopam in preventing CIN.\textsuperscript{48} There is also inconsistent evidence that the use of N-acetylcysteine (Mucomyst) is of benefit for preventing CIN.\textsuperscript{49,50} One small, randomized trial showed that and the use of hydration with sodium bicarbonate can prevent CIN; however, this needs to be confirmed in larger studies.\textsuperscript{51} At present, it is recommended that patients with a glomerular filtration rate of <50 mL/1.73 m\textsuperscript{2}, should avoid iodinated contrast agents if possible. If conventional angiography is required, a low/iso-osmolar agent should be used at the minimal dose, nonsteroidal anti-inflammatory drugs and diuretics should be withheld, and \(\sim 1\) mL/kg of 0.9% saline should be administered starting at least 3 hours prior to the procedure and continuing 12 hours after the procedure.\textsuperscript{52}

REFERENCES


29. Beales JS, Adcock FA, Frawley JS, et al. The radiological assessment of


Although coronary angiography remains the reference standard for diagnosing critical epicardial coronary artery disease (CAD), it has a number of limitations. Identifying functionally significant intermediate coronary narrowings, characterizing plaque morphology, detecting moderate diffuse intimal thickening, evaluating the results of percutaneous coronary intervention (PCI), and assessing the status of the microvasculature all remain challenging with coronary angiography alone.\textsuperscript{1-6} Technologic advancements have made several adjunctive diagnostic techniques available that allow the interventional cardiologist to address the limitations of coronary angiography and more thoroughly assess the coronary circulation.

In this chapter we will focus on the role of the coronary pressure wire to measure fractional flow reserve (FFR) and guide decisions regarding coronary revascularization. The background and derivation of FFR were already covered in Chapter 6. We will briefly review the concept of FFR and then detail how to measure FFR, outline the clinical indications for FFR assessment, and present data supporting its role in the cardiac catheterization laboratory.

HISTORICAL BACKGROUND

The significance of intracoronary pressure gradients and their reflection of
the severity of underlying CAD has been appreciated for many years. However, it was not until the advent of miniaturized pressure sensors that allowed a wire-based approach to measuring coronary pressure and not until the development and validation of the FFR index by Pijls and De Bruyne that intracoronary pressure measurements have become a routine procedure in many catheterization laboratories.

DERIVATION OF FFR

FFR is defined as the fraction of maximal blood flow perfusing the myocardium in the presence of stenosis compared with the maximal blood flow that would reach the myocardium in the theoretical absence of the stenosis. Because the measurement is made at maximal vasodilation, resistance is minimized and flow becomes proportional to pressure. In a normal epicardial artery, there is little pressure decrement along the vessel, and distal pressure is roughly equal to proximal pressure. Therefore, in a diseased vessel, one can estimate the distal flow or pressure in the theoretical absence of the disease by measuring the proximal pressure. FFR then can be calculated easily in a diseased vessel by dividing the distal pressure, measured with a coronary pressure wire, by the proximal pressure, measured with the guiding catheter during peak hyperemia.

Compared with other techniques for determining the functional significance of a coronary narrowing, measuring FFR has several inherent advantages. It has an absolute normal value of 1.0 and a narrow range of normal values extending from 0.94 to 1.0. Because the measurements are made at maximal vasodilation, the effects of resting hemodynamics are eliminated, making FFR an extremely reproducible index, independent of blood pressure and heart rate. Compared with measuring CFR to evaluate intermediate coronary lesions, FFR is advantageous because it is epicardial artery-specific and independent of the microcirculation (Table 24-1). As described in more detail below, FFR has a narrow cutoff range for identifying ischemia-producing lesions. Numerous studies have shown that an FFR less than 0.75 to 0.80 correlates strongly with the presence of ischemia on a variety of noninvasive stress tests and predicts clinical outcome with or without percutaneous coronary intervention (PCI).
Table 24-1 Important Characteristics of Fractional Flow Reserve (FFR)

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Normal value of 1.0 in every vessel and every patient</td>
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<tr>
<td>Narrow ischemic threshold at &lt;0.75-0.80</td>
</tr>
<tr>
<td>Independent of hemodynamic changes</td>
</tr>
<tr>
<td>Extremely reproducible</td>
</tr>
<tr>
<td>Specific for the epicardial vessel</td>
</tr>
<tr>
<td>Independent of the microvasculature</td>
</tr>
<tr>
<td>Accounts for collateral flow</td>
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HOW TO MEASURE FFR: EQUIPMENT AND TECHNIQUE

The coronary pressure wire is a standard 0.014-in angioplasty guidewire with a high-fidelity pressure transducer mounted 3 cm from the tip of the wire, at the junction of the radiopaque and radiolucent segments. There are now multiple manufacturers of pressure wires, each of which have their own consoles which analyze and display the pressure recordings. The 2 oldest and most commonly used ones (St. Jude Medical Systems and Philips Healthcare) incorporate piezoelectric technology to measure intracoronary pressure. More recently introduced wires (Opsens and Boston Scientific) utilize optical sensors to measure pressure. The potential advantages of these newer wires are less propensity for pressure drift and improved wire handling characteristics. Finally, a micro catheter (Acist Medical Systems) with an optical pressure sensor mounted near its tip has been introduced and has the added advantage of allowing measurement of distal pressure by advancing the microcatheter over a workhorse wire. However, it has the theoretical disadvantage of increasing stenosis severity (because of its larger crossing profile compared to a 0.014-inch wire alone) and lowering FFR, particularly in smaller vessels and more severe lesions.

To measure FFR, it is traditionally necessary to connect the pressure console to the catheterization laboratory pressure monitoring system and to calibrate the guiding catheter and pressure wire. Newer wireless systems and
integrated consoles allow the pressure wire to communicate with the cath lab system without external connectors and facilitate this process. After administering intravenous heparin (or another antithrombotic agent) and intracoronary nitroglycerin (100-200 micrograms), the pressure wire should be advanced out of the guiding catheter so that the pressure transducer is positioned at the ostium of the guiding catheter. At this location, both the pressure wire and the guiding catheter should display identical pressures. One should flush the guiding catheter with saline to ensure an accurate pressure recording. If this is not the case, the pressure wire can be equalized to the guiding catheter. This step can be performed with the catheter and wire in the aorta in the presence of ostial coronary disease. The pressure wire is then advanced to the distal part of the vessel and a vasodilating agent such as adenosine is administered. It is important to start with the sensor in the distal two-thirds of the vessel so that not only the lesion in question, but also any other atherosclerosis in the vessel can be interrogated. The FFR of the vessel is the lowest value achieved by dividing the simultaneously measured mean distal pressure by the mean proximal pressure during maximal steady state hyperemia (Fig. 24-1). Occasionally with intravenous adenosine variability in the delivery of and/or response to adenosine results in fluctuations in the $P_d/P_a$ ratio. If this occurs, the lowest $P_d/P_a$ should be taken as the FFR. At times, the pressure wire console will record an inaccurate FFR because of an artifact in the pressure tracing, such as can occur when the manifold is open in order to inject intracoronary adenosine. For this reason, it is always important for the operator to review the tracing and determine the correct FFR.
FIGURE 24-1 Example of fractional flow reserve (FFR) determination. The upper red tracing represents the mean and phasic pressure recorded from the guiding catheter and the lower green tracing represents the mean and phasic pressure recorded from the pressure wire in a patient with a physiologically significant stenosis of the left anterior descending artery. The nearly horizontal yellow line above the 2 tracings represents the continuous distal pressure divided by proximal pressure calculation, and the vertical line marks the peak gradient and represents the FFR of 0.72.

If it is not possible to manipulate the pressure wire down the desired vessel, one can remove the pressure wire after equalization and wire the vessel with a more maneuverable wire through an exchange microcatheter. Once the wire and microcatheter have been advanced to the desired location, the more maneuverable wire can be removed. The pressure wire can then be advanced through the microcatheter to the desired location and the microcatheter can then be pulled back into the guiding catheter. At this point, FFR can be measured in the usual fashion. Alternatively, one can use the Navvus microcatheter (ACIST RXi) to measure pressure over the more maneuverable workhorse wire.

Achieving maximal hyperemia is critical in order to accurately measure FFR. If hyperemia is submaximal, the gradient across the stenosis in question will be underestimated and FFR will be overestimated. The reference standard agent for achieving peak vasodilatation is intravenous adenosine. Ideally, it is administered through a central vein or large bore peripheral line.
Peak hyperemia typically occurs within 1 minute and is signaled by the onset of chest pain (not due to ischemia) and or shortness of breath. These symptoms are generally well tolerated, particularly if the patient is forewarned and can be helpful in that they assure the operator that hyperemia has occurred. Because the hyperemia lasts as long as the infusion continues, intravenous adenosine is advantageous in that it allows more careful determination of the peak gradient. In addition, it affords the operator the ability to slowly pull back the pressure wire proximally in order to identify the area of stenosis. This can be particularly useful if there is diffuse disease or multiple lesions in the vessel (Fig. 24-2). Finally, in the setting of ostial left or right coronary lesions, it allows the operator time to remove the guide catheter from the ostium of the vessel in order to accurately measure FFR.
Intracoronary adenosine is another common method for measuring FFR which in the United States is less expensive and easier to administer. Its major drawback is its short peak effect, which is roughly 10 to 15 seconds. In addition, because it is given via the coronary artery, the potential exists for incomplete administration down the coronary artery and partial injection or reflux into the aorta. Recently, it has been shown that higher doses than previously used are necessary to achieve peak hyperemia, but typically 100 micrograms in the right coronary artery and 200 micrograms in the left coronary are adequate. If there is any doubt regarding adequate hyperemia, it is important to use either intravenous adenosine or an alternative agent, such as intracoronary papaverine.

Using intracoronary papaverine to measure FFR is advantageous because its peak effect is longer lasting than intracoronary adenosine, roughly 45 seconds, which makes more accurate determination of FFR possible and which allows time to perform a slow pullback of the pressure sensor. In addition, papaverine is inexpensive and easy to prepare and administer. Its major drawback is its potential arrhythmogenic effect. In an older series, the incidence of a serious arrhythmia (ventricular tachycardia or torsades de pointes) was approximately 1%. Fortunately, these arrhythmias were usually self-limited. Papaverine can precipitate in ionic contrast medium, which may induce the arrhythmia.

A newer hyperemic agent, regadenoson, has been recently introduced. It is an agonist specific for the adenosine A2A receptor and has the potential advantage of inducing less bronchoconstriction than adenosine. A recent study demonstrated equivalent hyperemia compared to intravenous (IV) adenosine with excellent reproducibility. An advantage is that it can be given as a single peripheral IV bolus. A potential drawback is that the hyperemic effect lasts between 45 seconds and 10 minutes, but its duration is unpredictable. A number of other agents are available for achieving hyperemia and are listed in Table 24-2.

Table 24-2  Agents for Inducing Hyperemia
If the FFR is abnormal and PCI is necessary, the operator can disconnect the pressure wire from the interface coupler and a balloon catheter or stent can be advanced over the pressure wire in the usual fashion. During balloon inflation the pressure wire can be reconnected and the coronary wedge pressure, a reflection of collateral flow, can be recorded. After completing the PCI, the pressure wire can be reconnected and FFR remeasured. Finally, it is important after measuring FFR, whether or not PCI has been performed, to reposition the pressure sensor at the ostium of the guiding catheter before removing the wire completely, to ensure that equal pressures are recorded from the guiding catheter and the pressure wire (ie, that no “drift” in either pressure recording system has occurred). If there is a difference greater than 0.05, then one should consider reequalizing the pressure wire and remeasuring FFR.

### INDICATIONS FOR MEASURING FFR

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Adenosine</td>
<td>IV infusion</td>
<td>140 µg/kg/min</td>
<td>Reference standard. Side effects include dyspnea and chest pain. Prolonged hyperemia allows pressure wire pullback.</td>
</tr>
<tr>
<td>Adenosine</td>
<td>IC bolus</td>
<td>&gt;100-200 µg</td>
<td>Easy to use, inexpensive, and no significant side effects. Transient heart block at high doses. Hyperemia lasts only 10-15 seconds.</td>
</tr>
<tr>
<td>Adenosine</td>
<td>IC infusion</td>
<td>240-360 µg/min</td>
<td>Inconvenient set-up. Fewer side effects compared to IV infusion. Prolonged hyperemia allows pullback. Not well-validated.</td>
</tr>
<tr>
<td>Regadenoson</td>
<td>IV bolus</td>
<td>400 µg</td>
<td>Convenient, single IV bolus. Expensive. Side effects similar to IV adenosine but less severe and briefer. Hyperemia lasts 20 seconds-10 min.</td>
</tr>
<tr>
<td>Papaverine</td>
<td>IC bolus</td>
<td>10-20 mg</td>
<td>Easy to use, inexpensive. Rare, but significant side effect of polymorphic VT. Hyperemia lasts 30 seconds, allowing pullback.</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>IC bolus</td>
<td>0.3-0.9 µg/kg</td>
<td>Easy to use, inexpensive. Major side effect is hypotension. Hyperemia lasts 50 seconds allowing pullback. Not well-validated.</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>IV infusion</td>
<td>50 µg/kg/min</td>
<td>Inconvenient as it takes time for onset an offset. Side effects include palpitations and hypotension. Not well-validated for FFR.</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>IC bolus</td>
<td>2 mg</td>
<td>Not available in United States. Fewer side effects compared to IV adenosine. Hyperemia lasts 30 seconds. Not well-validated.</td>
</tr>
</tbody>
</table>

IC: intracoronary; IV: intravenous; µg: microgram; mg: milligram; min: minute; VT: ventricular tachycardia.
Indications for measuring FFR are listed in Table 24-3. The most common indication for measuring FFR is to determine the physiologic significance of an intermediate coronary lesion. As many more patients present to the catheterization laboratory without a prior noninvasive assessment for myocardial ischemia and with an awareness of the limitations of angiography alone to identify functionally important moderate lesions, the role of a relatively simple method, such as measuring FFR, for interrogating this challenging subset has expanded. Pijls and colleagues performed a landmark trial comparing FFR with 3 noninvasive stress tests. They showed that an FFR less than 0.75 is 100% specific for predicting myocardial ischemia; the sensitivity was 88% and the predictive accuracy was 93%. Since this seminal report, clinical experience and subsequent studies have found a “grey zone” for FFR between 0.75 and 0.80. If the FFR falls in this range, one should use clinical judgment to decide if revascularization is warranted. If the patient has typical symptoms and a proximal lesion in a large vessel that is amenable to stenting, then revascularization should be performed. If the patient has no symptoms, atypical symptoms, and/or the lesion is located in a small or distal vessel, then medical therapy may be more appropriate. If the FFR is greater than 0.80, it is extremely unlikely that significant ischemia is present. FFR is not a dichotomous variable but a continuous one reflecting the fact that lower FFR values correspond with higher event rates in patients treated medically. This concept is an important one that has recently been highlighted.

Table 24-3 Common Indications for Measuring Fractional Flow Reserve (FFR)

<table>
<thead>
<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>Coronary lesion of unclear significance</td>
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<tr>
<td>Multiple lesion assessment in multivessel coronary artery disease (CAD)</td>
</tr>
<tr>
<td>Indeterminate left main coronary stenosis</td>
</tr>
<tr>
<td>“Jailed” sidebranch evaluation</td>
</tr>
<tr>
<td>After percutaneous coronary intervention</td>
</tr>
<tr>
<td>Nonculprit lesions at the time of acute myocardial infarction</td>
</tr>
<tr>
<td>Investigate for angiographically silent diffuse disease</td>
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Intermediate Lesions
To determine the safety of employing FFR to guide the operator’s decision to defer PCI, Bech and colleagues, in the DEFER trial, measured FFR in 325 patients with chest pain, no prior stress test, and intermediate coronary lesions who had been referred for PCI. One hundred and forty-four of these patients had an FFR less than 0.75, underwent PCI as planned, and formed a reference group. One hundred and eighty-one had an FFR of 0.75 or greater and were randomized to deferral of PCI (n = 91) or performance of PCI (n = 90). The deferral group had a greater freedom from major adverse cardiac events at 2 years, although not statistically significant, compared with the performance group: 89% versus 83%, respectively. The reference group had a significantly worse event-free survival compared with the deferral group (78% vs 89%, \( P = 0.03 \)), presumably because they had more significant CAD. Five-year follow-up from this study was reported and found that the rate of cardiac death or myocardial infarction (MI) in the deferral group was less than half of the rate in the performance group (3.3% vs 7.9%, \( P = 0.21 \)). Recently, the 15-year follow-up from this trial has been published, revealing no difference in long-term mortality between the two groups, but a significantly lower rate of MI in the patients assigned to deferral of PCI (2.2% vs 10%, \( P = 0.03 \)). This trial clearly showed that it is safe to defer PCI in stable patients with an intermediate lesion and an FFR of 0.75 or greater. Numerous other registries have confirmed the findings in the DEFER trial.

**Multivessel CAD**

The FFR versus Angiography for Multivessel Evaluation (FAME) trial established the role of routine FFR measurement for guiding PCI in patients with multivessel CAD amenable to PCI. In the FAME trial, 1005 patients with coronary lesions of >50% diameter stenosis in 2 or 3 major epicardial vessels which were amenable to PCI with drug-eluting stents were randomized to either the standard of care, angiography-guided PCI, or to FFR-guided PCI. Angiography-guided PCI was performed based on the noninvasive clinical data and the angiographic appearance of the lesions. For the FFR-guided PCI arm, FFR was measured across every stenosis and only if the FFR was \( \leq 0.80 \) was PCI performed on the particular stenosis.

There were approximately 3 lesions identified per patient in both groups, but the angiography-guided PCI group received significantly more stents per
patient, 2.7 ± 1.2 versus 1.9 ± 1.3, \( P < 0.001 \). In addition, significantly more contrast media was administered to the angiography-guided PCI patients, 302 ± 127 versus 272 ± 133 mL, \( P < 0.001 \). Importantly, the duration of the procedure was identical between the two groups—although measuring FFR adds time to the procedure, avoiding unnecessary PCI saves time. Despite the fewer stents, the percentage of patients free of angina at 1 year was numerically higher in patients randomized to FFR guidance (81.3% vs 77.9%, \( P = 0.20 \)).

The primary endpoint of the FAME trial was the 1-year rate of death, MI or repeat revascularization, which occurred in 18.3% of the angiography-guided PCI patients as compared to 13.2% of the FFR-guided PCI patients, \( P < 0.02 \) (Fig. 24-3). This significant reduction resulted from 30% to 40% relative risk reductions in each component of the composite endpoint. In addition, the rate of death and MI was reduced significantly in the FFR-guided PCI group (7.3% vs 11.1%, \( P = 0.04 \)). Subsequently, the 2-year results of FAME were reported and revealed a persistent reduction in the composite of death, MI and repeat revascularization (17.9% vs 22.4%, \( P = 0.08 \)). Importantly, the hard endpoints of death and MI remained significantly lower in the FFR-guided PCI patients (8.4% vs 12.9%, \( P = 0.02 \)). The Kaplan-Meier curves at 1 and 2 years showed that the benefit attributed to FFR guidance occurred early, due to fewer procedural-related events, and continued during follow-up, due to fewer late events. Recently, the 5-year follow-up from the FAME trial has been published and found continued separation of the curves with respect to major adverse cardiac events between the two groups, without any significant late catch-up in events in the FFR-guided PCI group.\(^{24}\)
FIGURE 24-3 One-year outcomes in the FFR versus Angiography for Multivessel Evaluation (FAME) 1 trial comparing angiography-guided percutaneous coronary intervention (PCI) to fractional flow reserve (FFR)-guided PCI.

The FAME trial further highlighted the limitations of coronary angiography alone for identifying lesions responsible for ischemia. Approximately 35% of the lesions graded between 50% and 70% narrowed had an ischemic FFR, while roughly 20% of the lesions between 71% and 90% narrowed had nonischemic FFR values (Fig. 24-4). This would suggest that all lesions between 50% and 90% narrowed could benefit from FFR measurement to accurately determine their functional significance.

FIGURE 24-4 A breakdown of lesions in the fractional flow reserve (FFR)-guided arm of patients in the FFR versus Angiography for Multivessel Evaluation (FAME) 1 trial demonstrating their FFR values based on their visual diameter stenosis on the
The FAME trial raised awareness about the differences between anatomic complete revascularization and “functionally” complete revascularization. In patients with multi-vessel coronary disease, this is particularly relevant because many of our treatment decisions regarding revascularization are made based on angiographic (or anatomic) assessment of the severity of coronary disease. For example, the SYNTAX score is an angiography-based scoring system designed to quantify the complexity of coronary disease; those patients with high SYNTAX scores tend to have better outcomes with coronary artery bypass graft (CABG) surgery, while those patients with low scores appear to do equally well with PCI.26

Because the SYNTAX score is based on visual interpretation of the angiogram, it is inherently limited by the inaccuracy of the angiogram. A substudy from the FAME trial asked whether incorporating FFR into the SYNTAX score and calculating a “Functional SYNTAX Score (FSS)” might convert higher-risk SYNTAX score patients to a lower risk, and whether it might improve the risk stratification of patients with multi-vessel coronary disease undergoing PCI.27

In the 497 patients in the FFR-guided arm of FAME, the SYNTAX score was calculated in the usual fashion and the patients were divided into tertiles, based on the SYNTAX score. The FSS was then determined by recalculating the SYNTAX score taking into account only those lesions with an FFR ≤0.80. More than one third of patients moved from a higher risk group to a lower one after calculation of the FSS. In addition, the FSS was a significant predictor of death or MI, while the classic SYNTAX score was not (Fig. 24-5). In this manner, the FSS simplifies the approach to PCI in many of these challenging multi-vessel disease patients and may make PCI a more appropriate treatment than CABG. This hypothesis is now being tested prospectively in the FAME 3 trial, comparing FFR-guided PCI to CABG in patients with 3-vessel coronary disease (www.clinicaltrials.gov: NCT02100722).
A comparison of the classic SYNTAX score and the Functional SYNTAX Score for their abilities to discriminate the risk for death and myocardial infarction. Of note, the percentage of patients falling into the highest risk functional SYNTAX score group is smaller than in the highest risk SYNTAX score group and the percentage of patients in the lowest risk group is much larger.

**Acute Coronary Syndromes**

The majority of PCI involves patients presenting with acute coronary syndromes (ACS). The role of FFR in these settings depends on whether the patient is presenting with ST segment elevation myocardial infarction (STEMI) or a non-ST elevation ACS (NSTEMI) and whether one is evaluating the culprit vessel or the nonculprit vessel. In the setting of STEMI, acute microvascular dysfunction can occur which will affect the peak flow achievable down the culprit vessel. This will result in a lower gradient and higher FFR for a given stenosis. Over time, some of the transient microvascular dysfunction can improve and the peak flow can increase leading to a larger gradient and lower FFR. For this reason, in the acute setting of a STEMI, measuring FFR in the culprit vessel is not recommended. Studies have shown that typically a number of days after STEMI, most of the transient microvascular dysfunction has resolved and one is left with chronic microvascular damage. In this setting, although the peak flow across a given stenosis may be lower, the gradient less and the FFR higher, the FFR remains accurate and is a reflection of the smaller amount of viable myocardium subtended by the vessel. Therefore, in the nonacute setting, FFR down the culprit vessel remains reliable.
There has been some concern regarding the role of FFR in the nonculprit vessel of patients presenting with STEMI. Older studies suggested that with STEMI, some degree of global microvascular dysfunction occurred which might affect the accuracy of FFR even in the nonculprit study. However, in a series of 101 ACS patients, Ntalianis and colleagues measured FFR in a nonculprit vessel in the acute setting and then repeated the measurement an average of 1 month later. They found only 2 cases in which the FFR was >0.80 in the acute setting and <0.75 at the time of follow-up, suggesting that in the vast majority of cases FFR can be measured accurately in the nonculprit vessel of a patient presenting with STEMI.

In a recent clinical trial, 627 STEMI patients with multivessel CAD were randomized to PCI of the culprit vessel only versus culprit vessel PCI and FFR-guided management of the nonculprit disease. These investigators found a significantly lower rate of the composite endpoint of death, reinfarction, and ischemia-driven revascularization of the nonculprit vessels at a median follow-up of 27 months in the functionally completely revascularized patients (13% vs 22%, \( P = 0.004 \)). This difference was primarily a result of lower rates of ischemia-driven revascularization in the patients with FFR guidance, but the study reinforces the safety and benefit of FFR guidance of nonculprit stenoses in the setting of STEMI.

**Tandem Lesions**

Tandem lesions or serial stenoses in the same vessel can be challenging to interrogate independent of each other with FFR. This is because each lesion affects flow across the other, and removal of one lesion may result in increased flow across the remaining lesion and a persistently low FFR. Predicting the contribution of each lesion to an FFR value is not practical because it requires complex equations and measurement of the coronary wedge pressure. For these reasons, when one is faced with serial narrowings, one should first measure FFR with the pressure sensor distal to both lesions. If the FFR is not ischemic, then the combination of the two lesions is not functionally significant and medical therapy is warranted. If the FFR is ischemic, then a slow pullback of the wire during maximal hyperemia (typically with IV infusion of adenosine) should be performed. Whichever lesion is responsible for more than 50% of the gradient (>0.10 contribution to the abnormal FFR) should be stented first, if technically feasible. It is then
critical to measure FFR again because with the increased flow down the vessel due to the relief of 1 stenosis, the FFR across the other lesion may still be in the ischemic range (Table 24-4).

Table 24-4 Approach to Serial or Tandem Coronary Lesions of Unclear Significance

<table>
<thead>
<tr>
<th>Fractional Flow Reserve (FFR) Assessment of Serial Lesions</th>
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<tbody>
<tr>
<td>1. Measure FFR of the entire vessel.</td>
</tr>
<tr>
<td>2. If FFR &gt; 0.80, revascularization is not indicated.</td>
</tr>
<tr>
<td>3. If FFR ≤ 0.80, then perform slow pullback of the wire during hyperemia.</td>
</tr>
<tr>
<td>4. Determine which lesion is responsible for the majority of the gradient (ideally &gt;0.15).</td>
</tr>
<tr>
<td>5. Perform percutaneous coronary intervention (PCI) on the lesion which is physiologically more severe.</td>
</tr>
<tr>
<td>6. Remeasure FFR after PCI of the first lesion and if ≤0.80 then treat the second lesion.</td>
</tr>
</tbody>
</table>

Left Main Disease

Another challenging group of patients in which FFR measurement can be helpful is the subset with intermediate left main coronary disease. Left main disease is particularly difficult to evaluate with angiography and noninvasive testing. Intravascular ultrasound has been an alternative method for obtaining more anatomic information regarding lumen compromise; however, it provides no functional data and is hampered by the lack of a clear cutoff value applicable to all patients. FFR has been evaluated in a number of registries and found to be a safe method for deferring revascularization if the value is in the nonischemic range. In the presence of downstream disease in both the left anterior descending (LAD) and the circumflex arteries, isolating the contribution of the intermediate left main disease to an abnormal FFR can be difficult, just as occurs with tandem lesions not involving the left main. However, if downstream disease is present only in the LAD, for example, the operator can place the wire in the nondiseased downstream circumflex vessel
and measure FFR accurately in most cases. Studies have shown that if the LAD disease is severe (resulting in an FFR down the LAD < 0.50 range), then it may decrease flow across the left main and raise the FFR down the circumflex.\textsuperscript{36,37,38} If the operator stents the LAD and remeasures FFR of the left main down the circumflex, it may now be slightly lower. Fortunately, the clinical relevance of this effect appears to be small.\textsuperscript{38}

**Stable CAD**

Controversy exists regarding the appropriate initial management of patients with stable angina and CAD. Based on the COURAGE trial results, some argue medical therapy should be optimized in favor of performing PCI.\textsuperscript{39} However, others have criticized the COURAGE trial because it may have enrolled lower-risk patients without significant ischemia and because PCI may have been performed in a suboptimal fashion. The FAME 2 trial was designed specifically to ensure the inclusion of patients with a large burden of ischemia and utilizing current generation drug-eluting stents and PCI techniques, such as FFR.\textsuperscript{40} This was achieved by randomizing only patients with at least 1 lesion in 1 of the 3 major epicardial vessels with >50% narrowing and an FFR ≤0.80. Those patients with narrowings of >50% but with an FFR >0.80 were not included in the randomized portion of the study, but followed in a registry and treated with best medical therapy. The goal was to randomize roughly 1600 patients and follow them for 2 years with a primary composite endpoint of death, MI or unplanned hospitalization requiring urgent revascularization.

After 888 patients had been randomized, recruitment into FAME 2 was stopped prematurely by the data and safety monitoring board because of a highly significant difference in the primary endpoint between the 2 groups. After a mean follow-up of only 7 months, the primary endpoint occurred in 12.7% of patients in the best medical therapy arm compared to 4.3% in the PCI plus best medical therapy arm. There was no significant difference in death (0.7% vs 0.2%, \(P = 0.31\)) or MI (3.2% vs 3.4%, \(P = 0.89\)), but a highly significant difference in the rate of unplanned hospitalization requiring urgent revascularization (11.1% vs 1.6%, \(P < 0.001\)) between the best medical therapy arm and PCI arm, respectively. The rate of any revascularization was also significantly higher in the best medical therapy arm (19.5% vs 3.1%, \(P < 0.001\)).
Both groups in FAME 2 received excellent medical therapy, with the vast majority prescribed aspirin, a statin, a beta-blocker, and an angiotensin-converting enzyme (ACE) inhibitor in similar rates to what was seen in the COURAGE trial. The majority of the best medical therapy arm also received a calcium channel blocker and/or nitrate for refractory angina. Despite this, the hospitalization rate for an acute coronary syndrome requiring urgent revascularization in the best medical therapy arm was 11.1% at just 7 months. In comparison, in the COURAGE trial, the rate of an acute coronary syndrome at a median follow-up of 4.6 years was only 11.8%. This difference is likely because in the FAME 2 trial, by measuring FFR first, patients with a larger burden of ischemia were randomized.

The concept of more severe ischemia resulting in worse outcomes is supported further by the fact that stratifying outcomes in FAME 2 based on an FFR value of 0.65 demonstrated a significant interaction, meaning that those patients with more severe ischemia at baseline had even greater benefit with PCI as compared to medical therapy alone.

Importantly, there were 332 patients in the FAME 2 trial with angiographic coronary disease which was not significant based on FFR assessment and 166 of these were randomly assigned follow-up in a registry receiving best medical therapy alone. The primary endpoint occurred in only 3.0% of these registry patients with a 2.4% rate of urgent revascularization. This finding further emphasizes the importance of not only identifying angiographic evidence of coronary disease, but further characterizing whether the disease is responsible for ischemia. Patients with these types of lesions benefit from PCI, while patients with angiographic disease which is not functionally significant based on FFR respond well to medical therapy alone.

The complete 2-year follow-up of the FAME 2 study was recently published and showed a continued highly significant difference in the composite endpoint of death, MI, and urgent revascularization between the FFR-guided PCI arm and the medical therapy arm (8.1% vs 19.5%, \( P < 0.001 \)). Additionally, a landmark analysis evaluating the difference in the rate of death and MI alone, found that after 7 days (eliminating periprocedural MI from the FFR-guided PCI arm) there was a significantly low rate of death or MI in the FFR-guided PCI arm (4.6% vs 8.0%, \( P = 0.04 \)) (Fig. 24-6). These findings further highlight the increased risk for adverse events due to lesions with a low FFR which are treated with medicine alone.
FIGURE 24-6 Landmark analysis starting 1 week after treatment (and thereby eliminating periprocedural myocardial infarctions) from the FFR versus Angiography for Multivessel Evaluation (FAME) 2 trial. The data demonstrates an increased risk of death and myocardial infarction in the medical therapy arm compared to the percutaneous coronary intervention (PCI) arm.

An economic evaluation of the FAME 2 trial was performed.\textsuperscript{42} Although performing PCI initially costs more compared to medical therapy alone, because patients receiving PCI have significant improvement in quality of life and because they have fewer adverse events during follow-up, the incremental cost-effectiveness ratio for the PCI arm was favorable at $36,000 per quality-adjusted life year. This finding was robust in bootstrap replications and sensitivity analyses.

The role of routine measurement of FFR in stable patients undergoing coronary angiography also has been tested in two registries.\textsuperscript{43,44} Both found that the additional information from FFR measurement can have a dramatic impact on treatment strategies. For example, in one study of 1,075 patients, the final treatment strategy (medical therapy, PCI, or coronary artery bypass) was changed in 43% of cases after the operators were made aware of the FFR results.\textsuperscript{44} These findings further highlight the limitations of the coronary angiogram and argue for more routine utilization of FFR in the diagnostic setting.
**FFR After PCI**

A number of studies have compared FFR after stenting with intravascular ultrasound criteria for determining optimal stent deployment and have found a significant correlation between the two techniques.\(^45\)\(^-\)\(^47\) However, the strongest evidence supporting a role for measuring FFR after PCI comes from a registry in which 750 patients who had FFR measured after bare-metal stenting were followed for 6 months to determine the relationship between the post-procedure FFR and clinical outcomes.\(^5\) Multivariate analysis showed that FFR was the strongest predictor of major adverse cardiac events. In the 36% of patients with a final FFR of more than 0.95, the 6-month adverse event rate (after bare-metal stenting) was 4.9%, and in the 32% with a final FFR between 0.90 and 0.95, the event rate was 6.2%. In comparison, if the final FFR was less than 0.90, the event rate was 20.3%, and in the 6% of patients with a final FFR of less than 0.80, the event rate was 29.5%. Of note, angiographic results were not at all predictive of adverse events. Subsequent studies evaluating FFR measured after drug-eluting stenting have demonstrated similar findings, with low event rates if the final FFR is \(>0.90.\)\(^48\),\(^49\)

**LIMITATIONS OF FFR**

Although no invasive index for assessing the functional significance of a coronary stenosis is perfect, FFR is widely perceived to be the reference standard. There are some aspects related to the theory of FFR and to its actual measurement which have created controversy. First, FFR theory states that during maximal hyperemia, when myocardial resistance is minimized and coronary autoregulation abolished, coronary pressure becomes proportional to flow, and therefore myocardial flow in the presence of a stenosis can be determined by measuring distal coronary pressure. However, some have argued that this assumption is invalid because at low perfusion pressures the relationship between pressure and flow is no longer linear.\(^50\) In other words, coronary flow will stop before coronary pressure equals 0. This is because of the backpressure resulting from the myocardium and the coronary venous system. However, within the physiologic range of pressures where FFR is measured, the linear relationship between pressure and flow exists and
therefore this theoretical concern has not had clinical implications on the validity of FFR.

There has also been controversy over whether the minimal achievable microvascular resistance in the presence of a stenosis is equivalent to the resistance in the hypothetical absence of a stenosis.\textsuperscript{50,51} One study measuring microvascular resistance before and after uncomplicated PCI found lower levels of minimal resistance after PCI.\textsuperscript{52} This finding may be due to measurement error that occurred by not taking into account the contribution of collateral flow, which is greater in the presence of a stenosis and which, when neglected, leads to apparently higher levels of microvascular resistance. Earlier work\textsuperscript{53} and a number of follow-up studies performed by different investigators in both animals and humans have found that microvascular resistance is equivalent in both the presence and absence of an epicardial stenosis when collateral flow is incorporated into the measurement.\textsuperscript{54-57}

Another concern regarding the actual measurement of FFR is its theoretical reliance on achieving maximal hyperemia. If maximal hyperemia does not occur, the flow across the stenosis may be less, the pressure gradient lower and the FFR overestimated. For these reasons, it is critical that when FFR is measured the hyperemic agent is administered correctly and in an adequate dosage. If one is concerned that maximal hyperemia has not been achieved, an alternative pharmacologic agent can be delivered. If there is still concern, microvascular resistance can be measured simultaneously with the same pressure wire, for example, by calculating the index of microcirculatory resistance (IMR)\textsuperscript{58} using a thermodilution technique; in this manner, one can assess whether resistance is minimized and flow maximized. If the FFR is higher than expected based on the angiographic findings and the IMR is low, then one can be reassured that hyperemia has been achieved and the FFR result is valid. If FFR is high and IMR is high, then likely microvascular dysfunction is present, which may explain the presence of symptoms and/or ischemia. In this scenario, the use of IV adenosine is helpful because the symptoms and hemodynamic changes which often occur are reassuring that hyperemia has been achieved. FFR is still valid in that it informs the operator that there is little to be gained by performing PCI; a number of studies demonstrate that PCI of the epicardial stenosis in this setting does not improve outcomes.\textsuperscript{19,22,41} To circumvent this requirement for maximal hyperemia, combined pressure and Doppler flow indices have been
proposed. These require further validation and improvements in technology before they are used to augment FFR measurement.

Another issue raised about the need for maximal hyperemia concerns the fact that adenosine may not completely abolish autoregulation and minimize microvascular resistance. Prolonged coronary occlusion likely produces the greatest degree of hyperemia, but is not practical in the clinical setting. The addition of other vasodilators on top of adenosine has been proposed and may further reduce FFR; however, in theory this would require recalibration of the FFR cutoff value for identifying lesions capable of causing MI. It is unlikely that an additional agent would create enough additional hyperemia such that an FFR which with adenosine alone is >0.80 would drop to <0.75. This may explain why measuring FFR with adenosine alone has proven to be so useful clinically, despite the theoretical possibility that in a small proportion of patients truly maximal hyperemia was not achieved.

CONCLUSION

By providing information regarding the ischemic potential of a coronary stenosis, FFR measurement improves our management of patients with CAD. Is FFR required for all patients with coronary disease undergoing coronary angiography? In the culprit vessel of a patient with STEMI, FFR is not recommended. In a patient with angina, single-vessel CAD with an angiographically significant coronary stenosis, and a noninvasive stress test with ischemia in the territory subtended by the vessel with the stenosis, FFR is not necessary. But these scenarios occur less frequently than the patient with an equivocal noninvasive stress test, or the patient with multivessel coronary disease, where FFR measurement to guide PCI clearly improves outcomes and saves resources.

REFERENCES


2. Metz JA, Yock PG, Fitzgerald PJ. Intravascular ultrasound: Basic


**MULTIPLE CHOICE QUESTIONS**

1. Which statement is correct with respect to the derivation of fractional flow reserve (FFR)?
   A. During maximal vasodilation, resistance is maximized and flow becomes proportional to pressure.
   B. In a normal epicardial vessel, there is little pressure loss along its course (ie, distal pressure is similar to proximal pressure).
   C. FFR is calculated as the proximal coronary or aortic pressure divided by the distal coronary pressure during maximal hyperemia.
   D. FFR is defined as the maximum flow in a diseased vessel compared to the maximum flow in an adjacent nondiseased vessel.
   E. FFR is defined as maximal flow down the vessel divided by resting flow down the vessel.

2. Which of the following is a feature of fractional flow reserve (FFR)?
A. It has a normal value of less than 0.80.
B. It is affected by changes in heart rate and blood pressure.
C. It is an index specific for epicardial coronary disease.
D. It has an ischemic cutoff value at 1.0.
E. It has high variability and is not very reproducible.

3. Which of the following is true when measuring fractional flow reserve (FFR)?
   A. The sensor is positioned just beyond the stenosis and not in the distal two-thirds of the vessel.
   B. Nitroglycerin is not routinely administered.
   C. The optimal dose of intracoronary adenosine is 12 micrograms (μg) for the right coronary artery and 16 μg for the left coronary artery.
   D. It is important to keep the guide catheter well-seated when assessing an aorto-ostial coronary stenosis.
   E. A continuous intravenous administration of adenosine has the advantage of allowing a slow pullback of the pressure sensor to identify the location of the most significant pressure drop.

4. The FFR versus Angiography for Multivessel Evaluation (FAME) trial did which of the following?
   A. Compared fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) to angiography-guided coronary PCI in patients with stable, single-vessel coronary disease.
   B. Demonstrated that the FFR-guided procedure significantly prolonged the procedure compared to the angiography-guided strategy.
   C. Found that the angiography-guided arm received significantly fewer stents.
   D. Found that the FFR-guided arm utilized significantly more contrast media.
   E. Showed a significant reduction in major adverse cardiac events at 1 year in patients randomized to FFR-guided PCI.

5. The FFR versus Angiography for Multivessel Evaluation 2 (FAME 2) trial did which of the following?
   A. Compared fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) to medical therapy in patients with acute
coronary syndromes.
B. Enrolled only patients with single vessel coronary artery disease.
C. Found that FFR-guided PCI led to significantly lower rates of the composite of death, myocardial infarction and urgent revascularization compared with best medical therapy alone.
D. Showed that medically treated patients without any lesion with an FFR less than or equal to 0.80 had higher event rates than medically treated patients with at least 1 lesion with an FFR less than or equal to 0.80.
E. Revealed an unfavorable cost-effectiveness ratio for FFR-guided PCI of greater than $100,000 per quality adjusted life year gained.

ANSWERS

1. B
2. C
3. E
4. E
5. C
Adjunctive Diagnostic Techniques: Intravascular Ultrasound, Optical Coherence Tomography, and Spectroscopy

Yuhei Kobayashi
Peter J. Fitzgerald
Yasuhiro Honda

The limitations inherent to angiography served as a technological springboard for the development of other devices in search of better visualization, quantification, and identification of the coronary vasculature and assessment of the efficacy of subsequent clinical therapeutics. Intravascular ultrasound (IVUS) was invented and introduced to clinical practice in the late 1980s as an invasive intravascular imaging device. As a front-runner in this field, IVUS has greatly contributed to the investigation of the pathophysiology of coronary artery disease in symptomatic patients and to the guidance of percutaneous coronary interventions (PCI).

Since the early 2000s, optical coherence tomography (OCT), which was first introduced in the ophthalmology field, has been applied to human intravascular imaging. Apart from these intravascular imaging systems, spectroscopy has also begun to gather attention as a device to determine plaque components. Spectroscopy provides adjunctive information when used with IVUS, though current clinical applications are limited to the detection of cholesterol within the vessel wall.
This chapter will provide information related to concrete usage and tips of adjunctive intravascular imaging devices as well as to review evidence and rationale for use as a procedural guide in the cardiac interventional setting.

**INTRAVASCULAR ULTRASOUND**

After the first initial clinical experience by Yock et al. in 1988,\(^1\) IVUS has become established as an adjunctive diagnostic device as well as an essential research tool in the cardiac catheterization laboratory. Moreover, its development and findings have been a driving force in the expansion of the intravascular diagnostic field. With a miniaturized ultrasound probe equipped at a tip of an IVUS catheter, a high-frequency ultrasound beam ranging from 20 to 45 megahertz (MHz) is transmitted radially from the probe to a vessel wall and its reflection sound waves are reconstructed to depict a cross-sectional image. The higher frequency ultrasound beam (shorter wave length) than those utilized in noninvasive echocardiography (2-5 MHz, longer wave length) potentiates its high resolution to visualize vessel and intravascular structures, which leads to its low radial penetration of 4 to 8 mm from the IVUS catheter. To improve the resolution of IVUS images, adoption of ultrasound with higher frequency (55-60 MHz) than conventional IVUS is currently underway; this will possibly lead to better interpretation of gray-scale IVUS imaging by improving tissue and plaque differentiation.

There are several intermediate resolution/penetration ultrasound catheter devices for peripheral (15-20 MHz) or intracardiac (intracardiac echocardiography [ICE], 5-10 MHz) uses, specifically developed to guide catheter-based treatments of peripheral vessels and structural heart disease, or catheter ablation. Detailed descriptions of ICE can be found elsewhere in this textbook (see **Chapter 13**).

**Imaging Systems and Image Acquisition Procedure**

IVUS imaging systems consist of 3 components: an imaging catheter, a console for imaging reconstruction/display/recording/analysis, and a catheter interface unit with motorized transducer pullback capability. Specifically, 2 types of imaging acquisition processes are applied to commercially available IVUS catheters: a solid-state dynamic aperture and a mechanically rotating
single transducer system (Table 25-1). Currently, only 1 company (Volcano Corp., San Diego, CA) provides the solid-state catheter system that has 64 phased-array transducers mounted around the catheter tip. It utilizes a rapid-exchange design and the guidewire is inserted through a circumferential array of transducer elements. On the other hand, mechanical catheter systems are available from 4 companies with slightly varying configurations (Boston Scientific Corp., Marlborough, MA; Infraredx Inc., Burlington, MA; Terumo Corp., Tokyo, Japan; and Volcano Corp./Royal Philips). In mechanical systems, there is only one transducer equipped at the tip of the catheter, which rotates inside of a protective sheath, and it incorporates a rapid-exchange design with the guidewire running alongside the imaging window; therefore, this system can have several inherent artifacts from its structure (eg, non-uniform rotational distortion, guidewire shadow). In general, however, image quality is superior to the solid-state system because of the higher frequency ultrasound (40-45 MHz vs 20 MHz) and the larger effective aperture of a transducer element used in the mechanical system. In addition, longitudinal lesion length assessment is more accurate in the mechanical system, because the transducer pullback is performed within the stationary protective sheath.

Table 25-1 Comparison Between the Mechanically Rotating Single-Transducer System and the Solid-State Dynamic Aperture System for Coronary Applications

<table>
<thead>
<tr>
<th></th>
<th>Mechanically Rotating Single-Transducer System</th>
<th>Solid-State Dynamic Aperture System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features</strong></td>
<td>Higher image resolution</td>
<td>Shorter preparation time</td>
</tr>
<tr>
<td></td>
<td>Protective sheath (air flushing requirement)</td>
<td>Digital subtraction requirement</td>
</tr>
<tr>
<td></td>
<td>Better longitudinal length assessment</td>
<td>to mask ring-down artifact</td>
</tr>
<tr>
<td><strong>Artifacts</strong></td>
<td>Air bubbles</td>
<td>Ring-down artifact</td>
</tr>
<tr>
<td></td>
<td>Guidewire artifact</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-uniform rotational distortion (NURD)</td>
<td></td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Boston Scientific</td>
<td>Volcano</td>
</tr>
<tr>
<td>Console</td>
<td>iLab™</td>
<td>Visiwave™</td>
</tr>
<tr>
<td>Catheter</td>
<td>OptiCross™</td>
<td>Revolution</td>
</tr>
<tr>
<td>Frequency</td>
<td>40 MHz</td>
<td>Eagle Eye™ Platinum</td>
</tr>
<tr>
<td>Guide compatibility</td>
<td>5 F</td>
<td>Eagle Eye™ Platinum ST</td>
</tr>
<tr>
<td>Tissue or plaque characterization</td>
<td>iMap™</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: F, fluorescence profile; MHz, megahertz.
In terms of preparing the IVUS catheter prior to use, there are differences between the mechanical system and the solid-state system owing to their designs. The mechanical system requires a saline flush to remove air bubbles between the protective sheath and the transducer before IVUS catheter insertion, whereas the solid-state system requires a step to mask ring-down artifact before insertion of IVUS catheter into the coronary artery, which is usually performed in the aorta or in the left main. It is generally recommended that residual air bubbles should be flushed outside of the body so as to avoid an air embolization. Similar to standard interventional procedures, intravenous heparin (5000-10,000 units) and intracoronary nitroglycerin (100-200 micrograms) should be administered beforehand. Thereafter, a 0.014-inch guidewire is advanced distally to the target vessel, followed by IVUS catheter insertion. Pullback IVUS scan should be started from at least 10 mm distally to the target lesion and to the aorta for complete target vessel interrogation. Automated pullback speeds of 0.5 mm/sec and 1.0 mm/sec are available. When assessing an ostial lesion, it is important to disengage the guide catheter slightly from the ostium so that the target lesion can be fully visualized.

**Artifacts**

Differentiating among the types of artifacts and addressing them properly are important aspects to achieve precise interpretation of IVUS images. Artifacts of IVUS mainly derive from IVUS design, feature of ultrasound, or inappropriate preparations (Fig. 25-1).
FIGURE 25-1  Examples of common IVUS artifacts. A. Acoustic shadowing is an image blank behind strong ultrasound reflectors. B. Air bubbles are the artifact that blurs an IVUS image, when residual air bubbles exist between an outer sheath and a transducer in mechanical IVUS systems. C. Blood speckles can be observed as an unexpectedly high-echoic area within a lumen, and, as a result, the border between lumen and intima may become obscure. D. Multiple ghost images called reverberations (white arrowheads), spaced radially at regular intervals, can be observed in a calcified lesion with a smooth surface (red arrowhead) or a lesion with a metal stent. E. Non-uniform rotational distortion (NURD) is an artifact that can be seen as a partial or entire distortion of the cross-sectional image, resulting from mechanical binding of the drive cable that rotates the transducer inside the protective sheath. F. Ring-down artifact can be observed as a ring adjacent to an IVUS catheter and may be caused by residual air bubbles within the protective sheath or the sheath itself in mechanical IVUS systems, or by interference of ultrasound in the solid-state system. G. Side lobe artifact is an artifact observed laterally to stent struts or a calcification. When a strong reflector exists, a side lobe ultrasound can create a lateral ghost image. H. A guidewire can be the cause of acoustic shadowing (see Part A) called guidewire artifact, stemming from the reflection of the ultrasound beam by the guidewire.

A)  Acoustic shadowing (see Fig. 25-1A).
Acoustic shadowing is an image blank behind a calcification, a metal stent, or a guidewire. IVUS beam cannot penetrate such strong ultrasound reflectors, generating the image blank observed behind these structures.

B)  Air bubbles (see Fig. 25-1B).
Air bubbles are the artifact that blurs an IVUS image. When residual
air bubbles exist between an outer sheath and a transducer in
mechanical IVUS systems, adequate ultrasound beam emission and
image acquisition are inhibited. Repeat saline flushes are necessary to
fully remove the residual bubbles.

C) Blood speckles (see Fig. 25-1C).
Blood speckles can be observed as an unexpectedly high-echoic area
within a lumen, and, as a result, the border between lumen and intima
may become obscure. It is usually observed when using an ultrasound
system with higher frequency (>40 MHz), or in lesions with stagnant
coronary flow from severe stenosis where rouleaux formation of red
blood cells occurs. An injection of saline or contrast will help to
identify the lumen border.

D) Multiple reverberations (see Fig. 25-1D).
When analyzing a calcified lesion with smooth surface or a lesion with
a metal stent, multiple ghost images, spaced at radially regular
intervals, can be observed. These ghost images are called multiple
reverberations, and care should be taken to not misinterpret these
findings as true structures. This phenomenon is caused by multiple
reflections of the ultrasound beam between the transducer and a strong
reflector.

E) Non-uniform rotational distortion (NURD) (see Fig. 25-1E).
NURD is an artifact that can be seen as a partial or entire distortion of
the cross-sectional image. This artifact is unique to the mechanical
IVUS systems, resulting from mechanical binding of the drive cable
that rotates the transducer inside the protective sheath. This is usually
observed in a tortuous artery or from a kink in the imaging catheter. To
avoid this artifact, it is important to straighten the IVUS catheter
outside of body, or to unfasten the Y-connector to release torque.

F) Ring-down artifact (see Fig. 25-1F).
Ring-down artifact can be observed as a ring adjacent to an IVUS
catheter and may be caused by residual air bubbles within the
protective sheath or the sheath itself in mechanical IVUS systems, or
by interference of ultrasound in the solid-state system. This may be
treated with additional saline flushing in mechanical systems, or digital
mask adjustment in the solid-state system.
G) Side lobe artifact (see Fig. 25-1G). 
Side lobe artifact is an artifact observed laterally to stent struts or a calcification, which can possibly lead to an inaccurate assessment of a stent area because of pseudo-protruding struts to the lumen. When a strong reflector exists, a side lobe ultrasound can create a lateral ghost image.

H) Guidewire artifact (see Fig. 25-1H). 
A guidewire can be the cause of acoustic shadowing (see Fig. 25-1A), stemming from the reflection of the ultrasound beam by the guidewire, resulting in the blank image behind it. This artifact is only seen in the mechanical IVUS system, because a guidewire runs alongside the transducer.

**Image Interpretation**

Arterial three-layer structures (intima, media, and adventitia) correspond to high-low-high echoic findings by IVUS (Fig. 25-2). It is usually difficult to distinguish adventitia from extravascular matrix. In some cases, the media may appear artifactually thin because of “blooming”—an intense reflection from the intima. In other cases, the media can contrarily appear thick because of signal attenuation from the intima and the weak reflectivity of the internal elastic membrane (IEM). Particularly in younger normal subjects, the vessel wall may have a single-layer appearance, since the intima is thinner than the resolution of IVUS. IEM and external elastic membrane (EEM), just adjacent to the media, cannot be observed by IVUS. In some cases, the media may be destroyed partially in association with development of atherosclerosis, and it no longer appears as a distinct layer.
FIGURE 25-2 Typical cross-sectional IVUS image and its interpretation. A. A cross-sectional IVUS image with schematic diagram. B. Demonstrates the classic high-low-high, three-layered appearance. C. Histologic correlations with intima, media, and adventitia. The media has lower ultrasound reflectance owing to less collagen and elastin as compared with the neighboring layers. Because the intimal layer reflects ultrasound more strongly than does the media, there is a spillover in the image, which results in a slight overestimation of the thickness of the intima and a corresponding underestimation of the medial thickness.

In order to determine image orientation within the artery, recognition of perivascular structures (eg, branches, veins, pericardium, and myocardium) are of clinical importance, especially during interventional procedures or in repeated recordings over time (Fig. 25-3).

An IVUS image is reconstructed as a cross-sectional image as if the interpreters look down into a coronary artery in a proximal-to-distal direction. As an example in a typical case, a diagonal branch is located at approximately 90° to 120° clockwise to a septal branch. In contrast to side branches, veins are susceptible to compression during the cardiac cycle and do not merge with arteries when assessed longitudinally. While the pericardium appears to be a high echoic thick layer with pericardial space between an interrogated vessel and pericardium, the myocardium is viewed on an opposite side of the vessel as a low echoic homogeneous structure.
FIGURE 25-3 Perivascular structures. A. **Diagonal and septal branch** can be observed in the left anterior descending artery. A diagonal branch is located at approximately 90°-120° clockwise to a septal branch. B. While the **pericardium** appears to be a high echoic thick layer with pericardial space between an interrogated vessel and pericardium, the **myocardium** is viewed on an opposite side of the vessel as a low echoic homogeneous structure. C. **Right ventricular (RV) vein** overlying the right coronary artery. D. **Great cardiac vein (GCV)** observed from the left circumflex artery. In contrast to side branches, veins are susceptible to compression during the cardiac cycle and do not merge with
Quantitative Assessment

With an intrinsic distance calibration, diameter and cross-sectional area (CSA) can be measured in a cross-sectional IVUS image. Measurements will be repeated in the tightest cross-section within the lesion, and in proximal and distal reference segments. Reference segments are usually selected as the most “normal-looking” cross-section within 10 mm from the interrogated lesion without any major intervening side branches. The average area of proximal and distal reference is often used. Vascular remodeling, originally identified and proposed in autopsy specimens, can also be evaluated by IVUS. When serial IVUS images are available, vascular remodeling can be defined as a ratio of follow-up EEM CSA to baseline EEM CSA. When it is not available, it can be defined using a following formula: Remodeling index=lesion EEM CSA/reference EEM CSA. If the lesion EEM CSA exceeds the reference EEM CSA, remodeling index becomes >1.0, which is defined as positive remodeling of the vessel. On the other hand, negative remodeling is defined as a remodeling index <1.0. Instead of this cutoff, positive remodeling of >1.05 and negative remodeling of <0.95 can be employed.\(^5\)

After determination of the interface between the lumen and the leading edge of intima, lumen measurements can be performed. In addition to lumen CSA, minimum, maximum, and mean diameters as well as eccentricity can be obtained. Because the interface between the adventitia and extravascular matrix is usually obscure, EEM area is used as an alternative to vessel area. EEM area is defined as the area enclosed by the outermost interface between media and adventitia. Circumferential EEM may not be measured precisely, especially at a bifurcation or calcified lesion. Because IEM is not well delineated by IVUS, the area between the leading edge of the lumen and EEM is defined as atheroma, based on the fact that the media represents only a very small fraction of the atheroma CSA. Accordingly, the term “plaque plus media” is used to represent plaque in a cross-section. In terms of stent measurements, metallic stent struts are strong reflectors of ultrasound, and thus, high gain setting should be avoided to reduce side-lobe artifacts. Typical IVUS measurements for lumen, plaque, and stent are summarized in Figure 25-4 and Table 25-2.
FIGURE 25-4 Examples of quantitative IVUS assessment. Quantitative IVUS measurements for non-stented (A-D) and stented (E-H) segments. Area measurements are performed with computer planimetry. External elastic membrane (EEM) area is defined as the area enclosed by the outermost interface between media and adventitia (B), while lumen area (C and G) is determined by tracing the leading edge of the blood/intima border. Plaque + media area (D) is calculated as the difference between EEM and lumen areas. Stent area (F) is measured by tracing the leading edge of the stent struts, and neointimal area (H) is calculated as the difference between stent and lumen areas. For EEM, lumen, and stent, the maximum (solid arrows) and minimum (dotted arrows) diameters are determined. For plaque + media and neointima, the maximum (solid arrows) and minimum (dotted arrows) thickness are measured.

Table 25-2 Quantitative Assessment of Lumen, Plaque, and Stent by IVUS
In addition to cross-sectional assessments, longitudinal lesion length is an important aspect of a quantitative assessment. In mechanical IVUS systems, longitudinal lesion length can be measured automatically or manually by pulling back a transducer inside the protective sheath, whereas the solid-state system requires the pullback of the catheter itself. Care should be taken in assessing a tortuous lesion, where constant transducer pullback is not warranted. In addition, lesion length can be affected by the longitudinal catheter movement due to heartbeats. With the Eagle Eye® Platinum solid-state catheters (Volcano Corp.), 3 radiopaque markers at 1-cm intervals on the catheter shaft proximal to the transducer may be utilized to estimate the lesion length based on the angiogram.

**Qualitative Assessment by Gray-Scale IVUS**

With conventional gray-scale IVUS, plaques are typically classified into 4 types: (1) soft plaque; (2) fibrous plaque; (3) calcified plaque; and (4) mixed plaques.
plaque. However, this classification is fundamentally different from the histology, thus necessitates careful interpretation. Soft (echolucent) plaque refers to a low echoic plaque (lower than the adventitia) which derives from high lipid content and contrary low collagen and elastin (Fig. 25-5A). Fibrous plaque refers to an intermediate echoic plaque (echogenicity between the soft plaque and the calcified plaque) and represents the majority of atherosclerotic lesions (Fig. 25-5B). Usually, echogenicity increases according to the increment of fibrous tissue content. Calcified plaque has higher echogenicity than the adventitia and is accompanied by acoustic shadowing (Fig. 25-5C). Calcified plaque can be classified based on depth and its circumferential extent. Depending on the location of the leading edge of calcification, calcified plaque is categorized as superficial (within 50% of plaque plus media) or deep (deeper than 50% of plaque plus media). Because IVUS may not accurately delineate the border of calcification, and the angle is dependent of the distance from the center of the lumen, the extent of calcium may be semi-quantitatively expressed as 4 quadrants; 0°<90°, 90° to 180°, 180° to 270°, and >270°. If the extent of calcium is more than 90°, vessel contour should not be assessed. Calcification less than 90° is called spotty calcification, which is recognized as a feature of unstable plaque in acute coronary syndrome. It is worth noting that highly dense fibrous plaques may have acoustic shadowing and similar echogenicity with calcified plaques due to the high content of fibrous tissue. Some plaques consisting of multiple components are called “mixed plaques” (Fig. 25-5D), and are classified as fibrocalcific or fibrofatty plaques.
FIGURE 25-5 Examples of qualitative plaque characteristics assessment by gray-scale IVUS. With conventional gray-scale IVUS, plaques are typically classified into 4 types: A. soft plaque; B. fibrous plaque; C. calcified plaque; and D. mixed plaque. Soft (echolucent) plaque refers to a low echoic plaque (lower than the adventitia) which derives from high lipid content and contrary low collagen and elastin. Fibrous plaque refers to an intermediate echoic plaque (echogenicity between the soft plaque and the calcified plaque) and represents the majority of atherosclerotic lesions. Calcified plaque has higher echogenicity than the adventitia and is accompanied by acoustic shadowing. Calcified plaque can be classified based on depth and its circumferential extent. Depending on the
location of the leading edge of calcification, calcified plaque is categorized as superficial (within 50% of plaque plus media) or deep (deeper than 50% of plaque plus media).

**Tissue Characterization**

As IVUS-guided intervention matures, there is growing attention to acquiring more detailed plaque characterization. To date, 3 different tissue characterization techniques, which employ computer-assisted analysis of raw radiofrequency (RF) signals in the reflected ultrasound beam, are commercially available: Virtual Histology™ (VH) (Volcano Corp.), iMAP™ (Boston Scientific Corp.), and Integrated Backscatter (Terumo Corp.). A comparison of the 3 tissue characterization techniques and representative images are shown in Table 25-3 and Figure 25-6.

**Table 25-3 Comparison Among 3 Tissue Characterization Techniques**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Virtual Histology™ (VH)</th>
<th>iMAP™</th>
<th>Integrated Backscatter (IB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Console</td>
<td>s5™</td>
<td>iLab™</td>
<td>VISIWave™</td>
</tr>
<tr>
<td>Catheter</td>
<td>Eagle Eye® Platinum (20 MHz)</td>
<td>OptiCross™ (40 MHz)</td>
<td>ViewIT™ (40 MHz)</td>
</tr>
<tr>
<td>Tissue classification Method</td>
<td>Classification based on a dedicated spectral radiofrequency analysis tree algorithm using multiple radiofrequency signal characteristics developed from ex vivo coronary datasets</td>
<td>Classification based on the degree of spectral similarity between the backscattered signal and a reference library of spectra from preserved histological data</td>
<td>Classification based upon integrated backscatter values, calculated as the average power of the backscattered ultrasound signal from a sample tissue volume</td>
</tr>
<tr>
<td>Color-mapped presentation</td>
<td>Fibrous (green) Fibrofatty (yellow) Necrotic core (red) Dense-calcium (white)</td>
<td>Fibrotic (green) Lipidic (yellow) Necrotic (red) Calcified (blue)</td>
<td>Fibrous (green) Mixed lesion (yellow) Lipid (blue) Calcification (red)</td>
</tr>
<tr>
<td>Features</td>
<td>No guidewire artifact Low resolution</td>
<td>Guidewire artifact High resolution</td>
<td>Guidewire artifact High resolution</td>
</tr>
</tbody>
</table>
Clinical applications of tissue characterization techniques have been mainly focused on the prediction of future coronary events or slow-flow phenomenon after an interventional procedure by stratifying high-risk coronary plaques. In particular, among the three techniques, the VH-IVUS system has demonstrated the ability to predict future coronary events in a large-scale prospective multicenter trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree: PROSPECT) where 697 patients with acute coronary syndrome underwent three-vessel gray-scale and VH-IVUS after PCI. The 3-year cumulative rate of major adverse cardiac events was 20.4%, with nearly half of these events being associated with nonculprit lesions, most of which appeared to be mild by baseline angiography. On multivariate analysis, nonculprit lesions with recurrent events were significantly associated with 3 characteristics: (1) plaque burden of 70% or greater; (2) minimal luminal area of 4.0 mm² or less; and (3) VH-determined thin-cap fibroatheroma. In another study of investigating 190 consecutive patients with acute coronary syndrome (ACS), a no-reflow phenomenon was observed in 24 patients after stent implantation. VH-detected absolute and % necrotic core (NC) areas at the minimum lumen area (MLA) site as well as volumetric parameters of these variables were significantly greater in patients with no reflow. In the multivariable analysis, % NC volume was the only independent predictor of no reflow (OR=1.126, 95% CI: 1.045-1.214, $P = 0.002$).
There are several inherent limitations to these tissue characterization techniques: limited spatial resolution (100-250 μm) for detection of thin fibrous caps, no classification for thrombus or stent struts, and misclassification of plaque beyond severe calcification due to limited ultrasound signal penetration.

**Clinical IVUS Applications**

IVUS-guided PCI with both bare metal stents (BMS) and drug-eluting stents (DES) has demonstrated to be associated with better long-term outcomes compared to angiography-guided PCI. In the literature-based meta-analysis including nine studies, Casella et al. showed that IVUS-guided PCI with BMS reduced target lesion revascularization, major adverse cardiac events, and binary restenosis at 6 months, although deaths and nonfatal MI was similar between the two groups.\(^8\) In the recently published meta-analysis of IVUS-guided DES implantation including three randomized trials and 12 observational studies with 24,849 patients, Jang et al. found significant reduction of all-cause mortality (odds ratio [OR]=0.64, 95% confidence interval [CI] 0.51-0.81, \(P < 0.001\)), major adverse cardiac events (OR=0.79, 95% CI 0.69-0.91, \(P = 0.001\)), and stent thrombosis (OR=0.59, 95% CI 0.42-0.82, \(P = 0.002\)).\(^9\) It must be emphasized that careful and accurate interpretation of IVUS images is mandatory to maximize the benefit of IVUS-guided intervention. One additional aspect of IVUS-guided PCI is the potential to minimize the amount of contrast media during the procedure, which may also impact short- and/or long-term outcomes of our patients.

**Pre-Interventional Assessment**

In terms of preinterventional assessment, IVUS enables the interventionalist to determine the optimal device, its size, and other observations related to predicting favorable outcomes for a given procedure (Fig. 25-7). For example, if the IVUS catheter does not pass the target lesion, stent delivery and deployment may be affected. In this case, lesion preparation with balloon pre-dilatation or rotational ablation with the Rotablator® (Boston Scientific, Marlborough, MA) may be utilized, depending on the angiographic findings. After passing the target lesion, both qualitative and quantitative lesion morphology should be assessed. Additionally, when examining a tortuous
artery, a pseudo-stenosis caused by the accordion phenomenon should be kept to avert a misdiagnosis of a stenosis. On the IVUS image, a crescent-shaped lesion can be observed due to the folding of vessel wall. After removal of the IVUS catheter and guidewire, the lesion should be re-evaluated with an angiogram.

**FIGURE 25-7** Flow chart of preinterventional IVUS assessment.

### Qualitative Assessment

Common preinterventional qualitative assessment includes 1) high-risk features for distal embolization, 2) calcified plaque, and 3) plaque morphology with high risk of side branch occlusion. It is reported that plaque volume, a lipid pool-like image, ultrasound attenuation, and thrombus detected by IVUS are thought to be contributing factors to slow flow and no reflow. A lipid pool may be observed as an echolucent (or low echoic) zone inside the plaque in cases with high-quality images. However, detection of a lipid pool only by gray-scale IVUS imaging has low accuracy. Echo-
attenuated plaque can be identified by absence of the ultrasound signal behind the plaque that was either hypoechoic or isoechoic to the adventitia, despite absence of calcium, and is usually found in patients with acute coronary syndrome (Fig. 25-8A). One group recently reported that histopathologically, 91.4% of echo-attenuated plaques corresponded to either a fibroatheroma (FA) with an NC or pathological intimal thickening with a lipid pool; almost all segments with superficial echo attenuation indicated the presence of an FA with an advanced NC. Another group proposed that ultrasound attenuation with a longitudinal length of >5 mm and plaque rupture were significantly associated with no-reflow phenomenon. IVUS findings for a thrombus vary depending on the morphology; however, it is described as an intraluminal mass with a layered, lobulated, or pedunculated appearance (Fig. 25-8B). Adjunctive intracoronary drug administration or using a distal protection device may be warranted in this setting. In treating the heavily calcified lesion, especially circumferential calcification, called “napkin ring appearance” (Fig. 25-8C), application of the Rotablator device may be considered as an adjunctive therapy. The IVUS catheter position within a cross section will be useful to predict the impact of guidewire bias for the ablation procedure. After the ablation of calcium, multiple reverberations may be observed due to the smooth surface of the calcification. With respect to side branch occlusion, 2 IVUS findings were reported to have a predictive value. By observing a side branch ostium from a main vessel (Fig. 25-8D), presence of an atherosclerotic plaque at the side branch ostium was associated with 35% occlusion rate, whereas only 8% of the side branches without the ostial plaque resulted in occlusion. However, this finding may not be reliable, since an observation of the side branch ostium from the main vessel is not necessarily the same as the direct observation of the side branch ostium. One study investigating left main bifurcation lesions with IVUS pullback from the main vessel and the side branch showed that IVUS evaluation of the side branch ostium from the main vessel is only moderately reliable. Another finding is the “eyebrow” sign, which can be identified in the longitudinal view as a carina with a spiky morphology (Fig. 25-8E). Protection with a guidewire or predilatation may be utilized to avoid the side branch occlusion. Coronary aneurysm can be observed in preinterventional IVUS imaging or in postinterventional long-term follow-up IVUS imaging, as a consequence of an interventional
procedure (Fig. 25-8F). True coronary aneurysm is defined as more than 50% of lumen area enlargement than the proximal reference with an intact vessel wall. In contrast, pseudoaneurysm shows a loss of vessel wall integrity and damage to adventitia or perivascular tissue.

**FIGURE 25-8** Examples of preinterventional qualitative IVUS assessment. A. Echoattenuated plaque is characterized by absence of the ultrasound signal behind the plaque that was either hypoechoic or isoechoic to the adventitia, despite absence of calcium, and is usually found in patients with acute coronary syndrome. B. IVUS findings of a thrombus vary depending on its content and age; however, acute thrombus often presents as an intraluminal mass with a layered, lobulated, or pedunculated appearance. Adjunctive intracoronary drug administration or using a distal protection device may be warranted in this setting. C. In treating a heavily calcified lesion, especially with circumferential calcification called “Napkin ring appearance,” plaque modification with rotational atherectomy may be considered as an adjunctive therapy. D. Presence of an atherosclerotic plaque at the side branch ostium may be associated with an increased risk of occlusion after main vessel stenting. Accurate assessment requires direct imaging of the side branch. E. “Eyebrow” sign, defined in the longitudinal view as a carina with a spiky morphology, was also reported to predict side branch encroachment by main vessel intervention. F.
Coronary aneurysm can be observed in preinterventional IVUS imaging, or in postinterventional long-term IVUS follow-up as a consequence of an interventional procedure.

Quantitative Assessment

As stated previously, optimal device selection in terms of type and size are achieved with data acquired from quantitative IVUS assessment of the target lesion. Information obtained from earlier IVUS studies include the mechanism of luminal gain after percutaneous transluminal coronary angioplasty (PTCA) or stent deployment consist of vessel expansion (EEM expansion) and decrement of plaque volume (axial redistribution, compression, and distal embolization).\(^{15}\)

Clinical Outcomes with Ultrasound Trial (CLOUT) by Stone et al. was the first clinical investigation which demonstrated the safety and usefulness of IVUS-guided angioplasty compared to angiography alone, in which a balloon sizing protocol of the average of the lumen and media-to-media diameters at the reference segment for cases without extensive calcification was employed.\(^{16}\) A subsequent randomized, multicenter clinical trial (Balloon Equivalent to STent [BEST] study) comparing IVUS-guided angioplasty vs stenting employed a balloon sizing protocol of media-to-media diameter measured at the lesion.\(^{17}\) This aggressive balloon strategy resulted in a 56% reduction of stent usage (crossover of 44% patients from angioplasty strategy to stenting) with similar 6-month angiographic and clinical outcomes. In a contemporary DES trial of complex lesions, known as the Angiography Versus IVUS Optimization (AVIO) trial, the size of the post-dilatation balloon was selected based on the average of the media-to-media diameters at multiple sites within the stented segment.\(^{18}\) Precise vessel size measurement is also critically important for size selection of self-expanding or because these devices are not amendable once underdeployed in the lesion.

Angiographically “normal” reference segments can show 35% to 51% of plaque burden when evaluated by IVUS, and therefore, assessment of true lesion length by IVUS dictates the exact length of stent necessary to appropriately scaffold a lesion. To date, several IVUS studies of DES have identified greater reference plaque burden (inflow/outflow disease) as an independent predictor of subsequent stent edge restenosis or thrombosis.\(^{19-21}\)
The Impact of Stent Deployment Techniques on Clinical Outcomes of Patient Treated With the Cypher Stent (STLLR) trial also demonstrated that geographic miss (defined as the length of injured or stenotic segment not fully covered by the DES) had a significant negative impact on both clinical efficacy and safety at 1 year following sirolimus-eluting stent implantation.\textsuperscript{18} Thus, stent length is commonly recommended to be long enough to cover the entire lesion. Importantly, however, longer stent length has also been reported to be independently associated with DES restenosis and thrombosis. One practical approach was proposed in a single-center registry, where unique stepwise IVUS criteria (plaque burden <50% as the primary target zone) determined the optimal landing zone for DES.\textsuperscript{23} Spot stenting may also be an alternative option, which has shown favorable clinical outcomes in the DES era.\textsuperscript{24}

Detailed assessment of left main coronary artery disease is one of the most clinically important applications of IVUS, since left main disease is directly related to patient mortality. Angulations, calcification, or spasm in this location often lead to poor catheter engagement and confound angiographic interpretation. Several studies have shown that high percentages of patients that appear normal on angiography have left main coronary artery disease detected by IVUS.\textsuperscript{25-27} Conversely, another IVUS study has demonstrated that only less than half of angiographically ambiguous left main stenosis have a significant stenosis.\textsuperscript{28} This was especially true for ostial left main coronary disease where only 36% of the lesions had a significant stenosis and 41% had plaque burden <50% when assessed by IVUS. Furthermore, a recent study also reported a slight overestimation of fractional flow reserve (FFR) for the functional assessment of left main disease when a significant downstream stenosis coexists in the proximal left anterior descending or circumflex artery.\textsuperscript{29} Plaque distribution in left main bifurcation lesions can also be evaluated more accurately with IVUS compared with conventional angiographic classifications.\textsuperscript{30}

**PostInterventional Assessment**

Immediately after PTCA or stent deployment in a given lesion, the interventionalist should consider two perspectives in postinterventional IVUS assessment: the detection of complications following the procedure and the
optimization of the treatment (Fig. 25-9). In long-term follow-up, chronic stent problems and neointimal proliferation may also be assessed in details.

**FIGURE 25-9** Flow chart of postinterventional IVUS assessment.

**Qualitative Assessment**

Although spontaneous coronary dissection may be a primary cause for coronary events in some cases, coronary dissection (Fig. 25-10A) is usually seen after interventional procedures. IVUS is able to visualize the presence, longitudinal extent, and severity of the dissection, which is often difficult to assess precisely by coronary angiogram alone. In the IVUS image, dissection appears as a fissure or separation within the intima or plaque, and its severity can be quantified according to the depth (intimal, medial, or adventitial). After PTCA, dissection typically arises between 2 components with different compliance, such as soft and calcified plaque, whereas after stent deployment, it typically originates near the stent edge. Generally speaking, utilization of IVUS is preferable to OCT when injection of contrast media may possibly worsen the severity of dissection. Intramural (intravascular)
hematoma can arise often as a result of proximal dissection into the media (entry point) and distal dead end (a lack of reentry), leading to an accumulation of blood within the medial space (Fig. 25-10B). Maehara et al reported that in 29% of the hematomas detected by IVUS, there was no significant angiographic abnormality. Intramural hematoma is typically crescent-shaped, with straightening of the internal elastic membrane and with a homogeneous and hyperechoic lesion caused by blood accumulation. In contrast, extramural (extravascular) hematoma results from perforation of the coronary artery with extravasation to the adventitial tissue, typically observed after PCI, such as atherectomy or recanalization of chronic total occlusion (CTO) lesions. It appears as an irregularly shaped, echo-dim pattern, owing to the dilution of red blood cell concentration and dissemination throughout an echogenic adventitia with a separation of media. There may be less luminal compression in an extramural hematoma than in intramural hematoma.
FIGURE 25-10 Examples of postinterventional qualitative IVUS assessment and myocardial bridge. A. **Coronary dissection** is often seen after interventional procedures. In the IVUS image, dissection appears as a fissure or separation within the intima or plaque, and its severity can be quantified according to the depth (intimal, medial, or adventitial). B. **Intramural (intravascular) hematoma** can arise often as a result of proximal dissection into the media (entry point) and distal dead end (a lack of reentry), leading to an accumulation of blood within the medial space. Intramural hematoma is typically crescent-shaped, with straightening of the internal elastic membrane and with a homogeneous and hyperechoic region caused by blood accumulation. C. Even after stent
optimization, baseline incomplete stent apposition (ISA) can be observed by IVUS in 8% to 30% of drug-eluting stent (DES) cases. ISA is defined by IVUS as one or more stent struts incompletely attached to the arterial wall with evidence of blood speckle behind the strut(s) in a segment not associated with any side branches. **D. Myocardial bridge** is gaining attention as a functional cause of angina, myocardial infarction (MI), conduction disturbances, and sudden death. Myocardial bridge is defined on IVUS as an echolucent band (halo) corresponding to muscle tissue, partially surrounding the artery, with a variable degree of systolic arterial compression during cardiac cycle.

Even after stent optimization, baseline incomplete stent apposition (ISA) (Fig. 25-10C) can be observed in 8% to 30% of DES cases by IVUS. ISA is defined by IVUS as one or more stent struts incompletely attached to the arterial wall with evidence of blood speckle behind the strut(s) in a segment not associated with any side branches. Despite its theoretical concern, there are no data directly linking this finding with unfavorable clinical events in the long term, especially for minor baseline ISA under dual antiplatelet regimens. However, a “permanent” gap between stents and the vessel wall might become problematic when rewiring the vessel is needed at later interventions.32

**Quantitative Assessment**

Stent expansions defined by minimum stent diameter (MSD) or area (MSA) of both BMS and DES are frequently smaller than expected from the compliance charts provided by the manufacturers (MSD; 71%-80%, MSA 61%-66%).33 MSA is reported to be a consistent IVUS-based predictor of ISR and thrombosis, both in conventional BMS and contemporary DES. Utilizing IVUS assessment can confirm the achievement of larger acute gain, thereby contributing to better long-term outcome.8,9 Historically, the predicted risk of ISR was reported to decrease 19% for every 1 mm$^2$ increase of MSA in BMS.34 As a consequence, the so-called “bigger is better” theory is typically applied in the optimization of lesions with BMS. In other words, it is generally recommended to achieve maximal stent expansion in a given lesion when treating with BMS.

Given that the variability of neointimal proliferation is reduced by the eluting drug, the predictive value of MSA for long-term lumen patency is thought to be magnified in DES. In the SIRIUS (Sirolimus-Coated BX VELOCITY Balloon-Expandable Stent in Treatment of de Novo Native
Coronary Artery Lesions) trial, while a significant positive correlation was observed between baseline MSA and follow-up MLA in both BMS and sirolimus-eluting stent (SES) groups \((P < 0.0001\) for both), SES showed a higher correlation than BMS \((0.80\) vs \(0.65\)) with a higher regression coefficient \((0.92\) vs \(0.59\)).\(^{35}\) In a retrospective IVUS analysis of lesions with restenosis of various DES, despite excessive intimal hyperplasia still identified as the dominant mechanism of ISR, stent underexpansion at the MLA site was observed in a considerable percentage of ISR lesions \((35\%\) in lesions with stent length \(>28\) mm). Thus, stent underexpansion is considered as an important preventable mechanism of ISR, particularly in lesions with long stents.\(^{36}\) One practical question is whether any definitive target MSA exists to assure long-term stent patency. To date, several investigators have reported diagnostic thresholds of MSA to predict long-term DES patency by utilizing receiver–operator characteristic (ROC) analysis.\(^{32,35}\) While these analyses are useful to compare the performance of various types of stent devices, the cutoff values determined by ROC curves do not necessarily represent procedural endpoints, since the sensitivity and specificity for predication of ISR are not equivalently important from a clinical perspective. An ideal procedural endpoint should be a clinically reasonable agreement of MSA in maximizing the probability of long-term stent patency while minimizing increased risk of complications associated with aggressive stent dilatation.\(^{37}\) The target MSA should also be modified based on clinical (eg, diabetes, renal failure) and targeted lesion characteristics (eg, lesion location, amount of downstream myocardium).

For left main stenting using either single- or 2-stent strategy, Kang et al proposed optimal stent areas to predict angiographic ISR. Among 403 patients enrolled in this study, MSA cutoffs to best predict ISR on a segmental basis were \(5.0\) mm\(^2\) for the ostial left circumflex artery, \(6.3\) mm\(^2\) for the ostial left anterior descending artery, \(7.2\) mm\(^2\) for the polygon of confluence, and \(8.2\) mm\(^2\) for the left main. Stent underexpansion was again an independent predictor for major adverse cardiac events \((\text{adjusted HR}=5.56, 95\% \text{ CI}, 1.99-15.49, P = 0.001)\).\(^{38}\) Another clinical study reported the impact of IVUS-guided stent implantation on long-term mortality of left main disease, using propensity-score matching. In 145 matched pairs of patients treated with DES, IVUS-guidance was associated with a significantly lower 3-year mortality as compared with angiography-guidance \((4.7\%\) vs
Follow-Up Assessment

The primary mechanism of restenosis can be accurately identified by IVUS, which significantly affects the treatment strategy in patients with restenotic lesions. An IVUS study of in-stent ISR lesions following BMS demonstrated that 20% of lesions had an MSA <5.0 mm$^2$ and an additional 4.5% had other mechanical problems that contributed to restenosis. In most of these cases, stent underexpansion or other mechanical problems were not suspected angiographically at the time of reintervention. In another IVUS study of DES restenosis, 21% of lesions had an MSA <5.0 mm$^2$, 38% of which were not associated with significant neointimal hyperplasia. For this type of ISR, mechanical optimization is the first priority, and IVUS can be helpful to differentiate mechanical issues from exaggerated neointimal proliferation that may truly require DES implantation within the original restenotic stent.

Serial IVUS studies have added the concept of classification of ISA according to the time course. At follow-up, baseline ISA may have resolved or may persist. Therefore, ISA observed at follow-up could be either persistent baseline ISA (persistent ISA) or newly developed ISA in the segment where struts were completely apposed to the vessel wall after the procedure (late-acquired ISA [LISA]). At present, however, it is still debatable whether LISA independently contributes to the occurrence of late adverse events: the majority of clinical trials failed to show a prospective association between LISA and later thrombotic events, whereas multiple IVUS studies have demonstrated that LISA is frequently observed in lesions of late DES thrombosis. This discrepancy clearly represents a multifactorial process of this phenomenon. Also, most prospective studies were underpowered to detect a possible relationship of LISA with rare thrombotic events. A literature-based meta-analysis, recently conducted to circumvent this issue, suggested a significantly higher risk of late or very late DES thrombosis in patients with LISA (persistent or late-acquired) compared with those without LISA (OR: 6.51, $P = 0.02$). Another potential methodological issue in investigating the clinical impact of LISA is lack of appropriate grading or classification: LISA consists of a wide spectrum ranging from tiny
ISA to extensive aneurysm formation, whereas thrombosis-associated LISA is often at the extreme end of this spectrum. Finally, the late development of ISA may simply represent a pathologic process within the arterial wall, such as chronic inflammation with endothelial dysfunction weakening the vessel structure, rather than serving as a direct cause of thrombosis. To accurately identify LISA posing a risk for future events across the spectrum, a better understanding of this phenomenon is essential.

Another IVUS-detected condition that may be of importance in DES is stent strut fracture after implantation. IVUS imaging can directly visualize stent struts, offering more detailed morphologic assessment and classifications of this phenomenon. By IVUS, strut fracture is defined as longitudinal strut discontinuity and can be categorized based upon its morphologic characteristics: (1) strut separation, (2) strut subluxation, or (3) strut intussusceptions. Another proposed classification focuses on potential mechanisms of the strut fracture, categorizing them on the basis of the presence or absence of aneurysm at the fracture site (type I and II, respectively). Theoretically, strut fracture of the DES can reduce the local drug dose delivered to the arterial wall, as well as affecting the mechanical scaffolding of the affected lesion segment. In addition, the irregular edge of the fractured struts may give chronic stimuli to the vessel wall under cardiac movement. Conversely, deployment of long and rigid stents in angulated lesions with hinge motion can lead to significant alteration of local physiology, and therefore, the strut fracture may help restore the original dynamic state in at least some cases. The exact incidence and clinical implications of strut fractures remain to be investigated in large clinical studies.

**Other Clinical Applications**

When treating a CTO lesion, IVUS has the potential to improve its success rate with real-time procedure guidance. In contrast to OCT, IVUS does not require contrast flush that may possibly aggravate subintimal dissection. If there is a branch located near the entry point of the CTO lesion, the IVUS catheter can be inserted into the side branch to examine the target for wire penetration. Also, the IVUS catheter can possibly be inserted into the subintimal space to determine the direction of the true lumen, to guide penetration of the 2nd guidewire, or to determine the balloon diameter in
order to make a connection between the intimal and the subintimal space. For this application, the short-tip solid-state catheter is often preferred. In addition, the longer monorail design of the solid-state catheter may offer better trackability and less frequent catheter trapping, which can occasionally be caused by separation of the IVUS catheter and guidewire. Finally, intramural or extramural hematoma (or perforation) can occur not infrequently during the CTO procedure. Early detection and precise assessment of these conditions are crucial for safe and effective treatment of patients with CTO.

Recently, myocardial bridge is gaining attention as a functional cause of angina, myocardial infarction (MI), conduction disturbances, and sudden death. Among 331 patients with de novo coronary lesions located in the left anterior descending artery, myocardial bridge was reported to be detected in 23% of patients by IVUS, whereas in 3% of patients by angiogram. Myocardial bridge is defined on IVUS as an echolucent band (halo), corresponding to muscle tissue, partially surrounding the artery (Fig. 25-10D). The direct assessment of muscle tissue by IVUS regarding length, thickness, and location, in combination with a functional measurement of systolic arterial compression, may enhance our understanding of this anomaly, provide prognostic information in specific patients, and determine the indication and strategy of treatment, especially when unroofing surgery is considered.

Assessment of vasculopathy after heart transplant is another common application of IVUS, since angiography often fails to detect diffuse progression of vasculopathy that involves the entire coronary tree. Rapidly progressive vasculopathy, defined by IVUS as an increment of >0.5 mm in intimal thickness within the first year after transplantation, was demonstrated to predict worse long-term outcome up to 5 years.

**Safety**

The IVUS procedure can be performed safely with general cautions for interventional procedures and careful catheter manipulation. The most frequently observed complication during the IVUS procedure is coronary spasm (2.9%), followed by other rare problems, such as acute occlusion, embolism, dissection, or thrombus formation (0.4%). Regarding possible endothelial injury and disease progression as a chronic complication of
intracoronary instrumentation, no acceleration in the progression of atheroma or allograft vasculopathy of arteries imaged by IVUS has been demonstrated compared with noninstrumented arteries.48

OPTICAL COHERENCE TOMOGRAPHY

Since the first description in 1991,49 the OCT technology has been applied clinically in ophthalmology, dermatology, gastroenterology, urology, and cardiology. By utilizing backscattered reflections of infrared light, the catheter-based OCT system generates real-time tomographic images with significantly higher resolution than conventional IVUS (10 times or more). However, this leads to a relatively low penetration ability and necessitates removal of blood during the image acquisition procedure. Thus, the relation between IVUS and OCT is thought to be complementary rather than alternative. The integration of IVUS and OCT on a single catheter is currently under investigation.

While OCT provides microscopic assessment of coronary artery disease, the impact of its application for PCI on clinical outcomes is yet to be demonstrated. Currently, an international multicenter registry (n=3,000) with 5 years clinical follow-up is underway to address its evidence in clinical utility. In addition, a multicenter randomized trial (n=800) comparing OCT-guided versus IVUS-guided PCI is ongoing.

Imaging Systems and Image Acquisition Procedure

OCT employs light in the near infrared (NIR) range, typically with wavelengths of approximately 1.3 micrometers (μm). Light emitted from the OCT system is split into 2 portions, so that 1 portion travels through tissue and the other portion travels through a predetermined distance as a reference. Reflected light from tissue is then collected and combined with the reference light to obtain an interference pattern between the 2 portions of light, which are then analyzed by the OCT system to determine the amount of backscattering as a function of delay time or depth within the tissue (A-line). First-generation OCT systems, called time domain (TD)-OCT, and 2nd
generation OCT systems, called frequency domain (FD)-OCT or optical frequency domain imaging (OFDI), employ similar systems. Second-generation systems have vastly improved the capability of obtaining A-lines at much higher speeds, facilitating rapid 3D pullback imaging. Both FD-OCT and OFDI systems have an axial resolution of 10 to 20 μm and a lateral resolution of 25 to 30 μm at the focus.

TD-OCT and FD-OCT/OFDI have different catheter configurations. The TD-OCT employs a wire type catheter with 0.016-in thickness and an imaging core at the tip of the wire. The FD-OCT/OFDI uses a rapid-exchange catheter that enables pullback imaging performed within a protective sheath, similar to the configuration of mechanical IVUS catheters.

For accurate measurements, the OCT image should be properly calibrated for the refractive index of the flushing media and Z offset. Since the refractive index differs among various flushing media, calculated distances in the images can vary, thus the distances need to be corrected. This correction is readily available in the OCT console provided by the manufacturer. Z offset refers to slight variations in the optical path length of the optical fiber within the catheter. Calibration can be achieved by adjusting the optical path length in the sample and/or reference arm, which can be performed automatically or manually before each OCT examination. Since the fiber length can also change during a single pullback, resulting in a varying z-offset across the OCT dataset, OCT images should be evaluated to verify the z-offset and to adjust it, if necessary, prior to quantitative analysis.

Unlike IVUS, OCT image acquisition mandates blood removal, since light emitted from the imaging core is strongly scattered/absorbed by red blood cells. Conventionally, the proximal balloon occlusion method has been used for TD-OCT, whereas continuous flushing technique is the standard for FD-OCT/OFDI. In the former method, the occlusion balloon catheter is advanced over a standard 0.014-in guidewire, followed by replacement of the guidewire to the "ImageWire". Careful manipulation is required when using the TD-OCT catheter because this imaging wire is fragile. In FD-OCT/OFDI, the monorail imaging catheter is inserted along a 0.014-in coronary guidewire. Owing to the much higher image acquisition rate of the FD-OCT/OFDI system enabling a rapid pullback of the imaging core, blood removal using a bolus injection of contrast media results in satisfactory image quality. Some operators prefer low-molecular weight dextrose or lactated Ringer’s solution to reduce the amount of contrast media for OCT imaging.
In contrast, using saline to flush the vessel is not generally recommended since QT-elongation or ventricular arrhythmia may occur during the procedure. Comparisons of different OCT systems are provided in Table 25-4.

**Table 25-4 Comparison Among 3 Optical Coherence Tomography (OCT) Systems**

<table>
<thead>
<tr>
<th></th>
<th>First Generation</th>
<th>Second Generation</th>
<th>Optical Frequency Domain Imaging (OFDI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>LightLab (St. Jude Medical)</td>
<td>St. Jude Medical</td>
<td>Terumo</td>
</tr>
<tr>
<td><strong>Console</strong></td>
<td>M3™</td>
<td>ILUMIEN™ OPTIS™</td>
<td>Lunawave™</td>
</tr>
<tr>
<td><strong>Catheter</strong></td>
<td>ImageWire™ (0.016-in)</td>
<td>Dragonfly Duo™ (2.7 F)</td>
<td>FastView™ (2.6 F)</td>
</tr>
<tr>
<td><strong>Frame rates</strong></td>
<td>20 frames/sec</td>
<td>100 frames/sec</td>
<td>160 frames/sec</td>
</tr>
<tr>
<td><strong>Maximal pullback speed</strong></td>
<td>1-3 mm/sec</td>
<td>36 mm/sec</td>
<td>40 mm/sec</td>
</tr>
<tr>
<td><strong>Tissue penetration</strong></td>
<td>1.0-2.0 mm</td>
<td>1.0-2.5 mm</td>
<td>1.0-2.5 mm</td>
</tr>
<tr>
<td><strong>Maximal scan diameter</strong></td>
<td>6.8 mm</td>
<td>10.5 mm</td>
<td>9.5 mm</td>
</tr>
<tr>
<td><strong>Features</strong></td>
<td>Blood removal with proximal balloon occlusion method Possible complications from balloon occlusion</td>
<td>Blood removal by flushing method Higher pullback speed</td>
<td>Blood removal by flushing method Higher pullback speed No need to flush inside the catheter</td>
</tr>
</tbody>
</table>

Abbreviations: F, fluorescence profile; mm, millimeters.

**Artifacts**

Similar to IVUS, OCT has several inherent artifacts from its catheter configuration and nature of light (Fig. 25-11).
FIGURE 25-11 Examples of common OCT artifacts. A. The OCT image can be blurry when the flushing of the catheter is insufficient. Repeat flushing with saline is necessary to fully remove the residual bubbles or blood inside the catheter. B. With residual blood inside the vessel lumen, high-density, variably shaped structures within the lumen are observed, precluding visualization of entire vessel structures. This artifact often results from insufficient injection of flushing media. C. In the FD-OCT/OFDI system, the guidewire artifact is always observed as a point artifact with signal void behind it. In contrast, the guidewire artifact is not observed in the TD-OCT system, since the original guidewire is exchanged with the image wire. D. When assessing a lesion with a metal stent, multiple ghost images of stent struts, radially spaced at regular intervals, can be observed. These ghost images are called reverberations. Unlike with intravascular ultrasound (IVUS), this phenomenon is observed beyond metal struts but not beyond calcium, since OCT light can penetrate the calcium. E. Saturation artifacts are linear streaks of high and/or low intensities seen along the axial direction. This phenomenon occurs when a strong reflector of light, such as a guidewire or metal stent struts, backscatter at too high intensity to be accurately detected by the system. F. Seam-line or sew-up artifact appears as an axial discontinuity at the location of the transition between the first and the last A-line. This is caused by catheter motion during acquisition of a single cross-sectional image. G. Eccentric catheter position within the lumen may result in an artifact termed “sunflower” or “merry-go-round” artifact, where stent struts form a pinwheel pattern, appearing to face the imaging probe. H. Tangential signal dropout occurs when the optical beam is directed nearly parallel to the tissue surface and can resemble the OCT appearance of thin-cap fibroatheroma (TCFA). Careful interpretation is necessary so as not to misdiagnose this finding as a TCFA.
A) Bubbles or blood inside the catheter (see Fig. 25-11A).
The OCT image can be blurry when the flushing of the catheter is insufficient. Repeat flushing with saline is necessary to fully remove the residual bubbles or blood inside the catheter.

B) Blood within the lumen (see Fig. 25-11B).
With residual blood inside the vessel lumen, high-density, variably shaped structures within the lumen are observed, precluding visualization of entire vessel structures. This artifact often results from insufficient injection of flushing media. In some cases, a severe stenosis proximal to the imaging core may cause this phenomenon. It is important to ensure proper engagement of the guide catheter prior to increasing the injection speed of flushing media.

C) Guidewire artifact (see Fig. 25-11C).
In the FD-OCT/OFDI system, the guidewire is always observed as a point artifact with signal void behind it. This artifact is derived from its rapid-exchange design at the distal portion of the catheter, and is also seen in the reconstructed 3D image. In contrast, the guidewire artifact is not observed in the TD-OCT system, since the original guidewire is exchanged with the image wire.

D) Multiple reverberations (see Fig. 25-11D).
When assessing a lesion with a metal stent, multiple ghost images of stent struts, radially spaced at regular intervals, can be observed. These ghost images are called multiple reverberations. This phenomenon is caused by the multiple reflections of light between the transducer and a strong reflector. Unlike IVUS, this phenomenon is observed beyond metal struts but not beyond calcium, since OCT light can penetrate the calcium.

E) Saturation (see Fig. 25-11E).
Saturation artifacts are linear streaks of high and/or low intensities seen along the axial direction. This phenomenon occurs when a strong reflector of light, such as a guidewire or metal stent struts, backscatter at too high intensity to be accurately detected by the system.

F) Seam-line (sew-up) (see Fig. 25-11F).
Seam-line or sew-up artifact appears as an axial discontinuity at the location of the transition between the first and the last A-line. This is caused by catheter motion during acquisition of a single cross-sectional
image.

G) Sunflower (merry-go-round) (see Fig. 25-11G). Eccentric catheter position within the lumen may result in an artifact termed as “sunflower” or “merry-go-round” where stent struts form a pinwheel pattern, appearing to face the imaging probe.

H) Tangential signal dropout (see Fig. 25-11H). This occurs when the optical beam is directed nearly parallel to the tissue surface and can resemble the OCT appearance of thin-cap fibroatheroma (TCFA). Careful interpretation is necessary so as not to misdiagnose this finding as a TCFA (see below).

I) Non-uniform rotational distortion (NURD). NURD is an artifact which can be seen as a partial or whole distortion of the cross-sectional image, as occasionally seen with mechanical IVUS. This artifact results from mechanical binding of the drive cable that rotates the imaging core inside the protective sheath, and is usually observed in a tortuous artery or from kinking of the imaging catheter. To avoid this artifact, it is important to straighten the OCT catheter outside of body, or to unfasten the Y-connector to release torque.

**Image Interpretation**

In a normal coronary artery, three-layer vessel wall structures (intima, media, and adventitia) correspond to high–low–high backscattering layers by OCT image, similar to that seen with IVUS (Fig. 25-12). Owing to much higher resolution than IVUS, OCT can visualize microscopic vessel layer structures, such as IEM or EEM seen as a thin high-intensity layer, and periadventitial adipocytes as large, clear structures. In contrast, lower signal penetration of OCT than IVUS may inhibit observation of the entire vessel wall or perivascular structures (eg, branches, veins, pericardium, and myocardium).
FIGURE 25-12 **Typical cross-sectional OCT image and its interpretation.** A cross-sectional OCT image (A) with schematic diagram (B) demonstrates the classic high–low–high, 3-layered appearance. Histologic correlations with intima, media, and adventitia are also shown (C). Owing to much higher resolution than intravascular ultrasound (IVUS), OCT can visualize microscopic vessel layer structures, such as internal elastic membrane (IEM) or external elastic membrane (EEM) seen as a thin high-intensity layer, and periadventitial adipocytes as large clear structures. In contrast, lower signal penetration of OCT than IVUS may inhibit observation of the entire vessel wall or perivascular structures.

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**Quantitative Assessment**

Quantitative assessment methods of OCT are generally similar to those for IVUS. Current OCT systems provide automatic lumen contour detection and subsequent measurements of lumen area and diameter (minimum and maximum diameters) of every cross-section immediately after image acquisition, owing to better delineation of lumen contour by blood removal and higher resolutions. On the other hand, its low signal penetration within the tissue often results in difficulty assessing plaque burden or vessel remodeling precisely. To optimize the high-quality imaging of OCT, complete blood removal and calibration of the catheter are necessary. Also, care should be taken when assessing the lesion with the TD-OCT system, since the vessel may shrink by obstructing the blood with a proximal balloon.

Unlike IVUS, either or both the IEM and EEM may be visualized in the OCT image. By employing the EEM for measurements, the definition of plaque area is the same as IVUS measurement, whereas by employing the IEM, plaque volume will be more accurate in terms of the pathologic definition of atherosclerosis.
Qualitative Assessment

A fibrous plaque (Fig. 25-13A) has high backscattering and a relatively homogeneous OCT signal, which mainly derives from collagen. Unlike ultrasound, OCT signal can penetrate a calcified plaque (Fig. 25-13B) without shadowing, thus it is defined as a well-delineated, signal-poor region with sharp borders. Kume et al demonstrated that OCT is superior to IVUS in quantifying the calcification area within a cross-sectional image as referenced to histology specimen.\(^{51}\) A lipid plaque (Fig. 25-13C) is visualized as a signal-poor region with a diffuse border by which a calcified plaque can be differentiated. Due to signal attenuation from the lipid plaque, quantitative assessment of lipid volume is usually difficult in OCT.

A thin-cap fibroatheroma (TCFA) is defined as an OCT-delineated lipid or NC with an overlying thin fibrous cap, which is thought to be one of the features of unstable plaque. E. Thrombus appears as a lobulated structure that attaches to the luminal
surface or is floating within the lumen. Red thrombus (red blood cell-rich) is typically observed as a high backscattering and high attenuation structure, whereas white thrombus (platelet-rich) is seen as a less backscattering and homogeneous mass with less attenuation. **F. Cholesterol crystals** are high backscattering, thin, and linear structures within the plaque, typically accompanied with a fibrous cap or necrotic core. **G. Intimal vasculature** can be observed as signal-poor voids that are delineated clearly and can be identified in multiple continuous frames. **H. Macrophage accumulations** are seen as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise. Since macrophages attenuate the light significantly, superficial accumulations of macrophages may be falsely interpreted as a TCFA in some cases.

A fibrous cap is visualized by OCT as a signal-rich tissue layer overlying a signal-poor region such as a lipid pool or calcium. One important aspect of OCT image interpretation is the diagnosis of vulnerable plaque. A TCFA (Fig. 25-13D) is defined as an OCT-delineated lipid or NC with an overlying thin fibrous cap, which is thought to be one of the features of unstable plaque. With respect to the thickness of a “thin-cap,” 65 μm is proposed as a cutoff from a pathological study. However, the pathological cutoffs may require some adjustments when applied to in vivo OCT images, since tissue shrinkage of 10% to 20% can occur during histopathologic processing. One OCT study reported that, in ruptured plaques, the median thinnest cap thickness was 54 μm (50-60), and that the thinnest cap thickness was <80 μm in 95% of ruptured plaques. In several studies, an additional parameter was used for the diagnosis of OCT-defined TCFA, such as distribution of lipid (or NC) of >90° or involvement of more than one quadrant of the vessel circumference. As described earlier, misdiagnosis can happen when the tangential signal dropout artifact is observed.

Thrombus (Fig. 25-13E) appears as a lobulated structure which attaches to the luminal surface or is floating within the lumen. Depending on the content of thrombus, the OCT image will appear differently. Red thrombus (red blood cell-rich) is typically observed as a high backscattering and high attenuation structure, whereas white thrombus (platelet-rich) is seen as a less backscattering and homogeneous mass with less attenuation. Minute structures such as cholesterol crystals, intimal vasculature, or macrophage accumulations can also be seen by OCT (Fig. 25-13F-H). Cholesterol crystals are high backscattering, thin, and linear structures within the plaque, typically accompanied with a fibrous cap or NC. Intimal vasculature can be observed as signal-poor voids that are delineated clearly and can be identified in
multiple continuous frames. Association of this finding with active inflammation and the vasa vasorum are currently under investigation. Macrophage accumulations are seen as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise. Since macrophages attenuate the light significantly, superficial accumulations of macrophages may be falsely interpreted as a TCFA in some cases.

Clinical OCT Applications

Preinterventional Assessment

OCT may offer unique preinterventional information regarding vulnerable plaque, culprit lesion assessment of patients with acute coronary syndrome, and the extent of calcification. Several studies have demonstrated the relation between OCT-defined TCFAs and distal embolization during intervention. Its high resolution feature often enables the operator to identify the culprit lesion of acute coronary syndrome by visualizing the ruptured plaque. Detailed assessment and quantification of calcified plaque by OCT may help determine the appropriate treatment strategy of calcified plaque, including the employment of aggressive preprocedural lesion modification with Rotablator® or cutting balloon. On the other hand, there is a possibility that device sizing based on OCT imaging tend to be smaller than IVUS-guided intervention, because the low penetration of OCT light makes the determination of true vessel size difficult in cases with large plaque burden.

Postinterventional Assessment

Higher resolution of OCT than IVUS contributes to more precise detection of coronary dissection (Fig. 25-14A), tissue protrusion (Fig. 25-14B), and ISA after stent implantation; however, its impact on clinical outcomes has yet to be determined. For example, the minor abnormal findings noted only on OCT (not detectable by IVUS) were reported to be healed or resolved without any restenosis or thrombus formation (Fig. 25-14C). Also, while the higher resolution of OCT can enhance the detection of those abnormal morphologies, interobserver variability of qualitative analysis may also increase for less experienced analysts.
FIGURE 25-14 Examples of post-interventional OCT assessment. Higher resolution and contrast of OCT than intravascular ultrasound (IVUS) contribute to more precise detection of coronary dissection (A), tissue protrusion (B), thrombus formation (C), and incomplete strut apposition after stent implantation. At long-term follow-up of drug-eluting stent (DES), multiple interstrut hollows (D) defined as multiple hollows (the maximum depth >0.5 mm) existing between and outside well-apposed stent struts, can be observed.

After stent deployment, stent strut apposition is precisely assessed by
direct measurement of the distance between the stent strut and the lumen border. Because OCT light can create a blooming artifact of the stent strut both proximally and distally, the highest intensity point within the strut image is often used as the endoluminal surface of the stent strut. The measured distance is compared with the nominal strut thickness (metal plus polymer thickness in DES) to distinguish incomplete from complete strut apposition. The latest OCT systems can also provide immediate 3-dimensional stent reconstruction in the catheterization laboratory, which potentially facilitates appropriate guidewire insertion through the jailed orifice of a side branch for further bifurcation intervention.

Quantitative OCT analysis for polymeric bioresorbable vascular scaffolds (BRS) may slightly be different from conventional analysis methods for permanent metallic stents. For example, the scaffold area is often measured by tracing the backside of struts, while the stent area of metallic devices is drawn by connecting the endoluminal surface of strut. Strut core area and flow area can also be measured since polymeric struts appear on OCT as a black-box region surrounded by bright reflecting frames without shadowing, enabling the direct measurement of the strut core area as well as the precise assessment of luminal area even behind the struts. In addition, unlike the apposition assessment of metallic struts using the distance measurement, apposition of polymeric struts can be assessed directly owing to its optical transparency. To compare these two different implantation devices, a standardized comparative methodology should be applied to avoid systematic analysis biases.

**Follow-Up Assessment**

The definition of ISA described above is also applied to the assessment of chronic stent apposition, combined with tissue coverage of the struts: (i) apposed and covered; (ii) apposed and uncovered; (iii) non-apposed (protruded) but covered; (iv) non-apposed and uncovered (Fig. 25-15). At long-term follow-up of SES, an angiographic finding named peri-stent contrast staining (PSS) has been identified as an important imaging marker of very late stent thrombosis, possibly reflecting chronic inflammatory response of the vessel wall after the implantation. Two OCT findings of PSS lesions were reported in the literature; one is ISA, and the other is multiple interstrut hollows defined as multiple hollows (the maximum depth >0.5 mm) existing
between and outside well-apposed stent struts (Fig. 25-14D). On the other hand, conflicting results were also reported in an OCT study of acute and late ISA, in which OCT-detected LISA was not significantly associated with adverse clinical outcome.

Another unique and potentially important application of OCT at follow-up is the detailed characterization of neointimal tissue after stent implantation. Unlike homogeneous neointimal proliferation typically seen after BMS implantation, neointimal tissue within DES can be heterogeneous, representing proteoglycan-rich tissue, organized thrombus, smooth muscle cells, atheroma, inflammatory cells, or fibrinoid. Particularly, advanced neoatherosclerosis of neointimal tissue observed by OCT may be predisposed to late coronary events after DES implantation. In a study investigating 50 lesions with in-stent DES restenosis, 52% of lesions had at least 1 OCT-defined in-stent TCFA and 58% had at least 1 in-stent neointimal rupture.
within median follow-up of 32.2 months. In addition, fibrous cap thickness measured by OCT negatively correlated with follow-up time ($r = -0.318$, $P = 0.024$).\textsuperscript{58}

In BRS, minute structural changes of polymeric struts over time, such as the processes of strut degradation and absorption, and their interaction with the vessel wall can readily be monitored by OCT.\textsuperscript{59}

**Other Applications**

OCT is now being utilized for the assessment of cardiac allograft vasculopathy as well. In a prospective observational study of heart transplant patients, prevalence of vulnerable plaque features (ie, TCFA, macrophages, and microchannels) and complicated coronary lesion morphologies (ie, intimal laceration, intraluminal thrombus, layered complex plaque, and plaque rupture) increased over time, suggesting the development of atherosclerosis beyond the typical concentric and fibrosing vasculopathy changes.\textsuperscript{60}

By utilizing OCT, conformational changes of arterial layers in vasospastic lesions can also be investigated in detail. An OCT study of lesions with vs without spasm suggested that medial contraction occurs even in an asymptomatic state and facilitates the formation of an intimal bump in patients with vasospastic angina.\textsuperscript{61} Luminal narrowing during spasm was associated with intimal gathering, but without alteration of intimal area.

**Safety**

The safety of TD-OCT has been reported in a multicenter retrospective registry.\textsuperscript{62} Among 468 patients undergoing OCT examination, 54.7% of examinations were performed utilizing the balloon occlusion technique, whereas 45.3% were performed with the non-occlusive flush technique with a mean contrast volume of 36.6±9.4 mL. Although minor adverse events of transient chest pain (47.6%) and electrocardiographic changes (45.5%) were frequently observed, major complications were rare. Ventricular fibrillation occurred due to balloon occlusion and/or deep guide catheter engagement in 5 cases (1.1%), air embolus in 3 cases (0.6%), and vessel dissection only in 1 case (0.2%). No coronary spasm or major adverse cardiac event was
As for FD-OCT, a single center registry of 90 patients reported no major complications in terms of death, MI, emergency revascularization, embolization, life-threatening arrhythmia, coronary dissection, prolonged and severe vessel spasm, and contrast-induced nephropathy.

Compared with IVUS, additional considerations are required specific to OCT imaging procedures. First, additional contrast media usage should be taken into account when using OCT in patients with renal dysfunction or heart failure. Second, if there is coronary dissection in the investigating artery, there is a possibility of extending the dissection when flushing contrast media during the imaging.

SPECTROSCOPY

Spectroscopy, developed within the field of analytical chemistry for identification of mixed samples or unknown molecules, has recently been adapted for tissue characterization in interventional cardiology. Analyzing the spectra induced by the interaction of electromagnetic radiation or light with tissue materials, spectroscopy enables the determination of the chemical composition of plaque substances. Several forms of photonic spectroscopy have been applied for the characterization of atherosclerotic plaques, represented by diffuse reflectance near-infrared, Raman, and fluorescence spectroscopy.

Among these newly developed optical techniques, the diffuse reflectance near-infrared spectroscopy (NIRS) is the frontrunner for invasive intracoronary imaging, for which an FDA-approved catheter-based NIRS system (Infraredx, Inc., Burlington, MA) is clinically available in the US. Since its initial experience with detecting lipid content of an atherosclerotic plaque in an experimental animal study in 1993, its usefulness to identify lipid core plaque (LCP) has been validated with human atherosclerotic plaques in autopsy specimens through blood and in vivo. NIRS provides a two-dimensional map of the vessel, called a “chemogram,” to demonstrate the lipid component in atherosclerotic plaques.

Other spectroscopic techniques are still under preclinical evaluation. Raman spectroscopy has a theoretical advantage in direct quantification of individual plaque components. Recently, a prototype of an intravascular
Raman spectroscopy catheter system and diagnostic algorithms for high wave number Raman spectra have been developed.\(^{65}\) Ongoing efforts are also directed at the application of fluorescence molecular imaging to catheter-based diagnostics by adopting intravascular near-infrared fluorescence (NIRF) techniques.

**Imaging Systems and Image Acquisition Procedure**

The commercially available NIRS system (Infraredx, Inc.) incorporates a dual-modality imaging catheter that provides simultaneous gray-scale IVUS and NIRS imaging for co-registered acquisition of structural and compositional information. NIRS-IVUS is the first clinically available hybrid intravascular imaging system, which is an area of growing attention in the field of coronary imaging. Combined data are obtained with a rapid-exchange 3.2F imaging catheter system (TVC Insight™) on which both ultrasound and NIRS probes are equipped. The catheter design and image acquisition procedure are similar to conventional IVUS systems. The imaging catheter is compatible with a 6-Fr guide catheter and can be inserted using a 0.014-in guidewire. After insertion of the catheter distally to the target lesion, catheter pullback is performed at 0.5 mm/s via an automated rotational pullback unit. Unlike other light-based imaging techniques such as OCT and angioscopy, NIRS does not require removal of blood from the imaging field.

The current NIRS system is specialized to detect lipid-rich plaque (cholesterol) that is displayed as yellow on a two-dimensional map of the vessel (called a “chemogram”) with spatial (circumferential and longitudinal) information (Fig. 25-16). A color scale from red to yellow indicates increasing algorithmic probability of a lipid component in the vessel wall. The chemogram data, laid in a halo surrounding the cross-sectional IVUS image, is readily applicable in a real-time manner on a dedicated console (TVC Composite™). A summary of the results for each 2-mm section of artery is presented as a block chemogram, which also is portrayed in the central catheter artifact of the cross-sectional IVUS image. In addition, a lipid core burden index (LCBI) is computed as the fraction of valid pixels within the scanned region that exceed a lipid probability of 0.6, multiplied by 1,000. Since the chemogram lacks depth information, precise assessment of lipid core plaque volume as well as the depth of lipid core (thickness of fibrous cap) is currently limited. However, a new algorithm to differentiate the cap
thickness of lipid core plaque using the amount of collagen signal contribution has recently been developed and is under preclinical validation.

**FIGURE 25-16** Example images of combined IVUS/NIR spectroscopy. A. The current NIRS system is specialized to detect lipid-rich plaque (cholesterol). A color scale from red to yellow indicates increasing algorithmic probability of a lipid component in the vessel wall. The color-coded data laid in a halo surrounding the cross-sectional IVUS image is readily applicable in a real-time manner. B. On a two-dimensional map of the vessel called “chemogram,” the spatial distribution of lipid is displayed with circumferential and longitudinal information. C. A summary of the results for each 2-mm section of artery is presented as a block chemogram, which is portrayed in the central catheter artifact of the cross-sectional and longitudinal IVUS images.

**Clinical NIRS Applications**

Other than research applications of NIRS-IVUS, three primary areas are being investigated for clinical applications: (i) in vivo detection and quantification of lipid-rich vulnerable plaque as well as guidance for PCI such as prediction of periprocedural distal embolization, (ii) determination of optimal stent length to avoid residual lipid-rich plaques at the treatment margins, and (iii) the risk stratification for side branch compromise during PCI based upon NIRS findings of plaques located in proximity to the side branches.
Madder et al demonstrated that target lesions of ACS patients were more frequently composed of LCP than those with stable angina (84.4% vs 52.8%, \( P = 0.004 \)). LCPs remote from the target lesion were also found more frequently in ACS patients (73.3% vs 17.6%, \( P = 0.002 \)). In another study of culprit lesions of ST-segment elevation MI, the maximal LCBI measured for each of the 4-mm longitudinal segments in the treatment zone (maxLCBI4mm) was 5.8-fold higher than in nonculprit segments within the same vessel (523 vs 90, \( P < 0.001 \)) and 87-fold higher than in autopsy segments free of large LCP by histology (523 vs 6, \( P < 0.001 \)). Based on these findings, this investigator group proposed the maxLCBI4mm=400 as a cutoff to detect the culprit segments of ST-segment elevation MI.\(^67\)

With respect to PCI applications, a substudy of the COLOR (Chemometric Observations of Lipid Core Plaque of Interest in Native Coronary Arteries) registry proposed the maxLCBI4mm=500 as a useful cutoff to stratify patients with high risk of periprocedural MI. In this study, periprocedural MI occurred in 7 of 14 patients (50%) with the maxLCBI4mm ≥500, compared with only 2 of 48 patients (4.2%) with the lower maxLCBI4mm \( (P=0.0002) \).\(^68\) This preliminary finding was further evaluated in the CANARY (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow) study in which a moderate relationship was again demonstrated between the automated NIRS lipid parameters and periprocedural MI. In this cohort, 31 patients with a maxLCBI4mm ≥600 were further randomized to PCI with vs without distal protection. Although this small study failed to demonstrate a significant reduction of periprocedural MI with the adjunctive distal protection, the potential utility of NIRS in this application warrants further investigation.

Unlike other modalities such as OCT or VH-IVUS, NIRS offers automated lipid-rich plaque detection that can be easily interpreted, both in a cross-sectional image and in longitudinal distribution on chemogram. This feature may possibly reduce interobserver variability between experienced and less experienced interventional cardiologists. Accordingly, LCBI may be used as an objective surrogate marker for assessing the efficacy of anti-atherosclerotic drug therapeutics, such as intensive statin therapy.\(^69\) In-stent thin-cap neoatheroma as a mechanism for late DES failure may also be assessed using this technology.\(^70\)
Safety

The safety of catheter-based spectroscopy has been reported in a standalone NIRS system. The SPECTACL (SPECTroscopic Assessment of Coronary Lipid) study that examined 106 patients with the standalone NIRS catheter showed no major adverse events related to NIRS imaging. On the other hand, a relatively high rate of failure (16%) to obtain adequate data was reported in this early clinical experience. The safety and performance of the newer dual-modality NIRS–IVUS system are currently being evaluated in the SAVOIR (Simultaneous Acquisition of Intravascular Ultrasound and Near Infrared Spectroscopy Data in the Coronary Artery) study.

ACKNOWLEDGEMENT

The authors appreciate Heidi N. Bonneau, RN, MS, CCA, and Teruyoshi Kume, MD, PhD, for the review and figure preparation of this chapter.

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**MULTIPLE CHOICE QUESTIONS**

1. Which of the following statements is correct in terms of intravascular ultrasound (IVUS) findings of the coronary artery?
   A. Arterial 3-layer structures (intima, media, and adventitia) generally correspond to a high–low–high echoic appearance of the arterial wall on IVUS images.
   B. The thickness of intima decreases with age.
   C. The media is clearly observed as a distinct layer, especially in atherosclerotic lesions.
   D. Plaque vulnerability can be accurately evaluated by conventional gray-scale IVUS.

2. An intravascular ultrasound (IVUS) image was obtained within a stented segment from a patient who underwent stent implantation 12 months ago. What is the area indicated in yellow?
A. Stent area
B. Neointimal hyperplasia (or thrombus) area
C. Lumen area
D. Plaque plus media area

3. In comparison of features between intravascular ultrasound (IVUS) and optical coherence tomography (OCT), all of the following statements are true, EXCEPT:
   A. OCT has higher resolution than IVUS.
   B. OCT requires blood removal whereas IVUS does not.
   C. Fibrous cap thickness can be measured by both IVUS and OCT.
   D. IVUS is more suitable for assessment of vessel remodeling than OCT.

4. In this optical coherence tomography (OCT) image, the coronary lumen is mainly occupied by which of the following?
   A. Thrombus
   B. Contrast medium
   C. Ruptured plaque material
   D. Residual blood
5. This is a representative image of combined intravascular ultrasound (IVUS)/near-infrared spectroscopy (NIRS). What does the yellow color represent in a halo surrounding the cross-sectional IVUS image?

A. Calcified plaque
B. Lipid-rich plaque
C. Stent struts
D. Neointima
E. Thrombus

ANSWERS

1. A
Interpretation of intravascular ultrasound (IVUS) images relies on the fact that arterial wall structures can be identified as separate layers. Typically, the differences in acoustic impedance of intima, media, and adventitia of coronary arteries give rise to a characteristic 3-layered (high–low–high) appearance on IVUS images (choice A). In muscular arteries such as the coronary tree, the media generally stands out as a thin dark layer since it contains much less echo-reflective material (collagen and elastin) than the neighboring intima and adventitia. However, this layered appearance may be undetectable in truly normal coronary arteries wherein the intimal thickness is below the effective resolution of IVUS. Also, with progression of atherosclerosis and/or patient age, the intima/plaque layer increases in thickness (choice B), and the media may be destroyed so that it may not appear as a distinct layer around the full circumference of the vessel (choice C). With respect to plaque vulnerability assessment, visual interpretation of conventional gray-scale IVUS images is limited in the precise detection and quantification of specific plaque components (choice D). Low echogenicity of plaque may represent its lipid content, but a similar appearance can result from other conditions, such as acoustic shadowing from microcalcifications or an adjacent region of calcification or fibrosis.

2. B
On intravascular ultrasound (IVUS) scan, metallic stent struts are visualized as bright, focal points in a circular-arrayed pattern, and the stent area measurement is performed at the leading edge of these distinct echoes (a blue line on the right panel). Neointimal hyperplasia within the stent has low echo-reflectivity at follow-up IVUS imaging, and the area is calculated as the difference between stent and lumen areas (choice B and C). Differential diagnoses include plaque prolapse, stagnant blood flow, and thrombus. Acute thrombus usually appears as a relatively echo-dense intraluminal mass often
showing a layered, lobulated, or pedunculated appearance with speckling, scintillation, clefts or microchannels, while old organized thrombus may have a darker, more homogenous ultrasound appearance, similar to that of neointimal hyperplasia. Plaque and media are located outside the stent area (choice D).

3. C

By utilizing backscattered reflections of infrared light, intravascular optical coherence tomography (OCT) systems generate real-time tomographic images similar to intravascular ultrasound (IVUS) but with significantly higher resolution (choice A). Thus, OCT is more suitable for microscopic assessment such as the thickness of a thin fibrous cap (choice C). On the other hand, this advantage is achieved at the expense of limited beam penetration within the tissue, often resulting in insufficient visualization of vessel area for the assessment of vessel remodeling (choice D). The imaging procedure of intravascular OCT is similar to that of IVUS, except that blood must be displaced by optically transparent liquid (e.g., contrast medium) while imaging, since red blood cells cause significant scattering of infrared light, leading to very large signal loss (choice B).

4. D

Unlike intravascular ultrasound (IVUS), optical coherence tomography (OCT) image acquisition mandates blood removal from the lumen, since light emitted from the imaging core is strongly scattered/absorbed by red blood cells. With residual blood inside the vessel lumen, high-density, variably-shaped structures within the lumen are observed, precluding visualization of entire vessel structures, as seen in this image (choice D). This artifact often results from insufficient injection of flushing media; therefore, operators should be careful not to interpret this artifact as real tissue structure. Contrast medium is optically transparent and is typically used to remove blood from the lumen (choice B). Thrombus, or plaque rupture complicated with thrombus accumulation, often appears as a lobulated intraluminal mass that attaches to the lacerated plaque surface or is floating within the lumen (choices A and C). Red thrombus (red blood cell-rich thrombus) is typically observed as a high backscattering and high attenuation structure, whereas white thrombus (platelet-rich thrombus) is seen as a less backscattering and
homogeneous mass with less signal attenuation.

5. B

The commercially available coronary spectroscopy system incorporates a dual-modality imaging catheter that provides simultaneous intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) imaging for co-registered acquisition of structural and compositional information. The current system is specifically designed for the detection of lipid-rich plaque that is exhibited yellow on a color-coded halo surrounding the cross-sectional IVUS image. The color scale from red to yellow indicates increasing algorithm probability of a lipid component of the vessel wall (choice B). At present, the ability of coronary spectroscopy to detect and differentiate various other plaque components or pathological features of plaque vulnerability remains to be determined.
INTRODUCTION

Adjunctive physiologic and intravascular imaging modalities as described in Chapters 24 and 25 enable operators to 1) direct ischemia-guided revascularization; 2) diagnose microvascular disease, coronary vasospasm, diffuse endothelial dysfunction, myocardial bridging or any combination of these entities; 3) characterize plaque morphology and severity; and 4) optimize acute and long-term percutaneous coronary intervention results. Herein we describe emerging clinical applications of in vivo physiologic and imaging modalities in the settings of stable ischemic heart disease, symptomatic myocardial ischemia without obstructive epicardial atherosclerosis, and acute coronary syndromes.

STABLE ISCHEMIC HEART DISEASE

Physiologic Evaluation of Intermediate Stenoses
As discussed in Chapter 24, fractional flow reserve (FFR) can accurately assess the hemodynamic significance of intermediate coronary lesions (40%-80% diameter stenosis) and guide coronary revascularization in patients with single vessel, multi-vessel, and left main disease. Physiologic assessment can also help simplify and determine the overall interventional approach for complex bifurcation lesions by converting them into a predominantly single lesion. In addition, FFR can be used to assess the need for intervention of jailed side-branches.

Considered the gold standard for invasive physiologic assessment, FFR has been preferred over other coronary indices such as hyperemic stenosis resistance (HSR), coronary flow reserve (CFR) and the instantaneous wave-free ratio (iFR) because it has a normal reference value of 1.00, is reproducible and relatively easy to perform, and has robust literature supporting its use for safely deferring and guiding revascularization.\(^1\)-\(^4\) While HSR may be even more accurate in predicting the hemodynamic significance of an epicardial lesion, it requires both pressure and flow sensors for measurement and currently does not have substantial data supporting its clinical use.\(^5\),\(^6\)

In patients with contraindications to adenosine use, non-hyperemic indices such as whole cycle distal pressure to aortic pressure ratio (Pd/Pa) or iFR may be preferable for intermediate lesion assessment. Although predictive of FFR with a diagnostic accuracy of 75% to 85%, Pd/Pa has a narrower gradient window and smaller signal-to-noise ratio, resulting in less robustness for ischemia prediction. For example, a pressure wire drift of ±2 mm Hg resulted in 31% of misclassified study lesions using Pd/Pa, compared to 21% for FFR (\(P < 0.001\)).\(^7\)

Another non-hyperemic index, iFR measures the difference between distal and aortic coronary pressure during a specific mid to late diastolic period of the cardiac cycle, known as the wave-free period, when the resting resistance is relatively constant and low. Several studies have suggested that iFR has a diagnostic accuracy of 75% to 85% for identifying a hemodynamically significant FFR.\(^8\)-\(^11\) The VERIFY study, however, reported a weaker correlation between iFR and FFR and recommended against its use for clinical decision making.\(^12\) Due to the variability of reported correlations between FFR, iFR, and Pd/Pa, the RESOLVE study was undertaken with analysis in a core laboratory to help settle questions surrounding the
diagnostic accuracy of iFR and Pd/Pa compared to FFR. In this retrospective multi-center study, an optimal iFR cut point of 0.90 and Pd/Pa cut point of 0.92 demonstrated overall accuracies of 80.4% and 81.5%, respectively, when compared with FFR.\textsuperscript{13} The ADVISE II study, a prospective multicenter trial, also observed similar diagnostic accuracies for an iFR cut point of 0.89 and Pd/Pa cut point of 0.91 (82.5% vs 83.2%).\textsuperscript{14,15} The role of iFR was recently clarified following the results of two studies: DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation)\textsuperscript{16} and iFR-Swedeheart (Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI).\textsuperscript{17} Both studies prospectively compared intermediate lesion assessment between FFR- and iFR-guided percutaneous coronary intervention. Two thousand four hundred patients were enrolled in the DEFINE-FLAIR trial and the primary endpoint was the 1-year risk of major adverse cardiac events which were a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization. At 1-year, the primary end point occurred in 6.8% in the iFR group and 7.0% in the FFR group (difference in risk, −0.2 percentage points; 95% confidence interval [CI], −2.3 to 1.8; \( p<0.001 \) for noninferiority; hazard ratio, 0.95; 95% CI, 0.68 to 1.33; \( p=0.78 \)) indicating for the first time that iFR guided revascularization is non-inferior to FFR-guided revascularization. This finding was further illustrated with the iFR-Swedeheart where 2037 patients with stable angina or acute coronary syndrome were randomized to undergo revascularization guided by either iFR or FFR. The primary end point was the rate of a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 1-year after the procedure. The primary endpoint in the iFR group occurred in 6.7% vs. 6.1% in the FFR group. Following completion of these randomized trials, it became evident that iFR is a promising non-hyperemic index and the technology appears to be quicker and as safe as the established FFR.

**Intravascular Imaging for Intermediate Stenoses**

The pressure gradient across a stenosis depends on the reference vessel area, stenosis area and length, blood flow velocity and viscosity, entrance effects, and flow separation (Fig. 26-1).\textsuperscript{3} One might thus expect an imperfect correlation between stenosis geometry and FFR.\textsuperscript{18-22} Therefore, it is now
accepted that physiologic evaluation is more reliable than anatomic evaluation for assessing intermediate lesion severity. Nevertheless, we discuss below the evidence derived from anatomic lesion assessment.

**FIGURE 26-1 Factors producing resistance to coronary blood flow.** The angiographic 2-dimensional images cannot account for the multiple factors that produce resistance to coronary blood flow and loss of pressure across a stenosis. The eccentric and irregular stenosis (upper panel) shows arrows designating entrance effects, friction, and zones of turbulence accounting for separation energy loss. The calculation of pressure loss ($\delta P$) across a stenosis (lower right panel) incorporates length ($l$), areas stenosis ($A_s$), reference area ($A_n$), flow ($Q$), and coefficients of viscous friction and laminar separation ($f_1$ and $f_2$) as contributors to resistance and hence pressure loss. (Reproduced from Kern MJ, Samady H. Current Concepts of Integrated Coronary Physiology in the Catheterization Laboratory. *J Am Coll Cardiol.* 2010;55(3):173-185. Copyright © 2010, with permission from American College of Cardiology Foundation.)

**Non-Left Main Lesions**
In a study of 167 patients with intermediate lesions randomized to undergo PCI based on cutoff values of FFR 0.80 or intravascular ultrasound (IVUS)-derived minimum lumen area (MLA) 4.0 mm$^2$, neither cohort had increased incidence of major adverse cardiac events, but the IVUS group underwent significantly more revascularization procedures. While studies suggest that an IVUS-MLA ≥4.0 mm$^2$ can accurately identify non-ischemic lesions for which PCI can be safely deferred, further investigations have supported the importance of considering additional vessel information beyond MLA. A meta-analysis of 11 clinical trials demonstrated that the mean MLA of non-left main lesions was 2.6 mm$^2$, with a pooled sensitivity of 0.79 and specificity of 0.65. Use of IVUS-MLA was observed to misclassify up to 20% of coronary lesions. Given the aforementioned discordances, physiologic evaluation remains superior to anatomic assessment with imaging for intermediate coronary lesions. Anatomic measurements with optical coherence tomography (OCT) imaging are smaller than those with IVUS and correlate better with true anatomic representations from phantom measurements.

**Bifurcation Lesions**

Coronary bifurcations are challenging lesion subsets accounting for 20% of interventional procedures. Pre-intervention intravascular imaging can help select the optimal bifurcation PCI strategy by visualizing the spatial distribution of the mother and daughter vessels as well as identifying carina shifts as a mechanism for side branch compromise. Koo et al have demonstrated that jailed side branches with <75% diameter stenosis are almost never hemodynamically significant and therefore often do not need further assessment or treatment. Similarly, provisional side branch PCI can usually be deferred if the pre-intervention side branch IVUS-MLA is ≥2.4 mm$^2$.

**Left Main Lesions**

In addition to difficulty in accurate angiographic assessment as demonstrated by substantial interobserver variability, decision making regarding the hemodynamic significance of left main lesions are often more critical.
Therefore, adjunctive imaging and physiology modalities have emerged as highly useful tools allowing operators to more confidently and accurately evaluate lesions and direct revascularization. Initial studies suggested that left main MLA <7.5 mm² was hemodynamically significant. A subsequent study observed that left main FFR cut point of 0.75 correlated with IVUS-MLA cut point of 5.9 mm². More recent data suggest that an IVUS MLA ≤4.5 mm² in the left main artery of Asian patients may correspond to an FFR value of ≤0.80, and that ruptured left main plaque and plaque burden also correlate with FFR. An observational outcomes study found that using an IVUS-MLA cut point of 6 mm² to direct or defer revascularization was safe.

Most of the support for the use of IVUS and FFR in left main disease has been derived from small trials and observational studies, so there remain several unanswered questions regarding optimal ischemic cut-off values and long-term safety, efficacy and cost-effectiveness. Nevertheless, even for intermediate left main lesions, FFR is considered the gold standard and can be used to guide decision making with regard to the need for revascularization. Importantly, the FFR of left main artery has to be taken in the context of tandem daughter vessel disease (see Chapter 25). Randomized clinical trials directed toward invasive physiologic and anatomic assessment for left main disease are warranted. In the interim, it may be appropriate to start with FFR for angiographically indeterminate left main lesions. If the FFR value is greater than 0.80, then PCI should be deferred, while if it is less than 0.75, the lesion should be revascularized. If the FFR value falls in the grey zone between 0.75 and 0.80, IVUS or other noninvasive functional testing may be helpful (Fig. 26-2).
Physiologic and intravascular ultrasound assessment of left main lesions. In this algorithm of left main assessment, we recommend performing fractional flow reserve (FFR) for indeterminate left main lesions. If the FFR value is greater than 0.80, then PCI should be deferred while if it is less than 0.75 the lesion should be revascularized. If the FFR value falls between 0.75 and 0.80, intravascular ultrasound (IVUS) or other non-invasive functional testing may be helpful. In particular, we recommend revascularization for an IVUS minimum luminal area (MLA) of <4.5 mm² and deferring if the MLA is >6.0 mm². For those lesions that fall in the grey zone of IVUS MLA 4.5 to 6.0 mm², the clinical context should be considered with respect to revascularization or further non-invasive testing.

MYOCARDIAL ISCHEMIA IN THE ABSENCE OF OBSTRUCTIVE EPICARDIAL CORONARY ARTERY DISEASE

Patients with anginal syndromes in the absence of significant epicardial disease (<40% diameter stenosis by visual assessment with angiography)
likely have myocardial ischemia derived from coronary microvascular disease, vasospasm and/or endothelial dysfunction, or from structural abnormalities such as myocardial bridging, coronary aneurysms, or coronary artery anomalies. Patients with non-obstructive atherosclerosis have longterm outcomes similar to those with obstructive coronary artery disease; anginal symptoms in these patients have been associated with increased mortality, higher frequency of emergency room visits and hospitalizations, increased costs, and worse quality of life when compared to normal subjects.\textsuperscript{33,34} Obtaining a definitive diagnosis in such patients can guide targeted intensified lifestyle modification counseling and medical treatment.\textsuperscript{35} Figure 26-3 outlines a diagnostic approach in the cardiac catheterization laboratory.

\textbf{FIGURE 26-3} Testing algorithm for patients with mild stenoses. For patients presenting with angina but no flow limiting coronary lesions, we recommend coronary reactivity testing, first with acetylcholine and then with adenosine. Normal coronary arteries vasodilate in response to acetylcholine. Therefore, observations of vasoconstriction in combination with symptoms or electrocardiogram (ECG) changes are highly suggestive of endothelial dysfunction and vasospastic disease. Additionally, patients with coronary flow velocity reserve <2.5 are considered to have microvascular disease. If this occurs without notable findings in response to acetylcholine, then the patient has endothelium-independent microvascular dysfunction. On the other hand, if it occurs with vasoconstriction to acetylcholine, then the patient is considered to have both endothelial and microvascular dysfunction. Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve. (Based on
Endothelium-independent microvascular assessment is performed with adenosine to induce hyperemia through smooth muscle cell relaxation and microcirculatory vasodilatation. Several indices have been developed to evaluate microvascular function in patients with and without epicardial disease. One established index is CFR, which reflects the combined ability of the epicardial artery and the microcirculation to achieve maximal blood flow in response to stress. In the absence of significant epicardial disease (FFR >0.80), CFR may be used as an index of predominantly microvascular disease, with a CFR <2.0 suggestive of coronary microvascular disease.

There are other indices that have been developed in recent years to assess microvascular function in patients with or without epicardial lesions. The index of microcirculatory resistance (IMR) can be assessed using a pressure wire and reproducibly measures microvascular function in patients with or without epicardial stenosis; although there are no established cut-off values for IMR, it is emerging as a very practical invasive tool for microvascular testing. Hyperemic microcirculatory resistance (HMR) is also an attractive index that can measure microvascular function independently of epicardial stenosis, but it relies on a combination of pressure and Doppler velocity wire that requires some technical expertise and does not account for collateral reserve. Microvascular assessments with IMR or HMR are primarily utilized in research cases only.

Endothelial dysfunction is a common cause of microvascular disease and angina in patients with no significant coronary atherosclerotic lesions. Endothelial function testing requires pharmacological interrogation of the endothelium using intracoronary acetylcholine (off-label use) and thus is generally performed in specialized centers or in research protocols. The healthy endothelium in the presence of acetylcholine induces vasodilatation through stimulation of nitric oxide and cyclic guanosine monophosphate. In patients with endothelial dysfunction, acetylcholine paradoxically fails to cause vasodilatation and may even result in vasoconstriction through interaction on muscarinic receptors of arterial smooth muscle cells. Endothelial dysfunction is therefore characterized by the vessel response to intracoronary acetylcholine: epicardial if there is no change or a decrease in
diameter as visualized by angiography; and microvascular if there is no change or a decrease in coronary blood flow as determined by angiography in combination with a Doppler velocity wire.\textsuperscript{37,38}

During acetylcholine administration, vasospasm is identified by reproduction of symptoms or ischemic electrocardiogram changes and classified as epicardial or microvascular depending on the degree of coronary artery diameter reduction in response to acetylcholine. Patients with severe vasospasm may demonstrate complete obliteration of the coronary artery that can be quickly reversed with nitroglycerin.

\textbf{Myocardial Bridging}

While only a minority of myocardial bridges will cause myocardial ischemia, identification of those with hemodynamic relevance is of paramount importance in the diagnosis and management of symptomatic patients.\textsuperscript{36,39} Angiography likely underestimates the prevalence of myocardial bridges given its lower detection rate (0.5%-16.0%) compared to autopsy (40%-80%).\textsuperscript{36} Angiographic manifestations of myocardial bridges include the characteristic step down/step up “U” sign on lateral projections and “coronary milking,” a periodic decrease in luminal dimensions that can be amplified with administration of intracoronary nitroglycerine. Compared to angiography, IVUS is more sensitive in detecting myocardial bridges and can more accurately assess lumen dimensions of the intramyocardial segment.\textsuperscript{40-43} IVUS frequently reveals a hypoechoic “half-moon” image adjacent to the arterial wall within the tunneled segment and has been instrumental in demonstrating the prolongation of luminal obliteration in myocardial bridging during the early- and mid-systolic phase of the cardiac cycle.

Similar to fixed coronary stenoses, the angiographic severity of myocardial bridge does not correlate well with its functional relevance. On the other hand, the physiology of myocardial bridging is significantly different and more complex compared to that of fixed stenoses. During systole, myocardial compression results in highly resistive microcirculation and markedly higher intracoronary pressure, which is observed as a negative pressure gradient across the myocardial bridge where distal pressure is higher than aortic pressure.\textsuperscript{44} Although myocardial bridges exert extravascular coronary compression primarily during systole, this compression also extends
into diastole resulting in compromised luminal area and blood flow with
positive pressure gradients during the early- and mid-diastolic phases.\textsuperscript{36,44,45} Since conventional FFR calculation is based on time-averaged pressures, the
negative systolic pressure gradients will invariably affect the detection of the
positive diastolic ones if only mean pressures are used.

As a myocardial bridge is a dynamic stenosis that depends on the
contractile status of the myocardium and the length of diastole, the
hemodynamic consequences of myocardial bridging may only get expressed
under stress during increased inotropy and tachycardia, which shortens the
diastolic period. Therefore, the hemodynamic significance of a myocardial
bridge with FFR should include a dobutamine challenge, which increases
coronary blood flow and ionotropy but does not modify epicardial vessel or
stenotic dimensions.\textsuperscript{44,46} Still, when using conventional FFR, a negative
result even after dobutamine challenge does not preclude the possibility of a
false negative, and should be interpreted with caution.

In myocardial bridging, this problem can be circumvented by using
diastolic FFR with an optimal cutoff value of 0.76.\textsuperscript{44,47} The restriction of
measurements to diastole not only avoids the influence of negative systolic
gradients on overall pressure measurements, but also allows identification
and quantification of the effect of the myocardial bridge on the diastolic
coronary blood flow.

Intracoronary Doppler has been used to evaluate vessels with myocardial
bridging.\textsuperscript{41,42,48,49} Flow velocity immediately proximal to the myocardial
bridge shows systolic flow reversal, resulting from epicardial blood being
squeezed from the compressed coronary segment.\textsuperscript{40} Characteristic abrupt
eyearly diastolic flow acceleration has been documented within the myocardial
bridge segment in Doppler tracings, reflecting the decreased luminal
dimensions caused by the myocardial bridge at that stage of the cardiac
cycle.\textsuperscript{49} Additionally, the velocity waveform within myocardial bridge shows
a characteristic “fingertip” spike pattern, which denotes a higher flow
velocity during early-mid diastole resulting from decreased luminal
dimensions during extravascular vessel compression.\textsuperscript{36,45} CFR has been
observed to be decreased as a consequence of the hemodynamic effect of the
myocardial bridge.
ACUTE CORONARY SYNDROMES

Intravascular imaging has been increasingly used in the management of patients presenting with acute coronary syndromes (ACS). Both IVUS and OCT can help the operator identify the location and morphology of the culprit lesion, appropriately select the stent size and optimize stent deployment. Furthermore, innovations in hybrid intravascular imaging and multi-modality fusion may facilitate precise morphologic visualization and phenotypic characterization of culprit lesions. These advances enable decision-making strategies during PCI which potentially reduce rates of late cardiovascular events such as myocardial infarction related to clinical restenosis or stent thrombosis.

Assessing Pathogenesis of the Culprit Lesion

Intravascular imaging has allowed in vivo evaluation of ruptured thin cap fibroatheromas and plaque erosions, which are the most common precursors of coronary occlusions resulting in fatal acute myocardial infarctions. For anatomic assessment, intravascular OCT with its superior spatial resolution (10 vs 100 microns for IVUS) allows accurate measurement of the fibrous cap thickness. In contrast, OCT’s lower image penetration depth (1-3 vs 4-8 mm for IVUS) limits its ability to reliably evaluate the entire plaque/media area and vessel remodeling. Clinical OCT observations demonstrate that 50% of culprit lesions in STEMI patients are due to plaque rupture and 25% to plaque erosions (Fig. 26-4).
Culprit plaque phenotype underlying coronary thrombosis stratified by sex. Optical coherence tomography (OCT) can highlight the different etiologies for the presentation of acute coronary syndrome. In the Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty (OCTAVIA) trial of 140 age-matched men and women undergoing percutaneous coronary intervention (PCI) for ST-Elevation myocardial infarction (STEMI), there was no significant difference in culprit plaque morphology between men and women. About 50% were plaque rupture, 25% plaque erosion and 25% unclassifiable. A total of 2 spontaneous dissection cases were observed in this study. (Reproduced from Guagliumi G, et al. Mechanisms of Atherothrombosis and Vascular Response to Primary Percutaneous Coronary Intervention in Women Versus Men With Acute Myocardial Infarction Results of the OCTAVIA Study. JACC: Cardiovascular Interventions. 2014;7(9):958-968. Copyright © 2014, with permission from American College of Cardiology Foundation.)

Several clinical applications of intravascular imaging have emerged to better identify high-risk atherosclerotic plaques. Advancements in IVUS technology to improve plaque morphological characterization include virtual histology IVUS, which uses radiofrequency backscatter analysis, and near-infrared spectroscopy, which estimates the lipid content through a lipid core burden index. An interesting advancement in OCT technology is the hybridization of OCT with near-infrared autofluorescence, which allows high resolution plaque morphologic visualization with accurate phenotypic characterization.

The quest for modalities with spatial resolution sufficient for cell level visualization has introduced micro-OCT, which uses ultra-broadband light
sources and common-path spectral-domain OCT to achieve an axial resolution of less than 1 micron. Micro-OCT can visualize the cellular and subcellular features of the coronary artery wall associated with atherogenesis and thrombosis as well as responses to interventional therapy, suggesting that it can complement existing diagnostic techniques for investigating progressive atherosclerotic lesions.

**Spontaneous Coronary Artery Dissection**

Spontaneous coronary artery dissection (SCAD) is an uncommon ACS presentation, with a reported prevalence of approximately 0.3% in patients undergoing angiography for the first time. Angiography can detect SCAD; however, when angiography is inconclusive, OCT can enhance the diagnostic accuracy by visualizing a double-lumen or an intramural hematoma, identifying the rupture site and measuring the extent of thrombi, true and false lumens. A potential concern when performing OCT in patients suspected with SCAD is the propagation of the dissection through contrast injection. Nevertheless, an algorithm has been proposed (Fig. 26-5) to utilizing intravascular imaging in identifying and managing SCAD.
Suspected SCAD

Angiographic diagnosis → Inconclusive angiography

OCT/IVUS

(+), (-) Rx underlying condition

SCAD

Clinical setting

Acute/ongoing ischemia

Stabilized/asymptomatic

Angina/recurrent ischemia

Revascularization (*)

Medical management (*)

Associated medical treatment

Mid-term clinical follow-up

Angiography (OCT/IVUS)

Asymptomatic/no ischemia

Noninvasive imaging (MSCT)

Late clinical follow-up

FIGURE 26-5 SCAD Algorithm with the roles of IVUS and OCT. In patients with suspected spontaneous coronary artery dissection (SCAD), intravascular imaging such as optical coherence tomography (OCT) or intravascular ultrasound (IVUS) can help enhance the diagnosis accuracy. Depending on the clinical setting, a conservative approach of medical management and watchful waiting with possible imaging follow up has been shown to have excellent clinical and angiographic outcome. For those with acute, ongoing or recurrent ischemia, revascularization is indicated to restore the coronary blood flow and reduce infarct size. There are 3 options: 1) conservative stenting to cover only the entry door and segments showing severe lumen compromise, which may result in residual distal dissection, 2) aggressive stenting that may result in a “full metal jacket” due to propagation of an intramural hematoma, or 3) coronary artery bypass grafting for unstable patients with left main involvement or multiple severe and long dissections. Abbreviations: CABG, coronary artery bypass
STENT DEPLOYMENT AND OPTIMIZATION STRATEGIES

Physiologic evaluation can help the operator determine which coronary lesion to intervene upon. As mentioned previously, both FFR and iFR can guide PCI decision making in intermediate stenoses. In critical angiographic stenosis (>90% diameter stenosis by visual assessment), particularly in a symptomatic patient with evidence of myocardial ischemia, further intravascular physiologic testing is not required to decide on hemodynamic lesion severity. On the other hand, both FFR and iFR have been proposed to help perform spot stenting in patients with tandem lesions or diffuse severe disease. Whether physiologically guided spot stenting or anatomically guided “normal to normal” stenting results in superior outcomes has not been prospectively investigated.

In addition to physiology, IVUS and OCT can help guide and optimize PCI. Intravascular imaging co-registered with angiography can accurately measure required stent diameter and length, inform the decision of how aggressively to prepare the lesion prior to stenting, and direct poststent optimization with noncompliant balloon dilatation or adjunctive stenting. Intravascular OCT may be particularly helpful for selecting debulking strategies toward optimal stent expansion in patients with calcified coronary lesions. At the time of stent implantation, intravascular imaging can identify stent underexpansion, edge dissections, strut malapposition, tissue prolapse and incomplete lesion coverage.60,61

**Bifurcation and Left Main PCI**

Intravascular imaging can assist during bifurcation PCI by: 1) estimating the degree of carina shift and daughter-vessel pinching after main branch stenting; 2) assessing the neocarina when 2-stent techniques are implemented
such as culotte or crush stenting; and 3) selecting the most distal stent cell to postdilate when optimization techniques are needed after stent deployment. In a propensity-matched analysis of patients undergoing PCI of non-left main bifurcations with drug-eluting stents, the IVUS-guided PCI strategy was associated with larger poststent lumen diameters as well as lower rates of death or myocardial infarction compared to the angiography-guided PCI strategy.\textsuperscript{26,62}

OCT excels at identifying which strut to rewire when reaccessing bifurcation side branches.\textsuperscript{63} This is particularly true with bioresorbable scaffolds, where OCT is superior to IVUS in detecting polymer-based struts. Bioresorbable scaffolds due to their larger strut size, are associated with a higher incidence of postprocedural side branch obstruction. This was recently demonstrated in the ABSORB—Extend trial where BVS-treated vessels demonstrated a higher incidence of postprocedural side branch obstruction compared with Xience V-treated vessels in small side branches with reference vessel diameters ≤0.5 mm (10.5% vs 3.9%, \(P = 0.03\)).\textsuperscript{64,65}

In unprotected left main coronary artery PCI, the adverse consequences related to suboptimal stent deployment are more dramatic and thus increase the utility of IVUS-guided PCI. During lesion preparation, IVUS can highlight the degree of calcification as well as the distribution, burden, and composition of atherosclerotic plaque within the left main and at the branch areas. Several observational studies have reported a wide range of clinical benefit of IVUS-guided PCI in unprotected left main disease.\textsuperscript{32,66-68} In particular, a post-hoc analysis of the multicenter MAIN-COMPARE registry, patients undergoing IVUS-guided unprotected left main PCI suggested a trend toward lower 3-year mortality compared to those undergoing angiography-guided PCI.\textsuperscript{67} Although OCT is not usually used to guide left main PCI, limited data suggest that it is comparable to IVUS in assessing and guiding left main PCI with respect to 1-year clinical event rates.\textsuperscript{69}

**Post-PCI Impairment of the Microvasculature**

There has been significant concern about the microcirculatory functional status after PCI in acute myocardial infarction patients because microvascular dysfunctions can occur in up to half of these patients and are associated with adverse ventricular remodeling and poorer patient prognosis.\textsuperscript{70} Impaired
microvascular function can include microvascular obstruction, myocardial compression, or hemorrhage. On angiography, microvascular obstruction can be observed as reduced or no-reflow and can be semiquantitated using the TIMI flow and/or blush grade.

While there is currently no consensus on the best way to detect and quantify microvascular dysfunction after PCI, IMR might provide more accurate measurements of the impairment and, thus, better prognostication. Defined as distal coronary pressure multiplied by the hyperemic mean transit time, IMR is measured using the thermodilution technique with a pressure sensor/thermistor-tipped wire. Several small studies have suggested that higher IMR values are associated with more microvascular obstruction. In 29 patients undergoing primary PCI for STEMI, IMR value >32 U was a predictor of acute and 3-month followup microvascular damage after STEMI. Another study of 50 patients undergoing elective PCI demonstrated that pre-PCI IMR values ≥27 U compared to lower values were associated with higher risk of developing periprocedural MI (HR 22.7, 95% CI 3.9-133.9). It has also been observed in patients undergoing PCI for STEMI that IMR values >36 U compared to lower IMR values were associated with higher rates of microvascular obstruction (93% vs 39%, \( P = 0.001 \)). Other physiologic indices such as zero-flow pressure and HMR measured at the time of primary PCI have been suggested to be superior to IMR for predicting the extent of myocardial infarction and warrant further investigation.

**Stent Underexpansion**

Several standardized criteria have been proposed to define stent underexpansion. These include the Multicenter Ultrasound Stenting in Coronaries (MUSIC) criteria and the more aggressive AVIO criteria (Table 26-1). The recent ADAPT-DES, a prospective non-randomized study of 8,583 patients undergoing PCI, found that IVUS caused the operator to alter the PCI strategy in 74% of cases, either by choosing a larger or longer stent, using higher balloon inflation pressures, performing additional post-stent dilatation, or implanting an additional stent. At 1-year follow up, the IVUS-guided cohort experienced lower rates of myocardial infarction (adjusted HR 0.66; 95% CI 0.49-0.88; \( P = 0.004 \)), definite or probable stent thrombosis.
(adjusted HR 0.40; 95% CI 0.29-0.73; \( P = 0.003 \)), and major adverse cardiovascular events (adjusted HR 0.70; 95% CI 0.55-0.88; \( P = 0.002 \)). Several studies have now suggested significant benefit of IVUS-guided PCI compared to angiography alone in patients presenting with complex target lesions.\(^{60,81-83} \)

Table 26-1 IVUS Criteria for Optimal Stent Deployment

<table>
<thead>
<tr>
<th>MUSIC Criteria</th>
<th>AV/iO Criteria</th>
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<tbody>
<tr>
<td>Complete apposition of stent</td>
<td>Minimal post-stent area &gt;70% of the balloon cross-sectional area used to post-dilate the stent</td>
</tr>
<tr>
<td>Adequate stent expansion</td>
<td>The noncompliant post-dilation balloon size selected according to the average of the maximum and minimum media-to-media diameter at the following points:</td>
</tr>
</tbody>
</table>
| MSA \( \geq 90\% \) of the average reference lumen area or \( \geq 100\% \) of reference segment with the lowest area when the MSA is <9 mm\(^2\) or MSA \( \geq 80\% \) of the average reference lumen area or \( \geq 90\% \) of reference segment with the lowest area when the MSA is >9 mm\(^2\) | 1. Distal in-stent segment  
2. Proximal in-stent segment  
3. In-stent of maximal narrowing |
| Symmetrical stent expansion defined by minimum lumen diameter divided by maximum lumen diameter \( \geq 0.7 \) |  |


Compared to IVUS-guided PCI, OCT guidance result in smaller lumen dimensional measurements, leading to smaller stent sizing and less lumen gain.\(^{84} \) The ILUMIEN studies have shed additional information on the use of OCT in stent optimization. ILUMIEN-1 was a prospective multicenter observational study to determine which OCT parameters were most useful for improving near-term clinical outcomes.\(^{85} \) Of the 418 patients enrolled in this study, 65 patients (16%) underwent both OCT-guided pre-PCI lesion assessment and post-PCI optimization and had significantly reduced rates of myocardial infarction at 1-year followup compared to those without OCT guidance (0% vs 12%, \( P = 0.03 \)). Interestingly, the post-PCI MLA was significantly smaller in those procedures guided by OCT compared to those with angiographic guidance without pre- or post-OCT guidance (5 ± 2 vs 6 ± 3 mm\(^2\), \( P = 0.004 \)). This conundrum spurred the design of ILUMIEN-2, a post-hoc study of ILUMIEN-1 and ADAPT-DES, comparing the relative degree of stent expansion from OCT- and IVUS-guided PCI.\(^ {86} \) This analysis determined that there were no major differences between OCT and IVUS
with respect to post-PCI stent expansion (73% vs 71%, $P = 0.84$), in-stent MLD (2.5 vs 2.6 mm, $P = 0.78$), in-stent acute gain (1.6 vs 1.6 mm, $P = 0.60$). The ILUMIEN-3, a prospective randomized clinical trial (NCT02471586) which was completed in 2016 and is pending analysis and publication, randomizes patients undergoing PCI to 1 of 3 arms: 1) OCT pre- and post-PCI guidance, 2) IVUS pre- and post-PCI guidance, or 3) angiography guidance. Patients in all arms will undergo post-PCI OCT to allow blinded core lab comparison of OCT measurements of the post-PCI minimal stent areas achieved from angiography-, IVUS-, or OCT-guided PCI.

**Strut Malapposition**

Malapposition, also known as incomplete stent apposition, occurs when there is no contact between the stent struts and the lumen wall. The extent of strut malapposition can be measured as the distance between the strut and the vessel wall, taking into account strut thickness and intravascular imaging resolution limits. Malapposition can occur acutely after stent deployment or develop over time from positive arterial remodeling or thrombus resolution, and are categorized accordingly. Acute malapposition is detected immediately after stent implantation and attributed to suboptimal stent implantation. Late–persistent malapposition is an acute stent malapposition that remains malapposed at follow-up evaluation, and late–acquired malapposition is malapposition identified at follow-up assessment despite complete strut apposition during the initial procedure. ILUMIEN II demonstrated that, compared to IVUS, OCT post-PCI imaging detected more malapposition of any type (14% vs 27%, $P = 0.0002$) but comparable major malapposition with a >20% distance-to-lumen ratio (0.7% vs 1.4%, $P = 0.69$). Clinically, it is debatable how malapposition affects future healing and long-term outcomes, as there have been several conflicting studies on the relationship between acute or late malapposition and the rates of stent thrombosis. Regardless of this uncertainty, most operators strive to achieve full apposition of all stent struts after stent deployment, thereby minimizing acute and late-persistent malapposition.

**Tissue Prolapse**
Tissue prolapse occurs after stent implantation where the tissue of the arterial wall and plaque protrudes between the stent struts. In postmortem and OCT studies, the observed rates of tissue prolapse immediately after stent implantation was 94% to 97%. Most cases of tissue prolapse detected immediately after PCI were found to have resolved during the study follow-up periods and do not appear to significantly impact clinical outcomes. However, large natural history studies of tissue prolapse are not available and are warranted.

**Edge Dissections**

A classification system for intimal tears was proposed by the Coronary Angioplasty Registry to help manage dissections observed after balloon angioplasty. This angiographically-based system has evolved into the National Heart, Lung, and Blood Institute (NHLBI) grading system for coronary dissections. Minor tears are categorized as type A or B dissections and are considered to be clinically benign. Higher-grade intimal tears include types C-F dissections, which have been associated with greater rates of acute closure or stent thrombosis early after PCI. With the improved resolution of intravascular imaging, higher incidences of edge dissections have been reported; however, most of these fall into the lower grade edge dissection categories have thus far have not been associated with higher rates of adverse events. The CLI-OPCI II Study evaluated 1,002 lesions in 832 patients by OCT, which showed suboptimal stent implantation in 31% of these lesions. On regression analysis, dissection >200 microns at the distal stent edge was associated with increased adverse cardiac events (HR 2.54, \( P = 0.004 \)) but not those at the proximal edge (HR: 0.83, \( P = 0.65 \)). While high-grade edge dissections continue to be intervened upon, there is no consensus on the optimal management of low grade and angiographically silent edge dissections, so it remains to be seen whether edge dissections that are observed only on intravascular imaging are clinically relevant.

**Stent Failure**

**In-Stent Restenosis**
Smaller minimal stent area is commonly associated with target vessel failure at follow-up, and larger post-PCI areas consistently predict lower rates of restenosis. Smaller minimal stent areas may represent stent underexpansion, which can be detected on IVUS or OCT and treated with appropriate post dilatation. Additionally, intravascular imaging can assist in the differentiation of restenosis related predominantly to intimal hyperplasia versus mechanical complications such as stent fracture or stent underexpansion, which can help the operator determine which approach to take to treat the in-stent restenosis.

**Stent Thrombosis**

Smaller stent areas have consistently been associated with higher rates of stent thrombosis, implicating stent underexpansion in the pathogenesis of both early and late stent thrombosis. Stent underexpansion and malapposition with uncovered struts are hypothesized to be more likely to incite thrombosis within the stent. IVUS studies have agreed with autopsy studies linking in-stent thrombosis with uncovered malapposed struts, while OCT has demonstrated that patients presenting with unstable angina are more likely to have stents with uncovered struts than those with stable angina. Clinically, intravascular imaging-guided PCI may reduce rates of stent thrombosis by identifying and managing suboptimal stent deployment.

**Neoatherosclerosis**

Within implanted stents, atherosclerotic changes of neointimal tissue has been hypothesized to contribute to late in-stent restenosis and stent thrombosis. In the SIRTAX-LATE OCT study, in-stent neoatherosclerosis was assessed by OCT 5 years after the initial PCI procedure with either sirolimus- or paclitaxel-eluting stents (SIRTAX trial conducted in 2003-2004). Defined as the presence of fibroatheroma or fibrocalcific plaque within the neointima of stented segments on OCT, neoatherosclerosis was identified in 16% of follow-up lesions and determined to be more common among patients with angiographic and clinical evidence of native atherosclerosis progression. OCT may therefore be a useful adjunctive tool in
distinguishing between in-stent restenosis and neoatherosclerosis.

**Stent Fracture**

Fracturing of metallic stents is relatively uncommon with a reported rate of about 4%;\textsuperscript{113} however, there are heightened concerns about stent fractures in the bioresorbable scaffolds.\textsuperscript{114} Because visualization of the stent on fluoroscopy can be limited and variable, the use of intravascular imaging increases the rate of stent fracture detection and provides additional information such as neointimal tissue formation, vascular remodeling, or strut characteristics that may help deduce the mechanism of stent fracture. Traditionally, IVUS has been used to evaluate suspected stent fracture cases; however, with the novel bioresorbable scaffolds, OCT may prove the better modality to visualize the non-metallic struts.

**CONCLUSION AND FUTURE DIRECTIONS**

Coronary angiography remains a cornerstone assessment for patients with coronary artery disease; however, given its inherent limitations, there is a strong rationale for incorporating adjunctive diagnostic tools for lesion assessment and PCI optimization. The use of physiological indices, especially FFR measurements, to direct coronary revascularization is seeing growing use in routine clinical practices as well as in more complex cases. Patients with recurrent angina symptoms and non-obstructive coronary artery disease may benefit from microvascular function testing and endothelial function assessment to guide targeted medical therapy. Intravascular imaging plays an important role in visualizing plaque characteristics and optimizing stent deployment to reduce the risk of in-stent stenosis and thrombosis. OCT may also be helpful to visualize plaque erosion or coronary dissection in patients presenting with ACS. It has therefore become critical for clinicians to understand the potential applications of adjunctive diagnostic tools in the cardiac catheterization laboratory in order to best incorporate these modalities into their current practice.
COMPETENCY STATEMENTS

ACS-MK1—Know the epidemiology, causes, pathophysiology, and natural history of ACS, including the roles of plaque rupture or erosion and platelet activation and thrombosis.

INV/INT-MK7—Know the angiographic features of coronary artery disease and how to assess its anatomic and physiologic severity.

ISCHEM-MK15—Know the anatomic and physiologic catheterization findings indicating significant coronary artery obstruction and the coronary angiographic features indicative of a high-risk state.

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**MULTIPLE CHOICE QUESTIONS**

1. Which of the following describes the best use of intravascular imaging in a patient presenting with acute myocardial infarction?
   A. Intravascular ultrasound (IVUS) to measure the fibrous cap thickness of a fibroatheroma
   B. IVUS to assess for myocardial bridging
   C. IVUS to detect edge dissections
   D. Optical coherence tomography (OCT) to measure the total plaque volume
   E. OCT to identify plaque erosions

2. Which of the following statements is correct regarding fractional flow reserve (FFR)?
   A. FFR requires more fluoroscopy and total procedure time compared to regular angiography, thus making it an overall less cost-effective solution over a 15-year period.
B. FFR can be accurately measured in patients presenting with acute myocardial infarction complicated by cardiogenic shock.
C. FFR can simplify and direct the revascularization approach to complex coronary bifurcation lesions.
D. FFR is normal if its measurement is 0.80 or above.
E. FFR should not be used to assess left main disease.

3. Which of the following statements is correct regarding left main lesions?
   A. Left main lesions may hide on angiography significant amounts of complex atherosclerotic plaque that increase the risk of a future adverse event.
   B. Left main lesions should almost always be treated with coronary artery bypass grafting.
   C. Left main lesions can be accurately evaluated with coronary flow reserve.
   D. Left main lesions do not benefit from intravascular ultrasound guided percutaneous coronary intervention.
   E. Left main lesions can be reliably assessed on angiography with respect to disease severity if one is a very experienced operator.

4. Which of the following statements is correct regarding stent underexpansion?
   A. Stent underexpansion can be readily detected using intravascular ultrasound.
   B. Stent underexpansion can be readily detected using fractional flow reserve.
   C. Stent underexpansion has little impact on stent thrombosis rates.
   D. Stent underexpansion has little impact on in-stent restenosis rates.

5. Which of the following statements is true regarding edge dissections detected on optical coherence tomography?
   A. There are fewer edge dissections detected on optical coherence tomography compared to intravascular ultrasound.
   B. Edge dissections detected on optical coherence tomography are considered National Heart, Lung, and Blood Institute (NHLBI) type E dissections.
   C. Most edge dissections detected only on optical coherence tomography
can be deferred from further intervention.
D. Edge dissections detected only on optical coherence tomography have higher event rates than those detected on angiography.

**ANSWERS**

1. E
2. C
3. A
4. A
5. C
Appropriate selection and manipulation of equipment is critical to successful percutaneous coronary intervention (PCI) outcomes and low complication rates. The guidewire is the first piece of interventional equipment to contact the lesion to be treated. Proper intraluminal advancement of the guidewire through the lesion and into the distal vessel allows the coronary guidewire to serve as the backbone for the safe delivery of diagnostic and therapeutic devices while maintaining secure and safe access to the vessel lumen. Although the current standard 0.014-inch wires are suitable for the majority of interventions, operator familiarity and facility with guidewire selection and manipulation are still paramount. The advent of specialty guidewires, such as those designed for chronic total occlusions (CTOs), has furthered our ability to successfully treat more complex lesions, but the use of these wires requires an understanding of specific wire performance features and the possible complications that can result from their use. Given the wide variety of guidewires that are available, knowledge of their design, materials and structure aids the operator in understanding unique differences in performance and ultimately in making the proper selection for an individual patient or lesion.

In this chapter, we will review specific characteristics of coronary guidewires including their construction and properties that favor different clinical situations. In order to optimize guidewire selection, we have developed a general classification scheme based on wire performance
features. We will discuss techniques for guidewire manipulation in selected subsets of coronary lesions with the caveat that minimal comparative literature is available. As with other aspects of interventional cardiology, there are multiple guidewires that can be used for each lesion, and operator selection may change with experience or as technologic advances are made.

**HISTORY OF THE GUIDEWIRE**

More than 30 years have passed since the introduction of a catheter system allowing an independently movable, flexible-tipped guidewire for coronary intervention. Unlike the initial balloon catheters with fixed-wire tips, the 2 component balloons and independent, steerable guidewire systems greatly enhanced coronary artery and lesion accessibility. Guidewires are designed to allow the tip to be shaped or curved so that the wire could be purposefully directed into the desired artery and across the target lesion using rotation and advancement. The independent catheter–guidewire system also brought increased safety with the ability to exchange devices without recrossing the coronary lesion.

The first guidewire for angioplasty, available from 1979 to 1982, was a 0.018-inch standard wire (Cook Group Inc.). This wire had a safety wire at its tip—a precursor to the shaping ribbon—that allowed it to be shaped but resulted in added tip stiffness. The next wire to be developed (ACS) was a standard wire that replaced the safety wire with a metal ribbon. This change made the tip more flexible while retaining the ability for shaping. Further advances included construction of a floppier wire, which lacked a shaping ribbon, and had greater flexibility and safety but sacrificed some directional control. Thus the objective was to develop wires that combined flexible and safe tips while maintaining shapability and torsional control. Currently, as no guidewire meets all needs or preferences, several manufacturers offer a line of coronary guidewires, many with subtle variations, to allow artery- or lesion-specific guidewire selection.
Knowledge of the underlying construction of a guidewire provides an understanding of the expected performance features including steerability and trackability. *Steerability* relates to the ability to direct the wire to a desired location within an artery or lesion. *Trackability* is the ability of a wire to follow the course of an artery during advancement with minimal resistance or buckling. Multiple characteristics including flexibility, radiopacity, torquability and kink resistance, and the frictional resistance of the guidewire within the system it is used, all contribute to the fundamental properties that result in maneuverability of guidewires (Fig. 27-1). *Torquability* is a term that describes the relationship between rotational movement of the proximal wire (the site where the operator grasps the wire) to the tip. Torquability that is 1:1 means that for every degree rotation by the operator, a similar rotation will occur at the tip.

**FIGURE 27-1** Guidewire performance. Multiple characteristics contribute to the fundamental properties that result in the steerability and maneuverability of a guidewire.

Coronary guidewires are composed of 3 main components, a central core that tapers distally, a flexible tip which includes a spring, and the external surface or coating (Fig. 27-2). These components all influence the ability of a
wire to reach and cross a lesion and also to support the delivery of balloon catheters and other devices to the lesion. For example, the core provides the support for device advancement but is also integrally related to trackability, steerability, and torque transmission.

**FIGURE 27-2** Coronary guidewires are composed of 3 main components: a central core, a flexible tip, and a lubricious coating.

The core may be constructed as a single continuous unit or have more than one segment. As the core extends distally, the diameter tapers and the degree of tapering and the location of tapering vary. These variations in core diameter, length and degree of tapering affect performance. Cores that extend to the distal wire tip provide extra support and torque transmission but are stiff. Cores that do not extent to the distal tip and that gradually taper are more flexible and retain more trackability than wire cores that abruptly end. For this reason, wires that have a single core construction have the smoothest transition into the flexible preshaped tip and provide a high degree of steerability and trackability. The core strength also varies with the core material and diameter, and as stiffness increases, flexibility may be compromised, but vessel straightening and device delivery improve. The core
wire is commonly composed of stainless steel or alternative alloys such as nitinol. The nitinol core increases wire trackability, including the ability to traverse acute artery angulations without wire prolapse. Nitinol wires, therefore, might be more capable of entering a retroflexed circumflex takeoff than a stainless steel core wire.

The tip of the wire is composed of a coil or spring that provides a flexible leading tip that enhances safety and steerability. The ability to shape the tip into a retainable and variably shaped curve is accomplished with a shaping ribbon. This thin metallic strip that runs parallel to the longitudinal axis of the wire allows the tip to retain a curved shape or “J” configuration that provides directionality to the guidewire. The degree to which the tip retains its shape during use relates to the properties of the shaping ribbon, the material of the distal tapered core, and, additionally, to the coatings, which are discussed below. Wires with straight tips and shaping ribbons can be shaped to more acute angles, or sequential bends can be placed to negotiate unusual or severe (<90°) instances of vessel tortuosity. Wires that have preshaped tips are also available. These wires lack a shaping ribbon, which results in less ability to alter the tip shape.

The wire tip also varies in stiffness. Highly flexible tips are termed floppy or soft and these wires are particularly safe and atraumatic in that the likelihood of subintimal dissection or vessel perforation is very low. Commonly such wires include a core of moderate flexibility and support and are accordingly used as “workhorse wires.” Because of enhanced tip flexibility, they can prolapse or form a large “J” configuration when advanced. Such a configuration, if it occurs after the wire crosses the lesion to be treated, is an advantage in that the wire can be readily and safely advanced into the distal artery without the need for steering.

Other potential features of the wire tip that may be manipulated include the distal diameter and weight of force, or tip load. Guidewire tips can have a tapered coil from the shaft of 0.014-inch down to 0.009-inch. There are also lines of wires that are designed with incremental tip loads, or grams of force at the wire tip. These wires with reduced profile or increased tip load, discussed below, are designed to improve crossing of subtotally or totally occluded arteries. Caution must be exercised with these wires to avoid coronary dissection or perforation.

The distal coil segment is constructed of platinum, tungsten, or an alternative radiopaque material. Radiopacity is critical for monitoring fine
wire manipulation and advancement. The standard wire has a radiopaque tip of 2 to 3 cm in length, and although the entire wire is visible with fluoroscopy, the entire length of the wire may be difficult to follow. Problems with the wire such as kinks or the development of loops, particularly outside the guiding catheter and within the aorta, may be difficult to detect. These situations, however, are usually recognized by accompanying clues such as loss of 1:1 torque, pushability, guide stability, or the ability to deliver devices. The benefit of a short radiopaque tip is that it can be advanced past the target lesion so as not to influence the identification of devices or evaluation of the targeted lesion. The radiopaque segment may also interfere with the ability to perform quantitative coronary angiography. Certain wires have longer radiopaque tips of 11 to 40 cm. This “high radiopacity” feature is found on more aggressive wires where more force may be applied to wire advancement, and intense monitoring of the entire length of the wire in the coronary and guiding sheath is needed for safety. Besides the safety issue, the longer radiopaque tip does not offer additional benefits.

The third component of the coronary wire is the coating, which can be silicone, Teflon, polytetrafluoroethylene (PTFE), or a hydrophilic polymer. The coating decreases the friction, making the surface lubricious within the device lumen and across lesions, and improves wire and device tracking in tortuous vessels. The hydrophilic wires are well suited for severe stenoses and total occlusions, but they may create vessel dissections or perforations if not manipulated cautiously. As with other aspects of wire construction, each feature may improve one or more clinical aspects of the wire, but at the expense of another.

**GENERAL GUIDEWIRE FEATURES**

The majority of coronary wires are 0.014-inch diameter for compatibility with low-profile coronary balloon and stent systems. Larger diameter specialty wires such as the Glidewire® Gold 0.016 to 0.018 inch (Boston Scientific Corporation) and the Magnum wire (Schneider) 0.021 previously used for recanalization of chronic total occlusions (CTOs), have been replaced by 0.014 wires engineered specifically for CTOs. Wires come in 2 general lengths. Standard length guidewires are 175 to 190 cm and exchange length wires are 270 to 300 cm. Longer wires, 335 to 350 cm, are available.
for specific procedures that require guidewire externalization such as retrograde CTO interventions. The choice of wire length depends largely on operator preference and the balloon catheter system chosen, single operator or rapid exchange (RX) versus over the wire (OTW). Details of these techniques are discussed in the next section. Importantly, most, but not all, standard length guidewires can be extended with compatible extension wires if conversion to an OTW technique is required. If a standard length wire is not compatible with an extension wire, there are techniques, discussed below, that can be used to remove OTW devices or to exchange the wire without uncrossing the target lesion or losing access to the distal vessel. Additional features on some wires include marker bands that can reduce fluoroscopy time. These bands are generally placed at 90 and/or 100 cm, the length of a guiding catheter, to allow passage of the wire through the guide or balloon to the appropriate distance without fluoroscopy, ensuring that the wire has not exited from the guide catheter. Wires can also be designed with radiopaque markers at the distal tip that are a known distance, apart allowing for estimation of lesion length. These wires are termed marker wires.

GUIDEWIRE TECHNIQUES FOR OVER-THE-WIRE AND RAPID-EXCHANGE SYSTEMS

**OTW Systems**

In an OTW system the wire traverses the entire length of the balloon catheter lumen, which is generally 135 to 150 cm. Standard coronary balloon and stent catheters are designed for 0.014-inch wires. Often the tolerances of the balloon catheter lumens and the guidewires overlap such that there is little clearance between lumen and wire. There are 2 approaches to using an OTW system. In the more common approach, the operator first places the guide wire through the balloon lumen and then the guidewire-loaded device is advanced into the guiding catheter to the coronary ostium. The guidewire is manipulated through the vessel across the target lesion, and, with the wire fixed in place, the balloon can be advanced across the lesion for dilation. The
advantage of this technique is that the balloon catheter can be advanced over
the wire into the coronary for more precise guidewire manipulation.
Additionally, if the operator requires a different guidewire, the balloon
catheter can be left in place within the coronary to maintain access. For
example, OTW balloon catheters are of special value when attempting
difficult anatomy including calcified, tortuous, or highly stenotic vessels and
especially chronic total occlusions. The greatest challenge for successfully
treating such lesions is to cross the lesion with a guidewire, and, accordingly,
an assortment of different guidewires is often necessary in these cases. The
OTW catheter can be positioned directly proximal to a total occlusion to
facilitate guidewire exchanges.

Either a standard length wire (175-100 cm) or an exchange length wire
(300 cm) can be used to cross the lesion with the OTW system. If a standard
wire successfully crosses the target lesion, the wire can be extended with an
extension wire to remove the balloon catheter or the balloon can be advanced
distal to the lesion and the wire can be exchanged through the balloon for an
exchange-length wire prior to balloon withdrawal. Another method for
removing an OTW device from a standard length wire is to use a trapping
balloon. This method is commonly used in CTO interventions, where
meticulous care is required to prevent vessel injury or perforation from
unintended migration of stiff or polymer coated wires. To perform this
technique, a rapid exchange balloon is advanced to the distal tip of the
guiding catheter on its own, not over a wire. For an 8-French (Fr) guiding
catheter, a 3.0-mm balloon is used, and, for 7-Fr or smaller, a 2.5-mm balloon
is recommended. The OTW device is retracted proximal to the trapping
balloon, then the trapping balloon is inflated to 14 atmospheres, pinning the
wire against the guiding catheter to maintain position. Then, the OTW device
is withdrawn from the guide, followed by deflation and removal of the
trapping balloon. During the trapping, the guidewire pressure will be damped,
and, following device removal, the system should be cleared of potential
trapped air. Another advantage of this method is that fluoroscopy can be
minimized and radiation exposure reduced. An alternative technique to
preloading the guidewire in the OTW device is one where the operator
advances a guidewire alone into the guiding catheter and across the target
lesion. In this “bare-wire technique,” the balloon or stent is then advanced
over the wire into the lesion. This approach allows better visualization in
smaller diameter guiding catheters, but given the low profile of current OTW
balloons, the advantage of this approach is minimized. Passage and removal of OTW balloon catheters over standard length wires has been reported using other techniques, such as the hydro-glide method. This method uses hydrostatic pressure applied to the central lumen of the balloon catheter with a saline-filled syringe or inflation device.\textsuperscript{8,9} Loss of wire position is the main drawback of this approach. Since this situation can lead to loss of vessel access it should be avoided, and a rapid-exchange catheter or trapping balloon should be used in these situations.

**Rapid Exchange Systems (RX)**

The RX system is commonly referred to as a single-operator exchange system. The coronary balloon and stent catheters are labeled \textit{RX} (for rapid exchange) or \textit{Monorail} and are compatible with 0.014-inch wires. The catheters were modified from the OTW type and the distal portion is similar, with the guidewire traversing through the balloon lumen. The OTW segment, however, is short, and the remainder of the wire tracks outside the catheter adjacent to the balloon lumen. The RX system is ideal for the single operator and can reduce fluoroscopy time. A standard length guidewire can be used for all RX intracoronary catheters. Initially, the bare wire technique is used to cross the lesion, and then the balloon catheter is loaded on the distal end of the guidewire. The catheter is advanced until the wire exits the catheter lumen and the wire is then fixed in place as the remainder of the catheter is advanced across the lesion. Although the RX catheters may have less pushability and trackability and cannot act as a device for exchanging wires, the current balloon catheters are low profile, easy to deliver, and can be used in the majority of cases.

When using an RX system, the operator must be prepared to change to an OTW system when necessary. In certain situations, such as inability to cross a lesion with a wire or balloon or an unanticipated non-dilatable lesion, the wire may need to be exchanged for a specialty wire, such as an extra support wire or rotational atherectomy wire. If balloon inflations have been performed, and, in particular, if a dissection in the vessel is present, maintenance of distal wire position is essential. Normally these situations pose no problem, as the majority or standard length wires can be extended to exchange length with extension wires, and a microcatheter or OTW balloon catheter can be used to secure position during the wire exchange. Another
option is to use a dual lumen catheter such as the Twin-Pass (Vascular Solutions, Minneapolis, MN) which has both an RX and OTW lumen. The Twin-Pass can be placed on the standard length wire through the RX lumen and advanced distal to the lesion, then a long wire can be placed in the OTW lumen of the catheter.

GUIDEWIRE SELECTION

There may be many appropriate guidewire choices for each coronary intervention. Categorizing the guidewires into groups according to their general performance features and becoming familiar with a few wires from each group is a sound initial approach. Subsequently, each operator may find subtle differences among the guidewires in each group and develop a personal preference for a specific guidewire. Most operators will choose an “all-purpose” guidewire for the majority of cases and then have preferred wires for circumstances where “extra support” is needed or for specific lesion subsets. A guidewire classification grouping according to the general performance features is given in Table 27-1.

Table 27-1 Guidewire Classification

<table>
<thead>
<tr>
<th>General description</th>
<th>Desired use</th>
<th>Examples: Name (Manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tip Light support core</td>
<td>Simple to complex lesions</td>
<td>Runthrough NS (Terumo) Asahi Prowater (Abbott Vascular) Asahi Light (Abbott Vascular)</td>
</tr>
<tr>
<td>Non-polymer coated</td>
<td></td>
<td>Choice Floppy (Boston Scientific) Forté Floppy (Boston Scientific) ATW (Cordis) Cougar (Medtronic)</td>
</tr>
<tr>
<td>Soft tip Moderate support</td>
<td>Simple to complex lesions</td>
<td>WIZDOM Soft (Cordis) Hi-Torque Balance Middle Weight (Abbott Vascular) Hi-Torque Floppy II (Abbott Vascular) Stabilizer BP (Cordis) Intuition (Medtronic)</td>
</tr>
<tr>
<td>core Non-polymer coated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-polymer coated</td>
<td>device delivery</td>
<td></td>
</tr>
<tr>
<td>Soft tip Light to moderate</td>
<td>Complex lesions Severe</td>
<td>Hi-Torque WISPER (Abbott Vascular) Hi Torque Pilot 50 (Abbott Vascular) PT Graphix (Boston Scientific)</td>
</tr>
<tr>
<td>support core Hydrophilic</td>
<td>tortuosity Side branch</td>
<td></td>
</tr>
<tr>
<td>polymer coated</td>
<td>access Severe stenosis</td>
<td></td>
</tr>
</tbody>
</table>
**Specialty Wires for Total Occlusions**

There are many wires that have been developed to cross severely narrowed or totally occluded coronary stenosis. These wires are generally classified by the coating and tip characteristics such as style and stiffness (Table 27-2). This section will review examples of these types of wires.

**Table 27-2 Guidewires for Complex Interventions Including Chronic Total Occlusions**

<table>
<thead>
<tr>
<th>Polymer Coated Wires</th>
<th>Tip type</th>
<th>Tip stiffness (identifier)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fielder XT</td>
<td>Tapered</td>
<td>1.2 g</td>
<td>Asahi/Abbott Vascular</td>
</tr>
<tr>
<td>Fielder FC</td>
<td>Non-tapered</td>
<td>1.6 g</td>
<td>Asahi/Abbott Vascular</td>
</tr>
<tr>
<td>Whisper</td>
<td>Non-tapered</td>
<td>0.8 g (LS), 1.0 g (MS), 1.2 g (ES)</td>
<td>Abbott Vascular</td>
</tr>
<tr>
<td>Pilot</td>
<td>Non-tapered</td>
<td>1.5 g (50), 2.7 g (150), 4.1 g (200)</td>
<td>Abbott Vascular</td>
</tr>
<tr>
<td>Choice PT</td>
<td>Non-tapered</td>
<td>2.1 g</td>
<td>Boston Scientific</td>
</tr>
<tr>
<td>PT Graphix</td>
<td>Non-tapered</td>
<td>1.7 G, 2.9 G (Intermediate)</td>
<td>Boston Scientific</td>
</tr>
<tr>
<td>Crosswire NT</td>
<td>Non-tapered</td>
<td>7.7 g</td>
<td>Terumo</td>
</tr>
<tr>
<td>Shinobi</td>
<td>Non-tapered</td>
<td>6.8 g</td>
<td>Cordis</td>
</tr>
</tbody>
</table>

**Open Coil (no polymer cover)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Tip type</th>
<th>Tip stiffness (identifier)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>SION</td>
<td>Non-tapered</td>
<td>0.8 g</td>
<td>Asahi/Abbott Vascular</td>
</tr>
<tr>
<td>CROSS-IT 100</td>
<td>Tapered</td>
<td>1.7 g</td>
<td>Abbott Vascular</td>
</tr>
<tr>
<td>MiracleBros</td>
<td>Non-tapered</td>
<td>3.9 g (3), 4.4 g (4.5), 8.8 g (6), 13 g (12)</td>
<td>Asahi/Abbott Vascular</td>
</tr>
<tr>
<td>Confianza</td>
<td>Non-tapered</td>
<td>8.6 g (9)</td>
<td>Asahi/Abbott Vascular</td>
</tr>
<tr>
<td></td>
<td>Tapered</td>
<td>9.3 g (Pro 9), 12.4 g (Pro 12)</td>
<td>Asahi/Abbott Vascular</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Non-tapered</td>
<td>5.5 g (40), 9.7 g (80), 13.9 g (12)</td>
<td>Abbott Vascular</td>
</tr>
<tr>
<td></td>
<td>Tapered</td>
<td>12.5 g (140T), 13.3 g (200T)</td>
<td>Abbott Vascular</td>
</tr>
<tr>
<td>Persuader</td>
<td>Non-tapered</td>
<td>8.3 g (3), 9.1 g (6)</td>
<td>Medtronic</td>
</tr>
<tr>
<td></td>
<td>Tapered</td>
<td>9.1 g (9)</td>
<td></td>
</tr>
</tbody>
</table>

**Polymer-Coated Wires**

Several polymer jacketed wires are available for use in challenging anatomy, and are particularly suited for CTO interventions. The wires either have a standard 0.014-inch tip or taper to a .009- to .010-inch tip to assist in probing microchannels. The Asahi Fielder XT wire (Abbott Vascular, Lake Bluff, IL) is an example of a tapered-tip wire that can be manipulated in a CTO in
attempt to cross non-visible microchannels. The drawback of these types of wires is the potential for subintimal dissection. The Fielder FC (Abbott Vascular), which has a non-tapered tip, is suited for crossing small vessels, such as septals and collaterals, with less risk of dissection (Fig. 27-3). The Pilot series of wires (Abbott Vascular) come in 3 different tip loads and are stiffer than the Fielder wires. The increasing stiffness results in greater ability to penetrate occlusions with the negative consequence of risk of complications. Several additional polymer-coated wires are available with tip stiffness ranging from 0.8 g to 7.0 g (Table 27-2).

FIGURE 27-3 Cineangiograms from a percutaneous coronary intervention in a
patient with a chronic total occlusion of the right coronary artery (RCA) treated with a retrograde approach. A. A Fielder FC wire and Corsair microcatheter were used to atraumatically cross the septal collaterals. B. A Pilot 200 wire was used for retrograde subintimal tracking. A ViperWire was used for guidewire externalization (not shown). C. Final result after overlapping drug-eluting stents to the RCA.

**Open Coil Non-Polymer Coated Wires**

Stiff- tipped non-polymer coated wires may be more steerable than the “glide” type wires and are well suited for total occlusions. They also offer more secure positioning for device delivery. As with other wire types, the tip configuration may tapered or non-tapered with a range of stiffness. The Asahi SION wire (Abbott Vascular) was designed for small vessels. It tracks well through tortuosity and is used for septal and collateral wiring. The CROSS-IT wire (Abbott Vascular) has the lowest tip stiffness, and is tapered and can be used to probe visible microchannels in CTOs. Wire escalation to wires with increasing stiffness is a reasonable strategy but operators should be cautious not to extend fluoroscopy time by continuing to work with a wire that does not have the characteristics needed to cross the occlusion.

**Asahi MiracleBros and Confianza Line**

The Asahi Miraclebros line (Abbott Vascular) of 0.014-inch wires is also designed for highly stenosed or occluded vessels. The wires have a single continuous core construction with a jointless spring coil for tracking; silicone, fluororesin, and hydrophilic coatings to reduce friction; and a highly radiopaque 11-cm tip. The wires are manufactured according to a tip load—or the weight of force required to deflect the tip—with 3-g, 4.5-g, 6-g, and 12-g size available (ie, Miraclebros 3 has a tip load of approximately 3 g). The wires have reduced flexibility and increased support as the tip weight increases. The progression in tip load translates to greater retention of tip shape, responsiveness, and ability to push the wire in a desired direction. The Asahi Confianza wires (Abbott Vascular) which come in 9-g and 12-g tips, have tapered tips and high penetration ability for CTO caps. The radiopaque segment is 20 cm long to allow visualization of movement and wire displacement with manipulation. Use of these wires is based on a strategy of crossing total occlusions that differs from the conventional approach where emphasis is placed on detecting the original lumen and slipping through that
segment of the total occlusion. The Asahi concept features blunt but highly
direct dissection. This technique is more complex and technically demanding,
but may achieve success when others fail. If the course of the vessel is
unknown, the risk of complications from these aggressive wires is increased.

Externalization Wires

The retrograde approach to CTOs requires that a guidewire have sufficient
length for externalization outside the body. There are 2 wires available in the
United States. The R350 wire (Vascular Solutions) is 0.013 inch in diameter,
350 cm in length, and has a 5-cm radiopaque platinum coil tip. The Viper
Advance wire (CSI) is 0.014 inch in diameter and 335 cm in length.

GUIDEWIRE SHAPING TECHNIQUES

The majority of wires have a straight tip that can be shaped; however, some
are available with a preshaped curve. The advantage of the straight wire is
that the tip shape can be customized for the vessel morphology. In general,
the thumb and index finger are used to place rotational traction on the distal
wire over a mandrel or through the introducer tool (Fig. 27-4). For the
majority of interventions, a 30° to 60° smooth curve over the distal 4 to 5 mm
of the wire is sufficient. For larger or more angulated vessel, a longer curve, a
larger angle, or a secondary curve may be required. A different technique is
used when stiff-tipped wires are needed for severely stenosed or chronically
occluded vessels. A bend rather than a curve is placed on the distal 1.0 to 1.5
mm of the wire with an angle 30° to 45°.
GUIDEWIRE MANIPULATION TECHNIQUES

Universal Techniques

The “workhorse” wires are flexible tipped 0.014-inch wires that are often the initial wires of choice as they offer adequate support, excellent steerability, and are atraumatic. Some vessels and lesions, however, are particularly challenging and require alternative wires and techniques. The operator should be familiar with alternative wires and have a logical stepwise approach planned to accomplish a complicated intervention. In addition to wire choice, appropriate selection of additional equipment such as a guiding catheter with sufficient back-up is needed. Common lesion subsets are discussed below.

Tortuous Vessels and Distal Lesions

Severely angulated or tortuous vessels and distal lesions may be technically difficult to access. Even proximal lesions may pose a challenge if the origin of the left anterior descending artery, or more commonly the left circumflex, arises from the left main at an extreme angle. Although the tip of the flexible guidewire can be shaped to accommodate increased angulation, the guidewire will often prolapse into the alternative artery or branch rather than advance into the target branch. Stiffer-tipped or nitinol wires may prolapse less in >90° angulation, but even these wires will have poor tip steerability.

Distal lesions in tortuous arteries may represent the greatest challenge for access, because as the wire traverses curved segments, steerability is lost. For these reasons, additional support and ability for wire exchange is offered by an OTW approach. A low-profile OTW balloon can be advanced near the guidewire tip to decrease wire prolapse and to make wire removal and reshaping easier. The OTW system will also increase the torque responsiveness and decrease frictional drag of the wire. On occasion even
low profile OTW balloons cannot be advanced without compromising guide or wire position. Alternatively placing a second wire adjacent to the initial wire, the “buddy wire” technique may augment access. A third option advocated by many operators is the use of a more flexible system in these cases. Microcatheters have been used successfully in these difficult cases.\textsuperscript{10-12} There are currently several low-profile microcatheters available, including the FineCross (Terumo) which has a hydrophilic coating and tip that tapers to 1.8-Fr for crossing tortuous vessels. Delivery of devices such as balloons and stents may also be difficult in tortuous arteries or distal lesions. Vessel straightening and increased support can be achieved by exchanging the initial wire for an extra-support wire. The use of dual wires, or a buddy wire, can also be used in tortuous vessels to keep the balloon tips free.

**Chronic Total Occlusions**

Approximately 10% of percutaneous coronary interventions are for CTOs.\textsuperscript{13} The success rate for these lesions is lower than for other lesion subsets and ranges from 40% to 80% in various studies.\textsuperscript{14-19} The most common reason for failure in a CTO is inability to cross the lesion with a guidewire.\textsuperscript{20} Careful evaluation of the pre-intervention angiogram should help determine the appropriate course of the occluded vessel segment. If a previous angiogram was done prior to vessel occlusion, this should be reviewed to gain information regarding the vessel course and characteristics. Dual coronary injection is often required to simultaneously visualize antegrade and collateral flow.\textsuperscript{21,22} Recanalization of CTOs requires the availability of a broader range of coronary wires as discussed above. An example of a left anterior descending CTO case in which contralateral coronary injections and the Asahi Confianza wire (Abbott Vascular) were used is shown in Figure 27-5.
FIGURE 27-5 Cineangiograms from a percutaneous coronary intervention in a patient with a chronic total occlusion of the left anterior descending artery (LAD) treated with an antegrade approach. A. Simultaneous injections of the left and right coronary arteries allow visualization of the length of the LAD occlusion. The small arrow shows antegrade filling from the left and the large arrow shows retrograde filling from the right. B. Double arrows show the tip of the Asahi Confianza wire partially through the coronary total occlusion through an over-the-wire (OTW) balloon (*). C. Guidewire exiting LAD into diagonal artery demonstrated by contralateral injection. D. The Confianza wire was redirected into the distal LAD successfully. Note the long radiopaque segment of the wire (double arrows). E. The wire was exchanged to a floppy wire using the OTW balloon so that the LAD could be better visualized. A dissection was seen by angiography (**) that was confirmed by intravascular ultrasound. F. Several drug-eluting stents were delivered over a floppy guidewire (tip in distal LAD, arrow).

Hydrophilic wires have been used successfully in lesions previously attempted with conventional wires. In several series, lesions previously uncrossable with conventional wires were crossed with clinical success in 39% to 79% of cases.\textsuperscript{23,24} Coronary perforations were higher than previously reported at approximately 2%. In a larger series of 106 patients with CTOs
and previous PCI failure, a hydrophilic wire was employed and 42% of these attempts were successful. In a multivariate regression analysis, TIMI flow grade and occlusion age were independent predictors of success. In 5 cases, pericardial contrast staining due to vessel perforation occurred.\textsuperscript{25} Whether to use a hydrophilic wire as the initial wire in CTOs is debatable, but in one small randomized study of 88 patients, this strategy resulted in a lower number of guidewires being used, a trend toward shorter procedural and fluoroscopy times, and decreased use of contrast media compared to a strategy of using 1 or 2 0.014-inch soft or intermediate tip guidewires.\textsuperscript{26} Since that time, many non-hydrophilic wires suitable for CTOs have been developed and may offer the same success rate in crossing CTOs as the hydrophilic wires with more directability and less risk for dissection or perforation. These include wires such as the CROSS-IT and Asahi MiracleBros series (both from Abbott Vascular).

Since multiple wires are generally needed for a CTO intervention, microcatheters are often used. The Corsair microcatheter (Asahi Intecc USA), designed for CTO interventions, is a proprietary braided catheter that can track wires into microchannels or collaterals and provides support for wire manipulation or exchanges.

**Stents**

Advancing the guidewire through new or previously placed stents must be done cautiously. Even in situations of in-stent restenosis, the guidewire may exit through the stent struts, which will prohibit delivery of balloons and other devices and may even lead to stent avulsion.\textsuperscript{27} One manipulation technique that may decrease the chances of the wire advancing through stent struts is to place a large “J” curve on the wire in attempt to loop or prolapse the wire through the stent. Another option is to use a Wiggle Wire (Guidant, Inc.), which is manufactured with a distal core that has multiple undulations or bends, a shapeable flexible tip, and a low friction coating. This wire may be more trackable and prevent wire tip entrapment within stent struts.

**Bifurcation Lesions and Side Branch Access**

Dual coronary guidewires are often needed for bifurcation lesions. If provisional stenting is going to be used for the side branch, then the side
branch wire should be removed prior to stenting the main artery to avoid wire entrapment. Some operators, however, believe this cautionary step is not necessary and that leaving the side branch wire in place improves side branch patency during stent placement. A non-polymer coated, core-to-tip wire is preferred when wire jailing behind a stent is planned to prevent embolization of the coating and reduce the risk of wire tip separation during removal from behind-the-stent struts. With either method, removal or jailing, the side branch must be rewired prior to performing a final kissing balloon inflation of the main and side branch.

A complication that may occur with dual wires in bifurcation lesions or with the use of a buddy wire is wire braiding. This occurs when the two wires become entwined and cannot be manipulated independently. This phenomenon occurs mostly with RX systems and must be recognized to avoid inadvertent removal of both wires.

GUIDEWIRE COMPLICATIONS

Recognition and management of guidewire-related complications are critical to patient safety and successful procedural outcomes.

Coronary Vasospasm and Pseudostenosis

Coronary vasospasm occurs in <5% of interventions and is mostly at the target lesion or the distal vessel. Vessel closure secondary to spasm is uncommon—less than 2%—even with rotational atherectomy. Guidewire-induced vasospasm is uncommon and the presentation is not uniform. Rare instances of diffuse coronary vasospasm solely due to guidewire insertion and responsive to nitrates has been described. Additionally, wire-induced spasm may accompany angioplasty, making the recognition of the vasospasm more difficult. Multiple sites of spasm remote for the target lesion occur and may be due to wire or equipment manipulation. Most vasospasm is responsive to intracoronary vasodilators such as nitroglycerin 100 to 200 μg, but some patients may require higher doses or a continuous intravenous infusion. The calcium channel blockers verapamil, 100 μg/min up to 1.0-1.5 mg, and diltiazem, 0.5-2.5 mg over 1 minute, up to 5-10 mg, have also been
Vasospasm distal to the dilated lesion during PTCA may be refractory to vasodilators if the guidewire is contributing to the spasm, and, in that case, guidewire removal is necessary. Distinguishing newly acquired coronary narrowing due to vasospasm from coronary dissection is important. Removal of the guidewire, a potential therapy for wire-induced spasm, may be detrimental if a dissection, thrombus, or other mechanical complication is not recognized. Intravascular ultrasound may be helpful in this situation to rule out a dissection prior to wire removal. The recognition of this phenomenon of guidewire-induced vasospasm is important so that it does not interfere with selection of appropriate balloon and stent sizes or result in unnecessary interventions for “pseudolesions.”

Another well-described cause of coronary narrowing attributable to a guidewire is pseudostenosis. Tortuous vessels including the right coronary, left circumflex, and internal mammary arteries are prone to these artifacts. Pseudostenosis results from the creation of pleats or kinks in the artery due to artificial straightening induced by passage of the straight section of the guidewire through a tortuous or redundant arterial segment. In addition, stiffer guidewires, which are often used for the purpose of improved device delivery in more complicated cases such as calcified or tortuous vessels, are more likely to cause these false lesions. The lesions often appear as a linear defect and may be difficult to distinguish from a dissection, thrombus, or vasospasm. Pseudostenosis will usually resolve once the guidewire is removed, however, it can also result in erroneous hemodynamic measurements or incorrect assessment of stenosis severity.

Prior to complete removal of the wire, a few approaches can be taken to evaluate for a true lesion. If a stiff or extra-support wire is being used, it can be exchanged for a floppy wire to see if less vessel straightening resolves the lesion. Relief of pseudostenosis may occur with a transit catheter or OTW balloon catheter. The catheter can be placed distal to the lesion in question and the wire removed. This technique is particularly useful if the catheter has been used during the case so that an additional wire is not needed. Another approach is to partially withdraw the wire so that the flexible tip enters the segment of concern and the pseudostenosis disappears as the segment assumes its normal tortuous configuration (Fig. 27-6). Such an approach is not suitable for clarifying multiple lesions. If the etiology is still unclear,
IVUS can be helpful.\textsuperscript{49}

\textbf{FIGURE 27-6} Procedural cineangiograms of a right coronary intervention. A. Diagnostic angiography shows a tortuous right coronary artery (RCA) with a culprit lesion mid vessel (\textit{arrow}). B. After the stent was delivered over an extra-support wire (radiopaque floppy tip, \textit{double arrows}) 2 lesions were noted proximally (*). C. The diagnosis of pseudo-lesions was made by progressively withdrawing the guidewire until its floppy segment rested equally on either side of the suspect lesion(s).

\textbf{Wire Perforations}

Coronary perforations are a rare complication of PCI, occurring in 0.3% of patients in 12,658 cases, more with debulking devices (1%) than with balloon angioplasty and stent techniques (0.2%).\textsuperscript{50} Importantly, this study observed that 51% of the coronary perforations were guidewire-related. The majority of guidewire perforations result from distal migration and buckling of the wire during exchanges and delivery of devices. In this situation, the wire is advanced through progressively smaller arterial branches until it exceeds the lumen diameter and penetrates the thin wall of the distal branch. Perforations can also occur attempting to cross a CTO. Guidewires that have a distal hydrophilic polymer coating are more prone to cause perforations because of the wire properties and that they are generally used in more complex lesions. Operator experience is also a factor. In fact, reports of perforation often follow the release of new wires.\textsuperscript{51} As with other coronary perforations, wire perforations are can be classified as type I through III with an increasing risk of tamponade with higher classification. Importantly, wire perforations may not be readily apparent during or at the end of the PCI procedure. Patients with undetected perforations may present with features of cardiac tamponade,
notably hypotension, several hours after they completed what was judged to be an uncomplicated intervention. A high index of suspicion is essential for the prompt diagnosis and management of these patients.

Initial treatment of perforation should consist of a prolonged balloon inflation—up to 15 minutes—which in the case of a distal or CTO perforation should not result in significant ischemia. Wire-induced perforations typically do not require a covered stent. An OTW balloon should be used if time allows so that the wire can be removed, but, if an RX balloon is in place, the wire can be withdrawn into the distal balloon lumen. Further management is individualized, but if a significant pericardial effusion or tamponade is present, a pericardiocentesis should be performed.

For perforations that persist despite prolonged inflations, particularly when immediate reversal of anticoagulation is not possible such as with administration of a glycoprotein (GP) IIb/IIIa inhibitor, several unique treatment strategies have been reported. In 2 cases, a small dose (100-300 IU) of thrombin was injected via the lumen of a balloon catheter during prolonged low-pressure balloon inflation, just proximal to the wire perforation site. The thrombin can be prepared at a concentration of 50 to 00 IU/ml with a delivery of 2 to 5 ml and a 10- to 20-min balloon inflation following the thrombin injection to prevent retrograde effects of the activated thrombin. In one case report, 2-mm pieces of GelFoam (Pfizer, New York, NY) soaked in contrast were injected into the distal vessel via a transit catheter, with successful sealing of the perforation. Microcoil embolization, distal delivery of polyvinyl alcohol, or the patient’s organized thrombus has also been used successfully to treat wire perforations.

Wire Fractures, Emboli, and Retained Fragments

Guidewire entrapment or embolization is a rare complication of PCI that may be related to operator technique or, less commonly, to manufacturing flaws or wire component failure. Tip entrapment may occur when the wire is advanced into a small side branch or distal vessel due to resultant vessel vasospasm or with excessive rotation in total occlusions. Initially, an attempt to release the wire should include administration of intracoronary nitroglycerin with gentle retraction. Another possible technique is to advance a low profile over the wire balloon close to the wire tip and then retract the
wire into the balloon catheter. After removal of the wire, angiography should be performed to exclude vessel perforation. Attempts to remove an entrapped wire may lead to fracture and unwinding of the distal tip ribbon or wire embolization. Another situation that can lead to wire entrapment is the use of a wire to maintain side branch patency during stenting, as discussed above. A wire may also become inadvertently trapped behind a stent if a loop in the non-radiopaque segment goes unrecognized. The authors had this experience once during treatment of a bifurcation lesion and the stent entrapped wire fractured during attempted removal. Fracture of a coronary guidewire during thrombectomy of an occluded coronary bypass graft with the X-Sizer catheter (Genç Medikal, Ankara, Turkey) has also been reported and resulted from entrapment with a coronary stent. \(^{59}\) Guidewire transection can also occur during rotational atherectomy if the wire prolapses or kinks in the path of the rotoburr. \(^{60}\)

The optimal strategy for retrieval of wire fragments and the consequences of retained fragments are unclear, as the largest series reported outcomes in only 8 patients. \(^{61}\) Four of five extraction procedures were successful, including retrieval of a wire segment totally contained within a distal coronary artery. Retrieval of wires with segments extending into the coronary guide or aorta has been achieved with bioptomes, or compression of the wire in the guiding catheter by inflation of a balloon within the guide and simultaneous withdrawal of the balloon and catheter. \(^{62}\) Guidewire segments retained totally within the coronary circulation can be removed with improvised or commercially available snares that can be looped around the wire fragment. \(^{63}\) Some retained fragments may be benign, particularly if within the coronary or in total occlusions. At late follow-up in the observations of Hartzler et al \(^{61}\) up to 5 years, 5 patients with retained wire segments had no sequela attributable to the PTCA component debris.

**SUMMARY**

The guidewire is one of the most critical instruments in coronary intervention. This chapter reviewed the construction and fundamental physical properties of guidewires, general manipulation techniques, and potential guidewire complications. As coronary anatomy becomes more challenging, an understanding of the advantages and limitations of available
guidewires can complement operator experience and increase successful outcomes.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. Which of the following statements is true about guidewire cores?
   A. Those that extend to the tip add wire flexibility.
   B. Tapering detracts from trackability.
   C. Cores that extend to the tip provide better torque transmission.
   D. A wire with a nitinol core is less trackable than one with a stainless steel core.

2. Which of the following wire features is not helpful for crossing a total occlusion?
   A. Very flexible tip
   B. Polymer jacket
   C. Tapered tip
   D. Continuous core

3. Which of the following lesion locations would be the most difficult to cross with a guidewire?
   A. Origin of the posterior descending artery
   B. Distal left anterior descending
   C. Proximal retroflexed circumflex
   D. Internal mammary-left anterior descending anastomosis

4. The best way to determine if guidewire “kinking” is responsible for apparent coronary narrowing is to:
A. Inflate a balloon in area of narrowing and look for balloon compression.
B. Perform fractional flow reserve measurement.
C. Withdraw floppy segment of wire into area of narrowing.
D. Administer intravenous nitroglycerine.

5. Which of the following are true about guidewire perforation?
   A. Less frequent with polymer coated wires.
   B. More common with subtotal than totally occluded lesions.
   C. More common during wire exchanges.
   D. Are usually obvious.

ANSWERS

1. C
2. A
3. C
4. C
5. C
Percutaneous transluminal coronary angioplasty (PTCA) was first described by Andreas Gruentzig in 1976, when he reported the successful application of the new technique in canine coronary experiments. Dr. Gruentzig designed and assembled balloon dilation catheters in his own kitchen. He performed the first coronary angioplasty in a conscious human patient in September 1977 in Zurich, Switzerland. The dilation catheter consisted of a balloon attached to a long shaft and a short wire attached to its tip. Soon after, balloon catheters were designed with a central guidewire lumen. Since the introduction of balloon angioplasty, major advancements have taken place in the field of percutaneous coronary interventions, but the majority of cases still require dilatation of the lesion with a balloon catheter even when a stent or other devices are used. In many instances, lesion preparation is crucial prior to stent deployment.

**BALLOON CHARACTERISTICS**

**Coronary Balloon Material**

Challenging lesions require a balloon with optimal performance in terms of:

- Catheter *pushability* in order to transmit the force applied by the interventionalist’s hand to the distal end of the catheter, especially when guiding support is not adequate;
• Catheter trackability over the guidewire through tortuous segments; and
• Lesion crossability, especially in cases of calcified lesions with severe stenosis.

Therefore, despite the fact that standalone “plain old balloon angioplasty” (POBA) is mostly a thing of the past, there is an ongoing effort to manufacture more user-friendly balloon catheters that can address preparation of complex lesions to complement newer percutaneous technology. Several balloon catheter characteristics are considered in the manufacturing process.

Over-the-Wire and Rapid Exchange Systems

In an over-the-wire (OTW) system, the balloon catheter has a central lumen permitting free guidewire movement. This system is helpful when crossing difficult anatomy such as a chronic total occlusion, where balloon support is helpful and wire exchange is anticipated. On the other hand, the rapid exchange (RX) balloon catheter system is preferred by most single operators. The lesion is crossed with a standard-length guidewire. The wire is then fixed with one hand while the balloon catheter is advanced with the other. The wire exits a few centimeters from the distal end of the balloon catheter rather than its proximal end. The main disadvantage is that the wire cannot be pulled out for reshaping and cannot be exchanged for another wire without taking the entire system out. Balloon support may not be as good as with a full-length OTW system, since the balloon catheter is tracking over a relatively short distance of the wire. Therefore, the shaft design plays a fundamental role in balancing several characteristics for optimal catheter performance. These include pushability of the proximal shaft and flexibility as well as trackability of the distal shaft. Other important characteristics are lubricity, torque transmission and kink resistance. Factors that improve crossability include a smooth transition from the distal shaft to the balloon and a low profile of the very distal catheter tip.

Balloon Material

The first balloon catheter used by Andreas Gruentzig was made of polyvinylchloride, a low compliance plastic polymer. Most balloon catheters available on the market today are derived from 1 of 4 families of balloon
materials: polyolefin, nylon, polyester, and urethane. It is the type of balloon material derived from these categories of plastic that largely determine the characteristics that differentiate dilatation catheters. Noncompliant balloons are usually made of polyethylene terephthalate, a widely used resin in plastic soda bottles. The strength of the material allows the balloon to be used in calcified lesions at high pressures. The maximum recommended pressure is provided by the manufacturer. Relatively high-pressure balloons can be made out of nylon, although the strength of the material is somewhat less than that of polyethylene terephthalate; therefore, nylon balloons are characterized as semicompliant. Compliant balloons are made out of polyethylene or polyolefin copolymer, allowing for lower profile, more flexibility, and a lower tendency to “wing” after deflation. This allows for more effective rewrapping of semicompliant as compared to noncompliant balloons. The disadvantage of a compliant balloon is the reduced ability to dilate hard lesions with a greater tendency to “dog-bone” since the distending force may stretch the balloon longitudinally rather than concentrating the force circumferentially on the atherosclerotic plaque. Manufacturers also use hydrophilic surface coating for better crossability, however this is balanced against creating slippage during balloon inflation especially in hard lesions.

Each balloon comes with a compliance chart that correlates the balloon diameter to the inflation pressure. The nominal pressure is the atmospheric pressure at which the balloon reaches its nominal preset diameter as tested in vitro. Because of their stretching properties, compliant balloons attain a larger diameter with higher pressures compared to non-compliant balloons. The rated burst pressure is the maximum allowed pressure below which there is a high confidence that 99.9% of balloons will not rupture. Balloon rupture can be caused by specific lesion morphology\(^1,2\) such as the sharp edge of a calcium spicule. Most commonly, however, a rupture takes place at pressures exceeding the burst pressure in the form of a pinhole or a longitudinal tear in the balloon. Balloon rupture can cause dye staining which is usually benign or can cause an intramural hematoma and, very rarely, vessel perforation.

**Cutting Balloons**

The cutting balloon was first described by Barath in 1991\(^3\). It consists of a balloon catheter with 3 or 4 microtomes—sharp metal blades mounted longitudinally on the surface of the balloon. The balloon is inflated slowly,
allowing the blades to “cut” into the lesion before actual balloon dilation (Fig. 28-1). It is felt that these controlled microsurgical incisions may limit overall vessel stretch and vascular injury,\(^4\) therefore reducing the balloon dissection rate and possibly also the elastic recoil. The balloon uses lower inflation pressure than conventional balloons and achieves a trend toward larger lumen gain with increased plaque reduction.\(^5\) The cutting balloon has gained popularity for angioplasty of in-stent restenosis. In these situations, it has the advantage of preventing “watermelon seeding” of the balloon and may result in better dilatation.\(^6\) It is not felt to reduce the rate of angiographic restenosis compared to conventional balloons.\(^6-8\) It is important to keep in mind that the device is stiff and has a high crossing profile. Some anatomic situations, such as lesions in very tortuous segments, may be out of reach with the cutting balloon.

![FIGURE 28-1](image) Normal peripheral artery of a pig 4 hours after using the cutting balloon at low pressure without effective balloon dilatation. The arrows point to 2 incisions that extend to the media. (Reproduced from Barath, P., M.C. Fishbein, S. Vari, and J.S. Forrester, Cutting balloon: a novel approach to percutaneous angioplasty. Am J Cardiol. 1991. 68(11): 1249-1252, copyright © 1991, with permission from Elsevier.)
Scoring Balloons

The AngioSculpt Scoring Balloon Catheter (Angio-Score, Inc., Fremont, CA) consists of a minimally compliant balloon housed in 3 low-profile spirally arranged nitinol wires (Fig. 28-2). In theory, during balloon expansion, the dilating force is concentrated focally in the wires resulting in the scoring effect on the vessel lumen surface. This mechanism can result in a controlled expansion of the lumen with reduced barotrauma and lower dissection rates. As with cutting balloon angioplasty, device slippage is reduced, especially in in-stent restenosis. Optical coherence tomography (OCT) images show lumen expansion and imprints caused by the scoring elements of the nitinol wire cage (Fig. 28-3). The scoring balloon is lower in profile and more deliverable than the cutting balloon. It has been proposed for lesion preparation prior to stent delivery. In an observational study, predilation with the AngioSculpt balloon, compared with either direct stenting or conventional balloon predilation, resulted in better stent expansion by intravascular ultrasound (IVUS) measurements, irrespective of plaque morphology. This technology has also been proposed in complex bifurcation lesions with dilatation of the side branch with the scoring balloon prior to implantation of a drug-eluting stent in the main vessel. In a prospective clinical trial that enrolled 93 patients, this strategy was associated with a favorable procedure success rate of 91.4%. Dissections were observed in 8.2% of cases in the main branch and 6% in the side branch post scoring balloon angioplasty. Bailout stenting in the side branch was required in 10.8% of cases. At 9 months, the composite major adverse cardiac events (MACE) rate was 5.4%. A similar “simple provisional” strategy in true bifurcation lesions was tested in a pooled analysis of the Nordic Bifurcation and the British Bifurcation Coronary randomized trials. Both trials compared provisional T-stenting versus a complex strategy of bifurcating drug-eluting stents. In the simple strategy group (n = 457), stenting the main vessel was performed first, followed by provisional dilatation of the side branch with a conventional balloon, then stenting if necessary. This strategy resulted in 128 patients (28%) undergoing ballooning of the side branch, and 16 patients (3.5%) requiring a T-stent. At 9 months—the composite endpoint of all-cause death—myocardial infarction and target vessel revascularization occurred in 10.1% of the simple strategy group versus 17.3% of the complex group (P = 0.001). While most evidence
supports the simple strategy approach in bifurcating lesions, it is difficult to properly evaluate the place of the scoring balloon compared to the conventional balloon in the absence of a randomized clinical trial.


**FIGURE 28-3** Angiographic and optical coherence tomographic findings before and
after scoring balloon angioplasty. A–C. Before the procedure, an angiogram shows 2 severe stenoses in the right coronary artery (A). Optical coherence tomography (OCT) shows that the proximal lesion is composed mainly of fibrous tissue. No stent struts are seen at this de novo lesion (B). Thick neointimal proliferation inside the stent struts (black arrowheads) is revealed via OCT (C). D–F. After scoring balloon angioplasty, an angiogram shows the disappearance of both stenoses. There are no major dissections or visible recoil (D). In OCT analyses, the minimum lumen areas of the de novo lesion and in-stent restenosis increase from 1.18 to 2.75 mm$^2$, and from 1.51 to 4.09 mm$^2$, respectively. Marks caused by the scoring elements (white arrowheads) are clearly visible via OCT (E and F). (Reproduced from Takano, M., M. Yamamoto, D. Murakami, et al., Optical coherence tomography after new scoring balloon angioplasty for in-stent restenosis and de novo coronary lesions. *Int J Cardiol*. 2010. 141(3): e51-e53. Copyright © 2013 with permission from Elsevier.)

Drug-coated scoring balloon catheters are discussed in Chapter 32.

**MECHANISM OF CORONARY BALLOON ANGIOPLASTY**

The mechanism of coronary angioplasty is intriguing. In the original 1964 publication describing the transluminal treatment of arteriosclerotic peripheral artery obstructions with serial dilating catheters, Charles Dotter and Melvin Judkins speculated the following mechanism: “relatively non-traumatic remodeling and lateral displacement of the encircling atheromatous material.” However, soon after the inception of coronary balloon angioplasty, the theory of vessel injury gained momentum. In one of his publications, Andreas Gruentzig wrote: “the atherosclerotic material is compressed and pressed into the vessel wall, thereby partly disrupting and dissecting the intima and overstretching the media.” Gruentzig refers to this as “controlled injury.” The notion of plaque compression has since been largely refuted for lack of experimental evidence. Human coronary arteries studied postmortem after successful angioplasty demonstrated splitting of the atheromatous plaque at the point of least resistance. Morphologic studies are never conclusive, primarily because atherosclerotic plaques differ in their composition. In acute coronary syndrome for example, the plaque may have already ruptured and may have varying degrees of superimposed thrombotic material. These types of plaques may respond differently to balloon
angioplasty than those in stable coronary artery disease situations where fibrosis and calcifications usually prevail. Nevertheless, the body of evidence, especially from IVUS data, supports the mechanism of lumen enlargement with balloon angioplasty to be largely the result of endothelial desquamation, plaque fissuring and arterial wall dissection, stretching of the vessel wall through the elasticity of both the media and adventitia, and axial plaque redistribution. Recent work addressed the dissection mechanisms triggered during the early stages of angioplasty in an atherosclerotic coronary artery 2-dimensional geometric-based computational model. The study showed that the onset of dissection damage occurs very early. Plaque detachment at the shoulder region results in an intimal flap or partial dissection of the plaque from the media, but what is interesting is the occurrence, very early on during balloon inflation, of damage within the wall of the media layer itself. This again stresses the probability of several injury mechanisms at different locations. The degree to which each of these various mechanisms play a role varies with each lesion morphology and atherosclerotic plaque composition as well as with balloon pressure and sizing.

COMPLICATIONS OF BALLOON ANGIOPLASTY

Procedural Complications

Intimal tears and arterial wall dissections are commonly identified by IVUS following balloon angioplasty. Some form of plaque disruption is seen in 50% to 75% of cases. Intramural hematomas have also been described by IVUS. These can result from a medial dissection with blood accumulating in the medial space and extending into the contiguous normal arterial wall, especially in the absence of a clear re-entry point. Coronary dissections pose a risk for acute or subacute vessel closure, one of the most dreaded complications of balloon angioplasty. In particular, intramural hematomas predict a high rate of non–Q-wave myocardial infarction, need for repeat revascularization, and sudden death. By providing scaffolding to “tack up” dissections, coronary stents have largely resolved the problem of acute vessel
closure that is caused by a coronary dissection with or without intramural hematoma. However, before the stent era, PTCA resulted in a significant complication rate. In the first 1500 patients enrolled in the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry (1977-1981), major complications occurred in 9.2% of patients and were in the form of myocardial infarction, urgent revascularization, or in-hospital death. Emergency surgery was required in 6.8%. It is interesting to note that in this very early experience, success rate was reported in only 63% of cases. Despite refinement in balloon technology, the incidence of periprocedural vessel occlusion after angioplasty remained relatively high at 6.8% through 1985 to 1986, with roughly two-thirds of the vessel occlusions occurring in the cardiac catheterization laboratory. Acute vessel closure was associated with a high risk of major complications, including bypass surgery in 35% and mortality in 5%, which was substantially higher than the 1% mortality reported in PTCA patients without vessel closure.

Acute vessel closure with balloon angioplasty is primarily caused by severe coronary dissections. Less common reasons include thrombus formation and coronary spasm. Acute closure occurring in a proximal location of a large vessel can result in ST-segment elevation and significant hemodynamic compromise, especially if the area of myocardium supplied by the vessel is substantial and/or collaterals are absent. If the wire is still across the lesion, redilatation with a properly sized balloon was the only thing that could be tried in the vessel before the availability of stents. In the early era of coronary angioplasty, heparin was administered generously (10,000 units at the beginning of the procedure and 5000 units every hour). Automatic coagulation timer (ACT) machines were not widely available in cardiac catheterization laboratories, and a weight-based heparin approach was not routine. Prolonged balloon inflations were the norm as long as the hemodynamic situation allowed. Intra-aortic balloon pumps were frequently used. A fully staffed operating room was kept on standby and the surgery and anesthesia teams were alerted as soon as a major complication took place. Even now, recrossing a lesion during acute vessel closure when the wire is no longer across the lesion remains potentially very challenging, as the wire may inadvertently advance through the false lumen, resulting in propagation of the dissection. In the very early period of balloon angioplasty, the rate of emergency bypass surgery was high, either as a result of procedure failure or due to acute vessel closure.
In 1988, Stack RS et al described the coronary perfusion balloon that allows passive myocardial perfusion during balloon inflation. Perfusion holes are distributed on the catheter shaft proximal to the balloon. Blood enters through the holes and exits distally from the wire lumen, perfusing the distal artery bed beyond the inflated balloon. Early results were encouraging in terms of improving the hemodynamic condition of the patient or reducing the angiographic severity of the dissection.

The laser balloon was another modality that was proposed for sealing severe coronary dissections and reversing abrupt closure. It works by heating tissues with an Nd:YAG laser during balloon inflation and welding plaque-arterial wall separation. However, restenosis following successful treatment with the laser balloon was relatively high. The experimental device was discontinued before entering the clinical market.

Significant improvement in clinical outcome and reduction in major complications were not seen until coronary stents were introduced to clinical practice. This was shown when 1559 consecutive patients in the 1997-1998 Dynamic Registry who were having percutaneous interventions including use of stents in de novo lesions were compared to 2431 patients in the 1985-1986 National Heart, Lung, and Blood Institute (NHLBI) Registry of patients undergoing PTCA in the prestent era. Patients in the Dynamic Registry were on average older, clinical presentation was more unstable and lesions were more complex than patients in the NHLBI PTCA registry. Coronary stents were used in 70.5% of patients in this early era. Procedural success was higher in the Dynamic Registry (92.0% vs 81.8%; \( P < 0.001 \)) and the rate of major in-hospital complications was lower (4.9% vs 7.9%; \( P = 0.001 \)) compared to the NHLBI registry. Similarly, the 1-year rate for coronary artery bypass grafting (CABG) was nearly cut in half in the early stent era (6.9% vs 12.6%; \( P = < 0.001 \)) compared to the prestent era.

In contemporary percutaneous coronary interventions, the in-hospital major cardiac event rate is very low compared to that of the balloon angioplasty era.

**Predictors of Procedural Complications With Balloon Angioplasty**

Several angiographic and clinical predictors have been found to be associated
with balloon angioplasty procedural complications. In 1988, new American College of Cardiology/American Heart Association guidelines on PTCA emerged. The guidelines described lesion morphologies that can affect both the success and complication rates with PTCA. These angiographic characteristics were grouped into three types: A, B, and C reflecting an anticipated low, moderate, or high procedural risk (Table 28-1). Ellis et al assessed the procedural outcome in patients with multivessel disease undergoing PTCA. Three hundred and fifty consecutive patients (1100 stenoses) from 4 clinical sites were analyzed. A modified ACC/AHA score was applied whereby type B lesions were sub-grouped into type B₁ (having 1 type B characteristic) and type B₂ (having ≥2 type B characteristics). The distribution was as follows: type A, 28.7%; type B₁, 34.1%; type B₂, 26.6%; and type C, 10.6%. The influence of lesion characteristics according to the modified score on the procedural success and complication rates are shown in Figures 28-4 and 28-5.

Table 28-1 ACC/AHA Lesion Specific Characteristics 1988
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<thead>
<tr>
<th>Type A Lesion Characteristics (High Success, &gt;85%; Low Risk)</th>
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<tbody>
<tr>
<td>Discrete (&lt;10 mm length)</td>
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<tr>
<td>Concentric</td>
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<tr>
<td>Readily accessible</td>
</tr>
<tr>
<td>Nonangulated segment, &lt;45°</td>
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<tr>
<td>Smooth contour</td>
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<table>
<thead>
<tr>
<th>Type B Lesion Characteristics (Moderate Success, 60%-85%; Moderate Risk)</th>
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<tr>
<td>Tubular (10-20 mm length)</td>
</tr>
<tr>
<td>Eccentric</td>
</tr>
<tr>
<td>Moderate tortuosity of proximal segment</td>
</tr>
<tr>
<td>Moderately angulated segment, &gt;45°, &lt;90°</td>
</tr>
<tr>
<td>Irregular contour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type C Lesion Characteristics (Low Success, &lt;60%; High Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse (&gt;2 cm length)</td>
</tr>
<tr>
<td>Excessive tortuosity of proximal segment</td>
</tr>
<tr>
<td>Extremely angulated segments &gt;90°</td>
</tr>
</tbody>
</table>

In-hospital mortality was 1.1% in this study. Major ischemic complications (death, myocardial infarction, or emergency bypass surgery) occurred in 30 patients (8.6%). The only variables that were independently predictive of procedural outcome were the modified scoring system and the presence of diabetes mellitus. Consequently, this modified ACC/AHA score
became widely applicable. However, as experience matured, there was practically less reliance on a scoring system and more on lesion-specific morphologic characteristics to predict clinical outcome with angioplasty.\textsuperscript{42}

In a review of databases of patients undergoing PTCA, Kleiman et al\textsuperscript{43} reported the multivariate predictors of complications. It was evident that clinical factors such as acute coronary syndrome presentation played an important role in increasing the complication risk by creating a thrombogenic milieu. Other clinical factors included female gender, age, diabetes, chronic renal failure, low ejection fraction, and jeopardy score.

\section*{Restenosis}

\subsection*{Occurrence of Restenosis With Balloon Angioplasty}

Since the early days of PTCA, it became readily apparent that longterm efficacy after a successful procedure was primarily limited by recurrence of the original lesion. The definition of angiographic restenosis evolved over time. In one of the early reports of the PTCA registry,\textsuperscript{44} Holmes et al applied the definition of an increase of at least 30\% from the immediate post-PTCA stenosis to the follow-up stenosis or a loss of at least 50\% of the gain achieved at PTCA. In 557 patients with successful PTCA and follow-up angiography in 84\%, the restenosis rate was reported as 33.6\% of patients. In another study of patients who underwent elective PTCA to native coronary arteries between July 1980 and July 1984\textsuperscript{45} and angiographic follow-up in 57\%, angiographic restenosis was seen in 302 patients (30.3\%), according to the more traditional definition of luminal narrowing greater than 50\% at the time of follow-up angiography. A more complete angiographic follow-up rate of 90\% was achieved in the CAVEAT trial that randomized 1012 patients to directional coronary atherectomy versus percutaneous balloon angioplasty.\textsuperscript{46} Based on the classic definition of greater than 50\% diameter stenosis 6 months after an initially successful procedure, the restenosis rate was 57\% in the balloon angioplasty group. This rate was viewed as surprisingly high at the time of study publication, but it was probably more reflective of the true incidence of angiographic restenosis with balloon angioplasty.

The clinical relevance of angiographic restenosis is measured in terms of associated anginal symptoms, demonstration of ischemia and/or the need for
target lesion revascularization (TLR). Binary restenosis according to the classic definition of lesion recurrence ≥50% in diameter stenosis does not always result in TLR. Hemodynamically significant lesions usually correlate with a diameter stenosis ≥70%. We analyzed 3363 patients who had a successful elective balloon angioplasty procedure at Emory University Hospitals between 1980 and 1990 and who had a repeat angiographic evaluation for different indications at 4 to 12 months. Angiographic restenosis was seen in 1570 patients (47%). In patients with restenosis, 71% had angina versus 39% in patients without restenosis ($P < 0.0001$). At 6 years, the survival in patients with and without restenosis was not statistically different (93% vs 95% respectively $P = 0.16$). These data support the well-accepted notion that restenosis after PTCA does not increase short- or long-term mortality.

**Pathophysiology of Restenosis**

Our understanding of restenosis following coronary interventions continues to evolve. Indeed, despite the fact that many mechanisms have been elucidated, many others remain obscure or incompletely understood. The most accepted theory is that coronary arteries dilated with a balloon are prone to restenosis through acute lumen loss from elastic recoil and through late loss from intimal hyperplasia and negative vessel remodeling. IVUS technology has also helped shed some light on the different patterns of remodeling that can occur after angioplasty and the complex nature of the restenotic process.

Restenosis occurs in response to deep arterial wall injury to the intima and media which often creates a strong thrombogenic response. Lesion-specific characteristics as well as regional flow dynamics and wall shear stress contribute to the extent of injury. Longitudinal plaque fissures that commonly occur with balloon angioplasty expose the subendothelial and medial components including collagen, elastin, and smooth muscle cells to the circulating blood. Platelets deposit and aggregate at the site of balloon injury and release various cytokines, chemokines, and growth factors. Thromboxane A2, a very powerful platelet aggregator and vasoconstrictor, is released. Platelets also release platelet-derived growth factor, transforming growth factor-β1, and insulin-like growth factor 1. Inflammatory cells also
release a wide variety of mitogens. Thrombin, which is the most potent known platelet activator, plays a key role following balloon injury and endothelial denudation. Thrombin activity and thrombin receptor expression are upregulated. Thrombin facilitates several biologic responses that can induce vascular lesion formation, including being a direct smooth muscle mitogenesis. Growth factors and mitogens, in turn, will stimulate cell migration and proliferation. Vascular smooth muscle cells will migrate from the media to the intima and deposit extracellular connective tissue matrix proteins. This results in what is referred to as intimal hyperplasia.

Geometric remodeling occurs after balloon expansion, as the area circumscribed by the internal elastic lamina increases. Beyond acute lumen loss, however, the mechanism that leads to chronic remodeling after balloon injury is not very well understood. In de novo atherosclerosis, compensatory vessel enlargement occurs in the early stages in response to progressive plaque expansion. Following balloon angioplasty, the same mechanism of chronic positive arterial remodeling can be instigated by the release of proteolytic enzymes as part of the inflammatory process caused by the balloon injury. But arterial remodeling following balloon angioplasty can also consist of chronic arterial constriction. It is the magnitude of neointimal proliferation and hyperplasia, as well as the degree and direction of geometric remodeling that will determine which lesions will progress to clinically important restenosis following balloon angioplasty. Elastic recoil and geometric remodeling are thought to be virtually eliminated by coronary stenting.

**Temporal Features of Restenosis**

Restenosis following coronary balloon angioplasty usually occurs within the first few months, most commonly between 6 and 12 weeks. Noboyushi et al studied 229 patients with coronary angiography on day 1 and again at 1-, 3-, and 6-month intervals, and at 1 year after successful PTCA. The authors concluded that restenosis is most prevalent between 1 and 3 months and rarely occurs beyond 3 months. We have shown that if a lesion treated with balloon angioplasty does not recur within the first few months, the chance of restenosis thereafter is dramatically reduced to less than 3%. It is very unusual for restenosis to present as an acute myocardial infarction. Rather,
the recurrence of a lesion treated with angioplasty is often uncovered by the reappearance of symptoms or by functional testing.

**Predictors of Restenosis**

The risk factors that could potentially play a role in restenosis are many and range from clinical, angiographic, morphologic and procedural variables to biologic and geometric variables. The mechanism of restenosis following balloon angioplasty is so complex that to this date many of these factors remain poorly defined or totally unknown. It is likely that a confluence of factors has a synergetic effect in causing restenosis. Previous studies that have attempted to identify the importance of clinical variables have found some that correlated with restenosis, such as unstable angina, insulin-dependent diabetes, chronic hemodialysis, hyperlipidemia, hypertension, and prior restenosis. Angiographic variables that seem to increase the risk of restenosis following balloon angioplasty include long lesions, ostial and bifurcating lesions, small vessels with diffuse disease, total occlusions, and degenerate saphenous vein grafts. The predictive power of many of these variables is poor and derived from small studies. The one concept that is probably most accepted is that achieving a larger lumen after angioplasty favors a lower restenosis rate. This may be explained by the fact that for the same degree of intimal hyperplasia, a larger residual lumen will less likely cause significant luminal renarrowing. The theory of “bigger is better” is probably unrelated to the type of device used in a percutaneous coronary intervention.

**Prevention of Restenosis**

During the PTCA days, numerous studies were conducted in an effort to find a pharmacologic solution to restenosis following balloon angioplasty. These studies tested agents that could alter 1 or more of the multiple pathways that are believed to play a role in the restenotic process. Although many animal studies showed promising results, human studies were largely disappointing. Probulcol, an agent with antioxidant and lipid-lowering properties, and AGI-1067, a metabolically stable modification of probucol, may reduce restenosis if administered a few weeks prior to balloon angioplasty. Cilostazol, an antiplatelet agent and an inhibitor of intracellular
phosphodiesterase activity, has been shown to reduce restenosis following balloon angioplasty.\textsuperscript{78} In addition, in the randomized Cilostazol for R\textsc{E}STenosis (CREST) trial,\textsuperscript{79-81} cilostazol was shown to reduce restenosis when used as adjunct therapy with bare-metal stenting.

**PERCUTANEOUS BALLOON ANGIOPLASTY IN THE DRUG-ELUTING STENT ERA**

Since Andreas Gruentzig performed the first coronary balloon angioplasty on a living human in September of 1977, a balloon remains a fundamental tool in almost any percutaneous revascularization procedure.

As previously mentioned, stents have significantly reduced the problem of acute closure or threatened vessel closure. Incrementally, bare-metal and subsequently drug-eluting stents have reduced the problem of restenosis. However, in some situations, percutaneous coronary interventions still rely on POBA. Some examples include:

- The use of a plain balloon or a cutting balloon in a bifurcation lesion with disease in the ostium of the side branch without main branch stenosis, particularly if the strategy is to avoid stenting the side branch and encroachment on the main branch.
- Treatment of in-stent restenosis.
- Small vessel lesions.
- Distal lesions in which severe proximal tortuosities, especially with calcifications, prohibit the advancement of a stent.
- Poorly dilatable lesions in which placing a stent is felt to be inadvisable because of the risk of poor stent expansion.
- Some bifurcating lesions, when a balloon result is adequate and a stent is avoided to prevent jailing of the side branch.
- Treatment of lesions at the anastomosis of the left internal mammary artery (LIMA) or more distally in the native artery. In such instances, advancing a stent in a tortuous LIMA may be difficult. Moreover, data suggest that the longterm result with stenting is not favorable over
ballooning in LIMA anastomosis lesions.
• Rare situations in which prolonged antiplatelet therapy is contraindicated, such as in the presence of severe thrombocytopenia, the potential for active bleeding, or the anticipation of certain types of nonelective surgeries post angioplasty.

These examples, as well as others, lead to the performance of percutaneous coronary angioplasty without placing a stent. With that in mind, the interventionalist needs to be familiar with what to expect from a balloon result both in the short and long term.

SPECIAL LESION SUBSETS

Ostial Lesions and Bifurcating Lesions

The current era of stent and new technology has considerably limited the use of balloon angioplasty in aorto-ostial lesions. This stems from the fact that aorto-ostial lesions in locations such as the right coronary artery posed a big challenge for balloon technology. In one study from the pre-stent era involving 53 patients who underwent percutaneous transluminal angioplasty of a right coronary artery ostial stenosis, the procedure success rate was only 79%. Emergency coronary artery bypass grafting was needed in 5 patients because of abrupt closure. One-year follow-up revealed clinical recurrence of angina in 20 patients (48%) and restenosis in 16 (38%). A non-randomized study that compared different strategies, including balloon angioplasty in right coronary artery ostial lesions, reported that stenting provided the best short- and long-term outcomes. However, even with the current use of drug-eluting stents, aorto-ostial lesions are still associated with poorer long-term outcomes than ostial LAD and nonostial coronary lesions, as evidenced by a significantly higher restenosis and lower cardiovascular event-free survival rates.

For non–aorto-ostial lesions located at bifurcation points, such as the ostium of the left anterior descending or circumflex arteries, stenting poses a particular challenge. Possibilities of an untoward outcome in such situations include a proximal stent edge tear that could propagate into the left main artery, plaque shift into the adjacent large vessel, and complete or partial
jailing of the bifurcating artery. Carina shift is another potential problem that seems to be more important than once thought. In a volumetric IVUS analysis of bifurcating lesions, carina shift was found to be the major mechanism of side branch ostial compromise after main vessel stent implantation. There was no clear correlation with plaque shift in this study.

These problems can at times be circumvented by avoiding use of a stent altogether. For example, one way to approach an ostial left anterior descending artery would be to debulk the lesion with rotational atherectomy prior to balloon angioplasty. Use of a stent would follow only if a suboptimal result was obtained post balloon angioplasty. Another approach would be to use cutting balloon angioplasty with provisional stenting. No randomized trials have been performed to test these different strategies. But in current practice, the vast majority of cases are performed using coronary stenting in order to reduce the chance of future revascularization procedures. Exceptions include cases of isolated branch ostial lesions such as in diagonal or obtuse marginal arteries where placing a stent to cover the ostium fully may result in stent protrusion into a non-diseased main vessel. A stent that is positioned slightly more distally in the side branch artery will miss the ostium. In such instances, stenting could be avoided and conservative medical management or provisional cutting balloon angioplasty could be considered.

Ostial lesions have been excluded from the landmark randomized trials of drug-eluting stents. The efficacy of such stents in challenging anatomic subsets is being studied from large post-market registry data.

**Long Lesions**

A long lesion with diffuse disease is one of the most powerful predictors of a reduced procedural success rate, increased risk of hemodynamically important dissections, and acute closure as well as increased risk of restenosis with balloon angioplasty. Treatment of long lesions with long balloons and prolonged balloon inflations may be correlated with improved success rate without influencing the restenosis rate. Until the emergence of coronary stents, adjunctive debulking devices such as the excimer laser and rotational atherectomy have been applied to long lesions but without achieving significant gains in procedural success or restenosis. It was not until the introduction of coronary stents that the chance of dissections in long
lesions was dramatically reduced and the restenosis rate significantly dropped, especially with drug-eluting stents which seem for now to be the treatment of choice in long coronary artery obstructions.

**Diffuse Small Vessel Coronary Artery Disease**

Small vessel disease and diffuse coronary atherosclerosis can be seen in a number of clinical situations, but most importantly in patients with diabetes mellitus. Chronic hyperglycemia sets the stage for a proinflammatory and prothrombotic state and increases the risk of exaggerated neointimal hyperplasia and diffuse coronary artery disease and a potential for inferior clinical outcome with revascularization.

Optimal medical therapy may be the ideal approach in patients with stable small vessel coronary artery disease when considering the limitation of the invasive percutaneous approach. But in acute coronary syndrome or when symptomatic patients fail medical therapy, small vessels, especially with coexisting diffuse disease, pose a genuine challenge. In general, percutaneous revascularization of small coronary vessels carries a lower chance of success and a relatively higher risk of major adverse cardiac events compared with revascularization of large vessels, specifically when located in proximal coronary segments. Consequently, a distinction must be made between a small vessel supplying a small amount of myocardium and a proximal lesion in a small artery that supplies a large amount of myocardium, either because it travels a considerable length or it supplies important collaterals. In the first case, where the amount of myocardium in jeopardy is small, the benefit from an angioplasty may not outweigh the risks, and medical therapy is most often the first choice. The second case, in which a large amount of myocardium is at risk, presents a challenging problem for the interventionalist. When performing percutaneous revascularization to a small vessel, especially in association with diffuse disease, options are limited because of the risk of dissection, acute closure, and restenosis with balloon angioplasty, as well as debulking techniques. Furthermore, deployment of stents in this situation is fraught with the risk of underexpansion and the possibility of subacute thrombosis. Another concern is the risk of perforation when stents are oversized and overexpanded in small vessels. In the early stent era, the French multicenter registry reported a subacute stent thrombosis rate of 10% in vessels with diameters less than 2.5 mm. Comparison of balloon
angioplasty of small coronary vessels with bare-metal stenting can be derived from sub-analysis of randomized trials such as BENESTENT, which showed that decreasing vessel size was associated with an increasing risk of cardiac events for both the stent and balloon angioplasty groups. A more contemporary analysis of bare-metal stents versus drug-eluting stents in vessels ≤2.25 mm demonstrated the mid-term advantage of drug-eluting stents over bare-metal stents; however the benefit was not sustained at 5 years. In particular, diffuse atherosclerosis in patients with diabetes mellitus is a strong risk factor for restenosis following coronary stenting, despite the recent advances in drug-eluting stent technology.

Coronary artery bypass surgery is also inadequate, especially in terms of longterm graft patency when the target arteries are complex and diffusely diseased. A recent meta-analysis of observational studies reporting on the combination of coronary endarterectomy with bypass surgery in patients with extensive diffuse coronary atheroma reported an increased 30-day mortality and postoperative MI compared with coronary artery bypass surgery alone. Furthermore, angiographic patency at follow-up was reduced in the adjunctive coronary endarterectomy group. All these limitations stress the need to properly evaluate the clinical indication while considering any of the available revascularization strategies.

**Saphenous Vein Grafts**

One of the main limitations of coronary artery bypass surgery is the lifespan of the saphenous vein graft. At 10 years post-surgery, more than half of these bypass grafts are severely diseased or completely closed. Since the early days of percutaneous transluminal revascularization, balloon angioplasty of saphenous vein grafts was viewed as a logical approach in selected cases compared with the less-attractive alternative of repeat bypass surgery. However, the procedure was associated with more significant risks than balloon angioplasty of native coronary vessels. The short-term risks included distal embolization, no-reflow phenomenon, and myocardial infarction. Angiographic predictors of procedural complications included a diffusely diseased vein graft, presence of thrombus, irregular or ulcerated lesion surface, large plaque burden and marked lesion eccentricity. Older saphenous vein bypass grafts were prone to more complications. In the long term, there was a significant occurrence of late cardiac events and a
restenosis rate that could exceed 50%. It became clear that balloon angioplasty treatment of saphenous vein grafts was a suboptimal solution that had significant limitations.

With the advent of stents, the SAphenous VEin De Novo (SAVED) randomized trial compared the safety and efficacy of the Palmaz-Schatz stent with balloon angioplasty in 220 venous bypasses. There was no significant improvement in angiographic restenosis, which was the primary endpoint of the study. However, stenting was associated with more favorable procedural outcomes, a larger gain in luminal diameter, and a reduction in major cardiac events. This advantage, seen with stenting, led to the widespread use of stents in saphenous vein grafts. The emergence of distal embolic protection technology has allowed the treatment of more complex saphenous vein graft disease with safer procedural outcome.

The comparison of bare-metal stents to drug-eluting stents in the treatment of saphenous vein bypass lesions has yielded conflicting results. In the absence of large randomized trials, one can derive some limited conclusions from the existing studies. A report from a US multicenter registry suggests that the short-term benefit of drug-eluting stents in SVG may be limited to SVGs < 3.5 mm in diameter with loss of target vessel revascularization benefit after 9 months. The long-term results of percutaneous intervention in saphenous vein grafts have remained suboptimal compared to the outcome in native vessels. One important reason is that the long-term failure of saphenous vein grafts post intervention correlates not only with restenosis, but also with the natural course that these bypasses follow in the years following surgery.

**Balloon Angioplasty Through a LIMA Bypass**

The challenge posed by performing percutaneous angioplasty to a native artery via an internal mammary artery bypass is primarily correlated with the tortuosities of the conduit. Severe bends may be prohibitive and bear the increased risk of acute closure of the bypass during angioplasty. Moderate tortuosities may allow advancement of a low-profile balloon without permitting advancement of a stent, therefore limiting the chance of a bailout for acute vessel closure during angioplasty. Relatively straight internal mammary conduits are usually approachable with stents. A good balloon result at the anastomosis with the native vessel does not necessarily need to
be followed by stenting.

A retrospective analysis\textsuperscript{108} of 50 patients who underwent percutaneous revascularization of the LAD artery via a LIMA bypass (16 patients) or at the anastomosis site (34 patients), reported a success rate of 88%. The main reasons for failure were lack of adequate guide catheter support and excessive tortuosities of the LIMA. Thirty-four of the successfully treated patients were restudied with angiography. Restenosis was documented in 14 patients (41%). The restenosis rate was significantly higher if stenting was performed (65% vs 18%; $P = 0.005$). In particular, lesions at the anastomosis did better with balloon angioplasty compared to stenting (restenosis rate 14% vs 80%; $P = 0.001$). Other studies have also reported good short- and long-term outcomes with balloon angioplasty.\textsuperscript{109} A study specifically addressed the LIMA to LAD anastomotic site in 56 consecutive patients.\textsuperscript{110} Balloon angioplasty alone was successful in 15 patients (28.8%), and stenting was required in 37 patients (71.2%). Procedural results were similar in the 17 patients where bare-metal stents were used and in the 20 who received drug-eluting stents. At 1 year, there was no significant difference in target lesion revascularization with BMS and DES (26.6% vs 25% respectively; $P = 0.99$). Two late stent thrombosis were reported after placement of drug-eluting stents. Target lesion failure was lower with plain balloon angioplasty (6.7%) although this was not statistically significant. Therefore, a good acute result following plain balloon angioplasty of a LIMA to LAD anastomotic lesion without stenting may be considered an acceptable strategy.

**CONCLUSION**

Ever since the birth of transluminal coronary angioplasty, a balloon remains a fundamental tool in almost any percutaneous revascularization procedure. This is true even in the event of primary stenting, because most stents are balloon expandable. It is also true when adjunctive methods such as rotational atherectomy are used, because these rarely consist of standalone devices. A balloon is used to predilate a lesion or postdilate a stent. The evolving technology has resulted in newer modalities of treatment. Stents have significantly reduced the problem of acute closure or threatened vessel closure. Drug-eluting stents, in particular, have dramatically improved the problem of restenosis. Significant advances have also been witnessed in
adjunctive pharmacotherapy. Bypass surgery techniques are going through continuous refinement and the approach to secondary prevention has become more aggressive. Despite the fact that the bearing of the balloon has diminished with time, in some situations, percutaneous coronary revascularizations still rely on “plain old balloon angioplasty.”

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**MULTIPLE CHOICE QUESTIONS**

1. A 62-year-old woman taking oral hypoglycemic agents for known diabetes presents with a 2-h history of retrosternal chest pain and nausea to an emergency department without a cardiac catheterization laboratory. On presentation, she did not appear to be in any distress. Her vital signs: BP 135/88 mm Hg, HR 90/mn regular, respiratory rate 18/minute, and she was afebrile. Her ECG is shown in **Figure 1**. She was started on anti-platelets and anti-thrombotic agents and was transferred to the cardiac
catheterization laboratory where angiographic images showed a small area of inferior akinesis and a non-dominant right coronary artery. The left system is shown in Figure 2. The totally occluded second obtuse marginal was pre-dilated then stented with a 2.75 × 23 mm drug-eluting stent. The angiogram taken after stent deployment is shown in Figure 3. The interventional cardiologist administers intracoronary nitroglycerin without appreciable improvement in the lesion distal to the stent. At this point the most appropriate next step is to:

A. Dilate the lesion distal to the stent with a 2.0 mm non-compliant balloon.
B. Directly stent the lesion distal to the stent with a 2.25 mm × 12 mm drug-eluting stent.
C. Withdraw the wire and obtain a coronary angiogram.
D. Use a thrombus aspiration catheter.

2. A 57-year-old man presented with unstable angina. He receives treatment for chronic hypertension and dyslipidemia. He has a strong family history of coronary artery disease. At coronary angiography he was found to have a bifurcating lesion in the left anterior descending artery (LAD)/diagonal distribution (Figure 4). The rest of his coronary arteries are free of hemodynamically significant coronary obstructions. His ejection fraction is 60%. The revascularization options were discussed with the patient who consented to percutaneous coronary intervention. In planning for the procedure, which of the following options would be considered INCORRECT?
FIGURE 2
FIGURE 4

A. Apply the Nordic and BBC trial protocols by stenting the LAD first followed by provisional dilatation of the side branch with a conventional balloon, then T-stenting if necessary.
B. Apply the AGILITY trial methodology by stenting the LAD first followed by provisional dilatation of the side branch with a scoring balloon then stenting if necessary.

C. Plan bifurcating stenting using the mini-crush technique.
D. Plan bifurcating stenting using the TAP technique (T And Protrude).

3. A 73-year-old woman receives treatment for hypertension and dyslipidemia. She presents to her primary care physician for a checkup. She is totally asymptomatic from the cardiac standpoint and has a good exercise tolerance. Her ECG shows minor non-specific ST-T wave
abnormalities. Her physician orders stress echo. Baseline images show a normal left ventricular systolic function with no regional wall motion abnormality and significant anterior wall hypokinesis at peak stress. A cardiac catheter identifies a focal non-calcified 70% proximal LAD lesion. In evaluating the management options, which of the following statements is correct?

A. The COURAGE trial cannot be applied in this situation since proximal LAD disease was excluded.
B. The COURAGE nuclear substudy showed that ischemia reduction ≥5% is associated with lower risk of death/MI.
C. LIMA to the LAD in this patient is preferable to percutaneous coronary intervention because it confers a survival benefit at 1 year.
D. Percutaneous coronary intervention plus optimal medical therapy in this patient is associated with a survival benefit at 1 year compared to optimal medical therapy alone.

ANSWERS

1. C

New unexpected lesions in the course of a coronary intervention should raise the suspicion of a pseudo-lesion. The clue is moderate-to-severe coronary tortuosity at baseline before introducing the guidewire. Pseudo-lesion is the result of straightening of a tortuous coronary artery over the stiff part of the guidewire. It is also referred to as pseudo-narrowing or accordion effect. The differential diagnosis includes spasm, a coronary dissection and thrombus formation/embolization. But if a pseudo-lesion is not suspected or considered in the differential diagnosis, unnecessary interventions may take place, possibly subjecting the patient to inadvertent complications. Pseudo-lesions can be severe and can cause total obstruction of coronary flow with resultant chest pain and electrocardiogram changes. When suspected, the guidewire may be withdrawn while keeping the soft part across the suspected lesion. The soft part of the wire will cause less straightening, therefore improving the angiographic appearance of the pseudo-lesion. In case this is not confirmed, the wire can be safely re-advanced since it is already across the lesion. Figure 5 shows the angiographic appearance of the artery after withdrawing the wire.
2. B

The protocol in the AGILITY trial in complex bifurcation lesions consisted of dilatation of the side branch with the scoring balloon prior to implantation of a drug-eluting stent in the main vessel. Bailout stenting of the side branch was performed after stenting the main branch if the result in the side branch was felt to be suboptimal. Crossing the side branch with a scoring balloon to dilate the struts of a stent is not advisable.

3. B

The COURAGE trial randomized patients with ≥70% stenosis in ≥1 proximal epicardial vessel and objective evidence of ischemia (or ≥80% stenosis + CCS class III angina without provocation testing) to optimal medical therapy (OMT) plus percutaneous coronary intervention (PCI) or medical therapy alone. About a third had proximal LAD disease. The study concluded that PCI added to optimal medical therapy did not reduce risk of death, MI, or other major CV events compared with optimal medical therapy alone (Boden
INTRODUCTION

The technical goal of coronary stenting should be to eliminate or lessen ischemic symptoms in the short/intermediate term and possibly reduce the risk of death or myocardial infarction, while not exposing the patient to excess short- or long-term risk. Yet major adverse cardiac events (MACE) occur in 4% to 20% of stented sites within a year,\(^1,2\) and stent underexpansion\(^3,4\) and axial misalignment (“geographic miss”)\(^5\) account for nearly half of these. Although a discussion of choosing percutaneous intervention instead of bypass surgery or optimal medical therapy alone is beyond the scope of this chapter, we will address various issues to be considered to provide the patient with an optimal technical result.

CHOICE OF VASCULAR ACCESS

Improvements in guide catheter and wire support, as well as balloon and stent deliverability, have facilitated small-caliber device intervention and, in particular, radial access–based intervention. The result has been a dramatic reduction in bleeding complications and red cell transfusion–induced inflammation and perhaps even a reduction in patient mortality under some circumstances (especially primary percutaneous coronary intervention [PCI] for ST-segment elevation myocardial infarction [STEMI]).\(^6\) Except when
anatomy precludes it, radial access should be the preferred route of vascular access. Femoral, brachial, and axillary access can at times be reasonable alternatives.

**ADJUNCT PHARMACOLOGY**

Both antiplatelet and antithrombin therapies are required for safe stent implantation and healing. Aspirin and clopidogrel are usually sufficient antiplatelet therapy for patients with stable ischemic symptoms. Second-generation P2Y\textsubscript{12} inhibitors have been shown to be superior to clopidogrel in unstable angina patients but not, in general, in stable patients.\textsuperscript{7,8}

Although direct thrombin inhibitors have several potential advantages over unfractionated heparin as the requisite antithrombin agent to accompany coronary stenting, with good dual antiplatelet therapy, heparin alone is almost always adequate to prevent complications\textsuperscript{9} and is cost effective.\textsuperscript{10} The situation with STEMI patients is perhaps less clear, with a recent post HEAT-PPCI (Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention) meta-analysis showing no difference between bivalirudin and heparin for the end points of death or myocardial infarction, but more stent thrombosis and less bleeding with bivalirudin.\textsuperscript{11} Although disputed by some,\textsuperscript{12} most operators use activated clotting time monitoring to assure satisfactory antithrombin effect (200-250 seconds for the commonly used HemoTec) (Medtronic, Dublin, Ireland system) (the Hemochron [Accriva, Piscataway, NJ] system measures 50 seconds longer),\textsuperscript{13} with higher levels for complex interventions (eg, acute coronary syndrome)\textsuperscript{14} or those requiring multiple guide wires in the same coronary artery.

**SIZING**

**Stent Length**

In general, stents should be chosen to cover the lesion, from (angiographic) “normal to normal” vessel. Assessing where “normal” begins and ends is sometimes challenging, and intravascular imaging can often be helpful. Stent
ends should not be deployed in areas of obvious plaque buildup, in vessel
bends, or ideally in sites compressing thin-capped plaque or areas of necrotic
debris (“lipid-rich plaque”). Subsequent studies have demonstrated that stents should also be deployed to cover the
length of artery traumatized by predilatation ballooning or atherectomy, so as to avoid the “geographic miss” found in the STLLR (Stent Deployment Techniques on Clinical Outcomes of Patients Treated With the Cypher Stent) study that doubled the risk of MACE (Fig. 29-1). For longer lesions, it is often difficult to anticipate the stent length needed. One can use the length of the radiopaque part of the coronary guide wire (30 mm for most) or the known length of the predilation balloon for a “ruler.”

![Figure 29-1](image)

**FIGURE 29-1** A total 1557 patients from 41 US hospitals with protocol-based careful angiographic technique were reviewed to assess the impact of geographic miss on patient outcomes. Longitudinal geographic miss (L-GM) was identified in 47.6% of patients and was associated with more than doubling of risk of target vessel revascularization at 1 year and any GM tripled the risk of MI within that time frame. GM, geographic miss; MI, myocardial infarction; TVR, target vessel revascularization.

**Diameter**
To a large extent, the degree of luminal late loss after stenting is related to biologic processes such as the presence of diabetes and not to the extent of stent expansion (within limits)\(^\text{17}\); hence, the general adage has become “bigger is better.” But how big is big enough? Studies from a decade or more ago reliably found that what appeared angiographically to be a very good stent result (<10% stenosis) not infrequently left the stent undersized, underexpanded, or both when viewed by intravascular ultrasound (IVUS).\(^\text{18}\) In addition, meta-analysis of the 7 moderate-sized randomized controlled trials of IVUS versus angiographic guidance for bare metal stent implantation found that IVUS modestly reduced restenosis\(^\text{19}\); hence, we rely a lot on IVUS findings to answer this question. Importantly, IVUS has shown that balloon postdilation at 14 to 16 atm for a nominally sized stent delivery balloon typically results in the stent achieving only about 75% of predicted (out of the body) diameter (Fig. 29-2).\(^\text{20}\) In the drug-eluting stent era, Hong et al\(^\text{21}\) found that the best IVUS cross-sectional area (CSA) cutoff value discriminating risk of restenosis or no restenosis was \(5.5 \text{ mm}^2\) (length also was a risk factor). However, the implications of achieving that value are not the same for a patient with a 2.25- or 3.5-mm diameter vessel and further leave the patient with an average rather than ideal risk of restenosis. Other criteria have been proposed, ranging from the classic but difficult to achieve MUSIC (Multicenter Ultrasound Stenting in Coronaries) criteria (complete stent apposition and CSA \(\geq 80\%\) of the average of proximal and distal “normal” reference areas\(^\text{22}\)), achieved in only about 60% of cases,\(^\text{23}\) and the easier to achieve \(\geq 55\%\) CSA of the reference segment proposed by Moussa et al.\(^\text{24}\)
FIGURE 29-2 Intravascular ultrasound (IVUS) data from comparing final stent diameter with manufacturer’s predicted stent diameter in patients with direct stenting, balloon predilation, and AngioSculpt predilation in whom Taxus (Boston Scientific, Marlborough, MA) or Cypher (Cordis, Hialeah, FL) stents were implanted. IVUS-based diameters are approximately 75% of “nominal.” Consider also that IVUS overestimates stent size by 10% to 15%. Very similar data can be found for most other coronary stents. (Reproduced with permission from Costa JR, Mintz GS, Carlier SG, et al. Nonrandomized comparison of coronary stenting under intravascular ultrasound guidance of direct stenting without predilation versus conventional predilation with a semi-compliant balloon versus predilation with a new scoring balloon. Am J Cardiol. 2007;100:812-817.)

IVUS studies have also linked poor stent expansion to risk of early stent thrombosis, finding, for instance, increased risk with failure to achieve 80% reference CSA or CSA <5 mm.25-27 Dimensions obtained via optical coherence tomography (OCT) are likely helpful in this regard, because they more closely reflect actual dimension compared with IVUS, which overestimates vessel diameter by 10% to 15%.

However, in the current era of cost containment, IVUS or OCT cannot be
justifiably used in all cases, so many advocate their use principally to clarify angiographic ambiguities, and evaluate pre- or poststent anatomy, and treated lesions that are at high risk of restenosis (diabetes, long lesions) or are anatomically high risk (left main stenosis).

Although perhaps not as well validated as one might like, we favor using angiographic step-up and step-down as a surrogate for adequate stent expansion, as initially put forward by Antonio Colombo’s group\textsuperscript{18} and, more recently, supported by work of Haldis et al.\textsuperscript{28} This approach has led to a 90\% likelihood of successful implant by MUSIC criteria, albeit with an increased risk of OCT-detected small edge dissections.\textsuperscript{29}

**PRETREATMENT: LESION MODIFICATION/DEBULKING**

The role of predilatation/pretreatment before stenting should be to both allow stent delivery and also full expansion, without extending the treatment area via dissection or slippage. Balloon inflation, sized at 0.25 to 0.50 mm less than vessel diameter, usually suffices. Several devices other than plain old balloon angioplasty (POBA) have been proposed to improve the likelihood of achieving this goal, but all come with increased cost and hence should be used judiciously. Of these, perhaps the easiest to use is the AngioSculpt (Angioscore, Fremont, CA). Studies have shown greater stent expansion with pretreatment using this device compared with POBA (eg, 88\% vs 77\% of expected CSA in moderately complex lesions, irrespective of lesion morphology\textsuperscript{20}; Fig. 29-3). It should be noted that there were few heavily calcified lesions in this study, and we and others have encountered difficulties with the device in heavily calcified lesions, including device entrapment.\textsuperscript{30} The Cutting Balloon (Boston Scientific, Marlborough, MA) cuts more deeply and is less deliverable than the AngioSculpt, but in general, it has the same benefits and limitations. Both devices are particularly useful to prevent device slippage in the setting of in-stent restenosis (ISR) and for side branch treatment in conjunction with provisional stenting of bifurcation lesions.
FIGURE 29-3 Intravascular ultrasound (IVUS) data depicting percent nominal minimum stent diameter (MSD) achieved for Taxus or Cypher stents according to predilation strategy and IVUS morphology. (Reproduced with permission from Costa JR, Mintz GS, Carlier SG, et al. Nonrandomized comparison of coronary stenting under intravascular ultrasound guidance of direct stenting without predilation versus conventional predilation with a semi-compliant balloon versus predilation with a new scoring balloon. *Am J Cardiol.* 2007;100:812-817.)

More heavily calcified or difficult to cross lesions often require rotational atherectomy with the Rotablator (Boston Scientific) or Orbital Atherectomy Device (Cardiovascular Systems Inc [CSI], Saint Paul, MN) before stenting. An arc of calcium >180° by IVUS has been associated with poor stent expansion, but this may be hard to predict with angiography alone (suggested with somewhat limited sensitivity and specificity by angiographic calcium visible across the diameter using still frame imaging) and is more common in patients with renal insufficiency and in the elderly. A randomized trial comparing Rotablator (mean burr size, 1.5 mm) versus POBA in calcified lesions before drug-eluting stent implantation showed an increase in acute gain that was largely offset by more late loss and no difference in restenosis or stent thrombosis. However, because poor stent expansion is a risk factor for stent thrombosis and restenosis, atherectomy for lesions at risk
for poor stent expansion may be beneficial.

The CSI speed-expansive rotational atherectomy device competes with the older device, being simpler to set up and use and providing for generally more ablation, but with greater risk of vessel perforation (1.8% in the ORBIT-2 [Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions] study).\textsuperscript{34}

We will often resort to a trial of balloon inflation to 6 to 10 atm to see if the vessel “yields” if we are uncertain about the need for atherectomy. Although there is a small risk of creating a dissection without adequate vessel enlargement with this maneuver, atherectomy with the Rotablator seems to be safe in this setting.

A more complete discussion of the role of rotational atherectomy is provided in Chapter 34.

**ROLE OF DIRECT STENTING**

For moderately stenotic noncalcified lesions, direct stenting without predilatation or atherectomy has been advocated, largely as a time- and cost-saving approach (generally about 20% for both).\textsuperscript{35} A recent meta-analysis of randomized controlled trials evaluating this approach found a significant 20% to 25% reduction in periprocedural myocardial infarction or death, but no difference in late target vessel revascularization.\textsuperscript{36} The downsides to this approach are occasionally being unable to deliver the stent, potentially misjudging the length of the stent due to lack of the balloon marker “ruler,” and rarely, discovering a difficult-to-dilate lesion after the stent has been placed. Used judiciously, this approach appears to have merit.

**PROPER MANAGEMENT OF STENT EDGES**

Both failing to fully dilate the edges of a stent and dilating beyond the edges (“geographic miss”) are fairly common.\textsuperscript{5} To minimize risk of edge trauma, the delivery balloon should generally be inflated to only 10 to 14 atm (the low end for somewhat oversized stents). Higher pressure inflation risks “dog-
boning” and edge dissection, because the balloons on which contemporary stents are mounted are semi-compliant. Postdilatation is generally required unless angiographic step-up/step-down has already been achieved. Noncompliant balloons with a diameter approximately 0.25 mm larger than apparent vessel diameter should be used, inflated to nearly maximal pressure, for postdilatation. High-quality angiographic imaging (Stent Boost [Philips, Amsterdam, the Netherlands], or equivalent) should be used to assure that dilatation (outside edge of balloon marker) has extended to, but not beyond, the stent edge.

ROLES OF FRACTIONAL FLOW RESERVE, IVUS, OCT, AND INFRARED SPECTROSCOPY

The role of adjunctive imaging techniques is addressed in Chapter 26. Fractional flow reserve (FFR) has been shown in several setting to be highly useful in discerning which lesions require revascularization, but the optimal role of the 3 imaging modalities remains uncertain for routine and uncomplicated situations. We favor the use of IVUS for high-risk anatomic situations (eg, left main stenoses), for use in settings at high risk for restenosis (eg, long lesions, small but important vessels, diabetics), evaluation of the etiology of ISR, and in situations of ambiguous anatomy before or after PCI by angiography alone. OCT yields much better near-field resolution, often finds poststent luminal disruptions, and may be helpful in assessing which persistent dissections need further stents (Fig. 29-4). Infrared spectroscopy allows for identification of lipid-rich plaque, the placement of a stent into which leads to an increased risk of debris embolization.
FIGURE 29-4 A. Optical coherence tomography (OCT) image depicting measurement technique for dissection width. B. Relationship of risk of major adverse cardiac events (MACE) with dissection width as assessed by OCT.39

INFLOW AND OUTFLOW

Both inflow and outflow narrowing, variably defined, have been found to be associated with heightened risk of stent thrombosis, although they are generally less powerfully predictive than poor stent expansion, residual dissections, and slow flow.38 For example, using a definition of >40% plaque burden by IVUS, Alfonso and colleagues found inflow and or outflow narrowing in most of their stent thrombosis patients.40,41 Similarly, Fujii et al42 found reference vessel CSA <4 mm² by IVUS to be an independent measure of risk (67% of stent thrombosis cases vs 9% of controls).42 Some have also advocated poststent FFR <0.90 as an overall (stent plus adjacent vessel) correlate of MACE.43 Taken together and admitting the limitations of angiography, one should generally attempt to treat all “significant” narrowing
that might potentially impact stent-related blood flow.

**EMBOLIC PROTECTION**

Embolic protection is discussed in Chapter 62.

**PRIORITIZING AND ORDERING LESION TREATMENT**

The issue of optimally sequencing lesion treatment often arises when treating patients with multivessel disease. Generally, it is best to treat the most severe lesion in a major vessel first, so if the procedure has to be halted at that point, at least the worst of the ischemia should have been eliminated. There are at least 2 exceptions, however. First, if the most severe lesion is such that if it were to close for more than a short while hemodynamic instability would likely result and one could lessen that risk by treating another lesion, then the latter lesion should be treated first. Second (and this is less common with improving chronic total occlusion [CTO] results), if there is a CTO that, if unsuccessfully treated, would prompt referral for coronary artery bypass grafting, then the CTO should be attempted first. In general, the overall revascularization goal should be a physiologic SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score of <8.44

**DELIVERY ISSUES**

*Guide Catheters and Adjuncts*

A key to stent delivery is adequate guide catheter support. Various diameters (generally 5-8 Fr) and shapes are available for radial and femoral approaches, and detailed selection is somewhat beyond the scope of this chapter. Active (deep seating as necessary) support with 5- to 6-Fr catheters has generally superseded passive (catheter placed at or outside the coronary ostium only)
support as a means to decrease access site complications. Without deep seating, support is largely dependent on 3 factors: guide catheter diameter, coaxiality and fit into the coronary ostium, and support off the contralateral aortic wall as reflected by contact length and the cosine of the angle of engagement. We generally use 6-Fr catheters unless the lesion requires bulky equipment (eg, a 1.75-mm Rotablator burr or 2 stents are a very tight fit in a 0.71-inch 6-Fr guide catheter [any bending or kinking of the guide catheter may make device advancement impossible]). From the radial approach, we generally favor extra support/extra backup (XB/EBU) catheters for the left coronary artery (LCA). Right coronary access requires a greater variety of catheters to provide support for downward, horizontal, and upward takeoffs. Specialty radial catheters such as the Tiger and Ikari series are also often very useful. From the femoral approach, XB/EBU catheters generally supply adequate support for the LCA, but AL 1.5-2 catheters are sometimes required. JR4-5 or Amplatz AR1-2, ALR, or AL1 catheters are useful for right coronary artery lesions. A summary of radial guide catheter use from a relatively recent international registry is provided in Table 29-1. A useful tip when a right coronary guide catheter appears to be engaged and coaxial in the left anterior oblique view but is not providing adequate support is to check in the 30° right anterior oblique view to be sure it is “pointed at” the operator (unless the right coronary originates anteriorly). The availability of several “mother and child” devices such as the Guideliner catheter (Vascular Solutions, Minneapolis, MN) has greatly enhanced device delivery (Fig. 29-5). These can be placed over the coronary guide wire or drawn in over a (previously inflated) coronary balloon, fairly deeply into the coronary as long as proximal stenosis is absent. In challenging cases where the stent “hangs up” on rough/calcific plaque proximal to the target, often the Guideliner can be advanced across the lesion, with the stent brought forward and then “unsheathed” and deployed after the Guideliner is withdrawn proximally. It is important to remember, however, that use of this device reduces the internal diameter of the guide catheter by about 0.012 inch. An alternative approach that is less expensive but generally provides less support is to use a buddy wire in the target or adjacent coronary artery.

Table 29-1 Guide Catheter Use from Radial Approach
<table>
<thead>
<tr>
<th></th>
<th>All (%)</th>
<th>US (%)</th>
<th>Canada-Europe (%)</th>
</tr>
</thead>
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<td></td>
<td></td>
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</tr>
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<td>XB 3.0</td>
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<td>18.2</td>
<td>26.6</td>
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</tr>
<tr>
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<td>2.5</td>
<td>1.3</td>
</tr>
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<td>Tiger II</td>
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<td>0.5</td>
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<td>35.4</td>
<td>26.9</td>
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<td>7.9</td>
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<tr>
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<td></td>
<td></td>
</tr>
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<td>11.0</td>
</tr>
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</tr>
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</tr>
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<tr>
<td><strong>RCA</strong></td>
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<td>70.3</td>
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<tr>
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<td>7.6</td>
<td>5.4</td>
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<tr>
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<td>2.6</td>
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<tr>
<td>Kimny</td>
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<td>3.8</td>
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<tr>
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<td>7.5</td>
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<tr>
<td><strong>Left SVG</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left bypass graft</td>
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<td>16.5</td>
<td>21.0</td>
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<td><strong>Right SVG</strong></td>
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<tr>
<td>Left bypass graft</td>
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<td>3.1</td>
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<tr>
<td>Other</td>
<td>6.9</td>
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<td>4.6</td>
</tr>
</tbody>
</table>
Figure 29-5 Forty-year-old woman initially with spontaneous coronary dissection, with focal in-stent restenosis (ISR) at site of stent fracture among 3 layers of drug-eluting stent (DES). A. Right anterior oblique (RAO) projection showing obtuse margin stents with bend in systole, likely fracture, and stenosis (7-Fr AL1 guide catheter). B. As in panel A, in diastole. C. Left anterior oblique (LAO) projection, systole. D. LAO projection, diastole. E. RAO, Guideliner advanced into obtuse margin for support. F. RAO, final result after placement of 3.0 × 32 mm DES.

67 year old male with renal insufficiency and calcified proximal and mid right coronary artery stenosis. G. LAO projection showing multiple right coronary artery (RCA) stenoses. H. LAO projection, 1.75-mm Rotablator. Guide catheter is 7-Fr JR4. I. LAO projection, post-Rotablator result. J. Guideliner advanced to allow 3.0 × 33 mm DES placement. K. Final result.

Guide Wires

Guide wire use is reviewed in detail in Chapter 27. Specific to stent delivery, however, “workhorse” wires such as the Prowater (Abbott Vascular, Santa Clara, CA), Runthrough (Terumo, Somerset, NJ), BMW (Abbott), or Sion Blue (Abbott) generally provide sufficient support. Stiffer wires (eg, Grand Slam [Abbott], others) are sometimes needed to deliver stents distally or through areas of tortuosity, but it must be recalled that they also may cause “wire bias,” forcing the stent into the inner curvature of the artery. When that aspect of the vessel is roughened or calcified, this may actually impair stent delivery.

Completion Angiography

After stent implantation and postdilatation, angiography should be performed in 2 (nearly) orthogonal views, specifically looking for guide catheter trauma (common if the guide catheter jumped forward when initially engaging the coronary or was pulled forward during the removal of stiff or partially engaged equipment), stent expansion and edge trauma, and guide wire trauma (eg, perforation, particularly with hydrophilic guide wires). The guide wire should have been removed at least prior to the last injection so as not to be fooled by missing a dissection that had been “propped open” by the guide wire. Angiography should also be somewhat prolonged so as to allow inspection of sites where the guide wire tip might have caused an occult...
perforation. Management of complications occurring before or noted with completion of angiography is covered elsewhere in this text. However, it is important to note that the operator must remain vigilant and the catheter lab must be equipped with covered stents, coils, injectable thrombin, and pericardiocentesis equipment to manage the occasional tamponade, with intra-aortic balloon pump and Impella (Abiomed, Danvers, MA) support devices for hemodynamic compromise, as well as a wide variety of coronary stents, fibrinolytics, and intravenous antiplatelet agents to manage more common dissection- and thrombus-related complications. Finally, plans to rapidly activate the surgical team must always be in place.

OTHER IMPORTANT ISSUES

Prevention of radiation-related complications is dealt with in Chapter 11, and prevention of contrast-induced nephropathy is discussed in Chapter 19. Treatment of especially complex anatomy and management of PCI-related complications are discussed in Chapters 37 to 42.

REFERENCES


15. Uetani T, Amano T, Ando H, et al. The correlation between lipid volumes in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in


**MULTIPLE CHOICE QUESTIONS**

1. When used for pretreatment before stenting, how does use of the AngioSculpt compare to balloon angioplasty?
   A. With comparable-sized devices, resultant cross-sectional areas (CSAs) are similar.
   B. With comparable-sized devices, cross-sectional area is greater with AngioSculpt regardless of lesion complexity.
   C. With comparable-sized devices, results with AngioSculpt are better in calcified or long lesions, but not other lesions.
   D. When used with comparable-sized devices, high-pressure balloon angioplasty generally results in larger CSA than AngioSculpt.

2. After inflation to 16 atm with typical balloons, what is the average ratio of in vivo versus ex vivo minimum lumen diameter?
   A. 0.75
   B. 0.85
   C. 0.95
   D. 1.00

3. To minimize the risk of DES restenosis using IVUS, what is the best approach to follow?
   A. Attempt to achieve minimal in-stent cross sectional area of >5.5 mm² for all stents.
   B. Attempt to achieve minimal in-stent cross sectional area of >5.5 in vessels with reference diameters 2.25-3.00 mm.
   C. Attempt to achieve in-stent cross sectional area of >80% of adjacent normal reference segments.

4. Which of the following imaging modalities most closely approximates in-vivo vessel dimensions?
   A. QCA
B. IVUS
C. OCT
D. CTA

5. Which of the following is least closely related to the risk of stent thrombosis?
   A. Outflow narrowing.
   B. Poor stent expansion.
   C. Residual dissection.
   D. Slow flow.

**ANSWERS**

1. B (see reference 20)

2. A (see reference 20)

3. C

4. C

5. A (see reference 38)
Drug-Eluting Coronary Stents

Arie Steinvil
Ron Waksman

INTRODUCTION

Several major leaps in technology and immense research and development have led to the current wide use of drug-eluting stents (DES). Stents were initially developed to reduce the high rates of restenosis and acute vessel closure following balloon angioplasty–induced endothelial cell denudation and coronary artery medial layer tearing. The first bare metal stent (BMS) implantation in a coronary artery was reported by Sigwart et al in 1987, and the first randomized trial comparing balloon angioplasty and BMS was reported by Fischman et al in 1994. As compared to balloon angioplasty, BMS implantation was associated with an improved rate of procedural success, a lower rate of angiographically detected restenosis, similar rates of clinical events after 6 months, and a less frequent need for target vessel revascularization (TVR). These results eventually led to the use of BMS as the standard of care for the treatment of de novo coronary stenosis. The use of BMS, however, was associated with a high incidence of in-stent restenosis (ISR) mainly due to intimal hyperplasia. The high ISR rates in BMS eventually led to the idea of coating the BMS with antiproliferative agents. Therefore, the primary purpose of DES has been the prevention of vessel recoil, negative remodeling, and ISR. First introduced in 2002, first-generation DES have been shown to be superior to BMS with respect to lower rates of clinical and angiographic restenosis and target lesion
revascularizations (TLR) as compared to BMS.\textsuperscript{5,6} However, following real-world experience, concerns regarding high rates of late stent thrombosis (ST) have emerged,\textsuperscript{7} leading to a change in the recommendations for dual antiplatelet therapy following DES implantation.\textsuperscript{8} The vast research and development leading to a newer generations of DES, better understanding of the mechanisms of ST, and advances in technology, technique, adjunctive pharmacology, and operator experience have resulted in improved outcomes and the widespread use of DES. This eventually lead to the fact that the vast majority of stents being implanted during percutaneous coronary intervention (PCI) in the United States are DES\textsuperscript{9} as well as to the wide endorsement for the use of these stents in US and European clinical guidelines.\textsuperscript{10,11}

**DRUG-ELUTING STENT STRUCTURE**

The basic structure of DES includes a metallic strut platform, a polymer, and the drug. Due to the concept of persistent arterial wall inflammation attributed to the polymer and the risk for ST, novel DES designs have been introduced and include the biodegradable polymer and polymer-free DES,\textsuperscript{12} discussed later, and the bioresorbable vascular scaffold systems.\textsuperscript{13} A design summary for the first- and second-generation DES available in the United States for clinical use as well as newer platforms with bioresorbable polymer and polymer-free DES are presented in Table 30-1 and Figures 30-1 and 30-2.

**Table 30-1** Basic Structure of Selected Drug-Eluting Stents, Bioabsorbable Polymer Drug-Eluting Stents, and Polymer-Free Stents
<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Brand Name</th>
<th>Alloy</th>
<th>Drug Eluted</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-generation durable polymer drug-eluting stents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cypher</td>
<td>Stainless</td>
<td>Siroliimus</td>
<td>PEVA and PBMA</td>
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<tr>
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<td>Stainless</td>
<td>Paclitaxel</td>
<td>Triblock polymer matrix</td>
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<tr>
<td><strong>Second-generation durable polymer drug-eluting stents</strong></td>
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<td>Endeavour</td>
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Abbreviations: PBMA, poly n-butyl methacrylate; PEVA, poly-ethylene-co-vinyl acetate.

**FIGURE 30-2** Drug-eluting stents with durable or biodegradable polymer coatings. BES, Biolimus-eluting stent; CoCr, cobalt chromium; EES, everolimus-eluting stent; PLLA, poly-L-lactic acid; PtCr, platinum chromium; SES, sirolimus-eluting stent;
**Stent Platform**

Drug-eluting stents were initially constructed on a stainless steel platform due to their mechanical radial force properties and corrosion resistance. However, these stainless steel stents contained and released nickel, chromate, or molybdenum ions, causing a local inflammatory response leading to ISR. Currently, most second-generation DES are built on a cobalt-chromium platform, which exhibits superior radial strength with remarkably thinner struts (~80 μm) and improves deliverability. Some novel DES are constructed on a platinum-chromium platform. A meta-analysis has shown that compared with BMS, the use of cobalt-chromium everolimus-eluting stents (EES) improves global cardiovascular outcomes, including cardiac survival, myocardial infarction, and overall ST. Novel structural designs feature thinner struts and less metal, offering increased flexibility and deliverability, and thus, they are both more efficacious and safer.

Currently, all available DESs are balloon expandable. Symmetric expansion of stents with homogeneous distribution of struts is required for optimal drug delivery. Stent design can be either a closed- or open-cell configuration. A closed-cell stent design has a uniform cell expansion and constant cell spacing when deployed in a curved vessel, which gives uniform drug distribution. An open-cell design has variation in the surface coverage between inner and outer curvatures in the curved vessel but has better conformability to a curved surface at the expense of less uniform distribution. Current second-generation DESs are based on an open-cell design to minimize strut deformation after deployment while maintaining conformability, radial support, and flexibility.

**Stent Polymers**

Stent polymers are large compounds that carry the drug and control the kinetics of its elution. Both first- and second-generation DESs use durable polymers (see Table 30-1). First-generation DESs, compared to second-generation DESs, have thicker and more durable polymers that control the
release of sirolimus and paclitaxel. The durable polymers used in first-generation DESs have been associated with nonuniform coating, resulting in erratic drug distribution. In addition, they have been associated with perpetuating local vascular inflammatory reaction and potentially inducing the occurrence of late and very late ST.\textsuperscript{18} Therefore, the ideal DES would entirely inhibit restenosis while at the same time promote vascular healing with minimal risk of thrombus formation. DESs have evolved on this premise, initially with thinner polymers to enhance biocompatibility to fully bioabsorbable polymers and scaffolds to eliminate hypersensitivity reactions and local inflammatory response.

**Drug Coating of DES**

The antiproliferative agents that are used for the platforms of DESs are molecules that are distributed into the arterial wall and exert either immunosuppressive effects (inhibitors of mammalian target of rapamycin [mTOR]) or antiproliferative effects (paclitaxel) on smooth muscle cells. Paclitaxel and the “limus” drugs (eg, sirolimus, everolimus, zotarolimus, umirolimus) are lipophilic agents. In general, the degree of lipophilicity is higher with newer generations of DES. Eventually these substances inhibit migration and proliferation of vascular smooth muscle cells (VSMC). However, their mode of action is different.\textsuperscript{19} The limus drugs intracellularly bind to the FK-binding protein 12 (FKBP12) prior to blocking the mTOR pathway and ultimately interrupting the cell cycle. The inhibition of mTOR prevents the degradation of p27kip1, a cyclin-dependent kinase inhibitor that plays an important role in regulating VSMC migration and proliferation. More pertinent to the process of arterial healing, sirolimus is also a potent inhibitor of endothelial cell proliferation by deactivating the p70 S6 kinase pathway, an essential step for cell cycle progression in response to growth factors. Paclitaxel binds to microtubules and stabilizes their structure by shifting the dynamic equilibrium between soluble and insoluble tubulin, thereby enhancing microtubule assembly, resulting in inhibition of cellular replication. Most antimitotic agents used in DES are bonded to a matrix polymer, which acts as a reservoir to ensure drug retention during deployment and uniform distribution on the stent. The type of polymer will determine the drug-eluting kinetics.
CELLULAR RESPONSE TO DRUG-ELUTING STENT DEPLOYMENT

The cellular and molecular response to vascular injury is direct repair and vascular healing. However, dysregulation of these responses can result in adverse arterial remodeling, neointimal proliferation, and restenosis. The cellular cascade response to mechanical vascular injury initiated immediately after PCI can be divided into 3 different time phases: (1) an early phase consisting of platelet activation and inflammation, (2) an intermediate phase of granulation tissue corresponding to smooth muscle cell migration and proliferation, and (3) a late phase of tissue remodeling. During the early phase, the endothelium undergoes denudation, reendothelialization, and the formation of neoendothelium. After this early phase, endothelial cells proliferate and migrate over the injured areas, while smooth muscle cells and macrophages replace the fibrin clot with granulation tissue. The smooth muscle cells secrete proteoglycans that interact and stabilize the fibrin-rich extracellular matrix. This allows more smooth muscle cells to bind and proliferate while trapping inflammatory cells, which release matrix metalloproteinases that digest proteoglycans and hyaluronan. Ultimately, a more permanent matrix from collagen type I and III production occurs, allowing the wound to completely heal with eventual fibrosis.

The inhibition of intimal hyperplasia of the DES disrupts the physiologic arterial healing of the vessel wall, limiting endothelial coverage of all stent struts (Fig. 30-3). Their antiproliferative effect and the persistence of stent components have been shown to lead to chronic inflammation and impaired arterial healing, with the attendant risk of thrombotic events. The understanding of the pathophysiology of late ST of the first-generation polymer-based sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES) has been derived from animal and human pathologic samples taken after implantation of these devices. The data indicate that both of these first-generation DESs cause substantial impairment in arterial healing characterized by lack of complete reendothelialization and persistence of fibrin when compared with BMS. This delayed healing was the primary substrate underlying all cases of late DES thrombosis at autopsy. However, additional barriers to physiologic healing and late ST have been described, such as penetration of necrotic core, stent malapposition, overlapping stent
placement, excessive stent length, and bifurcation lesions. Second-generation DESs covered with everolimus (EES) and zotarolimus (zotarolimus-eluting stent [ZES]) have shown improved endothelial coverage following implantation with the use of sequential optical coherence tomography (OCT). With OCT, both ZES and EES showed comparable neointimal thickness and low rates of uncovered stent struts (3%) at 9 months after stent implantation.

![Imagery of vascular response to durable stent polymers]

**FIGURE 30-3** Vascular response to durable stent polymers. The images show (*from left to right*) focal inflammation with eosinophils at 4 months after drug-eluting stent (DES) implantation; chronic inflammation with giant cells secondary to polymer delamination at 3 months after implantation; foamy macrophage accumulation indicating neoatherosclerosis at 6 months after implantation; and antemortem slide demonstrating a 6-month late stent thrombosis event in an everolimus-eluting stent implanted within a paclitaxel-eluting DES. (Slides used with permission from Renu Virmani, MD.)

**FIRST-GENERATION DRUG-ELUTING STENTS**

The Cypher SES (Cordis Medical, Fremont, CA) and the TAXUS PES (Boston Scientific, Marlborough, MA) were the first US Food and Drug Administration (FDA)-approved DESs. Their major pivotal trials are summarized in **Table 30-2**.

**Table 30-2  Selected First-Generation Drug-Eluting Stent Trials**
The Cypher (Cordis) SES uses a stainless steel platform and poly(ethylene-covinyl acetate) (PEVA) and poly(n-butyl methacrylate) (PBMA) as the polymer that carries the drug. The SES was the first FDA-approved DES in the United States. The RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) trial was the first randomized comparison of an SES with a standard BMS. At 6 months, the degree of neointimal proliferation, manifested as the mean (± standard deviation [SD]) late luminal loss, was significantly lower in the SES group (–0.01 ± 0.33 mm) than in the BMS group (0.80 ± 0.53 mm; \( P < .001 \)). None of the patients in the SES group, as compared with 26.6% of the BMS group, had restenosis of 50% of the luminal diameter (\( P < .001 \)). There were no episodes of ST. The overall rate of major adverse cardiac events (MACE) was substantially reduced in the SES group versus the BMS group (5.8% vs 28.8%; \( P < .001 \)). This difference was driven by a higher rate of TVR in the BMS group. Five-year follow-up of the RAVEL cohort showed 1-, 3-, and 5-year rates of survival free from TLR of 99.2%, 93.8%, and 89.7% in the SES group versus 75.9%, 75.0%, and 74.0% in the BMS group, respectively (log-rank \( P < .001 \)). Rates of all MACE at 5 years were 25.8% in patients treated with SES versus 35.2% in patients assigned to BMS (log-rank \( P = .03 \)).

### Sirolimus-Eluting Stent

The Cypher (Cordis) SES uses a stainless steel platform and poly(ethylene-covinyl acetate) (PEVA) and poly(n-butyl methacrylate) (PBMA) as the polymer that carries the drug. The SES was the first FDA-approved DES in the United States. The RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) trial was the first randomized comparison of an SES with a standard BMS. At 6 months, the degree of neointimal proliferation, manifested as the mean (± standard deviation [SD]) late luminal loss, was significantly lower in the SES group (–0.01 ± 0.33 mm) than in the BMS group (0.80 ± 0.53 mm; \( P < .001 \)). None of the patients in the SES group, as compared with 26.6% of the BMS group, had restenosis of 50% of the luminal diameter (\( P < .001 \)). There were no episodes of ST. The overall rate of major adverse cardiac events (MACE) was substantially reduced in the SES group versus the BMS group (5.8% vs 28.8%; \( P < .001 \)). This difference was driven by a higher rate of TVR in the BMS group. Five-year follow-up of the RAVEL cohort showed 1-, 3-, and 5-year rates of survival free from TLR of 99.2%, 93.8%, and 89.7% in the SES group versus 75.9%, 75.0%, and 74.0% in the BMS group, respectively (log-rank \( P < .001 \)). Rates of all MACE at 5 years were 25.8% in patients treated with SES versus 35.2% in patients assigned to BMS (log-rank \( P = .03 \)).
Additional long-term data were provided by the SIRIUS (Sirolimus-Eluting Stent In Coronary Lesions) family of trials (see Table 30-2) and the SIRIUS extension data\(^{25}\) showing that at 5 years TLR rates were 9.4% versus 24% for SES versus BMS (\(P < .001\)) and target vessel failure (TVF) rates were 22.5% versus 33.5% (\(P < .001\)).

Increased interest in SES and BMS comparisons led to the evaluation and safety of SES in subgroups of patients at higher risk of restenosis. The C-SIRUS trial\(^{26}\) described that in patients with long lesions in small vessels at higher risk of restenosis the SES significantly reduces angiographic restenosis (2.3% vs 52.3%; \(P < .001\)) and TLR (4% vs 18%; \(P = .05\)). The Italian DESSERT study\(^{27}\) and the German SCORPIUS study\(^{28}\) showed that SES significantly decreases restenosis rates in diabetic patients compared to BMS. However, use of the SES in the setting of ST-segment elevation myocardial infarction examined in the MISSION trial\(^{29}\) failed to demonstrate superiority of SES as compared to BMS. In that trial, survival rates were comparable between SES and BMS groups (94.3% vs 92.8%, respectively; \(P = .57\)), as were the rates of repeat myocardial infarction (10.6% vs 13.7%; \(P = .40\)), freedom from death or myocardial infarction (84.4% vs 79.8%, \(P = .29\)), and TVF (14.9% vs 21.7%; \(P = .11\)). Likewise, rates of overall ST (5.4% vs 2.7%; \(P = .28\)) and very late ST (4.1% vs 0.7%; \(P = .07\)) did not significantly differ between the SES and BMS groups.

**Paclitaxel-Eluting Stent**

The TAXUS Liberté (Boston Scientific) PES was approved a few months after the Cypher SES. The family group of trials comparing this PES to BMS were the TAXUS I through TAXUS VI trials.\(^{6,30,31}\) The TAXUS IV trial\(^{32}\) led to the final FDA approval of the DES. In the TAXUS IV trial, 1314 patients were prospectively randomized to PES or BMS. The PES reduced the 12-month rates of TLR by 73% (4.4% vs 15.1%; \(P < .0001\)), TVR by 62% (7.1% vs 17.1%; \(P < .0001\)), TVF by 52% (10.0% vs 19.4%; \(P < .0001\)), and composite MACE by 49% (10.8% vs 20.0%; \(P < .0001\)). The 1-year rates of cardiac death (1.4% vs 1.3%), myocardial infarction (3.5% vs 4.7%), and ST (0.6% vs 0.8%) were similar between the PES and BMS groups. Long-term follow-up data from the TAXUS IV trial\(^{31}\) also showed that compared with BMS, the significant reduction of TVR with PES was maintained.
through 5 years (27.4% vs 16.9%; \( P < .0001 \)). Similar patterns were observed for the composite MACE (32.8% BMS vs 24.0% PES; \( P = .0001 \) at 5 years). ST was comparable as well at 5 years (2.1% BMS vs 2.2% PES; \( P = .87 \)). The overall revascularization benefits of PES were consistent across multiple subgroups, including gender, diabetes, left anterior descending artery lesion location, reference vessel diameter, lesion length, and multiple stents.

**Safety Concerns of First-Generation DES**

A concern that first-generation DESs may cause pronounced endothelial dysfunction because of delayed endothelialization has been raised.\(^{33}\) Comparisons between SES and BMS suggest that endothelial function is significantly impaired with SES, especially distal to the stent.\(^{34,35}\) In addition, first-generation DESs historically had slight increased risk of ST. Many large meta-analyses have addressed the differences in the rates of ST and clinical outcomes between SES and PES versus BMS. The largest one to date was published in 2007 by Stettler and colleagues\(^{36}\) and included 38 trials (18,023 patients) with a follow-up of up to 4 years. That analysis reported no mortality or ST differences between the 3 groups and that SES was associated with the lowest risk of myocardial infarction. However, the risk of late definite ST (>30 days) was increased with PES. The reduction in TLR was more pronounced with the SES than with the PES. Similarly another meta-analysis on 33 randomized controlled trials involving 31,379 patients compared first-generation to second-generation DESs.\(^{37}\) In that report, similar to the comparison with BMS, no differences in mortality among devices were found. In the overall class comparison, second-generation DESs were associated with a 22% reduction of odds of myocardial infarction; EES reduced the odds of definite/probable ST compared with PES; and first-generation SES along with second-generation EES and ZES showed similar efficacy in decreasing the odds of repeat revascularization. Overall, therefore, it seems that second-generation DESs offer similar levels of efficacy compared with first-generation DESs; however, second-generation DESs may be much safer than the first-generation DESs.

**SECOND-GENERATION DRUG-**
ELUTING STENTS

Zotarolimus-Eluting Stent

Zotarolimus is a derivative of sirolimus with a similar mechanism of action. The Endeavor ZES (E-ZES; Medtronic Cardiovascular, Santa Rosa, CA) was evaluated in the ENDEAVOR trials and was compared to BMS and first-generation DES. In the ENDEAVOR II trial, 1197 patients treated for single coronary artery stenosis were randomized to E-ZES versus BMS. As compared to BMS, almost all outcomes measures were reduced by the E-ZES, including the primary end point of TVF at 9 months (15.1% vs 7.9%; \( P = .0001 \)), MACE (14.4% vs 7.3%; \( P = .0001 \)), and TLR (11.8% vs 4.6%; \( P = .0001 \)). The rate of ST was 0.5% with the E-ZES, which was not significantly different from the rate of 1.2% with the BMS. In 531 patients submitted to angiographic follow-up, late loss was reduced from 1.03 ± 0.58 to 0.61 ± 0.46 (\( P < .001 \)) in stent and from 0.72 ± 0.61 to 0.36 ± 0.46 (\( P < .001 \)) in segment. The rate of in-segment restenosis was reduced from 35.0% to 13.2% with the E-ZES. Differences in clinical outcome were maintained at 12 and 24 months (\( P < .0001 \)).

The E-ZES was compared to SES in the ENDEAVOR III and SORT-OUT III trials. The ENDEAVOR III was a multicenter 3:1 randomized trial conducted to evaluate the safety and efficacy of E-ZES (n = 323) relative to SES (n = 113) in 436 patients undergoing elective PCI. The primary end point of 8-month angiographic in-segment late lumen loss was significantly higher among patients treated with E-ZES compared with SES (0.34 ± 0.44 mm vs 0.13 ± 0.32 mm, respectively; \( P < .001 \)). In-hospital MACE was significantly lower among patients treated with E-ZES (0.6% vs 3.5%; \( P = .04 \)). TLR rates at 9 months were 9.8% and 3.5% for the E-ZES and SES groups, respectively (\( P = .04 \)). However, the results for clinically driven TLR (6.3% vs 3.5%; \( P = .34 \)) and TVF (12.0% vs 11.5%; \( P = 1.0 \)) did not differ significantly for E-ZES and SES, respectively. Similarly, the SORT-OUT III trial randomized 2332 patients to E-ZES (n = 1162) or SES (n = 1170). In that trial, the E-ZES underperformed when compared to SES. At 3-year follow-up, the MACE rate was higher in patients treated with the E-ZES than in patients treated with SES (12.9% vs 10.1%; \( P = .022 \)). TVR was more frequent in the E-ZES group compared with the SES group (9.1% vs 6.7%; \( P = .0001 \)).
= .025), whereas the occurrence of myocardial infarction (3.8% vs 3.3%) and cardiac death (2.8% vs 2.8%) did not differ significantly. Although the rate of definite ST was similar at 3-year follow-up (1.1% vs 1.4%), very late (12 to 36 months) definite ST occurred in no patients (0%) in the E-ZES group versus 12 patients (1.1%) in the SES group ($P = .0005$). In addition, 5-year long-term follow-up registry data have shown significant differences in cardiac death, myocardial infarction, and composite end points favoring treatment with E-ZES over the comparators BMS and DES.\(^{41}\) In that report, the rates of clinical restenosis and safety events, including ST beyond the first year of revascularization, remained stable with E-ZES, leading to significant differences compared with first-generation DES.

The discouraging clinical results from previous trials as compared to first-generation SESs have led to the development of a newer zotarolimus-coated DES, the Resolute ZES (R-ZES; Medtronic Cardiovascular). Tada et al\(^ {42}\) have compared the R-ZES versus the E-ZES in 1000 patients who were enrolled in the ISAR-TEST 2 and ISAR-TEST 5 trials. His results have suggested that the R-ZES as compared to the E-ZES displayed overall superior antirestenotic efficacy with TLR rates of 12% versus 16% at 2 years ($P = .052$). Both devices were associated with a similar low risk of adverse safety events through 2 years. In a randomized trial including 2292 patients,\(^ {43}\) the R-ZES was compared with the Xience EES (X-EES; Abbott Vascular, Santa Clara, CA). The R-ZES was found to be noninferior to X-EES for the primary outcome of cardiac death, myocardial infarction, or TLR (8.2% vs 8.3%; $P$ for noninferiority = .001) or the rate of ISR (21.65% vs 19.76%; $P$ for noninferiority = .04). The R-ZES had a similar ST rate as the X-EES (2.3% vs 1.5%; $P = .17$). In longer follow-up experience from the RESOLUTE All-Comers trial,\(^ {44}\) R-ZES ($n = 1140$) and X-EES ($n = 1152$) demonstrated similar safety and efficacy throughout 4 years. At 4 years, the rates of target lesion failure (TLF; 15.2% vs 14.6%; $P = .68$), cardiac death (5.4% vs 4.7%; $P = .44$), target vessel myocardial infarction (5.3% vs 5.4%; $P = 1.00$), clinically indicated TLR (7.0% vs 6.5%; $P = .62$), and definite/probable ST (2.3% vs 1.6%; $P = .23$) were similar in the R-ZES and X-EES arms. Table 30-3 shows a comparison of the outcomes of the key trials examining the safety and efficacy of the E-ZES and R-ZES as well as EES.

Table 30-3 Selected Second-Generation Drug-Eluting Stent Trials

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\(^{41}\) A. Ahmad, F. Steinhubl, L. Wang, et al. 2015. \(^{42}\) Tada et al. 2015. \(^{43}\) Tada et al. 2015. \(^{44}\) Tada et al. 2017.
The new-generation Resolute Onyx (RO-ZES; Medtronic Cardiovascular) DES was built on the clinical performance and deliverability of the R-ZES and features CoreWire Technology that allows it to have a denser core metal surrounded by a cobalt alloy outer layer. The CoreWire Technology builds on the R-ZES’ continuous sinusoid technology (CST), a method of stent manufacturing first introduced with the R-ZES, which molds one single strand of wire into a sinusoidal wave enabling a continuous range of motion. This technology enables the stent to have better radiopacity during the procedure and have thinner struts and improves deliverability without compromising radial and longitudinal strength. Safety and efficacy studies of the RO-ZES for lesions under 2.0 mm and between 2.25 and 4.0 mm have been launched in 2015 (ClinicalTrials.gov identifiers: NCT02412501, NCT02419521).

### Everolimus-Eluting Stent

The X-EES is built on a cobalt-chromium platform, whereas the PROMUS Element and the PROMUS Premier EES (P-EES; Boston Scientific) are novel EESs built on a platinum-chromium platform.

<table>
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<th>Trial Name</th>
<th>Year</th>
<th>Population</th>
<th>Maximal Follow-Up</th>
<th>Stent Groups</th>
<th>TLR (%)</th>
<th>MACE (%)</th>
<th>ST (%)</th>
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<td>Endeavour II</td>
<td>2006</td>
<td>Stable de novo lesions</td>
<td>9 months</td>
<td>E-ZES (n = 598), BMS (n = 599)</td>
<td>4.6 vs 11.8 (P = .0001)</td>
<td>7.3 vs 14.4 (P = .0001)</td>
<td>0.5 vs 1.2 (P = .22)</td>
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<td>2011</td>
<td>Stable de novo lesions</td>
<td>5 years</td>
<td>E-ZES (n = 323), SES (n = 113)</td>
<td>8.1 vs 6.5 (P = .68)</td>
<td>14 vs 22 (P = .05)</td>
<td>0.7 vs 0.9 (P = 1.0)</td>
</tr>
<tr>
<td>Endeavour IV</td>
<td>2013</td>
<td>Stable de novo lesions</td>
<td>5 years</td>
<td>E-ZES (n = 722), PES (n = 718)</td>
<td>7.8 vs 8.4 (P = .69)</td>
<td>17.9 vs 20.3 (P = .25)</td>
<td>4.6 vs 4.6 (P = 1.0)</td>
</tr>
<tr>
<td>SORT-OUT III</td>
<td>2012</td>
<td>All comers</td>
<td>3 years</td>
<td>E-ZES (n = 1162), SES (n = 1170)</td>
<td>6.8 vs 3.9 (P = .001)</td>
<td>12.9 vs 10.1 (P = .02)</td>
<td>1.1 vs 1.4 (P = .61)</td>
</tr>
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<td>ZEST</td>
<td>2010</td>
<td>Stable de novo lesions</td>
<td>12 months</td>
<td>E-ZES (n = 883), SES (n = 878), PES (n = 884)</td>
<td>4.9 vs 1.4 vs 7.5 (P &lt; .001)</td>
<td>10.2 vs 8.3 (P = .001)</td>
<td>0.7 vs 0 vs 0.8 (P = .22)</td>
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<td>RESOLUTE All Comers</td>
<td>2011</td>
<td>All comers</td>
<td>2 years</td>
<td>R-ZES (n = 1140), EES (n = 1152)</td>
<td>10 vs 9.1 (P = .51)</td>
<td>12.5 vs 12.9 (P = .75)</td>
<td>1.9 vs 1 (P = .07)</td>
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<td>Tada et al</td>
<td>2013</td>
<td>Stable de novo lesions</td>
<td>2 years</td>
<td>R-ZES (n = 1000), E-ZES (n = 339)</td>
<td>12 vs 16 (P = .052)</td>
<td>5.5 vs 4.8 (P = .62)</td>
<td>0.4 vs 0.6 (P = .66)</td>
</tr>
</tbody>
</table>

**Everolimus Stent Trials**

**SPIRIT II** 2009 Stable de novo lesions 3 years EES (n = 223), PES (n = 77) 3.1 vs 7.2 (P = .16) 7.2 vs 15.9 (P = .05) 1 vs 2.9 (P = .28)

**SPIRIT III** 2011 Stable and unstable angina 3 years EES (n = 293), PES (n = 141) 4 vs 7.7 (P = .15) 4.9 vs 12.4 (P = .009) 0.7 vs 0 (P = NS)

**SPIRIT IV** 2011 Stable de novo lesions 2 years EES (n = 2450), PES (n = 1229) 4.5 vs 6.9 (P = .004) 7.1 vs 10.1 (P = .003) 0.42 vs 1.23 (P = .008)

**COMPARE** 2010 Stable de novo lesions 12 months EES (n = 897), PES (n = 903) 2 vs 5 (P = .0002) 6 vs 9 (P = .02) 0.7 vs 3 (P = .002)

**EXCELLENT** 2011 Stable de novo lesions 12 months EES (n = 1070), SES (n = 364) 2.4 vs 1.6 (P = .39) 2 vs 2.4 (P = .06) 0.3 vs 0 (P = .38)

**PLATINUM** 2011 Stable de novo lesions 12 months X-EES (n = 762), P-EES (n = 768) 1.9 vs 1.9 (P = .96) 4.9 vs 5.0 (P = .07) 0.4 vs 0.4 (P = .1)

**EES vs R-ZES**

**DUTCH PEERS** 2013 All comers 12 months R-ZES (n = 900), EES (n = 905) 3 vs 3 (P = .77) 5 vs 6 (P = .15) 0.7 vs 0.3 (P = .34)

**HOST-ASSURE** 2014 All comers 12 months R-ZES (n = 1252), EES (n = 2503) 1.2 vs 1.2 (P = .9) 5.4 vs 4.3 (P = .187) 0.4 vs 0.7 (P = .22)

**Abbreviations:** BMS, bare metal stent; EES, everolimus-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent; MACE, major adverse cardiac events; NS, not significant; P-EES, PROMUS Premier everolimus-eluting stent; PES, paclitaxel-eluting stent; R-ZES, Resolute zotarolimus-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; TLR, target lesion revascularization; X-EES, Xience everolimus-eluting stent.
The X-EES was studied in the SPIRIT family of trials. In SPIRIT IV, 3687 patients were randomized to X-EES versus PES. X-EES was superior to PES in the primary end point of TLF (4.2% vs 6.8%; \( P = .001 \)), as well as in the major secondary end point of the 1-year rate of ischemia-driven TLR (\( P = .001 \)), and was noninferior with respect to the major secondary end point of the 1-year composite rate of cardiac death or target vessel myocardial infarction. The 1-year rates of myocardial infarction and ST were also lower with X-EES than with PES (1.9% vs 3.1%, \( P = .02 \) for myocardial infarction; 0.17% vs 0.85%, \( P = .004 \) for ST). Similar results were seen in the meta-analysis of the final 3-year results from the SPIRIT II, III, and IV clinical trials. In that report, patient data from 4989 patients who were prospectively randomized to treatment with X-EES (n = 3350) or PES (n = 1639) were pooled for analysis. In this large data set with 3-year follow-up, coronary implantation of X-EES compared with PES resulted in reduced rates of all-cause mortality, myocardial infarction, ischemia-driven TLR, ST, and TLF. Real-world registry data have similarly shown the safety and efficacy of the X-EES over previous stent design.

The platinum-chromium–based P-EES was compared with a cobalt-chromium strut design in the PLATINUM trial (vs X-EES) as well as against another cobalt-chromium second-generation stent in the DUTCH-PEERS and HOST-ASSURE trials (vs R-ZES). In the PLATINUM trial, a total of 1530 patients were randomized to the cobalt-chromium X-EES (n = 762) or the platinum-chromium P-EES (n = 768). The platinum-chromium P-EES was found to be noninferior to the cobalt-chromium X-EES for the primary end point of 12-month TLF (3.4% vs 2.9%; \( P \) for noninferiority = .001, \( P \) for superiority = .60) or for any other outcome measures of safety and efficacy through 12-month follow-up after PCI. A 3-year follow-up of that trial showed comparable safety and efficacy outcomes for both EESs. In the DUTCH-PEERS trial, 1811 eligible all-comer patients were randomized to P-EES versus R-ZES. The primary end point of TVF occurred in 5% and 6% of patients, respectively (\( P \) for noninferiority = .006), with no significant differences in individual components of the primary end point. Definite ST occurred in 0.7% and 0.3% of P-EES and R-ZES patients, respectively (\( P = .34 \)). Similarly, in the HOST ASSURE trial, 3755 all-comer patients were randomized to P-EES versus R-ZES. At 1 year, TLF occurred in 2.9% of each group, meeting the noninferiority margin, with
no significant differences in the individual components of TLF noted.

THIRD-GENERATION DRUG-ELUTING STENTS

The biodegradable polymer DES, the polymer-free DES, and drug-coated stents represent a true leap in stent technology and are commonly referred to as the third generation of DESs (Table 30-4).

Table 30-4 Selected Biodegradable Polymer Drug-Eluting Stent Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Year</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Stent Groups</th>
<th>TLR (%)</th>
<th>MACE (%)</th>
<th>ST (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomatrix</td>
<td>2008</td>
<td>Stable or ACS</td>
<td>9 months</td>
<td>B-BES (n = 857) SES (n = 850)</td>
<td>4.6 vs 5.5 (P = .29)</td>
<td>5.3 vs 6.0 (P = .51)</td>
<td>1.9 vs 2.0 (P = .84)</td>
</tr>
<tr>
<td>LEADERS</td>
<td>2012</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>B-BES (n = 575)</td>
<td>1.6 vs 5.7 (P &lt; .001)</td>
<td>4.3 vs 8.7 (P = .04)</td>
<td>0.9 vs 2.1 (P = .10)</td>
</tr>
<tr>
<td>COMFORTABLE AMI</td>
<td>2015</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>B-BES (n = 1,497) R-ZES (n = 1,502)</td>
<td>1.1 vs 1.4 (P = .41)</td>
<td>5.0 vs 5.3 (P = .72)</td>
<td>0.1 vs 0.3 (P = .27)</td>
</tr>
<tr>
<td>SORT OUT VI</td>
<td>2015</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>B-BES (n = 1,497) R-ZES (n = 1,502)</td>
<td>1.1 vs 1.4 (P = .41)</td>
<td>5.0 vs 5.3 (P = .72)</td>
<td>0.1 vs 0.3 (P = .27)</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>2015</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>S-EES (n = 846) P-EES (n = 838)</td>
<td>6.7 vs 6.5 (P = .005)</td>
<td>5.5 vs 4.8 (P = .62)</td>
<td>0.2 vs 0.2 (P = .99)</td>
</tr>
<tr>
<td>EVOLVE II</td>
<td>2015</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>O-S-SES (n = 1,063) X-EES (n = 1,056)</td>
<td>4.0 vs 3.1 (P = .27)</td>
<td>11.8 vs 10.2 (P = .227)</td>
<td>0.9 vs 0.4 (P = .16)</td>
</tr>
<tr>
<td>Oniro</td>
<td>2014</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>O-S-SES (n = 298) X-EES (n = 154)</td>
<td>3.8 vs 5.4 (P = .46)</td>
<td>6.5 vs 8.1 (P = .58)</td>
<td>0 vs 0 (P = 1.0)</td>
</tr>
<tr>
<td>BIOSCIENCE</td>
<td>2014</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>O-S-SES (n = 1,063) X-EES (n = 1,056)</td>
<td>4.0 vs 3.1 (P = .27)</td>
<td>11.8 vs 10.2 (P = .227)</td>
<td>0.9 vs 0.4 (P = .16)</td>
</tr>
<tr>
<td>BioFlow II</td>
<td>2015</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>O-S-SES (n = 298) X-EES (n = 154)</td>
<td>3.8 vs 5.4 (P = .46)</td>
<td>6.5 vs 8.1 (P = .58)</td>
<td>0 vs 0 (P = 1.0)</td>
</tr>
<tr>
<td>Nobori</td>
<td>2013</td>
<td>Stable or ACS</td>
<td>12 months</td>
<td>N-BES (n = 1,229) SES (n = 1,229)</td>
<td>0.9 vs 0.6 (P = .34)</td>
<td>4.1 vs 3.1 (P = .06)</td>
<td>0.7 vs 0.2 (P = .03)</td>
</tr>
<tr>
<td>COMPARE II</td>
<td>2013</td>
<td>Eligible for PCI</td>
<td>12 months</td>
<td>N-BES (n = 1,795) X-EES (n = 912)</td>
<td>2.7 vs 2.4 (P = .69)</td>
<td>5.2 vs 4.8 (P = .54)</td>
<td>0.8 vs 1.0 (P = .38)</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; B-BES, Biomatrix Biolimus-eluting stent; BMS, bare metal stent; MACE, major adverse cardiac events; N-BES, Nobori Biolimus-eluting biodegradable polymer stent; O-S-SES, Oniro sirolimus-eluting stent; PCI, percutaneous coronary intervention; P-EES, Promus Premier everolimus-eluting stent; R-ZES, Resolute zotarolimus-eluting stent; S-EES, SYNERGY everolimus-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; STEM, STE segment elevation myocardial infarction; X-EES, Xience everolimus-eluting stent.

Biodegradable Polymer Stents

The Biomatrix DES is a Biolimus-eluting stent (B-BES; Biosensors, San Diego, CA) with a biodegradable polymer. The B-BES was evaluated versus SES in 1707 patients in the LEADERS trial. The primary end point of a composite of cardiac death, myocardial infarction, or TLR at 9 months occurred in 9% versus 11% of patients in the B-BES and SES arms, respectively (P for noninferiority = .003, P for superiority = .39). Components of the primary outcome did not differ between groups as well. Similarly, in the SORT OUT IV trial, the Biomatrix was also found to be noninferior to R-ZES for the primary composite end point of cardiac death, myocardial infarction, and TLR at 12 months in an unselected population of 1502 patients randomized to both stents (5.3% vs 5.0%; P for noninferiority = .004 for the B-BES vs the R-ZES, respectively). Compared with a BMS, the use of B-BES also resulted in a lower rate of the composite of MACE at 1
year among patients with ST-segment elevation myocardial infarction undergoing primary PCI in the COMFORTABLE AMI randomized trial. The SYNERGY DES is a thin-strut, platinum-chromium metal alloy platform with an ultrathin bioabsorbable poly(D,L-lactide-co-glycolide) abluminal everolimus-eluting polymer (S-EES; Boston Scientific). The EVOLVE II trial randomized 1684 patients to the S-EES stent versus the platinum-chromium P-EES. The primary end point of 12-month TLF was observed in 6.7% of the S-EES patients and 6.5% of the P-EES patients (P for noninferiority = .0005). Both TLR and ST rates were similar as well (2.6% vs 1.7%, P = .21; 0.4% vs 0.6%, P = .5 for the S-EES vs P-EES, respectively).

The Orsiro stent is a newly developed, ultrathin strut, cobalt-chromium stent releasing sirolimus (O-SES; Biotronik, Bulach, Switzerland) and featuring a unique dual-polymer matrix. An active bioabsorbable polymer delivers the antiproliferative drug via controlled release, while a passive biocompatible polymeric coating shields the metallic strut from surrounding tissue, preventing interaction. The O-SES has been found to be noninferior to the durable polymer X-EES in the BIOSCIENCE trial, as well as in the BIO-FLOW II trial. The ongoing BIO-FLOW V trial is a prospective, randomized, investigational device exemption trial that will study the O-SES versus X-EES. Finally, the SORT OUT VII trial will study the O-SES versus the N-BES biodegradable polymer stent.

Additional biodegradable polymer stents have been reported as well. The Nobori Biolimus-eluting biodegradable polymer stent (N-BES; Terumo, Tokyo, Japan) did not improve clinical results compared to the durable polymer first-generation SES in the SORT-OUT V trial. However, the N-BES was further evaluated versus X-EES in the COMPARE II trial, which randomized 2707 patients to either the N-BES or X-EES. The primary end point occurred in 5.2% and 4.8% of stents, respectively (P for noninferiority <.0001). The ISAR-TEST 4 trial compared the efficacy and safety of the biodegradable polymer SES Yukon Choice PC (YC-SES; Translumina, Hechingen, Germany) versus X-EES and SES. At 5-year follow-up, the YC-SES and permanent polymer X-EES stents showed comparable clinical outcomes, whereas the SES showed numerically higher rates of device-related adverse events. The Excel stent, a biodegradable polymer sirolimus-coated DES (E-SES; JW Medical Systems, Weihai, China) was evaluated in
the CREATE registry enrolling 2070 patients. The rates of cardiac death, myocardial infarction, TLR, and overall MACE at 5-year follow-up were 3.0%, 1.5%, 3.7%, and 7.4%, respectively. Five-year definite and probable ST rates were 1.1% and 0.3%, respectively. Finally, the Combo Stent Platform (OrbusNeich, Fort Lauderdale, FL) is a 100-μg-thick strut stainless steel stent covered abluminally with a biodegradable polymer that releases sirolimus. An additional circumferential layer of anti-D34 antibodies is applied on the stent strut on top of the polymer aiming to accelerate endothelialization. This stent was tested in the REMEDEE trial randomizing 100 patients in a 2:1 ratio to the Combo versus PES. The Combo stent was found to be noninferior to the PES regarding 9-month angiographic in-stent late lumen loss (0.39 ± 0.45 mm vs 0.44 ± 0.56 mm; \( P \) for noninferiority = .0012). At 12 months, the occurrence of MACE was 8.9% versus 10.2% (\( P = .8 \)) in the Combo group versus the PES group, respectively, with no difference in mortality, occurrence of myocardial infarction, or TLR. No ST was reported in either group.

**Polymer-Free Stents and Drug-Coated Stents**

Several technologies have been developed to design polymer-free DESs, such as the use of microporous stents and inorganic coatings that can be drug loaded. Polymer-free systems have included drug coatings with Biolimus, paclitaxel, tacrolimus, sirolimus, and a combination of Sirolimus and Probucol.

The BioFreedom stent (Biosensors) is a polymer-free, Biolimus-coated DES. This stent has been studied in the LEADERS FREE trial. In this randomized, double-blind trial, the stent was compared with a BMS in 2466 patients with a high risk of bleeding who underwent PCI and received 1 month of dual antiplatelet therapy. At 390 days, the primary safety end point (composite of cardiac death, myocardial infarction, or ST) occurred in 9.4% and 12.9% of the DES and BMS patients, respectively (\( P < .001 \) for noninferiority and \( P = .005 \) for superiority). During the same time period, TLR occurred in 5.1% and 9.8% of DES and BMS patients, respectively (\( P < .001 \)).

Other polymer-free stents have reached human testing. The VESTAsync system (MIV Therapeutics, Atlanta, GA) was evaluated in the VESTAsync II
feasibility observational trial,\textsuperscript{66,67} showing the VESTAsync stent to be effective in reducing late lumen loss and neointimal hyperplasia. The polymer-free sirolimus Yukon stent was evaluated in the ISAR-TEST trial versus PES,\textsuperscript{68} showing both systems to be equivalent. In fact, at 5 years, there were no significant differences in clinical outcomes.\textsuperscript{69} Byrne et al\textsuperscript{70} have reported their experience with a polymer-free rapamycin-eluting DES as compared to a durable polymer rapamycin-eluting DES and PES.

Finally, a novel drug-filled stent (DFS) has been presented at the 2015 Transcatheter Cardiovascular Therapeutics (TCT) conference. The new DFS, studied in the RevElution trial (NCT02480348), has a novel trilayer wire design, which allows the inner sacrificial layer to become a lumen continuously coated with drug. The drug (sirolimus) is contained on the inside of the stent and is released from a single continuous inner lumen through multiple laser-drilled holes on the abluminal side (outer surface) of the stent. This allows for a controlled and sustained polymer-free drug elution over a desired period of time directly into the arterial wall, thereby potentially avoiding chronic inflammation and adverse vascular responses. The initial report presented at TCT 2015 showed that the optical coherence tomography data demonstrate an early healing profile with an average of 90% strut coverage at 1 month, with a low rate of malapposed struts (2%) in the 6 patients analyzed.

**SUMMARY**

Considerable progress has been made in the development of new-generation DESs. The initial experience with balloon angioplasty and BMS set the groundwork for the development of metal struts with drug-eluting capability to prevent restenosis. Leaps in technology have brought forward new generations of DES. These leaps gave rise to the novel strut design, allowing greater stent deliverability and use of newer polymers and thereafter biodegradable polymers and polymer-free stents, reducing the local inflammatory effect of these materials, allowing shorter duration of dual antiplatelet therapy, and finally, allowing use of highly lipophilic drugs, which enhances drug absorption capabilities. All of these leaps in technology have been accompanied by extensive research and development that has shown the long-term safety and efficacy of the newer generation of DESs.
Available data suggest that DESs can be used safely and effectively in a wide array of patient and lesion subsets. The advances in the field have also led to the endorsement for the use of these stents in the practice guidelines in the United States and Europe. As continuous advances in technology change clinical practice, it remains to be seen whether older technologies, such as the BMS, will eventually become obsolete and whether novel technologies, such as the bioresorbable vascular scaffold systems, will eventually replace the durable framed DES.

REFERENCES


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Special Stents: Bioresorbable Coronary Scaffolds

Bill D. Gogas
Habib Samady

INTRODUCTION

Despite innovations in stent design, including reduction in strut thickness, novel antiproliferative agents, and more recently, the development of bioresorbable polymers, permanent metallic stents remain a nidus for sustained vascular inflammation, in-stent neoatherosclerosis, and impaired coronary vasomotor function. Therefore, the concept of a drug-eluting bioresorbable scaffold (BRS) with properties of medium-term temporary vascular scaffolding and long-term vascular reparative properties is appealing.

Several drug-eluting scaffolds, made of either biodegradable polymers or biocorrodible metals, have been developed and tested in first-in-man (FIM) studies showing comparable performance with current-generation drug-eluting stents (DES) in selected clinical subsets. More recently, large-scale randomized trials have demonstrated noninferiority of BRS compared to current-generation DES with respect to safety and efficacy. This cumulative evidence indicates the gradual maturation of the novel field of vascular reparative therapy.
RATIONALE FOR TRANSIENT BIORESORBABLE SCAFFOLDS

The impetus for developing drug-eluting BRS was driven by the need for more elastic and conformable platforms instead of stiff and permanent metallic implants to prevent acute and late recoil, seal post-procedural dissections derived from vascular barotrauma, and inhibit in-segment restenosis using appropriate drug elution.¹ This technologic endeavor would overcome mid- and long-term effects of rigid metal caging over a previously pulsatile vascular tissue.

As early as 1996, van der Giessen et al² reported on deploying synthetic polymer-based scaffolds in porcine coronary arteries. His preliminary observations demonstrated marked inflammatory reactions and subsequent intense neointimal proliferation. Further bench studies indicated that lower molecular weight polymers were an important determinant of these adverse vascular responses.² Current polymeric BRSs are therefore engineered using high-molecular-weight polymers, with poly-L-lactic acid (PLLA) being the most commonly used material. Other polymeric BRSs include tyrosine-derived polycarbonates and poly(anhydride-esters) composed of salicylic acid. Furthermore, an alternative approach to polymeric materials has been the use of magnesium metallic alloys (Table 31-1). Long-term potential advantages of BRS over permanent metal stents have been proposed based on preliminary observations from multicenter registries.

| Table 31-1 | Bioresorbable Coronary Scaffolds in Clinical Development |
Physiologic Restoration of Vascular Function

First- and second-generation metallic DESs have been associated with midterm endothelial dysfunction as well as a blunted vasodilatory response to endothelial-independent vasodilators such as nitroglycerine. Experimental models and clinical studies indicate that both polymeric and magnesium-based BRSs result in improved endothelial function, restoration of non–endothelial-dependent coronary vasoreactivity, and retained vessel pulsatility within and adjacent to the BRS deployed coronary segments. In addition to the pure biomechanical advantages of a more compliant platform, it is postulated that certain endothelial cell signaling and mechanotransduction pathways may be favorably affected by BRS. Finally, compensatory adaptive expansive remodeling with regression of plaque between the struts and the vessel wall resulting in incremental lumen gain has been described in observational studies.

Restoration of Original Vascular Anatomy

Wentzel and colleagues first demonstrated, in a porcine model, that alterations of vessel geometry following stenting resulted in unfavorable rheologic profiles in the treated segments. The authors found that permanent metallic stent implantations changed the 3-dimensional coronary geometry at the proximal edge by 121% and the distal edge by 100%, inducing regions of
low wall shear stress with subsequent development of neointimal hyperplasia and asymmetric patterns of in-stent restenosis. In contrast, both polymeric- and magnesium-based scaffolds were found to result in improved retention of baseline vascular curvature and angulation, with increased gain over 12 months in the ABSORB Cohort B.\textsuperscript{5,7} It is hypothesized that such improvement in vascular conformability will translate into more physiologic vascular flow patterns, which, in turn, can facilitate homogenous long-term scaffold healing patterns. These vessel-level differences in post–device deployment flow patterns, as well as strut-level hemodynamic differences, between BRS and permanent metallic stents are being investigated prospectively in ongoing studies.\textsuperscript{8,9}

\textbf{Reduction of In-Scaffold Neoatherosclerotic Risk}

In-stent neoatherosclerosis has been observed with both metallic DESs and bare metal stents (BMS). The timing of neoatherosclerosis appears to be earlier with DES (6-24 months) compared with BMS (>24 months)\textsuperscript{10} (Fig. 31-1). The mechanism of neoatherosclerosis is not fully elucidated; however, incomplete endothelial coverage and sustained endothelial dysfunction are thought to play important roles. Although selected cases with neoatherosclerosis following BRS deployment have been published,\textsuperscript{11} intravascular imaging data from limited but consecutive patient cohorts treated with BRS do not demonstrate evidence of neoatherosclerosis (ABSORB Cohort B). It is hypothesized that the combination of complete scaffold resorption, regenerated intact endothelium with restored vasomotor function, and plaque passivation has the potential to reduce the risk of neoatherosclerosis.\textsuperscript{12,13}
**FIGURE 31-1** Distal stent edge neoatherosclerosis 6 years after bare metal stent implantation. A. Distal right coronary artery (RCA); the trilaminar vascular structure is preserved between 1 and 5 o’clock. B. The total circumference of the distal edge appears to be occupied by neoatheroma consistent with a lipid-core plaque (white asterisk). Signs of neovascularization are observed at 1 o’clock. C. Distal edge occlusion as a consequence of plaque growth (white asterisk) at the side of the right ventricular branch takeoff. D. Distal stent edge neoatherosclerosis. The white arrows demonstrate the shadow behind the metallic struts. E-I, K. Metallic struts at different stages of healing. J. Delayed strut healing. AM=acute marginal; GWS=guide wire shadow.

**Pediatric Applications**

Absorbable scaffolds appear as more appropriate technologies for the treatment of pediatric obstructive vascular lesions such as premature coronary atherosclerosis, aortic coarctation, and pulmonary artery stenosis. Permanent metallic implants limit vessel growth and require future surgical removal, in contrast to BRS, which may allow natural vessel growth after the time of radial strength elimination and further resorption.

**Other Potential Advantages of BRS**
There are additional proposed advantages of BRS. First, they provide options for coronary artery bypass surgery in patients with advanced distal disease. This may seem esoteric, but not infrequently patients undergo percutaneous interventions with metallic stents that extend into the distal vessels, limiting targets for future coronary bypass. BRS for treatment of such distal diffuse disease may allow future bypass after resorption of the scaffold. The second advantage is the feasibility of computed tomographic imaging of the coronary arteries. With continued improvements in computed tomography angiography (CTA), including postprocessed computational techniques for hemodynamic lesion assessment, it is anticipated that noninvasive assessment of coronary arteries and bypass grafts will increase.\textsuperscript{14,15} Presently, coronary segments with metallic stents cannot be visualized by CTA, but segments treated with BRS can be adequately visualized, thereby reducing the need for invasive coronary angiography in patients with prior percutaneous coronary intervention (PCI).\textsuperscript{16} The third advantage is percutaneous treatment of large bifurcation lesions. The rationale is that one might achieve adequate revascularization with a 2-scaffold technique, with careful lesion preparation and image-guided postdilatation limiting risk of in-stent restenosis and with bioresorption over time not incurring long-term risk of stent thrombosis or neoatherosclerosis.\textsuperscript{17} The final advantage is a reduction of angina due to the favorable effects of BRS in the microvasculature. The observation that for similar epicardial revascularization, patients treated with BRS had lower rates of angina at follow-up was derived from the 1-year interim analysis of the ABSORB II randomized clinical trial, which compared a BRS with Xience metallic DESs (Abbott Vascular, Santa Clara, CA).\textsuperscript{18} However, this was not confirmed in the larger ABSORB III clinical trial, and ABSORB IV is currently under way to further evaluate this hypothesis.

**MECHANICAL PROPERTIES OF BRS**

Polymers have specific mechanical properties defined by 2 parameters. First is the Young tensile modulus of elasticity, which describes the material’s \textit{transient} deformation in response to an applied force. The Young modulus quantifies the elastic property or measure of stiffness of the material and is highly dependent on temperature. Second is the tensile strength, which quantifies the amount of stress the material will endure before suffering
permanent deformation. The spectrum of the Young tensile modulus of elasticity and tensile strength for polymeric and metallic scaffolds as well as permanent metallic implants is shown in Table 31-2.

Table 31-2 Summary of Major Randomized Controlled Trials of DCB in the Femoropopliteal Territory

<table>
<thead>
<tr>
<th>Material</th>
<th>Tensile Modulus of Elasticity (GPa)</th>
<th>Tensile Strength (MPa)</th>
<th>Elongation at Break (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly-$\alpha$-lactic acid</td>
<td>3.1-3.7</td>
<td>60-70</td>
<td>6</td>
</tr>
<tr>
<td>Poly-$\beta$-lactide</td>
<td>3.1-3.7</td>
<td>45-55</td>
<td>6</td>
</tr>
<tr>
<td>Poly (glycolide)</td>
<td>6.5-7.0</td>
<td>90-110</td>
<td>2</td>
</tr>
<tr>
<td>Cobalt-chromium</td>
<td>210-235</td>
<td>1449</td>
<td>40</td>
</tr>
<tr>
<td>Stainless steel 316L</td>
<td>193</td>
<td>668</td>
<td>40+</td>
</tr>
<tr>
<td>Nitinol</td>
<td>45</td>
<td>700-1100</td>
<td>20</td>
</tr>
<tr>
<td>Magnesium alloy</td>
<td>40-45</td>
<td>220-330</td>
<td>20</td>
</tr>
</tbody>
</table>

CHEMICAL PROPERTIES AND BIODEGRADATION OF BRS

**Polymer-Based BRS**

The chemical properties of scaffolds inform the site where degradation begins as well as the rate of degradation. Hydrolytic degradation favors the amorphous tie chains of the polymer that connect the crystal lamellae (Fig. 31-2). Once these tie chains are hydrolyzed, then bulk degradation of the crystal lamellae takes place starting from the inside core of the strut progressing to the strut surface. The surface polymer in which the antiproliferative agent is blended consists of both $D$ (dextro) and $L$ (levo) isomers of polylactic acid (PDLLA). PDLLA is fully amorphous, lacking crystalline structures, which results in relatively rapid degradation.\(^{19}\)
**FIGURE 31-2** Bench bioresorption of poly-L-lactic acid. A. The pathway of ester bond hydrolysis of poly-L-lactic acid. B. Poly-L-lactic acid is semicrystalline (70% crystallinity) consisting of amorphous tie chains linking the semicrystalline phased polymer. Degradation process starts at the sites of amorphous tie chains. C. Graph showing the change of radial support, molecular weight, and mass loss over time after hydrolysis. The device retains its radial support until 6 months; after this time point, it is transformed to a passive implant with no supportive properties.

**Hydrolytic Degradation of PLLA**

The first stage in the process of polymer bioresorption is hydration. Polylactides are relatively hydrophilic; thus water diffuses into the less dense amorphous regions of the implant and hydrolyzes the ester bonds. Random
chain scissions occur at this stage, leading to reduction of the polymer’s molecular weight. The second stage is characterized by continuous cleavage of the amorphous tie chains reducing the radial strength of the scaffold, leading to structural discontinuities. During the third stage, polymer chains that have been hydrolyzed to short lengths diffuse out of the implant (mass loss) as they are increasingly hydrophilic and soluble in aqueous solution. Following these sequential stages, oligomeric polylactic acid molecules hydrolyze to lactic acid monomers, which deprotonate (release of a proton [\(\text{H}^+\)]) to lactate. Lactate is converted to pyruvate and enters the citric acid cycle (Krebs cycle) and is further metabolized in carbon dioxide and water excreted through the lungs and kidneys, respectively.\(^{20}\)

In vivo polymer bioresorption has been analyzed by histology and visualized with optical coherence tomography (OCT). In the first experimental study that investigated the PLLA-based Absorb\textsuperscript{TM} bioabsorbable vascular scaffold (BVS) biodegradation process, 35 polymeric scaffolds (3.0 × 12 mm) were implanted in the main coronary arteries of 17 healthy Yucatan minipigs. OCT was performed after the procedure (n = 2) and at 28 days (n = 2), 2 years (n = 3), 3 years (n = 5), and 5 years (n = 5).\(^{21}\) Struts imaged with OCT, had a box-shaped appearance after implantation with sharply defined borders. At 28 days, 82% of the struts visualized with OCT remained box-shaped, whereas by histology, all struts appeared intact with no evidence of resorption. At 2 years, 80% of the struts still had a box-shaped appearance; however, polylactide was not able to be detected by gel permeation chromatography. Histology confirmed that PLLA had been replaced by proteoglycan-rich matrix (glycoconjugate) that stained positive with Alcian blue. At 3 years, only 5% of strut voids were box-shaped imaged with OCT, whereas 44% showed dissolved black box, 35% showed dissolved bright box, and 16% displayed an open box appearance.

Pathologic assessment at this time point showed that connective tissue had replaced the resorption sites previously occupied by proteoglycan-rich matrix. At 4 years histology revealed that strut voids are minimally discernible as foci of hypocellular connective tissue. These observations provide evidence of complete polylactide resorption at 2 years, whereas at 4 years, both in vivo OCT and ex vivo histology confirmed complete integration of the strut voids into the arterial wall.\(^{22,23}\)
**Igaki-Tamai Scaffold**

The Igaki-Tamai (Kyoto Medical Planning Co, Kyoto, Japan) scaffold was the first polymer-based device that underwent FIM evaluation. The material of the scaffold was PLLA, had a helical zig-zag design with sinusoidal hoops linked by 3 connectors, and carried 2 radiopaque cylindrical gold markers at the proximal and distal ends (Fig. 31-3A). The device was mounted over a conventional angioplasty balloon and was self-expanding following heated contrast injections (up to 70°C or 158°F) to inflate the delivery balloon. Importantly, this first BRS was not a drug-eluting device.

**FIGURE 31-3** Ten-year follow-up of the Igaki-Tamai scaffold. A. Macroscopic view of the polymeric scaffold demonstrating a helical zig-zag design interconnected with straight bridges. B. Angiographic view of the right coronary artery (RCA) demonstrating a significant mid-RCA lesion before procedure and the excellent angiographic result after implantation of the 2 Igaki-Tamai scaffolds. B’ and B”. Angiographic views 10 years after implantation of the Igaki-Tamai scaffolds without evidence of in-scaffold restenosis. Yellow asterisks demonstrate the gold markers at each proximal and distal scaffold end. Red asterisk demonstrates the outgrowth of a side branch. I-VI. Optical coherence tomographic views of the RCA after 10 years of
The FIM study was performed in 15 patients (19 lesions, 25 scaffolds implanted) demonstrating absence of major adverse cardiac events (MACE) or scaffold thrombosis defined by angiographic follow-up at 30 days. Longitudinal evaluation at 6 months demonstrated an acceptable angiographic loss index (late loss/acute gain) of $0.48 \pm 0.32$, which was comparable to BMS. Interestingly, intravascular ultrasound (IVUS) demonstrated scaffold expansion from post-deployment to 6-month follow-up ($7.42 \pm 1.51 \text{ mm}^2$ to $8.13 \pm 2.52 \text{ mm}^2$), a finding observed for the first time with coronary implantable devices. Target lesion revascularization (TLR) rates reached 6.7%, and 4-year MACE-free survival rates were 82%. The long-term clinical follow-up (>10 years) of 84 Igaki-Tamai scaffolds implanted in 63 lesions was recently reported showing a 10-year MACE rate of 50%, with a TLR rate of 38% and 2 cases of scaffold thrombosis (Fig. 31-3B).

Although the technology did obtain the Conformité Européenne (CE) mark for peripheral interventions, it failed to do so for coronary revascularization largely due to the need for heat to induce scaffold expansion and the requirement for 8-Fr guide catheters for scaffold deployment.

**Absorbable Magnesium-Based Scaffolds**

Magnesium (Mg), the lightest metal, is alloyed with rare earth metals, including aluminum, manganese, lithium, zinc, and zirconium. This class of bioresorbable devices belongs to biocorrodible metals characterized by high corrosion rates (complete biodegradation within 3 months), with end products being elemental Mg and inorganic salts (Fig. 31-4). The earliest proof-of-mechanism that demonstrated the biocompatibility of these materials with vascular tissue was introduced by Heublein et al who employed absorbable Mg devices in porcine coronary arteries and demonstrated rapid endothelialization with low inflammatory response.
FIGURE 31-4 Schematic representation of magnesium (Mg)-based scaffold bioresorption. The end product following magnesium scaffold bioresorption facilitated by hydrolysis is amorphous hydroxyapatite. The whole process takes up to 9 months with the first-generation DREAMS scaffold. Drug elution occurs within 3 months after device implantation.

The PROGRESS AMS (Clinical Performance and Angiographic Results of Coronary Stenting With Absorbable Metal Stents) trial was a nonrandomized, multicenter, prospective FIM trial that assessed the safety, efficacy, and performance of the first absorbable Mg stent (AMS-1; BIOTRONIK, Berlin, Germany). The AMS-1 platform was 93% Mg and 7% rare earth metals, the strut thickness was 165 μm. Sixty-three patients with stable coronary artery disease (CAD) were treated with 71 stents. The angiographic in-stent lumen loss was 1.08 ± 0.49 mm at 4 months, and IVUS imaging suggested that most of the struts were fully resorbed, with only strut remnants being visible and fully embedded into the neointimal layer. TLR rates were rather high (24% at 4 months and 45% at 1 year).
Although this study demonstrated safety of AMS-1, with no reported death, myocardial infarction, or stent thrombosis, imaging and clinical results raised concerns over the further use of this generation in coronary interventions as increased neointimal formation and vessel recoil became evident. Subsequently, AMS-2 and AMS-3 were developed to overcome the aforementioned limitations primarily caused by the lack of drug elution and early loss of radial strength. AMS-2 provided an improved Mg alloy with higher collapse pressure of 1.5 bar (compared to 0.8 bar with AMS-1), a slower degradation rate with expected absorption after 9 to 12 months, and a reduced strut thickness of 125 μm with rectangular shape to enhance stent integrity. The AMS-3 was designed to address the issue of excessive neointimal proliferation; thus, a bioresorbable matrix for controlled release of paclitaxel was added to the previous AMS-2. The new device was named drug-eluting AMS (DREAMS) 1.0. It was evaluated for safety, feasibility, and efficacy in the prospective, multicenter, FIM BIOSOLVE-I trial (Safety and Performance of the Drug-Eluting Absorbable Metal Scaffold [DREAMS] in Patients With De Novo Coronary Lesions). Forty-six patients with stable or unstable CAD or silent ischemia were treated with 47 stents. The angiographic in-stent lumen loss was 0.64 ± 0.50 mm at 6 months and 0.52 ± 0.49 mm at 1 year, which represents a 61% reduction compared to the 4-month results of AMS-1. Serial IVUS imaging confirmed the angiographic observations showing in-scaffold area obstruction of only 6.2% ($P < .0001$) at 1 year, attributed to neointimal formation with extra-scaffold plaque area increase. The TLR rate reached 7% with no reported episodes of scaffold thrombosis at 3 years of follow-up.

An important part of BIOSOLVE-I trial included the evaluation of anatomic changes induced by the scaffold from before to after the procedure and at follow-up. In particular, vessel curvatures showed a significant change of –32.1% ($P < .0001$) from before to after the procedure and returned to the pre-implantation levels at the 12-month follow-up. Vessel angulation similarly changed significantly by –40.5% ($P < .0001$) from before to after the procedure (vessel straightening) and increased by 33.1% at 12-month follow-up. These findings reflect the restoration of vessel anatomy after DREAMS scaffold bioresorption, which, from a rheologic perspective, potentially translates into improved flow patterns over the scaffolded segments and the transition zones. The beneficial hemodynamic implications
of these conformable materials may minimize the flow-dependent changes of wall shear stress, which precipitate neointimal formation and subsequent silent or clinical restenosis; however, this hypothesis-generating concept remains to be proven by future clinical trials.29

A second-generation DREAMS device has been recently developed that elutes sirolimus, carries 2 tantalum radiopaque markers at both ends, and provides higher bending flexibility and slower resorption rate compared to the previous generation. Preclinical data are encouraging, showing increased endothelialization rates and decreased inflammatory scores, and the BIOSOLVE-II study has been designed to assess the safety, efficacy, and feasibility of this generation in 123 patients, with follow-up investigations scheduled at 1, 6, 12, 24, and 36 months. IVUS, OCT, and vasmotion testing were completed in a subset of patients at 6 months. The primary end point of in-segment late lumen loss at 6 months was 0.27 ± 0.37 mm. The 2nd generation DREAMS scaffold aka Magmaris received CE mark regulatory approval in 2016.

Current evidence suggests that biocorrodible metallic scaffolds can be safely implanted in patients with favorable clinical outcomes. Despite the encouraging preliminary observations, further randomized clinical trials with head-to-head comparisons with newer generation DESs will define whether these technologies will be adopted over contemporary metallic stents.30

Absorb™ Bioresorbable Vascular Scaffold

The first-generation Absorb BVS (Abbott Vascular) was Absorb BVS 1.0 (Fig. 31-5). The device had circumferential out-of-phase sinusoidal hoops linked either directly or by straight polymeric bridges. The strut thickness including the polymer drug coating was 156 μm, and the crossing profile of 1.4 mm (crimped stage) was slightly larger compared to that of contemporary metallic stents. The device had to be kept refrigerated at −20°C to prevent early aging because room temperature is a precipitating factor for polymer cracking during scaffold deployment.20 The Absorb BVS 1.0 was evaluated in 30 patients with simple de novo native coronary artery stenosis for safety, feasibility, and efficacy in the ABSORB Cohort A. Follow-up included invasive angiography, IVUS, virtual histology IVUS (VH-IVUS), and OCT at 6 months and 2 years, and clinical end points were assessed at 6 months
and 1 and 2 years. Noninvasive coronary angiography with multislice computed tomography was also performed at 18 months and 5 years.

**FIGURE 31-5** Multi-imaging assessment of the Absorb™ bioresorbable vascular scaffold (BVS). The Absorb BVS 1.0 was the first-generation device used in the ABSORB Cohort A trial. The second-generation Absorb BVS 1.1 has been redesigned and is currently under clinical use. Intravascular imaging modalities such as intravascular ultrasound (IVUS), virtual histology IVUS (VH-IVUS), and optical coherence tomography (OCT) have provided important insights in the evaluation of bioresorbable scaffolds. The top panel of cross-sections shows IVUS, VH-IVUS, and OCT following Absorb BVS implantation, whereas the bottom panel shows 6-month follow-up. Polymeric materials, as opposed to metal materials, do not reflect sound or light; thus, shadow behind the struts is not visible. Guide wires and platinum markers are the only components that generate shadow over the circumference of the cross-section. VH-IVUS detects polymeric struts as a dense calcium tissue component similar to metal stents; in contrast to metal stents, this unique property is a surrogate marker of bioresorption with biodegradable scaffolds.

The angiographic in-scaffold lumen loss with Absorb BVS 1.0 was $0.44 \pm 0.35$ mm at 6 months, which was significantly greater than that observed with metallic everolimus-eluting stents (0.11 mm) but less than late loss with BMS (0.85 mm).\(^{31}\) IVUS imaging demonstrated both reduction of scaffold shrinkage by 12% and neointimal proliferation, which combined resulted in a 24% reduction in minimal luminal area.\(^{32}\) At 2 years, the in-scaffold angiographic late loss remained $0.48 \pm 0.28$ mm, which was not significantly
worse than at 6 months. Additional important findings from this FIM registry showed the following: (1) restoration of vasomotor function of the scaffolded segment in response to methergine or acetylcholine; (2) plaque area regression behind the struts between 6 months and 2 years; (3) a low MACE rate of 3.4% at 4 years without any scaffold thrombosis; and (4) feasibility of noninvasive imaging with CTA. Despite the favorable clinical performance of Absorb BVS 1.0, early scaffold shrinkage, premature loss of radial support, and robust neointimal growth raised the need for development of a second-generation Absorb BVS to overcome these shortcomings.

The second-generation Absorb™ BVS 1.1 device was constructed from the same polymer (PLLA) as the previous generation but with a different processing that delayed the rate of ester bond hydrolysis, increasing the duration of mechanical support and scaffold resorption. Although strut thickness remained at 156 μm, the backbone of the second-generation device was redesigned to reduce the circular unsupported surface area (area between 2 sequential rings) and be replaced by in-phase zig-zag hoops linked by 3 longitudinal bridges that allowed more uniform vessel support. Although the implant remained radiolucent, 2 platinum markers at each end of the scaffold were added for visualization during angiography.

The ABSORB Cohort B trial tested the Absorb™ BVS 1.1 in 101 patients. This cohort was split into 2 subgroups: cohort B₁ (n = 45), which underwent imaging with angiography, IVUS, VH-IVUS, and OCT after the procedure and at 6 months and 2 years, and cohort B₂ (n = 56), which underwent the same imaging after the procedure and at 1 year and 3 years. Additionally, CTA was performed in both groups at 18 months of follow-up. Angiographic in-scaffold lumen loss was 0.19 ± 0.18 mm at 6 months and 0.27 ± 0.20 mm at 2 years, and remained relatively unchanged at 3 years at 0.29 ± 0.43 mm. IVUS imaging revealed an increase of neointimal generation at 3 years from 0.08 ± 0.13 to 0.28 ± 0.41 mm² (Δ = 0.20 ± 0.41 mm²; P < .002), which was compensated by an increase in the scaffold area by 0.80 ± 1.26 mm² (from 6.29 ± 0.91 to 7.08 ± 1.55 mm²; P < .001), allowing lumen dimensions to remain preserved. The angiographic in-segment restenosis rate in the entire cohort B at 3 years was 6%, and the 3-year MACE rate was 10% without any events of scaffold thrombosis. The results of the ABSORB Cohort B trial indicated the dynamic nature of vessel wall changes following implantation of a fully
bioresorbable device showing low restenosis rates and low clinical adverse events up to 3 years.\textsuperscript{35}

**Randomized Clinical Trials with the First-Generation Absorb\textsuperscript{TM} Bioresorbable Vascular Scaffold**

Despite CE mark approval of the Absorb\textsuperscript{TM} BVS 1.1 in 2012 for revascularization of noncomplex lesions, the paucity of randomized comparisons of BRS with metallic DES in “low-risk” patients and early concerns for higher very late scaffold thrombosis rates resulted in questions regarding the merit of this technology.\textsuperscript{36} It was not until 2015 that the results from international large-scale randomized trials from the United States, China, and Japan were published.

**ABSORB III**

The ABSORB III was the first large-scale, multicenter, randomized trial designed to support the Absorb\textsuperscript{TM} BVS transition from the stage of premarket approval, to complete US FDA clearance for clinical use in the United States. Two thousand and eight patients with stable or unstable angina were randomly assigned to receive in a 2:1 ratio an everolimus-eluting metallic stent (Xience) or the Absorb\textsuperscript{TM} BVS 1.1. The primary end point was target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (TV-MI), or ischemia-driven TLR, tested for both noninferiority and superiority at 1 year. The treated lesions were relatively complex, with the majority being type B2. Only very complex lesion subsets, such as very long or heavily calcified lesions, chronic total occlusions, left main disease, and large bifurcations, were excluded.\textsuperscript{37}

The Absorb\textsuperscript{TM} BVS was found to be noninferior to Xience at 1 year, meeting the primary end point of noninferiority albeit with a generous noninferiority margin of 4.5%. TLF occurred in 7.8% versus 6.1% of patients in the Absorb BVS arm versus the Xience arm, respectively (difference, 1.7%; 95% confidence interval [CI], –0.5% to 3.9%; \(P = .007\) for noninferiority and \(P = .16\) for superiority). Individual components of TLF were not significantly different among both arms at 1 year. More specifically, rates of cardiac death in the Absorb BVS arm versus Xience arm were 0.6%
versus 0.1% (P = .29), respectively. TV-MI event rates in the Absorb BVS arm versus the Xience arm were 6.0% versus 4.6% (P = .18), respectively, and TLR rates were 3.0% versus 2.5% (P = .50), respectively. Device thrombosis among the groups reached 1.5% in the Absorb BVS arm versus 0.7% in the Xience arm (P = .13). Interestingly, 25% (n = 375) of the vessels treated in the ABSORB III trial had a reference diameter of <2.25 mm. Device thrombosis rates in these smaller vessels were significantly different, reaching 4.65% in the Absorb BVS arm versus 1.55% in the Xience V arm. This subanalysis demonstrates the importance of vessel sizing, suggesting avoidance of vessels <2.5 mm for BRS deployment.

In summary, the ABSORB III trial demonstrated the clinical safety and efficacy of Absorb™ BVS implanted in moderately complex lesions at 1 year. Although device thrombosis rates were numerically larger than the best-in-class metallic stent, there was no statistically significant difference among the treated groups. Obviously, long-term evaluation of both cohorts will determine whether the rates of late clinical events will decline in the Absorb BVS arm, an expectation based on the encouraging observations from FIM registries related to the reparative properties of the Absorb BVS.

**ABSORB China**

ABSORB China enrolled 480 patients randomized for elective PCI to receive in a 1:1 ratio an Absorb™ BVS or an Xience V stent. The trial was designed to assess in a noninferior fashion the angiographic efficacy and clinical safety of Absorb BVS compared with the Xience V stent in order to receive regulatory approval in China. The primary end point was angiographic in-segment late lumen loss powered for noninferiority with a margin of 0.15 mm. The Absorb™ BVS was noninferior to the Xience V stent at 1 year, meeting the primary end point of noninferiority. In-segment late lumen loss (in device + 5-mm proximal and distal edge vascular responses) was 0.19 ± 0.38 mm versus 0.13 ± 0.38 mm in the Absorb BVS versus the Xience V stent, respectively (P for noninferiority = .01). There were no definite scaffold or stent thromboses during the 1-year follow-up period. TLF rates and individual components of cardiac death, TV-MI, and TLR were similar among the groups at 1 year.38,39
**ABSORB Japan**

ABSORB Japan enrolled 400 patients randomized for elective PCI to receive in a 2:1 ratio an Absorb™ BVS or an Xience V stent. The trial was designed to assess in a noninferior fashion the clinical safety and angiographic efficacy of Absorb BVS compared with the Xience V stent in order to receive regulatory approval in Japan. The primary clinical end point was TLF at 1 year, whereas the secondary efficacy end point was angiographic in-segment late lumen loss at 13 months. The Absorb BVS was noninferior to the Xience V stent at 1 year, meeting the primary end point of noninferiority. The secondary end point of in-segment late lumen loss (in device +5-mm proximal and distal edge vascular responses) did not differ among the groups and was 0.13 ± 0.30 mm versus 0.12 ± 0.32 mm in the Absorb BVS versus Xience V stent groups, respectively ($P = .74$). Similarly, in-device late lumen loss (excluding the 5-mm proximal and distal edge vascular responses) was not significantly different among the Absorb BVS versus Xience V stent groups ($0.19 ± 0.31$ mm vs $0.16 ± 0.33$ mm, respectively; $P = .35$). There were no differences in the rates of stent or scaffold thrombosis among the arms.

**ABSORB Clinical Trial Data in Aggregate**

In a recent meta-analysis including the ABSORB II and III, ABSORB China, ABSORB Japan, EVERBIO II, and TROFI II randomized trials, the Absorb™ BVS was compared with a best-in-class cobalt-chromium DES in 3738 patients. The average follow-up was 1 year. Both devices had similar efficacy outcomes. However, the primary safety outcome of early (<30 days) definite/probable thrombosis was higher with the Absorb™ BVS compared with DES (1.3% vs 0.5%; odds ratio, 1.99; 95% CI, 1.00-3.98; $P = .05$).

**DESolve Scaffold**

The DESolve bioresorbable coronary scaffolds (Elixir Medical Corporation, Sunnyvale, CA) include the first-generation device made of PLLA eluting the antiproliferative agent Myolimus (Novartis, Basel, Switzerland) and the second-generation which elutes a novel macrocyclic lactone Novolimus (Elixir Medical) at a dose of 5 μg/mm. The scaffold design incorporates...
sinusoidal in-phase hoops with straight connectors, the strut thickness is 150 μm, and the expected strut resorption is 1 year, as indicated in porcine models. Despite the radiolucency of the device, it has 2 radiopaque platinum markers at the proximal and distal edges for appropriate visualization.

Both systems have a crossing profile of 1.47 mm and are 6-Fr compatible. The degradation process resembles that of the Absorb BVS undergoing polymer hydrolysis, and further metabolism occurs in the Krebs cycle to end products of carbon dioxide and water. The DESolve Myolimus-eluting scaffold was tested for efficacy, feasibility, and safety in the DESolve FIM trial (A Nonrandomized, Consecutive Enrollment Evaluation of the DESolve Myolimus-Eluting Bioresorbable Coronary Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions), which enrolled 16 patients with a single de novo coronary lesion. Multi-imaging assessment with IVUS, VH-IVUS, and OCT was serially performed at the 6-month follow-up. Multislice computed tomography (MSCT) was performed at 12 months and will be repeated at 24 months, whereas clinical end points were assessed at 30 days and 6 months and will be assessed annually for up to 5 years. The angiographic late lumen loss at 6-month follow-up was 0.19 ± 0.19 mm, similar to that of contemporary DES (Xience V everolimus-eluting stent) and far less than that of paclitaxel-eluting stents, which is in the range of 0.35 to 0.40 mm, with no evidence of scaffold shrinkage as indicated by serial IVUS assessment. MSCT at 12 months demonstrated comparable in-scaffold lumen diameters with the angiographically derived 6-month results (2.40 ± 0.28 mm vs 2.41 ± 0.28 mm, respectively).

In view of these encouraging results, the second generation Novolimus-eluting scaffold was developed and further evaluated in the DESolveNx study, which recruited 126 patients with single de novo coronary artery lesions. The primary end point of in-scaffold late lumen loss was 0.21 ± 0.34 mm at 6 months, and IVUS-based assessment in a subset of 40 patients indicated significant increases in scaffold and lumen areas of 16% and 9%, respectively. DESolve has recently received CE mark approval for coronary interventions in Europe.

Poly(Anhydride-Esters) Composed of Salicylic Acid for Engineering BRS
Poly(anhydride-esters) are biodegradable polymeric compounds composed of a trimer of 2 salicylic acid molecules joined by a linker molecule. The Bioabsorbable Therapeutic Inc. (BTI) scaffold (Bioabsorbable Therapeutic Inc., Menlo Park, CA) consists of 2 components: (1) the core composed of salicylic acid bridged with sebacic acid and (2) the coating composed of salicylic acid linked with adipic acid and 1:1 ratio of sirolimus in a total dose density of 8.3 μg/mm of scaffold length (Fig. 31-6). The bioresorbable coating, which is salicylate based, has previously proved its compatibility and efficacy in bench studies showing reduced inflammatory responses compared to BMSs (Multi-Link Vision stent; Abbott Vascular) attributed to the salicylic acid compound, which is an anti-inflammatory agent.

FIGURE 31-6 Poly(anhydride-ester) salicylic acid for engineering bioresorbable scaffolds. The first-generation BTI scaffold and the second-generation Ideal BioStent are shown. The scaffolds are composed of a top layer, which is a blend of polymer (salicylic acid linked with adipic acid) and sirolimus, and another layer, which is the scaffold backbone made of salicylic acid linked with sebacic acid. The chemical structures of poly(anhydride-esters) made of salicylic acid are illustrated.
The scaffold has a strut thickness of 200 μm, a crossing profile of 1.83 mm (3.0-mm scaffold) or 1.98 mm (3.5-mm scaffold), and is compatible with 8-Fr guiding catheters. The WHISPER FIM trial conducted in 2008 included 11 patients and confirmed the safety and efficacy of the device. However, high restenosis rates attributed to exaggerated neointimal proliferation subsequent to lower concentrations of sirolimus (25% less than the dose of the Cypher stent) drove the development of the second-generation scaffold.43

The Ideal BioStent (Xenogenics Corporation, Canton, MA) is thinner, with a thickness of 175 μm; has a smaller crossing profile (1.52 mm for 3.0-mm scaffold), which makes it compatible with 6-Fr guiding catheters; and has a higher drug dose of sirolimus and longer scaffold length, which are associated with slower release rates. Preclinical evaluation of the device is currently under way, with plans for clinical assessment in 2016. The poly(anhydride-ester) comprised of salicylic acid has not received either CE mark or US FDA regulatory approval.

Tyrosine-Derived Polymers for Engineering Polymeric Scaffolds

Tyrosine-derived polycarbonates are a group of homologous carbonate-amid copolymers differing in the length of their respective alkyl ester pendent chains. The REVA scaffold (REVA Medical, San Diego, CA) is made of tyrosine-derived polycarbonate polymer and designed with slide-and-lock expansion technology. The polymer undergoes hydrolysis, which produces iodinated desaminotyrosyl-tyrosine ethyl ester (I$_2$DTE) and carbon dioxide. The esters in the presence of water are further hydrolyzed to iodinated desaminotyrosyl-tyrosine (I$_2$DT), which is gradually converted to tyrosine and iodinated desaminotyrosine (I$_2$DAT). I$_2$DAT enters the Krebs cycle, with final products of carbon dioxide and water. The resorption pathway is similar to that of poly-lactic acid–based scaffolds, with early loss of the polymer’s molecular weight mediated by hydrolysis, followed by reduction of radial strength and gradual mass loss.

Resorption time may take up to 18 months. Bench studies in large animal models have demonstrated low inflammatory rates and complete endothelialization at 30 days, whereas serial IVUS imaging confirmed lumen gain from after implantation to 12 months. Another appealing property of the
REVA scaffold is its radiopacity (Fig. 31-7).

**FIGURE 31-7** Tyrosine-derived polymers for engineering bioresorbable scaffolds. A. The ReZolve (second-generation) tyrosine-derived polycarbonate scaffold showing the “slide and spiral lock” design. B. The chemical structure of the amino acid tyrosine, carbonate, and phenyl group, which provides the backbone for the tyrosine-derived polycarbonate polymer. C. The ReZolve scaffold is radiopaque, attributed to the iodination of tyrosine. The metabolic pathway of tyrosine-derived polycarbonates undergoes hydrolysis with end products of carbon dioxide and water. The resorption pathway is similar to polylactide-based scaffolds, with initial loss of molecular weight followed by mass loss and excretion by the lungs and kidneys.

These encouraging observations drove the technology in the clinical setting, with the FIM RESORB (REVA Endovascular Study of a Bioresorbable Coronary Stent) study being performed in 30 patients with de novo CAD. Focal mechanical failure of the technology due to polymer embrittlement led to high TLR rates of 66.7%, which drove the development of the second-generation device ReZolve (REVA Medical) scaffold. ReZolve provided a more robust polymer, acquired a “slide and spiral lock” mechanism, eluted the antiproliferative agent sirolimus, and was compatible with 6-Fr guiding catheters. The safety of this scaffold was evaluated in the FIM RESTORE (ReZolve Sirolimus-Eluting Bioresorbable Coronary
Scaffold) pilot study, which included 22 patients. The primary end point was freedom from ischemia-driven TLR at 6 months and angiographic late lumen loss at 12 months, which was $0.29 \pm 0.33$ mm with minimal acute recoil of 3.79%. The second-generation sirolimus-eluting FANTOM scaffold is undergoing safety and efficacy evaluation in the FANTOM II registry intending to enroll 240 patients from 28 clinical centers. The primary endpoint of MACE at 6 months was 2.1% and late lumen loss was $0.25 \pm 0.40$ mm. The 9-month secondary endpoints of MACE and late lumen loss are anticipated after completion of the follow-up. Following these encouraging observations, the technology received recently CE mark approval.

**PDLLA ART Scaffold**

The ART scaffold (Arterial Remodeling Technologies, Paris, France) is a polymer-based, non–drug-eluting device made of amorphous PDLLA. The scaffold has a strut thickness of 170 μm, consists of out-of-phase zig-zag hoops, and is compatible with 6-Fr guiding catheters. Preclinical assessment has shown early endothelialization, low inflammatory rates, and complete scaffold resorption at 18 months. The second-generation ART18Z is currently undergoing FIM evaluation in the ARTDIVA (Arterial Remodeling Transient Dismantling Vascular Angioplasty; ClinicalTrials.gov identifier: NCT01761578) trial, which intends to recruit 30 patients with de novo CAD.44

**NOVEL ASSESSMENT OF CORONARY BRS**

Both blood fluid dynamics and plaque/vessel solid mechanics adjacent to an implantable vascular device affect vascular healing around the device. Therefore, an important design element of BRS is platform flexibility, which induces alterations in angulation, curvature, and vessel compliance to a lesser degree compared to metal stents. Scaffold material properties, strut thickness, design, and resorption are properties that regulate the scaffold’s flexibility, further influencing vascular responses and healing.

The impact of stiffer metallic materials on vessel anatomy and the local
hemodynamic implications of these stiffer metalloids were first described by Wentzel and colleagues, who showed alterations of vessel geometry following stenting with subsequent unfavorable rheologic profiles at the stented segments. Polymer and Mg-based BRSs are made of elastic materials, providing a more conformable platform compared to metal stents. For example, Absorb BVS has shown a significantly lower modification of vessel angulation and numerically lesser change in curvature from before to after procedure compared to metal stents.

Strut thickness is an important determinant of scaffold flexibility; thus, current-generation DESs are manufactured with thinner struts in the range of 75 to 90 μm. BRSs were first introduced in the interventional market with strut thickness in the range of 140 to 150 μm to provide additional radial strength because these materials have inferior tensile strength compared to cobalt-chromium or stainless steel alloys.

Despite the larger struts resulting in more disturbed strut level flow after implantation, gradual scaffold resorption and neointima in between the struts result in more laminar flow patterns over time, which promote homogenous vascular healing. Indeed, we have recently described and quantified, using finite element methods and advanced computational fluid dynamic simulations, the device-flow interaction over time in a virtual model. Additionally, we have demonstrated the feasibility of assessing these rheologic patterns by fusing angiographic with optical-based imaging (Fig. 31-8).
FIGURE 31-8 Wall shear stress (WSS) derived from angiographic and optical coherence tomography (OCT) imaging data using computational fluid dynamics modeling techniques following implantation of the Absorb bioresorbable vascular scaffold (BVS). A, A’. Two-dimensional (2-D) angiographic views of the significant proximal left circumflex (LCx) lesion (A) and the scaffolded segment following implantation of the 3.0 × 18 mm Absorb BVS (A’). B, B’. Three-dimensional (3-D) angiographic views before (B) and after (B’) scaffold implantation. C. The Absorb BVS. D, D’. Time-averaged WSS (TAWSS) magnitude distribution from angiographically derived 3-D geometries before (D) and after (D’) scaffold deployment. Velocity profiles before and after implantation of the Absorb BVS are superimposed. E. 2-D OCT cross-section with embedded polymeric struts demonstrating in a 3-D pattern the distribution of TAWSS between the polymeric struts. The quantified color coding demonstrates low WSS regions (blue color). The matched OCT cross-section is superimposed. E’. Reconstructed stream lines of the velocity field demonstrating altered flow patterns in the proximity of the arterial wall induced by the polymeric struts. (Reproduced by permission from Gogas BD, King SB 3rd, Timmins LH, et al. JACC Cardiovasc Interv. 2013 Jul;6(7):760-761.)
The RESTORATION (Evaluation and Comparison of Three-Dimensional Wall Shear Stress Patterns and Neointimal Healing Following Percutaneous Coronary Intervention With Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold Compared to Xience V or XiencePrime Everolimus-Eluting Metallic Stent) study was designed to address the changes induced by BRS versus a permanent metallic stent in local hemodynamic conditions, vessel compliance, and angulation form after the procedure to 3 years of follow-up in selected patients enrolled in the ABSORB III randomized controlled trial. This head-to-head comparison will precisely describe the association of poststent wall shear stress with vessel healing using a combination of angiography and IVUS or high-resolution optical imaging and will add further insights in the field of vascular reparative therapy.

COST EFFECTIVENESS OF EVOLVING STENT TECHNOLOGIES

The reduction in the economic burden of restenosis with DES compared with BMS has been shown to compensate for the higher upfront cost of DES. Market competition has resulted in further reduction in costs of newer generation DESs. BRS technologies in clinical use within the European market are more expensive than current-generation DESs. Given that there is no expectation for BRS to clinically outperform current-generation DESs within the first year, one would not expect a compensation for the greater upfront cost, as was seen with DES compared with BMS in the early time period. However, if in the long-term BRSs reduce the ongoing 2% per year event rate related to DES technology, one might expect downstream cost savings that might offset the upfront additional cost. Long-term outcomes and cost-effectiveness analyses will shed light on this prospect.

SUMMARY

Interventional cardiovascular medicine has witnessed tremendous progress over the past 20 years. Undoubtedly, metal stents have revolutionized the practice of interventional cardiology over the past decade. However, concerns
of late stent thrombosis, neoatherosclerosis, metallic caging of long segments of vessels, lack of physiologic vasomotion, and ongoing endothelial dysfunction remain. The premise for BRS is to address these long-term concerns with metallic stents. However, ongoing refinement and research should address the following 2 major remaining issues: (1) strut thickness—efforts are under way to reduce strut thickness while maintaining mechanical properties to prevent acute scaffold recoil; and (2) strut integrity—polymer-based scaffolds have limited expansion properties, and therefore, overdilatation entails the risk of strut fracture or discontinuity. Aggressive lesion preparation and close attention to accurate BRS sizing with use of intravascular imaging will optimize strut integrity and scaffold expansion, likely improving outcomes.

CONCLUSION

BRSs have been heralded as the fourth revolution in interventional cardiovascular medicine following DES, BMS, and balloon angioplasty. Although BRS technologies are in their early stages, further developments will mature this novel field of vascular reparation therapy with scaffolds that are intended to “do their job and disappear.”

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MULTIPLE CHOICE QUESTIONS

1. Which of the following statements regarding polymer-based scaffold bioresorption is true?
   A. Polymer-based scaffolds undergo bulk degradation following polymer hydrolysis.
   B. The end products of polymer-based degradation are elemental magnesium and inorganic salts.
   C. The average resorption time of poly-l-lactic acid is 1 year, as indicated by gel permeation chromatography. Regions previously occupied by polymeric struts are replaced by functional connective tissue at 2 years.
   D. Continuous cleavage of polymer’s amorphous tie chains leads to oligomeric molecules that enter the Cori cycle with end products carbon dioxide and water.
   E. Continuous cleavage of polymer’s amorphous tie chains increases the scaffold’s radial strength, enabling sufficient vessel support.

2. The ABSORB III trial randomized 2008 patients with stable or unstable angina to receive in a 2:1 ratio the everolimus-eluting bioresorbable vascular scaffold (BVS; Absorb) or the metallic Xience V stent. The findings of this trial include all of the following except:
   A. The primary end point was target-lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (TV-MI), or ischemia-driven target lesion revascularization (TLR).
   B. TLF occurred in 7.8% of patients in the Absorb BVS arm versus 6.1%
of patients in the Xience arm (difference, 1.7 percentage points; 95% confidence interval, −0.5 to 3.9; \(P = .007\) for noninferiority and \(P = .16\) for superiority).

C. Device thrombosis among the groups reached 1.5% in the Absorb BVS arm versus 0.7% in the Xience arm (\(P = .13\)).

D. Device thrombosis rates in vessels with a reference vessel diameter (RVD) of \(<2.25\) mm did not differ among the groups, and the Absorb BVS is indicated in small vessels as well as in vessels with RVD \(>2.5\) mm.

E. The Absorb BVS was found to be noninferior to Xience at 1 year, meeting the primary end point of noninferiority, albeit with a generous noninferiority margin of 4.5%.

3. The ABSORB China trial randomized 480 patients to receive in a 1:1 ratio an Absorb BVS or an Xience V stent. Which of the following was the primary end point?
   A. The efficacy end point of in-stent late lumen loss at 1 year
   B. The safety end point of in-segment late lumen loss at 2 years
   C. The efficacy end point of in-segment late lumen loss at 1 year
   D. The safety end point of in-stent late lumen loss at 2 years
   E. The efficacy end point of scaffold thrombosis at 2 years

4. Which of the following statements regarding the DESolve scaffold is false?
   A. The DESolve scaffold has 2 radiopaque platinum markers at the proximal and distal edges for appropriate visualization.
   B. The DESolve scaffold incorporates sinusoidal in-phase hoops with straight connectors, and the strut thickness is 150 \(\mu\)m.
   C. The DESolve first-in-man trial enrolled 16 patients, and the angiographic late lumen loss at 6 months was similar to that of contemporary drug-eluting stents (DES).
   D. The DESolve scaffold is made of tyrosine-derived polycarbonate. The first-generation device eluted everolimus, whereas the second-generation scaffold elutes Myolimus.
   E. The DESolve Myolimus-eluting scaffold has acquired the CE mark for clinical use in Europe.
5. The second-generation DREAMS device is a:
   A. Tyrosine polycarbonate scaffold that elutes paclitaxel and provides similar bending flexibility and slower resorption rate compared with the DREAMS I device.
   B. Hybrid of three lactide polymers that elutes sirolimus.
   C. Magnesium-based scaffold that elutes Myolimus with higher resorption rate compared with the DREAMS I device.
   D. Magnesium-based scaffold that has been studied in the BIOSOLVE-I trial.
   E. Magnesium-based scaffold that elutes sirolimus and provides higher bending flexibility and slower resorption rate compared with the DREAMS I device.
   F. Polymer-based scaffold that elutes everolimus and has a slower resorption rate compared with the DREAMS I device.

ANSWERS

1. A

Polymer-based scaffolds undergo bulk degradation after polymer hydration. The first stage in the process of polymer bioresorption is hydration. Polylactides are relatively hydrophilic; thus water diffuses into the less dense amorphous regions of the implant and hydrolyzes the ester bonds. Random chain scissions occur at this stage, leading to reduction of the polymer’s molecular weight. The second stage is characterized by continuous cleavage of the amorphous tie chains, reducing the radial strength of the scaffold and leading to structural discontinuities. During the third stage, polymer chains that have been hydrolyzed to short lengths diffuse out of the implant (mass loss) as they are increasingly hydrophilic and soluble in aqueous solution. Following these sequential stages, oligomeric polylactic acid molecules hydrolyze to lactic acid monomers, which deprotonate (release of a proton [H⁺]) to lactate. Lactate is converted to pyruvate and enters the citric acid cycle (Krebs cycle), which is further metabolized in CO₂ and H₂O excreted through lungs and kidneys. The end products of magnesium-based scaffolds are elemental magnesium and inorganic salts.
Device thrombosis rates in vessels with an RVD of <2.25 mm did not differ among the groups, and the Absorb BVS is indicated in small vessels as well as in vessels with RVD >2.5 mm. The ABSORB III was the first large-scale, multicenter, randomized trial designed to support the Absorb BVS transition from the stage of premarket approval, which allows the execution of phase III clinical trials, to complete Food and Drug Administration (FDA) clearance for clinical use in the United States. Two thousand eight patients with stable or unstable angina were randomly assigned to receive in a 2:1 ratio an everolimus-eluting metallic stent (Xience) or the Absorb BVS 1.1. The primary end point was target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (TV-MI), or ischemia-driven target lesion revascularization (TLR), tested for both noninferiority and superiority at 1 year. The treated lesions were relatively complex, with the majority being type B2. Only very complex lesion subsets, such as very long or heavily calcified lesions, chronic total occlusions, left main disease, and large bifurcations, were excluded. The Absorb BVS was found to be noninferior to Xience at 1 year, meeting the primary end point of noninferiority, albeit with a generous noninferiority margin of 4.5%. TLF occurred in 7.8% of patients in the Absorb BVS arm versus 6.1% of patients in the Xience arm (difference, 1.7 percentage points; 95% confidence interval, −0.5 to 3.9; \( P = .007 \) for noninferiority and \( P = .16 \) for superiority). Individual components of TLF were not significantly different among both arms at 1 year. More specifically, rates of cardiac death in the Absorb BVS arm versus Xience arm were 0.6% versus 0.1% (\( P = .29 \)), respectively. TV-MI event rates in the Absorb BVS arm versus the Xience arm were 6.0% versus 4.6%, respectively (\( P = .18 \)), with TLR rates reaching 3.0% versus 2.5%, respectively (\( P = .50 \)). Device thrombosis among the groups reached 1.5% in the Absorb BVS arm versus 0.7% in the Xience arm (\( P = .13 \)). Interestingly, 25% (\( n = 375 \)) of the vessels treated in the ABSORB III trial had a reference diameter of <2.25 mm. Device thrombosis rates in these smaller vessels were significantly different, reaching 4.65% in the Absorb BVS arm versus 1.55% in the Xience V arm. This subanalysis demonstrates the importance of vessel sizing, suggesting avoidance of vessels >2.5 mm for bioresorbable stent deployment.
In-segment late lumen loss at 1 year was the efficacy end point and the primary end point. The ABSORB China trial was designed to assess in a noninferior fashion the angiographic efficacy of Absorb BVS compared to the Xience V stent in order to receive regulatory approval in China. The primary end point was angiographic in-segment late lumen loss powered for noninferiority with a margin of 0.15 mm. The Absorb BVS was noninferior to the Xience V stent at 1 year, meeting the primary end point of noninferiority. In-segment late lumen loss (in-device + 5-mm proximal and distal edge vascular responses) was 0.19 ± 0.38 mm versus 0.13 ± 0.38 mm (P noninferiority = .01) in the Absorb BVS versus the Xience V stent arms, respectively.

4. D

The DESolve scaffold is made of poly-l-lacatic acid (PLLA). The first-generation device eluted everolimus, whereas the second-generation scaffold elutes Myolimus. The DESolve bioresorbable coronary scaffolds (Elixir Medical Corporation, Sunnyvale, CA) include the first-generation device made of PLLA eluting the antiproliferative agent Myolimus (Novartis, Basel, Switzerland) and the second-generation device, which has the same platform but elutes a novel macrocyclic lactone Novolimus (Elixir Medical Corporation, Sunnyvale, CA) at a dose of 5 μg/mm. The scaffold design incorporates sinusoidal in-phase hoops with straight connectors and a strut thickness of 150 μm, and the expected strut resorption is 1 year, as indicated in porcine models. Despite the radiolucency of the device, it has 2 radiopaque platinum markers at the proximal and distal edges for appropriate visualization. Both systems have a crossing profile of 1.47 mm and are 6-Fr compatible. Degradation process resembles that of Absorb BVS undergoing polymer hydrolysis and further metabolism in the Krebs cycle to end products of carbon dioxide and water. The DESolve Myolimus-eluting scaffold was tested for efficacy, feasibility, and safety in the DESolve FIM trial (A Nonrandomized, Consecutive Enrollment Evaluation of the DESolve Myolimus Eluting Bioresorbable Coronary Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions), which enrolled 16 patients with a single de novo coronary lesion. Multi-imaging assessment with intravascular ultrasound (IVUS), virtual histology IVUS, and optical coherence tomography was serially performed at 6-month follow-up. Multislice computed tomography was performed at 12 months and repeated
at 24 months, whereas clinical end points were assessed at 30 days, 6 months, and annually for up to 5 years.

5. E

The second-generation DREAMS device elutes sirolimus, carries two tantalum radiopaque markers at both ends, and provides higher bending flexibility and slower resorption rate compared with the previous generation DREAMS device. Preclinical data are encouraging and show increased endothelialization rates and decreased inflammatory scores, and the BIOSOLVE-II study has been designed to assess the safety, efficacy, and feasibility of this second-generation device in 120 patients. The primary end point of this trial is in-segment late lumen loss.
Drug-Coated Balloon Technologies: Technical Features and Clinical Applications

Juan F. Granada
Yanping Cheng
Bruno Scheller

HISTORICAL BACKGROUND

The concept of delivering antiproliferative drugs via balloon angioplasty has been around for several decades. However, the specific idea of developing a drug-coated balloon (DCB) system originated from the seminal work of professor Ulrich Speck in the use of contrast agents as carriers of antiproliferative drugs.\textsuperscript{1} At the early stages of his research, it was found that paclitaxel solubility was significantly increased when mixed when contrast agents. Experimental data showed that a repeated intracoronary bolus injection of a taxane-iopromide formulation resulted in significant reduction of neointimal proliferation in the porcine model of restenosis.\textsuperscript{2,3} In 2001, the concept of mixing iopromide with paclitaxel in a form of a balloon coating was reduced to practice and validated at the experimental level.\textsuperscript{4} This original DCB formulation was then clinically validated in small randomized controlled studies in the coronary in-stent restenosis\textsuperscript{5} and de novo superficial femoral artery stenosis settings.\textsuperscript{6,7} Stimulated by these early clinical results, several DCB programs were started following a similar technologic approach
of using hydrophilic carriers as a method to transport paclitaxel into the vessel wall after balloon dilatation.

**TECHNOLOGIC APPROACH**

The development of drug-eluting stents (DESs) dramatically reduced the long-term rate of reintervention and improved clinical outcomes among patients undergoing percutaneous coronary interventions. However, despite their continuous technologic evolution and well-validated clinical efficacy, long-term complications (eg, target lesion revascularization) continue to occur. Several autopsy and in vivo imaging studies suggest delayed healing of the permanently implanted stent as the most important biologic mechanism responsible for these events. As a result, stent-based drug delivery technologies continue to evolve aiming to minimize the amount of permanent implantable components (ie, polymer) left behind following DES implantation.

The concept of developing a balloon-based drug delivery system to prevent arterial restenosis was based on the hypothesis that a durable effect on neointimal proliferation could be achieved following single-drug delivery and potentially minimizing the impact of the chronically implantable components. This technologic approach appeared to contradict historical experimental and clinical data suggesting that sustained tissue exposure to therapeutic levels of drug was necessary to effectively inhibit neointimal proliferation. Due to its particular delivery mechanism and resulting pharmacokinetic profile, the promising results shown by the early DCB trials were originally challenged under the premise that sustained drug release was needed to attain long-term clinical efficacy.

**COATING FEATURES AND MECHANISM OF ACTION**

All DCBs developed to date use paclitaxel due to its high lipophilic profile, potent antiproliferative effect, and chemical stability following tissue delivery. Paclitaxel has shown to inhibit cell proliferation and migration
due to an irreversible stabilization of intracellular microtubules, resulting in inhibition of cell replication during metaphase and anaphase of mitosis.\textsuperscript{15} Early experimental data showed that drug carriers are needed to transfer and maintain paclitaxel tissue levels over time.\textsuperscript{16} Thus, the pharmacokinetic characteristics of each DCB largely depend on the carrier and manufacturing process used to develop the coating. DCBs achieve the short-term transfer and long-term retention of paclitaxel to the arterial wall by different biologic mechanisms.\textsuperscript{17} Experimental data have shown that paclitaxel transfer and retention are not necessarily interrelated phenomena and largely depend on drug morphology and resulting solubility attained during the coating process (Fig. 32-1).\textsuperscript{18,19} At present, although a potential mechanism of action explaining long-term drug retention yielding sustained biologic efficacy following DCB drug delivery is still a matter of debate, important lessons have been learned regarding the pharmacokinetic behavior of some of these technologies. Early experimental data confirmed that paclitaxel transfer into the vessel wall occurs rapidly following balloon inflation.\textsuperscript{4} In addition, several tissue pharmacokinetic studies showed that the short-term tissue levels of paclitaxel following balloon delivery were several-fold higher compared with DES.\textsuperscript{20} Finally, most of the pharmacokinetic studies using clinically available DCB technologies have confirmed that paclitaxel tissue levels are successfully maintained over time (Fig. 32-2).\textsuperscript{17}
FIGURE 32-1 Paclitaxel coating types by surface electron microscopy according to manufacturing process; crystalline (A), hybrid (B), amorphous (C), nanospheres (D), and microcrystals (E). Table describes potential impact of the coating features on biologic performance.

<table>
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<tr>
<th>Feature</th>
<th>Crystalline</th>
<th>Amorphous</th>
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<tr>
<td>Particles released</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Uniform coating</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Drug transfer to vessel</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Drug retention vs time</td>
<td>+++</td>
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<td>Biological effectiveness</td>
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<td>Vascular toxicity</td>
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Several experimental studies suggest that the presence of paclitaxel deposits on the surface of the vessel wall contribute to the biologic process of sustained local drug delivery. A recent study suggested that following DCB dilatation, a large proportion of the paclitaxel coating is retained on the vessel surface and is not actually dissolved into the tissue (Fig. 32-3). In this study, it seemed apparent that arterial tissue levels were directly related to the sustained retention of drug on the surface of the vessel wall, thereby providing a constant concentration gradient from the vessel surface into the arterial wall over time. Interestingly, at 7 days, vessel wall concentrations began to equalize to the vessel surface levels, providing an explanation regarding the lack of tissue toxic effects despite the apparent supratherapeutic tissue levels found in pharmacokinetic studies. These results largely depended on the degree of paclitaxel crystallinity and seemed to be consistent with previous reports showing that specific binding to intracellular proteins occurs primarily in the subintimal space and determines arterial transport properties and microtubule binding of paclitaxel. As a consequence, the observed tissue half-life of paclitaxel delivered by DCB relates to the slow dissolution of paclitaxel deposits from the vessel surface into arterial tissue in a time-dependent fashion. Thus, the proposed mechanism of action reconciles the apparent contradiction between the observed short term
supratherapeutic tissue levels seen right after balloon delivery and the resulting vessel healing profiles seen at the experimental level. However, the mechanism of action of DCB is likely technology dependent and likely will unveil several mechanistic pathways that will help the future development of DCB technologies.

FIGURE 32-3 Impact of crystallinity on paclitaxel (PTX) deposition on the vessel surface: vessel wall (A) versus vessel surface (B) on 2 different coatings.

VESSEL HEALING AND DISTAL
TISSUE EFFECTS

Vessel healing largely depends on the pharmacokinetic features of each DCB technology. Bench data suggest that during balloon transit to the target lesion, approximately 10% to 15% of the drug is lost into the bloodstream. Also, at the time of balloon inflation, coating fragmentation occurs and paclitaxel particles are either transferred to the vessel wall or lost into the distal bloodstream (Fig. 32-4).\textsuperscript{16} Despite the high paclitaxel tissue levels achieved immediately after DCB delivery, tissue levels rapidly decline in 72 hours, and most of the paclitaxel remains attached to the surface of the vessel wall.\textsuperscript{4} After 7 days, paclitaxel tissue levels are comparable (although slightly higher) to the ones reported for DES.\textsuperscript{20}

\textbf{FIGURE 32-4} Proposed mechanism of drug loss and particulate production in drug-coated balloon technologies. PCB, paclitaxel-coated balloon.

The vessel healing characteristics of arteries treated with DCB vary according to the presence or absence of stents. In the absence of the stent, the vessel healing profile is characterized by neointimal inhibition, presence of fibrin, and smooth muscle cell loss persistent over 90 days and resolving at 180 days.\textsuperscript{16} In contrast, the vascular healing profile of bare metal stents...
(BMSs) followed by DCB dilatation is similar to the one reported for paclitaxel-eluting stents (Fig. 32-5). Finally, a significant amount of emphasis has been put on the phenomenon of particulate embolization into the distal bloodstream. In vitro data have shown that the degree of particulate formation is significantly higher compared to DES. However, it has also been described that these particles are usually small and unlikely to be trapped into the distal microcirculation. Experimental data also suggest that microembolization is a rare finding and perhaps clinically irrelevant. However, due to the potential clinical adverse events derived from this phenomenon, the clinical introduction of these technologies for the treatment of specific critical vascular territories (eg, below the knee) has been slow and limited.

**FIGURE 32-5** Representative histologic pictures and vascular healing response of crystalline and amorphous coatings at 28 days of follow-up. NS, not significant; PCB, paclitaxel-coated balloon; POBA, plain old balloon angioplasty.

**CORONARY DCB APPLICATIONS**
Although current-generation coronary DESs are considered to be standard of care, significant challenges still remain in specific clinical subsets in which DES outcomes are still suboptimal (eg, in-stent restenosis). In addition, DCBs have the potential to improve clinical outcomes in patients in whom the use of long-term dual antiplatelet therapy is limited (eg, bleeding risk). Thus, at present, the use of DCB has been limited to this specific population subset. In addition, although the use of DCB for the treatment of de novo lesions without the use of stents (“leaving nothing behind”) is theoretically appealing, the risk of abrupt vessel closure following balloon angioplasty and the high clinical success of DES have largely limited the introduction of this approach.

**In-Stent Restenosis**

The first publication of DCB use in humans was described for BMS in-stent restenosis (ISR). In this multicenter study, 52 patients with coronary BMS-ISR were randomized to receive angioplasty with either an uncoated balloon or an iopromide-paclitaxel–coated DCB. At 6 months, the DCB group demonstrated a significant benefit in the primary end point of angiographic in-segment late lumen loss (LLL) (0.74 ± 0.86 vs 0.03 ± 0.48 mm; \( P = .002 \)) as well as in the 6-month secondary end points of minimal lumen diameter (MLD) and binary restenosis. An additional 56 patients with coronary ISR were randomized, and the combined cohort of 108 patients was followed for 5 years, confirming the durability of the antiproliferative effect.

The PEPCAD (Paclitaxel-Eluting Percutaneous Transluminal Coronary Angioplasty Catheter in Coronary Disease) trial program investigated the SeQuent Please DCB (B. Braun, Berlin, Germany) using the same iopromide-paclitaxel coating. PEPCAD II was a multicenter, randomized trial of the DCB versus the Taxus DES (Boston Scientific, Marlborough, MA) in 131 patients with coronary BMS-ISR. The primary end point of 6-month in-segment LLL was significantly less with the DCB compared with the DES (0.17 ± 0.42 vs 0.38 ± 0.61 mm; \( P = .03 \)). At 12 months, target lesion revascularization (TLR) trended in favor of the DCB (6% vs 15%; \( P = .15 \)), suggesting that the DCB was at least as effective as the DES for BMS-ISR and avoiding the need of a second DES implantation. Since then, 8 randomized trials have been published studying the SeQuent Please DCB in
BMS-ISR\textsuperscript{25,26,28} and DES-ISR.\textsuperscript{29-34} A meta-analysis\textsuperscript{35,36} to assess the clinical efficacy of DCB for the treatment of DES-ISR from 5 studies\textsuperscript{29-34} including a total of 864 patients showed that DCB was superior to plain old balloon angioplasty (POBA) and comparable to first-generation DES for treatment of DES restenosis. Based on these trials, the 2014 European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines on myocardial revascularization state (Class I, Level of Evidence A) that DCBs are clinically recommended for the treatment of ISR (within BMS or DES).\textsuperscript{24} Almalla et al\textsuperscript{37} reported that treatment of 86 patients with DES-ISR using the SeQuent DCB is associated with lower rates of major adverse cardiac events (MACE) and TLR at 1-year follow-up compared to second-generation DES (Xience V; Abbott Vascular, Santa Clara, CA). However, the latest results of the RIBS IV trial,\textsuperscript{38} which compared SeQuent DCB with the Xience Prime DES in 309 patients with DES-ISR, showed that patients treated with everolimus-eluting stents achieved superior 9-month LLL compared to DCB (everolimus-eluting stent 2.03 vs DCB 1.80; $P = .004$). At 1 year, freedom from TLR was higher in the patients treated with everolimus-eluting stents than in the DCB group (96% vs 87%; $P = .008$; Table 32-1). As a result, the use of DCB for DES-ISR needs to be considered on individual basis and the decision based on specific anatomic and clinical characteristics of each patient.

**Table 32-1** Summary of Major DCB Studies in DES-ISR
De Novo Coronary Lesions

The initial concept for the use of DCB in coronary de novo lesions included the combination with a BMS to create a “polymer-free” DES. However, results from the PEPCAD III trial comparing such a BMS/DCB combination with the Cypher DES (Cordis, Hialeah, FL) showed this concept to be an inferior approach. Other concepts combining BMS and DCB as primary therapies have also shown similar results. These results have been partially explained by suboptimal percutaneous coronary intervention (PCI) technique (ie, geographic miss) and/or inferior DCB coatings. Nevertheless, even with optimized PCI techniques and more advanced coatings, the biologic effect of the DCB/BMS combination has proven to be clinically inferior compared to current-generation DESs. The PEPCAD I study was a nonrandomized study investigating the safety and efficacy of the SeQuent Please DCB with provisional BMS implantation in small vessel (mean reference vessel diameter, 2.36 mm) de novo lesions in 120 patients. At 6 months of follow-up, in-segment LLL was significantly less with DCB alone compared with DCB plus BMS (0.18 and 0.73 mm, respectively), with
the majority of the ISR being noted at the stent edges. In patients with adjunctive BMS implantation, geographical miss was thought to be a strong predictor of the occurrence of future ISR.\textsuperscript{48,49}

As a consequence of these findings, the so-called “DCB-only” strategy has been favored for the coronary use of DCB technologies. This concept includes careful lesion preparation, and depending on the result after predilatation, the operator can decide whether to proceed with DCB only in case of an acceptable angiographic result or use a stent or scaffold in case of major dissection (type C or higher), significant residual stenosis, or reduced flow. This approach aims to avoid the use of unnecessary stents and shorten the duration of dual antiplatelet therapy (~4 weeks in DCB-only procedures).\textsuperscript{50,51} This strategy was successfully investigated in 2 large registries\textsuperscript{52,53} and the randomized BELLO study. In this trial, 182 patients with small coronary vessel disease were treated with either the IN.PACT Falcon balloon (Medtronic, Dublin, Ireland) applying the DCB-only approach or the Taxus stent. The primary end point of LLL at 6 months was significantly lower in the DCB arm (0.08 ± 0.38 vs 0.29 ± 0.44 mm; \(P = .001\)), demonstrating superiority of the DCB-only approach over DES in terms of angiographic end points.\textsuperscript{54} Three-year follow-up (N. Ruparelia, unpublished data, May 2015) has been recently completed in more than 90% of the patients and shows a lower incidence of MACE events in the DCB group compared with the paclitaxel-eluting stent group (14.4% vs 30.4%; \(P = .015\)). However, TLR rates in the DCB group were comparable to those in the paclitaxel-eluting stent group at 6 months, 1 year, and 3 years (4.4% vs 7.6%, \(P = .37\); 4.4% vs 9.8%, \(P = .25\); 6.7% vs 13.0%, \(P = .14\), respectively). An interesting application is in the setting of ST-segment elevation myocardial infarction (STEMI). First results of the DEB-AMI (Drug-Eluting Balloon in Acute ST-Segment Elevation Myocardial Infarction) trial\textsuperscript{55} showed that in STEMI patients, DCB followed by BMS implantation failed to show angiographic superiority to BMS only. Six-month angiographic (LLL: DES 0.21 ± 0.32 mm vs BMS 0.74 ± 0.57 mm and DCB+BMS 0.64 ± 0.56 mm; \(P < .01\)) and clinical results of DES (MACE: DES 4.1% vs BMS 23.5% and DCB+BMS 20.0%; \(P = .02\)) were superior to both BMS and DCB. In a recent report, Camaro and colleagues (unpublished data, May 2015) assessed the angiographic and clinical outcomes of the use of DCB in the STEMI setting. In this study, a total of 130 patients were randomly assigned to predilatation with a paclitaxel-coated balloon (PCB) versus POBA, followed by
implantation of a Genous endothelial progenitor cell capture stent (OrbusNeich, Fort Lauderdale, FL; the DEBORA 2 randomized trial). At 9 months, the mean minimal lumen late loss was 0.18 ± 0.60 mm in the DCB group and 0.55 ± 0.52 mm in the POBA group ($P < .01$). No significant difference with regard to MACE was observed between groups (8.1% vs 9.5%; $P = .773$) at any time interval of clinical follow-up to 12 months. Finally, although the potential favorable vascular effects of the DCB-only strategy (eg, positive remodeling) have been shown in small observational studies, the lack of prospective comparative data has limited DCB use to specific clinical applications at the present time.

PERIPHERAL DCB APPLICATIONS

In contrast to the coronary field, peripheral vascular interventions are less dependent on the use of metallic stents. In long femoropopliteal lesions, the regular use of metallic stents has resulted in high mechanical and clinical failures rates. In addition, the treatment of ISR is a major clinical problem with no clear therapeutic alternatives. Thus, the use of DCB in the peripheral territory has gained more traction compared to the coronary field. However, the most important limitation of DCB use in this vascular territory is the potential for suboptimal angiographic results and dissections, leading to the use of “spot” metallic stenting. Although the use of DCB for de novo lesions has been clinically validated, the combination with BMS for this particular application is less clear. In addition, the use of adjunctive atherectomy and other lesion preparation techniques has also been proposed as a way to reduce the incidence of adjunctive stenting and enable the wider use of DCB in this particular vascular territory.

Femoropopliteal Disease

Several first-in-human randomized trials using different DCB technologies in femoropopliteal lesions have validated the safety and efficacy of this technology compared to POBA (Fig. 32-6). A meta-analysis including 381 patients (DCB, n = 186; POBA, n = 195) and using TLR as the primary end point has been recently published. At a median follow-up of 10.3 months, DCB use versus POBA reduced TLR (12.2% vs 27.7%; odds ratio
[OR], 0.22; 95% confidence interval [CI], 0.13-0.38; \( P < .00001 \)), angiographic restenosis (18.7% vs 45.5%; OR, 0.26; 95% CI, 0.14-0.48; \( P < .00001 \)), and 6-month LLL (–0.05-0.50 mm vs 0.61-1.7 mm; mean difference, –0.75 mm; 95% CI, –1.06 to –0.45; \( P < .00001 \)). In addition, the first DCB study performed in the superficial femoral artery (SFA) territory (THUNDER) has already reached 5-year follow-up demonstrating durability of the drug effect (TLR: DCB 21% vs POBA 56%; \( P = .0005 \)).

FIGURE 32-6 Primary efficacy end points of major drug-coated balloon (DCB) first-in-human clinical studies in the femoropopliteal vascular territory. BTCH, butyryltrin-hexyl citrate; LLL, late lumen loss; POBA, plain old balloon angioplasty; PTX, paclitaxel; TLR, target lesion revascularization.
Two large-scale randomized controlled trials have already completed 12-month clinical follow-up (Table 32-2). The LEVANT II trial\textsuperscript{64} enrolled a total of 476 patients, and the IN.PACT SFA II trial\textsuperscript{65} enrolled a total of 331 patients with a 2:1 randomization. In the LEVANT II trial, the primary vessel patency at 12 months, defined as freedom from both restenosis and TLR, was 65.2\% for DCB and 52.6\% for POBA ($P = .015$). At 12 months, the freedom from clinically driven TLR in the DCB group was attenuated and similar to the control group (87.7\% vs 83.2\%; $P = .208$). In this study, despite that both the safety (freedom from death, amputation, and reintervention) and efficacy primary end points were met, clinical efficacy was not demonstrated. The pooled randomized multicenter IN.PACT SFA I and II trials revealed that clinically driven TLR rates were significantly lower in the DCB group compared to the POBA group (2.4\% vs 20.6\%; $P < .001$). Similarly, the primary patency rate achieved with the IN.PACT Admiral balloon was 82.2\% versus 52.45\% in the POBA group ($P < .001$). In these studies, no safety issues were identified. The safety and efficacy of the use of DCB in long lesions have been recently presented (A. Micari, unpublished data, May 2015). In this study, 105 symptomatic patients with SFA lesions greater than 15 cm were enrolled. Angioplasty success was 84.8\%, the mean total lesion length was 252 mm, and the mean total treated length was 263 mm. The rate of primary patency at 12 months was 83.2\%, with 96\% free of TLR and 84.2\% free of restenosis. The primary patency rate was also reported in the IN.PACT SFA trial (D. Scheinert, unpublished data, May 2015) in 157 patients with long lesions. The 360-day primary patency rate was 91.1\%. Freedom from adverse safety events was 94\%; rates of all-cause death and any TLR were 4.5\% and 6.0\%, respectively. Those results demonstrate remarkable overall effectiveness and safety for patients treated with this technology in this lesion subset.

Table 32-2 \textbf{Summary of Major Randomized Controlled Trials of DCB in the Femoropopliteal Territory}
<table>
<thead>
<tr>
<th></th>
<th>IN.PACT SFA Trial</th>
<th>PTA</th>
<th>P Value</th>
<th>Lutonix SFA Trial</th>
<th>PTA</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline Clinical Characteristics</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age, years, mean ± SD (no.)</td>
<td>67.5 ± 9.5</td>
<td>68.0 ± 9.2</td>
<td>.612</td>
<td>67.8 ± 10.0 (316)</td>
<td>69.0 ± 9.0 (160)</td>
<td>.207</td>
</tr>
<tr>
<td>Male sex, % (no./ No.)</td>
<td>65.0% (143/220)</td>
<td>67.6% (75/111)</td>
<td>.713</td>
<td>61.1% (193/316)</td>
<td>66.9% (107/160)</td>
<td>.216</td>
</tr>
<tr>
<td>Diabetes, % (no./ No.)</td>
<td>40.5% (89/220)</td>
<td>48.6% (54/111)</td>
<td>.161</td>
<td>43.4% (137/316)</td>
<td>41.9% (67/160)</td>
<td>.758</td>
</tr>
<tr>
<td>ABI/TBI, mean ± SD (no.)</td>
<td>0.769 ± 0.228</td>
<td>0.744 ± 0.189</td>
<td>.308</td>
<td>0.7 ± 0.2 (306)</td>
<td>0.7 ± 0.2 (156)</td>
<td>.364</td>
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<tr>
<td>Rutherford grade, % (no./No.)</td>
<td></td>
<td></td>
<td>.898</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>37.7% (83/220)</td>
<td>37.8% (42/111)</td>
<td>.521</td>
<td>29.4% (93/316)</td>
<td>34.4% (55/160)</td>
<td>.521</td>
</tr>
<tr>
<td>3</td>
<td>57.3% (126/220)</td>
<td>55.9% (62/111)</td>
<td></td>
<td>62.7% (198/316)</td>
<td>57.5% (92/160)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.0% (11/220)</td>
<td>5.4% (6/111)</td>
<td></td>
<td>7.9% (25/316)</td>
<td>8.1% (13/160)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Angiographic Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion length, cm, mean ± SD (no.)</td>
<td>8.94 ± 4.89</td>
<td>8.81 ± 5.12</td>
<td>.815</td>
<td>62.9 ± 41.5 (315)</td>
<td>63.6 ± 40.3 (160)</td>
<td>.866</td>
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<tr>
<td>Total occlusions, % (no./No.)</td>
<td>25.8% (57/221)</td>
<td>19.5% (22/113)</td>
<td>.222</td>
<td>20.6% (65/316)</td>
<td>21.9% (35/160)</td>
<td>.741</td>
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<td>Severe calcification, % (no./No.)</td>
<td>8.1% (18/221)</td>
<td>6.2% (7/113)</td>
<td>.662</td>
<td>59.2% (187/316)</td>
<td>57.5% (92/160)</td>
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<td>Diameter stenosis before treatment, %, mean ± SD</td>
<td>81.1 ± 15.5</td>
<td>81.3 ± 13.7</td>
<td>.946</td>
<td></td>
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<td>Diameter stenosis after treatment, %, mean ± SD</td>
<td>19.9 ± 10.4</td>
<td>19.1 ± 10.3</td>
<td>.535</td>
<td>23.4 ± 12.3 (316)</td>
<td>23.8 ± 12.3 (158)</td>
<td>.703</td>
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<tr>
<td>Ball-out stenting, % (no./No.)</td>
<td>7.3% (16/220)</td>
<td>12.6% (14/111)</td>
<td>.11</td>
<td>2.5% (8/316)</td>
<td>6.9% (11/160)</td>
<td>.022</td>
</tr>
<tr>
<td>Device success, % (no./No.)</td>
<td>99.0% (308/311)</td>
<td>98.5% (128/130)</td>
<td>.302</td>
<td>99.5% (430/432)</td>
<td>100% (180/180)</td>
<td>.367</td>
</tr>
<tr>
<td>Procedure success, % (no./No.)</td>
<td>99.5% (219/220)</td>
<td>98.2% (109/111)</td>
<td>.111</td>
<td>88.9% (281/316)</td>
<td>86.8% (138/159)</td>
<td>.497</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12-Month Outcomes</th>
<th>IN.PACT SFA Trial</th>
<th>PTA</th>
<th>P Value</th>
<th>LEVANT II Trial</th>
<th>PTA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary patency, % (no./No.)</strong></td>
<td>82.2% (157/191)</td>
<td>52.4% (54/103)</td>
<td>&lt;.001</td>
<td>Primary patency, %</td>
<td>73.5%</td>
<td>56.8%</td>
</tr>
<tr>
<td>Clinically driven TLR, % (no./No.)</td>
<td>2.4% (5/207)</td>
<td>20.6% (22/107)</td>
<td>&lt;.001</td>
<td>Freedom from TLR, %</td>
<td>89.70%</td>
<td>84.30%</td>
</tr>
<tr>
<td>Primary safety composite, % (no./No.)</td>
<td>95.7% (198/207)</td>
<td>76.6% (82/107)</td>
<td>&lt;.001</td>
<td>Freedom from primary safety event, %</td>
<td>86.70%</td>
<td>81.50%</td>
</tr>
</tbody>
</table>
One recent publication addressed the issue of dissections following DCB use. In a subgroup analysis of the THUNDER trial, dissections did not negatively impact the efficacy of DCB angioplasty if left alone without stent placement. At 6 months, patients displaying dissections of any grade after treatment with DCB (n = 43) had significantly lower LLL than patients with dissection following POBA (n = 43; 0.4 vs 1.9 mm; \( P = .001 \)). In addition, patients displaying severe dissections (grade C-E) also had lower LLL with DCB compared to POBA (0.4 vs 2.4 mm; \( P = .05 \)). At the 2-year follow-up, TLR rates were 56% in the POBA group versus 10% in the DCB group (\( P = .002 \)). Although intriguing, it is important to note that the lesions included in this study were relatively short and noncalcific and thus not representative of the real-world population.

The efficacy of the adjunctive use of BMS plus DCB has been reported in a prospective, randomized, international trial (J. Tacke, unpublished data, May 2015). A total of 200 patients were enrolled and randomized equally to primary BMS implantation followed by either DCB (Freeway; Eurocor, Bonn, Germany) or POBA after dilatation. The results highly favored the use of DCB over POBA based on clinically driven TLR (5.1% vs 11.0% at 6 months and 9.1% vs 18.0% at 12 months) and primary patency rates (88.3% vs 70.0% at 6 months; \( P = .008 \)).

The efficacy of DCB in ISR lesions has also been recently tested. ISR occurs in up to 40% of femoropopliteal lesions treated with BMS within 1 year. In addition, the risk of ISR increases with lesion complexity and treated length. Parallel to the development of more aggressive recanalization techniques, the use of femoropopliteal stenting continues to increase. Thus, the occurrence of ISR has become a common clinical issue in SFA intervention. The optimal treatment of this condition remains elusive as multiple modalities have failed to provide durable results. Early preliminary
data supported the use of DCB for this clinical indication. A single-center prospective registry, including 39 patients, reported a 1-year primary patency rate of 92.1% and a 2-year primary patency rate of 70.3%. A more recent randomized controlled study (FAIR: DCB vs POBA for Superficial Femoral Artery In-Stent Restenosis) was presented including 119 patients with ISR mean lesion length of 8.2 cm in both study cohorts. The 6-month restenosis rate (primary end point) favored the DCB arm compared to POBA (15.4% vs 44.7%; \( P = .002 \)). At 1 year, restenosis rates were 29.5% and 62.5%, respectively (\( P = .004 \)), and freedom from clinically driven TLR rates at 390 days were 90.8% and 52.6%, respectively (\( P = .0001 \)).

**Ancillary Use of Atherectomy Devices**

The combination of debulking followed by PCB technology to achieve the best outcome for both acute and long-term success seems an attractive approach for these patients. Early, small, single-center reports of the combination of directional atherectomy (DA) and DCB have shown some promise of this approach for patients with lower limb arterial disease. In one study, the combination of DA and DCB (\( n = 60 \)) was compared with DA with non-DCB angioplasty (\( n = 29 \)). The outcomes were primary patency of 84.7% in the DCB group compared with 43.8% in the non-DCB group. In addition, in heavily calcified lesions, the combination of DCB provided a 90% freedom from clinically driven TLR in 30 patients studied from a single center. Thus, the combination of DA with the added technology of DCB seems to be an attractive approach in patients with significant arterial obstructive disease. Clearly, the scientific data are still scarce, and the cost-benefit analysis of this approach deserves further evaluation. The DEFINITIVE AR study (T. Zeller, unpublished data, November 2014) is a prospective, multicenter, pilot feasibility study designed to assess and estimate the effect of treating vessels with DA prior to a DCB. Claudicants with 7- to 15-cm SFA and/or popliteal lesions were randomized 1:1 to either DA+DCB or to DCB alone. Subjects with severely calcified lesions were assigned to a nonrandomized registry arm and were treated with DA+DCB. One hundred twenty-one subjects were enrolled, 48 in the DA+DCB arm, 54 in the DCB arm, and 19 in the severely calcified lesion DA+DCB registry group. Mean lesion length ranged from 9.7 to 11.9 cm. In the randomized groups, the primary end point, percent stenosis at 12 months, was similar in
both cohorts. Angiographic patency (≤50% stenosis and without TLR) was 82.4% in the DA+DCB arm and 71.8% in the DCB arm. The major adverse event rate, defined as a composite of clinically driven TLR, death, and major amputation, was 11.6% for the randomized DA+DCB arm, 9.8% for the randomized DCB arm, and 5.9% for the severely calcified lesion registry arm. This pilot study suggests an added benefit for combination therapy (DA+DCB) in long and calcified lesions that was not observed in the DCB-alone subgroup. Further investigation in larger, prospective, statistically powered randomized trials is warranted.

**Below-the-Knee Disease**

Multiple biologic aspects of below-the-knee (BTK) disease impact the performance of DCB in this vascular territory. The management of long calcified lesions in multiple small-caliber, low-flow arteries with a high-resistance outflow bed influences tissue pharmacokinetics. In addition, BTK arteries represent a tapering system with smaller arteries at the ankle and foot. If the artery significantly tapers in a long diseased segment, drug delivery and distribution may not be uniform. In addition, the presence of multiple lesions throughout the length of an artery and few anatomic landmarks may lead to geographic miss. In addition, medial calcification is a common finding among diabetics with BTK lesions. It is not clear whether these complex biologic components affect drug pharmacokinetics.

The use of DCB in the treatment of BTK occlusive disease and critical limb ischemia syndrome is still under debate. From a technical point of view, particulate formation leading to microvessel embolization may play a more significant role compared to DCB use in other vascular territories. Especially among patients with poor vascular runoff, the dislodgment of a large amount of particles may lead to the mechanical occlusion of microvessels vital for tissue survival. In addition, paclitaxel accumulation in hypoxic tissue may either delay or worsen healing in patients with evidence of tissue loss. Many questions need to be answered before the wide adoption of DCB in BTK intervention.

In BTK intervention, restenosis following POBA ranges from 42% to 69% at 12 months according to the lesion length. A meta-analysis of BTK angioplasty studies indicated that the overall 1-year patency of POBA was 58.1% ± 4.6% and the limb salvage rate was 86.0% ± 2.7%. Despite the
large amount of activity in the DCB field, data in the BTK territory are limited and controversial. Early noncontrolled studies suggested that restenosis following DCB use was lower compared to POBA, and recurrences tended to be more focal. A study including long lesions (mean, 17.3 cm) showed a 3-month angiographic restenosis rate of 27.4%. In this study, most of the restenosis (61%) was focal, and only 8% of the DCB failures presented as total vessel occlusion. In the DEBATE BTK trial, a randomized controlled trial of DCB versus POBA, both restenosis (27% vs 74%; \( P = .001 \)) and TLR (18% vs 43%; \( P = .003 \)) were drastically reduced at 1 year. Moreover, vessel occlusion was 17% versus 55% \(( P < .001 \)) complete wound healing occurred in 86% versus 67% of patients \(( P = .01 \)), and there were no significant differences in terms of major limb amputation.

The IN.PACT DEEP multicenter randomized controlled trial used a similar device and failed to confirm the positive early clinical data. This study compared the performance of the IN.PACT Amphirion DCB with POBA in a 2:1 randomization ratio in 358 patients with prespecified primary end points for efficacy (TLR and LLL) and safety (all-cause death, major amputations, or TLR). All patients were assessed at 1-year follow-up for clinical end points. A subgroup of patients with lesions ≤10 cm in length underwent angiographic follow-up. Significant baseline differences between the DCB and POBA cohorts included mean lesion length (10.2 vs 12.9 cm; \( P = .002 \)), impaired inflow (40.7% vs 28.8%; \( P = .035 \)), and previous target limb revascularization (32.2% vs 21.8%; \( P = .047 \)). Primary efficacy results of DCB versus POBA were clinically driven TLR of 9.2% versus 13.1% \(( P = .291 \)) and LLL of 0.61 ± 0.78 mm versus 0.62 ± 0.78 mm \(( P = .950 \)). The primary composite safety end point was 17.7% versus 15.8% \(( P = .021 \)) and met the noninferiority hypothesis. A safety signal driven by major amputations through 1 year was observed in the DCB versus POBA arm (8.8% vs 3.6%; \( P = .080 \); Table 32-3).

Table 32-3 Summary of Major Randomized Controlled Trials of DCB in the Treatment of Below-The-Knee Disease
DCB use in the most distal arteries (ankle and foot) seems to lead to lower patency rates compared to the most proximal arteries. It has been hypothesized that the small size of the arteries causing increased friction and
higher drug losses may be responsible for these findings. However, the low patency of these very distal arteries may also be due to a mechanical effect (external forces, impingement, and constant movement) that cannot be solved by DCB. In any case, the clinical use of DCB in very distal vessels is still unknown. In conclusion, although there is a widespread opinion that suggests that DCB can substantially improve the success of endovascular procedures for BTK disease, the recent results of the IN.PACT DEEP study, which caused alarme in terms of safety and lack of efficacy, suggest that an abundance of caution is reasonable.

**FUTURE PERSPECTIVES**

To date, the use of DCB in the coronary territory is limited to patients with ISR (Class I, Level A recommendation)\(^24\) and other “niche” clinical subsets. Clinical adoption involving other indication will largely depend on the evolution of these technologies toward safer and more predictable local drug delivery devices. Significant technologic improvements are under development and include low-dose, low-particulate coating technologies and sirolimus-based local drug delivery devices. Regardless, comparative randomized studies against traditional DES therapies will be needed in order to introduce these technologies as workhorse devices. In contrast, in the peripheral field, DCB use is a more widely accepted and clinically validated strategy. As in the coronary territory, DCBs are limited by the potential use of extra stents and the additional cost incurred by this approach. However, DCBs have taken a lead for this particular vascular application in which the use of stents is less desirable. Finally, the DCB field continues to evolve toward the development of more precise delivery methods and alternative drugs that permit the expansion to other vascular territories and clinical applications.

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Kleber FX, Rittger H, Bonaventura K, et al. Drug-coated balloons for


40. Virga V, Stabile E, Biamino G, et al. Drug-eluting balloons for the


**MULTIPLE CHOICE QUESTIONS**

1. Commercially available DCBs developed to date use the anti-proliferative drug, paclitaxel. Which of the following paclitaxel formulations is more effective in maintaining the drug in the vessel wall for a longer time?
   - A. Solid phase (crystalline) paclitaxel
   - B. Amorphous phase paclitaxel
   - C. High dose of liquid phase paclitaxel
   - D. Crystalline paclitaxel without a carrier

2. Which of the following statements is *true* regarding the application of DCBs in coronary diseases?
   - A. DCB has shown to be superior to EES for the treatment of in-stent restenosis
   - B. DCB and BMS combination is superior to BMS in acute myocardial infarction
   - C. DCB has shown to be superior to standard angioplasty for the treatment of in-stent restenosis
   - D. The DCB-only has no benefit to treat atherosclerotic disease involving small coronary vessels

3. Which of the following statements is *false* regarding the potential advantages of DCB over DES?
   - A. Polymer-free single time drug delivery
   - B. Completely prevents the use of ancillary stents
   - C. Allow the treatment of long segments leaving nothing behind
   - D. Does not preclude re-intervention of the treated segment in case restenosis occurs
4. Which of the following is true in regards to the outcomes from the IN.PACT SFA randomized trial?
   A. DCB was not effective in all important patient subgroups
   B. DCB required extensive use of adjunctive stenting in all participating patients
   C. The outcomes from the 1-year follow-up analysis did not confirm the durable effect of the DCB
   D. DCB was superior to standard angioplasty in terms of primary patency and safety composite end point

5. What was the major outcome from the randomized IN.PACT DEEP trial?
   A. DCB was superior to PTA in terms of primary efficacy and safety composite end point
   B. DCB had comparable efficacy to PTA in terms of primary efficacy and safety composite end point
   C. The outcomes from the subgroup did not meet the primary efficacy endpoint
   D. DCB was inferior to PTA in 12 month efficacy results

**ANSWERS**

1. A

   Solid phase drug provides a reproducible pharmacokinetic profile after balloon delivery and the drug stays in the vessel wall after the balloon inflation for a longer time compared with liquid phase drug that diffuses quickly into tissues. Addition of a carrier to crystalline paclitaxel keeps the drug in the vessel wall for a longer time and enhances drug intake.

2. C

   Randomized clinical trials have demonstrated the safety and efficacy profile of DCB over PTA for the treatment of in-stent restenosis. DCB appear to be as effective as paclitaxel-eluting stents in this particular application, however, re-intervention using EES was shown to be more effective in reducing angiographic restenosis compared to DCB. Small clinical studies support their use in other de novo clinical settings such small vessels, diffuse lesions
and bifurcation lesions, but until further refinements in DCB technology are made and larger randomized clinical trials are performed, the role of this technology remains to be completely understood.

3. B

Potential advantages of DCB include (a) single time drug transfer to the entire vessel wall; (b) rapid release of high concentrations of the drug sustained in the vessel wall; (c) absence of polymer could decrease chronic inflammation and the trigger for late thrombosis; (d) leave no implant; and (e) with local drug delivery.

4. D

Treatment effect of DCB was durable, few patients required adjunctive stenting, and the beneficial effect was observed across important patient groups including females and patients with diabetes. The 12-month follow-up results showed a significant benefit to patients treated with the DCB angioplasty compared with patients treated with the standard balloon angioplasty; higher primary patency ($P < 0.001$) and lower CD-TLR ($P < 0.001$).

5. B

The IN.PACT DEEP multicenter randomized controlled trial compared the performance of the IN.PACT Amphirion DCB with PTA in a 2:1 randomization ratio in 358 patients with pre-specified 2 primary endpoints for efficacy (TLR and LLL) and safety (all-cause death, major amputations or TLR). Primary efficacy results of DCB versus PTA were CD-TLR of 9.2% versus 13.1% ($P = 0.291$) and LLL of 0.61 ± 0.78 mm vs 0.62 ± 0.78 mm ($P = 0.950$). Primary safety endpoints were 17.7% vs 15.8% ($P = 0.021$) and met the noninferiority hypothesis.
In-Stent Restenosis

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INTRODUCTION

The safety and efficacy of percutaneous coronary interventions (PCI) have been drastically improved by the introduction of bare metal stent (BMSs) in clinical practice.\(^1\) However, a new pathologic entity arose with the implantation of BMSs within coronary arteries: in-stent restenosis (ISR).\(^2\) ISR can be defined as the in-stent lumen narrowing that pathobiologically relates to the phenomenon of neointimal hyperplasia (NIH).\(^3\) Biologic, mechanical, procedural, and stent-related factors interplay in determining the incidence, morphology, and clinical implications of ISR. Introduction of drug-eluting stents (DESs) in 2001 in clinical practice represented a technologic breakthrough. DESs critically improved the efficacy of percutaneous revascularization procedures by reducing the need of target lesion revascularization (TLR) and target vessel revascularization (TVR) at follow-up.\(^4\) However, a low rate of ISR after DES implantation still exists. With more than 3 million DESs implanted worldwide each year, DES-ISR represents a major public health issue. In this chapter, we comprehensively review the incidence, mechanisms, diagnosis, and potential treatment strategies of ISR, with a particular focus in the contemporary DES era.

DEFINITION AND CLASSIFICATION
The goal of percutaneous revascularization procedures is the relief of significant coronary artery obstructions. Effectiveness of PCI with stent implantation is expressed in terms of clinically significant restenosis assessed objectively as a requirement for ischemia-driven repeat revascularization either of the stented lesion itself (TLR) or of the stented vessels and its collateral branches (TVR). ISR can be defined as a lumen narrowing within the site of stent implantation induced by local vascular barotrauma with reactive NIH. The clinical consequence of ISR is the development of a new flow-limiting obstructive lesion and subsequent reduction of downstream myocardial perfusion.

ISRd differ in their morphologic pattern, which in turn is associated with important clinical, prognostic, and therapeutic implications. The most accepted morphologic classification of ISR is the one proposed by Mehran et al. Before the introduction of this classification, patterns of ISR were broadly classified as focal (in-stent lesion <10 mm in length) or diffuse (in-stent lesion >10 mm in length). The Mehran classification introduced the description of the topographic relation between NIH and the coronary stent implanted. This classification is as follows (Fig. 33-1):
FIGURE 33-1 Descriptive diagram of in-stent restenosis (ISR) angiographic patterns. Pattern I (focal type) is <10 mm in length and contains 4 subtypes (types IA-ID). Patterns II to IV (diffuse type) are >10 mm in length and are distinguished according to the relation with the stent and the vessel lumen. (Reproduced with permission from Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation. 1999;100:1872-1878.)

- Class I, focal ISR group: Lesions are ≤10 mm in length and are placed at the unscaffolded segment (articulation or gap) (type IA), the body of the stent (type IB), the proximal or distal margin (type IC), or a combination of these sites (type ID; multifocal ISR).
- Class II, diffuse ISR: Lesions are >10 mm in length and are confined to the stented segment, without extending outside the margin(s).
• Class III, diffuse proliferative ISR: Lesions are >10 mm in length and extend beyond the margin(s) of the stented segment.
• Class IV, ISR with total occlusion: Lesions with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0.

In order to quantitatively evaluate the magnitude of ISR, 2 parameters have to be taken into account: (1) binary angiographic restenosis, defined as a luminal narrowing of 50% or more measured by follow-up coronary angiography and (2) late lumen loss (LLL), defined as the difference in millimeters between the diameter of a stented segment immediately after PCI and the diameter measured by a follow-up coronary angiography.

Actually, the most widely used definition and classification of ISR is the one proposed by the Academic Research Consortium. This definition requires either a lumen narrowing of at least 50% of the vessel diameter associated with the evidence of functional significance (recurrent angina pectoris, objective signs of ischemia at rest or during exercise test [electrocardiographic (ECG) changes], abnormal fractional flow reserve [FFR <0.80] or intravascular ultrasound [IVUS]–assessed minimum cross-sectional area <4 mm²) or a luminal narrowing of at least 70% or greater in the absence of ischemic symptoms.

Clinical Significance of Morphologic Classification of In-Stent Restenosis

Morphologic classification of ISR is not exclusively descriptive; it also demonstrates a clinical prognostic value (Fig. 33-2). Diffuse intrastent, proliferative, and total occlusions represent a spectrum of increased ISR severity linked to an exaggerated NIH response. With BMS, a significant stepwise increase in TLR is associated with progressively greater levels of ISR in the Mehran classification (class I, 19%; class II, 35%; class III, 50%; class IV, 83%; \( P = .0001 \)).
FIGURE 33-2 The morphologic pattern of in-stent restenosis (ISR) predicts the outcome. A stepwise increase in the need for revascularization is observed in the transition from focal patterns of ISR to occlusive patterns. 1°G, first generation; 2°G, second generation; TLR, target lesion revascularization. BMS, bare metal stent; DES, drug-eluting stent.

Also in DES, the morphologic pattern of ISR is a significant predictor of outcome. Cosgrave et al demonstrated in first-generation DES a significantly higher ISR rate after treatment (with repeat DES stenting or plain old balloon angioplasty [POBA]) in patients with nonfocal DES-ISR as compared to patients with focal DES-ISR (51.1% vs 17.8%; \( P = .001 \)). In the same study, nonfocal pattern of ISR was a strong and independent predictor of TLR at follow-up, independently of the DES type. Latib et al observed in a large group of consecutive patients with DES-ISR treated with PCI (restenting or POBA) that recurrent ISR occurred in 29.1% of the focal type (class I), 45.8% \( (P = .007) \) of the diffuse type (class II and III), and 65.6% \( (P < .001) \) of the occlusive type (class IV) ISR. Accordingly, diffuse ISR was independently associated with a significant increase in TLR compared to focal ISR. In the same study, the investigators observed that the initial
presentation pattern of ISR also predicted the pattern of recurrent ISR after the initial treatment. Occlusive ISR recurred as a reocclusion in 66.7%, diffuse ISR (class II and III) recurred as diffuse or occlusive in 57.9%, and focal ISR (class I) recurred as recurrent focal ISR in 67.2% of patients.

Besides TLR, other main cardiovascular outcomes, such as death, myocardial infarction, and stent thrombosis (ST), seem to not be significantly different across ISR morphology patterns both in BMS and DES.\textsuperscript{5,7}

**PATHOPHYSIOLOGY OF IN-STENT RESTENOSIS**

NIH is the pathobiologic substrate of ISR. Different types of mechanisms account for the temporal development, severity, and distribution of NIH and subsequent ISR (see Fig. 33-2; Fig. 33-3). Stent implantation with local arterial injury represents the first trigger of NIH with activation of complex local inflammatory pathways (see Fig. 33-3).\textsuperscript{9,10} Neointimal development consists in the activation, proliferation, and migration of smooth muscle cells within the intimal layer. These processes are followed by local extracellular matrix (ECM) deposition and remodeling with subsequent restenotic tissue accumulation within the stent. At least 4 types of factors can be identified in the pathogenesis of reactive NIH and subsequent ISR (Fig. 33-4): (1) biologic factors, (2) vascular factors, (3) procedural factors, and (4) stent factors.
FIGURE 33-3 Pathogenic pathways leading to in-stent restenosis. ECM, extracellular matrix; NIH, neointimal hyperplasia; VSMC, vascular smooth muscle cell.
**Biologic Factors**

Biologic factors for ISR include drug resistance, hypersensitivity, and genetic substrate. An accurate knowledge of the biologic factors underlying ISR might allow a customized coronary revascularization strategy. In fact, patients with an intrinsic high risk of developing ISR might benefit from additional local antiproliferative drug release, particular procedural tricks, or surgical revascularization.

Resistance to antiproliferative drugs shares the same molecular mechanisms observed in chemotherapy resistance in oncologic medicine.\textsuperscript{11,12} Drug resistance can be primary (in genetically predisposed individuals) or secondary, following exposure to the antiproliferative drug. The molecular
pathways involved in drug resistance are complex, involving genes operating in drug absorption and metabolism, apoptosis regulation, DNA repair, and drug inactivation. Polymorphisms involving the genes encoding for mammalian target of rapamycin (mTOR) have been shown to be associated with paclitaxel or sirolimus resistance both in vitro and in vivo. Moreover, complex paracrine mechanisms involving cell survival signaling pathways and growth hormone response regulation influence the antiproliferative effect of the drug released by the stent platform.

Hypersensitivity reactions responsible for subsequent ISR may develop against 2 different targets: the DES polymer and the metallic stent platform. Implantation of a stent within a coronary artery induces a local barotrauma with endothelial denudation and subsequent activation of the inflammatory pathways with the distinctive foreign body reaction pattern with giant cell infiltration and granuloma formation. The inflammatory reaction occurring after arterial injury critically influences the burden of NIH. Persistence of local inflammation after 90 days is associated with a subsequent high risk of delayed endothelialization, ISR, and late or very late ST. First-generation DES polymers are strongly associated with an inflammatory response that persists beyond 180 days and for up to 2 years. This is in contrast to BMSs and second-generation DESs (which have a more biocompatible polymer), which are associated with an inflammatory reaction of 90 days and 12 months, respectively. Persistent inflammatory response represents a common pathways for the so-called “stent failure,” which include both ISR and ST. Hypersensitivity reactions to the metallic platform have also been described. Koster et al reported an association between nickel and molybdenum allergy and the risk of ISR with BMS. The evidence surrounding this issue is controversial and contradictory. With DES, no clear data exist. To date, a small study by Nakazawa et al found no association between the risk of ISR and the metallic platform allergy with sirolimus-eluting stents (SESs), suggesting that DESs prevent restenosis irrespective of metallic allergy.

The association between inflammatory and ECM remodeling biomarkers with ISR has been studied. The systemic inflammatory status assessed by means of C-reactive protein levels has not been consistently associated with ISR. Conversely, circulating matrix metalloproteinases (MMPs) have been shown to be useful in identifying patients at high risk of developing ISR. In
particular, MMP-2 and MMP-9 elevations after PCI have been associated with the risk of ISR after DES implantation. MMPs are expressed and released by vascular smooth muscle cells (VSMCs), endothelial cells, and macrophages in response to local vessel trauma.

**Arterial Factors**

Arterial factors determining ISR include vessel size, lesion type, local shear stress, neoatherosclerosis, vessel remodeling, and edge vascular response.

Vessel size is a critical factor determining the effectiveness of PCI with both BMS and DES (Fig. 33-5). Agostoni et al\(^{26}\) demonstrated that BMSs are superior to POBA in a large meta-analysis of randomized controlled trials. Biondi-Zoccai et al\(^{27}\) in another large meta-analysis of the use of DESs in small vessel disease, found that type of DES used has a substantial impact on PCI effectiveness. Pathologic mechanisms through which small vessel size influences PCI outcomes are small postprocedural minimal lumen area (MLA), higher degree of vessel injury and recoil, and higher metallic density.\(^{28}\) In particular, greater strut thickness has been associated with worse outcomes in small vessels.
Highly thrombotic lesions are associated with higher risk of stent failure with thrombosis or restenosis. High thrombus burden interferes with DES performance in several ways: (1) thrombus reduces the drug penetration and distribution by a magnitude of up to 10-fold; (2) thrombus interferes with stent expansion, potentially leading to stent underexpansion; and (3) stent underexpansion and late thrombus resolution significantly increase the incidence of incomplete stent apposition and the risk of ST and restenosis. Despite this, a significant benefit with DESs, especially new-generation DESs, has been observed in ST-segment elevation myocardial infarction (STEMI) in several studies and meta-analyses. Although high thrombotic burden significantly increases the risk of stent failure and need for revascularization, the factors independently associated with TVR in STEMI do not seem to differ from those observed in other PCI settings. Finally, the
use of thrombus aspiration does not seem to reduce the risk of thrombosis or restenosis after DES implantation.\textsuperscript{32}

Blood hemodynamics in relation to vessel geometry and stent strut design play a role in determining endothelial dysfunction, vessel remodeling, and restenosis (Fig. 33-6). Within the arterial vessel, the fluid velocity is maximal in the middle of the lumen and minimal in proximity to the vessel wall due to viscosity forces. Particular lesion subsets, such as bifurcations or ostial lesions, are associated with a significantly lower fluid velocity and endothelial shear stress (ESS).\textsuperscript{33,34} Reduced blood flow combined with local vessel injury may contribute to accumulation of growth factors, cytokines, and blood cells promoting NIH development and subsequent restenosis. The relationship between everolimus-eluting stents (EESs) and ISR has been demonstrated in several studies. Wentzel et al\textsuperscript{35} showed an inverse relationship between EES magnitude and the extent of ISR with BMS, which has been demonstrated by later investigations. Importantly, although ISR did not develop in sites with low ESS, not all sites of ISR originated from low ESS regions, showing the multifactorial contribution to ISR development. The relationship between low ESS regions and ISR was also demonstrated with SESs and paclitaxel-eluting stents (PESs). Apart from vessel anatomy, stent design critically influences ESS and ISR risk (see later Stent Factors section).
FIGURE 33-6 Effect of nonstreamlined (A) and streamlined (B) strut design on endothelial shear stress and risk of thrombosis and restenosis. EES, everolimus-eluting stent; ESS, endothelial shear stress. (Adapted from Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. J Am Coll Cardiol. 2012;59:1337-1349.)

Neoatherosclerosis (NA) emerged recently as a potential cause of late DES failure responsible for both restenosis and thrombosis of the stent platform.\(^{36}\) NA can be defined as the presence of an atherosclerotic lesion within the neointima of a stented vascular segment. NA can assume a pathologic feature ranging from simple intimal thickening with lipid infiltration to ruptured thin-cap fibroatheroma with thrombosis and acute clinical presentation. Pooling the evidences from histopathologic and endovascular imaging studies, NA seems to occur with both BMS and DES in which it can be responsible for lumen occlusion with restenosis and subsequent need for revascularization and plaque rupture with thrombotic occlusion of the stent. NA is carefully reviewed and discussed in the Histopathology of In-Stent Restenosis and Imaging of In-Stent Restenosis sections.

Vascular remodeling influences NIH formation.\(^{37-39}\) Large plaque burden is associated with positive arterial remodeling (PR). Okura et al\(^ {38}\) demonstrated that the presence of PR (defined as vessel area at the target lesion greater than that of average reference segments) is associated with adverse outcomes after IVUS-guided stent implantation. Following multivariable adjustment, remodeling index (defined as vessel area at the target lesion site divided by that of average reference segments) was the only independent predictor of TVR at 9 months. The association between PR and ISR may be explained by several mechanisms. First, PR is more frequent in unstable lesions; therefore, lesions with PR may be more biologically active and more prone to an exaggerated NIH response. Second, several studies demonstrated that the relative plaque burden outside the stent is proportional to the NIH that develops within the stent.

Edge vascular response (EVR) is defined as the pathologic changes occurring in the vascular tissue adjacent to the segment of stent implantation with subsequent focal lumen narrowing and need for revascularization of the target lesion.\(^ {40}\) EVR can occur in the presence or absence of longitudinal geographic miss (LGM) with uncovered plaque, and thus, it is only partially
dependent on the stent landing zone. The pathologic factors related to EVR include procedural factors (axial geographic miss or LGM, vascular injury, and plaque shift), stent factors (stent platform and eluted drug), and lesion factors (plaque burden). The TAXUS-II, -IV, -V, and -VI trials reported similar rates of LLL at both proximal and distal stent edges with BMS and PES. Conversely, the SIRIUS trial reported that ISR with SES had more commonly a focal pattern located at the proximal DES edge. In the ENDEAVOR-IV trial, the zotarolimus-eluting stent (ZES) was associated with comparable rates of LLL at both stent edges. Conversely, with bioresorbable vascular scaffolds (BVSs) in the ABSORB Cohort B1 study, LLL was significantly higher at the proximal edge. Compared to BMS, DES seems to be associated with lower distal LLL, most likely because of downstream drug effects related to drug release by the DES platform.

**Procedural Factors**

Optimal stent implantation is of paramount importance in reducing the risk of both restenosis and ST after PCI, as are directly modifiable factors. Procedural factors influencing the risk for ISR include stent underexpansion, LGM and axial geographic miss, unstented segment barotrauma with EVR, stent gap, and off-label DES implantation.

Stent underexpansion and smaller postprocedural minimal lumen diameter (MLD) are strongly associated with long-term DES patency and risk of ISR and ST.** IVUS use significantly improved stent deployment and achievement of an optimal postprocedural MLD. IVUS analyses from the SIRIUS trial and other studies identified an optimal cutoff of postprocedure minimum stent area to reduce the risk of restenosis of 5.0 to 5.5 mm². In a large meta-analysis comparing IVUS-guided with angiographic-guided BMS implantation, Casella et al demonstrated that IVUS use significantly reduces the risk of TVR, binary restenosis, and major adverse cardiac events (MACE) at 6 months of follow-up. Recently, a substudy from the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) trial, the largest observational study of IVUS to date, reported a significant reduction in 1-year rates of ST, myocardial infarction (MI), MACE, and repeated revascularization with IVUS use. Moreover, a large meta-analysis including 26,503 patients demonstrated a significant benefit with IVUS use during PCI with DES implantation. Conversely, results from randomized
clinical trials in the DES era are controversial. Some of them showed that the benefits of IVUS are observed in complex lesions, while others suggested that IVUS use per operator decision was associated with improved results (in the per-protocol analysis of the RESET [Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stent Implantation] IVUS trial). Until large-scale trials demonstrate a clear advantage of IVUS-guided procedures, its use will be at the discretion of the clinical and anatomic evaluation of the operator.

LGM (Fig. 33-7) is defined as the failure to cover the target lesion with intracoronary stent implantation. Failure to cover the lesion with the implanted stent is associated with a significant portion of the lesion remaining out of the stent margins and barotrauma of nondiseased vessel segments. Conversely, axial geographic miss (AGM; see Fig. 33-7) is defined as a final balloon-artery size ratio mismatch <0.9 or >1.3. In the STLLR study, LGM was observed in two-thirds of the study cohort, with half of the patients having LGM and more than one-third having AGM. Approximately 15% had both LGM and AGM. Patients with geographic miss had higher rates of TVR and MI at 1 year of follow-up. Among patients with geographic miss, most of the cases were observed in patients with LGM. Moreover, an additional subanalysis from the STLLR study showed that diabetic patients with LGM had significantly higher rates of TLR compared with nondiabetics, underscoring the importance of optimal stent implantation in high-risk patient subsets such as those with diabetes.
Stent gap can be defined as a discontinuous coverage between 2 DESs throughout the coronary vessel extension. A gap between 2 DESs leaves a small zone of the coronary vessel not exposed to the antiproliferative effects of the released drug and the mechanical support of the metallic strut. Considering that overlapping DESs have been demonstrated to be safe and effective, a gap between 2 DESs should be avoided.54

Finally, off-label DES use has been consistently associated with worse clinical outcomes after PCI. The STENT (Strategic Transcatheter Evaluation of New Therapies) Group is the largest prospective registry evaluating outcomes in patients undergoing DES implantation in the United States. Brodie et al,55 in an analysis from this registry, compared on-label and off-label (ostial, left main, chronic total occlusion, saphenous vein graft, small vessels, multivessel disease, and ISR lesions) indications for DES implantation and reported a significantly higher TVR rate in the off-label group at 2 years (11.8% vs 6.5%; P < .01).

**Stent Factors**
With DES, stent-related factors influencing ISR include strut thickness; drug release kinetics; drug type; stent fracture; polymer disruption, peeling, and cracking; and stent design.

The type of intracoronary stent influences the burden and temporal evolution of NIH. Angiographic and IVUS studies (Fig. 33-8) demonstrated a different pattern of NIH development with BMS and DES over time. IVUS studies with permanent polymer DES documented an increase in neointimal volume beyond the time point in which NIH is interrupted with BMS. Although with BMS the burden of NIH is significantly higher after the procedure and at long-term follow-up, it tends to reduce over time. Conversely, with early-generation DESs, neointimal volume tends to slowly increase years after the implantation. Finally, with bioresorbable polymer DESs, a stable behavior in neointimal volume has been observed. These differences might reflect the variable vascular response and inflammatory reaction to the DES polymer, which involves chronic inflammation associated with very-late restenosis in DES.

**FIGURE 33-8** Differences in neointimal volume at follow-up between bare metal stents (BMSs), first-generation drug-eluting stents, and new-generation drug-eluting stents (DESs). BES, biolimus-eluting stent; EES, everolimus-eluting stent; IVUS, intravascular ultrasound; NIH, neointimal hyperplasia; MR, moderate release; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SR, slow release.
The fine balance between the drug type, drug release kinetics, and dosage is a critical factor in DES design. Drug release kinetics critically influence the suppression of NIH even more than the total dose of drug released. To ensure an adequate suppression of NIH, a certain dose of drug has to be delivered to the vessel wall during a sufficient time period, during which strut endothelization is ongoing. The in-human PISCES trial tested 6 different polymer-drug release formulations and observed that a greater magnitude in the inhibition of neointimal formation was achieved with long-term drug-release formulations than with drug-polymer combinations with shorter eluting times. Similar results have also been observed by Waseda et al comparing different polymer formulations with ZES.

Although drug release kinetics is of critical importance in suppressing NIH, the type of drug also plays an important role. The antiproliferative drugs associated with the greatest effects are paclitaxel and limus family drugs. These drugs differ in their mechanism of action and intracellular pharmacodynamics. Paclitaxel acts by stabilizing the microtubule polymer and blocking the progression of mitosis, triggering apoptosis or reverting to the G phase of the cell cycle without reaching the cell division phase. Sirolimus, everolimus, biolimus A9, and zotarolimus all bind to the FKBP12 protein, which subsequently binds and inhibits mTOR, blocking the transition from the G1 to the S phase. Conversely, tacrolimus and pimecrolimus act by binding FKBP506, which subsequently inhibits the calcineurin receptor, leading to a reduced intracellular growth factor signaling pathway. In the PAINT trial, Lemos et al compared 2 DESs with the same metallic platform and polymer but different released drugs (paclitaxel or sirolimus) and a BMS with the same metallic stent. At 9 months, the DES eluting sirolimus was associated with a significantly lower late loss compared with the DES eluting paclitaxel and the BMS.

Stent fracture (SF) can be defined as a complete or partial discontinuation in the strut structure at follow-up. SF is associated with 2 consequences: (1) loss of the local vascular support provided by the metallic strut, and (2) severe impairment of the local drug delivery. The most common consequence of SF is focal restenosis due to the decreased local drug delivery and impairment in NIH suppression. At IVUS assessment, partial SF is defined as the absence of at least one-third or 120° of stent struts for at least 1 frame; conversely, complete SF is defined as the total absence of stent struts for at
The most common risk factors for SF are right coronary artery lesions, vessel tortuosity, lesion length, moderate or severe calcifications, longer stents, SES use (due to the closed-cell design, as opposed to an open-cell design), myocardial bridges, and overlapping stents. The incidence of SF ranges from 1% to 8% and is associated with a significant increase in need for revascularization at follow-up. In particular, the LONG-DES-II study, which evaluated incidence and predictors of DES fracture in long coronary lesions, reported an incidence of SF of 1.7% and a subsequent restenosis rate at 6-month follow-up of 14%. Finally, stent cell design critically influences the risk of SF. In fact, in a recent meta-analysis, the incidence of SF was of 0.1% with PES (open-cell design) and approximately 2.3% with SES (closed-cell design).

Polymer disruption has been demonstrated in bench studies with both old- and new-generation DES. Disruption and spreading of polymer components may be associated with reduced effectiveness of the drug release and increased local inflammation. Stent implantation failure was demonstrated to be associated with significant polymer damage. Bifurcation lesions have been associated with a high risk of polymer damage, nonuniform drug release, and focal restenosis. Guerin et al. in a bench study using scanning electron microscopy to evaluate the polymer integrity of 5 different types of DES, observed that a kissing balloon was associated with a significantly greater coating damage to the ostial portion of all the stents tested. In particular, the Endeavor stent (Medtronic, Dublin, Ireland) showed a subtotal disruption of the polymer on the luminal face, whereas the other DES showed a more localized pattern of polymer rupture.

The magnitude of stent-induced flow changes and vascular response is substantially dependent on strut design (see Fig. 33-6). Strut shape and thickness and the strut-strut intersection arrangement are all associated with ISR. Across stent types, stents with hemodynamically favorable designs are associated with homogeneous ESS across the inner platform surface and lower risk of ISR in clinical practice. Heterogeneous ESS is the result of flow disruption generating zones of high ESS and zones of low ESS (see Fig. 33-6A). A homogeneous ESS can be achieved by reducing strut thickness and a streamlined strut shape (see Fig. 33-6B). Several studies demonstrated that a nonstreamlined strut drastically increases low ESS to more than 80%. Strut connector length also influences in-stent hemodynamics. A computational
comparison of 5 stents used in clinical practice demonstrated that minimal connector length in the cross-flow direction decreased the percentage of in-stent area with low ESS.

**HISTOPATHOLOGY OF IN-STENT RESTENOSIS**

Underlying ISR histopathology relates to the angiographic appearance and clinical severity of ISR. ISR with BMS has been extensively studied in postmortem\(^9,74\) and endarterectomy\(^75,76\) specimens. Although the pathologic substrate of vessel restenosis with POBA was represented essentially by chronic vessel recoil with negative remodeling, VSMC proliferation is the dominant pathologic process leading to restenosis after BMS and DES implantation. The main identifiable cellular components of NIH are α-smooth muscle actin–positive cells embedded in a collagen-rich extracellular matrix (ECM). The composition of the hyperplastic restenotic tissue evolves over time. NIH evolution can be categorized into an *early stage*, characterized by high cellular density in active proliferation within a proteoglycan-rich ECM, and a *late stage*, characterized by a high burden of mature and dense ECM with lower cellular density and proliferation rate.\(^76\) Chung et al\(^76\) described the ECM changes in ISR tissue over time. Late ISR was composed mainly of large amounts of proteoglycan-rich and collagen-rich ECM alongside a low number of proliferative VSMCs. Interestingly, the investigators observed a significant correlation between ECM composition and ISR severity, instead of cellular proliferation.

Histopathology of ISR varies between BMS and DES. In an interesting study, van Beusekom et al\(^77\) compared the pathologic features of atherectomy specimens obtained from restenotic tissue in BMS, DES, and de novo atherosclerotic lesions. ECM in de novo atherosclerotic lesions was more commonly collagen-rich, whereas BMS- and DES-ISR tissue was more commonly proteoglycan-rich. With both BMS- and DES-ISR, the cellular component was mainly composed by proliferated VSMCs. However, DES-ISR tissue was richer in fibrinoid tissue, indicating a more persistent incomplete vascular healing response. Quantitatively, DES-ISR was significantly lower in terms of mass and volume compared with BMS-ISR.
This difference is most likely related to the more prevalent focal nature of ISR with DES compared with BMS (see later section In-Stent Restenosis With Bare Metal Stents and Drug-Eluting Stents).

Chieffo et al\textsuperscript{78} compared the histopathology of ISR with BMS and a wide range of DES by means of light microscopy specimens obtained through directional coronary atherectomy. In both BMS- and DES-ISR, specimens were composed mainly of proteoglycan-rich smooth muscle cells and a fibrolipidic stroma. The authors found significant differences in VSMC phenotype across stent types. In particular, restenotic tissue was mainly composed of intermediate-synthetic VSMC phenotype in BMS and PES, of intermediate VSMC phenotype in ZES, of contractile-intermediate VSMC phenotype in SES, and of mostly contractile VSMC phenotype in tacrolimus-eluting stents. These differences in VSMC phenotype might reflect the differential responses to stent types and, in the case of DES, to the antiproliferative drug. Both BMSs and PESs were associated with an intermediate-synthetic phenotype, potentially partially explaining the high NIH burden observed with these stents.

Local vascular inflammation induced by vessel barotrauma following intracoronary stent implantation is a critical factor influencing the burden of subsequent neointimal hyperplastic response. Moreover, persistence of an inflammatory milieu is related to greater NIH thickening, remodeling, and subsequent ISR. Farb et al\textsuperscript{9} demonstrated that early after stent implantation, features of acute inflammation at the interface of the stent and arterial wall were almost always present. Moreover, the authors underscored the importance of vascular medial layer damage. In fact, NIH thickness was significantly greater when medial damage (arterial medial laceration or rupture) occurred.\textsuperscript{9} Wilson et al\textsuperscript{79} further clarified the role of chronic inflammation associated with first-generation DES implantation. Histopathologic analysis of stented porcine coronary arteries showed features of chronic inflammation with giant cells, granulomas, and eosinophilic infiltrations at long-term follow-up (between 90 and 180 days), whereas no evidence of inflammation was present with BMS. The main trigger for arterial chronic inflammation is represented by the presence of the durable polymer. Durable polymers induce and sustain chronic inflammation over time, which in turn is responsible for both delayed endothelialization and greater burden of NIH. Therefore, bioresorbable polymer DES design could be an attractive option in reducing the polymer-related inflammatory
response and subsequent risk of thrombosis and restenosis. Bioresorbable polymer DESs seem to be associated with improved safety and efficacy profiles compared with first-generation DESs.\textsuperscript{80}

Another potential mechanism influencing the features of ISR with BMS and DES is the delayed endothelialization phenomenon. From an autopsy registry, Joner et al\textsuperscript{81} compared the vascular histopathology of DES and BMS, observing that after 30 days DESs were associated with significantly delayed vascular healing manifested by incomplete endothelialization and significant fibrin persistence and accumulation. These pathologic differences may account for both DES failure events—ST and ISR. The higher prevalence of thrombotic components within DES-ISR led to the theory of the “thromborestenosis phenomenon.” Oikawa et al\textsuperscript{82} demonstrated, by means of IVUS, angioscopy, and histopathologic analyses, that thrombus and fibrin deposition are substantially more frequent in ISR lesions of SES compared with BMS. Therefore, chronic thrombus formation may play a role in the pathogenesis of ISR in DES, especially when delayed endothelialization occurs.

Finally, in-stent NA emerged as a potential mechanism of stent failure, being associated with both ISR and ST, and may account for the “late catch-up phenomenon” observed in DES trials at long-term follow-up.\textsuperscript{83,84} NA is defined as the presence within the neointima of atherosclerotic plaque elements like foamy macrophages in clusters with or without calcification, fibroatheromas, and thin-cap fibroatheromas. The pathobiology of NA can be described as a form of accelerated atherosclerosis secondary to delayed reendothelialization and severe endothelial dysfunction. Nakazawa et al\textsuperscript{36} described the incidence of NA in BMS, SES, and PES postmortem pathologic specimens (Fig. 33-9). Compared with BMS, the incidence of NA was significantly higher with DES (31% vs 16%; \(P < .01\)), whereas no differences were present between the 2 types of first-generation DESs. Importantly, NA occurred earlier with DES compared with BMS. In fact, the median stent duration with NA was shorter in DES than BMS (DES: 420 days; BMS: 2160 days; \(P < .001\)). Interestingly, SES was associated with a greater NA change compared with PES for implant durations of 2 years or less (SES 37% vs PES 21%; \(P = .021\)). The earlier development of NA in DES may be due to delayed stent endothelialization with reduced cell-to-cell contact and increased lipidic and macrophage intimal infiltration. NA and its role and
evaluation in ISR will be further discussed in the Imaging of In-Stent Restenosis section.

**FIGURE 33-9** A to C. Histologic section from a paclitaxel-eluting stent (PES) implanted in a left circumflex artery 14 months antemortem: (A) patent lumen with presence of moderate neointimal growth; (B) foamy macrophage infiltration plus cholesterol clefts within the neointima; and (C) presence of CD68-positive macrophages in the neointima surrounding the strut (*asterisk*). D to F. Pathologic specimens from a sirolimus-eluting stent (SES) with superimposed thrombosis: (E) evidence of thin-cap fibroatheroma with cap rupture and (F) presence of CD68-positive macrophages in the fibrous cap and in the necrotic core. G to I. Pathologic specimens from a bare metal stent (BMS) implanted 8 years before death with superimposed stent thrombosis: (G) presence of occlusive thrombus within the stent lumen and (H and I) presence of ruptured plaque with a large number of macrophages at the site of cap disruption. (Reproduced from Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011;57:1314-1322, Copyright © 2011, with permission from Elsevier.)
Predictors of ISR with BMS and DES are illustrated in Table 33-1. Among other factors, diabetes mellitus (DM) has been consistently identified as a strong clinical predictor of ISR with both BMS and DES.\textsuperscript{85} Moreover, DM patients present more frequently with a worse morphologic pattern with a prevalent proliferative (type III) and occlusive ISR (type IV).\textsuperscript{5,86} Kornowski et al\textsuperscript{87} observed that ISR in DM patients, compared with ISR in non-DM patients, is associated with higher burden of NIH, underlying the influences of impaired glucose homeostasis and insulin resistance in promoting cellular proliferation after vascular injury. The accentuated neointimal hyperplastic response in diabetics has been documented in several studies. An IVUS-ISR study in patients treated with BMS showed substantial differences in the degree of neointimal hyperplasia among diabetics (5.1 ± 2.8 mm\textsuperscript{2}) compared to nondiabetics (2.1 ± 2.0 mm\textsuperscript{2}).\textsuperscript{87} Moreover higher prevalences of heterogeneous patterns have been observed among diabetics.\textsuperscript{88}

Table 33-1 Predictors of In-Stent Restenosis With Bare Metal Stents and Drug-Eluting Stents
<table>
<thead>
<tr>
<th>Predictors with BMS</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Diabetes mellitus</td>
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<tr>
<td></td>
<td>Female sex</td>
</tr>
<tr>
<td>Anatomic</td>
<td>Long lesions</td>
</tr>
<tr>
<td></td>
<td>Small vessels</td>
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<td></td>
<td>Baseline MLD</td>
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<td></td>
<td>Plaque burden</td>
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<td></td>
<td>Complex lesions (B2/C)</td>
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<td></td>
<td>Multivessel disease</td>
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<td></td>
<td>ISR lesions</td>
</tr>
<tr>
<td></td>
<td>Plaque burden</td>
</tr>
<tr>
<td>Procedural</td>
<td>Stent length</td>
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<tr>
<td></td>
<td>Postprocedural MLD</td>
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<td></td>
<td>Stent length/lesion length ratio</td>
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<tr>
<td></td>
<td>Coil stents</td>
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<tr>
<td>Predictors with DES</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
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<tr>
<td>Anatomic</td>
<td>Long lesions</td>
</tr>
<tr>
<td></td>
<td>Small vessels</td>
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<tr>
<td></td>
<td>Baseline MLD</td>
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<td></td>
<td>Plaque burden</td>
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<td></td>
<td>Complex lesions (B2/C)</td>
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<td></td>
<td>Multivessel disease</td>
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<tr>
<td></td>
<td>ISR lesions</td>
</tr>
<tr>
<td></td>
<td>Saphenous vein grafts</td>
</tr>
<tr>
<td>Procedural</td>
<td>Postprocedural MLD</td>
</tr>
<tr>
<td></td>
<td>Stent gap; stent fracture</td>
</tr>
<tr>
<td></td>
<td>Use of PES or E-ZES</td>
</tr>
<tr>
<td></td>
<td>Stent length</td>
</tr>
</tbody>
</table>

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent; ISR, in-stent restenosis; MLD, minimal lumen diameter; PES, paclitaxel-eluting stent.
Predictors From Bare Metal Stent Studies

Several factors are associated with specific morphologic patterns of ISR. Goldberg et al\(^89\) identified predictors of diffuse (≥10 mm) ISR and aggressive ISR (defined as the development of a longer or tighter lesion at follow-up compared with baseline) with BMS. Predictors of diffuse ISR were longer baseline lesion length, smaller final result achieved, and the use of coil stents. Conversely, predictors of aggressive ISR were female sex, MLD at baseline, lesion length, and stent length/lesion length ratio. Among these, MLD at baseline was the strongest predictor. The role of MLD as a predictor of TVR for ISR was confirmed in the CRUISE (Can Routine Ultrasound Influence Stent Expansion) trial.\(^90\) In this study, final in-stent MLD was also demonstrated to be a significant predictor of TVR.

Lesion-related characteristics impact the risk of ISR and specific ISR morphology. Elezi et al\(^91\) demonstrated in a study of 2602 patients the important influence of vessel size on ISR rate. In this study, patients with small-size vessels (<2.8 mm) had a significantly higher restenosis rate compared with patients with mid-size (2.8-3.2 mm) and large-size (>3.2 mm) vessels (38.6% vs 28.4% vs 20.4%, respectively; \(P < .001\)). The association persisted following multivariable adjustment. Within small vessels, a subsequent study performed by Hausleiter et al\(^92\) demonstrated that the main predictors in this lesion subset are diabetes, complex lesions (type B2/C), vessel stenosis diameter before intervention, stented segment length, balloon/vessel ratio, and stent design.

Finally, Hoffmann et al\(^93\) explored angiographic and IVUS predictors of ISR demonstrating 3 imaging variables consistently associated with ISR: ostial lesion location (odds ratio [OR], 4.01; \(P = .015\)), lesion site plaque burden (plaque/total arterial area) assessed by IVUS (OR, 1.25; \(P = .008\)), and final lumen area or MLD assessed by IVUS (OR, 0.24; \(P = .013\)). These predictors underscore the importance of IVUS-guided procedures to optimize PCI outcomes.

Predictors From Drug-Eluting Stent Studies

Predictors of ISR with DES are similar to those with BMS (see Table 33-1),\(^94\) in which clinical, procedural, and anatomic factors have been consistently
identified as independent predictors of restenosis and revascularization. However, with DES, procedural factors seem to have relatively more impact on the risk of restenosis compared with BMS. Kastrati et al, who analyzed predictors of ISR with SES and PES in a cohort of 1845 and 2093 target lesions, respectively, found that baseline clinical characteristics were not as strong predictors of ISR compared with angiographic factors such as vessel size, complex lesions, and final angiographic results. Moreover, differences in ISR rate among DESs might be more evident in small coronary arteries. Other potential risk factors for restenosis with SES were evaluated by Lemos et al in the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) trial. The investigators identified treatment of ISR, DM, and total stented length as independent predictors of ISR ostial lesions.

Compared with BMS, DESs are more commonly associated with a focal pattern of ISR. Investigators studied the predictors of nonfocal ISR in DES. The investigators identified female sex, overlapping stent implantation, and PES use as independent predictors of nonfocal ISR. Lesion complexity is strongly associated with ISR with DES. In particular, PCI of chronic total occlusive lesions also carries a high risk of restenosis after successful stent implantation. In a prospective cohort of successfully revascularized chronic total occlusive lesions using DES, Lee et al reported an ISR incidence of 24% at 6 to 9 months, with a prevalence of diffuse ISR of 61%. Finally, in the new-generation DES era, the RESOLUTE-All Comers randomized trial reported insulin-treated diabetes, treatment of saphenous vein grafts, ostial lesions, ISR treatment, and right coronary artery as a target vessel as independent major predictors of TLR.

DES implantation appears to be effective in attenuating the burden of NIH compared with BMS. However, DM is still a strong independent predictor of TLR even in the DES era. Moreover, several reports have shown that the presence of DM may attenuate the benefits associated with newer versus first-generation DESs.

IN-STENT RESTENOSIS WITH BARE-METAL STENTS AND DRUG-ELUTING STENTS
Stent type critically influences the risk of ISR, its morphologic pattern, and its associated clinical outcomes. Introduction of DESs drastically reduced the incidence of ISR and subsequent need of TLR. However, even in the DES era, the risk of ISR still persists. SES and EES were demonstrated to be the 2 types of DES associated with the lowest incidence of TVR. However, over time, EES demonstrated a significant improvement in the safety profile compared with first-generation DESs. A summary of the incidence of ISR and relative prevalence of morphologic patterns with different types of DESs from randomized controlled trials is reported in Table 33-2, Figure 33-10, and Figure 33-11.

Table 33-2 Incidence of In-Stent Restenosis With Drug-Eluting Stents in Randomized Controlled Trials
<table>
<thead>
<tr>
<th></th>
<th>No. of DES-Treated Patients</th>
<th>Follow-Up Period</th>
<th>Binary ISR</th>
<th>In-Segment Restenosis</th>
<th>Longest Clinical Follow-Up (mo)</th>
<th>TLR at Longest Clinical Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVEL</td>
<td>120</td>
<td>6 months</td>
<td>0%</td>
<td>0%</td>
<td>60</td>
<td>10.3%</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>533</td>
<td>8 months</td>
<td>3.2%</td>
<td>8.9%</td>
<td>60</td>
<td>9.4%</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>175</td>
<td>8 months</td>
<td>3.9%</td>
<td>5.9%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>50</td>
<td>8 months</td>
<td>0%</td>
<td>2.3%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SES SMART</td>
<td>129</td>
<td>8 months</td>
<td>4.9%</td>
<td>9.8%</td>
<td>24</td>
<td>7.9%</td>
</tr>
<tr>
<td>DIABETES</td>
<td>80</td>
<td>9 months</td>
<td>3.9%</td>
<td>7.8%</td>
<td>48</td>
<td>8.1%</td>
</tr>
<tr>
<td>PES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXUS II SR</td>
<td>131</td>
<td>6 months</td>
<td>2.3%</td>
<td>5.5%</td>
<td>60</td>
<td>10.3%</td>
</tr>
<tr>
<td>TAXUS II MR</td>
<td>135</td>
<td>6 months</td>
<td>4.7%</td>
<td>8.6%</td>
<td>60</td>
<td>4.5%</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>662</td>
<td>9 months</td>
<td>5.5%</td>
<td>7.9%</td>
<td>60</td>
<td>9.1%</td>
</tr>
<tr>
<td>TAXUS V</td>
<td>577</td>
<td>9 months</td>
<td>13.7%</td>
<td>18.9%</td>
<td>60</td>
<td>17.0%</td>
</tr>
<tr>
<td>TAXUS V ISR</td>
<td>195</td>
<td>9 months</td>
<td>7.0%</td>
<td>14.5%</td>
<td>24</td>
<td>10.1%</td>
</tr>
<tr>
<td>TAXUS V</td>
<td>219</td>
<td>9 months</td>
<td>9.1%</td>
<td>12.4%</td>
<td>60</td>
<td>14.6%</td>
</tr>
<tr>
<td>ZES</td>
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<tr>
<td>ENDEAVOR II</td>
<td>598</td>
<td>8 months</td>
<td>9.4%</td>
<td>13.2%</td>
<td>60</td>
<td>7.5%</td>
</tr>
<tr>
<td>SES versus PES</td>
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<tr>
<td>REALITY</td>
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<tr>
<td>SES</td>
<td>648</td>
<td>8 months</td>
<td>7.0%</td>
<td>9.6%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PES</td>
<td>669</td>
<td>8 months</td>
<td>8.3%</td>
<td>11.1%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SIRIAX</td>
<td>503</td>
<td>8 months</td>
<td>3.2%</td>
<td>6.6%</td>
<td></td>
<td>14.9%</td>
</tr>
<tr>
<td>PES</td>
<td>569</td>
<td>8 months</td>
<td>7.5%</td>
<td>11.7%</td>
<td>60</td>
<td>17.9%</td>
</tr>
<tr>
<td>ISAR-DIABETIC</td>
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<tr>
<td>SES</td>
<td>180</td>
<td>6-8 months</td>
<td>8.0%</td>
<td>11.4%</td>
<td>–</td>
<td>–</td>
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<tr>
<td>PES</td>
<td>180</td>
<td>6-8 months</td>
<td>14.9%</td>
<td>19.0%</td>
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<td>–</td>
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<tr>
<td>ISAR-SMART</td>
<td></td>
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</tr>
<tr>
<td>SES</td>
<td>100</td>
<td>6-8 months</td>
<td>11.0%</td>
<td>14.3%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PES</td>
<td>100</td>
<td>6-8 months</td>
<td>18.5%</td>
<td>21.7%</td>
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<td>–</td>
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<tr>
<td>ISAR-DESIRE</td>
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<tr>
<td>SES</td>
<td>125</td>
<td>6-8 months</td>
<td>4.9%</td>
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<td>–</td>
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<tr>
<td>PES</td>
<td>125</td>
<td>6-8 months</td>
<td>13.6%</td>
<td>16.5%</td>
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<td>–</td>
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<tr>
<td>ZES</td>
<td>323</td>
<td>8 months</td>
<td>9.2%</td>
<td>11.7%</td>
<td>60</td>
<td>8.1%</td>
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<tr>
<td>SES</td>
<td>113</td>
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<td>4.3%</td>
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<td>6.5%</td>
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<td>ZES versus PES</td>
<td></td>
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<tr>
<td>ZES</td>
<td>770</td>
<td>8 months</td>
<td>13.3%</td>
<td>15.3%</td>
<td>36</td>
<td>6.5%</td>
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<tr>
<td>PES</td>
<td>772</td>
<td>8 months</td>
<td>6.7%</td>
<td>10.4%</td>
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<td>6.0%</td>
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<tr>
<td>EES versus PES</td>
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<td>SPIRIT II</td>
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<tr>
<td>EES</td>
<td>223</td>
<td>6 months</td>
<td>1.3%</td>
<td>3.4%</td>
<td>48</td>
<td>5.9%</td>
</tr>
<tr>
<td>PES</td>
<td>77</td>
<td>6 months</td>
<td>3.5%</td>
<td>5.8%</td>
<td></td>
<td>12.7%</td>
</tr>
</tbody>
</table>
FIGURE 33-10 Median target vessel revascularization rates per 1000 patient-years of follow-up with bare metal stents (BMS) and first- and second-generation drug-eluting stents. EES, everolimus-eluting stents; E-ZES, Endeavor zotarolimus-eluting stent; PES, paclitaxel-eluting stent; R-ZES, Resolute zotarolimus-eluting stent; SES, sirolimus-eluting stent. (Results from Ban galore S, Fusaro M, Amoroso N, et al. Response to letter regarding article, “Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison Analysis of 117,762 patient-years of follow-up from randomized trials.” Circulation. 2013;127:e447.)
FIGURE 33-11 Prevalence of morphologic patterns of in-stent restenosis with first-generation drug-eluting stents and bare metal stents (BMSs). PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

**General Comparison Between Bare Metal Stents and Drug-Eluting Stents**

There are 2 main differences in terms of ISR between BMSs and DESs: (1) the incidence (ISR is much more frequent with BMS), and (2) the morphology (diffuse patterns of ISR are more common in BMS, whereas DES-ISR is more frequently focal).\(^{104-110}\)

BMS-ISR is characterized by a uniformly distributed NIH along the stent longitude. ISR incidence and morphology with BMS vary across BMS generation. Early-generation BMSs were associated with higher incidence and diffuse patterns of ISR.\(^{111}\) However, even if later BMS platforms were associated a lower rate of ISR, a diffuse pattern remained the most commonly observed morphology.

Compared with BMS-ISR, DES-ISR is characterized by delayed development and a predominantly focal pattern. Park et al.\(^{105}\) described focal ISR in approximately 65% of 177 consecutive first-generation DESs, whereas Solinas et al.\(^{112}\) reported a focal ISR prevalence of 69.5% in 182 lesions. The different pattern of ISR between BMS and DES reflects the
delayed arterial endothelialization after DES implantation in relation to the effects of the antiproliferative drug and local polymer hypersensitivity.\textsuperscript{19,113-115} The pathobiology underlying the prevalent focal morphology of DES-ISR is most likely related to nonuniform drug delivery and subsequent local failure of the antirestenotic effect.\textsuperscript{19,115} Nonuniform drug delivery might be attributable to stent underexpansion, vessel barotrauma, repeated balloon postdilatation, extremely tortuous lesions, and SF.\textsuperscript{94,116,117}

\textbf{In-Stent Restenosis in First-Generation Drug-Eluting Stents}

Compared with PES, SES is associated with lower rates of ISR and with more prevalent focal morphology (see Fig. 33-11). A meta-analysis by Kastrati and colleagues\textsuperscript{118} reported an overall incidence of ISR of 9.3\% with SES and 13.1\% with PES (OR, 0.68; \textit{P} = .001). No differences were found in other outcomes. The superiority of SES over PES with respect to the ISR incidence was explained by the lower degree of LLL and a higher MLD with SES at follow-up. These findings were confirmed later in another larger meta-analysis.\textsuperscript{119} However, recently in the SIRTAX LATE (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) study, Raber and colleagues\textsuperscript{120,121} reported an ongoing reduction in the differences in MLD between PES and SES at 5 years. Although SES was superior in terms of LLL at 8 months, no differences were found at 5 years. This finding was explained by a late catch-up phenomenon and a higher delayed lumen loss observed with SES. Therefore, SES seems to be associated with superior NIH suppression and a lower risk of ISR compared with PES at mid-term, whereas this advantage is no longer maintained over a longer term follow-up.

Differences in ISR between SES and PES persisted across different lesion and patient subsets. The ISAR-DIABETES (Paclitaxel-Eluting Stent Versus Sirolimus-Eluting Stent for the Prevention of Restenosis in Diabetic Patients With Coronary Artery Disease) trial compared SES and PES in patients affected by DM.\textsuperscript{121} PES was associated with higher rates of LLL and a higher incidence of angiographic ISR (16.5\% vs 6.8\%). All patients with ISR in the SES group had a type I pattern (100\%). Conversely, among patients with PES-ISR, 76.4\% had type I, 5.8\% had type II, 5.8\% had type III, and 11.7\%
had type IV ISR. The ISAR-SMART 3 (Sirolimus- and Paclitaxel-Eluting Stents for Small Vessels) randomized trial reported lower LLL, ISR incidence, and TLR rates with SES.\textsuperscript{122} In particular, angiographic ISR was found in 19\% of the PES group compared with 11.4\% of the SES group. Regarding the pattern of ISR in the PES group, ISR type I was observed in 69.6\%, type II in 9\%, type III in 6\%, and type IV in 15\%. In the SES group, 80\% of lesions presented with type I pattern; of the remainder, 5\% had type III and 15\% had type IV ISR.

Differences in ISR between SES and PES may be related to several factors. First, the cellular mechanism of the 2 drugs is different. Sirolimus is an mTOR inhibitor, whereas paclitaxel is a microtubule-stabilizing agent leading to reduced cell division and mobility.\textsuperscript{123-126} In vitro studies show that VSMCs adopt a differentiated contractile phenotype under sirolimus and a synthetic phenotype under paclitaxel. Accordingly, a VSMC synthetic phenotype is more frequent in both PES-ISR and BMS-ISR as compared with SES, which may in turn influence the ISR pattern.\textsuperscript{78} Conversely, SES has been demonstrated to be associated with higher inhibition of NIH.\textsuperscript{127} Differences in polymer-triggered inflammatory response following PCI with PES and SES may also contribute to differences in ISR patterns. SES is more commonly associated with a granulomatous and eosinophilic reaction starting at 28 days, whereas PES is characterized by a lower inflammation burden but higher amounts of fibrin deposition, which was demonstrated to be a powerful inducer of cellular proliferation.\textsuperscript{16,17,19}

**In-Stent Restenosis in Second-Generation Drug-Eluting Stents**

New-generation DESs are associated with significantly improved efficacy and safety profiles compared with first-generation stent platforms. A meta-analysis including the COMPARE and SPIRIT II, III, and IV trials reported significantly lower rates of TLR with EES compared with PES.\textsuperscript{128} Conversely, many studies have shown that EES and SES are similar in terms of efficacy outcomes. A meta-analysis of 5 randomized trials comparing EES and SES showed no differences in terms of repeat revascularization between the 2 types of stents.\textsuperscript{129} However, an updated meta-analysis from the same authors reported significantly lower rates of definite ST with EES compared
with SES. Finally, a large meta-analysis of 13 randomized trials reported significant reduction in ST, TLR, and MI with use of EES compared with other types of DESs.

Regarding ZES, 2 versions of this stent platform exist: the Endeavor-ZES (E-ZES; Medtronic) and the Resolute ZES (R-ZES; Medtronic). The R-ZES actually largely replaced E-ZES due to a significant improvement in polymer composition and drug release kinetics. E-ZES demonstrated higher rates of ISR and TLR compared to SES. In addition, although the most common pattern of ISR was focal with both types of DES, E-ZES was associated with higher restenosis length (12.9 mm with ZES vs 6.46 mm with SES; \( P < .001 \)), higher percentage of volume obstruction (16.1% with ZES vs 2.7% with SES; \( P < .001 \)), and greater mean neointimal thickness (0.19 ± 0.07 mm vs 0.10 ± 0.06 mm; \( P < .001 \)). Compared to PES, E-ZES again showed a higher rate of ISR and higher in-segment LLL, NIH volume, and percent volume obstruction. These findings were attributed the intrinsic drug release kinetics of the E-ZES (95% eluted in the first 2 weeks after implantation). On the other hand, E-ZESs were associated with a lower rate of death or MI beyond 3 years, mainly due to lower rates of late ST and late MI events. Results of E-ZES from clinical trials drove the production of the R-ZES, which has an extended delivery of zotarolimus, with 85% of release occurring within 2 months and the remainder by 6 months. The initial results of the RESOLUTE clinical trial showed that R-ZESs were associated with lower LLL, ISR rates, and TLR compared with E-ZES. An IVUS-based study comparing E-ZES, R-ZES, ZoMaxx (Abbott, Chicago, IL), and Driver (Medtronic; all ZESs with different polymer and drug elution times) demonstrated lower NIH volume, percent neointimal obstruction, and LLL with the R-ZES. Interestingly, after multivariable adjustment, R-ZES correlated with neointimal suppression.

EES and R-ZES are actually the most commonly used commercially available new-generation DESs. Several randomized trials have reported that EES and R-ZES are similar in terms of efficacy profile, with comparable rates of restenosis and need of revascularization. The RESOLUTE-All Comers trial showed no differences in primary end point, showing the noninferiority of R-ZES compared with EES. However, R-ZES was associated with higher LLL at 13 months, but no significant difference in target lesion failure at 2 and 4 years (2 years, 12.6% R-ZES vs 12.2% EES; 4
years, 15.2% R-ZES vs 14.6% EES). An optical coherence tomography (OCT)-based substudy showed no differences in MLA, NIH volume, and percent neointimal volume obstruction between R-ZES and EES.\textsuperscript{142}

Observational studies related to patterns of ISR in first- and second-generation DESs are scarce. Lee et al\textsuperscript{143} reported an incidence of focal ISR of 50.5% with PES, 84.7% with SES, 84.6% with EES, and 85% with R-ZES, with a much lower incidence of diffuse intrastent ISR with second-generation DES (5.6% vs 40%).\textsuperscript{143} Of note, the proportion and distribution of margin-type focal ISR were similar between different generations of DES.

**In-Stent Restenosis in New-Generation Drug-Eluting Stents**

The emerging evidence of the effect of late polymer hypersensitivity on the risk of ST and the prolonged need of dual antiplatelet therapy led to the development of the bioresorbable polymer (BP) DES.\textsuperscript{144} The main potential advantages of BP-DESs are the avoidance of in situ chronic inflammation, delayed endothelialization and healing, and its associated pathologic consequences. The LEADERS (Limus Eluted From a Durable Versus erodable Stent Coating) trial compared the biodegradable polymer biolimus-eluting stent (BES) with SES.\textsuperscript{145} No differences were found in ISR rates, percentage stenosis, LLL, TLR, and TVR at 9 months. An OCT-based substudy of the LEADERS trial demonstrated that although the quantity of neointimal tissue was similar, BES was associated with improved stent strut coverage.\textsuperscript{146} Long-term results (1-4 years) have demonstrated a significant reduction in very late definite ST and TLR with BES compared with SES.\textsuperscript{147,148} These results were confirmed in 3 larges subsequent meta-analyses comparing BP-DES with first-generation and second-generation DESs using direct and indirect comparisons.\textsuperscript{80,149,150} In the same studies, there was no evidence of superiority of BP-DES over second-generation DESs.

Currently, BVS represents a technologic breakthrough in interventional cardiology. Early results with the BVS have been promising. The ABSORB trial, involving 101 patients, reported 2 cases of early ISR (<6 months; 2%), 1 case of late ISR (6-12 months; 1%), and 3 cases of very late ISR (>12 months; 3%).\textsuperscript{151,152} Two of the later cases of ISR were focal and located at
the proximal stent edge, suggesting that EVR may play a potential critical role in ISR with this class of stents. An OCT-based comparison at 1 year of BVS and EES showed similar rates of LLL, NIH thickness, and NIH composition.\textsuperscript{153} However, these studies to date have been small, and the processes leading to ISR in these devices warrant further investigation.\textsuperscript{152,154} Moreover, whether bioabsorbable stents have a role in treating ISR remains unknown.\textsuperscript{155}

\textbf{CLINICAL MANIFESTATIONS OF IN-STENT RESTENOSIS}

The time frame between stent implantation, ISR, and related symptoms is approximately 5 months with BMS and 8 to 13 months with DES.\textsuperscript{156-159} The pathophysiologic consequence of ISR is the development of obstructive coronary artery disease with reduction of myocardial perfusion and development of ischemic symptoms. ISR presentation ranges from stable angina to STEMI.\textsuperscript{158,159} The exact prevalence in clinical presentation of ISR with different types of stent is unclear. ISR with DES has a tendency to manifest more as a stable angina rather than with acute coronary syndrome (ACS). Conversely, studies evaluating ISR manifestations with BMS reported an unstable presentation as a prevalent finding.\textsuperscript{158-160} However, De Labriolle et al,\textsuperscript{161} in a study including more than 1900 patients hospitalized with BMS-ISR and 190 patients with DES-ISR, reported that an unstable presentation was noted in 78\% of patients. Patients with DES-ISR presented more often with an acute MI (4.3\% vs 1.6\%; \( P < .01 \)) and stable angina (30.9\% vs 19.1\%; \( P < .01 \)).\textsuperscript{161} Conversely, Rathore et al\textsuperscript{162} compared the clinical presentation, pattern, and angiographic outcomes in 838 patients with BMS-ISR (\( n = 487 \)) and SES-ISR (\( n = 351 \)). The authors found no differences in clinical presentation between the groups, and most of the patients had a stable presentation. With BMS, 2 larges prospective studies showed that more than 50\% of patients with BMS-ISR present with an ACS, with unstable angina being the prevalent clinical manifestation.\textsuperscript{160,163} Finally, Appleby and colleagues\textsuperscript{164} found no differences in clinical presentation between types of DES (SES and PES), and 78\% of patients had a chronic stable angina as the clinical presentation.
ISR presentation has a significant effect on clinical outcomes. A PRESTO (Prevention of Restenosis With Tranilast and Its Outcomes) trial substudy found that patients with ISR who presented with ACS had a higher incidence of recurrent MACE and binary restenosis compared with patients presenting with stable angina.165

IMAGING OF IN-STENT RESTENOSIS

Intravascular Ultrasound Assessment of In-Stent Restenosis

Intravascular imaging technologies have provided inestimable insights in coronary pathophysiology and underlying mechanisms in stent-induced vascular response, ST, and restenosis. In particular, IVUS analyses allowed the assessment of phenomena such as vascular remodeling, stent underexpansion, and the distribution and patterns of NIH. A classification system for DES-ISR according to IVUS has been proposed by Kang et al166:

- Focal ISR: defined as lumen area <4 mm$^2$ and length ≤10 mm, subcategorized by the location within the stent
  - Focal body type: confined to the body of stent
  - Focal marginal type: extending to the margins of stent
- Multifocal ISR: multiple focal lesions, with subcategories
  - Multifocal body type: confined to the body of the stent
  - Multifocal marginal type: involving stent margins
- Diffuse ISR: defined as MLA <4 mm$^2$ and length >10 mm, with subcategories
  - Diffuse body type: confined to the stent body
  - Diffuse marginal type: associated with stent involvement

In this study, which included 76 IVUS-assessed ISR lesions, a total of 42% had evidence of stent underexpansion and 93% had NIH area >50% of the stent. Importantly, total stent length was negatively correlated with minimal stent area. In patients with stent length >28 mm, underexpansion was evident
in 35% of minimum lumen sites. Therefore, the analysis showed that despite NIH being the predominant mechanism of ISR, a large portion of ISRs (~30%) show evidence of underexpansion, which is an important preventable mechanism of ISR. The same study evaluated NIH features according to the DES. Among SES, PES, and ZES, no differences in the angiographic or IVUS patterns of restenosis were observed, but a higher rate of significant NIH was found with PES. Moreover, PES and ZES were more commonly associated with >10 mm of significant NIH when compared to SES (32% vs 33% vs 9%; \( P = .038 \)). The same authors reported findings from 70 DES-ISR and 47 BMS-ISR lesions assessed by virtual histology IVUS (Fig. 33-12).\(^{167}\) DES-ISR featured more fibrous NIH, whereas a necrotic core and dense calcium were more prevalent in BMS-ISR. Importantly, older ISR lesions had in-stent tissue features characterized by the presence of necrotic core and dense calcium suggestive of NA (see Fig. 33-9).

**FIGURE 33-12** Virtual histologic intravascular ultrasound (IVUS) findings in a stent restenosis with evidence of neointimal neoatherosclerotic features at long-term follow-up. Follow-up of paclitaxel-eluting stent implantation at (A) 6 months, (B) 9 months, and (C) 22 months and bare metal stent implantation at (D) 48 months and (E) 57 months. Virtual histology IVUS analysis coded tissue as green (fibrotic), yellow-green...
(fibrofatty), white (dense calcium), and red (necrotic core). (Reproduced with permission from Kang SJ, Mintz GS, Park DW, et al. Tissue characterization of in-stent neointima using intravascular ultrasound radiofrequency data analysis. *Am J Cardiol*. 2010;106:1561-1565, Copyright © 2010, with permission from Elsevier.)

**Optical Coherence Tomography Assessment of In-Stent Restenosis**

OCT deepened our ability to characterize and understand the mechanisms and morphologic patterns of ISR. Gonzalo et al.\(^{168}\) proposed a morphologic classification according to quantitative and qualitative OCT parameters (Table 33-3 and Fig. 33-13). The relationship between OCT and angiographic ISR assessment was also evaluated (Fig. 33-14). The tissue coverage structure pattern at OCT was most commonly layered in diffuse ISR, homogeneous in marginal ISR, and similarly layered or heterogeneous in focal ISR. High backscatter was associated with diffuse ISR, whereas focal ISR was more likely to have low backscatter. Irregular lumen shape, intraluminal material, and microvessels were all more common in focal ISR. Irregular lumen shape and higher neointima symmetry ratio were also associated with unstable clinical presentation, whereas long ISR was correlated with stable presentation.
FIGURE 33-14 Focal (A) and diffuse (B) in-stent restenosis (ISR) evaluated with optical coherence tomography (OCT). Patient with angiographic focal ISR (A1, white arrow). Cross-sectional OCT image shows heterogeneous tissue with low backscatter (A2). Longitudinal OCT image shows a very focal restenosis (A3, white arrows).

Patient with angiographic diffuse ISR (B1, white bracket). Cross-sectional OCT image shows restenotic tissue with layered structure with high backscatter (B2).


Table 33-3 Qualitative and Quantitative Optical Coherence Tomography (OCT) Characterization of In-Stent Restenosis
### OCT Qualitative Assessment

| Restenotic tissue structure | • Homogeneous: uniform optical properties without focal variation in backscattering pattern  
|                           | • Heterogeneous: focal changes in optical properties and various backscattering pattern  
|                           | • Layered: concentric layers with adluminal high scattering layer and abluminal low scattering layer |
| Restenotic tissue backscatter | • High: predominant bright tissue with backscatter  
|                               | • Low: predominant dark tissue with low backscatter |
| Lumen shape                   | • Irregular: sharp delineation of lumen border that appears smooth and circular  
|                               | • Regular: irregular border with tissue protrusion from the vessel wall into the lumen |
| Intraluminal material         | • Presence: visible material within the vessel lumen  
|                               | • Absence: of same |
| Microvessels                  | • Presence: well-delineated structures <200 μm in diameter with a course within the vessel  
|                               | • Absence: of same |

### OCT Quantitative Assessment

- Mean lumen area (mm$^2$)
- Minimal lumen area (mm$^2$)
- Mean stent area (mm$^2$)
- Mean restenotic tissue area (mm$^2$)
- Restenotic tissue burden (%)
OCT characterization according to the time of clinical manifestation of ISR has also been studied. Gonzalo et al\textsuperscript{168} showed that early ISR (≤12 months) has a prevalent layered pattern (84.3%), whereas later ISR (>12 months) has a prevalent homogeneous pattern. At quantitative analysis, early ISR had a tendency to have smaller mean lumen area. No differences were found in restenosis length, restenotic tissue area, or restenotic tissue burden, according to timing of presentation.\textsuperscript{168} Habara et al\textsuperscript{169} also investigated the temporal relationships between DES-ISR (first generation) and OCT features. A total of 43 early (<1 year), 22 late (1-3 years), and 21 very late (>3 years) ISRs were compared. Angiography alone did not detect any differences between the groups. Conversely, quantitative OCT analysis showed differences in mean stent area, with the lowest area in the late ISR group and the highest in the very late ISR group. Qualitative OCT assessment showed that heterogenous intima with thin-cap fibroatheroma (TCFA)–like pattern, intraintimal microvessels, persistent ulcer-like appearance, disrupted intima with visible cavity, and intraluminal material were more common in very late ISR. These morphologic changes suggest a continuous remodeling of ISR tissue with the development of NA features.

OCT has been also used as a tool to characterize the relationship between ISR and NA. Kang et al\textsuperscript{170} reported a high prevalence of in-stent NA in very late DES-ISR (>20 months after PCI). A total of 52% of lesions had at least 1 site containing TCFA, 58% had at least 1 site of in-stent neointimal rupture, and 58% had evidence of thrombus. According to the interval time (<20 vs >20 months after PCI), patients with DES-ISR at >20 months had a higher incidence of single TCFA and multiple TCFA.

Similarly, an OCT study by Takano et al\textsuperscript{171} assessed the neointimal characteristics of BMS at an early (<6 months) and very late stage (>5 years). The investigators observed that the neointima often transforms over time into lipid-laden tissue with lumen narrowing. Interestingly, neovascularization processes expanded from the persistent area to intima with associated NA, suggesting that neoangiogenesis, which is closely associated with plaque progression, could also play a role in the development of in-stent NA. Finally, the authors found that lipid-laden intima was highly associated with ISR compared with no lipid-laden intima. These observations reinforce the theory that very late DES failure is strongly associated with in-stent neoatherosclerotic processes.
Alongside OCT, near-infrared spectroscopy (NIRS) has also been used to characterize the presence of NA within restenotic tissue. Ali et al\textsuperscript{172} characterized in-stent neoatheroma with OCT and NIRS in a consecutive series of patients with BMS- and DES-ISR. NA was defined at OCT as a signal-poor region with diffuse borders. The authors morphologically classified NA through OCT assessment as the following:

- Type I, thin-cap neoatheroma (TCNA): \geq 1 area of thin cap NA located between the lumen and the stent struts
- Type II, thick-cap neoatheroma (ThkNA): absence of thin cap; NA located between the lumen and the stent struts
- Type III, peristrut neoatheroma (PSNA): NA located around the stent struts
- Type IV, preexisting fibroatheroma (PEFA): native preexisting atherosclerosis displaying as poor region signals with diffuse border between the stent struts and the adventitia

The authors observed that NA was significantly more common in DES than BMS (68\% vs 36\%; \( P = .02 \)). Moreover, DES-ISR had a higher prevalence of TCNA. On NIRS assessment, DES-ISR had a greater total lipid burden and density. Finally, NA was more common at sites of culprit lesions in DES but not in BMS. Interestingly, the authors reported a correlation between the occurrence of periprocedural MI and NA type. Periprocedural MI occurred exclusively in DES, with almost half of the events attributable to luminal-type (I/II) NA within the target ISR lesion.

Differences in ISR OCT appearance between early- and new-generation DESs have also been evaluated. Kilickesmez et al\textsuperscript{173} compared OCT findings in ISR in first-generation DESs (SES and PES) versus second-generation DESs (ZES, EES, and BES) before and after 1 year. Features of NA were more prevalent with first-generation DESs, particularly in the early period; conversely, the prevalence of NA features was higher with second-generation DESs after 1 year. Over time, no differences were observed in the prevalence of lesions with NA features between stent generations.

In summary, the study of ISR morphology with OCT has greatly increased our understanding of the etiology and pathogenesis of ISR, particularly with respect to the nature and time course of NA with various stents. The relationship between ISR morphology determined at OCT and clinical
outcomes is a compelling and ongoing area of investigation.

**Computed Tomography Coronary Angiography Assessment**

Computed tomography coronary angiography (CTCA), despite several limitations, has been demonstrated to be useful in evaluating patients with previous intracoronary stent implantation developing new anginal symptoms with a suspicion of ISR. However, according to the present evidence, recommendations favoring a primary role in evaluating ISR are weak. Ehara et al demonstrated a negative predictive value (NPV) of CTCA for binary ISR of 98% alongside a relatively low positive predictive value (PPV) due to unassessable lesions. Artifacts in coronary stent evaluation include motion artifacts, beam hardening (artificial luminal narrowing and decreases in intraluminal attenuation values), and blooming. In particular, metal blooming (stents appear larger than they actually are) causes the stent to appear thicker, not allowing a proper evaluation of the stent lumen. Blooming artifact is more common in cases of overlapping stents, smaller stent diameter, and small vessels.

The role of 64-slice CTCA in evaluating ISR was explored in a large meta-analysis of observational studies (895 patients and 1447 stents) by Kumbhani et al. The overall sensitivity and specificity were both 91%, the NPV was 98%, and the PPV was moderately low at 68%. When nonassessable segments were included, overall sensitivity and specificity decreased to 87% and 84%, respectively, with a PPV of 53% and an NPV of 97%. The results of the present meta-analysis suggest that CTCA is useful to detect or exclude ISR; however, its PPV is low.

**MANAGEMENT OF IN-STENT RESTENOSIS**

The optimal treatment of ISR is still uncertain. DESs have been demonstrated to be safe and effective in the treatment of ISR. Current American College of Cardiology/American Heart Association guidelines gave a Class I recommendation for DES implantation in clinical restenosis after POBA or
BMS in patients able to comply with and tolerate a mandatory regimen of dual antiplatelet therapy (DAPT). For DES-ISR, the same guidelines gave a Class IIb recommendation for repeat PCI with balloon angioplasty, BMS, or DES containing the same drug or an alternative antiproliferative drug if anatomic factors are appropriate and the patient is able to comply with and tolerate DAPT. In every type of ISR, IVUS might be considered to determine the cause for ISR and help guide the treatment strategy.

ISR patterns may guide therapeutic strategies (Fig. 33-15). Focal DES-ISR, where mechanical factors, SFs, nonuniform strut distribution, and edge effects play a determinant role, might be effectively treated by POBA or drug-eluting balloon (DEB). Conversely, diffuse DES-ISR might be treated with repeat stent implantation. Drug resistance is another potential mechanism of DES failure; therefore, in this case, patients may benefit from repeated stenting with a DES eluting a different drug. Diffuse ISR has been shown to be associated with higher rates of TLR (up to 85%) after successful intervention. Of note, most of these studies used percutaneous transluminal coronary angioplasty as a treatment modality for ISR intervention. Kini et al reported a rate of TLR after treatment of ISR with rotational coronary atherectomy, directional coronary atherectomy, and excimer laser of 46% in diffuse-type ISR and 14% in focal-type ISR. However, irrespectively of the pattern of BMS-ISR, as confirmed by a meta-analysis performed by Dibra et al of 4 randomized studies comparing SES or PES with balloon angioplasty or vascular brachytherapy, DESs are markedly superior in terms of TLR and angiographic restenosis compared to conventional techniques (balloon angioplasty and vascular brachytherapy). Edge ISR represents a small subgroup of ISR lesions that apparently have benign angiographic appearance but are associated with high rates of TLR. A substudy from the RIBS (Restenosis Intra-Stent: Balloon Angioplasty Versus Elective Stenting) trial registry demonstrated that the use of stents in this subgroup of lesions significantly reduced the need for TLR when compared to balloon angioplasty. After multivariable correction for other confounders, stent implantation was the only independent predictor of freedom from TVR (hazard ratio, 0.15; \( P = .003 \)). The recent RIBS-V trial, which compared EES and paclitaxel-eluting balloon (PEB) in BMS-ISR, found that even though both techniques provided excellent results, EES appeared superior to PEB in terms of acute and late angiographic results. This result was also consistent
in patients with diffuse ISR.

Regarding ISR in DES (SES, PES, ZES, and BES), the recent ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis) III trial, which compared PEB, PES, and POBA, showed that, independent of the baseline pattern of ISR, PEB and PES are markedly superior to POBA in preventing recurrent TLR. Of note, POBA was more commonly associated with a higher incidence of recurrent ISR with diffuse pattern (POBA 39% vs PES 21% vs PEB 21%). Conversely, PES and PEB were more commonly associated with focal-type recurrent ISR (POBA 31% vs PES 41% vs PEB 46%); however, these differences were not statistical significant. Previously, the ISAR-DESIRE II trial demonstrated no differences in the treatment of SES-ISR with SES or PES. Of note, no significant differences were observed in the pattern of recurrent ISR between the 2 types of DES. The similar efficacy of both treatments was also recently confirmed in diabetic and nondiabetic patients by Kufner et al.
**Bare Metal Stent Restenosis**

Currently, PCI with DES implantation is the preferred treatment for BMS-ISR. The safety and efficacy of DES implantation for the treatment of BMS-ISR have been demonstrated in several randomized controlled trials. In the ISAR-DESIRE trial, 300 patients with BMS-ISR were randomized to treatment with SES, PES, or POBA alone. At 6 months, binary angiographic restenosis and TVR rates were significantly lower with DESs compared with POBA alone. Among DESs, SES was associated with a trend toward lower rate of binary angiographic restenosis and significantly lower rates of TVR and LLL compared with PES.\(^{184}\) Similarly, in the RIBS-II (Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) trial, 150 patients with ISR were randomized to treatment with SES or POBA. At 9 months of follow-up, SES was associated with lower rates of recurrent restenosis and higher MLD and lumen volume at IVUS assessment compared with POBA.\(^{185}\) Long-term follow-up at 4 years of the RIBS-II trial demonstrated sustained clinical efficacy with SES, with lower rates of TLR and MACE.\(^{186}\) Recently, results from the RIBS-V (Restenosis Intrastent of Bare Metal Stents: Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent) trial have been published.\(^{187}\) This study evaluated the safety and efficacy of DEB versus EES in patients with BMS-ISR. EES was associated with significantly larger MLD and lower percent diameter stenosis. However, LLL and binary restenosis rates were low and similar in both groups. Finally, no differences in TVR were observed between groups at 9 months. Therefore, this study demonstrated excellent clinical midterm results with both DEB and EES; however, EES provided superior late angiographic findings. Certainly, long-term follow-up is needed to characterize the efficacy of DEB over time.

Brachytherapy was initially proposed as a potential treatment for ISR. However, 2 randomized controlled trials comparing brachytherapy with DES implantation failed to show any benefit associated with this technique. The TAXUS V ISR trial randomly assigned 396 patients with clinical ISR to treatment with brachytherapy or PES.\(^{188}\) At 9 months, PES was associated with lower LLL, angiographic binary restenosis, and higher MLD. The angiographic superiority of PES over brachytherapy was confirmed at 2 years of follow-up, whereas no differences were observed in clinical outcomes.\(^{189}\) In the SIRS (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial, 384 patients with clinical BMS-ISR were randomly
assigned to either brachytherapy or SES-PCI. Similarly to the TAXUS V ISR trial, SES was associated with better clinical and angiographic outcomes at 9 months compared with brachytherapy. Conversely, at 5 years of follow-up, there were no significant differences in clinical outcomes between the 2 strategies. Considering the complexity and the costs associated with brachytherapy, DES implantation is the preferred strategy for treatment of BMS-ISR.

**Drug-Eluting Stent Restenosis**

DES-ISR is becoming an increasingly frequent problem because of the important number of DESs implanted worldwide each year. Moreover, the optimal treatment for DES restenosis is currently uncertain. As described previously in this chapter, endothelial antiproliferative drug resistance is a potential mechanism of DES-ISR. In the ISAR-DESIRE 2 study, the use of different DESs for the first DES-ISR has been tested. A total of 450 patients with clinical SES-ISR were randomized to either SES or PES implantation. At 6 to 8 months of follow-up, there were no differences between SES and PES in late loss, binary restenosis, or TLR. Moreover, no differences were observed in terms of clinical outcomes. Conversely, the RIBS-III (Restenosis Intrastent: Balloon Angioplasty Versus Drug-Eluting Stent) trial, a prospective, multicenter nonrandomized study, yielded different results. A total of 363 patients were included. The different DES strategy was used in 274 patients (75%), whereas implantation of a DES with similar drug elution was used in 89 patients (25%). At a median follow-up of 278 days, the different DES strategy was associated with greater MLD and lower recurrent restenosis rates. These results remained consistent following adjustment for baseline confounders; however, the nonrandomized nature of this study makes these results less reliable.

Another important issue in the management of ISR is the duration of DAPT following ISR treatment. A substudy from the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial reported a lower incidence of the composite of death, MI, or stroke in patients with ISR treated with long (24 months) DAPT compared with a short (6 months) regimen. Despite the limitation of this analysis (only 224 patients with ISR were included), these data provide preliminary evidence that patients treated for ISR might benefit from prolonged DAPT.
Finally, a very recent network meta-analysis of randomized controlled trials has shown that DEB and DES for ISR treatment (both BMS- and DES-ISR) are associated with significantly lower TLR rates compared with POBA, whereas no differences in MI or mortality were observed. Interestingly, the risk for MI or all-cause mortality was lowest with DEB but this did not reach statistical significance.

Currently, 2 randomized controlled trials evaluating different treatments for DES-ISR are ongoing. The ISAR-DESIRE IV (ClinicalTrials.gov identifier: NCT01632371) trials will test the superiority of cutting balloon plus PEB versus PEB alone for the treatment of ISR within limus-eluting stents. Therefore, this trial will test the efficacy of cutting balloon in the treatment of ISR associated with the release of an antiproliferative drug of a different family compared with the restenotic DES. Theoretically, the application of a cutting balloon prior to deployment of PEB may increase the bioavailability of paclitaxel within the restenotic tissue with subsequent improvement in the efficacy of PEB. Conversely, the RIBS-IV (ClinicalTrials.gov identifier: NCT01239940) trial will randomize 310 patients with DES-ISR to receive treatment with DES or EES implantation.

**CONCLUSIONS**

DESs critically improved the safety and efficacy of PCI by reducing the need for TLR and TVR across all types of coronary lesions and patient subsets. In a contemporary era, the rates of ISR with DES are less than 8 to 10% at 3 to 4 years of follow-up. However, limitations still exist, especially in very complex lesions and diabetic patients. Next-generation stent platforms have to further improve DES performance by implementing novel antiproliferative drugs, thinner stent struts, more favorable stent designs, and improved stent material biocompatibility. Routine implementation of intracoronary imaging may be critical in optimizing stent implantation and improve long-term PCI outcomes. Finally, BVSs, which represent a technologic breakthrough in the field of coronary stents, have the potential advantages of similar efficacy in treating coronary stenosis along with the ability to restore native vascular physiology. Further studies are warranted to better identify the factors associated with ISR in the current era and establish the optimal strategies for its prevention and treatment.
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Coronary Atherectomy: Concepts and Practice

Creighton W. Don
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Mark Reisman

BACKGROUND

Coronary atherectomy continues to be an important tool for percutaneous coronary intervention (PCI), particularly as the population ages and more patients present with complex calcified coronary artery disease. Early studies using rotational and laser atherectomy failed to demonstrate a clear advantage over angioplasty alone, and as such, atherectomy of straightforward atherosclerotic disease is not commonly used. With the very low restenosis rates of second-generation drug-eluting stents (DESs) in many lesion types, contemporary practice is to use atherectomy primarily as adjunctive therapy for plaque modification of calcific lesions that cannot be crossed with devices or dilated with balloons to enable DES delivery.

Utilization of atherectomy composes approximately 3% of PCIs in the United States and between 0.8% and 3.1% worldwide (Table 34-1). Yet, as the population ages, more PCIs are performed in higher risk patients with more complex coronary artery disease, and in a recent evaluation of patients undergoing PCI, 33% were found to have moderate to severe coronary calcification (Fig. 34-1). Furthermore, the extent of vessel calcification is often underappreciated fluoroscopically. In one study, significant
calcification seen by intravascular ultrasound (IVUS) was seen only 50% of the time fluoroscopically,\textsuperscript{5} which is often the cause for “rota-regret” when a stent cannot be delivered or dilated.

**FIGURE 34-1** Prevalence of moderate to severe calcification in 1800 patients undergoing percutaneous coronary intervention (COMPARE study).\textsuperscript{4} ACC, American College of Cardiology; AHA, American Heart Association; CTO, chronic total occlusion.

Table 34-1 Percentage of Atherectomy by Total Percutaneous Coronary Interventions by Country
Vessel calcification remains a major independent predictor of PCI failure and adverse outcomes (Fig. 34-2), and atherectomy is a critical component to improve PCI success in these situations. Some studies are already starting to show an increasing trend in the number of operators and centers performing atherectomy.

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>3.1%</td>
</tr>
<tr>
<td>United States</td>
<td>3.0%</td>
</tr>
<tr>
<td>France</td>
<td>2.9%</td>
</tr>
<tr>
<td>Spain</td>
<td>2.3%</td>
</tr>
<tr>
<td>Austria</td>
<td>1.8%</td>
</tr>
<tr>
<td>Italy</td>
<td>1.3%</td>
</tr>
<tr>
<td>Australia</td>
<td>1.0%</td>
</tr>
<tr>
<td>Germany</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

**FIGURE 34-2** Increasing risk associated with degree of lesion calcification among patients being treated with percutaneous coronary intervention (HORIZONS-AMI and ACUITY studies). $^7$ P < .05 for all comparisons. MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion
revascularization.

Rotational atherectomy is the most widely used form of atherectomy, although utilization of laser and orbital atherectomy has been increasing. The majority of clinical data regarding coronary atherectomy is based on evaluation of the Rotablator device (Boston Scientific, Marlborough, MA). As such, this chapter will focus primarily on rotational atherectomy, with more brief discussion of the potential utility of other atherectomy devices.

**RATIONALE FOR AThERECTOMY**

The early experience with coronary atherectomy focused on plaque reduction and lesion debulking, given the residual stenosis and need for repeat revascularization in an era in which PCI was limited to balloon angioplasty. Several devices were developed and approved for use, but clinical trials found minimal benefit and potentially harm compared to angioplasty. Directional coronary atherectomy and laser atherectomy have fallen out of favor given their association with coronary perforations and similar rates of restenosis and adverse events compared with patients undergoing angioplasty alone.\(^{10}\)

In the coronary stenting era, in which restenosis rates with DES are less than 3% annually,\(^{11}\) atherectomy is used primarily for plaque modification and lesion preparation rather than debulking. Rotational atherectomy has remained a useful tool for its ability to preferentially ablate calcific and fibrotic disease to help facilitate stent delivery,\(^{12}\) avoiding the barotrauma caused by repeated high-pressure balloon inflations that can lead to vessel dissection or perforation.\(^{13,14}\)

Furthermore, forceful advancement of DES through narrow, calcified lesions may cause stent polymer damage, which could be avoided with proper lesion preparation using atherectomy.\(^{15}\) In the ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) study, among patients who underwent an angioplasty-stenting strategy, stent loss was observed in 2.5% of patients, and 12.5% of these patients ultimately crossed over to atherectomy, whereas no stent loss was observed among patients randomized to the atherectomy strategy.\(^{12}\)

The ROTATE Multicenter Registry demonstrated that patients undergoing
planned rotational atherectomy had fewer balloon inflations, less radiation exposure, lower contrast volumes, and shorter procedure times than those undergoing provisional atherectomy for device delivery failure or balloon expansion failure (Fig. 34-3).\textsuperscript{16}
In addition to this, atherectomy would potentially modify a calcified lesion to allow optimal stent expansion and improve lumen gain.\textsuperscript{12,17} This may have particular benefits for PCI with bioresorbable scaffolds that may have lower radial strength and greater recoil than metal stents that demand more complete vessel preparation to allow stent delivery and more complete apposition.\textsuperscript{18,19} Although the use of atherectomy for debulking atherosclerotic tissue has fallen out of favor in the era of DES, plaque reduction remains useful in specific situations such as bifurcations or ostial disease, reducing disease at the carina to avoid geographic miss, and plaque shift.\textsuperscript{20-22} The list of potential benefits of atherectomy to optimize PCI are listed in Table 34-2.

Table 34-2 Potential Benefits of Atherectomy to Optimize Percutaneous Coronary Interventions (PCIs)

<table>
<thead>
<tr>
<th>Potential Benefits of Atherectomy to Optimize PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allow device delivery\textsuperscript{12,16}</td>
</tr>
<tr>
<td>• Improve stent expansion and apposition\textsuperscript{12,17}</td>
</tr>
<tr>
<td>• Improve procedure efficiency</td>
</tr>
<tr>
<td>• Shorter procedures, fewer balloons, less radiation, less contrast\textsuperscript{16}</td>
</tr>
<tr>
<td>• Reduce balloon-induced dissections\textsuperscript{14}</td>
</tr>
<tr>
<td>• Ostial lesions</td>
</tr>
<tr>
<td>• Reduce plaque shift and geographic miss\textsuperscript{20-22}</td>
</tr>
<tr>
<td>• Bifurcation disease</td>
</tr>
<tr>
<td>• Debulk plaque at carina and reduce plaque shift\textsuperscript{20,67}</td>
</tr>
<tr>
<td>• Reduce stent loss\textsuperscript{12}</td>
</tr>
<tr>
<td>• Prevent stent polymer damage\textsuperscript{15}</td>
</tr>
</tbody>
</table>
ROTATIONAL AHERECTOMY

The Rotablator rotational atherectomy system was developed by David C. Auth, PhD, PE, at the University of Washington over a period of 13 years. After years of experimentation and animal studies, on January 6, 1988, Fourrier et al. performed the first procedure in a human coronary artery. At the same time, Zacca and colleagues performed the procedure in the peripheral vasculature in humans. Since then, multiple clinical trials and registries have demonstrated the efficacy of rotational atherectomy, which has become the most commonly used coronary atherectomy device worldwide.

The components of the Rotablator rotational atherectomy system include the burr, drive shaft, turbine, and console (Fig. 34-4).
FIGURE 34-4 Rotablator components.

**Burr**

The Rotablator burr is a nickel-plated brass ellipse coated with diamond.
crystals between 20 and 30 μm in size on the leading edge, on average extruding only 5 μm from the surface, forming an abrasive sanding surface. There are no diamond chips on the trailing edge, so atherectomy is only achieved with forward motion of the burr. For the coronary arteries, burrs are available in sizes of 1.25, 1.5, 1.75, 2.0, 2.15, 2.25, 2.38, and 2.5 mm. The inner diameter of the guide catheter must be at least 0.01 mm (0.004 in) greater than the burr size to provide adequate clearance for device advancement and withdrawal. The later section on guide catheters describes this in greater detail.

The burr is bonded to a drive shaft housed in a 4.3-Fr, 135-cm-length Teflon sheath and connected to a turbine within the advancer. Potential injury to the arterial wall (by the spinning drive shaft) is prevented by the Teflon sheath, which also acts as a conduit, delivering flush at 7 to 13 mL/min when activated.

**Advancer**

Compressed nitrogen powers a turbine within the advancer that rotates the shaft and burr at speeds of 150,000 to 200,000 rpm. The turbine is controlled by the console and activated by a foot pedal. The advancer has a knob that controls the movement of the burr during atherectomy. The knob can be locked down to avoid movement of the burr during advancement through the coronary guide. The back end of the advancer has a brake that locks the advancer onto the wire and prevents the coaxial guide wire from spinning along with the burr. The break is released by pressing the black button on the end of the advancer, which needs to be released when withdrawing the device.

**Console and Foot Pedal**

The console regulates the flow of compressed air, which controls the turbine speed. A fiberoptic light probe monitors the rotational speed and displays it on the console tachometer. Depressing the foot pedal initiates rotation of the burr and activates the breaking system. The button on the right of the foot pedal toggles between the rotation used for atherectomy and DynaGlide, which rotates the burr at a constant 30,000 rpm to prevent stalls. DynaGlide is used for withdrawing the system through the guide and helping to
disentangle an entrapped burr.

**BASIC PRINCIPLES AND MECHANISMS**

The high-speed rotations of the Rotablator are effective in increasing lumen diameter through plaque ablation but can also have deleterious effects that may weaken the vessel adventitia, leading to perforations and vessel aneurysms, or cause microcavitations, hematologic effects, and embolization of microparticulate debris that can lead to no reflow.

*Mechanisms and Physiologic Effects*

The Rotablator system is analogous to a low-powered rotary sander. High-speed rotational atherectomy effectively ablates calcified, inelastic atherosclerotic tissue while sparing healthy, elastic tissue, leading to lumen enlargement and reduction of cross-sectional atherosclerotic plaque area. There is also minimal trauma to normal “healthy” tissue. Data from human and animal studies confirm these findings.\(^{23-25}\)

The 2 principles that govern the operation and effectiveness of the Rotablator system are *differential cutting* and *orthogonal displacement of friction*.

**Differential Cutting**

Differential cutting is the ability to selectively ablate one material while preserving the integrity of the other, based on differences in the composition and texture of the substrate. The elasticity of the normal tissue deflects the ablative surface, whereas the inelastic properties of diseased tissue engage the cutting surface. A common analogy to differential cutting is shaving. Whiskers are relatively inelastic compared to skin, and a razor will preferentially cut these while sparing the skin. The atherectomy burr tends to spare healthy, elastic tissue, while calcium, fibrous tissue, fatty deposits, and intimal hyperplasia (restenotic tissue) increase the inelastic properties of vascular tissue, making it susceptible to ablation by the cutting edges of the
atherectomy burr.

**Orthogonal Displacement of Friction**

Orthogonal displacement of friction is essential in allowing easy passage of the burr through diseased and tortuous vascular segments. The sliding motion and high rotational speeds virtually eliminate the longitudinal friction vector, allowing for unhindered advancement and withdrawal of the burr. This principle is similar to a corkscrew, in which the twisting motion reduces the friction on the surfaces and facilitates movement of the corkscrew. The faster it is turned, the easier it is to remove it.

These 2 basic principles allow for the burr to effectively ablate diseased and atherosclerotic tissue, with lower risk of harming normal tissue. This was confirmed with early animal studies using cholesterol-fed New Zealand white rabbits. After treatment, the minimum lumen diameter (MLD) was reduced from 81% ± 9% to 38% ± 22% ($P < .001$, paired $t$ test). Histologic specimens showed effective intimal plaque removal, with minimal medial injury and no medial or intimal dissections. Similar results were shown by Ahn et al\textsuperscript{27} in cadaveric human coronary arteries.

**Debulking and Plaque Modification**

Quantitative coronary angiography has been used to evaluate the efficiency of rotational atherectomy in debulking lesions. Early studies using quantitative coronary angiography in 109 patients showed that a predictable MLD can be achieved across the range of burr sizes. Expressing MLD as a burr ratio (MLD/burr size), the Rotablator achieved immediate results of 72% ± 19% of the burr selected (ie, a 2.0-mm burr predicted an MLD of approximately 1.4 mm). Mintz et al\textsuperscript{25} confirmed this using IVUS. There was minimal injury to the media and adventitia of adjacent tissue. Measured 24 hours later, the burr ratio increased to 84% ± 15%.\textsuperscript{28}

Guide wire bias, however, preferentially orients the burr toward either the inner or outer curvature of an angulated lesion and causes unequal force to be exerted on one region of the vessel wall, resulting in a much larger, eccentric lumen. The Rotablator burr creates a force vector that not only ablates the vessel media and creates an elliptical lumen,\textsuperscript{29} but can also form deep vessel
dissections or “rota-gutters,” aneurysms, and perforations (Fig. 34-5).

**FIGURE 34-5** Formation of a deep vascular dissection by rotational atherectomy. A. Angiogram showing severe calcification along an angulated lesion (white solid arrow). There is a calcified plaque before atherectomy with the wire in contact with the vessel wall (I), and plaque modification after the debulking intervention with a channel formation (II). The diameter of the channel (solid white double arrow) is exactly the same diameter of the 1.25-mm burr that was used. After stent placement (III), some segments still showed the presence of the channel (asterisk) behind the struts (white dashed arrow). (Used with permission from Attizzani GF1, Patrício L, Bezerra HG. Optical coherence tomography assessment of calcified plaque modification after rotational atherectomy. *Catheter Cardiovasc Interv.* 2013;81(3):558-561.)

In some studies, sequential IVUS imaging and electron microscopy have shown not only plaque reduction, but also ablation of media volume and damage to the smooth muscle layer, albeit without change in the external elastic membrane diameter. Nevertheless, unequal ablation of tissue,
Atherectomy of calcium, and disruption of the media layer change vessel compliance in such a way that allows for device delivery and full expansion, even with minimal initial lumen gain. In more contemporary studies of atherectomy adjunctive to stenting, significant increases in lumen areas were documented despite use of primarily smaller 1.5-mm burrs.\textsuperscript{12,16,34} For these reasons, the maximal burr size should not exceed 70% of the vessel diameter, and floppy wires or guide and wire positioning techniques can be used to reduce eccentric cutting of the vessel media layer. Atherectomy of extremely angulated lesions may need to be avoided.

**Thermal Effects**

Thermal injury can lead to smooth muscle proliferation, increasing restenosis rates, as well as cause red blood cell aggregation and platelet activation.\textsuperscript{35-37} Increased temperatures are generated with longer, more continuous engagement of coronary lesions with the spinning burr and aggressive ablation with excessive decelerations (14,000-18,000 rpm), whereas an intermittent or oscillating “pecking” technique can limit decelerations and reduce the temperature changes.\textsuperscript{38} Minimizing thermal injury using this technique may prevent vessel trauma and smooth muscle proliferation that may increase restenosis.

**Microparticulate Debris**

The vast majority of microparticulate debris produced by rotational atherectomy is generally 2 to 10 μm and smaller, compared to red blood cells and capillaries, which are about 6 to 10 μm\textsuperscript{26,27}; however, about 2% to 10% of particles are 10 to 20 μm and larger when using the larger burr sizes.\textsuperscript{27,39} A recent study of the orbital atherectomy device reported an average particulate size of 2 μm, with approximately 1% of particles being larger than 9.5 μm. Most of this debris passes through the capillaries and is cleared by the reticuloendothelial system.\textsuperscript{27} Transient perfusion defects can be observed on single-photon emission computed tomography imaging, but these appear to resolve after 48 hours and are not necessarily clinically significant.\textsuperscript{40} Other studies have shown similar defects with PCI that may not differ significantly from rotational atherectomy.\textsuperscript{41}
The rapidly spinning Rotablator burr is also known to form relatively large gas bubbles dissolved in blood called microcavitations, which appear to collapse quickly. During activation of the burr, transient enhancement of echocardiographic contrast is seen in the area of the myocardium subtended by the artery, which disappears immediately after the burr rotation is stopped. Microcavitations may transiently reduce myocardial blood flow.42

Nevertheless, more significant no reflow or vessel closure during the procedure, associated with hypotension, is clinically relevant, and steps should be taken to minimize such events. It is recommended that each atherectomy run last no longer than 30 seconds to restore normal myocardial blood flow and allow time for microparticles to clear from the distal vasculature. Administration of prophylactic vasodilators or mixing verapamil and nitroglycerine with the RotaGlide lubricant may help reduce no reflow.43,44

**Platelet Aggregation**

The high rotational speed of the burr establishes a shear field and affects both erythrocytes and platelets. A study using 8 samples of porcine blood exposed to a spinning burr demonstrated evidence of platelet aggregation as measured by optical microscopy.38 The number of aggregates was affected by the speed of the burr. Larger platelet aggregates (>60 μm in diameter) were seen in all 8 samples at 180,000 rpm and in only 1 of 8 samples at 140,000 rpm. These findings support the importance of lowering the burr speed to minimize the hematologic impact of rotational atherectomy. The combination of lower rotablation speeds and the use of glycoprotein IIb/IIIa inhibitors during atherectomy has also been shown to reduce platelet aggregation45 and the incidence of periprocedural myocardial ischemia46 and infarctions in patients.47

These observations establish the basic foundation for understanding the mechanism of rotational atherectomy and provide general principals to mitigate the untoward effects of atherectomy (Table 34-3). Smaller burr/artery ratios, management of guide wire bias, and avoidance of severely angulated lesions will help avoid significant damage to the vessel media layer. Heat generation and thermal injury can be minimized by advancing the device gently and intermittently and avoiding significant decelerations. Use
of smaller burrs, limiting atherectomy runs to 30 seconds, and prophylactic administration of vasodilators may reduce the impact of downstream microparticulate embolization. Platelet aggregation and other hematologic affects can be controlled by lowering the rotational speeds and the use of platelet inhibitors.

**Table 34-3 Recommended Techniques to Address Complications Associated With Atherectomy**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Causes</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Perforations and aneurysms**| Burr oversizing, forceful burr advancement, angulated lesions and guide wire bias causing deep fissures, and eccentric cutting of the vessel media layer | • Smaller burrs for angulated lesions  
• Start with smaller burrs for plaque modification, with maximal burr size <70% of the vessel diameter  
• Rota Floppy wire and guide wire positioning to reduce guide wire bias in angulated lesions  
• Avoidance of severely angulated vessels |
| **Restenosis**                 | Thermal injury predisposing to intimal hyperplasia                      | • Intermittent “pecking” technique rather than continuous lesion engagement  
• Limit each atherectomy run to 30 seconds  
• Avoid excessive decelerations |
| **Slow flow**                 | Microparticulate debris and platelet aggregation                        | • Use smaller burrs (~1.5) if possible  
• Limit each atherectomy run to 30 seconds  
• Start with lower burr speeds ~140,000 to 160,000 rpm  
• Appropriate platelet inhibition  
• Prophylactic vasodilators |
| **Burr entrapment**           | Forceful advancement of the rotational burr or atherectomy within a dissection | • Careful use of the 1.25 burr  
• Graded upsizing of the burr  
• Use of the Intermittent “pecking” technique  
• Avoid decelerations >5000 rpm |

**PROCEDURAL CONSIDERATIONS AND TECHNIQUE**

**Guide Catheters**

The internal diameter of the guiding catheter should be at least 0.01 mm (0.004 in) larger than the burr. Therefore, a 5-Fr guide with an inner diameter of 1.47 mm (0.058 in) can only allow delivery of the 1.25-mm burr. A 6-Fr guide with an inner diameter of 1.80 mm (0.071 in) can accommodate the 1.25-, 1.5-, and 1.75-mm burrs. A 7-Fr guide with an inner diameter of 2.05 mm (0.081 in) can accommodate up to a 2.0-mm burr; however, larger guides provide greater clearance to facilitate advancement of the burr through the
guide, so an 8-Fr guide may be preferable for the 1.75-mm burr. An 8-Fr guide with an inner diameter of 2.28 mm (0.090 in) can accommodate up to a 2.15-mm burr. A 9-Fr guide would be needed for the 2.25- and 2.38-mm burrs, and a 10-Fr guide would be needed for the 2.5-mm burr. Since 9-Fr and 10-Fr guides are rarely used in the coronaries in the contemporary era, the larger burr sizes are primarily used in peripheral interventions. Operators must be attentive to the specifications of guide catheters from different manufacturers as inner diameters may vary.

Guide extension catheters may facilitate burr delivery to distal, tortuous lesions, but the inner diameter of these catheters limits what sizes can be used. Although the inner diameter of the 6-Fr Guideliner (Vascular Solutions, Minneapolis, MN) is 1.42 mm (0.056 in) and that of the 6-Fr Guidezilla (Boston Scientific) is 1.45 mm (0.057 in), there is minimal clearance for the 4.3-Fr Rotablator drive shaft, and device advancement is not easy. The 8-Fr Guideliner inner diameter is 1.80 mm (0.071 in), which could allow for the 1.25- and 1.5-mm burrs to be advanced.

Coaxial guide positioning is important to ensure easy of passage of the Rotablator burr and avoid trauma to the coronary ostia. The guide can also be used to modify the trajectory of the guide wire to change the direction of the ablation plane, which is important in atherectomy of proximal lesions that are highly angulated or are affected by guide wire bias.

**Guide Wires**

The Rotablator spins over a 0.009-in stainless steel wire with a radiopaque platinum 0.014-in spring coiled tip. The larger tip diameter prevents the burr from spinning beyond the tip of the wire, so the radiopaque dip must be positioned distal to the lesion, because the burr cannot track over this larger segment. Every attempt should be made to keep the guide wire from prolapsing or coiling, because any rotation during burr activation can result in fracture or trapping of the tip in the vessel wall.

Two types of guide wires are currently available. The Floppy RotaWire (Boston Scientific) has a long, tapered shaft that maximizes flexibility to reduce vessel straightening and help relieve unfavorable wire bias in tortuous vessels. On the other hand, in highly calcified vessels, the floppy wire may bias the Rotablator vector preferentially toward normal tissue, leading to eccentric atherectomy or potential dissections. The RotaWire Extra Support
wire (Boston Scientific) is a stiffer-bodied wire that increases vessel straightening to help steer the burr through heavily calcified and ostial lesions, but it may create pseudolesions and lead to ablation of normal tissue.

It is possible to angle the guide catheter and manipulate the guide wire to orient the burr closer to the lesion, particularly when treating proximal eccentric and angulated lesions. Pulling or pushing on the wire can direct the burr force vector to the inner or outer curve of the lesion—a concept that has been referred to as *directional* rotational atherectomy.

**Burr Selection, Advancement, and Trouble Shooting**

Early plaque debulking strategies incorporated a 2-burr approach, with the burr-to-artery ratio of the first burr being approximately 0.5 to 0.6, and that of the second approximately 0.75 to 0.8. In the stenting era, in which the goal is plaque modification, a single burr with a burr-to-artery ratio of at most 0.6 to 0.7 is sufficient, in conjunction with angioplasty and stenting. A burr-to-artery ratio of less than 0.5 is helpful for total occlusions, sharply angulated lesions, or long lesions. Less aggressive atherectomy has been associated with lower rates of restenosis and helps reduce periprocedural complications. 48,49

Once the burr is advanced into the coronary artery, it should be placed just proximal to the lesion—the so-called *platform segment*. The burr is activated in this position, where it can rotate unimpeded, because if the burr is activated while in contact with the vessel wall, the risk of injury is significantly increased.

After positioning the burr in the proximal position, it is important to relieve the tension on the system by pulling back on the advancer knob to prevent the burr from jumping forward into the lesion when the device is activated, increasing the risk of dissection. Once the operator is certain that the tension on the burr has been released, the burr is activated in the platform segment and then advanced to the lesion. Rotation speeds of 140,000 to 160,000 rpm are ideal to optimize atherectomy and reduce complications.

Ablation of the lesion should be performed using a “pecking” technique to reduce thermal injury and embolization. Burr advancement should be gentle. Monitoring the decelerations and avoiding excessive decelerations of >5000 rpm helps to avoid aggressive atherectomy. Contrast injections can be performed to evaluate the progress of the burr and identify any problems with
burr orientation or burr-to-artery relationship. The duration of each run should last 15 to 30 seconds, with an interval of 30 seconds and longer between each run to allow for myocardial perfusion and clearance of microparticles. Longer rest periods may be needed to allow for electrocardiographic changes, hypotension, chest pain, or bradycardia to resolve. Once there is no tactile resistance as the burr crosses the treated segment or when no decrease in revolutions per minute are noted during burr advancement, the burr should be removed.

**Complications**

**Bradycardia**

Bradycardia and heart block are often seen in patients undergoing atherectomy of right or left dominant circumflex coronary arteries, most likely due to microparticulate emboli leading to a parasympathetic effect on the heart. Atherectomy using larger burrs, longer runs, or more revolutions per minute and treating lesions affecting a greater myocardial territory are more likely to induce heart block.

Routine temporary pacemakers are not required when using smaller burrs at lower revolutions per minute, but operators should stop atherectomy runs when transient atrioventricular nodal block occurs and be prepared to place a temporary wire or address this with pharmacologic (eg, atropine) or mechanical maneuvers (eg, coughing) if it does not resolve quickly.

**No Reflow**

The major clinical complication rates for rotational atherectomy are similar to those reported for balloon angioplasty and include death in 0.9% of patients, Q-wave myocardial infarction (MI) in 1.3%, and emergency bypass surgery in 1.9%, even in the context of higher risk lesions. There is, however, a trend toward a higher rate of non–Q-wave MI (6%), defined as a creatine kinase–myocardial band (CK-MB) level elevated to more than twice the normal value. Most of these complications can be avoided by using proper procedural technique and pharmacotherapy.

However, lesions with thrombus, with extensive dissection, and in
saphenous vein grafts should be avoided. The choice of guide catheter (eg, based on vessel takeoff, need for support), guide wire, and burr size should be determined at the start of the procedure.

It is worthwhile to note that use of glycoprotein IIb/IIIa inhibitors has been shown to reduce postprocedural elevation of cardiac enzymes by almost 50%, which may translate to a reduction in long-term adverse events.\textsuperscript{32,33} Glycoprotein IIb/IIIa use has also been shown to attenuate the transient wall motion abnormality sometimes associated with rotational atherectomy,\textsuperscript{34} and in vitro studies have shown that abciximab can reduce platelet activation caused by a high-speed burr.\textsuperscript{35} Although there is significant benefit in using these agents, care is needed when lesions are at high risk for perforation, because the level of anticoagulation could have catastrophic effects.

Vasospasm can sometimes complicate rotational atherectomy; therefore, it is important to have vasodilating agents such as nitroglycerine (100-200 μg) available during the procedure. Some operators prefer to use a cocktail of nitroglycerine, verapamil, and heparin in a flush solution for continuous infusion, and some data support this approach.\textsuperscript{36} Intracoronary adenosine administration has also been shown to reduce the rates of no reflow.\textsuperscript{37} RotaGlide lubricant is also usually added to the flush solution to reduce friction between the drive coil and guide wire. Vasopressors should also be readily available; dopamine, epinephrine, and phenylephrine are the usual agents.

**Burr Entrapment**

The Rotablator burr can be advanced forward too quickly, insufficiently atherectomizing the lesion, and then pushed beyond the lesion. Since the atherectomy surface on the Rotablator is only on the proximal surface, it is possible that the burr cannot be withdrawn back through the vessel in this situation. It is also possible that the burr becomes embedded in a fibrotic and calcified lesion and the device stalls and will not rotate. Extremely calcified lesions and tortuous vessels increase the risk for entrapment.\textsuperscript{50} A 1.25-mm burr is the most likely to inadvertently be forced through a lesion given its smaller size and lower profile shape compared to the larger burrs. Purposeful, but careful, burr advancement during atherectomy helps to avoid this complication, but it cannot always be avoided.
Gently withdrawing the burr using DynaGlide, with constant low revolutions per minute, typically will disentangle a stalled device; however, this is occasionally insufficient to remove the device.

Expanding the lesion with an angioplasty balloon may reduce the resistance of the lesion and allow the burr to be withdrawn. If an 8-Fr guide is used, a second wire and 1.5-mm balloon can be passed alongside the rotablation catheter, and an attempt can be made to pass a wire alongside the entrapped rotablation burr and angioplasty the resistant lesion. A second guide can be used from a second access site, or a smaller guide can be upsized by cutting the distal hub off of the rotablation burr, removing the smaller guide and advancing a larger guide over the rotablation shaft. Alternatively, once the distal hub of the rotablation burr is cut, the outer plastic sheath covering the burr can be removed. This will allow for a second wire and balloon to be passed through a 6- or 7-Fr guide.

A telescoping 5-Fr guide to provide countertraction and a gooseneck snare to provide negative traction have been described to successfully remove entrapped rotablation burrs. The hub of the rotablation catheter and the outer plastic sheath need to be removed so a telescoping “mother-in-child” guide can be advanced over the rotablation shaft assembly or the snare, and the snare microcatheter will fit alongside the Rotablator within the guide. Additionally, the distal end of the rotablation wire is 0.014 in and can be withdrawn and used to pull back on the rotablation burr, which has a 0.009-in lumen.

**CLINICAL STUDIES**

The first atherectomy device for coronary arteries was a directional atherectomy device approved by the US Food and Drug Administration (FDA) in 1990, followed by the approval of the excimer laser and Rotablator in 1993. There were no other coronary atherectomy devices approved until Cardiovascular Systems Incorporated’s Diamondback 360 in 2013.

The FDA approval of the Rotablator was based on several nonrandomized studies, the most important of which involved a multicenter registry that included 2953 procedures involving 3717 lesions from patients who underwent rotational atherectomy for primary treatment of coronary artery disease or as adjunctive therapy to balloon angioplasty. The study was
published in 1995 and compiled data from 1988 to 1993, at a time when angioplasty was the primary mode of coronary intervention and atherectomy was used as a sole therapy. The procedural success rate was 85% with atherectomy alone and 95% with adjunctive balloon angioplasty. The rate of periprocedural MI was 9.5%, mortality 0.8%, and urgent coronary artery bypass graft (CABG) 2.0%. Dissections were noted in 13.1%, perforations in 0.7%, and abrupt closure in 3.6% of patients.

The early use of atherectomy focused on plaque debulking using progressively larger burrs to maximize lumen gain with angioplasty. As stent technologies improved, the practice of aggressive atherectomy using burr-to-artery ratios >0.7 gave way to the practice of less aggressive atherectomy using lower ratios for plaque modification, in order to deliver and deploy stents. Short- and long-term complications associated with atherectomy have decreased significantly from its early use in the early 1990s. In the contemporary era, where optimal atherectomy techniques are employed and stents are used routinely, the frequency of acute complications such as no reflow, dissections, and perforations has been maintained at a low rate over the past 20 years (Fig. 34-6). The long-term major adverse cardiovascular events (MACE), mortality, and target vessel revascularization (TVR) rates have decreased, along with routine use of stents, less aggressive debulking strategies, and drug-eluting platforms (Table 34-4).

![FIGURE 34-6 Periprocedural and in-hospital outcomes in clinical studies of atherectomy between 1995 and 2014.](image)

Complication rates for the CARAT study reflect the “small burr” arm of the study. The dissection rate of the DART study refers to severe, flow-limiting dissections, similar to the definition used...
in other studies. The definition of myocardial infarction (MI), a major adverse cardiovascular events (MACE), varies across studies.

Table 34-4 Long-Term Outcomes After Atherectomy

<table>
<thead>
<tr>
<th>Compared Values</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-Up (mo)</th>
<th>MACE (%)</th>
<th>Death (%)</th>
<th>MI (%)</th>
<th>TVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotational atherectomy and angioplasty</td>
<td>1997</td>
<td>231</td>
<td>12</td>
<td>45.9</td>
<td>2.4</td>
<td>2.4</td>
<td>42.4</td>
</tr>
<tr>
<td>Reifart et al (ERBAC)</td>
<td>2000</td>
<td>252</td>
<td>6</td>
<td>0.3</td>
<td>2.7</td>
<td></td>
<td>21.0</td>
</tr>
<tr>
<td>Dill et al (COBRA)</td>
<td>2001</td>
<td>222</td>
<td>6</td>
<td>34.4</td>
<td>4.7</td>
<td>4.7</td>
<td>25.0</td>
</tr>
<tr>
<td>Safian et al (CARAT)</td>
<td>2001</td>
<td>497</td>
<td>6</td>
<td>24.2</td>
<td>2.6</td>
<td>1.6</td>
<td>22.2</td>
</tr>
<tr>
<td>Whitlow et al (STRATAS)</td>
<td>2003</td>
<td>227</td>
<td>12</td>
<td>26.0</td>
<td>0.9</td>
<td>3.1</td>
<td>24.7</td>
</tr>
<tr>
<td>Mauri et al (DART)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Rotational atherectomy and bare metal stenting

<table>
<thead>
<tr>
<th>Compared Values</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-Up (mo)</th>
<th>MACE (%)</th>
<th>Death (%)</th>
<th>MI (%)</th>
<th>TVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moussa et al</td>
<td>2009</td>
<td>75</td>
<td>6</td>
<td>24.0</td>
<td>1.3</td>
<td>1.3</td>
<td>21.0</td>
</tr>
<tr>
<td>Tamekiyo et al</td>
<td>2009</td>
<td>144</td>
<td>12</td>
<td>42.2</td>
<td>11.3</td>
<td>8.5</td>
<td>38.2</td>
</tr>
<tr>
<td>Rathore et al</td>
<td>2010</td>
<td>125</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mangiacapra et al</td>
<td>2012</td>
<td>83</td>
<td>12</td>
<td>23.5</td>
<td>6.3</td>
<td></td>
<td>12.3</td>
</tr>
</tbody>
</table>

Rotational atherectomy and drug-eluting stent placement

<table>
<thead>
<tr>
<th>Compared Values</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-Up (mo)</th>
<th>MACE (%)</th>
<th>Death (%)</th>
<th>MI (%)</th>
<th>TVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavijo et al</td>
<td>2006</td>
<td>81</td>
<td>6</td>
<td>11.0</td>
<td>6.8</td>
<td>1.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Tamekiyo et al</td>
<td>2009</td>
<td>79</td>
<td>12</td>
<td>23.5</td>
<td>11.5</td>
<td>9.4</td>
<td>21.2</td>
</tr>
<tr>
<td>Furuichi et al</td>
<td>2009</td>
<td>96</td>
<td>15</td>
<td>15.8</td>
<td>4.2</td>
<td>5.3</td>
<td>11.6</td>
</tr>
<tr>
<td>Vaquerizo et al</td>
<td>2010</td>
<td>63</td>
<td>15</td>
<td>9.5</td>
<td>6.3</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Benzeet al</td>
<td>2011</td>
<td>102</td>
<td>15</td>
<td>12.7</td>
<td>3.9</td>
<td>4.9</td>
<td>8.8</td>
</tr>
<tr>
<td>Dardas et al</td>
<td>2011</td>
<td>184</td>
<td>49</td>
<td>14.9</td>
<td>3.3</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Naito et al</td>
<td>2012</td>
<td>223</td>
<td>20</td>
<td>14.5</td>
<td>6.5</td>
<td>2.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Mangiacapra et al</td>
<td>2012</td>
<td>104</td>
<td>12</td>
<td>12.0</td>
<td></td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Abdel-Wahab et al (ROTAXUS)</td>
<td>2013</td>
<td>205</td>
<td>15</td>
<td>17.7</td>
<td>9.0</td>
<td>2.7</td>
<td>11.2</td>
</tr>
<tr>
<td>Kawamoto et al (ROTATE)</td>
<td>2016</td>
<td>667</td>
<td>12</td>
<td>14.5</td>
<td>4.0</td>
<td>1.5</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Orbital atherectomy and drug-eluting stent placement

<table>
<thead>
<tr>
<th>Compared Values</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-Up (mo)</th>
<th>MACE (%)</th>
<th>Death (%)</th>
<th>MI (%)</th>
<th>TVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genereux et al (ORBIT II)</td>
<td>2015</td>
<td>443</td>
<td>12</td>
<td>16.4</td>
<td>4.4</td>
<td>9.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Abbreviations: MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization.

With the availability of lower profile devices and routine use of stents, the use of atherectomy has generally moved away from plaque debulking to plaque modification, but it has also evolved into new uses such as treating in-stent restenosis, ostial and bifurcation lesions, saphenous vein grafts, or chronically occluded lesions.

**Atherectomy Versus Angioplasty**

Three major studies have compared angioplasty to atherectomy alone (see Table 34-4). The ERBAC (Excimer Laser, Rotational Atherectomy, and
Balloon Angioplasty Comparison) study compared 685 patients with symptomatic coronary disease randomized to balloon angioplasty, excimer laser, or rotational atherectomy.\textsuperscript{56} Patients who underwent rotational atherectomy had the highest rate of procedural success (89.2%), defined as a <50% residual stenosis, compared with those who underwent excimer laser angioplasty (77.2%) or balloon angioplasty (79.7%; \(P < .01\)). Acute inhospital complications were similar, but TVR was 42.4% in the rotational atherectomy group and 46.0% in the excimer laser group, which was higher than in the angioplasty group (31.9%; \(P = .01\)).

The COBRA (Comparison of Balloon Angioplasty Versus Rotational Atherectomy) multicenter randomized trial enrolled 502 patients with complex coronary artery disease to angioplasty or rotablation.\textsuperscript{57} Procedural success was higher with atherectomy (85\% vs 78\%; \(P = .04\)), and crossover from angioplasty to rotablation was 10\%, which was more than twice as frequent as the converse (\(P = .02\)). Patients undergoing high-pressure balloon angioplasty were also twice as likely to need bailout stenting (15\% vs 6\%; \(P < .01\)). Otherwise clinical outcomes, including TVR (percutaneous transluminal coronary angioplasty 51\% vs rotablation 49\%; \(P = .33\)), were the same at hospital and at 6-month follow-up.

The multicenter, randomized DART (Dilation Versus Ablation Revascularization Trial Targeting Restenosis) study compared rotational atherectomy with balloon angioplasty in 446 patients with lesions in small coronary arteries (<3 cm) without severe calcification.\textsuperscript{58} Procedural success, acute lumen gain, and long-term lumen diameter were similar between groups. In-hospital complications and 12-month mortality, MI, MACE, and TVR rates were similar (see Table 34-4).

It is clear that rotational atherectomy is safe compared to angioplasty, but it also has the potential to improve procedural success in complex coronary artery disease, particularly in lesions that are highly fibrotic or calcified where dissections are likely to occur with high-pressure balloon angioplasty.

**Debulking Versus Plaque Modification**

In the pre-stent era, larger atherectomy burrs could be used to maximize lumen gain or allow for greater stent expansion. Aggressive atherectomy, however, can increase the risk for deeper dissections, abrupt vessel closure, and increased distal embolization.
The STRATAS (Study to Determine Rotablator and Transluminal Angioplasty Strategy) study\(^{59}\) randomized patients to either an “aggressive” strategy (n = 249; maximum burr-to-artery ratio >0.7 alone, or with adjunctive inflation ≤1 atm of an oversized balloon) or a “routine” strategy (n = 248; maximum burr-to-artery ratio ≤0.70 and routine balloon inflation ≥4 atm). Final MLD was 1.97 mm for the routine strategy and 1.95 mm for the aggressive strategy, and clinical success was also equivalent. CK-MB elevations were greater in the patients receiving aggressive atherectomy, but MIs or other major complications were not significantly different. Emergency bypass surgery was needed in 2% of patients in the routine strategy and in none of the aggressive strategy patients.

At 6 months, 21.1% of the patients receiving routine atherectomy versus 23.5% of those receiving aggressive rotational atherectomy had target lesion revascularization. Angiographic follow-up showed MLD of 1.26 mm in the routine group versus 1.16 mm in the aggressive group. Excessive burr decelerations greater than 5000 rpm were significantly associated with restenosis (\(P = .01\)).

The Coronary Angioplasty and Rotablator Atherectomy Trial (CARAT)\(^{60}\) also compared a lesion-debulking strategy (burr-to-artery ratio >0.7) to achieve maximal debulking versus a lesion modification strategy, in which a burr-to-artery ratio ≤0.7 was used to modify lesion compliance. Among the 222 patients in the study, there were no differences in procedural success, the extent of immediate lumen enlargement, in-hospital ischemic complications, or late TVR. Patients randomized to the large-burr group, however, were more likely than the lesion modification group to experience serious angiographic complications (5.1% vs 12.7%; \(P < .01\)) immediately after atherectomy.

When aggressive atherectomy is combined with stenting, used electively or as a bailout for acute vessel closure, larger lumen diameters can be achieved while mitigating the impact of acute complications. Kobayashi et al\(^{49}\) retrospectively compared 126 patients who had undergone aggressive atherectomy with a burr-to-vessel ratio of ≥0.8 with 703 patients who had undergone routine atherectomy. There were more periprocedural MIs among patients with aggressive atherectomy but no other differences in clinical events. At follow-up, the MLD in the aggressive atherectomy group was significantly higher by 35% and late lumen loss significantly lower by 40%.\(^{49}\)
Although aggressive debulking can be harmful, stepwise burr selection and avoiding long passes and drops in rotation speed help to reduce the damage to the vessel wall and reduce the volume of microparticulate debris and platelet activation. Thus, even though aggressive atherectomy offers no advantage over more routine burr sizing for angioplasty, with careful technique and the use of stenting, more aggressive atherectomy can be performed. A burr-to-artery ratio <0.7 should generally be used to reduce acute periprocedural risks, but some situations may require more aggressive debulking to optimize stent delivery and maximal stent expansion.

**Atherectomy and Stenting**

Stenting can treat acute complications of atherectomy and improve long-term vessel patency. Early studies using bare metal stents showed only modest improvements over atherectomy with angioplasty (see Table 34-4). Moussa et al\(^6^1\) reported the earliest experience in using routine bare metal stents following atherectomy in 75 patients. Plaque modification was achieved using a burr-to-artery ration of 0.61 ± 0.12 and angioplasty prior to stenting. Stent implantation was successful in 93.4% of patients. Five patients had major complications, including a left main dissection, 2 acute vessel closures due to subintimal stenting, a vessel perforation, and acute stent thrombosis.

The frequency of these acute complications reported in studies over the past 20 years has not changed dramatically (see Fig. 34-6). More than 10 years after the study by Moussa et al,\(^6^1\) despite significant improvements in stent technology, other investigators reported similar rates of no reflow, abrupt closure, dissection, perforation, and periprocedural mortality in a retrospective study of 516 patients treated between 2003 and 2007. The long-term outcomes with bare metal stents were only modestly better than prior angioplasty studies, even in contemporary studies, demonstrating a similar long-term incidence of MACE to angioplasty studies, primarily due to the need for repeat revascularization. The TVR rates for atherectomy with bare metal stenting ranged from 12.3% to 38.2% (see Table 34-4).

DESs have improved the outcomes of patients undergoing atherectomy by reducing TVR. As a result, MACEs have also declined, even though mortality and MI rates have remained unchanged or are slightly higher. The long-term follow-up results of several observational studies are shown in Table 34-4. The later studies had longer lengths of follow-up, and several
studies primarily evaluated higher risk patients with significant calcification. The only randomized study comparing atherectomy to angioplasty in the era of routine use of DESs was the ROTAXUS trial (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease).\(^\text{12}\)

Abdel-Wahal et al\(^\text{12}\) randomized 240 patients to a strategy of balloon angioplasty/stenting or primary atherectomy followed by angioplasty/stenting with paclitaxel-eluting stents. Patients had moderate to severe calcification, and most patients had American College of Cardiology (ACC)/American Heart Association (AHA) type B2/C lesions. Acute complications were the same between both groups, including dissections, perforations, no/slow flow, and periprocedural MI (Table 34-5). There was no difference in MACE, MI, TVR, or mortality at 9-month follow-up (Fig. 34-7). Immediate gain in lumen diameter was higher in the atherectomy arm, but at angiographic follow-up, the late lumen loss was higher, making any gains in lumen size negligible.

**FIGURE 34-7** Nine-month follow-up from the ROTAXUS study comparing a strategy of rotational atherectomy (RA) with paclitaxel-eluting stent (PES) placement versus standard therapy with angioplasty and stenting. Cumulative incidence curves for
death (A), myocardial infarction (B), target vessel revascularization (C), and major adverse cardiac events (D) in the RA + PES and standard therapy groups. (Used with permission from Abdel-Wahab M, Richardt G, Joachim Büttner H, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. JACC Cardiovasc Interv. 2013;6(1):10-19.)

Table 34-5 Procedural Outcomes From the ROTAXUS Study Comparing a Strategy of Rotational Atherectomy (RA) With Paclitaxel-Eluting Stent (PES) Placement Versus Standard Therapy With Angioplasty and Stenting

<table>
<thead>
<tr>
<th></th>
<th>RA + PES (n = 120)</th>
<th>Standard Therapy (n = 120)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural duration, min</td>
<td>66.4 ± 44.5</td>
<td>57.4 ± 34.5</td>
<td>.05</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>22.8 ± 21.9</td>
<td>18.1 ± 16.7</td>
<td>.04</td>
</tr>
<tr>
<td>Contrast amount, mL</td>
<td>201.0 ± 113.6</td>
<td>181.8 ± 93.6</td>
<td>.11</td>
</tr>
<tr>
<td>Dissections</td>
<td>4 (3.3)</td>
<td>4 (3.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Perforations</td>
<td>2 (1.7)</td>
<td>1 (0.8)</td>
<td>.56</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>No/slow flow</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>.32</td>
</tr>
<tr>
<td>Persistent advanced atrioventricular block</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Angiographic success</td>
<td>116 (96.7)</td>
<td>116 (96.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Stent loss</td>
<td>0 (0)</td>
<td>3 (2.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Crossover</td>
<td>5 (4.2)</td>
<td>15 (12.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Strategy success</td>
<td>111 (92.5)</td>
<td>100 (83.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td>.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (1.7)</td>
<td>4 (3.4)</td>
<td>.68</td>
</tr>
<tr>
<td>Target vessel re-PCI</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>MACE</td>
<td>5 (4.2)</td>
<td>5 (4.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Access site complications</td>
<td>7 (5.9)</td>
<td>2 (1.7)</td>
<td>.17</td>
</tr>
</tbody>
</table>

Note. Values are numbers (percentages) or means ± standard deviations.

Abbreviations: CABG, coronary artery bypass graft; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.


Strategy success was significantly higher in the rotablation arm of the study (92.5% vs 83.3%; P = .03), with a 12.5% crossover rate from the routine angioplasty group to the rotablation arm (P = .02). Notably, stent loss was observed in 2.5% of patients receiving routine angioplasty group and in no patients receiving an atherectomy-first strategy.

Although these complications did not impact overall MACE rates, switching strategies adds time to the procedure, and stent loss can be a
potentially major surgical emergency. Planned atherectomy was shown to improve procedure efficiency and reduce contrast and x-ray exposure in the ROTATE registry of 667 patients from 8 centers who underwent rotational atherectomy and stenting for calcific coronary artery disease (see Table 34-3). Patients who underwent planned atherectomy were compared to those with ad hoc atherectomy. The planned atherectomy patients were more likely to have insulin-dependent diabetes (16.2% vs 10.7%; \( P = .04 \)), peripheral vascular disease (24.0% vs 16.8%; \( P = .02 \)), and renal insufficiency (33.2% vs 15.9%; \( P < .01 \)). The majority of patients had ACC/AHA type B2/C lesions. There were more patients with unprotected left main (12.0% vs 4.3%; \( P < .01 \)) and bifurcation lesions but fewer chronic total occlusions (CTOs) (5.3% vs 9.5%; \( P = .03 \)) among the planned atherectomy group. Despite these baseline differences, the hospital and 1-year MACE, mortality, MI, stroke, and TVR rates were the same.

In patients undergoing provisional rotational atherectomy, delivery device failure occurred in 73.1% of patients and balloon expansion failure occurred in 26.9%. Among patients with failed balloon expansion, adverse hospital outcomes were double those in patients with delivery device failure (in-hospital MACE: 7.1% vs 16.9%; \( P = .01 \); and MI: 6.2% vs 14.5%; \( P = .02 \)). In the propensity analysis, adjusting for baseline differences that may have contributed to selection bias, there was a trend toward increased periprocedural MACE for ad hoc atherectomy (odds ratio, 0.59; 95% confidence interval [CI], 0.33-1.05; \( P = .07 \)).

Patients with nondilatable lesions who undergo high-pressure balloon inflation may be more likely to have overt dissections or microdissections that may increase the risk for adverse complications during subsequent atherectomy. In this regard, there may be some benefit to a planned atherectomy approach upfront or a staged approach to allow for vessel healing after failed angioplasty.

**Orbital Atherectomy**

The FDA approved Cardiovascular Systems Incorporated’s Diamondback 360 orbital atherectomy device in 2013 for use in calcified coronary lesions based on data from the ORBIT I and ORBIT II studies. The device is available for peripheral arterial interventions and consists of an eccentrically mounted, diamond-coated burr that orbits over an atherectomy guide wire at
speeds of 80,000 to 130,000 rpm using an electrical drive (Fig. 34-8). The current device lacks burring elements on the polished stainless steel tip, but achieves atherectomy as the crown’s orbital diameter expands radially by centrifugal force, achieving channels 1.25 to 1.75 times greater than the crown size, depending on the number of revolutions per minute chosen and the speed of advancement (ie, higher revolutions per minute and slower advancement theoretically allow for larger lumen diameters). The device only requires a 6-Fr guide, so a larger radius of atherectomy can be achieved without changing burrs or guides.

**FIGURE 34-8** Cardiovascular Systems Incorporated’s Diamondback 360 orbital atherectomy device. (Reproduced with permission from Cardiovascular Systems, Inc., Saint Paul, MN.)

The ORBIT II study was a nonrandomized, single-arm, multicenter study
of 443 patients designed to show noninferiority to historical performance goals based on prior atherectomy studies in patients with calcified coronary lesions. All patients had fluoroscopic or IVUS evidence for severe calcification of a significant coronary lesion, with 74.1% of patients having ACC/AHA type B2/C lesions. Successful stent delivery was achieved in 97.7% of patients, and the rates of acute complications were similar to prior studies (see Fig. 34-6). The overall in-hospital MACE, MI, death, and TVR rates were 9.8%, 9.3%, 0.5%, and 0.7%, respectively. The outcomes at 12 months are in line with previously published studies of atherectomy in patients with severe calcification (see Table 34-4). Stent type was a strong predictor for TVR, as only 4.7% of patients receiving DESs required revascularization at 1 year, compared to 15.1% of patients receiving bare metal stents. At 2 years, the rates of MACE, MI, mortality, and TVR were 19.4%, 9.7%, 7.5%, and 8.1%, respectively. The 3-year follow-up has only been reported in abstract form at the time of writing.

Orbital atherectomy has been used in over 50,000 patients for peripheral arterial disease and, based on the ORBIT study, has been shown to have low periprocedural and long-term complication rates, consistent with contemporary studies of rotational atherectomy. The greater debulking that can be achieved with a single atherectomy crown passed through a 6-Fr guide allows for procedural efficiency and more interventions using radial access. Theoretically, the circumferential atherectomy may help overcome guide wire bias and differential atherectomy associated with the Rotablator. Nevertheless, it remains to be seen what specific advantages or disadvantages orbital atherectomy may have in general use.

**Excimer Laser Atherectomy**

Excimer laser atherectomy uses 308-nm ultraviolet light delivered through a fiberoptic catheter to deliver both photochemical and thermal energy to debulk atherosclerotic lesions. It is approved by the FDA for use in long and moderately calcified coronary atherosclerotic lesions, CTOs, saphenous vein grafts, balloon resistant lesions, and in-stent restenosis. It has been shown to have comparable results to rotational atherectomy in the ERBAC study. Although its use in native coronary artery disease had declined given early problems with coronary dissections and perforations, it is still used with some regularity for in-stent restenosis, balloon/device noncrossable lesions, and
Directional coronary atherectomy is rarely used for coronary interventions, and most devices are no longer available in the US market. The randomized studies comparing directional atherectomy to angioplasty showed increased lumen gain, but no differences in clinical outcomes or reductions in lesion revascularization, and coronary perforation rates of approximately 1%.\textsuperscript{10}

**ATHERECTOMY FOR SPECIFIC SITUATIONS**

Although the most common use of atherectomy is aimed at plaque modification of calcified coronary arteries to facilitate stent delivery and expansion, there are several less common indications where atherectomy remains uniquely useful. Niche applications for atherectomy include ostial lesions, bifurcations, in-stent restenosis, and CTOs.

**Ostial Lesions**

Ostial lesions are associated with a high incidence of recoil, and delivering a stent perfectly can be challenging, which contribute to the increased restenosis rates associated with these lesions.\textsuperscript{64} Reducing ostial calcium and fibrosis reduces slippage of the balloon or stent during deployment and facilitates more precise landing of stents.

In a small series of 63 patients, rotational atherectomy was used with angioplasty to achieve immediate angiographic success in 92\% of patients, but at 6 months, 43\% of patients had significant restenosis. A retrospective comparison of non–aorto-ostial lesions among 44 patients who underwent debulking prior to angioplasty and bare metal stenting versus 42 patients who underwent angioplasty and stenting alone demonstrated that atherectomy achieved larger lumen diameters (2.30 ± 0.91 mm vs 1.86 ± 0.80 mm; \( P = .03 \)) and a lower cumulative restenosis rate (39.5\% vs 59.5\%; \( P = .04 \)) at 6 months.\textsuperscript{65}
Despite the immediate benefits of reducing lesion recoil and plaque shift and optimizing stent delivery using atherectomy, the longer term restenosis rates remain high. Nevertheless, because treatment options for patients with significant ostial disease remain limited, atherectomy will continue to be a useful interventional tool for this patient subset.

**Bifurcation Lesions**

Bifurcation lesions pose a unique challenge because true Medina 1,1,1 lesions can lead to loss of side branches and have a high restenosis rate. Although dedicated stent strategies can achieve improved immediate results, they have been associated with higher restenosis. Atherectomy can facilitate stent delivery and full stent expansion to highly calcified and angulated bifurcations.

Atherectomy itself, however, can potentially cause plaque shift. Walton et al\(^6\) evaluated 418 patients with 320 side branches who underwent rotational atherectomy and reported a side branch occlusion rate of 7.5%. Side branch diameter of <2.0 mm and ostial narrowing ≥50% were associated with compromised flow. Among patients with side branch loss, 29% experienced MI.

Compared to routine angioplasty, however, the incidence of these complications may be reduced with atherectomy. Dauerman et al\(^6\) evaluated patients undergoing PCI of true bifurcation lesions involving both the main and side branches and compared patients who underwent atherectomy versus angioplasty alone. They reported more transient side branch occlusions but overall higher procedural success with atherectomy (97.5% vs 73.3%; \(P = .01\)), lower residual stenosis, and no differences in MI. At 12-month follow-up, MACE rates were 30% in the atherectomy group and 56% in the angioplasty group (\(P = .05\)), and TVR was nearly halved by atherectomy (27.5% vs 53.3%; \(P = .05\)).

One strategy to help maintain patency during main branch atherectomy or stenting is to debulk the side branch. In a retrospective study of 40 patients with bifurcation lesions who underwent stenting of a main branch with side branch rotational atherectomy,\(^2\) no acute side branch closures or perforations were observed, and 80% of side branches did not require stents. At mean follow-up of 21.3 months, mortality was 2.5%, MI was 2.5%, and TVR was 5%.
The routine use of DESs can improve the outcomes of bifurcation PCI. In a study of 337 patients who underwent atherectomy for bifurcation disease reported by Dai et al, significant reductions in TVR rates (5.0% vs 15.7%; \( P < .01 \)) and MACE rates (12.0% vs 20.2%; \( P = .04 \)) were observed among patients receiving DESs compared to those with bare metal stents or angioplasty alone at a mean follow-up of 52.2 months. The very low restenosis rates speak to the efficacy of DESs, but also affirm the safety of an atherectomy strategy that allows adequate stent delivery.

**In-Stent Restenosis**

Although DESs have reduced rates of in-stent restenosis (ISR), even in the best case scenario, ISR occurs in 2% to 4% of patients within the first year, and ISR that occurs much later is more likely to represent calcified and fibrotic neoatherosclerosis that may be resistant to high-pressure balloon angioplasty and require atherectomy.\(^{68,69}\) The early use of rotational atherectomy to treat ISR developed in an era prior to the availability of DESs, and so the ISR at that time most likely represented softer neointimal hyperplasia that yields easily to balloon angioplasty. The BARASTER (Balloon Angioplasty Versus Rotational Atherectomy for Intra-Stent Restenosis) multicenter registry demonstrated lower MACE and TVR rates among patients receiving atherectomy and angioplasty compared to angioplasty alone.\(^{70}\) The ROSTER study (Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis) showed improved acute lumen gain and lower revascularization compared to angioplasty (32% vs 45%; \( P = .04 \)).\(^{71}\) In contrast, the ARTIST study (European Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial)\(^{72}\) demonstrated worse outcomes with atherectomy.

Laser atherectomy has been shown to be superior to angioplasty in debulking restenotic tissue for increasing lumen diameter and stent expansion\(^{73}\) and may also prove useful for treating balloon-resistant ISR and improving long-term outcomes. In the EXCITE ISR (Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis) trial, angioplasty with adjunctive excimer laser atherectomy was compared to angioplasty alone for femoral nitinol stents.\(^{74}\) Adjunctive
Atherectomy was associated with a higher procedural success rate (93.5% vs 82.7%; \( P = .01 \)) with fewer complications, higher 6-month freedom from target lesion revascularization rate (73.5% vs 51.8%; \( P < .01 \)), and lower 30-day major adverse event rate (5.8% vs 20.5%; \( P < .01 \)).

Routine use of atherectomy for ISR is not common; however, the increasing presentation of neoatherosclerotic lesions may make this necessary in certain circumstances (Fig. 34-9) where it can prove to be highly effective.


**Underexpanded Stents**

Rotational atherectomy can be used for ablation of metal stents in situations
where highly calcified lesions have not been not properly treated and the deployed stent cannot be expanded further. This is particularly useful when multiple layers of stents have already been placed in an unexpanded lesion, as shown in the example of stepwise burr sizing and stent ablation in Figure 34-10. This should be performed with extreme caution given the risk for embolization of large metal fragments\textsuperscript{75} or burr entrapment in the metal stent.
FIGURE 34-10 Ablation of stents using rotational atherectomy in a patient with 4 layers of stents in a nondilatable lesion. A. Angiogram showing narrowed, subtotally occluded stent. B. After percutaneous coronary intervention (PCI): Angiogram showing expanded stent and improved flow. C. Narrowed segment of 4 unexpanded stents (3.9 mm², 1.8 × 2.5 mm). D. After PCI: Minimally changed narrowed segment of stent (cross-sectional area, 5.7 mm²; 1.9 × 3.4 mm). E. Four stent layers with tissue between each stent. F. After PCI: Multiple stent layers with reduced tissue between each stent. PCI involved stent ablation with rotational atherectomy using 1.5-, 1.75-, and 2.0-mm burrs, followed by laser atherectomy with contrast injections, high-pressure ballooning, drug-coated balloon deployment, and brachytherapy.
Laser atherectomy also has utility in treating underexpanded or nondilatable stents, where heat energy from the laser “bubble” can be used to modify tissue outside the stent struts, allowing balloon dilation of the lesion. The ELLEMENT registry (Excimer Laser Lesion Modification to Expand Nondilatable Stents) described 28 patients with underexpanded stents despite high-pressure balloon inflations who underwent laser-assisted stent dilatation. This technique was successful in 27 cases with an improvement in minimal stent diameter (from 1.6 ± 0.6 mm at baseline to 2.6 ± 0.6 mm after procedure) and stent area by IVUS (3.5 ± 1.1 mm² to 7.1 ± 1.9 mm²).

**Chronic Total Occlusions**

The presence of significant calcium is a major predictor of failure to open a CTO. CTOs are often highly calcified with flush occlusions that can be “balloon-uncrossable,” despite successful guide wire crossing. One example is shown in Figure 34-11. In this case, after crossing the calcified lesion into the true lumen distally, no balloon or microcatheter could be passed. A small balloon was ruptured in the proximal cap, but no gear could be passed distally. A 0.9-mm excimer laser catheter was used to perform atherectomy with contrast, which softened the proximal cap sufficiently to allow passage of a microcatheter tip just beyond the CTO, although no further. The coronary wire was exchanged for a Floppy RotaWire, and rotational atherectomy was performed using 1.25- and 1.5-mm burrs, which then allowed angioplasty and stenting.
FIGURE 34-11 Severely calcified chronic total occlusion requiring atherectomy. A. Severely calcified, chronically occluded circumflex. B. Wire is across lesion, but balloons and microcatheters could not cross, so a 0.9-mm excimer laser was used to perform atherectomy. C. A microcatheter was then advanced across the lesion, and rotational atherectomy was performed followed by angioplasty and stenting. D. Final angiogram.

The BAROCCO (Balloon Angioplasty Versus Rotational Angioplasty in Chronic Coronary Occlusions) study showed that in chronic coronary occlusions with stump-like occlusions, the primary success rate is higher with
the rotational atherectomy technique.\textsuperscript{79} The multicenter DOCTORS study evaluated 266 patients with CTOs deemed appropriate for atherectomy who were randomized to an angioplasty or atherectomy strategy (either rotational or directional) prior to stenting.\textsuperscript{80} There was more periprocedural MIs in the atherectomy group, but a trend toward lower TVR (23.8\% vs 34.6\%; \textit{P} = .07) at 6-month follow-up and lower MACE at 12-month follow-up (27.5\% vs 39.8\%; \textit{P} = .033). Periprocedural MI is typically higher in patients with CTOs undergoing atherectomy, but other acute complications appear to be similar to standard angioplasty in such patients.\textsuperscript{80,81}

CTOs are often fibrotic and calcified, making them resistant to wire crossing, stent delivery, and deployment. Once a coronary guide wire is positioned properly across a severely calcified CTO, atherectomy is frequently required, especially if the wire traverses the calcified “true” lumen, instead of a subintimal track that may bypass the calcium. In these cases, laser and rotational atherectomy can be key components in the CTO toolbox.

**Saphenous Vein Grafts**

The use of rotational atherectomy in saphenous vein grafts is contraindicated for the Rotablator, given concerns about embolization of soft, thrombotic debris. There are situations, however, when the lesion in a graft is highly fibrotic or calcified and resistant to balloon dilation. In such situations, rotational atherectomy has been used successfully without apparent embolization of significant debris (Fig. 34-12).\textsuperscript{82}

CONCLUSION

The clinical application of rotational atherectomy has evolved considerably, from being used as a primary debulking device to being used more adjuntively for plaque modification to facilitate stent delivery and optimize stent expansion. Yet as bioresorbable scaffolds are increasingly used, more aggressive vessel preparation and debulking may once again be obligatory to improve vessel compliance to allow complete scaffold expansion, giving atherectomy an even greater role as this technology is adopted. Furthermore, there are specific situations that will require atherectomy, such as dense fibrotic/calcific ISR, calcific complex lesions, and CTOs.

Atherectomy can be performed safely with optimal burr selection and proper ablation techniques, and as a result, complication rates have been significantly minimized, with few changes in the acute complications reported in contemporary studies. Although atherectomy devices have not changed dramatically over the past 25 years, the increasing prevalence of significant calcific and complex coronary artery disease has ensured that
these devices remain relevant to the contemporary practice of interventional cardiology.

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**MULTIPLE CHOICE QUESTIONS**
1. Which of the following rotational atherectomy techniques is associated with increased microparticulate debris and platelet aggregation?
   A. Using a burr-to-artery ratio <0.7
   B. Allowing decelerations of the burr >5,000 rpm
   C. Limiting atherectomy speeds to 140,000 to 160,000 rpm
   D. Limiting atherectomy runs to less than 30 seconds
   E. Using a back-and-forth pecking motion instead of continuous lesion engagement

2. Which of the following is not a complication associated with rotational atherectomy?
   A. Abrupt vessel closure and no reflow
   B. Coronary dissections and perforations
   C. Transient heart block
   D. Increased mortality
   E. Asymmetric atherectomy and formation of deep eccentric fissures and aneurysms

3. The ROTATE multicenter registry retrospectively compared patients undergoing percutaneous coronary intervention (PCI) who had planned atherectomy versus those who required ad hoc atherectomy. Which of the following was not associated with planned atherectomy?
   A. A 35% reduction in fluoroscopy time
   B. Reduction in average contrast use by 70 mL
   C. A slight increase in total procedure time
   D. No differences in major adverse cardiac events (MACE), death, myocardial infarction (MI), and stroke, but an increase in target vessel revascularization (TVR) at 1 year
   E. A significant reduction in in-hospital myocardial infarctions and MACE compared to patients who underwent rotational atherectomy after balloon expansion failure

4. The ROTAXUS study randomized patients with calcific coronary artery disease to a strategy of planned rotational atherectomy followed by angioplasty and stenting or to a strategy of angioplasty and stenting. The findings of this study include all of the following except:
   A. 2.5% of patients in the standard therapy group experienced stent loss,
whereas no patients in the atherectomy group experienced this complication.

B. Among patients with planned atherectomy, there was a larger increase in lumen diameter but greater late lumen loss compared to the standard therapy group.

C. No differences in mortality, MI, TVR, or MACE were seen between the 2 strategies at short- and long-term follow-up.

D. Strategy success was higher for the atherectomy group.

E. Coronary dissections, tamponade, and no/slow flow were more commonly associated with rotational atherectomy.

5. Which of the following statements about atherectomy is false?

A. Using atherectomy to achieve maximal debulking has been shown to be a superior strategy to plaque modification.

B. Differential cutting allows rotational and orbital atherectomy burrs to selectively ablate inelastic tissue while sparing elastic tissue.

C. Slower advancement of the orbital atherectomy burr achieves a larger area of atherectomy.

D. Orbital atherectomy achieves debulking by applying centrifugal force on the vessel wall.

E. Heat energy from laser atherectomy can be used to treat calcific and fibrotic tissue outside of underexpanded stents.

ANSWERS

1. B

Most clinical studies have reported no reflow and abrupt vessel closure rates associated with rotational atherectomy of approximately 1%. Larger burrs, a burr-to-artery ratio of 0.7 to 0.8, atherectomy speeds >160,000 rpm, and long continuous atherectomy runs have been shown to increase platelet aggregation. An increase in acute angiographic complications has been associated with larger burr sizes, but without an impact on clinical outcomes. Thermal injury can also be caused by long runs of continuous engagement of the coronary lesion with the atherectomy burr or by decelerations >5000 rpm, which indicate more friction and force being applied to the vessel wall.
Thermal injury can lead to red blood cell aggregation and platelet activation and has been associated with increased restenosis. Therefore, it is recommended that a back-and-forth pecking motion be used, instead of forceful advancement of the burr.

2. D

In the major clinical trials comparing a strategy using rotational atherectomy versus a strategy using routine therapy, there have been no differences in short- or long-term mortality. Abrupt vessel closure and no reflow occur about 1% of the time during atherectomy. Treatment with prophylactic vasodilators such as nitroprusside, adenosine, and verapamil has been shown to reduce the incidence of this complication. Coronary dissections and perforations were seen in 3.3% and 1.7% of patients, respectively, in the ROTAXUS study and 3.4% and 1.8% of patients, respectively, in the ORBIT II study. Transient heart block can be seen, particularly with interventions on the right coronary artery or dominant left circumflex. Smaller burr sizes and shorter runs significantly diminish the occurrence of these events such that many operators do not prophylactically place temporary pacemakers. When atherectomy is performed, however, a transvenous pacer and appropriate pharmacologic agents should be readily available. Wire bias in an angulated and eccentric lesion can lead to preferential atherectomy of the inner or outer curve of the lesion, which may dispose to fissures and aneurysms.

3. C

Planned atherectomy had lower fluoroscopy time, lower contrast use, and shorter procedure times than procedures in which atherectomy was used ad hoc for failure to deliver stents/devices or for balloon expansion failure. Patients with failed balloon expansion had worse outcomes compared with those who had atherectomy for device delivery failure (in-hospital MACE: 16.9% vs 7.1%; \( P = .01 \); in-hospital MI: 14.5% vs 6.2%; \( P = .02 \)). In-hospital MACE, MI, mortality, stroke, and TVR were equivalent between the planned and ad hoc atherectomy groups. At 1-year follow-up, the adjusted outcomes were similar with the exception of TVR, which was higher for the planned atherectomy group (odds ratio, 1.73; 95% confidence interval [CI], 1.04-2.89; \( P = .04 \)).

4. E
Coronary dissections and tamponade were the same between the 2 groups, and no/slow flow was actually higher in the standard therapy arm. There were no differences in clinical outcomes between the 2 randomized arms of the ROTAXUS study, but there were significant procedural differences noted. In the standard therapy group, stent loss was reported in 2.5% of cases, whereas no stent loss was observed among patients randomized to the atherectomy strategy. A total of 12.5% of patients in the standard therapy arm crossed over to atherectomy, and strategy success was inferior in this group (83.3% vs 92.5% for atherectomy; \( P = .03 \)). Periprocedural outcomes were similar between the standard therapy and atherectomy groups (dissection, 3.3% vs 3.3%; no/slow flow, 0.8% vs 0%; heart block, 0% vs 0.8%; perforations, 0.8% vs 1.7%; tamponade, 0.8% vs 0.8%; \( P = \) not significant for all comparisons). Acute luminal gain was larger for the atherectomy patients (1.56 ± 0.43 vs 1.44 ± 0.49 mm; \( P = .01 \)), but late lumen loss was greater at 9 months (0.44 ± 0.58 vs 0.31 ± 0.52 mm; \( P = .04 \)). At 2 years, MACE occurred in 29.4% of the atherectomy patients versus 34.3% of the angioplasty patients (\( P = .47 \)). Target lesion revascularization (TLR) was 13.8% versus 16.7% (\( P = .58 \)) and TVR was 19.3% versus 22.2% (\( P = .62 \)) for the atherectomy versus angioplasty strategies, respectively.

5. A

Aggressive atherectomy for debulking has not been shown to be equivalent to a less aggressive plaque modification strategy. The CARAT and STRATAS studies compared aggressive atherectomy using burr-to-artery ratios >0.7 with less aggressive atherectomy using burr-to-artery ratios <0.7. Aggressive atherectomy is associated with more complications without any improvement in clinical outcomes or minimal lumen diameter. Differential cutting is the ability to selectively ablate one material while preserving the integrity of the other, based on differences in the composition and texture of the substrate. The elasticity of the normal tissue deflects the ablative surface, whereas the inelastic properties of diseased tissue engages the cutting surface. The orbital atherectomy crown’s orbital diameter expands radially by centrifugal force, achieving channels 1.25 to 1.75 times greater than the crown size, depending on the rpm chosen and the speed of advancement (ie, higher rpm and slower advancement theoretically allow for larger lumen diameters). The ELLEMENT registry described expansion of underexpanded stents in balloon nondilatable lesions using laser-assisted stent dilatation.
Percutaneous Coronary Intervention in Chronic Total Occlusion

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A coronary artery chronic total occlusion (CTO) is defined as an occlusion present for 3 or more months, which will feature classic histopathologic changes (Fig. 35-1). Although considered separately in this book, the treatment decisions for coronary revascularization should focus on coronary physiology and ischemia rather than specific anatomic considerations. To that end, the indications for treatment of CTOs should be indistinguishable from 95% coronary lesions. However, once the decision to treat a CTO percutaneously is chosen, the technical aspects of this treatment diverge significantly from standard coronary intervention. For many interventionalists, CTOs continue to represent a major technical challenge.
FIGURE 35-1 Histopathology of preservation of vessel architecture, including a multilayered structure in which the intima and neointima (including atherosclerotic plaque) is distinguishable from the muscularis and adventitia and, importantly, in which the external elastic lamina remains intact. This preservation of gross architecture is the pathologic feature that most enables percutaneous recanalization.

Percutaneous coronary intervention (PCI) is invariably predicated upon a steerable guide wire spanning the target lesion and acting as a rail over which devices can be delivered. Typically, this wire is tracked in the vessel lumen using angiography as a guide. In the absence of a visible lumen during angiography, tracking the coronary vessel and ensuring an intraluminal position can be difficult. Thus, the primary challenge of CTO PCI lies in initially traversing the target lesion with a guide wire. In recent years, important strategic and technical advancements have been made that facilitate overcoming this essential challenge in a reproducible fashion.\(^1\) Most major PCI programs now have, or are planning for, specialized competence in contemporary CTO procedures. An understanding of the field has become
essential knowledge for all interventionalists and arguably for any cardiologist who advises patients regarding revascularization options. The goal of this chapter is to describe the technical and strategic considerations necessary to understand CTO PCI.

Angiography for CTO PCI should emphasize simultaneous dual injections to visualize the antegrade and retrograde coronary flow, thus defining the extent of the lesion. Access choice is up to the operator’s discretion recognizing that 2 arterial access points are typically required. Frequently, at least 1 of the access points is 8 Fr to facilitate specific techniques described below. The relative merits of potentially larger sheath/guide sizes via femoral access can be weighed against the reduction in vascular complications and improved patient comfort when radial access is used. When femoral access is chosen, long (45-cm) sheaths can overcome iliac tortuosity and increase guide catheter support. Guiding catheter size is usually limited to 6-Fr from the radial approach, although sheathless 7-Fr systems are increasingly common. Good passive support with coaxial alignment is crucial, especially in complex CTO procedures. Although the choice of the guiding catheter shape is generally dictated by personal experience, it is important for operators to seek a guide with optimal support at the onset of the procedure rather than accepting one with merely satisfactory support. The radial operator should be familiar with active guide manipulation to augment “pushability,” and all operators should be versed in balloon anchoring and mother-and-child techniques to improve support when needed.

Even if the distal vessel bed is opacified by ipsilateral collaterals, this opacification can be limited following wire or catheter advancement, resulting in preferential collateral shift to contralateral collaterals during the procedure. Therefore, to achieve the best diagnostic angiography (ie, to fill the entire collateral bed), contralateral injection should be performed at the start of the procedure if any visible contralateral collaterals are present. Operators from the EuroCTO Club have used contralateral injection in 62% of their cases, whereas dual injection was used in 78% of cases in a more recent North American series. Dual-injection collateral analysis is performed best using low magnification, so that the entire coronary tree is visualized without panning. Careful study of the collaterals not only provides important information in choosing the most appropriate collateral, but will also alert the operator to the risk of ischemia and hemodynamic or electrical instability if the wired collateral becomes occluded. Three typical collateral pathways are
demonstrated in Figures 35-2, 35-3, and 35-4. A careful and detailed review of the angiogram is critical for creating primary and alternative CTO treatment strategies to optimize the efficacy, efficiency, and safety of the procedure.

**FIGURE 35-2** Typical fine, moderately tortuous transseptal collateral connecting the left anterior descending artery (LAD) to the right posterior descending artery. Transseptals are the most commonly employed collaterals for retrograde chronic total occlusion techniques and can serve to access an occluded dominant right coronary artery or dominant left circumflex artery from the LAD, or in the opposite direction, to access an occluded LAD from a dominant right or left circumflex. Another transseptal is visible arising from the distal LAD. Because transseptal collaterals are generally contained within septal myocardium, their rupture rarely poses a hazard with respect to tamponade.
FIGURE 35-3 A large, dominant, and tortuous transapical epicardial collateral supplies the right posterior descending artery from the distal left anterior descending artery. This collateral is likely to become kinked and thus occlude when instrumented with a guide wire or microcatheter, resulting in loss of visualization of the distal target and the potential for ischemia. Collaterals of this configuration are rarely helpful as conduits for retrograde access.
Anticoagulation during CTO PCI is best achieved with unfractionated heparin (UFH) because it allows for titration of the anticoagulant effect. The desired activated clotting time (ACT) recommended by many operators during retrograde CTO PCI to minimize the risk of donor vessel (ie, the vessel that provides the collateral) and guide thrombosis is >350 seconds, as opposed to the more routine 250 seconds used in typical PCI. Bivalirudin requires ongoing coronary circulation and exposure to blood to maintain its pharmacotherapeutic effect and therefore has the potential for higher guide catheter thrombosis rates in CTO PCI. As with all PCI, preloading with a P2Y$_{12}$ adenosine diphosphate (ADP) receptor inhibitor and aspirin is important to reduce the risk of acute stent thrombosis and periprocedural myocardial infarction.
PREDICTION OF CHRONIC TOTAL OCCLUSION CROSSING DIFFICULTY

Predicting the difficulty of CTO crossing with a guide wire is important for case selection and procedural planning. The Multicenter CTO Registry of Japan (J-CTO) score is determined by assigning 1 point to each of the following 5 variables: (1) previously failed lesion, (2) blunt type of entry, (3) calcification, (4) bending, and (5) occlusion length. Patients are classified into 4 difficulty groups: easy (J-CTO score of 0), intermediate (a score of 1), difficult (a score of 2), and very difficult (a score of 3 or higher). The J-CTO score correlated well with the probability of successful guide wire crossing within 30 minutes (87.7%, 67.1%, 42.4%, and 10.0%, respectively)\(^8\) and was recently validated in an independent single-center Canadian cohort.\(^9\) Recent reports using a hybrid-based CTO algorithm have shown that the J-CTO score predicts an increasing need for retrograde procedures to achieve success (Fig. 35-5). More recently, the Prospective Global Registry for the Study of Chronic Total Occlusion (PROGRESS CTO) score has been developed to predict procedural success using hybrid methodologies.\(^10\)
The hybrid approach to chronic total occlusion (CTO) percutaneous coronary intervention (PCI) uses sentinel features of the coronary anatomy to guide the initial approach to CTO recanalization. Antegrade approaches are favored by a clearly identified nonostial occlusion inlet (proximal cap), a large and well-visualized target segment beyond the distal cap, the absence of severe calcification or tortuosity, and the absence of an important side branch adjacent to the distal cap that might be excluded during dilation and stenting of a subintimal tract. Retrograde approaches are favored when suitable collaterals or bypass grafts exist through which delivery of PCI equipment to the distal cap appears feasible and when the anatomy does not favor an antegrade approach. An important feature of hybrid CTO procedures is the predisposition to timely changes of strategy when progress toward the goal of recanalization stalls.

**SPECIFIC APPROACHES AND TECHNIQUES**
Antegrade Guide Wire Approach

Antegrade guide wire–based recanalization of CTOs has been and remains the most common approach worldwide.\textsuperscript{11-13} In general, an over-the-wire catheter is delivered to the proximal cap on a workhorse wire, and then CTO-specific wires and wire tip shapes are applied. The approach of gradually escalating wire stiffness to achieve crossing has been generally abandoned in favor of an antegrade wire modification strategy that employs 3 or 4 wires chosen so that each performs a specific and different function based on their different characteristics. Historically, operators have started with tapered soft polymer jacketed wires when attempting antegrade wire crossing of CTOs. Recent data have shown that this wire type has a very low initial success rate. As such, most high-volume CTO programs would typically start with a stiffer polymer jacketed wire or a Gaia second wire with a rapid escalation to a tapered stiff wire. Modern wire modification strategies, also referred to as step-up/step-down techniques, start as described earlier, but then may step up to stiff, spring-coil tapered wires to overcome any hard, calcified, or fibrotic segments of the occlusion. Such a step up should then be matched by a step down to a soft, polymer/hydrophilic wire once the microcatheter is delivered into the calcified cap so that one does not exit the vessel but instead continues tracking along the occluded segment.\textsuperscript{7} Due to a rapidly expanding range of CTO guide wires, it is incumbent on the CTO specialist to have an organized approach to wire choice that keeps pace with evolving global experience and new guide wire designs.\textsuperscript{14}

Balloons or catheters should never be advanced over a wire unless it is certain that the wire is in the architecture of the vessel (within the boundary of the external elastic lamina). Wire perforations that occur within the occluded segment are usually benign but can become catastrophic if larger equipment is advanced outside the vessel, thereby enlarging the breach. Moreover, once the distal true lumen is accessed, the CTO crossing wires should be exchanged for workhorse wires to avoid distal plaque disruption/dissection and, in particular, to prevent inadvertent distal perforation of small vessels and delayed tamponade.\textsuperscript{15}

Antegrade Dissection/Reentry

The primary mode of failure when recanalizing a chronically occluded vessel
is failure of the wire to enter the distal true lumen. Frequently, the wire may instead reside within plaque or the subintimal plane downstream from the occluded segment. Reentering the true lumen from this position with standard wire techniques can be extremely challenging. However this problem has been greatly simplified with the development of dedicated reentry technologies designed to overcome the challenges a subintimal position. The CrossBoss catheter, Stingray balloon, and Stingray reentry guidewire (Boston Scientific, Natick, MA) address this limitation and provide a much more reproducible and systematic method for successfully gaining reentry into the distal coronary lumen. The CrossBoss catheter is a metal-braided, over-the-wire support catheter with a 1-mm rounded distal tip that can be used to support standard guide wire manipulation or can be advanced using rapid rotation, with or without the wire lead (Fig. 35-6). Without the wire lead, this catheter can cross from a subintimal position into the distal true lumen in approximately 30% of lesions. But most frequently, when advancing this catheter without a leading wire, it will continue within the subintimal space, creating a controlled subintimal dissection plane. Alternatively, it can enter into a side branch, which is important to recognize to avoid perforation. If the CrossBoss catheter reaches the vessel distal to the chronic occlusion in a subintimal position, or if a standard wire strategy leads to subintimal or sublesional position beyond the occlusion, coronary reentry can be systematically achieved with the Stingray coronary reentry technologies. The Stingray balloon is a 1-mm thick, over-the-wire balloon catheter with 3 exit ports (1 distal port and 2 180° diametrically opposed side ports). When the balloon is inflated, it effectively wraps the artery with 1 of the 2 exit ports, necessarily directed toward the adventitia with the other port directed toward the lumen. Using fluoroscopy and collateral angiography, operators can select the luminal-facing port with the dedicated Stingray reentry wire to create a pathway from the subintimal position to the distal true lumen (Fig. 35-7). Occasionally, a subintimal position can cause hematoma of the tissue plane, which, when it extends downstream, can compress the distal vessel true lumen. Decompression of this subintimal hematoma can be performed with aspiration of this tissue plane through the equipment residing there. The Stingray balloon or other microcatheters within that tissue plane can be used for this purpose with a subintimal transcatheter withdrawal (STRAW) technique. In general, the antegrade dissection/reentry technologies have been highly successful at crossing chronically occluded segments and regaining
access to the distal vessel true lumen with low complication rates, even in early experiences and refractory cases.\textsuperscript{16,17}

**FIGURE 35-6** The CrossBoss Catheter shown here is used to make a controlled dissection at the point of the planned reentry with the Stingray balloon. This catheter uses blunt dissection to avoid perforation and ensures a small channel to prevent hematoma and compression of the reentry zone. (Image provided courtesy of Boston Scientific. Copyright © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.)
The BridgePoint (Boston Scientific) dedicated antegrade dissection and reentry system. After establishing an antegrade subintimal tract using a CrossBoss (A) or other low-profile catheter or small angioplasty balloon, the Stingray balloon (B) is delivered and inflated in a position adjacent to the preferred segment for reentry. The flat profile of the Stingray balloon leads to its self-orientation circumferentially within the arterial wall such that 1 of the exit ports inevitably faces the arterial lumen. This port can then be selected using the dedicated steerable Stingray guide wire designed to facilitate puncture back into the lumen.

The Retrograde Approach

In 2005, Katoh and colleagues pioneered the modern era of retrograde CTO recanalization by introducing new techniques such as targeted septal or epicardial collateral crossing, retrograde lesion crossing, and management of the subintimal space through the use of balloon dilation for connecting antegrade and retrograde channels. Currently, retrograde procedures account for 15% to 34% of specialist CTO PCI procedures recorded in dedicated European and US registries. These methods require access to the distal CTO vessel from a collateral or, occasionally, a bypass graft vessel.
with successful placement of a support microcatheter into the distal target vessel.\textsuperscript{23}

**Retrograde Wire Crossing**

The term \textit{retrograde wire crossing} refers to lesion crossing in a distal-to-proximal cap direction where the wire traverses directly into the proximal vessel true lumen. This phenomenon is relatively uncommon and is successful in less than 30\% of retrograde procedures.\textsuperscript{18} When it is successful, the standard approach after successful retrograde wire manipulation includes placing the wire followed by the microcatheter into the antegrade guide catheter ostium and then exchanging the wire for a long wire to be externalized in a retrograde to antegrade direction. The externalized wire, which for ease of use should be a specialized externalization wire, particularly the RG3 (Asahi Intecc, Nagoya, Japan) but may also be the R350 (Vascular Solutions, Minneapolis, MN) or ViperWire Advance (CSI, Saint Paul, MN), is then used as the interventional platform to complete the PCI procedure. It is important for the portion of the retrograde guide wire that is across the fine collaterals to remain covered by a microcatheter to protect that collateral vessel from laceration and perforation. Equally important is careful attention to the retrograde guide to prevent guide-induced donor vessel injury.

**Retrograde Dissection and Reentry Techniques**

Controlled antegrade and retrograde subintimal tracking (CART; Fig. 35-8) with intentional dissection followed by reentry has become the dominant retrograde technique for successful crossing of CTOs. The principle of this technique is to create a subintimal dissection at the occluded vessel segment with limited extension, thereby creating a channel for wire crossing. The current evolution of this technique, termed \textit{reverse CART}, uses retrograde delivery of a microcatheter from the distal vessel true lumen into the CTO segment either with traditional wire or so-called “knuckle-wire” techniques. An antegrade wire is then simultaneously advanced distal to the equipment delivered in retrograde fashion. Over the antegrade wire, balloon dilation of the subintimal occlusion segment can be performed. This balloon should be matched to the vessel size to create a large subintimal pathway around the
occlusion. This dissects the 2 spaces occupied by antegrade and retrograde equipment to create a single, common space that is in continuity with the proximal true lumen; the retrograde wire can then be advanced into the true lumen (see Fig. 35-8).

**FIGURE 35-8** Controlled antegrade and retrograde tracking (CART): (1) Through directed penetration or knuckling, antegrade and retrograde guide wires are brought into overlap within the occluded segment; wires may be on opposite sides of the internal elastic lamina (one subintimal and the other within the occluded true lumen, 1a), both within the occluded true lumen (1b), or both in a subintimal plane (1c). Regardless, a balloon is advanced over one or the other wire (2), inflated/deflated (3), and then withdrawn leaving behind iatrogenic dissection often including breaches of the internal elastic lamina within the occluded segment (4) that allow the retrograde wire to be moved into a plane common with the retrograde wire, and then advanced into the patent proximal true lumen (5) and ultimately externalized. CART was originally described with the balloon positioned on the retrograde wire; the term reverse CART refers to the now common practice of positioning the balloon on the antegrade wire.

Ultrasound observations suggest this maneuver is easiest when both the antegrade and retrograde guide wire are on the same side of the internal elastic lamina, either both within the subintimal space or both within the
original true lumen. The most common reason for failure of this technique is use of undersized balloons, a problem overcome with experience and use of intravascular ultrasound for optimal balloon sizing and positioning. After the retrograde wire is advanced into the antegrade guide, externalization of the retrograde wire is performed as described earlier. The use of an antegrade daughter catheter such as a GuideLiner (Vascular Solutions) positioned immediately proximal to the reverse CART segment can expedite retrograde wire capture and externalization.

**HYBRID STRATEGY FOR CHRONIC TOTAL OCCLUSION PERCUTANEOUS CORONARY INTERVENTION**

Contemporary antegrade, retrograde, and dissection and reentry techniques are complementary and necessary to meet the full spectrum of challenges inherent to CTO PCI. Exploring sequential CTO crossing options can increase success, shorten procedure times, and reduce radiation exposure. The CTO expert operator needs broad skill sets, versatility, and flexibility to accommodate the wide range of anatomic scenarios present in chronic occlusions. Although significant variability exists among many operators with respect to procedural approaches, the hybrid method for CTO PCI is an effort to standardize initial and provisional technique selection based on patient anatomy (see Fig. 35-5). The implementation of the hybrid method requires skill-set development in optimal wire manipulation, dissection/reentry strategies, and retrograde techniques. The development and adoption of only 1 or 2 of these skill sets will ultimately limit the operator who wishes to approach all patients with appropriate indications for revascularization. Failure to develop a comprehensive skill sets will likely lead to underutilization of revascularization in patient subgroups that may derive great benefit from revascularization.

**TREATMENT OF LESIONS RESISTANT TO DILATION**
Although the most common form of failure in CTO PCI is an inability to obtain wire control of the proximal and distal vessel true lumen, occasionally other challenges present themselves. An inability to deliver equipment or, once delivered, dilate a crossed lesion represents another potential obstacle to successful CTO PCI. It is paramount to confirm that the guide wire is in the vessel architecture or in the distal true lumen before ever proceeding with an over-the-wire catheter or before applying various dilation strategies. The vessel architecture can usually be determined fluoroscopically by observing calcium deposits or other signs of the vessel outline moving or “dancing” in sync with the interventional guide wire. The distal true lumen can be determined by contralateral angiography (antegrade angiography should be avoided in such scenarios to avoid hydraulic artery dissection). After maximizing guide catheter support with either guide extension or anchor balloon techniques, dottering the lesion with the initial over-the-wire system should be attempted. In general, if a Corsair microcatheter (Asahi Intecc) or Turnpike Spiral microcatheter (Vascular Solutions) will not cross the lesion, the initial step is to advance and inflate to high pressure (14-16 atm) a small balloon (1.2-1.5 mm in diameter) as deeply as possible within the lesion to modify the proximal cap. When using small balloons, it is important to use longer balloons (15-20 mm) because the largest profile of these balloons is at the midshaft marker, and thus, the balloon tip will often penetrate the occlusion more readily. If this fails to allow passage of larger balloons, the next maneuver is to intentionally rupture the small balloon so as to modify the plaque morphology with barotrauma. If this fails to enable crossing, the Tornus catheter (Asahi Intecc) or Turnpike HardTip (Vascular Solutions) may be useful. If these maneuvers fail, more aggressive techniques such as the use of coronary laser or rotational atherectomy can be used. Rotational atherectomy and laser can be used even when the wire is not in the distal lumen, provided it is still within the vessel architecture. The advantage of the excimer laser (eg, the 0.9-mm Turbo Elite; Spectranetics, Colorado Springs, CO) is that it may be used on any 0.014-inch guide wire. However, rotational atherectomy requires exchanging the guide wire to a dedicated rotowire, and this may not be feasible when a resistant lesion prevents distal placement of any microcatheter. In situations where the distal true lumen has not been reached, the last 2 cm of the radiopaque wire tip can be removed prior to placement in the artery, thereby providing further reach with the burr (a short segment of the radiopaque portion of the wire should be preserved to prevent
the burr from proceeding off the end of the guide wire). Alternatively, the wire can be looped further down the vessel prior to atherectomy. Rotational atherectomy in the subintimal space should only be attempted by very advanced CTO operators with extensive experience assessing wire position in relation to vessel architecture. Performing rotational atherectomy in this situation demands the use of small (1.25-1.5 mm) burrs, maintenance of a high number of revolutions per minute (>170,000 rpm), and scrupulous avoidance of stalling and thus trapping of the device in a distal subintimal position. If all of these techniques fail to achieve balloon crossing and/or balloon dilation of the lesion, success can often be achieved by deliberately entering the subintimal space proximal to the anatomic cap, effectively moving the functional cap proximally and bypassing the point of resistance. This is done in an antegrade direction by intentionally dissecting the coronary proximal to the cap with a 1:1 noncompliant balloon and then accessing the subintimal space with a prolapsed polymer jacketed wire. Reentry into the true lumen is then planned distal to the lesion in question but prior to any major branches using the Stingray reentry system or using a retrograde approach with retrograde dissection and reentry techniques. This concept essentially employs the subintimal space as a bypass tract to go around the uncrossable or undilatable lesion.

It is beyond the scope of this chapter to cover all the potential intraprocedural challenges that will occur while performing CTO PCI on a wide array of coronary anatomies. It is critical, however, that the expert CTO operator be facile with a wide array of technologic- and technique-based solutions to manage the numerous potential difficulties involved in revascularization of occluded coronary arteries.

**CONCLUSION**

Although still very challenging, a growing cohort of global interventional programs have developed high-volume CTO programs. This work, in concert with transcatheter structural therapies and peripheral programs, provides a full complement of treatments for patients with advanced cardiovascular disease. There is growing clinical evidence in regard to the importance of complete revascularization in patients with coronary atherosclerotic disease (Fig. 35-9). The ability to open CTOs has now led to an era where complete
revascularization can be achieved in most patients.

**FIGURE 35-9** Kaplan-Meier curve showing differences in mortality between those with failed versus successful percutaneous coronary intervention (PCI) procedures targeting a chronic total occlusion (CTO). Successful intervention was associated with a significant decrease in mortality (hazard ratio, 0.71; 95% confidence interval, 0.62-0.82; \( P < .001 \)). Data draw from nearly 15,000 patients enrolled in a population-based PCI registry from the United Kingdom.24

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Intervention in Venous and Arterial Grafts

John S. Douglas, Jr.

HISTORICAL DEVELOPMENT

The surgeon’s use of saphenous veins and a variety of arterial conduits to bypass obstructive coronary atherosclerotic disease preceded percutaneous revascularization by about a decade. In that relatively short period of time, the inferiority of venous compared to arterial grafts and the potential for atheroembolization with vein graft manipulation at surgery had become apparent. When Andreas Gruentzig reported the first 50 patients treated with percutaneous coronary angioplasty in 1979, 5 had undergone saphenous vein graft (SVG) dilatation, and 3 (60%) had developed restenosis, leading him to surmise “the different kind of disease may explain the high incidence of recurrence in graft stenosis” and to question the wisdom of percutaneous SVG intervention. In the more than 35 years since that observation, interventional cardiologists have struggled with the indications for SVG intervention because of higher acute complications, more restenosis than was observed in native coronary arteries and arterial grafts, rapid disease progression in nontarget sites, and high late cardiac event rates. By 1983, outcomes of SVG intervention had been more completely characterized, and the first left internal mammary artery intervention had been reported. In a subsequent summary of several thousand reported cases of balloon angioplasty in SVGs, procedural mortality was less than 1%, Q-wave
infarction occurred in less than 2% of cases, and emergency surgery was required in 0.3% to 4% of cases. A gradient was observed in SVG restenosis rates, with very high rates approaching 70% at proximal anastomoses and progressively lower rates in more distal locations (see discussion mid-SVG and distal anastomosis). Subsequent maturation of graft percutaneous coronary intervention (PCI) occurred with improved understanding of patient and lesion selection, application of stents and embolic protection strategies, prediction and prevention of complications, and use of intravascular imaging as discussed below. Unfortunately, the goal of procedural and long-term safety and optimal durability of graft PCI has been illusive following treatment with SVGs.

**BARE METAL STENTS IN SAPHENOUS VEIN GRAFTS**

Use of stents in SVG intervention was supported by the report in 1995 of the Palmaz-Schatz multicenter registry experience in over 500 patients with the following favorable outcomes: procedural success, 97%; stent thrombosis, 1.4%; in-hospital mortality, 1.7%; urgent surgery, 0.9%; and restenosis in 18% of de novo lesions and 46% of restenotic lesions. In the Saphenous Vein De Novo (SAVED) trial, 220 patients with SVG stenosis of at least 50% and angina or objective evidence of ischemia were randomized to deployment of a Palmaz-Schatz stent or balloon angioplasty. Patients with lesion lengths requiring more than 2 stents, myocardial infarction within 7 days, or graft thrombus were excluded. Patients who underwent stent implantation had a higher procedural efficacy, defined as a reduction in stenosis to less than 50% of the vessel diameter with the assigned therapy (92% vs 69%; \( P < .001 \)). Patients assigned to stents had a larger increase in lumen diameter immediately (1.92 vs 1.21 mm; \( P < .001 \)) and a greater net gain in lumen diameter at 6 months (0.85 vs 0.54 mm; \( P = .002 \)). There was more bleeding in stented patients due to warfarin anticoagulation. Major in-hospital complications were otherwise similar in the 2 groups, although there was a trend toward fewer non-Q-wave myocardial infarctions in the stent group. This observation led some operators to investigate a strategy of direct stenting in SVGs, attempting to minimize distal atheroembolization.
In the SAVED trial, restenosis occurred in 37% of stented patients and in 46% of patients treated with balloon angioplasty ($P = .24$). Event-free survival at 240 days (freedom from death, myocardial infarction [MI], or repeat revascularization) was significantly higher in stented patients (73% vs 58%; $P < .03$). It was noted that late lumen loss was significantly greater in patients who had high-pressure stent deployment (≥16 atm), suggesting that high-pressure stent expansion may be undesirable in SVGs. Less aggressive stent expansion was also supported by an intravascular ultrasound study of over 200 SVGs that showed that stent expansion to ≥100% of the reference cross-sectional area was associated with significantly more non–Q-wave infarctions (29% vs 17%; $P = .05$) and similar rates of target vessel revascularization at 1 year (31% vs 26%; $P = .3$).\(^7\)

Observational reports of intervention in SVGs suggested that outcomes were somewhat better in 1995 to 1998 compared to earlier years (1-year event-free survival of 71% vs 59%; $P < .001$) and that use of stents had a protective effect.\(^8\) However, in an analysis of over 600 SVG patients in 5 large randomized trials, major adverse cardiac event (MACE) rates were twice that observed in native-vessel intervention.\(^9\)

**EMBOLIC PROTECTION DEVICES**

In the past decade, the importance of atheroembolic MI complicating PCI has become increasingly apparent, especially in SVG interventions. In relatively simple SVG lesions, stenting resulted in MI in 15% to 20% of patients. The rate of MI increased with lesion complexity, length, and estimated plaque volume,\(^10\) and in approximately 1000 patients who underwent SVG intervention, creatine kinase (CK)-MB elevation was the best independent predictor of late mortality.\(^11\) Strategies to prevent atheroembolic infarction have evolved over the years from occlusion aspiration to the use of filters. The first embolic protection device (EPD) method tested was the PercuSurge Guardwire system (Medtronic, Dublin, Ireland), which used a 0.014-inch guide wire with a compliant distal occlusion balloon. Inflation of the guide wire balloon interrupted blood flow, and stent deployment was followed by aspiration and balloon deflation. Use of this system in 24 SVG stent procedures was found to prevent infarction in 23 patients, and 95% of aspirates had typical atherosclerotic debris.\(^12\) However, it was the Saphenous
Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial that unequivocally and singularly demonstrated in a randomized study the value of embolic protection during SVG intervention. In 801 patients randomized to PercuSurge Guardwire or unprotected stent implantation, 30-day MACE was reduced by 42% with use of the Guardwire (from 16.5% to 9.6%; \( P < .001 \), primarily due to reduced infarction from 14.7% to 8.6%; \( P = .008 \)).\(^{13}\) In SAFER, use of EPD was demonstrated to be beneficial over a wide range of lesion lengths (even very short lesions), and this strategy was shown to be cost effective. Advantages of this technique included its low profile, which permitted crossing severe stenoses, and the ability to capture small particles and soluble vasoactive molecules such as endothelin and serotonin as well as coagulation components that have been shown to be liberated during SVG PCI.\(^{14}\) Disadvantages included the need to completely occlude the vein graft for several minutes, which was not well tolerated by some patients, and the requirement for several disease-free centimeters beyond the lesion to place the occlusion balloon. The complexity of this form of embolic protection compared to filters led to underutilization, and it was eventually removed from the market.

The effectiveness of filter-based embolic protection during SVG stent implantation was evaluated in the FilterWire EX During Transluminal Intervention of Saphenous Vein Grafts (FIRE) trial, a randomized study of 650 patients in 65 centers.\(^{15}\) Thirty-day MACE rate was 9.9% with the filter-based EPD and 11.6% with PercuSurge with virtually identical rates of MI (9% vs 10%) and death (0.9% vs 0.9%). Advantages of filter-based EPD included ease of use, maintenance of flow, avoidance of ischemia during stenting, and good visualization. Disadvantages included the need to cross the lesion with a somewhat bulky filter device that might require predilation, which has been shown to increase MI; the need for a substantial “landing zone” beyond the lesion; and the inability to remove soluble factors and particles smaller than the filter pores (<100 μm) (Fig. 36-1). The latter factors may not be clinically important based on comparisons such as FIRE. In addition, there can be difficulty with filter withdrawal due to inability to pass the retrieval catheter through a newly placed stent. This is especially true when the stent is in an aorto-ostial location with stent struts protruding into the aorta. Guide catheter–induced distortion of the newly placed ostial stent or entrapment of the filter on the distal stent edge can lead to major complications including stent embolization and thrombosis.\(^{16}\) Finally, filters
have finite limits as to the amount of debris that can be captured with maintenance of flow. Large atheroembolic or thrombotic loads can result in filter occlusion and the appearance of no reflow (Figs. 36-2 and 36-3). The optimal strategies, should this occur, include aspiration of the stagnant “dye” column, which frequently contains suspended particles; removal of the filter; and placing another filter if more interventional work is required. A variety of filters are currently available and appear to be equally effective.

FIGURE 36-1 A 79-year-old woman with unstable angina was found to have severe stenosis in a saphenous vein graft (SVG) to the left anterior descending coronary
artery (upper left), which had been placed 24 years earlier. The right coronary artery was occluded. She was somewhat forgetful and was not judged to be a good candidate for repeat surgery. Following placement of a FilterWire (Boston Scientific, Marlborough, MA) for distal protection and using an Amplatz left guide catheter, the lesion was predilated safely (upper right). A stent was selected to extend from the SVG ostium well beyond the lesion (lower left). Note the position of the filter. Following stent deployment, an excellent angiographic result was obtained (lower right). There was a moderate amount of atherosclerotic debris in the filter and no evidence of periprocedural myocardial ischemia or infarction. Had the patient been younger and better suited for repeat surgery, this option may have been used. The current ability to offer distal protection to enhance procedural safety and drug-eluting stents to ameliorate restenosis has significantly improved SVG percutaneous coronary intervention outcomes.
Chest Pain and ST Elevation

No Reflow!
FIGURE 36-2 A. Very complex lesion in mid portion of saphenous vein graft (SVG) to left anterior descending artery in an elderly man who was not a good candidate for repeat coronary artery bypass grafting (CABG). The lesion was ulcerated, with large plaque volume and probable thrombus. B. A filter was placed distally, and a 4.0 × 20 bare metal stent was deployed. The patient developed chest pain and ST-segment elevation (C), and there was no flow in the SVG (D). A manual aspiration catheter was used to aspirate the “dye” column in the SVG, and no reflow persisted after administration of adenosine distally through the aspiration catheter (E). The filter was removed, and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was immediately restored and ST segments normalized. The filter contained a large amount of plaque material sufficient to prevent flow through the filter (see Fig. 36-3). Several factors probably contributed to no reflow: (1) large lesion volume resulting in atheroembolization; (2) obstruction of the filter by plaque material; (3) release of vasoconstrictors such as endothelin and serotonin; and (4) clot embolization. The patient had a small non–Q-wave myocardial infarction and no other complications. Strategies that may have minimized the risk of no reflow include (1) pretreatment with a small-vessel dilator such as nitroprusside, adenosine, or calcium channel blockers (see “No Reflow Following SVG PCI” section); and (2) a smaller stent, because this stent was slightly oversized.
FIGURE 36-3 A. The Filter-Wire (Boston Scientific, Marlborough, MA). B. Filter obstructed by embolized plaque material resulting in no reflow. Image provided courtesy of Boston Scientific. © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.

A third form of EPD, known as PROXIS, which used a proximal occluding balloon, was tested in a randomized trial and was comparable to either filter or Guardwire.\textsuperscript{17} Advantages of proximal occlusion included protection during wire passage, side branch protection, and no need for a distal parking segment, a problem in many patients that prevented use of filters and PercuSurge. Unfortunately, as with the Guardwire, the complexity of proximal occlusion-aspiration and the requirement for graft occlusion for several minutes resulted in little usage and withdrawal of the device from the market.

The early report of Liu et al\textsuperscript{10} showing that plaque volume was a predictor of MI in SVG PCI was extended by Coolong and colleagues.\textsuperscript{18} They showed
in about 4000 patients that degeneration score and plaque volume were the most important predictors of MI, but the presence of thrombus, advanced age, and active smoking also contributed. When the occurrence of MACE was analyzed relative to these predictors, embolic protection was beneficial across all risk groups, implying that embolic protection should be used routinely in all suitable patients undergoing PCI in old SVGs as recommended in the 2011 PCI guidelines. However, data from the National Cardiovascular Date Registry indicated that embolic protection was used in only 21% of 49,325 senior patients who underwent SVG PCI and that acute and 3-year outcomes were not better in propensity score–matched patients in whom EPDs were used. In addition, in the recent ISAR-CABG (Is Drug-Eluting Stenting Associated With Improved Results in Coronary Artery Bypass Grafts?) study in which 610 patients underwent stent implantation in SVGs, the occurrence of MACE at 30 days was only 4% despite the use of embolic protection in <5% of patients. These observations cause one to question whether practices in place at the time of SAFER may have led to an increased rate of MI in the control group. For example, 40% of control patients underwent postdeployment stent dilation, a practice currently avoided by most experienced operators because further stent expansion frequently leads to no reflow. In addition, postdilation was carried out with a balloon that had a mean diameter of 4.2 mm, whereas the mean reference vessel diameter was only 3.4 mm. Use of a balloon larger than the reference vessel increased MI in the study by Iakovau et al. In addition only 27% of patients in the Guardwire arm underwent postdilation of the stent. These practice patterns may have contributed to the higher rate of periprocedural MI in the SAFER control group.

**ATHEROABLATIVE AND THROMBECTOMY STRATEGIES**

Debulking procedures in SVGs using directional atherectomy, the transluminal extraction catheter, and the excimer laser have been shown to have increased complexity and costs without evidence of improved outcomes. Consequently, atheroablative strategies do not play a significant role in current percutaneous intervention in venous or arterial grafts.
Mechanical thrombectomy is currently feasible with a variety of techniques, including aspiration with guide catheter, guide catheter extenders, or monorail aspiration catheters or by Angiojet thrombectomy (Boston Scientific, Marlborough, MA) (Fig. 36-4). Although proof of benefit is lacking, anecdotal experiences have convinced most practitioners that proceeding with PCI in the face of a large thrombus burden is rarely advisable when mechanical thrombectomy or some other strategy to eliminate or reduce thrombus is feasible (see later “Large Thrombus Burden” section).

**FIGURE 36-4** More than a decade after coronary artery bypass graft (CABG) a 61-year-old man presented 12 hours after onset of crushing chest pain and was found to have a normal electrocardiogram and troponin I level of 5 ng/mL. The saphenous vein graft (SVG) to the right coronary artery was occluded (A). Other grafts were patent, and the inferior left ventricular wall was mildly hypokinetic. Aspiration thrombectomy restored normal flow and revealed 2 SVG stenoses (B). Following deployment of 2 stents, the SVG was widely patent throughout (C). There were no complications. A very large amount of thrombus was removed at the time of the initial aspiration (D). It is highly unlikely that percutaneous coronary intervention results would have been favorable without clot removal, yet there is a small risk of systemic embolization.

**DRUG-ELUTING STENTS IN SAPPHENOUS VEIN GRAFTS**

Observational studies of the use of drug-eluting stents (DESs) in SVGs
suggested that they were safe and relatively effective. A multicenter registry of over 1000 patients who underwent SVG PCI reported that, at 9 months, patients receiving DES had significantly lower rates of death or MI (hazard ratio [HR], 0.52) and target vessel revascularization (HR, 0.36) compared to patients treated with bare metal stents (BMSs), and at 2 years, the mortality rate was lower (HR, 0.60). Multiple meta-analyses comparing DES with BMS in SVG have been published. In a meta-analysis, Mamas and colleagues analyzed 20 studies with over 5000 patients and reported no safety concerns and a 36% decrease in MACE in DES-treated patients. Three randomized trials have been published comparing sirolimus-eluting stents (SESs) or paclitaxel-eluting stents (PESs) with BMS in SVGs. Vermeersch et al randomized 75 patients to SES or BMS and found reduced restenosis at 6 months with SES, but at 3 years, target vessel revascularization was similar, suggesting a “catch-up” phenomenon, and SES-treated patients had a higher mortality. In the second randomized trial, 80 patients were randomly assigned to receive PES or BMS, and at 1 year, outcomes were more favorable with PES with respect to restenosis (11% vs 57%; P < .0001) and target lesion revascularization (5% vs 28%; P = .003), and clinical outcomes were better in PES-treated patients at 3 years.

The third randomized trial, ISAR-CABG, was the only study powered to compare clinical outcomes. Six-hundred ten patients were enrolled and randomly assigned to receive a DES (sirolimus or paclitaxel eluting) or BMS. Inclusion criteria were broad, and clinical characteristics of the 2 groups were similar. Outcomes at 1 year are reported in Table 36-1. The incidence of MACE, the primary end point, was 15% with DES and 22% with BMS, a 36% risk reduction. Target lesion and target vessel revascularization rates were significantly lower in DES-treated patients. There were no significant differences in all-cause mortality, MI, or definite or probable stent thrombosis. The 36% reduction in MACE is the same reported in a meta-analysis and in the stent registry. It is important to note that follow-up in ISAR-CABG was only 1 year and that longer term outcomes are needed.

Table 36-1 Clinical Outcomes at 1 Year in ISAR-CABG
Three recent publications of large registries reported somewhat differing long-term results. In a Danish registry, there was no benefit of DES with respect to death or stent failure at 3 years.\textsuperscript{28} However, in a large cohort of 709 propensity score–matched pairs of patients, the need for target vessel revascularization at 4 years was significantly less in DES-treated patients (21% vs 28%; \( P = .004 \); a 24% risk reduction).\textsuperscript{29} In patients with diabetes or stented segments \( \geq 30 \) mm, the number of procedures needed to prevent a target vessel revascularization was 8 and 7, respectively. In a report of stent implantation in SVGs from 63 Veterans Affairs hospitals for a 4-year period ending in 2011, DES use was associated with lower mortality in propensity-matched patients.\textsuperscript{30} Whether some late erosion of benefit with DES in SVG is related to the well-described delay in neointimal hyperplasia observed with DES in SVG is uncertain but plausible.

Virtually all the data available regarding long-term pathologic and clinical studies of DES in SVGs involve first-generation SESs and PESs. However, second-generation stents, which have been shown to be superior in native coronary arteries, are currently being implanted in SVGs. In an observational single-center study, 2-year outcomes of patients receiving second-generation everolimus-eluting stents (EESs; \( n = 88 \)) were shown to be superior to those of patients receiving first-generation SESs or PESs (\( n = 243 \)) with respect to MACE (18% vs 35%; \( P = .003 \)), target lesion revascularization (1% vs 12%; \( P = .005 \)), and target vessel revascularization (7% vs 25%; \( P < .001 \)).\textsuperscript{31} However, patients in the 2 groups were treated at different time periods and subject to selection bias. Although the use of DES in SVGs is somewhat controversial,\textsuperscript{32} given the paucity of long-term clinical outcome data and cost-effectiveness of current stents in SVGs, they do appear to be safe and confer at least short-term benefit, and their use is supported by the 2011 PCI guidelines.\textsuperscript{19} Patients most likely to benefit are those with diabetes, long

<table>
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<tr>
<th></th>
<th>DES</th>
<th>BMS</th>
<th>( P ) Value</th>
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<tr>
<td>MACE</td>
<td>15%</td>
<td>22%</td>
<td>.02</td>
</tr>
<tr>
<td>Death</td>
<td>5.1%</td>
<td>4.7%</td>
<td>.83</td>
</tr>
<tr>
<td>MI</td>
<td>4.1%</td>
<td>6.0%</td>
<td>.27</td>
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<tr>
<td>TLR</td>
<td>6.8%</td>
<td>13.1%</td>
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<tr>
<td>TVR</td>
<td>9.6%</td>
<td>15.5%</td>
<td>.03</td>
</tr>
</tbody>
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Note: MACE is the primary end point, a composite of death, MI, or ischemia-driven TLR.
Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; ISAR-CABG, is Drug-Eluting Stenting Associated With Improved Results in Coronary Artery Bypass Grafts?; MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.
Data from Mehilli et al.\textsuperscript{21}
lesions, SVGs <3.5 mm in diameter, and the ability to comply with long-term dual antiplatelet therapy.

**COVERED STENTS**

The results of randomized trials comparing polytetrafluoroethylene (PTFE)-covered stents with BMSs in SVGs were not encouraging.\(^{33,34}\) Six-month MACE rates were higher in patients receiving covered stents due to more MIs and late occlusion. However, PTFE-covered stents remain an important, potentially lifesaving adjunct for treatment of patients with SVG or left internal mammary artery (LIMA) graft perforation.

**PATIENT AND LESION CHARACTERISTICS**

*Time Since Coronary Artery Bypass Graft*

The type of graft lesions encountered is largely determined by the length of time that has passed since the patient underwent coronary artery bypass graft (CABG) surgery. The longer the interval, the higher is the probability of encountering bulky, friable, thin-capped atherosclerotic SVG lesions with high atheroembolic potential. Recurrent myocardial ischemia within days of CABG is commonly due to acute SVG thrombosis, but venous or arterial anastomotic lesions or uncorrected native coronary disease may be encountered. Among 145 patients with early postoperative ischemia evaluated with coronary angiography, 60% had graft stenosis or occlusion, 10% had incomplete revascularization, and no cause was apparent in the remainder.\(^3\) Seventy-four patients underwent repeat revascularization (PCI or CABG). Similar experience was reported by Thielmann and colleagues,\(^{35}\) who performed urgent catheterization in 2% of over 5000 patients very early after CABG because of suspected graft failure. Graft failure was confirmed in 71 patients, and repeat revascularization was performed in 60%. PCI in this setting is a Class I indication in American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and can be lifesaving.
Some insight into the frequency and timing of graft failure in the modern era can be gleaned from the use of routine intraoperative angiography at Vanderbilt University and several reports of routine angiography performed at 1 year following surgery. Zhoa et al\textsuperscript{36} reported that in patients undergoing routine angiography in the operating room immediately after completion of bypass surgery, 12% of bypass grafts had problems severe enough to require some form of intervention, and one-half of patients underwent open-chest PCI. In 3 studies reporting angiographic results at 1 year (PREVENT IV, PRAGUE-4, and ROOBY), graft failure rates were surprisingly high (40%-50% of SVGs and up to 11% of LIMA grafts). These results are sobering and strongly support angiographic evaluation when postoperative ischemia is suspected. The need for treatment of anastomotic lesions early after surgery is more common with off-pump and minimally invasive surgery in our experience. Development of anastomosis edema is a confounder that should be considered (see later section “Distal Anastomosis Lesions”).

**Proximal Graft Lesions**

Lesions at the origin of LIMA or right internal mammary artery (RIMA) grafts are quite rare, but stent implantation at these sites has been described. In most cases, these lesions predated CABG, suggesting a need to ensure conduit patency before surgery, especially in patients with large atherosclerotic burdens. Aorto-ostial SVG lesions are much more common and are difficult to treat effectively due to elastic recoil and restenosis and difficulty in achieving optimal stent placement. In a study of 320 consecutive patients with stent implantation for SVG aorto-ostial stenoses, about half of whom had debulking with atherectomy, 1-year target lesion revascularization was about 20%, and event-free survival was 70%. Atherectomy prior to stenting conferred no benefit. Results of the use of DESs at this site in large numbers of patients have not been reported. Aorto-ostial lesions in older SVGs have a high risk of distal embolization, and use of filters is recommended for embolic protection in bulky lesions with the caveat that filter retrieval following ostial stent implantation may be difficult.\textsuperscript{16}

**Mid-Graft Lesions**

Internal mammary artery grafts are “immune” to atherosclerosis; mid-RIMA
or -LIMA graft lesions are rare and most likely the result of operative trauma. Atherosclerotic lesions in the shaft portion of SVGs appear with increasing frequency beginning about 3 years after CABG. Data from the SAFER trial showed that even with the shortest lesions (<10 mm in length), a 77% reduction in 30-day MACE was experienced when embolic protection with PercuSurge was used (2.2% vs 8.1%). Although the risk of atheroembolic MI is highest with complex lesions, this observation in simple lesions supports routine use of a distal protection strategy during stent implantation in most de novo SVG lesions where the anatomy permits it (see earlier “Embolic Protection Devices” section). Exceptions are the lesion appearing within a year or 2 of surgery and in-stent restenosis, where intimal hyperplasia is the usual pathology and embolic complications are rare. Most operators use DESs in mid-SVG lesions. However, higher restenosis rates of stented sites in SVG compared to native vessels and more rapid progression of untreated moderate lesions in SVGs strongly support PCI of native vessel sites rather than SVG whenever possible.

**Distal Anastomosis Lesions**

In our experience, PCI of distal anastomosis lesions in SVGs or LIMA grafts has been safe even immediately after surgery, but there are isolated reports of suture line disruption. In addition, the European guidelines caution against treatment at this time because of the risk of perforation. We have observed moderate imperfections in LIMA anastomosis a day or so postoperatively that disappear on subsequent restudy, suggesting the presence of edema. Japanese colleagues reported similar observations in a group of patients undergoing early routine catheterization to evaluate results of off-bypass versus on-bypass surgery, leading a noted surgeon to question, “Does the internal thoracic artery graft have self-reparative ability?” Recurrent symptoms 1 to 12 months following surgery are frequently due to anastomotic lesions, with 3 to 4 months being the most common time. If balloon angioplasty results are good, stent implantation is not required. Anastomotic lesions occurring years after surgery are increasingly atherosclerotic, and stent implantation is the preferred treatment. Results of DESs for this site have not been reported in significant numbers, but most operators use them routinely in older lesions. When a bulky and presumably atherosclerotic distal anastomosis lesion is encountered, there is no embolic
protection strategy available, and a very careful risk-benefit analysis should be carried out, including consideration of native-vessel PCI and surgery. If stent implantation is planned, direct stent implantation without predilation should be considered.

**Intermediate SVG Stenosis**

Patients with moderate untreated stenosis in SVGs have a much higher late cardiac event rate than those without (45% vs 2%), leading some operators to have a lower threshold for intervening with stent implantation. Rodes-Cabau et al conducted a pilot trial randomizing 57 patients with intermediate SVG stenosis (30%-60% narrowing) to DES or medical therapy alone and reported lower late cardiac events in stent-treated patients out to 3 years. A large prospective randomized trial was initiated to further explore this strategy. Fractional flow reserve and intravascular imaging strategies with optical coherence tomography, useful in guiding native coronary intervention, have not been adequately studied in SVGs.

**Large Thrombus Burden**

Lesion-associated thrombus is a predictor of complications, especially periprocedural MI. In the SAFER trial, baseline SVG thrombus was associated with higher mortality (3.0% vs 0.9%; \( P = .04 \)), more no reflow (9.9% vs 3.4%; \( P = .001 \)), and higher 30-day MACE (17.4% vs 10.4%; \( P = .006 \)). This striking difference in outcomes occurred despite the fact that 50% of patients in SAFER received embolic protection with PercuSurge, which reduced complications (odds ratio [OR], 0.625; \( P = .02 \)). Some experienced operators attempt to reduce thrombus prior to stent implantation by administration of antithrombotic therapy along with glycoprotein IIb/IIIa platelet receptor inhibitors for a few days or by infusing thrombolytic agents locally. However, mechanical thrombectomy was shown to be superior to thrombolytic therapy and is the most common approach, combined with a distal protection strategy if possible (see later section “Thrombectomy in Saphenous Vein Grafts”).

**The Restenosis Lesion**
Restenosis following stent implantation in an SVG is common. When disease in the SVG appears to be confined to the in-stent restenosis lesion, repeat intervention can be conducted with such a low risk of atheroembolization that distal protection is not routinely implemented. Exceptions include patients with restenosis many years following stent implantation in whom neoatherosclerosis may be the pathology. Because repeat restenosis following BMS implantation occurs subsequently in almost one-half of such patients, treatment with DESs has become standard therapy.

**ST-Segment Elevation MI in the Post-CABG Patient**

In a recently reported large observational study, Gruberg et al reported outcomes of 15,628 patients with ST-segment elevation MI (STEMI), 6% of whom (n = 969) had a history of prior CABG. Patients with prior CABG were older, had more comorbidities, and had longer door-to-balloon times, and the target vessel was a vein graft in 53%. In post-CABG patients, there was a trend for increased short-term mortality risk if the treated lesion was in a bypass graft (OR, 2.2; \( P = .07 \)), and a similar trend was reported at 1 year in a single-center study of 249 post-CABG patients. The ACC/AHA Task Force report on early management of acute MI classified primary PCI for vein graft recanalization to be a Class IIa indication, that is “acceptable, of uncertain efficacy and may be controversial; weight of evidence in favor of usefulness/efficacy.” Strategies that should be considered in primary SVG PCI include consideration of native-vessel options whenever possible and optimal management of the large thrombus burden frequently encountered (see above).

**Chronic Total SVG Occlusions**

Intervening on a recently occluded SVG in the setting of an acute coronary syndrome is frequently a formidable task due to the large amount of thrombus commonly present and its increasing resistant to removal or lysis as time goes by (Figs. 36-4 and 36-5). PCI in the presence of a large thrombus burden carries a risk of distal embolization with aspiration thrombectomy, and there is a small risk of systemic embolization. In the presence of a chronic SVG occlusion, problems are magnified, and the risk-benefit ratio becomes even less favorable, accounting for the Class III indication (not
helpful, possibly harmful) in the 2011 PCI guideline statement. However, in a recent summary of 4 reports of attempted PCI of chronic SVG occlusion with a total of 94 patients, successful recanalization was achieved in 72% with in-hospital MI in 7%, no in-hospital deaths, and improvement in angina in 80%.47

FIGURE 36-5 A 66-year-old man presented to the emergency department with chest pain of 2 hours in duration. Clopidogrel had been discontinued a few days earlier due to anticipated surgery related to diabetes and a poorly healing foot ulcer. There was a history of coronary artery bypass grafting (CABG) × 3 12 years earlier. Electrocardiogram revealed anterior ST-segment elevation (A), and emergency coronary angiography revealed an occluded saphenous vein graft (SVG) to the left
anterior descending artery (LAD) (B). The native coronary arteries were occluded. Radial artery graft to right coronary and left internal mammary artery to ramus intermedius artery were patent. Percutaneous coronary intervention was initiated, and immediately after guide wire passage, slight antegrade flow was observed in the SVG to LAD with large thrombus burden (C). Aspiration was performed with a large amount of clot removed (D), with return of a normal flow but significant proximal SVG stenosis (E). Following placement of a filter, a 3.5 × 23 drug-eluting stent was deployed with excellent angiographic results (G). Tirofiban was administered intravenously for 18 hours due to the large clot burden. Initial troponin of 0.55 ng/mL increased to 200 ng/mL 8 hours after procedure. Echocardiogram 1 year later revealed anterior hypokinesis and an ejection fraction of 45% to 50%.

**FIGURE 36-6** A. Severe stenosis was observed in the saphenous vein graft to the left anterior descending artery in an elderly man 16 years after coronary artery bypass grafting. B. A 3.5-mm stent was deployed with full expansion of the stent at 18 atm. C. A type 3 perforation was noted. Optimal treatment of this complication includes immediate balloon inflation and consideration of strategies to seal the perforations. Consideration of a second guide catheter for deployment of a covered stent is a good strategy.

**The Diabetic Patient**

A study of over 2000 patients who underwent PCI of SVG lesions at Emory University pointed out the poor 5-year survival of diabetics compared to nondiabetics (60% vs 82%; \( P = .001 \)). Event-free survival at 5 years was also significantly lower (23% vs 37%; \( P = .001 \)). DESs were not used during this experience.
EQUIPMENT

The guide wires, balloon catheters, stents, thrombectomy devices, and available distal protection equipment are described in detail in the chapters devoted to these topics. The reader is referred to these chapters for review of the devices themselves.

STEP-BY-STEP PROCEDURE

Periprocedural Pharmacotherapy

The author premedicates patients with clopidogrel 600 mg loading dose or another P2Y\textsubscript{12} inhibitor, aspirin 325 mg, diphenhydramine 50 mg, a calcium-blocking drug such as diltiazem 60 mg orally, and a thrombin inhibitor. Unfractionated heparin is preferred in graft intervention because it can be reversed in the event of graft perforation. Patients with obvious thrombus may receive glycoprotein IIb/IIIa platelet receptor inhibitors, but their routine use has not been shown to be beneficial in SVGs and has a Class III indication in the 2011 PCI guidelines.

Guide Catheter Selection and Manipulation

For in situ LIMA or RIMA interventions, 6- or 7-Fr internal mammary artery (IMA) catheters are used from a homolateral radial artery or femoral approach. A 0.035-inch angle tip glide wire facilitates entering the subclavian artery or innominate artery, if needed. If entry into the IMA is difficult, a straight lateral view is obtained, and the tip of the IMA catheter is rotated anteriorly. Extreme care is taken to avoid traumatizing the ostium of the IMA, especially when balloon catheters and guide wire are withdrawn and the guide catheter can be pulled into the IMA.

For SVG and free arterial graft intervention, 6- or 7-Fr multipurpose guide catheters are used for down-going grafts to the right coronary artery. Hockey stick or Amplatz shapes are used for grafts that arise from the anterior aorta and supply left anterior descending (LAD) or diagonal arteries (see Fig. 36-1), and Amplatz shapes are favored for grafts to the circumflex distribution,
especially when their initial portion is superiorly oriented. Amplatz guide catheters provide superior “backup,” which becomes especially important when embolic protection strategies are applied. If ostial narrowing is present or the graft is small, a side-hole guide catheter is preferred. It is important to keep in mind that a 7-Fr guide catheter is required to deliver larger covered stents (≥3.5 mm) to treat SVG perforations. Guide catheter extenders are occasionally helpful when anatomy is difficult.

**Selection of Optimal Views**

For LIMA or RIMA interventions at the distal anastomosis with LAD or diagonal arteries, a straight lateral view, with cranial angulation if needed, is one of the best views and is frequently coupled with a 30° right anterior oblique view to provide 2 roughly orthogonal views. When SVG intervention is carried out, at least 1 and preferably 2 views are needed that are roughly 90° from the longitudinal axis of the graft, free of overlap and foreshortening, and display the entire length of the lesion. With aorto-ostial lesions, it is difficult but critically important to avoid foreshortening, which prevents precise placement of the stent in relation to the ostium of the graft.

**Selection for Embolic Protection**

The reader is referred to the Chapter 35 for a more complete review of this topic. In general, an embolic protection strategy is recommended, when the anatomy is suitable, in all interventions on de novo lesions in SVGs 3 years old or older. A filter can be used even when it is anticipated that ischemia would not be well tolerated. Examples include grafts supplying large myocardial segments, moderate-sized myocardial segments in the presence of left ventricular dysfunction, or last remaining vessel. When there is insufficient room for a filter beyond the lesion, direct stent implantation without predilation is advisable, and the stent diameter should be equal or slightly smaller than the reference vessel. A slightly longer stent is recommended when the risk of atheroembolism is increased to avoid longitudinal plaque shift outside the stented segment.

**Guide Wire Selection**
In the presence of a very tortuous internal mammary artery graft, a 0.014-inch floppy guide wire with hydrophilic coating is frequently the best choice and usually permits passage of a balloon catheter. Routine use of over-the-wire balloons and stents is advisable in LIMA graft interventions to facilitate guide wire exchange. In order to be able to pass a stent, it may be necessary to exchange for a stiffer guide wire or insert a “buddy wire.” Use of a guide catheter extender may be helpful, but there is some risk of injuring the graft. Use of a stiff wire may straighten the IMA and even occlude it. When this happens, it may be necessary to change to a less stiff wire once the stent is in the approximate target site, to remove the buddy wire, or to deploy the stent using landmarks such as surgical clips. Removal of a stiff guide wire from a straightened IMA is best accomplished via an over-the-wire balloon catheter with care not to drag the guide catheter into the IMA origin. Selection of a guide wire for SVGs follows principles used in native-vessel intervention, with middle-weight wires commonly being chosen.

**THROMBECTOMY IN SAPHENOUS VEIN GRAFTS**

When a large thrombus burden is present, PCI is risky, as discussed earlier. Angiojet thrombectomy is the most effective method for clot removal and is favored when the thrombus is large. Placement of a temporary pacemaker is usually required for treatment of SVGs supplying right and dominant circumflex coronary arteries because of bradycardia caused by adenosine release from red cells. Placement of a filter should be considered in the presence of a large thrombus, but there is some risk of embolizing clot when placing the filter. Proximal thrombi may be aspirated by a guide catheter or guide catheter extender, and smaller distal thrombi can be removed by manual aspiration catheters. It is important to keep in mind that there is a risk of cerebral emboli when aspirating thrombi from grafts, and deep seating guide catheters is advisable when it can be safely accomplished. Consideration of native-vessel PCI is warranted when thrombus-laden SVGs are encountered.
STENT SELECTION

DESs have become the default strategy despite the lack of hard long-term data supporting their use in SVGs. Currently, their use in large SVGs is constrained by the geometric expansion limits of the available devices. As noted earlier, data from the SAVED trial and ultrasound studies suggest that in SVG PCI, stent sizing and expansion pressures should be conservative.\(^5\)\(^-\)\(^7\) This strategy will also minimize the risk of SVG perforation and avoid, to a degree, the extrusion of atheroma through stent struts with subsequent embolization. A thoughtful approach to SVG PCI is recommended, including direct stenting,\(^6\) minimal catheter manipulations, avoiding postdilation of stents, slightly longer stents to trap as much atheroma as possible, and routine use of embolic protection. When distal protection could not be applied in the past due to anatomic constraints, use of self-expanding stents without postdilation minimized the risk of atheroembolization in the author’s experience. Currently, a self-expanding coronary stent is not available.

THE VALUE OF INTRAVASCULAR IMAGING

Use of intravascular ultrasound (IVUS) is valuable in measurement of luminal diameter and percent stenosis and has shown that nominal or slight undersizing of stents in SVGs results in less plaque extrusion and periprocedural MI with similar long-term outcomes.\(^7\) IVUS has also demonstrated in SVGs that the mechanism that commonly underlies development of acute coronary syndromes (ie, plaque rupture) is similar in SVGs and native coronary arteries. Optical coherence tomography, which has higher resolution than IVUS, has demonstrated in SVGs increasingly frequent presence of thin fibrous caps and thrombus with increasing clinical acuity and much greater lesion complexity than was suggested angiographically.\(^42\)

AVOIDING AND TREATING
COMPLICATIONS

SVG Perforation

The preceding sections highlight some of the most important tips to avoid perforation, namely avoiding oversized balloons and stents and unnecessarily high pressure inflations. Despite these cautionary measures, SVG perforations are encountered, perhaps because of the frequent use of long balloons and stents and the capability of stent delivery balloons to reach pressures exceeding 20 atm. Accepting minor imperfections such as a short segment of incompletely expanded stent may be preferred over extremely high inflation pressures that risk perforation and balloon rupture–induced injury. With the use of long balloons and stents, long tears may occur that are difficult and sometimes impossible to seal, even with PTFE-covered stents. Long inflations, covered stents, and coils can be invaluable in the event of a serious perforation, and covered stents and coils should be immediately available. When a “free” perforation occurs, it is usually advisable to control it with the balloon that caused the perforation while gathering necessary tools to definitively seal it. In some cases, it is advisable to place a second larger diameter guide catheter from a femoral approach to accommodate the bulky, covered stent required to seal a large SVG that has been perforated. Placing a second guide catheter offers the major advantage of avoiding a too-hasty exchange for the covered stent, risking loss of guide wire position, which can be catastrophic.

No Reflow Following SVG PCI

The etiology of no-reflow during SVG intervention is multifactorial and includes vasospasm, but most important is microembolization of plaque and thrombus. As shown in SAFER, effective distal protection significantly reduces no reflow (from 9.9% to 3.4%; \( P < .001 \))\(^{13} \) and should be used whenever possible in SVG PCI procedures involving de novo lesions in SVGs in place for \( \geq 3 \) years. Participation of microvascular spasm in no reflow is strongly suggested by the fact that endothelin and serotonin, both vasoconstrictors, are liberated during SVG PCI,\(^ {14} \) by reduced no reflow when calcium channel blockers are administered prior to SVG PCI, by a beneficial
treatment effect of microvasculature dilators (nitroprusside, adenosine, and calcium blockers), and by the lack of benefit of nitroglycerin. When no reflow occurs or is anticipated, intracoronary administration of 100 to 300 μg of diltiazem, verapamil, or nitroprusside or 10 to 30 μg of adenosine is conservative and may be repeated. A prolonged intragraft high-dose infusion of adenosine (200 μg/min for 10 minutes) has been shown to protect microvascular function and prevent no reflow. Based on the work of Japanese colleagues, the author has adopted a strategy of aspirating the stagnant dye column when no reflow occurs. In patients with no reflow, direct aspiration of the dye column was more effective than calcium channel blockers in restoring flow and avoiding balloon pumping and death. Aspirates most often contained plaque gruel, with <10% containing thrombus. Although glycoprotein IIb/IIIa platelet receptor inhibitors are sometimes administered in patients with no reflow, this strategy has not been formally tested.

LONG-TERM PHARMACOTHERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION

Following graft intervention and stent implantation, patients are at risk for stent thrombosis and/or restenosis and progression of disease in other portions of the graft. Patients should routinely receive optimal lipid-lowering therapy and aspirin, and there is an accumulating body of evidence supporting extended dual antiplatelet therapy. In a recent long-term observational study of over 400 patients who were event free at various intervals following SVG PCI, cessation of clopidogrel was associated with a clustering of death or MI within 90 days.49 Five-year event-free survival was significantly better in patients who received long-term dual antiplatelet therapy.

CONCLUSION

Recurrence of symptoms following CABG is a commonly encountered clinical problem that can often be ameliorated by PCI. Safety of graft PCI has
been enhanced by the advent of distal protection strategies and more effective and easily applied thrombectomy devices. Intermediate-term results have been improved by DESs. Although the interventional cardiologist has never been in a better position to effectively treat this patient subgroup, outcomes following SVG PCI remain suboptimal compared to native coronary intervention, engendering caution in selection of this strategy and highlighting the need for further investigation and native-vessel intervention whenever possible. Following graft PCI, long-term lipid-lowering therapy and dual antiplatelet therapy are the norm.

REFERENCES


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**MULTIPLE CHOICE QUESTIONS**

1. The use of embolic protection in saphenous vein graft (SVG) stent implantation in the randomized SAFER trial was associated with which of the following outcomes?
   A. No impact on occurrence of major adverse cardiac events (MACE)
   B. 10% reduction in MACE
   C. 20% reduction in MACE
   D. 40% reduction in MACE

2. The rate of SVG failure at 1 year after coronary artery bypass graft (CABG) in routinely performed angiographic studies was shown to be which of the following?
   A. 5%
   B. 10%
   C. 15%
   D. ≥20%

3. Use of slightly oversized stents in SVGs has been associated with which of the following outcomes?
   A. Reduced target vessel revascularization
B. Reduced periprocedural infarction  
C. Increased periprocedural MACE  
D. Reduced restenosis  

4. Use of drug-eluting stents in SVGs compared to bare metal stents was associated with which of the following in randomized trials?  
   A. Reduced mortality  
   B. Reduced myocardial infarction  
   C. Reduced stent thrombosis  
   D. Reduced restenosis  

5. When used in SVGs prior to stent implantation, atheroablative strategies were shown to be associated with which of the following?  
   A. Increased cost and reduced restenosis  
   B. Increased cost and similar restenosis  
   C. Similar cost and outcome  
   D. Increased complications  

**ANSWERS**  
1. D  
2. D  
3. C  
4. D  
5. B
INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) composes approximately 25% to 40% of myocardial infarction (MI) presentations. There has been remarkable progress in the treatment and clinical outcomes in STEMI patients over the past 2 decades. Where available within a reasonable time period, reperfusion with percutaneous coronary intervention (PCI) has been accepted as the preferred reperfusion strategy for STEMI (Fig. 37-1). As the number of patients receiving primary PCI has increased, mortality has declined (Fig. 37-2). In-hospital and 1-year mortality rates are currently 4% to 6% and 7% to 18%, respectively.1-4 Few other interventions in clinical medicine require the complex organization of health care delivery systems and the high level of technical expertise to achieve optimum outcomes. In this chapter, we review the evidence for PCI in STEMI, including management of patients presenting to non–PCI-capable centers as well as selected technical aspects of PCI including adjunctive pharmacotherapy.
FIGURE 37-1 Reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI). Bold arrows and boxes are the preferred strategies. *Patients with cardiogenic shock or severe heart failure initially seen at a non-percutaneous coronary intervention (PCI)-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from myocardial infarction (MI) onset. †Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. CABG, coronary artery bypass graft; DIDO, door-in–door-out; FMC, first medical contact; LOE, level of evidence. (From Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol. 2016;67(10):1235-1250.)

### REPERFUSION STRATEGY

**PCI Versus Fibrinolysis Therapy**

PCI has been shown to be superior to fibrinolytic therapy in numerous large, randomized clinical trials in not only PCI-capable hospitals but also non–PCI-capable centers⁵⁻¹⁴ (Fig. 37-3). In the 2 largest trials, DANAMI-2 (Danish Acute Myocardial Infarction 2) and PRAGUE-2 (Primary Angioplasty After Transport of Patients from General Community Hospitals to Catheterization Units With/Without Emergency Thrombolysis Infusion), most of the patients presented to hospitals without PCI facilities.⁸⁻¹² A large 2009 meta-analysis of randomized controlled trials (RCT) and observational studies, comparing primary PCI (with balloon angioplasty or stenting) to
fibrinolysis, found that PCI was associated with significant reductions in short-term (≤6 weeks) mortality of 34% in RCTs and 23% in observational studies with significant reductions in long-term (>1 year) mortality (24%) and reinfarction (51%).

PCI has also been demonstrated to be superior to fibrinolysis in specific high-risk patient subgroups. There is substantial evidence of benefit for patients with anterior MI in subgroup analyses from randomized trials. For example, in the PAMI (Primary Angioplasty in Myocardial Infarction) trial, the benefit of primary percutaneous transluminal coronary angioplasty (PTCA) compared to fibrinolysis was limited to patients with anterior wall STEMI. Efficacy in anterior MI was directly addressed in a study in which 220 such patients were randomly assigned to primary PCI or alteplase. Primary PCI was associated with significant reductions in in-hospital mortality (2.8% vs 10.8%), postinfarction angina or positive exercise test (11.9% vs 25.2%), repeat revascularization (22% vs 47.7%), and, at 6 months, mortality (4.6% vs 11.7%) and revascularization (31.2% vs 55.9%). For patients with cardiogenic shock, a population in which fibrinolysis is generally not effective, observational data from the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded
Coronary Arteries) trial and the randomized SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) trial demonstrated benefit with an early invasive strategy with revascularization by either PCI or coronary artery bypass grafting (CABG).\textsuperscript{17-19}

**Management at Non–PCI-Capable Centers**

**Transfer for Primary PCI**

The results from randomized trials indicate that outcomes are better when patients with STEMI who present to non-PCI hospitals are transferred to a PCI facility for primary PCI compared with being given fibrinolytic therapy at the local hospital\textsuperscript{5,6,8-12} (Fig. 37-4). The additional treatment delay of primary PCI compared with fibrinolytic therapy (door-to-balloon [D2B] time minus door-to-needle [D2N] time) in these trials ranged from 55 to 103 minutes. There are currently many statewide and nationwide efforts to improve D2B times (Fig. 37-5), including transfer from noninterventional hospitals.\textsuperscript{20-25} It has been shown that with well-defined goals, commitment from administrative and clinical leaders, standardized protocols, integrated systems of transfer, and data feedback to monitor progress, D2B times can be improved not only at PCI centers but also for patients presenting to noninterventional hospitals.\textsuperscript{5,6} In 2013, a study of 96,738 STEMI patients undergoing PCI at 515 hospitals enrolled in the ACCCathPCI Registry showed that median D2B times decreased from 83 minutes from July 2005 to June 2006, to 67 minutes from July 2008 to June 2009 (\(P < .001\)). The percentage of patients who met the guideline recommendation of ≤90 minutes increased from 59.7% to 83.1% (\(P < .001\)).\textsuperscript{26} In contrast to PCI centers, recent evidence indicates that 40% to 75% of patients transferred from non-PCI facilities continue to have a total D2B >120 minutes\textsuperscript{27-29} (Fig. 37-6).
FIGURE 37-4 Meta-analysis of composite end point of death, reinfarction, and stroke when comparing percutaneous coronary intervention (PCI) to lysis. (Reproduced from: Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation. 2003;108(15):1809-1814. Copyright © American Heart Association, Inc. All rights reserved.)

FIGURE 37-5 Improvement in the percentage of patients with door-to-balloon (D2B)

**FIGURE 37-6** Cumulative proportion of patients who received primary percutaneous coronary intervention stratified by the estimated interhospital drive time. Each line represents a group of patients stratified by the estimated interhospital drive time. The x-axis represents the first door-to-balloon (DTB) time to primary percutaneous coronary intervention. The intersection of each line with the 120-minute mark represents the observed percentage of patients who achieved a first DTB time within 120 minutes in each estimated interhospital drive time group. (Reproduced from Vora AN, Holmes DN, Rokos I, et al. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. JAMA Intern Med. 2015;175(2):207-215. Copyright © American Heart Association, Inc. All rights reserved.)

Recommendations regarding triage of STEMI patients with an expected delay ≥120 minutes for fibrinolytic therapy versus transfer for primary PCI remains an area of some controversy. Propensity-matched data from the National Registry of Myocardial Infarction found no mortality benefit from primary PCI when the PCI-related delay (D2B-D2N time) exceeded 120 minutes (Fig. 37-7). The meta-analysis by Boersma of randomized trials comparing fibrinolytic therapy versus primary PCI also suggested that
primary PCI has a mortality advantage, with PCI-related delays of up to 2 hours.\textsuperscript{32} Data evaluating the impact of treatment delay with primary PCI on mortality suggest that patients presenting early after the onset of symptoms have much more impact than patients presenting late after the onset of symptoms.\textsuperscript{33,34} Currently, guidelines recommend that patients with cardiogenic shock, patients who are ineligible for fibrinolytic therapy, and patients who can be treated within 120 minutes should be transferred for primary PCI.\textsuperscript{5,6}

**FIGURE 37-7** Relationship between percutaneous coronary intervention (PCI)–related delay and in-hospital mortality. *Dotted lines represent 95% confidence intervals. XDB-DN, transfer door-to-balloon–door-to-needle time (indicates transfer delay).* (Reproduced from Pinto DS, Frederick PD, Chakrabarti AK, et al; for the National Registry of Myocardial Infarction Investigators. Benefit of Transferring ST-Segment-Elevation Myocardial Infarction Patients for Percutaneous Coronary Intervention Compared With Administration of Onsite Fibrinolytic Declines as Delays Increase. *Circulation.* 2011;124(23):2512-2521. Copyright © American Heart Association, Inc. All rights reserved.)

**Facilitated or Pharmacoinvasive PCI**

Most patients with acute MI (AMI) present to hospitals without interventional facilities, and the time delay required to transfer patients for
primary PCI has led to a great deal of interest in pharmacologic reperfusion combined with mechanical reperfusion (facilitated PCI). Facilitated PCI is the use of pharmacologic therapy to establish reperfusion as rapidly as possible followed by immediate PCI to maximize Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow rates and to stabilize the ruptured plaque\textsuperscript{34,35} (Fig. 37-8). Primary PCI has the advantage of >97% successful reperfusion, but the challenges of availability and time delay. Fibrinolysis has the advantage of availability and rapid treatment, but the disadvantage of incomplete reperfusion (50%-70%) and the increased risk of bleeding. Patients undergoing primary PCI for AMI who arrive at the catheterization laboratory with an open versus closed infarct-related artery have higher procedural success rates, better recovery of left ventricular function, and lower early and late mortality.\textsuperscript{36} These factors led to a series of trials to examine the benefit of facilitated PCI, which has now evolved to “pharmacoinvasive” PCI.\textsuperscript{30}
FIGURE 37-8  Effect of timing of reperfusion on myocardial salvage and mortality. Mortality reduction as a benefit of reperfusion therapy is greatest in the first 2 to 3 hours after the onset of symptoms of acute myocardial infarction (MI), most likely a
consequence of myocardial salvage. The exact duration of this critical early period may be modified by several factors, including the presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands, and duration of sustained ischemia. After this early period, the magnitude of the mortality benefit is much reduced, and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. If a treatment strategy, such as facilitated percutaneous coronary intervention (PCI), is able to move patients back up the curve, a benefit would be expected. The magnitude of the benefit will depend on how far up the curve the patient can be shifted. The benefit of a shift from points A or B to point C would be substantial, but the benefit of a shift from point A to point B would be small. A treatment strategy that delays therapy during the early critical period, such as patient transfer for PCI, would be harmful (shift from point D to point C or point B). Between 6 and 12 hours after the onset of symptoms, opening the infarct-related artery is the primary goal of reperfusion therapy, and primary PCI is preferred over fibrinolytic therapy. The possible contribution to mortality reduction of opening the infarct-related artery, independent of myocardial salvage, is not shown. (Reproduced from Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? JAMA. 2005;293(8):979-986. Copyright © American Heart Association, Inc. All rights reserved.)

The ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention) trial, which randomized patients to tenecteplase-facilitated PCI versus PCI alone found a higher incidence of death, reinfarction, and stroke with facilitated PCI.\(^{37}\) In a meta-analysis, facilitated PCI using a fibrinolytic or glycoprotein IIb/IIIa inhibitors in combination with PCI also was associated with higher rates of death, reinfarction, stroke, and bleeding compared with primary PCI alone.\(^{38}\) The major limitations of the meta-analysis were the heterogeneity of the treatment regiments, the lack of P2Y\(_{12}\) inhibitors, and the fact that most patients were treated at PCI centers. In addition, the meta-analysis included few patients with an expected delay >120 minutes, which is the specific patient population most likely to benefit from facilitated PCI.\(^{39}\) The FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) trial randomized patients to facilitated PCI with half-dose

### B. Theoretical advantages of pharmacoinvasive reperfusions. STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction. (Reproduced from Dauerman HL, Sobel BE. Synergistic treatment of ST-segment elevation myocardial infarction with pharmacoinvasive recanalization. J Am Coll Cardiol. 2003;42(4):646-51, Copyright © 2003, with permission from the American College of Cardiology Foundation.)
reteplase plus abciximab or abciximab alone versus primary PCI alone. Although the trial was underpowered due to slow enrollment, the 1-year mortality rates were 6.3%, 7.4%, and 7.0%, respectively ($P$ = not significant). However, there was a significant increase in TIMI major and minor bleeding in the group that received early administration of abciximab compared to the group that received abciximab at the time of primary PCI (10.1% vs 6.9%; $P$ = .008). A subsequent reanalysis of the 2452-patient FINESSE trial found a significant improvement in the 90-day composite end point (death, ventricular fibrillation after 48 hours, cardiogenic shock, and congestive heart failure) as well as mortality at 1 year with facilitated PCI in patients at high risk who presented early after the onset of symptoms.

Since that time, a number of large randomized trials have demonstrated the clinical benefit of a pharmacoinvasive strategy with fibrinolysis followed by routine coronary angiography with PCI compared with fibrinolysis alone. A meta-analysis of early routine PCI after fibrinolysis compared with fibrinolysis alone demonstrated a significant reduction in reinfarction and recurrent ischemia at 30 days with no significant increase in bleeding events. These benefits were maintained out to 12 months (Fig. 37-9).
Most recently, the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial compared a pharmacoinvasive strategy to primary PCI and found a trend in the primary end point (a composite of death, shock, heart failure, and reinfarction at 30 days), which was 12.4% versus 14.3%, but the pharmacoinvasive strategy was superior when delays were prolonged (≤55 minutes: 10.6% vs 10.3%; 55-97 minutes: 13.9% vs 17.9%; >97 minutes: 13.5% vs 16.2%). Therefore, the data currently support a pharmacoinvasive approach for the patient who cannot be treated with primary PCI within 120 minutes.

**Rescue PCI**

Rescue PCI is the mechanical reopening of an infarct artery after unsuccessful fibrinolytic therapy. Rescue PCI is differentiated from facilitated PCI in that rescue PCI is generally not planned. With current fibrinolytic therapy, successful reperfusion (TIMI grade 3 flow) is achieved in only 50% to 70% of patients. Consequently, almost half of patients who undergo fibrinolytic therapy may be candidates for rescue PCI.

In the initial experience with rescue PCI, procedural outcomes were often suboptimal, but with the introduction of stents and P2Y$_{12}$ inhibitors, procedural outcomes have improved, and several randomized trials documented improved outcomes with rescue PCI. The RESCUE (Randomized Evaluation of Salvage Angioplasty With Combined Utilization of Endpoints) trial investigators randomized 151 patients with anterior wall MI treated with fibrinolytic therapy who had an occluded infarct artery within 8 hours of symptom onset to rescue PCI versus conservative care. The rescue PCI group had a lower composite event rate of death or congestive heart failure and better exercise left ventricular ejection fraction (43% vs 38%; $P = .04$). These benefits occurred despite the fact that stents were not yet available and despite, what the authors felt, was a strong investigator bias not to randomize patients presenting very early after MI. The MERLIN (Middlesbrough Early Revascularization to Limit Infarction) trial investigators randomized patients with STEMI and failed thrombolysis (<50% ST-segment resolution at 60 minutes) to rescue PCI versus conservative care. There was no difference in 30-day mortality (the primary end point), but event-free survival was better with rescue PCI ($P = .02$). The REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial randomized patients with STEMI and failed fibrinolysis (<50% ST-segment resolution at 90 minutes) to rescue PCI, repeat fibrinolysis, or conservative care. Patients treated with rescue PCI had a lower incidence of the composite end point (death, reinfarction, stroke, or heart failure) than patients treated with either repeat fibrinolytic therapy or conservative care. The problem with a rescue strategy is that it is frequently challenging to determine which patient has successful reperfusion, and this leads to inherent delay. Unfortunately, in real life, only 11% to 35% of patients in need of rescue PCI actually receive it.
DETECTION OF FAILED THROMBOLYSIS

A major limitation of the rescue PCI approach is the lack of a reliable noninvasive method to detect reperfusion after thrombolytic therapy. The electrocardiogram is very specific in predicting patency of the infarct artery when there is complete (>70%) resolution of ST-segment elevation, but this occurs in only a minority of patients. In most patients, there is partial or no resolution of ST-segment elevation, and the patency status of the infarct artery is uncertain. Consequently, acute angiography is often required to determine infarct artery patency.

In summary, we have made remarkable progress in the treatment of STEMI by improving timely access to PCI. In 2016, patients who present to a PCI center should undergo PCI with a D2B time of ≤90 minutes, and patients from a non-PCI hospital should be transferred to a PCI hospital if they can be treated in ≤120 minutes.\textsuperscript{5,6} For patients beyond 120 minutes, it now appears that a pharmacoinvasive approach (fibrinolysis followed by PCI within 24 hours) is the best strategy, but the ideal regimen and timing of revascularization remain areas of controversy.\textsuperscript{30,39,48}

MANAGEMENT PATHWAY

Before Procedure

The electrocardiogram (ECG) is critical to establishing a diagnosis of STEMI and triggering a management cascade. Transmission of an ECG taken in the field by emergency medical services to a PCI-capable hospital can facilitate rapid mobilization of the catheterization laboratory, thereby reducing transit time through the emergency department and thereby overall D2B time. When primary PCI is planned for patients with known or suspected AMI, a limited history and physical examination should be performed to avoid delays in initiating the catheterization procedure. Patients are given 325 mg of soluble chewable aspirin, intravenous unfractionated heparin, and sublingual nitroglycerin and are transported promptly from the emergency department to
the catheterization laboratory. A P2Y<sub>12</sub> inhibitor should be given as soon as possible based on evidence from multiple trials, discussed later, since the rate of emergent CABG following primary PCI for STEMI is low.

**Procedural Considerations**

**Radial Versus Femoral Access**

Bleeding portends a worse prognosis in STEMI. Access site–related bleeding can be reduced via a radial approach. Evidence supporting better outcomes with radial catheterization comes from a 2015 meta-analysis of 4 large, contemporary, multicenter trials and trials of patients (n = 17,133) with acute coronary syndromes<sup>53-57</sup> (Fig. 37-10). Comparing radial with femoral access, the risk was lower in terms of major bleeding (relative risk [RR], 0.57; 95% confidence interval [CI], 0.37-0.88), death (RR, 0.73; 95% CI, 0.59-0.90), and major adverse cardiac events (MACE; RR, 0.86; 95% CI, 0.75-0.98). However, in certain clinical situations, such as a patient with cardiogenic shock or cardiac arrest, a transfemoral approach may be preferable to facilitate use of larger guide catheters and peripheral hemodynamic support devices that are not able to be delivered radially.

![FIGURE 37-10](image)

**FIGURE 37-10** Meta-analysis of pooled data from randomized studies showing the effect of radial versus femoral access approach on risk of major adverse cardiovascular event in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. (Reproduced from Karrowni W, Vyas A, Giacomino B, et al. Radial versus femoral access for primary percutaneous interventions in ST-segment elevation myocardial infarction patients: a meta-analysis of...
Aspiration Thrombectomy

Intracoronary thrombus is found in a significant proportion of patients with STEMI. Thrombus may obstruct distal blood flow and increases subsequent myocardial ischemia. Although aspiration thrombectomy may reduce thrombus burden, there is a lack of evidence to demonstrate a significant clinical benefit from routine use. The TOTAL (Randomized Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI Undergoing Primary PCI), TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia), and TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trials are the largest studies of manual thrombectomy in STEMI.  

In the TAPAS trial (n = 1071), the primary end point of a myocardial blush grade of 0 or 1 (defined as absent or minimal myocardial reperfusion, respectively) occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% of those in the conventional PCI group (P < .001). TAPAS showed a significant reduction in the rate of death from any cause at 1 year with thrombus aspiration, but this finding must be interpreted in the context of the trial being underpowered for hard clinical end points. In a 2013 meta-analysis of trials that included TAPAS but not TASTE or TOTAL (n = 3936), the risks of all-cause mortality (the primary end point) and MACE (a composite of death, MI, and target vessel revascularization) were lower with aspiration thrombectomy (risk ratio, 0.71; 95% CI, 0.51-0.99 vs 0.76; 95% CI, 0.63-0.92). However, limitations of the meta-analysis include the lack of inclusion of patient-level data and the inclusion of non-peer-reviewed trials. Subsequently, 2 much larger contemporary trials have shown no benefit.

In the TASTE trial (n = 7244), the primary end point of death from any cause at 30 days was similar in both groups (2.8% vs 3.0%, respectively; hazard ratio [HR], 0.61; 95% CI, 0.34-1.07). Similarly, there was no difference in mortality at 1 year (5.3% vs 5.6%, respectively; HR, 0.94; 95% CI, 0.78-1.15). Most recently, in the largest trial, TOTAL (n = 10,732), the primary outcome (a composite of cardiovascular death, recurrent MI,
cardiogenic shock, or New York Heart Association class IV heart failure within 180 days) occurred with similar frequency in both groups (347 vs 351 events, respectively; HR, 0.9; 95% CI, 0.85-1.15) among the 10,063 patients who underwent PCI. Stroke rates were higher at 30 days (33 vs 16 events; HR, 2.06; 95% CI, 1.13-3.75) and at 180 days in patients who received thrombectomy (52 vs 25 events; HR, 2.08; 95% CI, 1.29-3.35). The 2015 American College of Cardiology Foundation/American Heart Association/Society for Cardiac Angiography and Interventions focused update on primary PCI for patients with STEMI recommends against performing routine manual aspiration thrombectomy due to disparities in clinical data.

**Drug-Eluting Stents Versus Bare Metal Stents**

Drug-eluting stents (DESs) are generally preferred to bare metal stents (BMSs) for the majority of PCI procedures, due to reduced rates of restenosis and target vessel revascularization. In the era of first-generation DESs, rates of stent thrombosis were higher than with BMSs, and there was concern that this difference could be translated to patients with STEMI, in whom the risk of stent thrombosis is higher than in patients with stable disease due to higher platelet reactivity and a generalized proinflammatory state. However, the introduction of second-generation DESs has resulted in improved clinical outcomes and excellent clinical evidence to support the preferential use of DESs in STEMI. A 2013 comprehensive network meta-analysis of STEMI patients found that when comparing cobalt chromium everolimus-eluting stents (CoCr-EES) or phosphorylcholine polymer–based zotarolimus-eluting stents (PC-ZES) to BMS, the 1-year risk of cardiac death or MI was reduced (odds ratio [OR], 0.63; 95% CI, 0.42-0.92 vs 0.86; 95% CI, 0.50-1.49), the 1-year risk of target vessel revascularization was reduced (OR, 0.45; 95% CI, 0.29-0.66 vs 0.60; 95% CI, 0.34-1.05), and the 1-year risk of definite stent thrombosis was reduced (OR, 0.32; 95% CI, 0.11-0.78 vs 0.44; 95% CI, 0.12-1.79). There were trends toward lower 1-year rates of cardiac death or MI, definite stent thrombosis, and target vessel revascularization with CoCr-EES compared to PC-ZES (OR, 0.73; 95% CI, 0.40-1.30; OR, 0.72; 95% CI, 0.17-3.16; and OR, 0.74; 95% CI, 0.38-1.42, respectively; Fig. 37-11). Current evidence suggests the majority of patients with STEMI will benefit from a newer generation DES.
FIGURE 37-11 Meta-analysis for cardiac death (A) or myocardial infarction (MI) (B), definite stent thrombosis (C), and target vessel revascularization (TVR) (D). BMS, bare metal stent; CoCr EES, cobalt chromium everolimus-eluting stent; OR, odds ratio; PC-ZES, phosphorylcholine polymer-based zotarolimus-eluting stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent. (Reprinted from Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2013;62:496, Copyright © 2013, with permission from American College of Cardiology Foundation.)

Treatment of Nonculprit Lesions

Approximately 40% to 60% of patients presenting with STEMI have multivessel coronary artery disease with other nonculprit lesions that may be angiographically or physiologically significant. These patients are at greater risk of mortality and reinfarction than those with single-vessel disease. Observational studies, performed prior to the randomized trials and their meta-analyses, concluded that culprit-only PCI, as opposed to multivessel PCI, at the time of initial reperfusion led to better outcomes. However, when patients who were treated with staged PCI during the hospitalization were analyzed separately, short- and long-term outcomes favored multivessel revascularization compared with culprit-only strategy.

Eight published randomized trials of patients with multivessel disease, with DANAMI-3–PRIMULTI (Primary PCI in Multivessel Disease), PRAMI (Preventive Angioplasty in Acute Myocardial Infarction), and CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial) being the 3 largest, have compared culprit-only with complete revascularization. A 2015 meta-analysis of 7 randomized trials with 1303 patients (excluding DANAMI-3–PRIMULTI) reported that, at a median follow-up of 12 months, complete revascularization at the time of primary PCI reduced the odds of MACE (death, recurrent MI, and repeat revascularization; OR, 0.59; 95% CI, 0.36-0.97), driven principally by a reduction in recurrent MI (OR, 0.48) and repeat revascularization (OR, 0.51; Fig. 37-12). Furthermore, complete revascularization was associated with a nonsignificant trend toward reduced cardiovascular mortality (OR, 0.54; 95% CI, 0.26-1.10). However, questions remain as to the optimal timing of complete revascularization, value of fractional flow reserve (FFR) in the acute setting, and approach to chronic
total occlusions. In the absence of compelling evidence, a reasonable approach would involve complete revascularization in the same hospital admission, FFR of any intermediate lesions at a separate time from the index procedure, and intervention on chronic total occlusions where the occluded vessel subtends a large area of viable myocardium.

![Table and Figure](image)

**FIGURE 37-12** Analysis of the primary end point of MACE: (A) summary odds ratios (ORs) with confidence intervals (CIs) and (B) summary rate ratios with CIs adjusted for differences in follow-up duration between studies. CvLPRIT, Complete Versus Lesion-Only Primary PCI Trial; HELP AMI, Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction; MACE, major adverse cardiac events; MV-PCI, multivessel percutaneous coronary intervention; PRAMI, Preventive Angioplasty in Acute Myocardial Infarction. (Reproduced from Kowalewski M, Schulze V, Berti S, et al. Complete revascularisation in ST-elevation myocardial infarction and multivessel disease: meta-analysis of randomised controlled trials. *Heart*. 2015;101(16):1309-1317, Copyright © 2015, with permission from BMJ Publishing Group Ltd.)

**Complications**
No Reflow

No reflow (TIMI grade 0-1 flow) or slow reflow (TIMI grade 2 flow) may occur transiently or may persist after primary PCI for AMI in 10% to 25% of patients. This is generally due to microvascular dysfunction from spasm, distal embolization, or endothelial injury and is associated with poorer recovery of left ventricular function and a higher incidence of post-MI complications\(^\text{75}\) (Fig. 37-13). When slow reflow or no reflow occurs, TIMI grade 3 flow usually can be reestablished with the use of intracoronary verapamil (100-200 μg boluses), adenosine (10-20 μg boluses), nicardipine (200 μg boluses), or nitroprusside (50-100 μg boluses) given through the guiding catheter, an infusion catheter, or the distal lumen of the balloon catheter (for no reflow).\(^\text{76}\) The no-reflow phenomenon may sometimes be prevented by early administration of antiplatelet agents or by preadministration of adenosine or verapamil.\(^\text{77}\) Caution should be used in stenting lesions with no reflow, because poor run-off may increase the likelihood of stent thrombosis.
Cardiogenic Shock

The mortality of patients with STEMI complicated by cardiogenic shock approaches 50%. In addition to standard care measures for routine STEMI, prompt treatment of hypotension and resulting hypoperfusion is essential. Pharmacologic and mechanical means of circulatory support are available to maintain coronary perfusion and ultimately vital organ perfusion. Although the question of the optimal inotropic agent is controversial, in most cases, a vasopressor agent such as norepinephrine is the preferred first-line agent. Mechanical support options in the acute setting include intra-aortic balloon pump and percutaneous left ventricular assist devices (Impella, Abiomed, Danvers, MA; Tandem Heart, CardiacAssist, Pittsburg, PA). In the
subacute setting, percutaneous cardiopulmonary bypass with extracorporeal membranous oxygenation or surgically implanted left ventricular/biventricular assist devices may provide a bridge to recovery or further therapy.\textsuperscript{78}

**ADJUNCTIVE PHARMACOLOGIC THERAPY**

**Antiplatelets**

**Dual Antiplatelet Therapy**

Aspirin should be given immediately with a loading dose of 162 to 325 mg. Ideally, the first tablet should be chewed or crushed to rapidly establish an effective plasma concentration.

A platelet P2Y\textsubscript{12} receptor blocker (clopidogrel, prasugrel, or ticagrelor) should be given to all patients with STEMI, irrespective of treatment strategy. Benefits of P2Y\textsubscript{12} inhibitor therapy were first shown in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial\textsuperscript{79} in patients treated with a clopidogrel. Prasugrel and ticagrelor are newer oral antiplatelet agents that inhibit platelet aggregation more rapidly with greater potency than clopidogrel.\textsuperscript{79} Prasugrel was compared to clopidogrel in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel)–TIMI-38 trial of 13,608 moderate- to high-risk acute coronary syndrome patients undergoing PCI, including 3534 with STEMI.\textsuperscript{80} Prasugrel was given with a loading dose of 60 mg and maintenance dose of 10 mg/d, whereas clopidogrel was given with a 300-mg loading dose and a 75-mg/d maintenance dose (current guideline recommendations are for a clopidogrel loading dose of 600 mg). The primary efficacy end point of cardiovascular death, nonfatal MI, or nonfatal stroke occurred significantly less often in patients treated with prasugrel at 15-month follow-up (10% vs 12.4%; HR, 0.79; 95% CI, 0.65-0.97), driven primarily by a significant reduction in nonfatal MI (7.4% vs 9.7%). In the STEMI subgroup, there was no significant difference in the rate of major
bleeding (TIMI) unrelated to CABG at 30 days (HR, 1.11; 95% CI, 0.70-1.77), although the overall trial population did have a significantly increased risk of bleeding and transfusion requirements. In addition, the rate of definite or probable stent thrombosis was significantly reduced in the prasugrel group (1.6% vs 2.8%; \( P < .001 \)).

Ticagrelor was compared to clopidogrel in over 18,000 ACS patients in the PLATO (Platelet Inhibition and Patient Outcomes) trial, 38% of whom had STEMI with intended PCI. Patients were randomly assigned to ticagrelor 180 mg loading dose followed by 90 mg twice daily or clopidogrel 300 mg loading dose followed by 75 mg daily. As in the entire cohort of acute coronary syndrome patients, the primary end point (MI, stroke, or cardiovascular death) occurred less often with ticagrelor (9.4% vs 10.8%). There was no significant difference in the rate of non–CABG-related TIMI major bleeding between ticagrelor and clopidogrel in the subgroup of patients with STEMI (HR, 1.09; 95% CI, 0.80-1.48), although the overall trial population did experience a modest increase in non–CABG-related bleeding (HR, 1.25; \( P = .03 \)). Unfortunately, there are limited data that directly compare P2Y\(_{12}\) inhibitors in STEMI patients. A recent network meta-analysis of 37 studies including 88,402 patients indicates the strongest data are with prasugrel, but the presence of a black box warning regarding use in patients with previous cerebrovascular accident is a limitation (Fig. 37-14).
FIGURE 37-14 Meta-analysis results of major adverse cardiac events (MACE) between prasugrel with other P2Y$_{12}$ inhibitors stratifying studies by (A) randomized
trials only, (B) transradial (TR) access used ≥50%, (C) bivalirudin use ≥50%, (D) bivalirudin use <50%, (E) glycoprotein IIb/IIIa inhibitors (GPI) use ≥50%, (F) GPI use <50%, (G) drug-eluting stent (DES) use ≥50%, and (H) bare metal stent (BMS) use ≥50% patients. (Reproduced from Rafique AM, Nayyar P, Wang TY, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a network meta-analysis. *JACC Cardiovasc Interv*. 2016;9(10):1036-1046.)

Finally, cangrelor, an intravenous P2Y₁₂ inhibitor, has been recently approved based on the reduction of the primary end point of a composite of MI, ischemia-driven revascularization, and death at 48 hours in the CHAMPION-PHOENIX (Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention) trial.⁸⁴,⁸⁵ Cangrelor has the advantage of immediate onset with a very short half-life and consistent pharmacokinetics and may be particularly useful in patients with STEMI.

### Glycoprotein IIB/IIIa Inhibitors

The majority of trials favoring glycoprotein IIb/IIIa inhibitors to placebo were performed prior to the routine use of P2Y₁₂ inhibitors, particularly the more novel and effective platelet inhibitors such as prasugrel and ticagrelor. Evidence supporting the use of abciximab in patients with STEMI undergoing primary PCI with either balloon angioplasty or stenting who are not pretreated with a P2Y₁₂ inhibitor comes from a meta-analysis of over 27,000 patients in 11 trials that found that abciximab, compared to placebo, significantly lowered the rate of death at 30 days (2.4% vs 3.4%; OR, 0.68; 95% CI, 0.47-0.99).⁸⁶ There is less evidence of benefit from either tirofiban or eptifibatide.⁸⁷,⁸⁸ In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trials with P2Y₁₂ inhibitor loading, bivalirudin was generally superior to heparin plus glycoprotein IIb/IIIa inhibition.⁸⁹,⁹⁰ The BRIGHT (Bivalirudin in Acute Myocardial Infarction Versus Glycoprotein IIb/IIIa and Heparin Trial) study showed no benefit of adding glycoprotein inhibition to unfractionated heparin.⁹¹

However, some patients, such as those with significant thrombus burden
or persistent no reflow at time of PCI, may benefit from glycoprotein IIb/IIIa inhibitor.

Although there are no head-to-head trials for direct comparison, data from small randomized trials with surrogate end points and from observational studies suggest equivalent efficacy among abciximab, tirofiban, and eptifibatide.\textsuperscript{92}

\textbf{Anticoagulation}

\textbf{Heparin}

Intravenous unfractionated heparin is given immediately prior to and during the procedure to prevent acute vessel closure due to thrombosis. Dose adjustment and monitoring are usually performed via serial checks of the activated clotting time (ACT). Careful monitoring of the ACT is important because some patients have persistent thrombin activity despite heparin therapy.

\textbf{Bivalirudin}

A number of large trials (HORIZONS-AMI, EUROMAX, HEAT PPCI [How Effective Are Antithrombotic Therapies in Primary PCI], BRIGHT, and MATRIX) have examined the effectiveness of bivalirudin in the AMI setting, usually compared to heparin alone or, in some cases, heparin plus a glycoprotein IIb/IIIa inhibitor.\textsuperscript{89-91,93-96} A 2014 meta-analysis (published before MATRIX) of 16 trials involving nearly 34,000 patients (the majority with an acute coronary syndrome)\textsuperscript{90} found that when compared to heparin, bivalirudin was associated with an increase in the risk of the primary composite outcome of death, MI, ischemia-driven revascularization, and stent thrombosis at 30 days (risk ratio, 1.09; 95\% CI, 1.01-1.17). All components of the composite were increased except death. Bivalirudin was associated with an increase in the risk of stent thrombosis (risk ratio, 1.38; 95\% CI, 1.09-1.74), with most events being acute. Favoring bivalirudin was a decrease in the overall risk of major bleeding (risk ratio, 0.53; 95\% CI, 0.47-0.61; \(P < .0001\)), although this was compared to heparin plus glycoprotein IIb/IIIa inhibitor. However, when considering studies in which glycoprotein
IIb/IIIa inhibitor use was planned in both arms, there was no difference (risk ratio, 1.07; 95% CI, 0.87-1.31). In contrast, a recent comprehensive analysis of all the available data suggests a significant reduction in bleeding with or without glycoprotein IIb/IIIa inhibitors (Fig. 37-15A). Overall event rates are similar, but there was a significant reduction in mortality in both HORIZONS-AMI and MATRIX-STEMI with bivalirudin (Fig. 37-15B). The HEAT trial was an outlier in that it was a single-center trial with only a brief infusion of bivalirudin and no pretreatment with a P2Y$_{12}$ inhibitor. In summary, the optimal antithrombin regimen will continue to be an area of controversy. Although overall the data appear to support the use of bivalirudin, the significantly higher cost compared to heparin also impacts the decision.
FIGURE 37-15 A. Comparison of major bleeding rates at 30 days between bivalirudin and heparin in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) across major randomized controlled trials (RCTs). Note: Only significant P values (<.05) are shown in the figure. P values for the remaining comparisons are not statistically significant.
Bival, bivalirudin; GPI, glycoprotein IIb/IIIa inhibitor; UFH, unfractionated heparin. **B. Comparison of all-cause mortality at 30 days between bivalirudin and heparin in STEMI patients undergoing primary PCI across major RCTs.** Note: Only significant *P* values (<.05) are shown in the figure. *P* values for the remaining comparisons are not statistically significant.

**CONCLUSION**

In summary, over the past 2 decades, we have made remarkable progress in the treatment of STEMI through improvements in adjunctive pharmacology and stent technology but primarily by producing timely access to PCI. Still, there are opportunities to improve outcomes even further, in particular with transfer from non-PCI centers and treatment of multivessel disease as well as improvements in the care of patients with cardiogenic shock and out-of-hospital cardiac arrest.

**REFERENCES**


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MULTIPLE CHOICE QUESTIONS

1. Which of the following is the most appropriate management strategy for a patient presenting 180 minutes following the onset of symptoms to a non–percutaneous coronary intervention (PCI)–capable hospital located 60 minutes away from a PCI-capable hospital?
   A. Immediate transfer to a PCI-capable hospital
   B. Fibrinolysis
   C. Facilitated PCI
   D. Fibrinolysis with rescue PCI as indicated

2. Which of the following has not been demonstrated to be an advantage of a radial compared to a femoral approach in STEMI?
   A. Reduced rate of stroke
   B. Reduced rate of death
   C. Reduced rate of major adverse cardiac events (MACE)
   D. Reduced rate of bleeding

3. Which of the following drugs has not been shown to be effective for treatment of no-reflow phenomenon?
   A. Adenosine
B. Verapamil  
C. Nitroprusside  
D. Lignocaine

4. Which of the following antiplatelet agents is least appropriate for a patient with a prior history of stroke?  
   A. Clopidogrel  
   B. Ticagrelor  
   C. Prasugrel  
   D. Aspirin

5. Which of the following P2Y$_{12}$ inhibitors can be administered intravenously?  
   A. Prasugrel  
   B. Clopidogrel  
   C. Ticagrelor  
   D. Cangrelor

**ANSWERS**

1. A

   The results from randomized trials indicate that outcomes are better when patients with ST-segment elevation myocardial infarction (STEMI) who present to non-PCI hospitals are transferred to a PCI facility for primary PCI compared with being given fibrinolytic therapy at the local hospital. Current guidelines recommend the door-to-balloon (D2B) time be ≤90 minutes for patients presenting to a PCI facility and ≤120 minutes for patients transferred from a non-PCI facility. Currently, guidelines recommend that patients with cardiogenic shock, patients who are ineligible for fibrinolytic therapy, and patients who can be treated within 120 minutes be transferred for primary PCI.

2. A

   Evidence supporting better outcomes with radial catheterization comes from a 2015 meta-analysis of 4 large, contemporary, multicenter trials and trials of
patients. Comparing radial with femoral access, the risk was lower in terms of major bleeding (relative risk [RR], 0.57; 95% confidence interval [CI], 0.37-0.88), death (RR, 0.73; 95% CI, 0.59-0.90), and MACE (RR, 0.86; 95% CI, 0.75-0.98).

3. D

No reflow is generally due to microvascular dysfunction from spasm, distal embolization, or endothelial injury. No reflow usually can be reestablished with the use of intracoronary verapamil, adenosine, nicardipine, or nitroprusside given through the guiding catheter or an infusion catheter or the distal lumen of the balloon catheter.

4. C

Unfortunately, there are limited data that directly compare P2Y₁₂ inhibitors in STEMI patients. However, a recent network meta-analysis of 37 studies including 88,402 patients indicates the strongest data are with prasugrel, but the presence of a black box warning regarding use in patients with previous cerebrovascular accident is a limitation.

5. D

Cangrelor, an intravenous P2Y₁₂ inhibitor, has been recently approved based on the reduction of the primary end point of a composite of myocardial infarction, ischemia-driven revascularization, and death at 48 hours in the CHAMPION-PHOENIX trial. Cangrelor has the advantage of immediate onset with a very short half-life and consistent pharmacokinetics and may be particularly useful in patients with STEMI.
INTERVENTION FOR BIFURCATION LESIONS

Bifurcation lesions have been reported to constitute 15% to 20% of all percutaneous coronary interventions (PCI). Since they are associated with an increased risk of procedure-related complication, especially side branch (SB) occlusion after stent implantation, treating these distinct lesion subsets has been a significant challenge for interventional cardiologists. Rapid advancements in novel techniques, devices, and adjunctive pharmacotherapies have considerably reduced the risk of acute complications, restenosis, and stent thrombosis (ST), and ultimately have led to the extension of PCI’s clinical application for various complex bifurcation lesions. Moreover, interventional cardiologists have learned lessons from extensive clinical experiences in that many important anatomic features, including relative plaque distribution to the bifurcation, degree of SB angulation, and severity or length of SB lesion, should be taken into account.
for technical success and favorable clinical outcome.\(^2\) Considering that currently there are no clear guidelines to address the use of particular interventional techniques with regard to the specific anatomy of a given bifurcation lesion, every effort should be made to obtain understanding of the technical, clinical, and fundamental aspects of the management of bifurcation disease.

**Definition and Classification of Bifurcation Lesions**

According to the consensus of the European Bifurcation Club, bifurcation coronary lesion can be defined as “a coronary artery narrowing occurring at, or adjacent to, a significant division of a major epicardial coronary artery.” A “significant SB” is a branch that the operator does not want to lose in a global context of a particular patient (e.g., symptoms, comorbidity, diameter and length of SB, size of the myocardial mass supplied by the SB, location of ischemia, viability of the supplied myocardium, collateralizing vessel, left ventricular function, results of functional tests).\(^3\)

Although several classification systems of bifurcation lesions have been proposed to facilitate PCI, planning the treatment approach according to the angulation of the bifurcation and the degree of plaque burden seems to be most practical (Fig. 38-1). The Y-shaped lesion is defined when the SB and the main vessel (MV) angulation is less than 70%, while that of the T-shaped lesion is greater than 70%. In general, the risk of atheromatous plaque shifting (snow-plow effect) and deterioration of SB flow during stent implantation is higher in Y-shaped lesions. Furthermore, it is technically difficult to achieve the whole coverage of the SB ostium using popular T-stenting in these lesions. Although the risk of SB occlusion is relatively low in T-shaped lesions, wire access can be problematic when large plaque burden is present at a significant SB ostium. The location of stenosis in each of the 3 segments that constitute the bifurcation is also crucial for the treatment strategy, and 7 lesion types, with each type assumed to be associated with a specific treatment technique, have been described in the Medina classification, the simplest and most widely used classification system\(^4\) (Fig. 38-2).
FIGURE 38-1 Lesion description according to the angle between the main vessel and side branch (SB).

- T-shape
  - Difficult SB access
  - Less plaque shifting
  - T-stenting better

- Y-shape
  - Easier SB access
  - More plaque shifting
  - Culotte or crush better
The Medina classification for bifurcation lesions. The designation “1” indicates the presence of stenosis (diameter stenosis ≥50% by visual estimation), and “0” indicates the absence of stenosis. MV, main vessel; SB, side branch.

**One-Stent Simple Crossover Technique**

The most frequently used approach to treat a bifurcation lesion is to place a stent in the MV while covering the ostium of the SB with the stent (Fig. 38-3). Although this treatment strategy may be very useful in lesions involving a normal SB ostium, it can be used after the predilation in lesions with SB ostial stenosis. In case of significant flow limitation to the SB after MV stenting, further treatment of the SB with a balloon or additional stent (provisional stenting) may be performed. In contrast, even if the diameter stenosis of the SB is up to 70% to 80% after MV stenting, the long-term patency and clinical outcome are usually excellent if the stenosis is confined
to the ostium and the flow is not impaired. Therefore, treating such lesions with stent implantation is not recommended.

FIGURE 38-3 Single-stent implantation covering the side branch. Stent implantation in the main vessel (B) is performed with double-wire technique (A). After retrieval of the wire from the side branch, a new wire is inserted into the side branch through the stent strut. Thereafter, optional kissing balloon dilation can be performed (C and D).

Since SB compromise occurs to some extent unpredictably, a decision to protect the SB by placing a wire to be left in until the procedure on the MV has been completed, including high-pressure postdilation, should be made carefully. In general, an SB <2.0 mm in diameter and supplying a small amount of viable myocardium is rarely considered for protection, whereas relatively large SBs (≥2.5 mm in diameter) with an ostial diameter stenosis ≥50% need to be considered for protection in case of further specific treatment. The jailed wire in the SB can act as a marker of the occluded SB and straighten the angle between the SB and the MV to facilitate further access. In the provisional technique, rewiring through the distal strut (close to the carina) following the MV stenting is strongly recommended since it creates better SB scaffolding compared with the proximal wire crossing.

One- and Two-Stent Techniques: Clinical Trials in the Drug-Eluting Stent Era

The sirolimus-eluting stent bifurcation study was the first randomized trial that was conducted to assess the feasibility and safety of drug-eluting stent
(DES) implantation for bifurcation lesions. In this study, 22 of the 43 patients who were randomly assigned to the strategy of single stent implantation in the MV with balloon angioplasty for the SB (group B) were crossed over to the strategy of T-stenting in both branches with 2 stents (group A) due to flow impairment or >50% residual diameter stenosis in the SB after stent implantation into the MV. Overall, 63 patients were treated with 2 stents, and 22 patients were treated with 1 stent. Although the high crossover rate (51.2%) made it difficult to directly compare the 2 groups, the in-segment restenosis rate at 6 months did not differ significantly between the 2 treatment groups (28.0% in group A vs 18.7% in group B; \( P = .53 \)). The researchers in this study postulated that the relatively high restenosis rate at the SB in the 2-stent technique group was caused by the incomplete coverage of the ostium of the SB since T-stenting may leave a gap between the 2 stents at the bifurcation. To address this problem, other bifurcation stenting techniques have been introduced. In the Nordic Bifurcation Trial (NORDIC), the investigators randomized 413 patients with complex lesions to MV-only stenting (n = 207) versus MV and SB stenting using crush, culotte, Y, or other techniques (n = 206) with sirolimus-coated stents. In the MV-only treatment arm, the threshold for crossover to SB stenting was high and was allowed only if the Thrombolysis in Myocardial Infarction (TIMI) flow grade was 0 following SB dilation. Overall, only 4.4% of the patients in the MV-only stenting group received a stent in the SB. The combined rate of MV restenosis (stenosis >50% in diameter) and SB occlusion after 8 months was low and similar in both the provisional and routine 2-stented groups (5.3% vs 5.1%; \( P = \text{not significant} \)). Long-term results of the Nordic Bifurcation Study were recently published and showed comparable incidences of all-cause mortality (5.9% vs 10.4%; \( P = .16 \)), non–procedure-related myocardial infarction (MI; 4% vs 7.9%; \( P = .09 \)), target vessel revascularization (TVR; 13.4% vs 18.3%; \( P = .14 \)), and definite ST (3% vs 1.5%; \( P = .32 \)) over 5 years between the 1-stent (n = 202) and 2-stent (n = 202) approaches. The investigators therefore concluded that excellent clinical and angiographic results appeared to be obtained with the percutaneous treatment of de novo coronary artery bifurcation lesions, independent of the stenting strategy that was used. However, the 1-stent strategy was associated with reduced procedure and fluoroscopy times and lower rates of procedure-related biomarker elevation.

The BBC ONE (British Bifurcation Coronary Study: Old, New, and
Evolving Strategies) study further provided evidence for the preference of 1-stent technique for bifurcations. A total of 500 patients were randomized either to a simple or a complex stenting strategy (crush or culotte) using paclitaxel-eluting stents. At 9 months of clinical follow-up, there was a significant difference between the 2 groups in terms of the primary end point (a composite of death, MI, and target vessel failure; 8.0% in the simple group vs 15.2% in the complex group; hazard ratio [HR], 2.02; 95% confidence interval [CI], 1.17-3.47; \( P = .009 \)), MI (3.6% vs 11.2%; \( P = .001 \)), and inhospital major adverse cardiovascular events (MACE; 2.0% vs 8.0%; \( P = .002 \)). A meta-analysis of previous randomized studies demonstrated that a provisional 1-stent approach was comparable to a 2-stent approach in terms of mortality, repeat revascularization, and quality of life. However, the 1-stent technique was superior in regard to the risk of periprocedural MI and ST. Based on these studies, the 1-stent technique with provisional SB stenting is currently recommended as the primary approach for most bifurcation coronary lesions. However, it should be noted that the results of the randomized studies are limited in generalizability due to selective inclusion criteria. Because the aforementioned randomized studies could not include all patients with bifurcations, patients with complex anatomies who may have potentially benefited from the 2-stent approach might have been excluded in enrollment. Moreover, a lack of enough experience in 2-stent techniques across operators might have inflated the risk of adverse events for patients.

The 2-stent approach in provisional or planned situations is still a viable option for a minority of patients who have complex true bifurcations. In 1170 true bifurcation lesions from the Coronary Bifurcation Stenting (COBIS) registry, 17.3% of lesions were treated with 2-stent approaches. The types of 2-stent approaches were T-stenting (47.8%), crush technique (34.1%), V-stenting (14.7%), and culotte stenting (3.4%). There were no differences in the rates of death, MI, target lesion revascularization (TLR), and their composite of MACE. Even in the randomized studies, for patients assigned to a 1-stent approach, a 2-stent technique was eventually performed in 3.5% of patients from the NORDIC and BBC ONE studies and 31% from the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study by the operators’ decision. In the recently updated randomized Optimal Stenting Strategy for True Bifurcation Lesions (PERFECT) trial, 28.2% of patients with true bifurcation lesions who
were randomized to 1-stent approach eventually received SB stenting. The 2-stent approach can be attempted for bifurcation lesions if the operator is concerned about the acute complications, including hemodynamic compromise or periprocedural MI in the circumstances of SB loss. In the COBIS registry, SB occlusion occurred in 8.4% of 2227 bifurcation lesions after MV stenting during 1-stent treatment. Preprocedural percent diameter stenosis of the SB (≥50%) and SB lesion length were independent predictors of SB occlusion, with odds ratios of 2.34 and 1.03, respectively. Moreover, SB occlusion was associated with an increase in the adjusted HR of 2.34 (95% CI, 1.15-4.77; \( P = .02 \)) for the composite of cardiac death or MI and 6.19 (95% CI, 2.00-19.13; \( P = .002 \)) for ST. In the PERFECT randomized trial, patients treated with provisional SB stenting experienced greater procedural time and contrast amount than the planned 2-stent approach. These findings indicate that bifurcations with complex SB stenosis, which are expected to be compromised or occluded during the 1-stent approach based on angiography with or without intravascular ultrasound (IVUS), may be an indication for a planned 2-stent approach. In general, if the SB is large enough (reference diameter ≥2.5 mm), has significant stenosis extending beyond the ostium (10-20 mm or more), supplies sufficient size of the territory to justify stent implantation, and/or has an unfavorable angle for recrossing after MV stenting, the 2-stent technique can be considered.

Two-Stent Techniques

Current 2-stent techniques using DES include culotte, crush and its variants, T-stenting, and V-stenting or simultaneous kissing stent (SKS) techniques. Classic crush is now rarely performed, and variants of the crush technique, such as mini-crush, step crush, and double kissing (DK) crush techniques, are preferred. The potential advantages and disadvantages of each technique are summarized in Table 38-1. Because of lack of studies on the comparative outcomes of diverse 2-stent techniques, selection of proper stenting technique should be dependent on the patient’s clinical manifestation, bifurcation morphology, and operator’s preference. In the same context, since the favorable outcome is more related to the successful procedure itself, not with the type of 2-stent technique, a careful angiographic evaluation is required to identify disease severity, vessel size, and the angle of both branches before the treatment of bifurcation lesions with 2-stent technique.
### T-Stenting Technique

The technique of T-stenting is better suited to treat the SBs that originate with an angle close to 90°. The deployment of 2 stents in the SB and the MV can be performed in different steps. Since this method is most frequently used for provisional SB stenting, the majority of T-stenting is performed with MV stenting first. However, with the intention to treat with a 2-stent technique at the beginning, initial deployment of the SB stent is preferred to avoid re-crossing the stent strut in the MV (Fig. 38-4). The technique is safe and eliminates the difficulty of advancing the second stent. However, this strategy may carry the risk of incomplete coverage of the SB ostium. This small gap between the stent implanted in the MV and the one implanted in the SB may result in an uneven distribution of the drug, which leads to late restenosis at the SB ostium (Fig. 38-5).
technique is a modification of the T-stenting technique to overcome this limitation and is based on an intentional minimal protrusion (1-2 mm) of the SB stent within the MV.\textsuperscript{21}

**FIGURE 38-4** T-stenting technique. The first stent is advanced into the side branch, and a second stent is advanced into the main vessel covering the ostium of the side branch (A). The first stent is carefully positioned right at the ostium of the side branch or slightly within the main vessel and dilated (B). The balloon and wire are removed from the side branch, and then the stent in the main vessel is deployed (C). The side branch is rewired, and kissing balloon dilation of both branches can be performed (D).

**FIGURE 38-5** Limitation of T-stenting technique. A. Restenosis was most frequent at the junction between the 2 implanted stent (from SIRIUS bifurcation study). B. To prevent the potential gap at the ostial side branch, the first stent should cover the
The culotte technique can be a suitable approach when there is small discrepancy in vessel size between the proximal MV segment and SB (Fig. 38-6). This technique provides full coverage of the bifurcation at the expense of an excess of metal component in the proximal MV. The culotte technique is very useful for all angles of bifurcation lesions and can be applied either in the provisional SB stenting strategy or planned 2-stent technique. The more angulated branch is usually stented first. However, if predilation results in a dissection or occlusion in 1 branch, this branch should be stented first in case of the difficulty of rewiring through the stent struts. It is advisable to make minimal overlap of stents in proximal MV segment whenever possible.

**FIGURE 38-6** Culotte technique. After predilation (A), the wire is removed from the straighter branch and the more angulated branch is stented (B). After removing the wire from the stented branch, a wire is recrossed through the stent strut. The stent strut should be dilated toward the nonstented branch. A second stent is advanced and expanded into the nonstented branch (C). Finally, the first stented branch is rewired, and final kissing balloon inflation is performed (D).

**Crush Technique**

Crush technique is the most widely used 2-stent technique. Despite the complex procedural steps, this technique can be applied to any true
bifurcations requiring a 2-stent technique with complete lesion coverage for SB ostium (Figs. 38-7 and 38-8). Because of some limitations of the classic crush technique, its variants, such as mini-crush, step crush, or DK crush, are preferred. The mini-crush technique is recommended over classic crush to avoid the large area of 3 strut layers in the proximal MV. Using the step crush technique, in which the SB stent strut is crushed by MV balloon instead of stent, separate manipulation of 2 stents is possible and allows precise placement of each stent using 6-Fr guiding catheter (Fig. 38-9). The DK crush technique may aid rewiring into the SB after MV stenting and also increases the expanded stent cell area in front of the SB detectable at follow-up. In any crush techniques, final kissing balloon inflation (FKI) is mandatory because it allows better strut contact against the ostium of the SB and better drug delivery. FKI may also correct the stent deformation and ensure optimal stent scaffolding. As compared with the culotte technique, the mini-crush technique showed similar incidence of MACE (composite of death, MI, TVR, or ST) at 6 months (4.3% for crush vs 3.7% for culotte; \( P = .87 \)) in the NORDIC II randomized study. However, a recent DKCRUSH-III randomized study showed that DK crush (n = 210) was superior to the culotte technique (n = 209) in terms of 1-year MACE including death, MI, and TVR for unprotected distal left main (LM) bifurcation stenosis (6.2% vs 16.3%; \( P = .001 \)).

**FIGURE 38-7** Crush technique. A first stent is advanced into the side branch but not expanded, and a second stent is advanced into the main branch to fully cover the bifurcation (A). At this time, the proximal marker of the main vessel stent should be more proximal in the coronary tree than the proximal marker of the side branch stent. Assuring the appropriate position of the side branch stent, the balloon is
inflated and the stent is deployed (B). After stent implantation in the side branch, the delivery balloon and the wire are removed from the side branch. Then, the stent in the main branch is expanded, and the protruding struts from the side branch are crushed against the wall of the main vessel (C). (D) Final result after kissing balloon inflation.

FIGURE 38-8 Example of the crush technique. A and B. Baseline angiogram of a bifurcation lesion involving the left anterior descending artery (LAD) and a large diagonal branch. C and D. Predilation for each branch. E and F. Two stents are placed, with the stent in the LAD positioned more proximally than the stent in the diagonal branch. A side branch stent is deployed first following the main vessel stent implantation. G and H. Adjunctive poststenting balloon dilatation for each stent. I. Final kissing balloon inflation. J. Optimal final result.
FIGURE 38-9 Step crush technique. Similar to the standard crush technique, the stent in the side branch is deployed (A). The stent strut in the side branch is crushed by the main vessel balloon instead of the stent (B). The second stent is advanced in the main vessel and deployed (C). (D) Final result after kissing balloon inflation.

V-Stenting and SKS Technique

The V-stenting or SKS technique can be preferred for bifurcations with a large proximal MV such as LM stenosis.\textsuperscript{31,32} V-stenting is preferable for selected bifurcation lesions where the lesions are limited to the distal portion of the bifurcation and have a narrow angle (Fig. 38-10). If there is a proximal stenosis in the MV, the SKS technique is preferred (Fig. 38-11). Since the SKS technique has advantages of fast procedural time and no need of strut reopening, it may have potential benefit for hemodynamically unstable patients with large LM bifurcation stenosis. However, the risk of restenosis or ST may be relatively high compared with other techniques due to the formation of long metal carina; hence, the SKS technique is not recommended for routine 2-stent treatment.
FIGURE 38-10 V-stenting. After predilation of both branches, the 2 stents are positioned into the branches, with usually a slight protrusion of both stents in the main proximal vessel (A). Each stent is deployed alternatively. Final kissing balloon inflation is performed using the same pressure for both balloons (B and C).

FIGURE 38-11 Kissing stenting technique. Both branches are wired and dilated (A). The 2 unexpanded stents are positioned in bifurcation with parallel proximal stent edges (B). The stents are deployed alternately followed by the final kissing balloon inflation (C).

INTERVENTION FOR LEFT MAIN CORONARY ARTERY LESIONS

As a result of the long-term benefit of coronary artery bypass graft (CABG) surgery compared with medical therapy, CABG has been regarded as the standard therapy for unprotected left main coronary artery (LMCA)
However, because of easy anatomic accessibility and a relatively large vessel caliber, PCI for LMCA disease has become an attractive option for interventional cardiologists. In addition, technical advances in PCI and devices have emboldened physicians to test the feasibility of LMCA intervention and, coupled with the widespread availability of DESs, have led to a reevaluation of the role of PCI as a viable alternative treatment for unprotected LMCA disease. As a result, over the last decade, the prevalence of LMCA stenting has significantly increased worldwide. In addition, several recent large registries and randomized controlled trials have demonstrated that LMCA stenting yields comparable mortality and morbidity rates compared with CABG. This chapter will provide an overview of current techniques and contemporary outcomes of PCI with either bare metal stents (BMSs) or DESs.

**Assessment of Lesion Severity**

Clinically, significant LMCA disease has been found in 3% to 5% of all patients who undergo coronary angiography and in 10% to 30% of patients who undergo bypass surgery. Traditionally, angiographic diameter stenosis of 50% has been considered a cutoff for significant LMCA stenosis. However, conventional coronary angiogram is only a luminogram and has critical limitations in assessing lesion morphology and plaque characteristics. The LM trunk is often short in length and lacks a normal segment for comparison. In addition, contrast material in the aortic cusp sometimes obscures the ostium, and “streaming” of contrast may result in a false impression of luminal narrowing. As a result, marked discrepancy in interpretation of degree of stenosis of LMCA narrowing has been documented in several studies. Therefore, fractional flow reserve (FFR) and IVUS are often used to assess the severity of LMCA stenosis.

An FFR value of 0.75 to 0.80 or greater has been suggested to be a strong predictor of excellent survival and low event rates in patients with intermediate LMCA disease, making it a useful cutoff value to determine significant LMCA stenosis. In a study involving 213 patients with intermediate LMCA stenosis, 5-year survival rates of 138 patients treated medically with an FFR ≥0.80 and 75 patients treated surgically with an FFR <0.80 were 89.8% and 85.4%, respectively (\(P = .48\)). Several other studies...
using FFR cutoff values of 0.75 to 0.80 as a surrogate for revascularization showed similar outcomes, and as a result, FFR-guided decision making for the treatment of LMCA stenosis is generally accepted.\textsuperscript{55-58} Practically, the FFR of LMCA stenosis should be interpreted with caution because isolated LMCA disease is rare, with most stenosis associated with disease in the left anterior descending artery (LAD) and/or left circumflex artery (LCX), both of which tend to increase the FFR value measured across the LMCA stenosis. Therefore, in these situations, the functional significance of intermediate LMCA stenosis should be reassessed after the correction of distal coronary artery stenosis.\textsuperscript{59}

The IVUS-derived minimal lumen area (MLA) has frequently been used to determine the functional significance of intermediate LMCA stenosis, and traditionally, an MLA cutoff value of 6.0 mm$^2$ has been considered to represent functionally significant LMCA stenosis. This value was derived primarily from the Murray law, with an MLA of 4.0 mm$^2$ considered to represent the ischemic threshold of the LAD or LCX, and was supported by a clinical study conducted by Jasti et al.\textsuperscript{58} However, recent studies reported that the IVUS MLA value corresponding to ischemia-producing lesions of non-LM epicardial coronary arteries to be $<3$ mm$^2$, and application of the Murray law to these values suggests that the IVUS MLA of a stenotic LMCA should be $<5.0$ mm$^2$.\textsuperscript{60-62} Park et al\textsuperscript{63} attempted to determine the IVUS-derived MLA criteria corresponding to an FFR $<0.80$ in 112 patients with isolated intermediate LMCA stenosis who underwent preinterventional IVUS and FFR measurements. They found that the IVUS-derived MLA value within the LMCA that best predicted FFR $<0.80$ was $<4.5$ mm$^2$ (77% sensitivity, 82% specificity, 84% positive predictive value, and 75% negative predictive value; area under the curve, 0.83; 95% CI, 0.76-0.6; $P < .001$), which was similar to the theoretical cutoff of $<5.0$ mm$^2$. It is interesting to note that the positive predictive value of IVUS-measured MLA $<4.5$ mm$^2$ was acceptably high and the anatomic parameter provided by IVUS appeared to correlate well with functional significance of LMCA stenosis. Thus, in cases when FFR measurement is not feasible, IVUS-derived MLA criteria could possibly be used as a surrogate of functional significance of LMCA disease.

\textbf{Outcomes of Unprotected Left Main Intervention}
LMCA stenosis might be considered to be an attractive target for percutaneous intervention because of its large vessel size, short lesion length, and lack of tortuosity. Consequentially, LMCA intervention has been shown to be feasible and to have acceptable short- and mid-term outcomes in the BMS era. The ULTIMA registry enrolled 279 patients with unprotected LMCA stenosis who were treated with BMSs; 46% of the patients were inoperable or at high surgical risk. The in-hospital mortality rate was 13.7%, and the 1-year incidence of all-cause mortality was 24.2%. However, among the 32% of patients at relatively low risk (age <65 years, left ventricular ejection fraction >30%, and no shock), there were no periprocedural deaths, with a 1-year mortality rate of only 3.4%. Park and colleagues found that elective BMS stenting for LMCA bifurcation (n = 63) in highly selected patients with normal left ventricular ejection fraction and a large reference vessel might be safe and effective. In this report, the procedure was successful in all patients, and major in-hospital events did not occur in any patients. Moreover, no significant differences were noted in the rates of 2-year freedom from TLR among LMCA ostium, shaft, and bifurcation stenting (82%, 86%, and 85%, respectively). Several other studies also showed favorable short- or mid-term outcomes (in-hospital mortality, 0%-4.3%; mortality at 6-12 months, 2.5%-10.8%) in low-risk patients undergoing elective PCI using BMS for unprotected LMCA disease. However, considerable risk of restenosis (18%-31%) and repeat revascularization (7.3%-33.6%), which may lead to worst-case outcomes such as sudden death and acute MI, have limited the durability of LMCA stenting with BMSs. Therefore, LMCA stenting had to be reserved for selected patients who were not candidates for CABG or refused to receive CABG in the BMS era.

After the introduction of DESs, with a remarkable reduction of restenosis and repeat revascularization, PCI with DES has been widely performed for more complex clinical and anatomic subsets of LMCA disease. Although limited by their nonrandomized nature, small numbers of patients, and short follow-up periods, several early observational studies have shown promising outcomes after PCI using early-generation DES compared with BMS. Even after safety concerns regarding very late ST associated with early-generation DES, physicians’ threshold for performing PCI at the LMCA became less restrictive, and the worldwide frequency of LMCA stenting started to sharply increase. In a subsequent meta-analysis comparing
outcomes for DES and BMS after LMCA stenting, a total of 44 studies including 10,342 patients who received a DES or BMS were analyzed. The respective (DES vs BMS) cumulative event rates at 3 years were 8.8% and 12.7% for death, 4.0% and 3.4% for MI, 8.0% and 16.4% for TVR/TLR, and 21.4% and 31.6% for MACE. Adjusted outcomes at 3 years favored DES, including the reduction of mortality.

Regarding the differential benefit of DES for the prevention of restenosis, the 2 most widely applicable first-generation DESs (sirolimus- and paclitaxel-eluting stents) were evaluated in previous studies. An early study comparing the 2 DESs from a RESEARCH registry showed a comparable incidence of MACE, with a rate of 25% for sirolimus-eluting stents (n = 55) and 29% for paclitaxel-eluting stents (n = 55). The ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) study compared 305 patients receiving sirolimus-eluting stents and 302 patients receiving paclitaxel-eluting stents using a prospective randomized design. The study enrolled patients with relatively high-risk clinical (mean age of 69 years, 30% with diabetes, 40% with acute coronary syndrome, and 50% with prior PCI) and angiographic (63% with distal bifurcation stenosis and 70% with multivessel disease) characteristics. At 12-month follow-up, the rates of death (6.6% vs 5.0%), MI (4.6% vs 5.0%), stroke (1.0% vs 1.7%), and major cardiac events (death, MI, or revascularization; 15.8% vs 13.6%) were similar in the sirolimus- and paclitaxel-eluting stent groups, respectively, as were the angiographic restenosis rates at 6 to 9 months (19.4% vs 16.0%) and 2-year revascularization rates (7.8% vs 6.5%). The rates of definite (0.3% vs 0.7%) and probable (0% vs 0.3%) ST at 2 years were also similar in the 2 study arms.

Thereafter, several refined versions of DESs sharing common features of thinner struts and biocompatible polymers have been rapidly adopted in clinical practice, and newer generation DESs further decreased the risk of ST and restenosis compared to the previous stents. Although no randomized trial has specifically compared the outcomes of first-generation and second-generation DESs for LMCA disease, several observational studies have suggested better outcomes with newer versions of DESs for LMCA PCI. The multicenter randomized ISAR-LEFT MAIN 2 study compared the safety and efficacy of the zotarolimus-eluting stent (ZES) with the everolimus-
eluting stent (EES) for LMCA intervention. At 1 year, the cumulative incidence of death, MI, or TLR was 17.5% in the ZES group and 14.3% in the EES group (relative risk, 1.26; 95% CI, 0.85-1.85; \( P = .25 \)). All-cause mortality (5.6%; relative risk, 1.00; 95% CI, 0.52-1.93; \( P = .98 \)) and angiographic restenosis (21.5% vs 16.8%; relative risk, 1.28; 95% CI, 0.86-1.92; \( P = .24 \)) was comparable between the 2 groups at 1-year follow-up.

**Comparison Between PCI and Bypass Surgery**

Table 38-2 summarizes the key observational studies and randomized trials that compare PCI with DES and CABG. The representative study to assess the feasibility of PCI as an alternative to CABG came from the MAIN-COMPARE registry, which included 2240 patients with unprotected LMCA disease who underwent intervention (BMS, \( n = 318 \); DES, \( n = 784 \)) or CABG (\( n = 1138 \)) at 12 major cardiac centers in South Korea. The first 3-year outcome report after propensity score matching and the second 5-year report using the inverse probability of treatment weighting method showed that the risk of death and the combined risk of death, Q-wave MI, or stroke were not significantly different for patients undergoing PCI versus CABG. A similar pattern was observed in patients treated with either DES or BMS. However, the risk of repeat revascularization was significantly higher in the PCI group than in the CABG group, with HRs varying by the type of implanted stent, in that DES recipients were almost 6-fold more likely to require repeated revascularization and BMS recipients almost 10-fold more likely to require repeated revascularization compared to patients who underwent surgery. An interesting finding in this study was that the majority of PCI patients who needed repeat revascularization were treated with repeat PCI instead of CABG. Given the fact that the recommendation for CABG for unprotected LMCA disease has been based mostly on survival benefit compared with medical therapy, the lack of a statistically significant difference in mortality may support PCI as an alternative option to bypass surgery.

Table 38-2 **Comparative Studies of PCI With DES and CABG for Left Main Disease**
Four consecutive randomized clinical trials comparing early-generation DES and CABG reported similar results. The first randomized study comparing PCI (n = 52) with CABG (n = 53) for treatment of unprotected LMCA stenosis was conducted by Buszman and colleagues.\(^{50,88}\) PCI was performed using either BMS (65%) or DES (35%), and left internal mammary artery grafts were used in 72% of CABG patients. At 1 year, the primary end point of absolute change in left ventricular ejection fraction was significantly greater in the PCI group than in the CABG group (3.3% ± 6.7% vs 0.5% ± 0.8%; \(P = .047\)), whereas the secondary end points of survival and major adverse cardiac or cerebrovascular events (MACCE) were comparable between the 2 groups. These outcome findings were maintained at up to 10 years of follow-up. Although it provides valuable information, this trial only included patients with low to medium complexity of coexisting coronary artery disease and was underpowered by the small number of patients and the inconclusive primary end point chosen to evaluate comparative treatment effects. The SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) trial compared the outcomes of PCI using paclitaxel-eluting stents versus CABG for unprotected LMCA stenosis in a subgroup analysis from the randomized study cohort.\(^{40}\) In the subset of LMCA disease comprising 348 patients receiving CABG and 357 patients receiving PCI, PCI...
demonstrated an equivalent 12-month rate of MACCE compared with CABG (15.8% vs 13.7%). Of note, the higher rate of repeat revascularization with the use of PCI (11.8% vs 6.5%; \( P = .01 \)) was offset by a higher incidence of stroke with the use of CABG (2.7% vs 0.3%; \( P = .01 \)). Even when the follow-up was extended to 5 years, there were no significant differences in the rates of death (12.8% vs 14.6%; \( P = .94 \)), MI (8.2% vs 4.8%; \( P = .2 \)), and MACCE (36.9% vs 31.0%; \( P = .14 \)) between patients who received PCI and CABG. The incidence of stroke was lower (1.5% vs 4.3%; \( P = .03 \)), whereas the incidence of repeat revascularization was higher (26.7% vs 15.5%; \( P = .003 \)) in the PCI arm. When patients were stratified according to the SYNTAX score tertiles, the incidence of MACCE did not differ between the PCI and CABG groups in patients with low (0-22) and intermediate (23-32) scores, but significantly increased in PCI patients with high scores (≥33). These findings suggest that both treatment modalities are valid options for patients with LMCA disease and that the anatomic complexity should be considered when choosing PCI or CABG.

In the PRECOMBAT trial, 600 patients with unprotected LMCA disease were randomized to undergo either CABG or PCI with a sirolimus-eluting stent. The primary end point was MACCE, defined as a composite of all-cause death, MI, stroke, or ischemia-driven TVR. PCI was noninferior to CABG for the incidence of MACCE at 1 year (absolute risk difference, 2%; upper margin of 95% CI, 5.6%; HR, 1.56; \( P = .011 \) for noninferiority). At 5 years, the primary end point occurred in 52 patients in the PCI group and 42 patients in the CABG group (17.5% vs 14.3%, respectively; HR, 1.27; 95% CI, 0.84-1.90; \( P = .26 \)). The 2 groups did not significantly differ in terms of the composite of death from any cause, MI, or stroke. Ischemia-driven TVR occurred more frequently in the PCI group than in the CABG group (11.4% vs 5.5%, respectively; HR, 2.11; 95% CI, 1.16-3.84; \( P = .012 \)). Another small randomized trial by Boudriot et al compared sirolimus-eluting stenting (n = 100) with CABG (n = 101) for patients with unprotected LMCA disease. The primary end point was noninferiority in freedom from the composite of cardiac death, MI, and the need for TVR at 12 months. The incidence of the primary end point was 13.9% in the CABG group and 19.0% in the PCI group (\( P = .19 \) for noninferiority). The combined rates for death and MI were comparable (7.9% in CABG vs 5.0% in PCI), but PCI was inferior to CABG for repeat revascularization (5.9% vs 14.0%; noninferiority \( P = .35 \)).

Based on these registries and randomized studies showing PCI with DES
to be feasible and effective in the treatment of unprotected LMCA disease, the updated guidelines for the treatment of LMCA stenosis upgraded PCI as a reasonable or considerable treatment (Level of Evidence B) in prespecified patients to improve survival\textsuperscript{91,92} (Table 38-3). In summary, PCI using DES is currently considered an effective alternative option in anatomically suitable patients with significant LMCA disease. Two randomized trials comparing PCI with newer generation DES and CABG (the Nordic-Baltic-British Left Main Revascularization [NOBLE] and Evaluation of Xience Prime vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL] trials) are ongoing and will hopefully provide more information on the differential treatment effect of both strategies.

Table 38-3 Summary of PCI Guideline Recommendations for LMCA Disease

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Class of Recommendation</th>
<th>LOE</th>
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<tbody>
<tr>
<td>2011 ACCF/AHA/SCAI Guideline\textsuperscript{93}</td>
<td>Ila—For SIHD patients when both of the following are present: • Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score ( \leq 22 ), ostial or trunk left main stenosis) • Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality ( &gt;5% ))</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Ilb—For SIHD patients when both of the following are present: • Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of ( &lt;33 ), bifurcation left main stenosis) • Clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate-severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality ( &gt;2% ))</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>III—Harm—For SIHD patients (vs performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG</td>
<td>B</td>
</tr>
<tr>
<td>2014 ESC/EACTS Guideline\textsuperscript{94}</td>
<td>I—LMCA with a SYNTAX score ( \leq 22 )</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Ila—LMCA with a SYNTAX score 23–32</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>III—LMCA with a SYNTAX score ( \geq 33 )</td>
<td>B</td>
</tr>
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</table>

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CABG, coronary artery bypass graft; EACTS, European Association for Cardiothoracic Surgery; ESC, European Society of Cardiology; LMCA, left main coronary artery; LOE, level of evidence; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; SIHD, stable ischemic heart disease; STS, Society of Thoracic Surgeons; SYNTAX, Synergy Between PCI with Taxus and Cardiac Surgery.

**Technical Considerations**

During unprotected LMCA intervention, a femoral approach and use of guiding catheters with relatively large lumen (7 or 8 Fr) are preferred. The end of a thin guiding catheter may suddenly advance into the lesion, resulting in plaque dissection. In addition, multiple devices for complex procedures are
easily delivered through catheters with large lumens.

Patients with normal left ventricular function are usually tolerant of brief global ischemia during the balloon occlusion. Although an intra-aortic balloon pump is not routinely recommended during the procedure, prophylactic use should be considered to prevent hemodynamic collapse in patients with severe left ventricular dysfunction, critical right coronary artery disease, complex LMCA anatomy, or unstable presentations. In general, for provisional use, another femoral routine with small sheath for the rapid insertion of intra-aortic balloon pump is recommended before PCI for high-risk patients (low left ventricular ejection fraction, heavy calcified stenosis, or thrombus containing LMCA stenosis). New supporting devices, such as the TandemHeart PTVA system (CardiacAssist Inc., Pittsburgh, PA) or the Impella Recover System (Abiomed, Danvers, MA), can provide active circulatory support and may improve the feasibility of unprotected LMCA intervention.

Stenting of ostial or shaft LMCA lesions can be performed safely using careful hemodynamic monitoring and meticulous guiding technique. Coaxial alignment of the guiding catheter is important to minimize vessel injury and to ensure proper positioning of the stent. Once the balloon or stent is properly positioned, the guiding catheter can be retracted 1 to 2 cm into the aorta with gentle forward pressure on the balloon catheter. A brief (<30 seconds) and multiple (>3) balloon inflation is required to avoid ischemic complications. In ostial LMCA lesions, the stent is generally deployed to protrude 1 to 2 mm into the aorta for full lesion coverage. Further dilatation using a high-pressure balloon may be needed to achieve optimal stent cross-sectional area. Aorto-ostial coverage is not mandatory for treatment of disease limited to the shaft of the LMCA.

Stenting for LMCA bifurcation lesions is technically demanding and should be restricted to highly skilled interventional cardiologists. For LMCA bifurcation disease, the 1-stent strategy showed more favorable long-term clinical outcomes compared with the 2-stent strategy. Therefore, in real practice, the 1-stent crossover technique has been used more frequently, in approximately 60% of all LMCA bifurcation treatments. However, a notable rate of SB occlusion has been reported (187 of 2227 patients, 8.4%) from a real-world registry, the majority of which occurred in the true bifurcation lesion, and considering the possibility of circulatory collapse after SB occlusion in LM bifurcation lesions, the elective 2-stent technique is still
advocated as a viable option for this lesion subset. The selection of a 1- or 2-stent technique should be based on disease involvement of the LCX ostium because SB compromise after stent crossover is frequent in the setting of significant ostial disease of the SB (Table 38-4). Thus, to determine the appropriate stenting strategy, IVUS use is strongly recommended because it provides more accurate information of the disease status of the MV and SB as well as the degree of vascular remodeling compared with conventional angiogram. If possible, direct imaging from LCX is necessary because IVUS evaluation of an SB ostium from the MV is only moderately reliable.94

Table 38-4 Anatomic Features for Single-Stent or 2-Stent Strategy in the Treatment of Unprotected LMCA Bifurcation

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Anatomic Features</th>
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<tbody>
<tr>
<td>Single-stent</td>
<td>• Insignificant stenosis at the ostial LCX with Medina classification 1,1,0 or 1,0,0</td>
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<tr>
<td></td>
<td>• Small LCX with &lt;2.5 mm in diameter</td>
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<tr>
<td></td>
<td>• Diminutive LCX, right dominant coronary system</td>
</tr>
<tr>
<td></td>
<td>• Wide angle with LAD</td>
</tr>
<tr>
<td></td>
<td>• No concomitant disease or only focal disease in LCX</td>
</tr>
<tr>
<td>Two-stent</td>
<td>• Significant stenosis at the ostial LCX with Medina classification 1,1,1 or 1,0,1 or 0,1,1</td>
</tr>
<tr>
<td></td>
<td>• Large LCX with ≥2.5 mm in diameter</td>
</tr>
<tr>
<td></td>
<td>• Diseased left dominant coronary system</td>
</tr>
<tr>
<td></td>
<td>• Narrow angle with LAD</td>
</tr>
<tr>
<td></td>
<td>• Concomitant diffuse disease in LCX</td>
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Abbreviations: LCX, left circumflex artery; LMCA, left main coronary artery.

**IVUS-Guided Optimization of LMCA Stenting**

Optimal stent expansion was considered one of the most important factors in preventing restenosis or adverse clinical outcomes after PCI.95,96 However,
there were no data suggesting the optimal minimal stent area (MSA) cutoff for prediction of restenosis and long-term clinical outcome after DES implantation for LMCA stenosis until the recent report from Kang et al. After analyzing 403 patients undergoing sirolimus-eluting stent implantation for LMCA disease, the best IVUS-MSA criteria that predicted angiographic in-stent restenosis (ISR) on a segmental basis were found to be 5.0 mm$^2$ for the LCX ostium, 6.3 mm$^2$ for the LAD ostium, 7.2 mm$^2$ for the polygon of confluence (POC), and 8.2 mm$^2$ for the proximal LMCA above the POC (Fig. 38-12). Stent underexpansion was more frequent in the 2-stent group than in the 1-stent group (54% vs 27%, respectively; $P = .001$). In addition, in the 2-stent group, the LCX ostium was the most common site of underexpansion (37%), which may explain the greater risk of ISR when LMCA bifurcation lesions are treated with a 2-stent strategy. Overall, angiographic ISR was more frequent in lesions with underexpansion than in lesions without underexpansion (24.1% vs 5.4%, respectively; $P = .001$). Even in the 2-stent group, lesions with complete expansion at all sites showed only 6% of the ISR rate, which was similar to that of the single-stent group (6.3%) and in nonbifurcation LMCA lesions (4.5%).
FIGURE 38-12 A. Minimal stent area (MSA) cutoff values for the prediction of angiographic in-stent restenosis (ISR) on a segmental basis. B. Frequency of underexpansion in 2-stent group (n = 104). Left circumflex artery (LCX) ostium was the most common site of underexpansion (37%); ISR developed in 55% of the underexpanded LCX ostia. C. Frequency of underexpansion in the single-stent group (n = 289, including 67 nonbifurcation stents and 222 bifurcation lesions treated with a 1-stent crossover technique). The rate of underexpansion at the left anterior descending artery (LAD) ostium and polygon of confluence (POC) was significantly lower in the single-stent group compared with the 2-stent group (*P <.05). LM, left main artery.

Although there are some controversies regarding the clinical impact of IVUS-guided stenting for unprotected LMCA along with some cost-benefit issues, this adjuvant method recently gained support from many interventional cardiologists after associated publications. A subgroup analysis from the MAIN-COMPARE registry including 201 propensity-score matched pairs demonstrated that there was a strong tendency for lower risk of 3-year mortality with IVUS guidance compared with angiography guidance (6.3% vs 13.6%; log-rank P = .063; HR, 0.54; 95% CI, 0.28-1.03). In particular, for 145 matched pairs of patients receiving DES, the 3-year rate of mortality was significantly lower for IVUS guidance compared with angiography guidance (4.7% vs 16.0%; log-rank P = .048; HR, 0.39; 95% CI, 0.15-1.02). Of note, mortality started to diverge beyond 1 year after the procedure. Given that IVUS guidance did not reduce the risk of mortality in 47 matched pairs of patients receiving BMS (8.6% vs 10.8%; log-rank P = .35; HR, 0.59), this study indicates that IVUS guidance may play a role in reducing very late ST and subsequent long-term mortality. A recent IVUS-TRONCO-ICP Spanish study also demonstrated the importance of IVUS surveillance during LMCA stenting. The IVUS-guided group had a lower incidence of the composite of cardiac death, MI, and TLR and also ST at 3 years.

INTERVENTION FOR OSTIAL LESIONS

Ostial lesions have a reputation of being fibrotic, calcified, and relatively rigid. Because these unique characteristics contribute to resistant to dilatation and propensity for recoil, treatment of ostial lesions was associated with lower angiographic success and frequent procedural complications, such
as dissections and acute vessel closure, in the balloon angioplasty era. Although, significant progress in clinical outcomes has been made with the use of stents and adjunctive devices such as cutting balloons or IVUS, percutaneous intervention in ostial lesions still poses unique challenges as a result of technique considerations in catheter manipulation, lesion preparation, and stent positioning.

**Types of Ostial Lesions**

Traditionally, ostial disease is defined as a lesion arising within 3 to 5 mm of the vessel origin. Coronary ostial lesions can be classified by location as aorto-ostial and branch ostial lesions. Aorto-ostial lesions involve the junction between the aorta and the orifice of the right coronary artery, LMCA, or bypass grafts and histologically resemble the aortic wall, being rich in smooth muscle cells and elastic fibers. Isolated aorto-ostial disease is more frequently encountered in women and is more common at the right coronary artery than at the LMCA. Branch ostial lesions involve the junction between a large epicardial vessel and the orifice of a major branch and are frequently accompanied by various bifurcation lesions.

**Technical Tips for Branch Ostial Stenting**

Precise stent positioning to obtain full lesion coverage is of the utmost importance in branch ostial intervention. Unnecessary proximal extension may result in obstruction of major vessels. For example, in ostial LAD stenting, the stent should be deployed to cover the most proximal part of the LAD ostium without protrusion of the stent into the LMCA. Using multiple angiographic views to minimize foreshortening or overlap is necessary. In ostial LAD stenting, super-zooming angiography (magnification ×8) in the right or left anterior oblique and caudal views may be useful to facilitate the exact stent positioning. Proper positioning can be confirmed by a small amount of contrast injection in multiple projections. Occasionally, the stent becomes subject to an oscillating or rocking motion in time with the cardiac cycle, which makes accurate stent positioning impossible. Pharmacologic methods (such as esmolol, adenosine, and atropine) and rapid ventricular pacing to reduce or slow cardiac motion have been described. However, these methods have a short time window and can potentially distress the patient,
which can be counterproductive. Use of a large guiding catheter, deeper intubation of the guiding catheter, and use of a stiffer guide wire might allow the entire apparatus for angioplasty to swing with cardiac motion. The partial inflation technique is another option to overcome the cardiac cycle–related motion. Slight inflation of the stent balloon at 2 atm can increase the stent profile and reduce oscillation while allowing positional adjustment before full deployment. However, abrasion of the normal vessel intima by the stent or possible stent loss can be problematic.

**Technical Tips for Aorto-Ostial Stenting**

Because engagement of catheters at aorto-ostial sites can often provoke spasm and give a false impression of severe ostial disease, every effort should be made to confirm the true stenosis severity before intervention. Intracoronary nitroglycerin should be administered unless contraindicated; nonselective coronary injection into the aortic sinus or IVUS evaluation can be performed for this purpose.

Selection of an adequate guiding catheter is particularly important in aorto-ostial intervention. Generally, less aggressive catheters with a short tip are preferred to avoid deep engagement and wedging of the catheter within the lesion and to facilitate disengagement during stent deployment. Most native aorto-ostial lesions can be successfully approached with the Judkins catheter, whereas multipurpose right coronary bypass, left coronary bypass, or Amplatz left catheters are often used for aortocoronary bypass graft lesions. Pressure damping, which indicates wedging of the catheter within the lesion, can be a sign of flow occlusion, and catheters with side hole should be used for intervention. In general, coaxial alignment of the guides minimizes ostial injury, permits proper positioning of devices, and facilitates accurate assessment of the ostium. Once the balloon or stent is properly positioned, the guiding catheter can be gently retracted into the aorta. The balloon should not be fully inflated inside the catheter due to the possible risk of balloon rupture and air embolism (Fig. 38-13). After balloon angioplasty, stent implantation is strongly recommended in almost all cases of significant aorto-ostial lesions because of the specific characteristics of lesion rigidity and high elastic recoil. Guiding catheter disengagement can result in poor contrast opacification, which can hinder accurate stent positioning. Frequent and intense test injections of contrast in multiple angiographic views are required.
to verify proper stent positioning. The proximal 1 to 2 mm of the stent should extend into the aorta to ensure complete coverage of the ostial lesion (Fig. 38-14). Excessive stent protrusion into the aorta can cause difficulty in repeat catheterization or increase the risk for thromboembolic complications. IVUS evaluation to identify the correct reference vessel size and to confirm stent optimization can be very useful for favorable outcomes, especially for aorto-ostial intervention. However, operators should bear in mind that the need for catheter disengagement during IVUS pullback risks non-coaxial imaging of the ostium and overestimation of the luminal area (Fig. 38-15).

**FIGURE 38-13** Proper balloon dilation technique for aorto-ostial lesions. The catheter is gently retracted 1 to 2 cm into the aorta prior to the balloon inflation.

**FIGURE 38-14** Proper stenting technique in aorto-ostial lesions. A. The proximal 1 to 2 mm of the stent should extend into the aorta. The guiding catheter should be retracted 1 to 2 cm before stent implantation. B. After stent deployment, the delivery balloon is removed while maintaining backward tension of the guide to prevent it
from advancing into the ostium and damaging the stent. C. Perform adjunctive balloon dilation with a high pressure balloon. D. Final result.

**FIGURE 38-15** Example of aorto-ostial right coronary artery (RCA) stenting. (A) Baseline RCA angiogram showing significant stenosis at mid-portion and ostium. Preprocedural intravascular ultrasound examination for RCA revealed diffuse concentric plaque resulting in a minimal lumen area of 2.37 mm$^2$ and 1.69 mm$^2$ for mid-portion (B) and ostium (C), respectively. (D) Several predilations were done from mid to ostial RCA. (E) Distal stent was deployed first. (F) Proximal stent was deployed while securing both the full ostial coverage and overlap with the distal stent. (G) Optimal final result.
PCI Results for Coronary Ostial Lesions

The use of BMSs to treat ostial stenosis has been reported to have a high procedural success rate but also associated with a high rate of restenosis.\textsuperscript{105,106} To overcome this limitation, several studies were designed to evaluate the role of plaque modification and debulking strategy with use of adjunctive devices including excimer laser, directional coronary atherectomy, and rotational atherectomy. However, these devices increase procedural complexity and the risk of device-related complication, and the studies could not find consistent superiority of combining these devices over stenting alone.\textsuperscript{105,107-109}

The use of DES can reduce the rates of restenosis in a broad range of coronary lesions. Indeed, several studies reported improved outcomes of PCI with DES in ostial lesions compared with BMS, especially in terms of the rates of restenosis and repeat revascularization.\textsuperscript{110-113} In addition, despite the lack of adequate evidence, procedural and long-term outcomes of coronary ostial stenting in the DES era seem to be comparable to other coronary lesions so far.

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**MULTIPLE CHOICE QUESTIONS**

1. Which bifurcation stenting technique has a risk of incomplete side branch coverage?
   A. Culotte technique
   B. T-stenting technique
   C. Crush technique
   D. Simultaneous kissing stent technique
   E. Double kissing crush technique

2. Which anatomic feature of distal left main bifurcation would be favorable for a 2-stent strategy rather than single stenting?
   A. Wide angle with left anterior descending artery
B. Left circumflex artery <2.5 mm in diameter  
C. Medina classification 1,0,1  
D. Right dominant coronary artery system  

3. What site is most common for restenosis after distal left main stenting, and what is the intravascular ultrasound minimal stent area criterion to predict restenosis at that site?  
   A. Left circumflex artery ostium, 5.0 mm\(^2\)  
   B. Left circumflex artery ostium, 6.0 mm\(^2\)  
   C. Left anterior descending artery ostium, 6.0 mm\(^2\)  
   D. Left anterior descending artery ostium, 7.0 mm\(^2\)  
   E. Polygon of confluence, 7.0 mm\(^2\)  

4. Which circumstance is least reliable for additional side branch intervention in a provisional 1-stent approach for a distal left main bifurcation lesion?  
   A. Chest pain  
   B. New ST-segment depression on lead I  
   C. Side branch diameter stenosis of 70%  
   D. Fractional flow reserve (FFR) of 0.70  

5. For a stable patient with significant left main coronary artery disease, which outcome measure is most affected by different revascularization methods (ie, coronary artery bypass grafting [CABG] and PCI)?  
   A. All-cause death  
   B. Repeated revascularization  
   C. Myocardial infarction  
   D. Composite of death, myocardial infarction, and stroke  

**ANSWERS**  

1. B  

T-stenting technique is the most commonly used approach in the provisional stenting strategy, in which a single main vessel stent is deployed, with side branch stenting only used in cases of suboptimal angiographic results. A
technical consideration with T-stenting is the angulation of the side branch relative to the main vessel. Lesions that more closely resemble a true “T” configuration with a side branch angulation >70° will enable better coverage of the entire side branch than lesions with less angulation, which may carry a risk of incomplete side branch ostium coverage. The side branch ostium is the most common site for angiographic restenosis following stenting of bifurcation lesions, which is why adequate coverage of this region is important.

2. C

For distal left main bifurcation disease, the possibility of circulatory collapse after main vessel, attributable to the large myocardial volume supplied by the left circumflex artery in many patients, is always a concern. This is why 2-stent techniques are chosen relatively more frequently for left main bifurcation lesions than for non–left main lesions. In general, the provisional 1-stent approach would be preferred for left main bifurcations with insignificant stenosis at the ostial left circumflex artery or a nondominant left coronary system, whereas the elective 2-stent technique is preferred in patients with significant ostial stenosis of the left circumflex artery with a dominant left coronary arterial system. Medina class of 1,0,1 refers to a presence of significant stenosis at the side branch, a situation in which a 2-stent strategy should be considered.

3. A

Either after a single-stent crossover strategy or an elective 2-stent strategy, the most frequent site of restenosis is the ostium of the left circumflex artery. Based on our research results, stent underexpansion after percutaneous coronary intervention (PCI) was most common at that site and was more frequent in the 2-stent group than in the 1-stent group. This explains why the 1-stent strategy shows more favorable long-term clinical outcomes compared with the 2-stent strategy in relevant studies. The rule of “5-6-7-8” is a best intravascular ultrasound minimal stent area criterion after PCI that predicts angiographic in-stent restenosis on a segmental basis for left circumflex artery ostium (5 mm$^2$), left anterior descending artery ostium (6 mm$^2$), polygon of confluence (7 mm$^2$), and the left main coronary artery above the polygon of confluence, respectively.
Additional treatment for “functionally significant” side branch lesion would be the reasonable approach in this situation. If a patient develops ischemic symptoms or signs after left main stenting that are attributable to the compromise of the left circumflex artery, further intervention should definitely be performed. Currently, there are small observational studies suggesting the benefit of FFR-guided decision making for further left circumflex artery intervention after main vessel stenting. In these reports, considerable discrepancy between angiographic stenosis and FFR value was demonstrated in that only less than one-third of angiographically jailed left circumflex artery ostia were revealed to be functionally significant (FFR <0.80). In left main or non–left main bifurcations, even if the diameter stenosis of the side branch is up to 70% to 80% after main vessel stenting, the long-term patency and clinical outcome are usually excellent if the stenosis is confined to the ostium and the flow is not impaired.

There are robust data indicating the inherent weakness of stent-related treatment in left main coronary artery disease in that PCI, compared with CABG, consistently displayed a disadvantage for the risk of repeated revascularization. Accordingly, left main coronary artery disease patients with a high degree of anatomic complexity (eg, SYNTAX score >32) are recommended to undergo CABG rather than PCI by community guidelines, mainly because of the differential future outcome of repeated revascularization. However, this drawback for PCI did not translate into an increase in hard clinical end points in most comparative effectiveness studies.
Special Considerations: Small Vessel and Diffuse Disease

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Small vessel disease and diffuse coronary artery disease represent particularly challenging subsets for treatment with transcatheter coronary interventional therapies. This pathology is associated with higher risk comorbidities, such as diabetes, and is more frequently associated with female gender and diffuse coronary involvement. Small and diffusely diseased vessels are frequently noncompliant, calcified, tortuous, and distal in location, making these targets more technically challenging for intervention. Consequently, a higher incidence of acute complications, including significant vessel dissection, acute vessel closure, myocardial infarction, and emergent coronary bypass grafting, has historically complicated intervention in small and diffusely diseased vessels. Along with poorer acute outcomes, these subsets are plagued by high restenosis and thrombosis rates, often necessitating repeat intervention or bypass surgery. Despite the challenges and complexities inherent to small vessel intervention, the problem is common. Between 30% and 67% of all percutaneous coronary interventions involve small vessels, depending on the definition of a small vessel.

This chapter will review the definition and diagnostic approach to small and diffuse coronary artery disease. Acute and long-term outcomes associated with percutaneous interventional therapies, particularly the favorable impact of drug-eluting stents, will be reviewed. Finally, the future
role in the treatment of these subsets with drug-eluting balloons and bioabsorbable stents will be examined.

**DEFINITION OF SMALL VESSEL DISEASE**

The definition of what constitutes a small vessel in the context of coronary interventional therapy has been quite variable. A number of studies examining small vessel intervention have defined vessels less than 3.0 mm in reference size as being small, and this criterion is in part derived from early stent trials in which patients with vessels less than 3.0 mm were excluded from enrollment.\(^{10,11}\) Other studies have defined small vessels as those less than 2.5 to 2.8 mm in diameter.\(^{9,12-14}\) Certainly, less than 3.0 mm is the most sensitive descriptor, although necessarily less specific. Despite whatever arbitrary cutoff is used, the relationship between vessel size and outcome is not a step function; instead, a continuous inverse relationship exists between outcomes and size.\(^{8,15}\) Consequently, differences in the definition and enrollment criterion frequently help explain apparently conflicting results from various studies of small vessel intervention. Like the small vessel, diffuse disease has had various definitions; however, the most consistent definition is lesion length greater than 20 mm.\(^{16}\)

The definition of small vessel has been based on angiography; nevertheless, results of intravascular ultrasound (IVUS) have demonstrated that many angiographically small vessels are in fact “pseudosmall” as a result of angiographically undetected disease in the reference segment and positive remodeling at the lesion site.\(^{17}\) Briguori and colleagues\(^{18}\) compared 344 consecutive patients having 419 lesions in small vessels (angiographic reference vessel ≤2.75 mm) with 953 patients having 1161 lesions in large vessels (>2.75 mm); all underwent concomitant IVUS. The difference in angiographic and IVUS reference vessel dimension delta (IVUS-angiography) was calculated for all lesions.\(^{18}\) The tendency to underestimate vessel size was significantly greater for small vessels (difference between IVUS and angiography, 1.3 ± 0.5 mm vs 1.0 ± 0.6 mm; \(P < .001\)). Angiography underestimated vessel size by more than 1.0 mm in 71% of small vessels and in only 49% of large vessels (\(P < .001\)). There was a
stronger correlation between plaque burden and the delta (IVUS-angiography) in small vessels ($r = 0.80; P < .001$) than in large vessels ($r = 0.59; P < .001$). Predictors of delta (IVUS-angiography) were proximal or middle lesion location and female gender.\textsuperscript{19} Extending these observations, Moussa et al\textsuperscript{19} examined the predictors of large discrepancies between IVUS and angiography. Independent predictors of a delta (IVUS-angiography) greater than 1.0 mm were small vessel size ($<3.0$ mm), location of the lesion in the proximal vessel, and diabetes (Fig. 39-1). The authors suggested that IVUS might be particularly helpful in small vessel intervention when the lesion was proximally located or the patient had diabetes.

**FIGURE 39-1** Predictors of large discrepancies between intravascular ultrasound (IVUS) and angiography (angio) as reported in 1 study. Independent predictors of a delta $>1.0$ mm were small vessel size ($<3.0$ mm), location of the lesion in the proximal vessel, and diabetes mellitus (DM). (Reprinted from Moussa I, Kobayashi Y, Adamian M, et al. Characteristics of patients with a large discrepancy in coronary artery diameter between quantitative angiography and intravascular ultrasound. *Am J Cardiol*. 2001;88:294-302, Copyright © 2001, with permission from Elsevier.)

**NONSTENT INTERVENTION**

Early studies of percutaneous transluminal coronary angioplasty (PTCA) demonstrated higher risks associated with small vessel intervention.\textsuperscript{20} Overall procedural success with plain old balloon angioplasty (POBA) was significantly less for small vessels compared to interventions on larger
vessels. Additionally, major adverse cardiac events occurred more frequently in small vessel cohorts. Hypotheses explaining the higher event rates include the association of small vessels with other high-risk comorbidities, greater lesion complexity, and the higher incidence of diffuse plaquing. The combination of small vessel size and diffuse disease is particularly difficult, with a much higher incidence of abrupt closure compared to focal lesions. Strategies that have been shown to be beneficial in reducing these complications and improving restenosis rates include utilization of longer balloons, gradual and prolonged balloon angioplasty, and cutting balloon (CB) angioplasty. Data from the REDUCE (Restenosis Reduction by Cutting Balloon Evaluation) and CAPAS (Cutting Balloon Angioplasty Versus Plain Old Balloon Angioplasty Study) trials collectively suggested that CB angioplasty may be a superior technique to POBA, with fewer coronary dissections, improved binary restenosis rates, and reduced target lesion revascularization.

Because the results of POBA had been demonstrated to be suboptimal, interventional therapies using ablative techniques, particularly rotational atherectomy and laser angioplasty, have also been evaluated. Several studies done in the early 2000s, including a meta-analysis of trials examining PTCA versus atherectomy, CB angioplasty, or laser angioplasty, demonstrated higher acute complication rates without restenosis benefits in patients who underwent these procedures. Despite limited data to suggest plaque ablative techniques should be used routinely to treat small, diffuse disease, it continues to have a niche role in heavily calcified vessels, facilitating more complete dilation and delivery of stents.

**BARE METAL STENTS**

Early reports of stenting in small vessels suggested higher rates of complications and no improvement in restenosis. Diffuse disease treated with multiple or long stents was also associated with a higher risk of stent thrombosis as well. A meta-analysis of the Belgian-Netherlands Stent (BENESTENT) study and the Stent Restenosis Study (STRESS) suggested no improvement in restenosis in small vessels when elective stenting was compared with balloon angioplasty. These reports led to initial American College of Cardiology/American Heart Association recommendations that
small vessels should not be routinely stented.\textsuperscript{30}

Despite these mediocre results, subsequent reports of bailout stenting in
the setting of abrupt or threatened closure in small vessels were
encouraging.\textsuperscript{31,32} An analysis of small vessel lesions enrolled in the STRESS
I and II trials suggested that in vessels less than 3.0 mm, elective stenting was
beneficial.\textsuperscript{10} Angiographic restenosis was significantly less in those receiving
elective stenting (34\% vs 55\% restenosis for stent vs balloon; \(P < .0001\)), and
there was no difference in abrupt closure between the POBA and stent group
(3.6\% in both groups). Many other elective registries also suggested
favorable outcomes with stenting when compared to historical controls.\textsuperscript{33-42}

Following these early reports, there have subsequently been a large
number of randomized trials comparing bare metal stenting to PTCA.\textsuperscript{9,13,42-50} There has been considerable variability in the results of these studies. In
2004, a meta-analysis of these randomized trials was performed and included
3541 patients; 1672 patients were allocated to balloon angioplasty, and 1869
were allocated to bare metal stenting.\textsuperscript{51} Of these, 84\% had angiographic
follow-up. The pooled restenosis rate was 25.8\% in patients assigned to
stenting and 34.2\% in patients allocated to balloon angioplasty (relative risk,
0.75; 95\% confidence interval [CI], 0.67-0.84; \(P < .001\)). A smaller reference
vessel diameter at baseline was associated with higher risk reduction of
restenosis in the stent group (\(P = .012\)). In summary, these studies suggested
that stenting improves restenosis in small vessels, particularly when PTCA
outcomes are not optimal and possibly when reference vessel size is smaller.

\textbf{Stent Strategies}

Initially, the treatment of diffuse disease, particularly in small vessels, was
discouraging because of higher rates of stent thrombosis and restenosis.
Subsequent studies suggested more favorable results. In long lesions, Serruys
et al\textsuperscript{52} showed the superiority of IVUS-guided stenting compared to optimal
balloon angioplasty in the Additional Value of NIR Stents for Treatment of
Long Coronary Lesions (ADVANCE) trial.\textsuperscript{52} In this study, 437 patients with
lesions 20 to 50 mm in length were angioplastied with long balloons; 149 of
the patients (34\%) required bailout stenting for flow-limiting dissections. The
remaining 288 patients who achieved an optimal PTCA result were
randomized to IVUS-directed stenting or no further therapy. The restenosis
rate in the stent group was significantly lower than in the PTCA-only group (27% vs 42%; \( P = .022 \)), with no difference in early complications. Using IVUS guidance, Colombo et al\(^5\) described a technique whereby the vessel was aggressively dilated and segments within the lesion with minimal lumen areas less than 5.5 mm received spot stenting. Compared to usual stenting, spot stenting was associated with no difference in 30-day major adverse cardiac events (MACE) but with significantly less restenosis (25% vs 39%; \( P < .05 \)). Although single-center reports of spot stenting have been encouraging, the time-consuming and operator-dependent technique has not been embraced as a mainstream strategy.

Another strategy examined in the setting of small vessel intervention has been direct stenting.\(^5\) Garcia and colleagues\(^5\) randomized 350 patients with reference vessel sizes between 2.2 and 2.7 mm to either direct stenting or predilation followed by stenting using the Pixel stent (Abbott Vascular, Santa Clara, CA). Of those assigned to direct stenting, 83% were successfully stented without predilation. Binary angiographic restenosis at 180-day follow-up was 16% for direct stenting versus 25% for the control (\( P = \text{not significant} \ [\text{NS}] \)). Target lesion revascularization was low in both groups (3.4% vs 4.3% for direct stent vs control; \( P = \text{NS} \)).

Finally, the use of glycoprotein IIb/IIIa inhibitors as a routine strategy in small vessel intervention has not been shown to reduce restenosis. Hausleiter and colleagues\(^4\) randomized 502 patients in a 2 × 2 factorial design to stent (phosphochlorine-coated) versus PTCA and abciximab versus control. There was no difference in 30-day MACE, restenosis, or target vessel revascularization (TVR) between the abciximab and control groups.

**First-Generation Drug-Eluting Stents**

The fundamental problem with stenting in small arteries is that the amount of neointimal hyperplasia is independent of vessel size, with small arteries suffering on average the same amount of late loss (0.8 mm) as larger vessels.\(^8\) Because of lower postprocedure stent area, small vessels are less able to accommodate neointimal accumulation than larger arteries. Lesion length independently exacerbates the negative impact of smaller vessel size.\(^8\) Even when in-stent minimal vessel areas are large, small vessels have higher rates of TVR than larger vessels with similar postprocedural minimal in-stent
lumen areas (Fig. 39-2).  

FIGURE 39-2 Results of a study demonstrating that even when the in-stent minimal vessel areas are large, small vessels have higher rates of target vessel revascularization than larger vessels with similar postprocedural minimal in-stent lumen areas. (Based on data from Moussa I, Kobayashi Y, Adamian M, et al. Characteristics of patients with a large discrepancy in coronary artery diameter between quantitative angiography and intravascular ultrasound. Am J Cardiol. 2001;88:294-302.)

The solution to improving long-term outcomes in small and diffuse coronary artery stenting is to reduce neointimal proliferation, thereby attenuating late lumen loss. The site-specific application of antiproliferative agents such as sirolimus, paclitaxel, everolimus, and zotarolimus dramatically and unequivocally reduces restenosis in larger vessels. Subset analysis from randomized trials and subsequent small vessel–specific studies have demonstrated remarkable effectiveness in the setting of small vessel disease as well. Their impact on diffuse disease has been equally favorable.

An early analysis compared the use of sirolimus-eluting stent (SES) versus balloon angioplasty. In vessels with a reference size less than 3.0 mm, the effectiveness of the SES in the SIRIUS (Sirolimus) trial was compared to the results of balloon angioplasty in patients treated in BENESTENT I and II and STRESS. Subacute occlusion was 0.4% versus 1.4% (SES vs POBA), and the SES reduced target lesion revascularization (TLR) from 24% to 5.1% (difference, –18.9%; 95% CI, –23.5% to –14.3%), suggesting that the drug-
eluting stent was far more effective than balloon angioplasty.

In the evaluation of first-generation drug-eluting stents (DESs) on small vessel disease, the SIRIUS trial demonstrated that the Bx-VELOCITY SES (Cordis, Hialeah, FL) dramatically reduced in-stent late loss in smaller vessels with some attenuation of the effect over the analysis segment due to proximal edge restenosis (Fig. 39-3).\textsuperscript{58} TVR was reduced in a similar fashion, although the relative reduction was somewhat less for smaller vessels. Likewise, the results from the e-SIRIUS and c-SIRIUS trials, looking at the benefits of CYPHER stents (Cordis) in small vessels compared to the Bx-VELOCITY bare metal stents,\textsuperscript{61} demonstrated decreased late lumen loss across all vessel sizes, particularly small vessels (~2.2 mm), of 0.12 mm. The lack of edge restenosis shown in these studies suggests that avoiding geographic miss and stenting “normal to normal” is particularly important in small vessels.


Like the SES, the paclitaxel-eluting stent (PES) has been shown to be
Results from the TAXUS IV (Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent) trial demonstrated substantial reductions in in-segment restenosis, with no edge restenosis and with concomitant reductions in TVR and TLR (Fig. 39-4). However, older trials comparing PES with SES in small vessel and diffuse coronary disease were inconsistent. The REALITY trial randomized patients having a mean vessel diameter of 2.4 mm and a lesion length of 17 mm to either the TAXUS (Boston Scientific, Marlborough, MA) or CYPHER SES stent. Although the in-stent late loss was significantly less in the CYPHER group, there was no overall significant difference in binary angiographic restenosis and TLR; in particular, neither stent was superior in the subgroups of “long lesions” and “small vessel.” In contradistinction, the SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial exhibited that the angiographic restenosis and TLR associated with CYPHER was significantly lower overall in small vessels and long lesions compared to the PES.

**FIGURE 39-4** Results from TAXUS IV, which demonstrate significant reductions in in-segment restenosis. Although the relative reductions in restenosis were similar between vessel sizes, the absolute difference was greater with smaller vessel size. QCA, quantitative coronary angiography. (Based on data from Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38-42.)
**Newer Generation Drug-Eluting Stents**

The benefits of newer generation DESs in treating coronary stenosis by percutaneous transcatheter intervention compared to older therapies extend to the treatment of small vessel coronary disease, as well. The newer generation everolimus-eluting stents (EESs) have particularly been demonstrated to be effective in reducing clinical and angiographic events in diffuse, small vessel disease. The XIENCE V USA study was a “condition of approval” postmarket study involving 5054 patients to evaluate the safety of XIENCE V (Abbott Vascular), everolimus-eluting platform in a real-world setting. Two cohorts were identified; a small vessel cohort comprising 1869 patients who received at least one 2.5-mm XIENCE V stent and a non–small vessel cohort comprising 2905 patients who received XIENCE V stents larger than 2.5 mm. Baseline characteristics were similar between both patient populations, with the exception that small vessel patients were more likely to be women; had a higher prevalence of diabetes, hypertension, and anemia; and were more likely to have had a prior myocardial infarction, multivessel disease, and prior coronary artery bypass graft. Despite these differences in baseline characteristics and clinical risk factors, 1-year clinical outcomes were similar in both the small vessel and non–small vessel groups, which included stent thrombosis rates, and composite rates of cardiac death or Academic Research Consortium–defined myocardial infarction. TLR was higher in the small vessel group (4.9% vs 3.8%).

More consistent differences between drug-eluting platforms were demonstrated between EES and PES in a subset in a post hoc analysis of the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) III trial, which sought to compare clinical and angiographic outcomes in patients treated with 2.5-mm XIENCE V (EES) or TAXUS stents; lower rates of late loss were observed in vessels treated with EES. The subgroup of patients in the original trial who received at least one 2.5-mm stent consisted of 160 patients (total of 190 stents implanted) in the XIENCE V arm and 59 (total of 67 stents) in the TAXUS arm, with a mean vessel diameter of 2.36 ± 0.3 mm and 2.34 ± 0.33 mm in the XIENCE V and TAXUS arms, respectively. In-hospital and 30-day event rates for MACE and target vessel failure (TVF) were low and similar in both groups. Through 9 months of follow-up, however, TVF and MACE were significantly lower in
the group receiving EES compared to PES. The difference in MACE was driven mainly by a reduction in TLR (1.3% vs 12.5%; \( P = .0016 \)). Follow-up angiography also demonstrated a significant difference in in-stent and in-segment late loss between the stents, and binary in-segment angiographic restenosis was significantly lower for the EES group (4.1% vs 20.8%; \( P = .02 \); Fig. 39-5).

Another pooled analysis from both the SPIRIT III and SPIRIT IV trials also demonstrated reduced clinical adverse events in patients with small vessel disease treated with EES compared to PES. In this patient-level meta-analysis, which included 4689 patients, randomized 2:1 to EES versus PES, patients with small vessel intervention (n = 1019) were pooled, and the performance of these stents in single-lesion intervention was evaluated at 1 year. The use of EES was associated with a significant reduction in target lesion failure (4.4% vs 7.9%; \( P = .03 \)) in favor of EES. Target lesion revascularization was also significantly reduced by 56% in small vessels with EES compared to PES (2.4% vs 5.5%; \( P = .02 \)). It was concluded then that in
high-risk patients requiring percutaneous coronary intervention in small coronary arteries, EES results in significantly improved 1-year rates of event-free survival compared to PES, with evidence present for both enhanced safety and efficacy.

Similar data are available for the zotarolimus-eluting stents (ZES) and the treatment of small vessel disease. The ENDEAVOR IV and RESOLUTE trials looking at first- and second-generation ZES, respectively, demonstrated good outcomes and at least noninferiority when compared to PES, SES, or EES. However, the mean reference vessel diameter was 2.73 mm for ZES and 2.70 mm for PES in the ENDEAVOR IV trial and 2.59 mm for ZES in the RESOLUTE trial. The results of a small trial looking at the second-generation ZES RESOLUTE (R-ZES) in small vessel coronary artery disease were recently published. This study sought to examine the angiographic results of R-ZES in de novo coronary lesions of ≥50% diameter stenosis in target vessels ≤2.5 mm. The results on follow-up angiography performed on 143 lesions in 127 patients demonstrated an angiographic restenosis rate of 6.3%, with late lumen loss of 0.26 ± 0.34 mm. At 1-year follow-up, the MACE event rate was only 8.5%, which included 4 cardiovascular deaths, 2 nonfatal myocardial infarctions, and 6 repeated revascularizations. The results of a small trial looking at the second-generation R-ZES for treatment of small vessels compared to larger vessel intervention. Looking at 2-year clinical outcomes from 5 previously performed R-ZES studies comparing small vessel (reference vessel diameter [RVD] ≤2.5 mm; n = 1956) with larger vessel disease (RVD >2.5 mm; n = 3174), baseline characteristics revealed a higher incidence of comorbidities in the small vessel group. There was no significant difference in target lesion failure (TLF) (10.1% vs 8.7%; P = .54) at 2 years. When the subgroup of patients with diabetes was examined (n = 1553), there was no significant difference in 2-year TLF in small compared to large vessels (11.2% vs 11.1%; P = 0.17). Similarly, within the small vessel cohort, no significant difference was seen regarding TLF at 2 years between people with and without diabetes (11.2% vs 9.6%; P = .28).

The evidence supporting the use of second-generation DES, both EES and ZES, in treating small vessel coronary artery disease is encouraging. The use of these newer antiproliferative agents in the platforms of currently available DES appears superior to earlier generation DES as a treatment modality for
small vessel disease and certainly overcomes the inherent problems with balloon angioplasty alone in treating this difficult subset of patients.

**DRUG-ELUTING BALLOONS**

The success of drug-eluting stents in the treatment of coronary artery disease, mainly in the attenuation of cellularity and consequent neointimal hyperplasia, and thus reduction of restenosis and revascularization, is clear. Limitations to DES include the issue of late and very late stent thrombosis, as well as the difficulty in delivery and expandability of stents to tortuous, long calcified, and small vessels. Although treatment of small vessel disease has improved with the aforementioned newer generation agents, limitations of DES still exist.

Drug-eluting balloons (DEBs) have developed as a potential alternative that is intuitively attractive, especially for the treatment of in-stent restenosis of bare metal stents or DES. The use of DEB allows for the delivery of an antiproliferative agent, while potentially eliminating the nidus for late and very late stent thrombosis. For these reasons, as well as a relatively higher restenosis rate of small vessel coronary artery disease treated with DES, the use of DEB was thought to be an attractive alternative in this patient cohort.

Small vessel disease treated with a paclitaxel DEB has been shown to be associated with less angiographic late loss and similar rates of restenosis and revascularization as compared to PES. In the BELLO (Balloon Elution and Late Loss Optimization) trial, 182 patients with lesions located in small vessels (reference diameter <2.8 mm) were randomized to treatment with paclitaxel DEB and provisional bare metal stenting (n = 90) or PES implantation (n = 92). The primary end point was no inferiority of angiographic in-stent (in-balloon) late loss with a delta of 0.25 mm. Secondary end points were angiographic restenosis, target lesion revascularization, and MACE (death, myocardial infarction, TVR) at 6 months. Although the DEB group had smaller vessel sizes overall, the groups were otherwise well matched, and the majority of the treated lesions (89%) were <2.5 mm in diameter. The primary end point of in-device late loss was significantly less with DEB compared to PES ($P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .001$). At 6-month follow-up, the angiographic restenosis, TLR, and MACE rates were similar between DEB and PES. 73
The results of this trial, although encouraging for the use of DEB in the treatment of small vessel disease, contradict data from the earlier PICCOLETO trial. In the PICCOLETO trial, the Dior (Eurocor, Bonn, Germany) paclitaxel-covered balloon (PCB) failed to show no inferiority to paclitaxel DES regarding angiographic end points during percutaneous coronary intervention (PCI) of small coronary arteries. The trial was a small randomized study including patients with stable or unstable angina undergoing PCI of small coronary vessels (≤2.75 mm) who were randomized to Dior PCB (n = 28) or paclitaxel DES (n = 29). The primary study end point was stenosis diameter percentage at 6-month angiographic follow-up (noninferiority), with secondary end points being angiographic binary restenosis and occurrence of MACE (death, myocardial infarction, or TLR) at 9-month follow-up. The study was terminated early, after clear superiority in stenosis percentage of PES was observed (43.6% vs 24.3%; \( P = .029 \)) in two-thirds of enrolled patients. Angiographic restenosis and MACE were also significantly higher in the PCB group compared to the PES group\(^7\) (Fig. 39-6).

![The piccoleto trial](image)

**FIGURE 39-6** In the PICCOLETO trial, the Dior paclitaxel-eluting balloon (PEB) failed to show noninferiority to paclitaxel-eluting stent (PES) regarding angiographic end points during percutaneous coronary intervention of small coronary arteries. PES was superior to PEB in stenosis percentage (24.3% vs 43.6%; \( P = .029 \)). Angiographic restenosis and major adverse cardiac events were also significantly higher in the PEB group compared to the PES group. (Reproduced from Cortese B,

Although the widespread use of these devices may have a future niche role in treating in-stent restenosis, based on these 2 small trials, the data are certainly lacking to suggest a clear role for drug-eluting/drug-coated balloons in the treatment of small vessel coronary disease.

**BIOREABSORABLE POLYMERS AND STENTS**

The use of biodegradable polymers, as opposed to durable polymers, which serve as the vehicle for the elution of antiproliferative agents, has garnered interest in recent years as a way of minimizing the limitations of DES in the treatment of de novo coronary lesions. It is hypothesized that the eventual reabsorption of polymer not only removes a trigger of inflammation, but also decreases the risk of late and very late stent thrombosis, because endothelialization occurs sooner. Although DESs that are not permanent are intuitively attractive, good data are lacking regarding this technology as it relates to small vessel disease.

Finally, the use of bioabsorbable stent scaffolding represents a groundbreaking advance in the field of PCI. Long-term follow-up from the ABSORB I and II studies of bioresorbable vascular scaffold (BVS) suggested late plaque regression and favorable remodeling, which are attributes that would be particularly beneficial in the setting of small vessel disease. ABSORB III randomized 2008 patients 2:1 to the ABSORB BVS (Abbott Vascular) versus XIENCE in patients with uncomplicated lesions. The strut thickness of the ABSORB BVS is 150 μm. Although the overall trial suggested noninferiority of the bioresorbable stent compared to the XIENCE metallic platform, patients with small vessels (particularly <2.5 mm in diameter) had a higher stent thrombosis rate. This may have been due to the relatively high ratio of stent thickness to vessel lumen diameter in these small vessels, particularly when coupled with suboptimal stent dilatation. There are no trials to date specifically looking at bioresorbable scaffolding in the treatment of small vessel disease. As the strut thickness of these
bioresorbable scaffolds decreases and implantation techniques are optimized, we will have to see how these devices compare to the best metallic platforms. If their early safety is comparable, they may have an advantage if the promise of their long-term benefits is demonstrated (Fig. 39-7).

**FIGURE 39-7** ABSORB III 1-year events based on the reference vessel diameters (RVDs) of less than or greater than 2.25 mm. $P_{\text{int diff}}$, $P$ value for interaction difference; QCA, quantitative coronary angiography; ST, stent thrombosis; TLF, target lesion failure. (Based on data from Ellis S, Kereiakes D, Metzger C, et al. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. *N Engl J Med.* 2015;373:1905-1915.)

**WHAT PCI THERAPY IS BEST FOR SMALL VESSELS?**

To evaluate the most appropriate PCI in the treatment of small vessel coronary disease, Siontis and colleagues\(^76\) performed a pairwise meta-analysis followed by a network meta-analysis of small vessel PCI studies. Nineteen trials were included with over 5000 patients.\(^76\) The 5 identified interventions included and compared were (1) first-generation SES, (2) first-generation PES, (3) DCB, (4) bare metal stents, and (5) balloon angioplasty (BA). No dedicated trial was identified evaluating new-generation DESs.
Both angiographic and clinical outcomes were assessed. Early-generation SES yielded the best angiographic results according to percent diameter stenosis. For percent diameter stenosis, SES was ranked as the most effective treatment followed by PES and DCB. In terms of absolute differences, SES yielded a significant reduction of 18% in diameter stenosis compared to DCB. SES significantly reduced the risk of TLR versus PES, DCB, bare metal stent, and BA (Fig. 39-8).

**FIGURE 39-8** Network meta-analysis demonstrating superiority of sirolimus-eluting stent (SES) over other percutaneous coronary intervention PCI modalities. A. Ranking plots for all the outcomes of with respect to diameter stenosis. Interventions have been ranked according to the surface under the cumulative ranking curve (SUCRA) values. SES was superior to all other modalities; balloon angioplasty (BA) was least effective. B. Estimated odds ratios (95% confidence intervals [CIs]) for the secondary outcomes of the network meta-analysis (binary restenosis, target lesion revascularization, myocardial infarction, and overall mortality) of different percutaneous interventions compared to BA. BMS, bare-metal stent; DCB, drug-coated balloon; PES, paclitaxel-eluting stent; PrI, prediction interval; SMD, standardized mean difference. (Reprinted from Siontis G, Piccolo R, Praz F, et al. Percutaneous coronary interventions for the treatment of stenoses in small coronary arteries: a network meta-analysis. *JACC Cardiovasc Interv*. 2016;9(13):1324-1334, Copyright © 2016, with permission from American College of Cardiology Foundation.)

**SUMMARY**
Small vessel and diffuse coronary disease continue to be challenging subsets even in the era of advanced transcatheater therapies. Frequently, what is thought to be a small vessel by angiographic criterion is often incorrect, because unsuspected disease in the reference areas and positive remodeling at the lesion promote the underestimation of vessel size, particularly in the proximal coronary segments and in patients with diabetes. The acute risks and technical problems associated with percutaneous intervention of these lesions can be higher, although advances in stent design and the use of newer antiproliferative agents have attenuated these challenges. DESs have revolutionized the treatment of small and diffuse disease. Although the restenosis rates with DES in small vessels may be incrementally higher than in larger vessels, DESs dramatically improve angiographic outcomes and reduce repeat revascularization in small and diffuse vessel coronary intervention, particularly limus-eluting stents. Newer technologies, such as the use of biodegradable polymers or bioabsorbable stents, may play a significant role in the future of treating these lesions. Nonetheless, the use of DES has truly become the dominant technology used for these lesions and has broadened the indication for transcatheter therapy in many untreatable patients who suffer from the difficult problem of small and diffuse coronary disease.

REFERENCES


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Caputo R, Leon M, Serruys P, et al. TCT-639 two year outcomes following implantation of the resolute zotarolimus-eluting stent in vessels ≤2.5 mm diameter. *J Am Coll Cardiol.* 2012;60:17S.


MULTIPLE CHOICE QUESTIONS

1. Independent predictors of underestimating the true coronary vessel size based on a disparity between intravascular ultrasound (IVUS)–determined reference lumen diameter and coronary angiography include all of the following except:
   A. Diabetes
   B. Proximal left anterior descending artery (LAD) lesion location
   C. Coronary calcification
   D. Diffuse disease

2. True or false? Small vessel size has been associated with higher restenosis rates. However, equally expanded stents (equal minimum stent area) in different-sized arteries have equivalent restenosis risk.

3. True or false? For calcified small coronary lesions, prestent atherectomy has been associated with lower restenosis rate.

4. True or false? Compared to bare metal stents, percutaneous transluminal coronary angioplasty has a higher rate of target lesion revascularization.

5. True or false? Compared to drug-eluting stents, bare metal stents in small vessels have a lower incidence of negative remodeling over the first year.

6. The use of bioresorbable scaffolds in small vessels has been associated with higher stent thrombosis compared to metallic second-generation drug-eluting stents in vessels smaller than which size?
   A. 2.5 mm
   B. 2.75 mm
   C. 3.0 mm
   D. 3.25 mm

ANSWERS

1. C
2. False
3. False
4. False
5. True
6. A
Special Patient Subset: Diabetes Mellitus

Mark L. Villalon
Zoran S. Nedeljkovic
Alice K. Jacobs

PREVALENCE OF DIABETES MELLITUS

Diabetes mellitus affects a significant portion of the population; 1 in 10 adults in the United States has diabetes, with 90% to 95% of patients having type 2 diabetes.\(^1\) In 2012, nearly 20.1 million Americans ≥20 years of age were diagnosed with diabetes mellitus, 8.1 million Americans had undiagnosed diabetes mellitus, and an estimated 80.8 million (35.3%) had prediabetes (ie, fasting blood glucose of 100 to <126 mg/dL).\(^1\) The prevalence of diabetes mellitus is rapidly increasing and is attributed to the increased frequency of obesity, suboptimal nutritional habits, and aging of the population (Fig. 40-1).\(^2\) The total prevalence of diabetes mellitus in the United States is expected to more than double from 2005 to 2050 (from 5.6% to 12.0%) in all age, sex, and race/ethnicity groups, with minorities disproportionately affected.\(^1\) This increase, however, is not limited to the United States. The global prevalence of diabetes mellitus for all age groups is also increasing. In 2010, the prevalence of diabetes mellitus worldwide was estimated to be 6.4% and is projected to increase to 7.7% in 2030; the total
number of people with diabetes mellitus is projected to increase from 285 million in 2010 to 439 million in 2030.\textsuperscript{1,3}

**FIGURE 40-1** Numbers of people with diabetes (in millions) for 2000 and 2010 (top and middle values, respectively), and the percentage increase. (Reprinted by permission from Macmillan Publishers Ltd: Nature, Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414:782-787, Copyright © 2001.)

**DIABETES AND CARDIOVASCULAR DISEASE: GENERAL CONSIDERATIONS**

The interventional cardiologist often encounters patients with diabetes mellitus in more advanced stages, when vascular complications have already occurred. The pathophysiology of vascular disease involves derangements in endothelial, vascular smooth muscle cell, and platelet function.\textsuperscript{4} The hyperglycemia, increased availability of free fatty acids, and insulin resistance in the diabetic patient collectively decrease nitric oxide availability, increase oxidative stress, disrupt intracellular signal transduction,
and activate receptors for free radical–producing advanced glycation end products. In addition, several deregulatory factors play a part in the derangements of coagulation and platelet activity seen in patients with diabetes, mostly mediated by enhancement of the prothrombotic state due to insulin resistance and hyperglycemia. Subsequently, atherosclerosis ensues, and as such, the risk for adverse cardiovascular events increases.

The concept of diabetes as a coronary artery disease (CAD) risk equivalent has its roots in a landmark Finnish-based study that demonstrated that the presence of diabetes alone increased the 7-year risk of fatal and nonfatal myocardial infarction (MI). These results laid the foundation for the recommendation that patients with diabetes receive secondary level prevention per the Adult Treatment Panel III of the National Cholesterol Education Program.

Indeed, CAD is prevalent in the patient with diabetes even when asymptomatic. Occult CAD was discovered in asymptomatic patients with diabetes who underwent coronary computed tomography angiography despite having a normal stress test (using single-photon emission computed tomography pharmacologic stress testing), a normal electrocardiogram, a lack of symptoms, and a lack of peripheral arterial disease. A separate study of an autopsy cohort from Olmstead County, Minnesota, examined patients with diabetes without prior evidence of clinical CAD and found that they were more likely than their nondiabetic counterparts to have high-grade atherosclerosis (68% vs 46%; \( P < .001 \)) and more likely to have multivessel CAD (50% vs 31%; \( P < .001 \)).

Moreover, the presence of angina was not found to be predictive of future mortality or cardiac events. In a post hoc analysis of the Bypass Angioplasty Revascularization Investigation in Patients With Diabetes (BARI 2D) trial, the prognostic significance of angina or its equivalents was examined, and it was determined that the presence of angina did not significantly affect the 5-year risk of cardiovascular events or all-cause mortality.

The patient with diabetes and underlying ischemic heart disease is more likely to be female and have a higher prevalence of hypertension, hypercholesterolemia, renal insufficiency, peripheral vascular disease, and congestive heart failure. There is an excess mortality associated with CAD in patients with diabetes, particularly in patients with acute coronary syndromes (ACS), and females have a relative risk for fatal CAD that is
50% higher than males.  

**MEDICAL THERAPY**

It is well established that patients with CAD across the spectrum of stable ischemic heart disease, ACS, and ST-segment elevation MI (STEMI) should be treated with guideline-directed medical therapy (GDMT). However, in patients with diabetes, with more rapid progression of atherosclerosis and a higher incidence of adverse events, special considerations exist. It has been shown that diabetes is a clinical predictor of nonresponse to aspirin and clopidogrel therapy, suggesting that patients with diabetes may require more aggressive antiplatelet regimens. Using aggregation-based testing in a prospective evaluation of 635 patients with non-STEMI to evaluate the clinical predictors of nonresponse to aspirin and clopidogrel therapy, diabetes was associated with an attenuated response to these antiplatelet agents.

In addition, subgroup analysis of patients with diabetes in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) examined the net effect of diabetes on the efficacy and safety profiles of prasugrel as compared with clopidogrel. For patients with diabetes treated with prasugrel for high-risk ACS, the rate of cardiovascular death, nonfatal MI, and nonfatal stroke was significantly reduced as compared with clopidogrel (Fig. 40-2).
FIGURE 40-2 Kaplan-Meier curves for prasugrel versus clopidogrel stratified by diabetes status. A. Primary efficacy end point (cardiovascular death, nonfatal myocardial infarction [MI], or nonfatal stroke) stratified by diabetic status. B. MI (fatal or nonfatal). DM, diabetes mellitus; HR, hazard ratio. (Reproduced with permission Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial I. Circulation. 2008;118:1626-1636.)

The BARI 2D trial compared GDMT with and without coronary revascularization in a relatively low-risk population and revealed that an initial strategy of percutaneous coronary intervention (PCI; n = 1605) or coronary artery bypass graft (CABG; n = 763) plus GDMT did not improve
outcomes compared with GDMT alone (freedom from death, MI, or stroke: 77.2% vs 75.9%). However, in the CABG-stratified group (more advanced CAD and class C lesions), freedom from death, MI, or stroke was significantly lower in patients treated with CABG plus GDMT compared with GDMT alone (77.6% vs 69.5%), suggesting that patients with advanced CAD may benefit from CABG.\textsuperscript{20}

**CORONARY REVASCULARIZATION: SPECIAL CONSIDERATIONS**

Nearly 25\% of all revascularization procedures are performed in patients with diabetes\textsuperscript{1}; in the National Cardiovascular Data Registry, 36.2\% of patients undergoing PCI between 2010 and 2011 had diabetes.\textsuperscript{21} Although acute procedural success and complications are similar in patients with and without diabetes undergoing PCI,\textsuperscript{11,22} patients with diabetes are more likely to have advanced CAD, with more multivessel disease, total occlusions, and diffuse disease.\textsuperscript{11,23} This finding may translate to higher in-hospital mortality rates. In an analysis of the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, a significantly higher in-hospital mortality in patients with diabetes compared to patients without diabetes (diabetes 2.3\% vs no diabetes 1.3\%; $P = .02$) undergoing PCI was observed.\textsuperscript{11} Patients with diabetes who undergo PCI are at increased risk not only for death and MI during subsequent follow-up, but also for repeat revascularization and angiographic restenosis.\textsuperscript{11,24,25} Patients with diabetes, in particular type 1 diabetes with poor glycemic control, who underwent CABG had increased long-term risk of major adverse coronary events and all-cause mortality.\textsuperscript{26} In addition, patients with type 1 diabetes who underwent CABG were found to have a more than 2-fold increased risk of death at 6 years compared with the general population, whereas patients with type 2 diabetes had only a slightly worse prognosis after CABG.\textsuperscript{27}

Revascularization considerations for patients with diabetes across the spectrum of CAD have been noted earlier for patients with stable ischemic heart disease where CABG may play a role in patients with advanced disease. Although the last 2 decades have witnessed an innovative expansion of catheter-based therapy for CAD, for the patient with stable ischemic heart
disease, this expansion has not resulted in a survival improvement but rather a decrease in restenosis. A meta-analysis comparing these methods to medical therapy in stable CAD did not improve the rates of death or MI.²⁸

In patients with ACS, in whom 30-day mortality is higher in patients with diabetes compared to without diabetes, the benefit seen overall in terms of a decrease in major adverse cardiac events is similar in patients with and without diabetes. However, patients with diabetes experienced a reduction in nonfatal MI (relative risk [RR], 0.71; 95% confidence interval [CI], 0.55-0.92) not seen in patients without diabetes.²⁹ It is noteworthy that the American College of Cardiology/American Heart Association guidelines suggest that the invasive strategy is preferred in patients with diabetes and ACS.³⁰ For patients with STEMI and diabetes, management should be similar to that for patients without diabetes, where primary PCI is the preferred strategy if accomplished within guideline-recommended time to reperfusion.

**RESTENOSIS**

There is evidence that the metabolic abnormalities associated with the diabetic state (hyperglycemia and hyperinsulinemia) can lead to enhanced platelet adhesion, activation, and aggregation, in addition to thrombus formation, endothelial cell dysfunction, and alterations in local growth factor production.³¹ Smooth muscle cell proliferation and extracellular matrix deposition, crucial elements in the cellular response to vessel injury and subsequent development of restenosis following PCI, are also enhanced in diabetic patients.³¹ It has been observed that the mechanism of increased restenosis in patients with compared to without diabetes following coronary stent placement was due to increased late loss of minimal lumen diameter, suggesting more aggressive neointimal hyperplasia with diabetes.³²

The presence of diabetes is an independent risk factor for restenosis after PCI. Among patients with diabetes who underwent standard balloon angioplasty in the first report from the NHLBI Percutaneous Transluminal Coronary Angioplasty Registry in the early 1980s, restenosis occurred in 47%, compared with 32% in patients without diabetes.³³ This finding is not limited to patients undergoing balloon angioplasty, but extends to those who are treated with stents. In a study that included over 12,000 patients with
diabetes undergoing stent implantation (bare metal and first- and second-generation drug-eluting stents), diabetes was an independent risk factor for restenosis (odds ratio, 1.32; 95% CI, 1.19-1.46). Although drug-eluting stents have been shown to have significantly lower rates of restenosis as compared to bare metal stents, restenosis still occurs and may be related to longer stent length and small vessel size in patients with diabetes.

**DRUG-ELUTING STENTS**

In 2010, approximately 75% of stents used during PCI were drug-eluting stents and 25% were bare metal stents. As compared with bare metal stents, drug-eluting stents reduce cardiac events in a broad selection of patients with angina or ACS, a finding driven by a reduction in restenosis. In the patient with diabetes, the advantages of drug-eluting stents have also been observed. In all patients with diabetes who underwent PCI with stents between April 1, 2003, and September 30, 2004, in the state of Massachusetts, drug-eluting stents reduced mortality, MI, and revascularization compared with bare metal stents (Fig. 40-3).
FIGURE 40-3 Clinical outcomes after stenting in patients with diabetes mellitus. Cumulative incidence of mortality (A), myocardial infarction (B), and target vessel revascularization (C) at 3 years in the matched cohort of patients with diabetes. Solid lines indicate drug-eluting stents (DES); dashed lines indicate bare metal stents (BMS). Error bars are 95% confidence intervals. (Reproduced with permission from Garg P, Normand S-LT, Silbaugh TS, et al. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. Circulation. 2008;118:2277-2285.)

In a collaborative network meta-analysis of 35 trials, sirolimus- and paclitaxel-eluting stents were found to be safe and effective in both patients with and without diabetes when combined with greater than 6 months of dual antiplatelet therapy. In another analysis, the outcomes of various commercially available drug-eluting stents (including sirolimus-, paclitaxel-, zotarolimus-, and everolimus-eluting stents) were examined. In this mixed treatment comparative meta-analysis of 42 trials with over 10,000 patients...
with diabetes, all of the drug-eluting stents showed a reduction in target vessel revascularization compared with bare metal stents. The efficacy varied between stents, with everolimus-eluting stents having the lowest rate of target vessel revascularization compared to zotarolimus, sirolimus, and paclitaxel stents.³⁹

**PCI VERSUS CABG**

The optimal method of revascularization, percutaneous or surgical, has been debated for nearly 2 decades. Complicating the interpretation of the initial studies, which compared the outcomes of surgical versus percutaneous modalities of revascularization in the patient with diabetes, are the recent advances in both surgical and percutaneous techniques and materials. Table 40-1 presents an overview of the major trials comparing PCI with CABG in patients with diabetes and multivessel CAD.⁴⁰

**Table 40-1 Randomized Clinical Trials Comparing CABG Surgery with PCI in Patients with Diabetes and Significant Multivessel CAD**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Profile</th>
<th>Time, y</th>
<th>Groups*</th>
<th>Mortality, No. (%)</th>
<th>P Value</th>
<th>Repeat Revascularization, No. (%)</th>
<th>P Value</th>
<th>MACCE, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI Investigators, 2007 (BARI)</td>
<td>Symptomatic/Ischemic multivessel CAD (diabetic cohort)</td>
<td>10</td>
<td>CABG surgery (n = 180) Balloon (n = 173)</td>
<td>42.2% 54.5%</td>
<td>.03</td>
<td>(18.3%) (70.7%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kapur et al, 2010 (CARDia)</td>
<td>Diabetes and either multivessel CAD or complex single- vessel disease</td>
<td>1</td>
<td>CABG surgery (n = 249) BMS/sirolimus (n = 254)</td>
<td>81.2% 83.2%</td>
<td>.97</td>
<td>52(2.0%) 30(11.8%)</td>
<td>&lt;.01</td>
<td>28(11.3%) 49(19.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Farkouh et al, 2012 (FREEDOM)</td>
<td>Diabetes and multivessel CAD</td>
<td>5</td>
<td>CABG surgery (n = 947) Paclitaxel or sirolimus (n = 953)</td>
<td>8(10.9%) 11(16.3%)</td>
<td>.05</td>
<td>41(6.0%) 117(12.6%)</td>
<td>&lt;.01</td>
<td>106(11.8%) 157(16.8%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Kappetein et al, 2013 (SYNTAX)</td>
<td>Diabetes with left main and/or 3-vessel disease</td>
<td>5</td>
<td>CABG (n = 221) Paclitaxel (n = 231)</td>
<td>26(12.9%) 46(19.5%)</td>
<td>.07</td>
<td>28(14.6%) 75(35.3%)</td>
<td>&lt;.01</td>
<td>55(28.9%) 105(46.5%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Kamaleh et al, 2013 (Veterans Affairs study)</td>
<td>Diabetes multivessel CAD or isolated proximal left anterior descending disease</td>
<td>2</td>
<td>CABG (n = 97) DES (n = 101)</td>
<td>5% 21%</td>
<td>NR</td>
<td>19.5% 18.9%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: BMS, bare-metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease; significant multivessel CAD defined as >70% stenosis in ≥2 major epicardial coronary arteries; DES, drug-eluting stent; MACCE, major adverse cardiac and cerebrovascular events (defined as all-cause mortality, myocardial infarction, stroke, or repeat revascularization); NR, not reported; PCI, percutaneous coronary interventions; RCT, randomized clinical trials.

*Composites pertaining to the diabetic cohort reported.
*Subset of patients with treated diabetes.
*Only percentage was reported.
*Initially started with BMS and switched to sirolimus-eluting stents when they became available.
*All outcomes are defined at 1 year in this FREEDOM trial.
*Choice of any US Food and Drug Administration-approved DES.


The first major trial comparing the outcomes of the 2 revascularization strategies was a subset analysis of the initial BARI trial.⁴¹ In this landmark study, 1829 patients with symptomatic multivessel CAD were randomized to
either multivessel balloon angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) or CABG. Although the overall trial results showed no difference in mortality between the 2 revascularization strategies, analysis of the 353 patients with diabetes revealed a significantly lower 5-year survival in the group treated with PTCA compared with CABG (65.5% vs 80.6%).\textsuperscript{42} In a 10-year follow-up analysis, this survival disadvantage persisted in individuals managed with PTCA (PTCA 45.5% vs CABG 57.8%; \( P < .025 \)).\textsuperscript{43}

Additional findings from this study revealed that the benefit of surgery was greater in patients with diabetes treated with insulin compared to those treated with oral hypoglycemic agents and appeared to be limited to patients receiving a left internal mammary artery (LIMA) graft and to those with more diffuse disease defined by 4 or more lesions.\textsuperscript{42,44}

One possible explanation for the improved survival seen in patients with diabetes undergoing CABG may be related to progression of disease in patients undergoing PTCA. A retrospective analysis of 248 patients referred for diagnostic angiography >1 month after successful PTCA found a significantly higher rate of new lesions on the follow-up angiogram in patients with compared to without diabetes (22% vs 12%; \( P < .004 \)).\textsuperscript{45} PTCA appeared to increase the risk of new lesions distant from the treatment site, and the risk was additive in patients with diabetes. This may, in part, account for the possible survival advantage of CABG, especially when using the LIMA.

The Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI) and Emory Angioplasty versus Surgery Trial (EAST) trials were similar trials of PTCA versus CABG in patients with multivessel CAD.\textsuperscript{46,47} Although both trials showed a trend toward improved survival with CABG in the diabetes subset, the number of patients with diabetes in these trials was small, and the differences did not reach statistical significance.

Moreover, in a collaborative analysis of patient data from 10 randomized trials of PCI compared with CABG in patients with multivessel CAD, including 4 trials using bare metal stents in 7821 patients of whom 1233 were patients with diabetes, mortality was similar at a median follow-up of 5.9 years. However, in patients with diabetes, CABG was associated with significantly lower mortality (23% vs 29%; hazard ratio [HR], 0.7; 95% CI, 0.56-0.87) in comparison to PCI. While overall mortality was 50% lower in
the trial using bare metal stents, the relative advantage of CABG persisted overall and in patients with diabetes.\textsuperscript{48}

The majority of these early trials preceded the modern era of coronary stents and technical improvements in PCI and surgical revascularization. In the Arterial Revascularization Therapies (ART) Part-I and Part-II studies, bare metal stents, sirolimus-eluting stents, and surgical revascularization were compared. These studies included a total of 367 patients with diabetes, in whom there were 112 patients who received bare metal stents, 159 patients who received sirolimus-eluting stents, and 96 CABG patients.\textsuperscript{49} The rate of major adverse cardiovascular and cerebrovascular events favored the surgical revascularization group (bare metal stents 53.6\% vs CABG 23.4\% vs sirolimus-eluting stents 40.5\%; \( P < .01 \) for sirolimus-eluting stents vs bare metal stents and sirolimus-eluting stents vs CABG). Repeat revascularization was highest with the bare metal stent group at 43.5\%, compared with 33.2\% in the sirolimus-eluting stent group and 10.7\% in the CABG group (sirolimus-eluting stent vs bare metal stent, \( P < .02 \); sirolimus-eluting stent vs CABG, \( P < .01 \)). Of note, mortality was not significantly different between all 3 groups.

The CARDia (Coronary Artery Revascularization in Diabetes) trial was the first to enroll an all-diabetic cohort with CAD and randomize patients to CABG versus PCI plus stenting (with bare metal stents or sirolimus-eluting stents). Although 1-year results revealed all-cause mortality rates of 3.2\% for both groups, this study failed to show that PCI was noninferior to CABG. When repeat revascularization was added to the composite of death, MI, or stroke, there was a significant difference favoring CABG (11.3\% vs 19.3\% in the CABG and PCI groups, respectively; HR, 1.77; 95\% CI, 1.11-2.82; \( P = .02 \)).\textsuperscript{50}

In the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial, investigators compared PCI (with paclitaxel-eluting stents) with CABG in 1800 patients with de novo left main or 3-vessel CAD.\textsuperscript{51} After a follow-up of 5 years, the subset of patients with medically treated diabetes (\( n = 452, 26\% \)) had significantly higher rates of major adverse cardiac and cerebrovascular events when treated with PCI compared with CABG (PCI 46.5\% vs CABG 29.0\%; \( P = .001 \))\textsuperscript{52} driven by repeat revascularization. However, there remained no significant difference in all-cause mortality in this subgroup with diabetes (PCI 23.9\% vs CABG 19.1\%; \( P < .26 \)).
An interesting subgroup analysis of SYNTAX compared patients with and without diabetes with low (<22) SYNTAX scores. In this subgroup, management with PCI resulted in comparable major adverse cardiac and cerebral event rates (30.5% vs 29.8%; \( P < .98 \)), with no difference in repeat revascularization (Fig. 40-4).\textsuperscript{53} This suggests that PCI is a reasonable alternative to CABG in patients with diabetes with less complex 3-vessel or left main disease. However, these findings must be interpreted with caution in view of a small subset of patients with diabetes, use of first-generation drug-eluting stents, and an overall trial that did not meet its primary end point.
FIGURE 40-4 Three-year outcomes for patients with and without diabetes according to anatomic lesion complexity, as measured by the SYNTAX score: (A, D) major adverse cardiac and cerebrovascular events (MACCE); (B, E) composite of death, cerebrovascular accident (CVA), and myocardial infarction (MI); and (C, F) revascularization in patients with medically treated diabetes (A-C) and without medically treated diabetes (D-F). Rates are separated by SYNTAX scores, indicating low (≤22), intermediate (23–32), and high (≥33) anatomic lesion complexity. CABG, coronary artery bypass grafting (Blue); PCI, paclitaxel-eluting stent (Red).

(Reproduced with permission from Mack MJ, Banning AP, Serruys PW, et al. Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or...

The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, the largest randomized trial investigating revascularization strategies in patients with diabetes, consisted of 1900 patients with diabetes and multivessel CAD who were randomized to either PCI with drug-eluting stents (primarily sirolimus-eluting and paclitaxel-eluting stents) or CABG. This study concluded that CABG was the superior modality of revascularization in this specific patient population. The majority of the patients (83%) had 3-vessel disease, mean SYNTAX score was 26.2 with a symmetric distribution, nearly all had hypertension and/or dyslipidemia, 26% had a prior MI, 29% had a low-density lipoprotein level <70 mg/dL, and 95% of patients received a LIMA conduit. During a median follow-up of 3.8 years, the primary end point of death from any cause, nonfatal MI, or nonfatal stroke occurred more frequently in the PCI group compared with the CABG group (P = .005). The 5-year rate of all-cause mortality, MI, and stroke was 26.6% in the PCI arm and 18.7% in the CABG arm. Of note, the rate of stroke was higher in the CABG arm compared with the PCI arm (5.2% vs 2.4%; P = .03), mostly driven by the excess of stroke event rate (87% ischemic, 13% hemorrhagic) within the first 30 days after surgery. The superiority of CABG was not affected by the SYNTAX score. Moreover, the individual end points of mortality and MI were significantly lower in the CABG group.

Finally, a meta-analysis of 4 randomized trials of PCI using drug-eluting stents and CABG in >3000 patients with diabetes revealed that the major adverse coronary event rate (death, MI, or stroke) was higher in the PCI group (22.5% vs 16.8%; RR, 1.34; 95% CI, 1.16-1.54; P < .0001). The superiority of CABG compared with PCI was most evident with high SYNTAX scores.

In aggregate, these data suggest that in patients with diabetes and multivessel disease, CABG is the preferred strategy, particularly in patients at low or moderate risk for surgery with complex anatomy and 3-vessel disease and in patients who will receive a LIMA graft.

**PRACTICAL CONSIDERATIONS**
As described earlier, patients with diabetes undergoing PCI are at risk for periprocedural and long-term complications. Careful peri- and intraprocedural management can often mitigate some of the acute risk, and here we discuss strategies that we believe are helpful to consider.

Patients with diabetes should be in a euvolemic state prior to and following use of iodinated contrast agents. Volume depletion increases the risk for contrast-mediated renal insufficiency, which is a concern in patients with diabetes, particularly in those with chronic kidney disease. We recommend that diuretics be held the morning of the scheduled procedure, and if there is any baseline renal impairment, we consider withholding angiotensin-converting enzyme inhibitors. Our practice is to withhold metformin at least 24 hours prior to the procedure, if possible, and to withhold it for a minimum of 72 hours after the procedure. In addition, we routinely hold oral hypoglycemic agents and short-acting insulin preparations. Long-acting insulin can be administered at a reduced (half) dose. Our patients also routinely receive 0.9% isotonic saline (with dextrose added if insulin is administered), at a rate of 1 mL/kg/h prior to the start of the procedure. After the procedure, we administer a high volume of hydration with saline infusion (minimum 1-2 L), maintaining euvolemia with furosemide as needed (with positive or negative fluid balance at 12-24 hours after procedure determined by filling pressures). Serum electrolytes and creatinine are routinely measured on the day after the procedure.

Transradial catheterization is associated with a lower incidence of bleeding and vascular complications when compared with the transfemoral route, and this is preferred, especially in the patient with diabetes and peripheral arterial disease. Since diabetic patients are at increased risk for repeat revascularization, drug-eluting stents are our preferred revascularization strategy.

**RECOMMENDATIONS**

We prefer PCI in patients with diabetes with single- or selected double-vessel CAD, if the anatomy is suitable, and especially if they are candidates for treatment with drug-eluting stents. However, deciding on a revascularization strategy in a patient with diabetes with triple-vessel (and multilesion) CAD is more of a challenge. We strongly consider CABG for patients with diabetes
with multivessel diffuse disease, especially if there is involvement of the proximal left anterior descending artery, which would allow grafting with an internal mammary artery. We also prefer CABG for patients with complex multivessel disease and reduced left ventricular function.

The Fractional Flow Reserve Versus Angiography in Multivessel Evaluation 2 (FAME 2) trial revealed similar results in patients with and without diabetes and improvements in stent technology including bioabsorbable stents, new platforms, and new polymers, and newer and more effective thienopyridines are on the horizon. Notwithstanding these advancements, since the mechanism responsible for the advantage of CABG compared with PCI in patients with diabetes and multivessel disease is most likely protection of the myocardium against subsequent events, it is expected that CABG will continue to be associated with more favorable outcomes.

REFERENCES


53. Mack MJ, Banning AP, Serruys PW, et al. Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or


**MULTIPLE CHOICE QUESTIONS**

1. In comparison with percutaneous coronary intervention (PCI), which of the following best explains the benefit of coronary artery bypass grafting (CABG) in patients with diabetes mellitus and multivessel coronary artery disease (CAD)?
   A. Fewer procedural complications with CABG
   B. Progression of disease following PCI
   C. Superior long-term patency of saphenous vein conduits compared with drug-eluting stents
   D. Higher periprocedural mortality with PCI compared with CABG

2. Compared with bare metal stents, drug-eluting stents reduce the incidence of which of the following in patients with diabetes?
   A. Stent thrombosis
   B. Periprocedural myocardial infarction
   C. Restenosis
   D. Periprocedural bleeding complications
3. CABG surgery is preferred to PCI in which of the following clinical scenarios in patients with diabetes?
   A. A 45-year-old man with unstable angina and a 90% stenosis in the mid right coronary artery
   B. A 60-year-old woman with rheumatoid arthritis on steroids, unstable angina, and a 70% discrete stenosis in the proximal circumflex artery and 90% ulcerated stenosis in the proximal right coronary artery
   C. A 55-year-old man with stable angina and an 80% stenosis in the proximal left anterior descending artery, a 100% stenosis in the proximal right coronary artery, and a 70% stenosis in the proximal left circumflex artery
   D. An 80-year-old man with stable class III angina and a 100% chronic occlusion of the proximal right coronary artery

4. The Bypass Angioplasty Revascularization Investigation (BARI) study demonstrated which of the following outcomes in patients with diabetes treated with balloon angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) compared with CABG at 5-year follow-up?
   A. Decreased survival with PTCA
   B. Improved survival with PTCA
   C. Decreased rate of myocardial infarction (MI) with PTCA
   D. Decreased rate of MI with CABG

5. In the FREEDOM trial, which of the following was responsible for the benefit of CABG compared with PCI in patients with diabetes and multivessel CAD?
   A. Higher rate of death, MI, and stroke with PCI
   B. Lower rate of stroke with CABG
   C. Higher rate of stroke with PCI
   D. Lower rate of cardiovascular death with CABG

**ANSWERS**

1. B

Patients with diabetes mellitus treated with PCI are at increased risk for
progression of disease in nontreated segments of the coronary artery, which often leads to recurrent ischemic events and the need for subsequent repeat revascularization.

2. C

Bare metal stents were developed to reduce the incidence of restenosis following balloon angioplasty. Neointimal proliferation within the stent became an important limitation, leading to restenosis and need for subsequent revascularization, particularly in diabetic patients. Drug-eluting stents were developed to decrease the incidence neointimal proliferation and restenosis.

3. C

The 2011 American College of Cardiology Foundation/American Heart Association guidelines for CABG recommends CABG in preference to PCI to improve survival in patients with multivessel coronary artery disease and diabetes, particularly in patients in whom a left internal mammary arterial graft can be anastomosed to the left anterior descending artery (Class IIa, Level of Evidence B).

4. A

Although the overall BARI trial results showed no difference in mortality between the two revascularization strategies, subsequent post hoc analysis of the 353 diabetic patients revealed a significantly lower 5-year survival in the group treated with PTCA compared with CABG (65.5% vs 80.6%). In a 10-year follow-up analysis, this disadvantage persisted in those individuals managed with PTCA (PTCA 45.5% vs CABG 57.8%; P < .025).

5. A

The FREEDOM trial randomized patients with diabetes and multivessel CAD to either PCI with drug-eluting stents or CABG. During a median follow-up of 3.8 years, the primary end point of death from any cause, nonfatal MI, or nonfatal stroke occurred more frequently in the PCI group compared with the CABG group. The benefit of CABG was mostly driven by decreases in death and MI. The rate of stroke was higher in the CABG arm compared with the PCI arm, mostly driven by the excess of stroke event rate within the first 30
days after surgery.
The introduction of percutaneous balloon mitral valvuloplasty (BMV) by Inoue et al\textsuperscript{1} in 1982 has opened a new dimension in the treatment of patients with mitral stenosis. The body of data accrued to date has clearly established this invasive, nonsurgical procedure as the treatment of choice in symptomatic patients with moderate to severe mitral stenosis (mitral valve area $<1.5\text{ cm}^2$) and favorable valve morphology (noncalcified, pliable valve with minimal subvalvular disease and no or mild mitral regurgitation).\textsuperscript{2-5} The presence of either severe (grade $\geq 3$) angiographic mitral regurgitation or left atrial thrombus is considered to be a contraindication for BMV. However, several controversial issues in the use of this procedure exist, because the selection of patients for BMV in clinical practice continues to be a complex decision involving consideration of multiple variables, including clinical profile, operator skill, valve morphology, and severity of associated mitral regurgitation.

Among the multiple variables, valve morphology and severity of associated mitral regurgitation have, to a large extent, remained the principal determinants in patient selection. In patients with favorable valve morphology (pliable, noncalcified valve with minimal subvalvular disease) and no or mild mitral regurgitation, BMV predictably yields excellent results and a low risk of resultant severe mitral regurgitation. With successful balloon valve enlargement, there is generally a 2-fold increase in the mitral
valve area and an associated dramatic fall in transmitral valve gradient, left atrial pressure, and pulmonary artery pressure.\textsuperscript{2-5} These hemodynamic benefits are mirrored in clinical improvements in the patients’ symptoms and exercise tolerance.

This is not entirely surprising, considering the fact that BMV enlarges the stenosed mitral valve in the same manner as that afforded by surgical commissurotomy—namely that of commissural split. Several randomized trials\textsuperscript{6-11} comparing BMV and closed and/or open surgical commissurotomy in patients with favorable valve morphology have demonstrated that BMV is as efficacious, if not more so, than surgical mitral commissurotomy in acutely relieving the obstructed valve and achieving favorable clinical outcome. The long-term results of BMV are excellent, especially when the acute results are optimal and valve morphology is good. Long-term data in BMV have also indicated that after optimal mitral valve dilation, the restenosis rate is low and the acute symptomatic benefits are sustained.\textsuperscript{12-16} When restenosis is defined as mitral valve area less than 1.5 cm\textsuperscript{2}, the restenosis rate in patients with favorable valve morphology at 7-year follow-up in the randomized trial by Farhat et al\textsuperscript{11} was 6.6\% in patients who underwent BMV; this rate was similar in those who underwent open surgical commissurotomy and was far superior to the restenosis rate of 37\% observed after closed surgical commissurotomy. Hernandez and associates\textsuperscript{16} found that survival free of major events (cardiac death, mitral surgery, repeat BMV, or functional impairment) was 69\% at 7 years, ranging from 88\% to 40\% in different subgroups of patients. Mitral area loss, although mild (0.13 ± 0.21 cm\textsuperscript{2}), increased with time and was greater than or equal to 0.3 cm\textsuperscript{2} in 12\%, 22\%, and 27\% of patients at 3, 5, and 7 years, respectively.

In contrast to the usually excellent results obtained with the procedure in patients with favorable valve anatomy, the results of BMV in those with adverse valve morphology (heavily calcified leaflets and commissures and extensive subvalvular disease) are less predictable.\textsuperscript{17-20} BMV in the latter compared with the former patient subset tends to produce inferior acute and long-term results. Therefore, patients with unfavorable mitral morphology are, in general, better served with mitral valve replacement (but not surgical commissurotomy). Having said that, there remains a significant minority of patients with adverse valve morphology in whom BMV may yield acceptable hemodynamic outcome and may continue to gain long-term symptomatic
improvement. It is thus reasonable to perform BMV in these patients if they refuse surgery as a bridge to surgery at a later stage, particularly if urgent noncardiac surgery is required or if the risk of cardiac surgery is deemed to be prohibitively high because of other major medical comorbidities (Table 41-1). In fact, BMV may occasionally be the only option for some of these patients.

Table 41-1 Recommended Treatment Strategies for Various Subsets of Patients

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliable, noncalcified mitral valve with absent or mild subvalvular disease, and</td>
<td></td>
</tr>
<tr>
<td>a) Absent or mild MR</td>
<td>BMV</td>
</tr>
<tr>
<td>b) Moderate MR</td>
<td>Trial of BMV</td>
</tr>
<tr>
<td>c) With left atrial cavity thrombus</td>
<td>OSC with thrombectomy</td>
</tr>
<tr>
<td>Nonpliable, grossly calcified mitral valve with significant subvalvular disease, and</td>
<td></td>
</tr>
<tr>
<td>a) With or without moderate MR</td>
<td>MVR</td>
</tr>
<tr>
<td>b) In special clinical settings:</td>
<td>BMV</td>
</tr>
<tr>
<td>• High-surgical risk patients</td>
<td></td>
</tr>
<tr>
<td>• Urgent noncardiac surgery required</td>
<td></td>
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<tr>
<td>• Bridge procedure to mitral surgery</td>
<td></td>
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<tr>
<td>• Patient refusal for surgery</td>
<td></td>
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<tr>
<td>• Shortened lifespan from medical comorbidities</td>
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</tbody>
</table>

Abbreviations: BMV, percutaneous balloon mitral valvuloplasty; MR, mitral regurgitation; MVR, mitral valve replacement; OSC, open surgical commissurotomy.
Many centers performing BMV exclude patients with moderate (angiographic grade 2+) mitral regurgitation from the procedure for fear of increasing the severity of the mitral regurgitation and the need for emergency mitral valve surgery. In our centers, these patients with moderate mitral regurgitation but with otherwise favorable valve characteristics are not excluded from BMV. In our experience, the risk of resultant severe mitral regurgitation is minimal with the use of cautionary balloon sizing approach and the controlled stepwise dilation technique.\textsuperscript{21-23} However, should the procedure fail to provide optimal clinical results, patients can still be subjected to elective surgery without exposing them to any additional risk. Recent work suggests that even patients with severe mitral regurgitation and mitral stenosis can benefit from BMV.\textsuperscript{24}

The presence of left atrial thrombus has traditionally been considered a contraindication to BMV because of the heightened risk of cardioembolism with the procedure. In patients with nonpedunculated thrombi in the left atrial cavity, one may elect to administer long-term (3-6 months) warfarin therapy (targeting an international normalized ratio between 2 and 2.5), if their clinical and hemodynamic status does not warrant immediate surgery and the mitral valves are deemed suitable for BMV. When the thrombus is observed to have resolved with transthoracic echocardiographic reassessments performed at 3-month intervals, BMV can then be performed safely after confirmation of the absence of thrombi in the left atrial cavity with transesophageal echocardiography.\textsuperscript{23,25} Patients with lytic-resistant or mobile thrombi should be considered for open surgical commissurotomy with direct visual clot removal. Despite our safe and successful experience in performing Inoue-BMV in patients with left atrial thrombi confined to the appendage,\textsuperscript{23,26} the subject has remained controversial even among experienced operators of Inoue-BMV. Therefore, the alternative approach is either to subject patients with appendage thrombi to mitral valve surgery or to defer BMV for stable patients until resolution of the thrombi under warfarin treatment.\textsuperscript{23,27} Another clinical concern is pulmonary hypertension; successful BMV usually decreases the pulmonary pressure, although early intervention is better.\textsuperscript{28}

The best choice of technique for BMV remains a contentious issue. Beside the original Inoue technique using size-adjustable, self-positioning balloon catheters, various other techniques for performing BMV have been developed
that use fixed-size balloon catheters. These include the antegrade (transvenous) approaches with 1 or 2 balloon catheters through 1 or 2 interatrial septal punctures \textsuperscript{29,30} or the retrograde (transarterial) approaches with transseptal wiring or without transseptal access. \textsuperscript{31} An overview of the various comparative studies, both randomized and nonrandomized, does not reliably indicate that either the double-balloon or the Inoue-balloon technique is superior to the other in achieving a larger final mitral valve area. There is, however, persuasive evidence that the Inoue-balloon approach is technically less demanding and clearly simpler to perform; hence, it has a shorter irradiation and procedural time and is safer than the double-balloon approach. \textsuperscript{32-34} These advantages are vital in pregnant patients in whom the hazards of irradiation to the fetus are of paramount importance and for patients with pulmonary edema in whom swift and expeditious BMV is clearly desirable. Therefore, the transvenous Inoue-balloon approach has obtained its current position as the principal BMV technique.

Subsequent sections of the present chapter are drawn largely from our incremental experience in Inoue-BMV techniques and evolving technical refinements in BMV techniques. These have resulted in a nearly 100% technical success rate and a significant diminution in complications despite the presence of a significant number of technically demanding scenarios and high-risk comorbid conditions. \textsuperscript{12,22,23} Mainly discussed are the technical aspects of Inoue-BMV, the pitfalls and tricks to facilitate a successful procedure, and how to minimize procedure-related complications.

**TRANSSEPTAL ACCESS**

Transseptal catheterization is a vital component of BMV. Transseptal puncture must not only be executed safely to avoid cardiac perforation but also made at an appropriate interatrial septal site to facilitate balloon crossing of the stenosed mitral valve. \textsuperscript{35} To avert cardiac perforation, some operators have resorted to routine intraprocedural transesophageal echocardiography to facilitate optimal transseptal needle placement; however, even with the echocardiographic guidance, cardiac perforation may still occur. \textsuperscript{36} Recently developed intracardiac echocardiography is useful, but it is not widely available and its use adds to more cost. Therefore, acquisition of basic transseptal skill is essential. To perform transseptal procedure, biplane
fluoroscopic equipment is preferable, but single-plane fluoroscopy is usually sufficient.

The instruments used for the procedure include a Brockenbrough needle and a 7- or 8-Fr transseptal catheter. The use of an outer sheath is optional, but its utility is recommended, especially for inexperienced operators, for 2 reasons: (1) to prevent inadvertent perforation of the dilator by the needle during its insertion, and (2) to prevent left atrial perforation during insertion of the catheter/needle into the left atrium; the sheath tip works as a safety stopper at the septum.

Landmarks for Optimal Puncture Site

The puncture target site is usually located at the cross point of (1) a horizontal line crossing the center of the mitral annulus (M-line) and (2) a vertical line, assumed to divide the interatrial septum into anterior and posterior halves (“midline”). However, in individual cases, the puncture site may have to be adjusted. For example, in patients with giant left atria, the operator is often forced to make the interatrial septal puncture more caudal to the horizontal M-line. In patients with a more vertically oriented left ventricle and a relatively small left atrium, the operator may need to make the puncture site slightly more cephalad to the M-line and lateral to the vertical midline.

Definition of Horizontal M-Line

The line is derived from a diastolic stop frame of diagnostic left ventriculography obtained in 30° right anterior oblique (RAO) view (Fig. 41-1). This horizontal line level is memorized in relation to the vertebral body. The angiogram is also used as a road map during transseptal puncture and balloon catheter manipulation.
Definition of Vertical Midline

Inoue devised a specific transseptal puncture technique designed for the Inoue balloon BMV, incorporating the concept of a vertical “midline,” a line assumed to divide the interatrial septum into anterior and posterior halves. The midline is a vertical line crossing the midpoint of a horizontal line spanning the anterior and posterior limits of the septum. The upper end of the tricuspid is assumed to be the anterior septal limit in Inoue’s angiographic method, corresponding to the aortic valve in our modified fluoroscopic method.

Because the septum lies within the superimposed area between the 2 atria in both methods, the medial atrial silhouette (usually the left atrium) is used as the posterior limit (not necessarily the posterior border) because there is no septum beyond this silhouette. Infrequently, such as in patients with giant left atria or distorted cardiac anatomy, the right atrial border is medial to that of the left atrium, and thus, the right atrial border is used as the posterior limit.

1. Angiographic method (Fig. 41-2A-B): The midline is defined based on the landmarks obtained from frontal plane right atrial angiography during normal respiration.
**FIGURE 41-2** Definition of “midline.” Angiographic method (A and B): the upper end of the tricuspid valve at systole (point T, marked as asterisk) is determined on a stop-frame frontal right atrial (RA) image (A) and translated to a stop-frame left atrial (LA) image (B). On the latter image, a horizontal line is drawn from point T until point L, where the line intersects the LA silhouette. The “midline” (broken line) is the vertical line crossing at the midpoint between T and L. Fluoroscopic method (C): a horizontal line is drawn from the tip of the pigtail catheter (point A) to L, the LA silhouette (black arrows), to define the “midline.” The dotted line indicates the right atrial silhouette. (Used with permission from www.ptmv.org.)

2. Fluoroscopic method (Fig. 41-2C): In this method, the aortic valve is used to substitute the upper end of the tricuspid valve as the anterior septal limit because the 2 structures are in close proximity to each other. Therefore, a pigtail catheter is placed with its tip in the noncoronary sinus of Valsalva, touching the aortic valve. The midline thus derived is usually identical to that from Inoue’s angiographic method.

Because in most cases of mitral stenosis the left and right atrial silhouettes are visible under fluoroscopy (see Fig. 41-2C), the angiographic method is infrequently used and is reserved for the following situations: (1) for operators inexperienced with the transseptal puncture technique, (2) in cases in which atrial silhouettes are not well visualized under fluoroscopy, and (3) in extremely difficult cases of transseptal puncture (eg, in the presence of a giant left atrium and kyphoscoliosis). In these cases, it may be necessary to perform biplane (frontal and lateral) right angiography to properly visualize the atrial septal orientation and relative anatomic relationships of the atria, the tricuspid valve, and the aorta.
Confirmation of Optimal Puncture Site

Frontal View

Under frontal view, the needle-fitted transseptal catheter placed in the superior cava inserted from the right femoral vein is slowly withdrawn to align the catheter/needle on the midline. Reshaping of the distal Brockenbrough needle to make it more curved may be necessary to align the catheter tip with the midline. The needle tip should be constantly kept concealed slightly (2-3 mm) within the catheter tip before needle puncture.

The catheter tip should not be set medial to the midline to avoid puncturing the aorta, tricuspid valve, or coronary sinus. More importantly, the puncture site thus made is too close to the mitral valve, and this makes balloon crossing of the mitral valve difficult or even impossible. Slight lateral deviation of the puncture site to the midline is permissible, especially in patients with relatively small left atria. It is important to note that there may not be septum in an area near the inferior (caudal) border of the left atrium because the atrium often bulges caudally beyond the true septal boundary.

Thirty-Degree Right Anterior Oblique View

The catheter tip site is further examined in this view to confirm its optimal position (see Fig. 41-1B), also using the left ventriculogram as a road map (see Fig. 41-1A). The tip position is usually in front of the spinal column, and the distance between the intended puncture site and the mitral orifice (P to M in Fig. 41-1C) should exceed 1.3 times the vertebra width for easy catheter balloon crossing of the mitral valve. Because the catheter tip is away from the aorta, tricuspid valve, coronary sinus, and left atrial posterior border, needle puncture at this point pierces only the septum unless the puncture is made too caudally near the caudal edge of the left atrium in frontal view.

Confirmation of Catheter Tip at Septum

When setting of the catheter/needle at the septum is in doubt, septal flush or stain method may be used to examine the catheter/needle tip position. This is done by injecting a small amount of pure contrast medium contained in a 5-mL syringe attached to the proximal needle end.
**Septal Flush Method**

The contrast medium flushing outlines the right atrial margin of the septum, and the optimal puncture site is at the curving segment of the septal outline (Fig. 41-3A, right panel).
**FIGURE 41-3** Septal flush/stain method in frontal (*left panel*) and lateral (*right panel*) views. (A) Flushing of contrast medium outlines the right atrial margin of the septum (*white arrows, lateral view*). The optimal puncture site (*P, arrowhead*) is at the curved segment of the septal outline (*right*). The *dotted line* shows the left atrial caudal border. (B) Needle puncture at higher septum results in septal dissection as evidenced by staining of the septum in a more vertical orientation (*arrow*), and the catheter direction is aligned with the septal outline (*lateral view*). (C) Contrast staining of the septum after needle puncture made at more caudal site shows obliquely directed staining (*arrow*), indicating that the puncture is made at an optimal site at the curved segment of the septum. (Used with permission from www.ptmv.org.)

**Septal Stain Method**

After needle puncture is made, the needle is aspirated and contrast medium is injected to confirm its entry into the left atrium. If no blood is aspirated, the needle either has dissected the higher septum or is caught in the thickened septum (usually, in the muscular septum). Staining of the septum with injection of contrast medium easily distinguishes these 2 possibilities (*Fig. 41-3B-C*). If the catheter/needle is caught in the septum, it should be carefully forced across the septum. With pressure monitoring, it is not possible to differentiate high septal dissection from needle entrapment in the thick septum. This is another reason why the authors perform the transseptal puncture without constant pressure monitoring.

**Confirmation of Left Atrial Entry**

After entry of the needle in the left atrium is confirmed, first by contrast medium injection followed by pressure recording, the needle direction is set toward 3 o’clock (left side of the patient). If there is no or little resistance, the catheter/needle is advanced forward slightly into the left atrium. Then, the catheter alone is advanced until the tip of the sheath meets a resistance at the septum, while the needle is being withdrawn.

On needle removal, heparin, 100 U/kg body weight, is given immediately through the catheter. After baseline hemodynamic studies, BMV is performed. If the patient has been on warfarin prior to BMV, the drug is discontinued 2 to 3 days before the procedure and substituted with intravenous unfractionated or subcutaneous low-molecular-weight heparin until before the procedure.
SELECTION OF BALLOON CATHETER

Selection of an appropriate-sized balloon catheter for the controlled stepwise dilation technique is extremely important in order to avoid creating severe mitral regurgitation during BMV. Our balloon catheter selection methods have evolved from our continuing efforts to minimize this complication.12,21-23

Catheter Selection

Selection guidelines are based on balloon reference size (RS) derived from patient height, transthoracic echocardiographic findings of the mitral valve, fluoroscopic presence of valvular calcification, and degree of angiographic mitral regurgitation before the procedure. The RS is calculated according to the following simple formula12,22: patient height (cm) is rounded to the nearest zero and divided by 10, and 10 is added to the ratio to yield the RS (mm). (For example, if the patient’s height is 167 cm, then RS = 170/10 + 10 = 27 mm [Table 41-2].) In patients with pliable and noncalcified valves and with mitral regurgitation less than or equal to 1+, a catheter with a nominal balloon size at least that of the RS (an RS-matched catheter) is used. In contrast, in patients at high risk for creating severe mitral regurgitation (valvular calcification and/or severe subvalvular lesions, baseline 2+ mitral regurgitation), a balloon catheter 1 size smaller than an RS match is selected. Therefore, in the above example with an RS of 27 mm, a PTMC-28 catheter would be selected for a pliable, noncalcified valve, and a PTMC-26 catheter would be selected for a calcified valve and/or a valve with severe subvalvular disease.

Table 41-2 Catheter Selection and Balloon Sizing Based on Patient Height and Valvular Status
Pretesting for Balloon-Syringe Mismatch

Although the volume predefined by red marks on the syringe and its corresponding balloon size at full inflation have been tested by the manufacturer, balloon-syringe mismatch may occur. Although this mismatch is usually mild, gross mismatch may take place when the catheter and the syringe are from different packages. The mismatch, if undetected, may result in either underinflation or overinflation of the balloon. Therefore, before inserting the balloon catheter into each patient, the diameters of balloon inflated by injection of diluted contrast medium should be confirmed using a test; the balloon diameter chosen for the first inflation and the nominal diameter of the balloon should be compared. If there is a mismatch, the difference should be noted and adjusted.

### CATHETER PLACEMENT

#### Balloon Catheter Advancement

**Resistance at Groin Access Site**
To avoid creating a long subcutaneous tunnel, which may pose some resistance during insertion of the balloon catheter, the puncture needle is angled more vertically than usual during the initial vascular access (at about 60° to the skin surface). After insertion of the coiled-tip guide wire into the left atrium, the shorter subcutaneous track is then well stretched with an artery forceps alongside the wire. This is followed by use of the 12-Fr dilator, which is also used to dilate the atrial septum. When inserting the stretched balloon catheter, the guide wire should be held taut by an assistant. Use of a 14-Fr intravascular sheath for balloon catheter insertion is optional. During insertion of the catheter into the femoral vein, the catheter should never be twisted or the metal stretching tube or the guide wire will bend, thereby requiring replacement.

**Septal Passage and Resistance**

After placement of the coiled-tip guide wire in the left atrium, there may be some difficulty at times in advancing the balloon catheter across the septum, particularly when the latter is markedly thickened at the puncture site. When this occurs, forceful action is to be avoided. Rather, the balloon catheter should be turned slightly, usually in a clockwise direction, as it is pushed forward to overcome septal resistance. In the rare instances when this method also fails, the septum is redilated with the dilator. After passage across the septum, it is also important not to push the catheter tip up against the left atrial roof, or the guide wire may be bent into an acute angle.

**Deep Catheter Placement in Left Atrium**

The balloon catheter is introduced under frontal fluoroscopic view into the atrium over the coiled-tip guide wire to form a large loop with the tip medial to the mitral valve (Fig. 41-4). This placement has the following advantages: (1) the catheter thus positioned is less likely to flip to the left atrial appendage area when the stylet is inserted to the catheter tip; (2) the catheter does not enter the pulmonary veins; and (3) in subsequent manipulations to cross the valve, the catheter has already been advanced deep into the atrium, and it will need only to be withdrawn. Thus, the mitral valve crossing is attempted first with the vertical method, and potential catheter entrapment by a tough septum is avoided.
FIGURE 41-4 Deep catheter placement in left atrium and mitral valve crossing. A balloon catheter is introduced under frontal view into the atrium over a coiled-tip guide wire to form a large loop with the tip medial to the mitral valve (MV), pointing downward to a 6 to 7 o’clock direction (A). The catheter thus positioned is less likely to flip to the left atrial appendage area (open arrowhead). Subsequent catheter manipulations are done in 30° right anterior oblique (RAO) view. (B) Mitral valve crossing is attempted in order of vertical, horizontal, direct and posterior loop method (C1 to C4). The broken line indicates mitral orifice to left ventricular apex orientation. (Used with permission from www.ptmv.org.)

MITRAL VALVE CROSSING

Catheter manipulation is done in the 30° RAO view using the left ventriculogram as a road map. In difficult cases, such as in patients with giant left atria, additional use of lateral fluoroscopic view may be needed to facilitate valve crossing.

With the stylet inserted to the catheter tip, the partially inflated distal balloon is directed toward the anteriorly located mitral orifice. The balloon is directed anteriorly by applying a counterclockwise twist (usually 180°) to the stylet with one hand (usually the right), thus controlling the axial movement
of the catheter balloon (see Fig. 41-4). The catheter is then withdrawn gradually, using the other hand, to control the vertical motion of the balloon. Mitral valve crossing is then attempted using 4 methods in the order that they are described below.

**Vertical Method**

On further slight retraction of the catheter, the balloon is observed to move in (during diastole) and out of the left ventricle even though the catheter is not aligned with the orifice-apex axis of the left ventricle (black broken line in Fig. 41-4). Coincident with diastole, only the stylet is withdrawn. This allows the distal segment of the catheter to take on a more horizontal orientation to cross the valve and enter deep in the left ventricle. Having replaced the originally used direct method, the vertical method is now the most frequently used successful crossing method.

**Direct Method**

When the vertical method fails, the balloon catheter is further withdrawn until the catheter balloon is near the valve and the catheter is well aligned with the orifice-apex axis. At this time, a “woodpecking” sign is observed as the balloon moves away from the mitral orifice in systole and toward it in diastole along the axis between the mitral orifice and the left ventricular apex (orifice-apex axis). Once this sign is evident, the operator jerks the stylet back slightly as the balloon approaches the orifice and simultaneously advances the catheter with the left hand to drive the balloon across the valve and deep into the left ventricle.

**Horizontal (or Sliding) Method**

This method has proved to be effective, especially in cases in which the septal puncture is made too caudally and/or the left ventricle assumes a more horizontal orientation. The balloon is first directed toward the mitral valve by keeping the stylet twisted counterclockwise. The distal catheter segment is then made more flexible by withdrawing the stylet clear out of the balloon segment. Once the slightly inflated balloon is at the mitral orifice, cardiac contractions cause the balloon segment to tilt upward during systole. In
diastole, the balloon segment aligns with the catheter shaft. With the operator carefully watching the rhythmic motion of the cardiac cycle, only the catheter is advanced forward (with the stylet kept fixed) during diastole to cross the valve. The stylet is then advanced to help align the catheter with the orifice-apex axis.

**Posterior Loop Method**

First, a vertical loop is made (as in Fig. 41-4B) and the stylet is then withdrawn to a point 2 to 3 cm proximally to make the balloon segment more flexible. With the stylet twisted clockwise, the balloon tip is brought toward the posterior and inferior wall of the left atrium; thus, the catheter forms a loop in the left atrium.

With the stylet held firmly, only the balloon catheter is advanced, allowing the balloon to move forward to the mitral orifice. When the balloon enters the left ventricle, its tip usually points upward. The loop is then reduced by carefully withdrawing the catheter and slightly advancing the stylet to the balloon segment to align the distal catheter with the orifice-apex axis. This method is infrequently used in the authors’ experience.

**Discussion of the Methods**

In the vertical and direct methods, the major causes of valve crossing failure are (1) bending of the distal balloon segment, resulting in malalignment of the balloon segment with the mitral orifice, and (2) insufficient counterclockwise rotation of the stylet, thus failing to bring the catheter balloon segment sufficiently anteriorly to align toward the mitral orifice. Therefore, it is important to insert the stylet all the way to the balloon catheter tip to straighten the latter. Occasionally, however, the stylet may be too short to reach the catheter tip, thus making a slight bend in the catheter tip. If this occurs, the rubber grip at the proximal end of the stylet can be pulled further back to lengthen the exposed segment of the stylet, or failing that, the rubber grip can be cut at 1 to 2 mm from its distal end and removed. In addition, the stylet must be kept twisted at all times. An extra counterclockwise twist is occasionally needed to direct the catheter tip anteriorly. Less commonly, inappropriate stylet tip curving may also contribute to the failure. If this occurs, the stylet should be reshaped.
according to the positional relationship between the septal puncture site and the valve orifice.

In the catheter sliding or the posterior loop method, the catheter has a propensity to enter the left atrial appendage region during a failed valve-crossing attempt because the distal balloon catheter is more horizontally oriented. Therefore, the stylet should not be pulled back too vigorously to avoid excessive forward movement of the catheter toward the appendage region.

**BALLOON INFLATION PROCEDURES**

*Ensuring Free Balloon Movement in Left Ventricle*

Once the mitral valve has been crossed, the free movements of the partially inflated distal balloon in the left ventricle should be ascertained to prevent disastrous consequences (ie, rupture of chordae, papillary muscles, or leaflets) stemming from its subsequent full inflation within the chordae. This is done by simultaneously pushing the catheter and pulling the stylet slightly in opposite directions (“accordion” maneuver)\(^{22}\) to ensure that the partially inflated distal balloon slides freely along the orifice-apex axis.

After crossing the mitral valve, the catheter balloon may point more vertically and deviate away from the orifice-apex axis. This suggests that the catheter has strayed among the chordae. To correct this situation, the distal balloon is inflated larger to prevent the balloon from being inadvertently retracted into the atrium, and the catheter is carefully pulled back to assume a more horizontal orientation. After satisfactory alignment of the catheter with the orifice-apex axis, the catheter is advanced toward the apex, and the previously described accordion maneuver is performed before initiating the inflation procedure. Similarly, a twist in the balloon during the inflation process may also indicate that the catheter has tethered among the chordae. In this case, the inflation should be promptly aborted and the balloon repositioned.

*Reassessment of Subvalvular Status*

Before BMV, mitral valvular status is determined by preprocedural
transthoracic echocardiography and fluoroscopy (for the presence of valvular calcification), and an appropriate balloon catheter is then chosen accordingly. Extensive subvalvular disease has been found by various investigators to be a predictor of significant mitral regurgitation. Because echocardiography often underestimates the severity of subvalvular disease, severe mitral regurgitation may be created during BMV despite the presence of apparently favorable valve morphology. Therefore, during the actual balloon dilations, vigilance is required to identify the presence of previously undetected severe subvalvular disease. We and others have found other more reliable signs of significant subvalvular involvement. The most commonly encountered sign is a distorted balloon due to compression by severe subvalvular disease when it is being inflated. Even in patients in whom no severe subvalvular disease is demonstrated by echocardiography, when the presence of severe subvalvular disease is suspected during the balloon inflation process, the balloon dilation protocol should be altered accordingly as described below (see Balloon Sizing).

**Controlled Stepwise Dilations**

To avoid or minimize the complication of severe mitral regurgitation, the selection of an appropriate balloon catheter and the controlled stepwise dilation technique are mandatory. In addition, one should be familiar with the pressure-volume relationship and inflation limit of the catheter balloon.

**Balloon Pressure-Volume Relationship**

The intraballon pressure transits from the “low-pressure” to the “high-pressure” zone as the balloon is inflated to within 2 mm of its nominal size (eg, the 24- to 26-mm zone in a 26-mm balloon catheter). Each catheter can be safely inflated to a maximal diameter of 1 mm above the nominal size because of the built-in safety margin. Initial balloon inflation is never to be performed with balloon diameter in the high-pressure zone, regardless of the valvular morphology.

**Balloon Sizing**

As indicated earlier, balloon sizing for the stepwise dilation technique is
crucial in avoiding the complication of severe mitral regurgitation. By adhering to the cautionary methods outlined below, especially in patients with severe subvalvular disease, creation of significant mitral regurgitation (increase of ≥2+ angiographically) can be minimized.²³

1. Pliable, noncalcified valves. In patients with pliable, noncalcified valves and no severe subvalvular lesions, as determined by the subvalvular reassessment outlined earlier, an RS-matched balloon catheter is selected as stated previously. The initial inflated balloon diameter is RS minus 2 mm. In subsequent dilations, the balloon size is increased by 1 mm. When there is preexisting mitral regurgitation or any question of increase in the degree of mitral regurgitation, the increment should be 0.5 mm in the high-pressure zone. This approach also applies when unilateral commissural splitting occurs during the previous dilation, as observed by asymmetrical balloon waists on fluoroscopy. The final diameter is best kept within 1 mm above the RS to avoid oversizing; that is a risk factor for creating severe mitral regurgitation in this group of patients.¹²

2. Calcified valves and/or severe subvalvular disease. In patients with either fluoroscopically visible valvular calcification or severe subvalvular lesions as observed by transthoracic echocardiography, instead of an RS match, a balloon catheter 1 size smaller than the RS match is selected at the outset. For those whose subvalvular lesions are not detected by preprocedural echocardiography, the RS-matched catheter already placed in the patient may still be used if the dilation procedures are carried out with extra care. Ideally, the catheter should be exchanged for a smaller one, but this is quite costly.

For the first dilation, a balloon diameter 4 mm less than the RS is used. For subsequent dilations, the balloon size is increased by 1 mm in the low-pressure zone and by 0.5 mm in the high-pressure zone until satisfactory results are obtained or until mitral regurgitation develops or worsens. In cases where the gradient has already been reduced to one-half and several more dilation attempts have failed to reduce it further, the procedure is terminated to avoid creating severe mitral regurgitation. Reducing the mitral valve gradient by one-half should result in a 41% increase in the mitral valve area, as calculated by the Gorlin formula, provided that heart rate and cardiac output remain the same. Our previous study²¹ suggests that a 40% increase in
the valve area is sufficient for symptomatic improvements in patients with a more sedentary lifestyle.

**Exchange for Different-Sized Balloon Catheters**

Exchange of balloon catheters is carried out for 2 reasons. The first is to downsize the catheter in the presence of severe subvalvular disease that may have evaded detection by echocardiography but was noted during the BMV procedure itself. The second occurs in the rare instance when there is a need to upsize the balloon catheter to one that is 1 size larger because of inadequate hemodynamic improvement with the initial balloon catheter. In such a situation, before exchanging for a larger catheter, it is vital that the initial catheter’s final balloon diameter be remeasured and reverified after its complete removal from the patient, particularly when it has been inflated beyond its nominal size. This precautionary exercise is essential because, not uncommonly, despite pretesting, the balloon size is smaller than what it is supposed to be after in vivo usage. When this occurs, the original balloon catheter is retested to determine the actual volume of diluted contrast in the syringe necessary to achieve maximum balloon size (the balloon tolerates about 1-2 mm in excess of its nominal size before rupturing), the original balloon catheter is reintroduced into the patient, and the dilation process is repeated. However, if the balloon matches its predefined size, an exchange for a larger-sized catheter is made and dilations with the larger balloon are performed. Failing to reverify the maximum balloon size before inflating a much larger balloon may risk the creation of severe mitral regurgitation.

**Balloon “Popping” to Left Atrium**

When the mitral valve has already been enlarged by dilations, the balloon may occasionally slip into the left atrium during subsequent inflations with larger balloon diameters. To prevent the latter from occurring, the stylet is advanced far into the balloon segment to stiffen the catheter, and before the catheter is retracted to anchor the balloon at the orifice, the distal balloon is inflated to a diameter slightly larger than the previous one. As soon as the balloon assumes an hourglass configuration, the catheter is advanced slightly to prevent it from jerking out into the left atrium, and full balloon expansion is then executed. With this extra dilation, although the mitral gradient may be
unchanged, enhanced splitting of the commissures, as assessed by echocardiography, is often observed.

The balloon “popping” signals enlargement of the mitral orifice with wide splitting of the commissures. It is usually encountered in patients with pliable, noncalcified valves and foretells excellent BMV results. However, suboptimal hemodynamic results are occasionally observed despite the balloon “popping” sign, especially in the presence of atrial fibrillation. In these cases, although the mitral valve with split commissures can be forced to accommodate the fully inflated balloon, the effective mitral valve area is, in reality, limited by the thickened and stiff leaflets and by ineffective atrial contractions in the beating heart.

**Assessment After Each Valve Dilation Procedure**

After each balloon inflation procedure, the catheter balloon is withdrawn to the left atrium. The effects of the balloon dilation are assessed by observing the left atrial pressure waveforms, by measuring the transmitral gradient, and also by auscultation. If mitral regurgitation is suspected by the appearance of a large or giant “v” wave and by a new or worsening systolic murmur, echocardiography or left ventriculography may be performed. Although not essential, transthoracic or online transesophageal echocardiography is an excellent tool to assess and monitor the valve status after each balloon dilation if the logistics permit its use. However, the tool is too sensitive for detection of new or increasing mitral regurgitation, and thus, sole dependence on the echocardiography findings may result in premature termination of the procedure.

**AVOIDING LEFT ATRIAL APPENDAGE**

Left atrial appendage thrombus may be unsuspected when BMV candidates are screened only with insensitive transthoracic echocardiography. Balloon catheter encroachment on the left atrial appendage region must thus be avoided in order to minimize the risk of inadvertent thrombus dislodgement and systemic embolism. Under 30° RAO fluoroscopic view, the anterolaterally located appendage is cephalad to and right of the pigtail catheter segment in the left ventricle (see Fig. 41-4B). Therefore, the balloon
catheter tip should always be kept to the left of the pigtail catheter during catheter manipulation in the left atrium by adopting the following steps:

1. Deep placement of balloon catheter in the left atrium (see Fig. 41-4A).
2. Mitral valve crossing. The balloon catheter tip is more horizontally orientated when performing the catheter sliding or the posterior loop method (see Fig. 41-4) in crossing the mitral valve. The catheter tip is thus more prone to entering the left atrial appendage region during a failed valve-crossing attempt. Therefore, the stylet should not be pulled back too vigorously during the crossing attempt to avoid excessive forward movement of the catheter toward the appendage region.
3. Catheter withdrawal to the left ventricle. After each balloon inflation procedure, in order to exert better control over the catheter tip, the stylet is advanced halfway into the balloon segment and the catheter is withdrawn just out of the mitral orifice from the left ventricle. Then, a slight clockwise twist to the stylet is applied to direct the catheter tip posteriorly. The balloon catheter can then be safely retrieved to the atrium by cautiously withdrawing the catheter and the stylet in steps until the catheter stands straight upward.
4. Mitral valve gradient measurement. After each valve dilation procedure, a transmitral valve gradient measurement is performed without fluoroscopy. Thus, care should be exercised to avoid pushing the catheter forward into the appendage.

After the precautions have become rote, it is possible to perform BMV safely even in the presence of left atrial appendage thrombi. Despite our safe and successful experience in performing BMV in patients with thrombi confined to the appendage, the subject has remained controversial even among experienced operators of Inoue-BMV. Therefore, the alternative approaches are either to subject patients with appendage thrombi to mitral valve surgery or to defer BMV for stable patients until resolution of the thrombi after warfarin treatment.

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ETIOLOGY AND PATHOLOGY

Degenerative disease of the aortic valve occurs with age. Areas of cusp flexion over time develop fibrosis and calcification, impeding valve excursion and creating obstruction to left ventricular outflow. The most common cause of aortic stenosis (AS) is calcification of a normal trileaflet or congenital bicuspid valve. Calcific AS is an active disease process characterized by lipid accumulation, inflammation, and calcification, with many similarities to atherosclerosis. The degenerative process usually occurs in the sixth decade of life and beyond, but patients with additional valve pathology (bicuspid aortic valves, rheumatic heart valvular disease, radiation valvulopathy) can present much earlier in life with deterioration of valve function and consequent symptoms.

The 2 most common etiologies of AS amenable to percutaneous treatment are: (1) congenitally bicuspid aortic valves and (2) calcified tricuspid valves. Unicuspid or quadricuspid valves are not normally candidates for a percutaneous approach, with unicuspid disease typically associated with stenosis and quadricuspid valves with regurgitation. Isolated rheumatic AS, rare even in countries with a high prevalence of rheumatic heart disease, is highly amenable to percutaneous intervention because the mechanism of improvement is splitting of the fused commissures.
Bicuspid aortic valves occur in approximately 1.5% of the population, and associated stenosis presents much earlier in life than tricuspid aortic valve disease.\(^7\) AS in adolescents and young adults is usually noncalcific, is the result of fused bileaflet valves, and is highly amenable to percutaneous balloon intervention. In contrast, AS in bicuspid and tricuspid valves of adults is associated with calcification of the valve that results in thickening, rigidity, and immobility of leaflets, often without commissural fusion.

Balloon aortic valvuloplasty (BAV) has been shown to relieve obstruction of the stenotic valve by 3 mechanisms: (1) fracture of calcium deposits in the leaflets, (2) splitting of fused commissures, and (3) stretching of the aortic annulus.\(^8\)\(^9\) Calcium deposits are broken into separate fragments with balloon inflation, facilitating leaflet flexion and allowing better excursion during systole. Splitting of commissures is quite effective by BAV. Stretching of the valve may explain the early gains by BAV, but valve recoil can occur within hours to days, and in this case, results of BAV may be fleeting. Late restenosis (after several months) probably results from progression of the original lesions that produced stenosis.

**CLINICAL FEATURES AND INDICATIONS FOR TREATMENT**

The development of symptoms can trail the onset of degeneration of the aortic valve by several decades.\(^10\) When present, initial symptoms tend to be dyspnea on exertion and effort angina, although some patients may present with syncope or heart failure.\(^11\) Exertional fatigue may be the first manifestation of severe AS in the elderly. Once symptoms are detected, the prognosis is poor without intervention: patients often have mortality within 5 years of angina, 3 years of syncope, and 2 years of heart failure.\(^12\)\(^13\) Cohort B of the Placement of Aortic Transcatheter Valves Trial (PARTNER) consisted of inoperable patients randomized to transfemoral transcatheter aortic valve replacement (TF-TAVR) versus medical therapy (including BAV as necessary). The study demonstrated 50% mortality at 1 year with medical therapy including BAV.\(^14\) More recently, 2-year results from the PARTNER trial demonstrated a mortality of 68% with medical therapy and BAV.\(^15\)

Surgical aortic valve replacement (SAVR) has been the standard of care
for treatment of symptomatic patients with severe AS. SAVR is accepted to alleviate symptoms and prolong survival; however, up to one-third of patients are denied SAVR because of prohibitive surgical risk (eg, advanced age, significant left ventricular dysfunction). Results from the PARTNER trial have shown that transcatheter aortic valve replacement (TAVR; covered in Chapters 42 and 43) is the standard of care for extremely high-risk or “inoperable” patients and is a valid alternative to surgery for high-risk but “operable” patients with symptomatic AS. The introduction of TAVR has brought resurgence in the use and utility of BAV.

Standalone BAV has been reserved for a subset of patients who are too sick to undergo SAVR and are considered inappropriate patients for TAVR. BAV is used in contemporary practice as a bridge to subsequent SAVR or TAVR (class IIb indication). In the current era of percutaneous valve replacement, BAV may be used to assess initial clinical improvement and future candidacy for TAVR.

**Clinical Subsets**

Several important clinical subsets of patients with AS exist with mean aortic valve gradients of less than 40 mm Hg in whom BAV may be used as a diagnostic and therapeutic procedure.

An important group of patients are those with severe AS and secondary depression of left ventricular function. In this subset of patients, the aortic valve gradient is low due to the inability of the left ventricle to sufficiently open the stenotic valve. In this group, pharmacologic agents, such as dobutamine, that increase flow across the valve will result in a dramatic rise in gradient. These patients typically benefit from relief of aortic valve obstruction. In contrast, patients with moderate AS and left ventricular dysfunction do not have an increase in gradient with dobutamine and do not benefit from SAVR. In cases where there remains an uncertainty after dobutamine challenge, we have performed BAV to evaluate whether increasing the valve area correlates with improved clinical symptoms and ventricular recovery.

Another complicated group of patients has only been distinctly identified in the past several years. These patients have small hypertrophied ventricles, preserved ejection fraction, and low aortic valve gradients. This group
sometimes has high valvuloarterial impedance AS and has low gradient because of decreased stroke volume. In these patients, when an uncertainty exists about the degree of AS, we have performed BAV as a diagnostic procedure and have been aggressive with blood pressure control (afterload reduction). Those with an excellent clinical response can be sent for SAVR or TAVR with mortality benefit. BAV can be used to assess clinical response in patients with severe lung disease as well.

**HISTORY OF THE BAV PROCEDURE**

BAV was originally performed in 1985 and was initially proposed as an alternative to SAVR in patients who were considered too elderly or high risk with severe AS. Initial enthusiasm in the late 1980s was subsequently tempered by studies demonstrating high rates of complications, lack of durability, and little or no impact on long-term survival, particularly in centers with low experience. Until recently, the use of BAV had significantly waned; it was restricted to very-high-risk patients with severe heart failure or cardiogenic shock and was often used as a bridge to SAVR.

The introduction of TAVR in 2002 and technical improvements with reduction of sheath diameter, rapid pacing, and vascular closure devices have brought the nearly dormant BAV technique back into the mainstream. The problem of restenosis has been addressed by the advent of TAVR. Several very busy structural heart centers such as ours perform more than 200 BAVs a year, a volume that has been sufficient to train multiple attending physicians and fellows. For these trainees, BAV has been a gateway procedure for learning the essentials of TAVR.

**PREPROCEDURE EVALUATION**

The evaluation of AS begins with the patient history and physical examination. Often, only transthoracic echocardiography (TTE) is used to quantify the degree of stenosis as retrograde catheterization has been associated with an increased risk of stroke, particularly if prolonged attempts are needed to cross the aortic valve. If there is any discrepancy between the patient’s presentation and echocardiographic results, retrograde
catheterization should be performed to measure the simultaneous gradient across the aortic valve (class I indication), as described below. In patients with low transvalvular gradient and low cardiac output, dobutamine infusion can aid in diagnosing patients with true AS from those with “flow-dependent” stenosis. Assessment of concomitant coronary artery disease is important prior to BAV and can often be accomplished in the same session. Venous and arterial access sites should also be evaluated prior to the procedure.

After assessing candidacy for BAV, it is important to obtain and review multimodality imaging for optimal procedural planning. TTE is the initial, and often only, imaging modality of choice due to its ease and safety. TTE establishes the diagnosis of AS and allows assessment of valve morphology (ie, bicuspid, functionally bicuspid, or trileaflet valve), left ventricular outflow tract size, and baseline left ventricular function. Understanding valve morphology prior to BAV is critical as balloon dilatation of a bicuspid or functionally bicuspid valve with an oversized balloon may result in acute severe aortic regurgitation.

Computed tomography (CT) provides a wealth of cardiac, thoracic, and peripheral information in assessing a patient’s feasibility for TAVR and procedural planning. A CT scan will show in detail the aortic root anatomy (including annular, sinotubular, and sinus of Valsalva dimensions as well as coronary heights above the annulus), aortobifemoral anatomy, and details of arterial diameters and calcification. A gated, contrast CT with less than 1-mm slices will allow detailed 3-dimensional reconstruction, which can be invaluable for evaluation of the aortic annulus and peripheral arteries. Review of the CT scan prior to BAV aids in procedural planning. The lower extremity with larger diameter iliofemoral caliber is reserved for potential future TF-TAVR. Additionally, accurate assessment of the femoral bifurcation and areas of calcification will guide arterial access for BAV and successful percutaneous arteriotomy closure.

Factors contributing to limited reserve (ie, depressed left ventricular ejection fraction, last remaining coronary vessel/graft, biventricular failure, or hemodynamic shock) should be identified prior to BAV to assist with procedural planning. These patients tend to not tolerate pacing runs, and it may be more beneficial to perform BAV without rapid ventricular pacing. Additionally, in patients with hemodynamic shock or in those who cannot lay supine, hemodynamic support devices (intra-aortic balloon counterpulsation)
and a wedge may be used.

**TECHNIQUE OF BALLOON AORTIC VALVULOPLASTY**

Patients are prepared from the upper thigh to the subxiphoid area in case emergent pericardiocentesis is required. Defibrillator pads are placed in the anterior-posterior position to facilitate treatment of ventricular arrhythmias during the procedure. Patients with difficulty in breathing are positioned semi-recumbent with the assistance of a wedge cushion. The procedure begins with the administration of minimal conscious sedation and local anesthesia.

**Special Instruments and Pharmacologic Agents**

- “Micropuncture” access kits that use a 21-gauge needle and 0.018-inch wire for arterial entry are best for fluoroscopic or ultrasound-guided access.
- Percutaneous arteriotomy closure devices such as the Perclose ProGlide (Abbott Vascular, Abbott Park, IL), ProStar XL (Abbott Vascular), and Angio-Seal (St. Jude Medical, St. Paul, MN).
- For patients with depressed ejection fraction, low coronary reserve, or hemodynamic compromise, 10-mL syringes of norepinephrine (16 μg/mL) and epinephrine (0.1 mg/mL) are helpful when treating acute hypotension. Background low doses of norepinephrine continuous infusion may also be helpful to maintain blood pressure, particularly with escalating doses of sedation.

**Antithrombotic Therapy**

Unfractionated heparin (dose of 5000 IU) should be used after arterial access to maintain an activated clotting time (ACT) of 250 to 300 seconds. Direct thrombin inhibitors have been used in patients with heparin allergies. Cases can be performed without any anticoagulation, although stroke risk is higher. In those cases, frequent catheter exchanges are performed to minimize
clotting on the wire used during BAV, and procedure time is minimized.

**Vascular Access, Right Heart Catheterization, and Supra-aortic Angiography**

Right common femoral arterial access is obtained with a micropuncture access kit and cannulated with a 6- or 7-Fr sheath. If the right femoral artery is unavailable for access, the left femoral artery, the brachial artery, the axillary artery, or an antegrade transseptal approach via the femoral vein can be used. To limit vascular complications in the arm, we recommend a cut down and maximum sheath size of 10-Fr. Common femoral venous access is obtained and cannulated with a 7-Fr sheath. A 7-Fr Swan-Ganz catheter is advanced from the femoral vein, and baseline right-sided pressures are recorded. Cardiac output measurements using either thermodilution or the Fick principle should wait until the aortic valve has been crossed to reduce error if calculation of the aortic valve area is performed during catheterization. After a right heart catheterization is performed, a temporary pacing wire is advanced to a stable position in the right ventricular apex. Placement of the lead in the base of the right ventricular free wall can increase the risk of perforation or loss of capture. A 6-Fr pigtail catheter is then advanced from the femoral artery and placed superior to the aortic valve. Aortic angiography in the left anterior oblique projection is not mandatory but can be helpful to define the details of the valve anatomy and assess the degree of insufficiency (Fig. 41A-1). Patients with more than moderate aortic regurgitation are in general not considered for BAV. Patients with moderate aortic insufficiency or less are reasonable candidates for BAV, particularly if the valve is trileaflet.
A regular, J-tipped 0.035-inch wire is inserted at the main arterial access site, and the 6- or 7-Fr sheath is removed. The arteriotomy is “preclosed” using a percutaneous suture device. Over a stiff, 0.035-inch wire such as the Amplatz Extra-Stiff wire (Cook Medical, Bloomington, IN), the arteriotomy is serially dilated to accommodate the BAV sheath, which is 12 or 14-Fr (CheckFlow, Cook Medical). The use of a 12-Fr arterial introducer and routine preclosure of the arteriotomy have markedly decreased the rate of local complications at the femoral puncture site. Smaller sheath sizes have been used with lower profile balloons and may not require preclosure. Twelve- and 14-Fr sheaths can be postclosed with suture-based closure devices.\textsuperscript{19}

**Preclosure**

**Crossing the Native Valve**

Proper technique permits negotiation of the stenotic aortic valve within 60 seconds in all cases. This is achieved most commonly with a 6-Fr Amplatz left (AL) catheter, although multiple other catheters may be used, such as 7-
Fr Sones (B type), pigtail catheter, Judkins right, multipurpose, or hockey-stick. A straight, 0.035-inch wire is used to cross the stenotic valve (Figs. 41A-2 and 41A-3). If a hydrophilic wire is used, it is important to make sure that the wire passes through the valve orifice and does not pass through a leaflet perforation prior to advancement of any catheters. The starting position of the Amplatz catheter should be with the tip pointed at the orifice between the left and right cusps, and the starting position of the Sones catheter is in the left coronary cusp with the tip pointed superiorly. With either catheter, a slow pull back with clockwise rotation and careful probing with the guide wire should negotiate the stenotic orifice. The Amplatz catheter is more useful than the Sones catheter when the plane of the aortic valve is more vertical. Once the valve has been crossed, the wire position is confirmed in the right anterior oblique projection, and the crossing catheter is advanced into the left ventricle. Failure to cross the valve with the catheter usually means the wire has biased into a commissure. Repositioning the wire, which includes making a loop in the ventricle, may be required to move the wire more toward the central orifice. Care needs to be taken not to puncture the apex. If one cannot cross, alternative strategies include recrossing, exchanging for a smaller catheter, or torquing the catheter in the ascending aorta out of the commissure. With the crossing catheter in place or exchanged for a pigtail catheter, the transvalvular gradient can be obtained, using the lateral arm of the sheath to record aortic pressure.
FIGURE 41A-2 A. The Amplatz catheter (AL) is directed toward the aortic orifice (valve calcifications above the dotted line). B. The straight guide wire (GW) has passed through the stenotic orifice (valve calcifications above the dotted line).
The Sones catheter (SC) is advanced over a guide wire (GW) in the left coronary cusp in the left anterior oblique view. The guide wire is used to probe the valve orifice (above the dotted line). The guide wire has passed through the stenotic orifice (valve calcifications above the dotted line).

The straight guide wire is removed from the crossing catheter and replaced by a 0.035-inch, 260-cm Amplatz Extra-Stiff wire (Cook Medical). The flexible end of the guide wire is preshaped before introduction into an exaggerated pigtail curve using a standard hemostat or with the hand. The curve in the distal wire decreases the risk of left ventricular trauma, perforation, and ventricular arrhythmia. The stiff wire is important to provide adequate support during advancing or inflating of the balloon catheter. We do not advocate the routine use of wires that are stiffer than an Amplatz Extra-Stiff wire (Cook Medical).

**Balloon Catheters**

The balloon catheters used at our institution are the TYSHAK (B. Braun Interventional Systems, Bethlehem, PA), ZMED, ZMEDII (NuMed, Hopkinton, NY), Cristal (BALT, Montmorency, France), and TRUE (Bard Peripheral Vascular, Tempe, AZ) dilatation balloons. The TRUE balloons inflate and deflate faster and are highly resistant to ruptures, punctures, and tears. The TYSHAK and Cristal balloons are the lowest profile, although they are more compliant and prone to rupture. All balloons are inserted over the stiff guide wire and purged of air outside of the body or in the descending aorta. We use a 30-mL syringe filled with an adequate volume of contrast and saline (10:90 mixture) to easily and completely inflate the valvuloplasty balloon. This dilution of contrast is adequate for visualization of the balloon under fluoroscopy and also decreases the time of deflation.

The balloon should pass the stenotic orifice without difficulty in most cases. If the balloon does not pass, the wire is probably biased into a commissure. In this situation, an empty 20- or 30-mL syringe can provide additional negative pressure to decrease the balloon profile. The wire position can also be changed by advancing the wire further into the ventricle or tracking the wire during balloon advancement. In special cases, we have purged the balloon of air after crossing the native valve in order to facilitate crossing. In most valvuloplasties, we begin with a 23-mm balloon; however, in patients with a small aortic annulus (<20 mm by TTE) or heavily calcified
valve, sequential inflations starting with a 20-mm balloon are prudent. In these cases, progression to a large-size balloon is acceptable if the initial result is insufficient, the balloon size appears undersized, and there is no visible waist during inflation. We rarely inflate a balloon that is >3 mm larger than the aortic annulus as measured on long-axis views on TTE.

**Rapid Pacing and Balloon Inflation**

Maintaining the position of the balloon catheter during inflation is critical for effective dilatation. This positioning is facilitated by rapidly pacing the right ventricle causing electrically induced arrest of the heart. The pacing lead should be connected to an external pulse generator that is capable of pacing at rates >200 bpm. Starting at 180 stimulations per minute, the minimal rate that causes a rapid and predictable decrease in systolic pressure to 30 to 40 mm Hg should be found (Fig. 41A-4). Typically a rate of 200 to 220 bpm is needed, although some patients will require rates as low as 140 to 160 bpm for adequate capture and hypotension. A back up rate of 60 bpm should be set to prevent episodes of bradycardia after dilatation.

**FIGURE 41A-4** Aortic and electrocardiogram (ECG) tracing during rapid stimulation depicts a predictable and abrupt decrease in cardiac output during which balloon valvuloplasty can be performed safely.
With markers of the balloon on either side of the valve calcification (Fig. 41A-5), rapid stimulation is started and coupled with cine-angiographic imaging and maximal balloon inflation. Normally, balloon deflation and arrest of stimulation are done simultaneously. Maintaining wire position is important, and pushing of the wire to ensure that the wire is against the outer curvature of the aorta provides extra support to the balloon during inflation. Balloon sizing of the annulus during BAV may be particularly helpful prior to TAVR when the annulus is questionably too large for a given transcatheter valve: supravalvular aortography is performed during BAV with rapid pacing, and any leakage of contrast into the left ventricle suggests that a larger valve will be needed\textsuperscript{35} (Fig. 41A-6). Upon deflation, the balloon is quickly withdrawn from the valve orifice to promptly restore antegrade blood flow.

**FIGURE 41A-5** The balloon markers (BM) are centered around the aortic valve calcification (white dotted lines) prior to inflation. The guide wire tip (GW) has an exaggerated curve to prevent ventricular trauma or arrhythmia. PL, pacer lead; black dotted lines, mitral annulus calcification.
FIGURE 41A-6 Balloon aortic valvuloplasty to size the aortic valve annulus. If a supravalvular aortogram is completed during maximum inflation of an appropriately sized balloon (1 mm less than the proposed valve’s size), balloon valvuloplasty can be used to predict whether or not the proposed valve will seal the annulus. In panel A, the absence of any leak around a 22-mm balloon suggests that a 23-mm valve will be large enough. In panel A, the left coronary system fills with contrast at peak balloon inflation and suggests a low likelihood of obstruction. In panel B, contrast is leaking around a 25-mm balloon, which suggests that a 26-mm valve will be too small and may leave significant paravalvular leak.

The valve is dilated in the same fashion once or twice more, depending on the quality of dilatation (adequate balloon size without movement at maximal inflation) (Fig. 41A-7). The goal of valvuloplasty should be greater than 50% decrease in transvalvular gradient and a valve area ≥1.0 cm$^2$. To decrease the number of pacing runs, we escalate to the final and largest balloon size quickly. Two dilatations are performed with the largest size balloon. Even with perfect technique and strategy, adequate reduction of mean gradient may not be possible in 20% of patients.
FIGURE 41A-7 A. Lack of rapid pacing results in movement of the balloon catheter (BC) distal to the aortic valve (dotted lines, aortic valve calcification) and inadequate dilatation. GW, guide wire. B. Rapid pacing stabilizes the balloon during inflation, resulting in adequate valve dilatation. PL, pacing lead; arrow, aortic valve calcification.

Antegrade and Double-Balloon Dilatation

If arterial access is limiting, the aortic valve can be dilated via the antegrade route or a double balloon technique using lower profile systems. The antegrade route (Fig. 41A-8) requires venous access, transseptal catheterization, and a guide wire that is looped in the left ventricle and across the aortic valve. Although this method is not recommended for inexperienced operators because of potential damage to the atrial septum and mitral valve, we have performed this technique safely in patients under special circumstances. The double balloon technique requires the use of 2 smaller balloons such that the addition of the individual diameters is 1 to 2 mm larger than the aortic annular diameter as measured by TTE. This technique may be beneficial in the adult patient with bicuspid AS.
FIGURE 41A-8 The guide wire (GW) is seen entering the heart from the right atrium and then crosses the left atrium, mitral valve, left ventricle, and aortic valve. A balloon catheter is inflated in the aortic valve (arrows, valve calcification). A Sones catheter (SC) from the left femoral artery is used to stabilize the balloon during inflation, although this technique is not necessary for routine valvuloplasty. PL, pacing lead.

POSTPROCEDURE MANAGEMENT

The transvalvular gradient and cardiac output should be measured as previously described. A final supra-aortic angiogram should define the degree of aortic regurgitation. Some centers may choose to evaluate aortic regurgitation and mean gradient after BAV with TTE in the catheterization laboratory. Immediately after the procedure, the balloon catheters and arterial sheaths are removed. The femoral artery entry site is closed using the predelivered percutaneous sutures in the vast majority of cases. In case of technical failure, pneumatic compression devices are sufficient and protamine can also be administered to reverse the effects of heparin. When BAV is applied in the context of severely impaired left ventricular function or cardiogenic shock, inotropic support or intra-aortic balloon counterpulsation.
may be transitorily required in the days following the procedure. If high-degree atrioventricular block occurs, temporary pacing should be used for 24 to 48 hours; if there is no recovery of conduction, a permanent pacemaker should be considered. In uncomplicated cases, the patients can be discharged after 1 day. Long-term follow-up is sequentially assessed on clinical and echocardiographic evaluations. Only in patients in whom the recurrence of symptoms is delayed by 6 months or longer should repeat BAV be performed. In these cases, results are similar to initial BAV.  

COMPLICATIONS

Vascular Injury

The rate of complications associated with BAV has markedly decreased since initial registries. The incidence of major vascular injury, traditionally the most common complication, has been reduced to less than 2% by the use of lower profile arterial introducers and closure devices.  

Significant Aortic Regurgitation

Significant aortic regurgitation (AR) after BAV can be a fatal complication. In patients with small stature or heavily calcified valves, sequential dilatation is useful to prevent this problem. Acute, severe, native AR after BAV is best treated with implantation of a new valve. For this reason, some operators prefer to prepare the new valve for implantation prior to performing BAV in TAVR procedures. If balloon sizing is needed to determine the size of the newly implanted valve, then pre-BAV preparation of the new valve is not possible. Bradycardia should be avoided in the setting of significant AR, and pacing may be a helpful temporizing measure.

Cardiac or Proximal Aorta Trauma

While rare, it is important to consider cardiac trauma as the cause of hypotension during BAV. Right ventricular perforation from a temporary pacing wire may cause pericardial effusion or tamponade. Large inspiratory drops in systemic arterial pressure (pulsus paradoxus) suggest a
hemodynamically significant effusion, and echocardiography may be confirmatory. Treatment with pericardiocentesis is reasonable since the bleeding into the pericardium is often self-limited. If blood loss is substantial, blood may be autotransfused from the pericardium into a systemic vein while preparation is made for surgical exploration. The site of perforation may not be identifiable at surgery.

Aortic root trauma may be immediately catastrophic or may present subtly with thickening of the interatrial septum on echocardiography and subsequent development of pericardial effusion. Effusion may be treated as above, and surgical repair may be considered. Immediate treatment with protamine and blood pressure control are recommended for conservative management.

**Embolic Events**

In our experience, the occurrence of clinically apparent cerebral events (<1%) is less common with BAV than reported with retrograde catheterization.\textsuperscript{19,32} Intravenous heparin should be used at the beginning of the procedure, and the valve should be crossed with the minimal number of guide wire passes. Stroke can also occur during prolonged hypotension, manipulation of hardware across the diseased aorta (particularly in patients with extensive vascular disease or previous stroke), or balloon inflation. Preventing hypotension can be done by minimizing sedation or using background pharmacologic hemodynamic support for those who require deeper sedation. Shorter balloon inflation/deflation time, shorter rapid stimulation time (<10 seconds), and moving to the final balloon size without many inflations with intermediate sizes are also helpful. The development of neurologic changes should prompt urgent imaging and consultation with a neurologist, particularly in stroke centers where interventional removal of embolic debris can be done quickly and effectively.

New-generation embolic protection devices, such as the Montage Dual-Filter System (Claret Medical, Santa Rosa, CA), have shown some preliminary feasibility in deflecting or capturing emboli during TAVR and may serve a future role in BAV.\textsuperscript{39}

**Mortality**

Procedural death (within 24 hours), the result of fatal arrhythmia, progressive
heart failure, rupture of the aorta, or disruption of the aortic valve, can be seen in patients with severely depressed left ventricular function, cardiogenic shock, heavy calcification of the aortic valve, asymmetric bicuspid valves, and porcelain aorta. If hypotension occurs during the procedure, the etiology should be sought immediately. Liberal use of echocardiography is invaluable, and pericardiocentesis can be lifesaving, particularly as a bridge to surgical therapy.

The National Heart, Lung, and Blood Institute (NHLBI) registry reported an 11% cardiovascular mortality by 30 days, including 3% of patients dying on the catheterization table. In more recent registries, complication rates are significantly lower, with a mortality rate of <3% and, in our centers, <1%. Lower rates of complications in modern BAV are largely driven by lower vascular complications due to more slender arterial introducers and systematic use of vascular closure devices. The most important predictor of event-free survival after BAV is baseline left ventricular function (ejection fraction >25%).

In the PARTNER Cohort B (TF-TAVR vs medical management) trial, (inoperable) patients who were not randomized to TAVR had 50% 1-year mortality despite BAV in 84%. There is evidence to suggest that patients who undergo repeat BAV have higher long-term survival rates than those who undergo isolated BAV. Perhaps repeat BAV in these patients is a viable treatment strategy while awaiting definitive therapeutic options. The lack of sustained impact on mortality is most likely due to restenosis, and a plan for a more definitive solution should be part of the procedure discussion with patients and their families before they become symptomatic as signs and symptoms of AS can have an accelerated recurrence. For this reason we often meet patients at 4 to 6 weeks after BAV to discuss therapeutic options.

CONCLUSION

Current guidelines recommend BAV as a bridge to SAVR or TAVR in patients who are at high risk for surgery with severe symptomatic AS. Isolated BAV may also be considered as a palliative procedure in select individual cases where surgical and TAVR risk is prohibitive or ineffective secondary to severe comorbidities. In the TAVR era, BAV can serve both a
diagnostic purpose to predict the potential benefit of TAVR as well as a therapeutic purpose to temporize symptoms while awaiting definitive therapy. In particular, assessing improvement in impaired left ventricular function, severe pulmonary hypertension, mitral regurgitation, and cognitive dysfunction after BAV may help drive clinical decisions making. Further prospective randomized studies are warranted to better elucidate the indications and the potential benefit of BAV in the contemporary era of TAVR.

REFERENCES


Patient Selection, Procedural Techniques, and Complications of Balloon-Expandable Transcatheter Aortic Valve Replacement

Ayaz Rahman
Alain Cribier
Vasilis Babaliaros

HISTORY AND RATIONALE OF THE PROCEDURE

Aortic stenosis (AS) is the most common acquired valvular disease in adults.\(^1\) The incidence of AS has steadily increased along with population life expectancy and age, affecting almost 5% of patients over the age of 75 years.\(^2\) The most common cause of valvular AS in adults is calcification of a normal trileaflet valve or a congenital bicuspid valve.\(^3\) Severe symptomatic AS has a poor prognosis when treated medically, with a mortality of almost 80% at 2 years.\(^4\) Surgical aortic valve replacement (SAVR) is currently the standard of care and accepted to alleviate symptoms and prolong survival; however, up to one-third of patients are denied SAVR because of prohibitive surgical risk (eg, advanced age, significant left ventricular dysfunction).\(^5\)

In 2002, Cribier and colleagues\(^6\) successfully performed the first
transcatheter aortic valve replacement (TAVR) in an elderly inoperable patient for the treatment of severe AS. This approach marked the feasibility of percutaneous valve implantation, and TAVR has emerged as a less invasive alternative to conventional SAVR.\(^7\) Results from the Placement of Aortic Transcatheter Valves (PARTNER) trial have allowed TAVR to become the standard of care for extremely high-risk or “inoperable” patients, and TAVR is a valid alternative to surgery for selected high-risk but “operable” patients with symptomatic AS.\(^8,9\) TAVR has been performed for over 10 years with >100,000 implantations worldwide, and this innovative technology has allowed a paradigm shift in the treatment of AS.\(^10\)

**INDICATIONS FOR TREATMENT**

TAVR is recommended for patients with symptomatic, severe, calcific stenosis of a tricuspid aortic valve who have predicted survival >12 months and either prohibitive surgical risk (defined by >50% estimated risk of mortality or irreversible morbidity at 30 days, frailty, prior cobalt chest irradiation, porcelain aorta, coronary bypass graft adhesion to the posterior sternum preventing safe reentry into the chest, or severe pulmonary or hepatic disease) or high surgical risk (Society of Thoracic Surgeons [STS] mortality risk ≥8% with predicted actual mortality >15%).\(^11,12\) Trials are ongoing to evaluate TAVR in a medium-risk population (STS mortality risk 3%-8%; PARTNER II trials).

**AVAILABLE BALLOON-EXPANDABLE VALVES**

Currently, the most data available for TAVR are based on the balloon-expandable SAPIEN valves (Edwards Lifesciences, Irvine, CA; Fig. 42-1). The Edwards SAPIEN transcatheter heart valve system has been used extensively worldwide and was used in the PARTNER I trial.\(^7\) Based on this trial, the SAPIEN valve was the first transcatheter aortic valve to be granted approval by the US Food and Drug Administration (FDA) in November 2011 for use in surgically inoperable patients and in 2012 for use in surgically
The Edwards SAPIEN consists of a trileaflet, bovine pericardial valve mounted on a stainless steel stent with a polyethylene terephthalate skirt and seals at the aortic annulus with the stent frame deployed just beneath the coronary ostia. It was available in 2 sizes: 23 mm (for aortic annuli between 18 and 22 mm) and 26 mm (for aortic annuli between 21 and 25 mm) with a sheath and delivery catheter system of 22 Fr and 24 Fr, respectively. Dimensions and adequate requirements for the SAPIEN valve are provided in Table 42-1. More recently, the SAPIEN was replaced by the SAPIEN XT in Europe, Canada, and the United States (June 2014). Dimensions and adequate requirements for the SAPIEN XT valve are provided in Table 42-2. SAPIEN XT also consists of a bovine pericardial valve but is mounted to a thinner cobalt-chromium stent with fewer struts to allow for a lower profile delivery system. The SAPIEN XT is available in a wider range of sizes (23, 26, and 29 mm). Additionally, the Edwards eSheath (Edwards Lifesciences) combines a low profile with a dynamic expansion mechanism and is available in 16, 18, and 20 Fr (23-, 26-, and 29-mm valve, respectively). The eSheath allows for transient sheath expansion during delivery system passage and reduces the time the access vessel is expanded.

Table 42-1 Dimensions and Anatomic Requirements for Approved Edwards SAPIEN Transcatheter Heart Valves and Retroflex Delivery Systems
The most recent generation of the SAPIEN series of valves is the SAPIEN 3 (S3). The S3 consists of a bovine pericardial valve mounted on a cobalt-chromium stent with an outer skirt (polyethylene terephthalate) designed to enhance sealing and minimize paravalvular leak. The S3 is a taller valve (decreases the likelihood of native leaflet tissue prolapse) with 4 rows and 4 columns of cells between each commissure for high radial force. The S3 is available in 20, 23, 26, and 29 mm and can be delivered through a reduced profile 14- and 16-Fr (for the 29-mm valve) eSheath. Dimensions and adequate requirements for the S3 valve are provided in Table 42-3. In addition, the latest iteration of the delivery system (Commander) has several characteristics intended to facilitate accurate positioning, including increased flexion capability to engage the native valve coaxially and a fine alignment mechanism to make precise adjustments prior to deployment. The low-profile S3 valve and delivery system may facilitate fully percutaneous implantation in a broader range of patients with more accurate positioning and less paravalvular regurgitation. Improvements in valve technology will make it feasible for less experienced centers to make the transition to a complete

| Table 42-2 Dimensions and Anatomic Requirements for Approved Edwards SAPIEN X Transcatheter Heart Valves and NovaFlex Delivery Systems |
|-------------------------------|-----------------|-----------------|-----------------|
|                                | 23-mm Valve     | 26-mm Valve     | 29-mm Valve     |
| Acceptable aortic annular size range (by 2D TEE) | 18-22 mm        | 21-25 mm        | 24-27 mm        |
| Acceptable aortic annulus area by CT | 314-415 mm²     | 415-530 mm²     | 530-660 mm²     |
| Valve height                   | 14 mm (17 mm crimped) | 17 mm (20 mm crimped) | 19 mm (22 mm crimped) |
| eSheath outer diameter         | 6.7 mm          | 7.2 mm          | 8.0 mm          |
| Minimum access vessel diameter | 6.0 mm          | 6.5 mm          | 7.0 mm          |

Note: Aortic annular size is often more accurate and larger by transesophageal echocardiography (TEE) compared to transthoracic echocardiography (TTE). Computed tomography (CT) sizing is the most accurate, and optimal oversizing is 10% to 15%. The ranges suggested in this table are for general guidance and should not substitute for clinical judgment and experience.
percutaneous approach using local anesthesia and fluoroscopic guidance in the catheterization laboratory.

Table 42-3 Dimensions and Anatomic Requirements for Approved Edwards SAPIEN 3 Transcatheter Heart Valves and Commander Delivery Systems

<table>
<thead>
<tr>
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<th>20-mm Valve</th>
<th>23-mm Valve</th>
<th>26-mm Valve</th>
<th>29-mm Valve</th>
</tr>
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<tbody>
<tr>
<td>Acceptable aortic annular size range (by 2D TEE)</td>
<td>16-19 mm</td>
<td>18-22 mm</td>
<td>21-25 mm</td>
<td>24-28 mm</td>
</tr>
<tr>
<td>Nominal area</td>
<td>328 mm²</td>
<td>406 mm²</td>
<td>519 mm²</td>
<td>649 mm²</td>
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<tr>
<td>Acceptable aortic annular 3-dimensional area</td>
<td>273-345 mm²</td>
<td>338-430 mm²</td>
<td>430-546 mm²</td>
<td>540-680 mm²</td>
</tr>
<tr>
<td>Valve height</td>
<td>15.5 mm (21 mm crimped)</td>
<td>18 mm (24.5 mm crimped)</td>
<td>20 mm (27 mm crimped)</td>
<td>22.5 mm (31 mm crimped)</td>
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<td>eSheath outer diameter</td>
<td>6.0 mm</td>
<td>6.0 mm</td>
<td>6.0 mm</td>
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<tr>
<td>Minimum access vessel diameter</td>
<td>5.0 mm</td>
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Abbreviation: 2D TEE, 2-dimensional transesophageal echocardiography.

**BASELINE EVALUATION AND PATIENT SELECTION FOR TAVR**

The assessment of a patient’s surgical risk, clinical status, and feasibility for TAVR is best accomplished by a multidisciplinary heart team consisting of clinical cardiologists, cardiac imaging specialists, interventional cardiologists, and cardiothoracic surgeons. We begin to establish surgical risk using the STS Predicted Risk of Mortality (PROM) score, which evaluates factors such as age, renal function, type of surgery, and pulmonary function. An STS-PROM score (mortality rate) of >8% signifies high risk (as defined by the inclusion criteria of the PARTNER trial cohort A group), and a score of 4% to 8% signifies moderate surgical risk (as defined by the inclusion criteria of the PARTNER II trial cohort A group).

The STS-PROM scoring system provides a formal means of risk stratification; however, it fails to include several important patient characteristics, including frailty and disability, which are particularly relevant to the elderly AS cohort. Several standardized models of frailty exist, and all seem to indicate that frailty has a significant impact on outcomes after cardiac surgery. Elderly patients with a low level of independent functioning (Katz Index of independent activities of daily living) were found to have twice the
surgical mortality and 6 times the risk of prolonged institutional care following cardiac surgery.\textsuperscript{15} Even crude measures of disability, such as gait speed, have been found to increase the risk of mortality or major morbidity by 2 to 3 times for any given STS-PROM score after cardiac surgery.\textsuperscript{16} A high frailty score (which includes assessment of gait speed, grip strength, serum albumin, and activities of daily living) has been independently associated with increased 1-year mortality following TAVR.\textsuperscript{17} These findings serve to remind clinicians that although risk stratification begins with validated models, a comprehensive assessment must consider other factors that may not be so easily measured.

A small but significant number of patients with AS are unable to have surgery due to a myriad of anatomic and medical conditions. Reasons for technical inoperability include porcelain aorta, previous mediastinal radiation, chest wall deformity, and potential for injury to previous bypass graft on sternal reentry.\textsuperscript{18} Cirrhosis, lung disease, and frailty are other medical conditions that when present are often thought to imply excessive surgical risk. Patients undergoing TAVR secondary to anatomic and advanced medical comorbidities have significant survival benefit when compared to standard therapy.\textsuperscript{18} Patients with bicuspid aortic valves have been excluded from most TAVR registries and trials. However, there are data to suggest that TAVR can be performed with good clinical outcomes in patients with bicuspid aortic valves.\textsuperscript{19} Patients with moderate dementia who would not fare well after cardiopulmonary bypass can be considered for TAVR. Patients who cannot afford to have a prolonged recovery after SAVR due to ongoing chemotherapy, need for additional operations, and upcoming transplantation can be considered for TAVR. Consideration of such factors outside of formal risk prediction models makes it crucial to allow assessment of anticipated risk for SAVR or TAVR by an experienced heart team.

**PREPROCEDURAL PLANNING FOR TAVR**

Perhaps the 2 most significant challenges to TAVR are the larger size of the delivery sheaths and the reliance on indirect visualization of the heart. To overcome these obstacles and perform safe TAVR, meticulous preprocedure
planning and intraprocedure imaging are needed. Evaluation prior to TAVR should seek to determine several factors, including (1) iliofemoral vessel size, calcification, and tortuosity; (2) anatomic details of the aortic valve leaflets; (3) annulus, sinotubular, and sinus of Valsalva dimensions; and (4) distance from the aortic annulus to the coronary ostia.

TAVR was initially conceived as a fully percutaneous procedure performed through the iliofemoral vessels without the need for a vascular cutdown. The transfemoral (TF) approach is the preferred access route for TAVR because it is less invasive than alternative routes. For patients without adequate iliofemoral vessels, operators have investigated more novel routes for delivery of the SAPIEN bioprosthesis. The SAPIEN device can be deployed via a transapical (implantation through the cardiac apex after a lateral thoracotomy), transaortic (direct cannulation of the ascending aorta with a mini-sternotomy), transcarotid (following a cutdown with Javid shunt), transcaval, or transseptal approach. In earlier Edwards SAPIEN registries, 30% to 50% of patients required an alternative approach due to peripheral artery disease or vessels unable to accommodate the larger delivery sheaths available at the time. In more recent reports using the 16/18/20 Fr SAPIEN XT and 14/16 Fr S3 delivery sheaths, an alternative access site has been used in 7% to 10% of cases.

PREPROCEDURE IMAGING

To determine which patients are suitable for a true percutaneous approach and which would be best served by an alternative access approach, we propose multimodality imaging assessment as an important step in planning TAVR. Imaging guides both access route and device sizing.

Echocardiography

Transthoracic echocardiography (TTE) is the initial imaging modality of choice due to its ease and safety. TTE is important to establish the diagnosis of AS and valve morphology (ie, bicuspid vs trileaflet valve), assess aortic annulus size, and evaluate left ventricular function and other concomitant valvular disorders, right ventricular dysfunction, and pulmonary hypertension. TTE is useful in identifying the location of any large, calcific
nodules, their relationship to the coronary ostia, and calcium that tracks into the left ventricular outflow tract (Fig. 42-2). Precise sizing of the aortic annulus is crucial for proper valve prosthesis selection and in order to avoid complications of inappropriate sizing (see section on computed tomography [CT]). TTE tends to underestimate true open surgical sizing and transesophageal echocardiography (TEE) may be helpful to provide better assessment of the annulus (Fig. 42-3).\textsuperscript{23,24} Balloon sizing of the annulus during balloon aortic valvuloplasty may be particularly helpful when the annulus is questionably too large for a given valve; supravalvular aortography is performed during balloon aortic valvuloplasty with rapid pacing, and any leakage of contrast into the left ventricle suggests that a larger valve will be needed (Fig. 42-4).\textsuperscript{25} Invasive techniques to assess aortic annular sizing may not be necessary with the advent of cross-sectional 3-dimensional TEE and CT imaging.\textsuperscript{26}
FIGURE 42-2 Calcified nodules in the aortic valve leaflets. A and B. Images from the same patient show a calcified nodule associated with the right coronary leaflet. This nodule is relatively less likely to cause significant paravalvular leak since it may be displaced into the sinus with valve deployment. LA, left atrium; RA, right atrium;
RV, right ventricle.

**FIGURE 42-3** Aortic root anatomy by echocardiography. Transthoracic echocardiography with 2-dimensional imaging (A) can be used to measure the aortic valve annulus as well as the sinuses and sinotubular junction (STJ). The annulus is frequently elliptical, and 3-dimensional transesophageal echocardiography provides a more complete assessment including the annular area (B). For this patient, the annular area of 620 mm$^2$ suggests that a SAPIEN 26-mm valve (nominal area 530 mm$^2$) would be too small.
FIGURE 42-4 Balloon aortic valvuloplasty to size the aortic valve annulus. If a supravalvular aortogram is completed during maximum inflation of an appropriately sized balloon (1-2 mm less than the proposed valve’s size), balloon valvuloplasty can be used to predict whether or not the proposed valve will seal the annulus. In panel A, the absence of any leak around a 22-mm balloon suggests that a 23-mm valve will be large enough. In panel B, contrast is leaking around a 25-mm balloon, which suggests that a 26-mm valve will be too small and may leave significant paravalvular leak. Panel C shows deployment of a 29-mm bioprosthesis after balloon sizing with a 25-mm balloon. Panel D shows final supravalvular aortography after deployment of a 29-mm bioprosthesis with no evidence of paravalvular regurgitation.
Computed Tomography

CT provides a wealth of cardiac, thoracic, and peripheral information in assessing a patient’s feasibility for TAVR and procedural planning.\(^{26}\) A CT scan will show in detail the aortic root anatomy (including annular, sinotubular, and sinus of Valsalva dimensions as well as coronary heights above the annulus), aortobifemoral anatomy, and details of arterial diameters and calcification. A gated, contrast CT with less than 1-mm slices will allow detailed 3-dimensional reconstruction, which can be invaluable for evaluation of the aortic annulus and peripheral arteries. Given the ellipsoid shape of the aortic annulus, 2-dimensional imaging techniques, such as TTE, may not accurately represent the size of the annulus (Fig. 42-5). Three-dimensional gated CT imaging of the aortic root may provide even more accurate assessment than surgical sizing.\(^{27}\)
Computed tomography with 3-dimensional reconstruction of the aortic valve annulus may provide the most complete assessment of aortic root anatomy and, like 3-dimensional echocardiography, can be used to measure the annular area. For this patient, the annular area of 532 mm$^2$ suggests that a 29-mm valve (nominal area 649 mm$^2$) would provide 22% oversizing for the S3 valve.

An appreciation of the complex, 3-dimensional, and nearly uniformly ovoid shape of the aortic annulus is important for appropriate prosthesis sizing. Inappropriate prosthesis size selection is associated with
paravalvular regurgitation, aortic annular rupture, coronary occlusion, and
device embolization. CT annular area measurements are usually performed in
systole at 25% or 35% of the RR interval when the annulus is largest.\textsuperscript{29} 
Nominal external areas for the SAPIEN 23- and 26-mm valves are 415 and
531 mm\textsuperscript{2}, respectively, and for the SAPIEN XT 23-, 26-, and 29-mm valves,
they are 415, 531, and 661 mm\textsuperscript{2}, respectively. Area oversizing of 8% to 10%
is considered optimal; however, most patients will not meet this stringent
target due to the large increments between prostheses sizes, and therefore, a
range extending up to 20% oversizing is acceptable in proposed sizing
algorithms.\textsuperscript{30} For borderline aortic annular dimensions, intentional
underexpansion of balloon-expandable valves by reducing the balloon
volume by 10%, which results in an intermediate inflow diameter between
the fully expanded valve and the next smaller transcatheter valve, has been
proposed.\textsuperscript{30} The S3 valve incorporates a paravalvular sealing system, and the
target annular oversizing range is 5% to 15% (see Table 42-3 for nominal
area for the 20-, 23-, 26-, and 29-mm valves). If oversizing by 20% to 30% is
anticipated, underfilling the deployment balloon by 1 to 3 mL or undersizing
the prosthesis by up to 5% should be considered.\textsuperscript{31}

Another application of cardiac CT is to establish a fluoroscopic projection
that defines the precise aortic valve plane that is perpendicular to the axis of
implantation and allows optimal deployment of the valve prosthesis. By using
CT to determine the “deployment angle,” operators can avoid performing
multiple aortic root angiograms. Additionally, CT imaging provides
information such as leaflet length, leaflet calcification, and height from the
annulus to the coronary ostia. These factors may predict the complication of
coronary occlusion during TAVR. Generally, a distance from annulus to
ostium of 11 to 14 mm is considered reasonable, and less than 7 mm is
possibly prohibitive for TAVR, particularly with narrow sinuses of Valsalva
(see Table 42-1). Adverse root features, including more than minimal left
ventricular outflow tract calcification, increase the risk for aortic rupture and
paravalvular regurgitation.\textsuperscript{32}

CT assessment of the minimum diameter of the iliofemoral vasculature is
important in assessing the feasibility of TF TAVR. The Edwards SAPIEN
bioprosthesis requires a minimum diameter of 8 mm throughout the
iliofemoral system for the 26-mm valve and of 7.3 mm for the 23-mm valve
(see Table 42-1). The outer diameter of the 22- and 24-Fr Edwards delivery
sheaths are 8.4 and 9.2 mm, respectively (see Table 42-1). The SAPIEN XT requires a minimum of 6.0 mm for the 23-mm valve, 6.5 mm for the 26-mm valve, and 7.0 mm for the 29-mm valve (see Table 42-2). The S3 requires a minimum of 5.5 mm for the 23- and 26-mm valves and 6.0 mm for the 29-mm valve (see Table 42-3). It is also important to assess the degree of tortuosity and calcification of the pelvic vasculature. Extensive calcification in relatively straight common iliac arteries maybe acceptable as long as the dimension is larger than the outer diameter of the sheath. Moderate calcification in tortuous external iliac arteries (which frequently dive deep into the pelvis) may increase the likelihood of major vascular complications. A noncalcified artery will often stretch 1 mm without major complication using a nonexpandable sheath, although dissection can still occur postprocedure. With the e-Sheath, we have seen noncalcified arteries temporarily stretch >2 mm without complication. Contrast-enhanced CT is preferred in the assessment of the peripheral vasculature, but in patients with significant renal insufficiency, a noncontrast study may be adequate.

**Angiography**

Invasive coronary and bypass graft angiography is also needed to evaluate anatomy suggestive of a large burden of ischemic myocardium; however, complete revascularization may not be necessary prior to TAVR. An invasive, digitally subtracted distal abdominal aortobifemoral angiogram using a marked pigtail catheter can be complimentary to CT and very helpful in defining the size and course of the iliofemoral system. In patients with borderline diameter of the pelvic vessels, intravascular ultrasound may be helpful to determine candidacy for the TF approach.

**Carotid Ultrasound**

Carotid duplex ultrasound may identify severe, flow-limiting carotid disease that may increase the risk of stroke associated with significant cardiogenic shock during TAVR, although this is exceedingly rare with TF TAVR. Percutaneous or surgical carotid revascularization may be considered prior to TAVR; however, procedure-related hypotension may be devastating and, thus, this procedure is not recommended by our center. We also measure the diameter of the common carotid artery in addition to the disease burden of the
carotids to determine candidacy for a transcarotid approach if no other access is feasible or safe.

**ANESTHESIA**

TF TAVR is commonly performed under general anesthesia but may be safely performed in experienced centers using only local anesthesia and minimal or no sedation. The advantage of general anesthesia is that operators early in their experience can perform TAVR without being rushed or concerned about airway management if a complication occurs. TAVR performed with conscious sedation allows for quicker recovery and hospital discharge of the patient. It also decreases the utilization of resources for TAVR, which may have important economic implications.

**TF TAVR PROCEDURE**

The following text describes the practical aspects of TF TAVR for patients with native valve AS using the Edwards SAPIEN valve.

*Antibiotics*

Routine antibiotic prophylaxis should be administered immediately prior to the procedure. Often, the same antibiotics that are used perioperatively for open surgical aortic replacement are used (eg, cefuroxime). Drugs effective against gram-positive skin flora such as cefazolin and vancomycin (in cases of penicillin allergy) are appropriate when a fully percutaneous approach is used. Antibiotic prophylaxis for the implanted bioprosthesis is indicated with subsequent dental procedures according to intersociety guidelines.

*Patient Preparation*

Patients are prepared and draped in the supine position with exposure from the upper thigh through the subxiphoid area, which should be available if emergent pericardiocentesis is required. An adhesive, iodophor-impregnated incise drape may be helpful in preventing access site infection.
Intraoperative Echocardiography

Intraoperative echocardiography may be transesophageal or transthoracic and is helpful in positioning the new valve prior to deployment as well as in evaluating postdeployment valve function. In the setting of hypotension after valve deployment, echocardiography is critical in assessing for valvular regurgitation, pericardial effusion, left ventricular dysfunction, and injury to the aortic root. Aortic regurgitation, if present, should be identified as transvalvular or paravalvular, quantified, and treated appropriately; management of aortic regurgitation will be discussed later in this chapter.

Special Instruments

• “Micropuncture” access kits that use a 21-gauge needle and 0.018-inch wire for arterial entry facilitate fluoroscopy-guided access.
• Uninterrupted capture during rapid ventricular pacing is critical to stable valve deployment, and for this reason, a Mullins (transseptal) sheath may be placed across the tricuspid valve to support the temporary pacing wire.
• Suture-based, percutaneous arteriotomy closure devices such as the Perclose ProGlide and ProStar XL (Abbott Vascular, Abbott Park, IL) are needed for fully percutaneous TF TAVR procedures.
• When TF TAVR is performed without an anesthesiologist, prepared 10-mL syringes of norepinephrine (16 μg/mL) and epinephrine (0.1 mg/mL) are helpful when immediately available to operators for as-needed treatment of hypotension.

Antithrombotic Therapy

Unfractionated heparin should be used after arterial access is obtained to maintain an activated clotting time (ACT) of 250 to 300 seconds. Heparin administration based on baseline ACT levels results in a significantly lower occurrence of major bleeding with TAVR. Direct thrombin inhibitors have been used for those with heparin allergies. We routinely administer a loading dose of clopidogrel prior to TF TAVR based on anecdotal evidence. Dual antiplatelet therapy with aspirin and clopidogrel is indicated after TAVR to prevent thromboembolic complications, but there is no consensus on the indicated duration of therapy. Six months of therapy with aspirin and
clopidogrel after TF TAVR are reasonable in most patients, and aspirin is indicated indefinitely thereafter. Clopidogrel can probably be omitted for patients who will be therapeutically anticoagulated with warfarin.

**Arterial and Venous Access**

In addition to femoral arterial access for the valve’s delivery sheath, a second (typically 6 Fr) arterial access is needed for insertion of a pigtail catheter into the aortic root. Venous access is needed for insertion of the temporary pacing wire.

**Device Preparation**

The family of SAPIEN valves uses dedicated delivery systems, and the balloon inflation lumen is connected to an Atrion inflation device (Atrion Medical, Arab, AL). The balloon ends in a nose cone, which facilitates crossing of the stenotic native valve. A crimping tool is a compression device that symmetrically collapses the valve over the delivery balloon catheter. The crimper is composed of a crimp aperture, which allows compression by means of a rotary knob; a balloon gauge, which verifies the delivery balloon diameter at full inflation; and a crimp gauge to verify the size of the balloon/valve assembly and to ensure that the delivery system has been suitably crimped. The newer generation SAPIEN valves (XT and S3) do not require measurement of the delivery balloon prior to crimping as a predetermined volume in the balloon is adequate. The entire system needs to be de-aired carefully. It is important to always check to see if the valve is mounted correctly on the balloon (fabric skirt toward the nose cone for the TF approach). The SAPIEN valves can be fully crimped for 15 minutes before insertion without compromising subsequent valve performance. Preparation of the delivery system and valve should be timed appropriately with the flow of the case.

**Step by Step Procedure**

After appropriate anesthesia, arterial and venous accesses are obtained on the side contralateral to where the delivery sheath will be inserted. A temporary pacing wire is advanced to a stable position in the right ventricular apex,
tested, and secured. The wire may be placed through a Mullins sheath (positioned across the tricuspid valve) for stabilization. The most stable position for the pacer lead is at the right ventricular apex. Placement of the lead in the base of the right ventricle free wall can lead to loss of capture or perforation (Fig. 42-6).

![Optimal positioning of the temporary pacing wire](image)

**FIGURE 42-6** Optimal positioning of the temporary pacing wire. Hand injection of a small volume of contrast through a Mullins sheath (or other catheter) positioned across the tricuspid valve can reveal the location of the right ventricular apex and facilitate safe positioning of the temporary pacing wire there. Wire placement on the right ventricular free wall or outflow tract may increase risk of perforation and loss of capture, respectively. Loss of capture may lead to valve malpositioning or embolization during deployment.

For fully percutaneous procedures, a 6-Fr Judkins right number 4 or similar catheter is then advanced to the aortic-iliac bifurcation, where it is used to selectively engage the contralateral iliac artery and create a digital “roadmap” of the femoral artery where the delivery sheath will be inserted. Using this image, a 21-gauge needle is placed coaxially into the center of the common femoral artery under real-time fluoroscopic guidance. Using the CT
scan for preprocedure planning, the location of the puncture can be selected to avoid the superficial femoral artery/profunda bifurcation and avoid a high arteriotomy through the inguinal ligament. Proper location of this puncture is critical to facilitate subsequent arteriotomy closure. Areas of heavy calcification are purposefully avoided. A 6- or 7-Fr sheath is inserted. Surgical cutdown to the planned femoral access site or external iliac conduit may alternatively be performed (Fig. 42-7).

**FIGURE 42-7** Accessing the femoral artery for valve implantation. Digital fluoroscopy equipment allows a femoral angiogram (created with contrast injection from contralateral access) to be stored as a “roadmap,” as depicted in panel A, where the tip of the arrow indicates the ideal site of puncture (1 cm above the femoral bifurcation) and the direction of the dotted line indicates the ideal angle of approach with the 21-gauge needle (coaxial with the femoral artery at the site of the planned puncture). Front-wall (B) puncture is essential for percutaneous closure, which provides immediate hemostasis at the end of the procedure (C). Access can also be obtained surgically. Panels D-F show how the external iliac artery may be accessed surgically using a conduit, which is brought out through a second skin incision in the groin. This approach may be helpful when femoral disease precludes transfemoral sheath insertion.
The catheter in the aortic bifurcation is exchanged for a pigtail catheter, which is advanced into the aortic root. Often the deployment angle can be predetermined by CT to align all 3 aortic cusps without overlap, with the nadir of the cusps defining the annular plane. A shallow left anterior oblique/cranial or right anterior oblique/caudal projection is typical. With the catheter sitting in the right sinus, a hand-injection aortogram is completed, allowing more detailed assessment of annular perpendicularity to the image. If the right cusp is too aortic, the image intensifier is moved cranially, and supra-aortic angiography is repeated. If the right cusp is too ventricular, the camera is moved caudally. The image projection is changed, and aortography is repeated until the annulus is visualized perfectly on edge. This “deployment angle” is saved into a still frame as a guiding picture for later valve deployment (Fig. 42-8).

![FIGURE 42-8 Optimal projection for valve deployment. In panel A, the right cusp is too high and overlying the noncoronary cusp. By moving the image detector cranially by 5°, the right coronary cusp is lower but not in line with the other cusps (B). In panel C, the image detector is moved an additional 5° and the bases of all 3 sinuses are aligned.](image)

A regular, J-tipped 0.035-inch wire is inserted at the main arterial access site, and the 6- or 7-Fr sheath is removed. The arteriotomy is “preclosed” using a pair of offset percutaneous suture devices. The matched pairs of suture ends are fixed together and secured as each is deployed (Fig. 42-9). Over a stiff, 0.035-inch wire such as the Amplatz Extra-Stiff wire (Cook...
Medical, Bloomington, IN), the arteriotomy is serially dilated to accommodate the balloon aortic valvuloplasty (BAV) sheath, which may also be the valve delivery sheath.

![Image](https://via.placeholder.com/150)

**FIGURE 42-9** Suture-based, percutaneous arteriotomy closure. Perclose ProGlide devices can be placed at the arteriotomy site before it is dilated to accommodate the large sheath. Two sutures are typically placed at a 45° offset (A). More offset may lead to higher risk of suture-mediated stricture when the site is closed. The sutures are secured during valve replacement (B), noting which pair of sutures was placed second. The second suture is usually tied first after sheath removal. An angiogram is completed prior to removal of the access site wire and final tightening of the last suture (C).

Once the larger sheath is inserted, a 6-Fr Amplatz left number 1 (AL1) catheter is inserted into the ascending aorta over a regular, J-tipped 0.035-inch wire. The J-tipped wire is removed, and a straight, 0.035-inch wire is used to cross the stenotic valve (see Chapter 41A, which describes techniques for crossing the stenotic aortic valve). The AL1 catheter is advanced into the left ventricle, and the aortic valve gradient is measured by transducing pressures simultaneously from the AL1 catheter and the side port of the large
sheath.

The same, stiff, 0.035-inch wire is reshaped to include a pigtail curve at its tip with roughly the same diameter as the left ventricular apex. We have found that the smallest diameter curve that can be shaped in the wire is best, as often it will grow to fill the left ventricular apex. The reshaped wire is inserted via the AL1 catheter into the left ventricular apex, and the AL1 catheter is removed. The valvuloplasty balloon is advanced across the aortic valve under fluoroscopic guidance, and BAV is performed during rapid ventricular pacing. One predilation is adequate for the subsequent delivery of the TAVR. The valvuloplasty balloon is sized to the short axis of the annulus or smaller to avoid interim severe aortic insufficiency (20-mm balloon for 23-mm TAVR and 23-mm balloon for 26-mm TAVR). Larger balloons can be used for balloon sizing as an adjunct to noninvasive imaging for prosthesis selection. Balloon sizing of the annulus may be particularly helpful prior to TAVR when the annulus is questionably too large for a given transcatheter valve. Supravalvular aortography is performed simultaneously during BAV with rapid pacing, and any leakage of contrast into the left ventricle suggests that a larger valve will be needed.\textsuperscript{25,39}

After the balloon is removed, the new transcatheter valve delivery system is introduced through the large sheath. The SAPIEN XT and S3 valves involve aligning the stent on the balloon within the aorta and use the NovaFlex and Commander delivery systems (Edwards Lifesciences), respectively. The SAPIEN XT and S3 devices are delivered via the low-profile Edwards eSheath, as described earlier.

While the delivery system is introduced, it is important to note wire position in the left ventricle and to allow the wire to float without any traction during advancement of the device. Prior to crossing the aortic arch, delivery catheter flexion is initiated and a left anterior oblique projection is obtained while advancing with countertraction on the guide wire. This maneuver allows for precise guidance of the delivery system in the mid-aorta and avoidance of atheromatous/debris embolization. The only part of the delivery system that may be touching the aorta while advancing around the arch is the nose cone. Strategies to ensure that the final position of the prosthesis is coaxial to the left ventricular outflow tract and thus perpendicular to the aortic annulus include wire manipulation with traction during advancement, clockwise rotation of the entire delivery system, and changing catheter flexion. Every effort should be made to advance the transcatheter valve
through the center of the aortic valve to increase the possibility of coaxial positioning. After crossing the aortic valve, we return to the deployment angle, and it is the role of the primary operator to go through the “5 Ps” as a checklist immediately before deployment (appropriate deployment picture, pigtail in noncoronary cusp, pusher catheter withdrawn so as to not interfere with balloon inflation, pacer advanced to make contact with the right ventricle, and position of the prosthesis). The implanter then needs to focus on the base of the native annulus that is located by identifying the basal attachment points of the leaflets by fluoroscopy or by echocardiography. It is in relation to this annular plane that the transcatheter valve is placed. Ideal position for the SAPIEN and SAPIEN XT is 50%/50% aortic/ventricular. To optimize positioning, identifying the leaflet tips is important to ensure that the prosthesis covers the native leaflets and the native annulus. Alignment of the aortic end of the prosthesis with the tips of the native aortic valve leaflets can be confirmed by echocardiography. The S3 is a taller valve, and positioning is accomplished by lining the middle balloon marker with the nadir of the aortic cusp (marked by the pigtail catheter). In cases of significant oversizing and/or significant subannular calcification, the S3 valve is placed 1 to 2 mm more aortic. Because ventricular shortening of the S3 may be limited in these conditions, placing the S3 more aortic helps approximate the ventricular skirt with the annulus. Ideal valve positioning is determined by a combination of fluoroscopy, echocardiography, and aortic root angiography. Significant aortic regurgitation during valve positioning can be mitigated by increasing the baseline pacing rate, which decreases diastolic filling time and affords additional time for positioning. Rapid pacing and/or arrested respiration during aortic root angiography may be helpful when there is significant valve movement with cardiac or respiratory motion. After satisfactory positioning, the new valve is deployed during rapid ventricular pacing. The rapid pacing should cause controlled hypotension. If 1-to-1 capture with the ventricle does not occur with the burst pacing, the deployment attempt should be aborted and reattempted at a slower pacing rate. If the burst pacing rate captures ventricular excitation consistently but does not cause a significant drop in blood pressure, the rate can be increased with rapid pacing (eg, start burst pacing at 160 beats per minute and increase to 200 beats per minute after initial capture). Deployment can be “active” to correct excessive movement of the device. Adjustments can be made if the valve dives too ventricular by
pulling back the prosthesis or pushing the guide wire. Pushing the valve forward or pulling the wire will prevent excessive aortic motion. Simultaneous root injection of the pigtail catheter in the noncoronary cusp will allow detailed visualization during deployment. A stepwise or gradual inflation will allow active deployment techniques. A prolonged pacing sequence (>20 seconds), however, can result in slow ventricular recovery, particularly in patients with depressed ejection fraction.

FIGURE 42-10 Optimal valve position by fluoroscopy and supravalvular aortography. Hand-injection aortography and fluoroscopic correlation with calcified landmarks help to optimize predeployment valve positioning relative to the base of the annulus as well as areas of calcification and the leaflet tips. Valve positioning is too aortic in panel A and too ventricular in panel B. Valve positioning in panel C is good.
FIGURE 42-11 Optimal valve position by echocardiography. Echocardiography is also important in optimizing predeployment valve positioning, including coaxiality (which cannot be completely assessed by single-plane aortography). Valve positioning is too aortic in panel A and too ventricular in panel B. Valve positioning in panel C is appropriate.

After deployment, the delivery system is withdrawn from the annulus, and prosthesis function is assessed echocardiographically, angiographically, and by hemodynamics. It is critical to understand the degree of aortic insufficiency and origin of the regurgitant jets because of the long-term adverse clinical impact that has been reported. Importantly, it is easier to correct the regurgitation during the index procedure compared with re-intervening on the patient at a later date. Patients with an aortic regurgitation index (defined as [diastolic blood pressure – left ventricular end-diastolic pressure]/systolic blood pressure × 100) of less than 25 have a significantly increased 1-year mortality compared with patients who have an aortic regurgitation index of ≥25. If significant transvalvular regurgitation appears to be related to the stiff wire against the leaflets, the delivery system may be removed and the wire exchanged for a multipurpose or pigtail catheter. If paravalvular regurgitation is severe, repeat balloon inflation by adding 1 mL of volume to the balloon can be successful. Balloon postdilatation may only be effective in 50% of cases and may come at the expense of higher cerebrovascular events. In extreme cases, a second valve can be implanted with excellent resolution of regurgitation. The final aortic valve gradient is measured using a multipurpose or pigtail catheter and the large sheath’s side port.
**Closure**

The large sheath is removed over a wire, and the arteriotomy is closed with the previously deployed sutures. The contralateral arterial access is used to perform a digitally subtracted, aortobifemoral angiogram after removal of the large sheath, thereby identifying any major vascular complications immediately. If the operator has a high level of suspicion for vascular rupture, contrast injections can be done gently through the large sheath during withdrawal. Protamine may be given if bleeding concerns outweigh thrombotic concerns. The pacing wire and contralateral sheaths are removed subsequently.

If the preplaced sutures do not provide hemostasis, additional suture(s) may be placed. With additional percutaneous sutures comes additional risk of creating a stricture or occlusion at the arteriotomy site, particularly if the sutures are deployed angulated. If arteriotomy closure remains incomplete after 3 or 4 sutures have been deployed, the partially closed arteriotomy may be occluded by insertion of a short, smaller (4-8 Fr) sheath. The smaller sheath may be removed and manual hemostasis achieved when the ACT is normalized. In cases of completely failed hemostasis, the larger sheath can be reintroduced and the patient can be sent for surgical repair of the arteriotomy. If concern for hemostasis exists, an adjunctive crossover balloon occlusion technique can be used with a wire and balloon from contralateral arterial access for tamponade and hemostasis of the arteriotomy site.44

**Postoperative Management**

Patients are typically transferred to a cardiovascular intensive care unit after TF TAVR, but uncomplicated cases may be transferred to regular telemetry beds in experienced centers. Systemic inflammatory response syndrome (SIRS) may be seen after TAVR and may manifest with leukocytosis, low-grade fever, hyperventilation, tachycardia, and vasodilation. Post-TAVR SIRS is a strong predictor of mortality and can be easily identified by a significant increase in the leukocyte count and treated with fluid and/or vasopressor support.45 Mild SIRS often resolves by the second day after TAVR. Continuation or late presentation of fever should prompt an investigation for infection. Acquired thrombocytopenia is common after TAVR and mostly resolves at patient discharge. However, nadir platelet
count of less than $50 \times 10^9/L$ may be predictive of higher 30-day and 1-year mortality.\textsuperscript{46} The duration of hospitalization after TF TAVR is determined by the patient’s baseline status and post-TAVR course, but patients may be discharged as early as postoperative day 1.

**TRANSAPICAL TAVR PROCEDURE**

The transapical (TA) approach has the advantages of facilitated implantation of a bioprosthetic device in patients who do not have favorable lower extremity access. TA TAVR procedures are performed by a team of cardiac surgeons, cardiologists, and anesthesiologists. The procedure is most favorably performed in a hybrid room with both fixed fluoroscopic imaging and TEE.

The patient is placed supine on the operating room table and prepped from the chin to the ankles. The chest, groin, and both legs are draped into the surgical field. Femoral arterial and venous access is obtained, the patient is anticoagulated with heparin to maintain an ACT of $>250$, a transvenous pacing wire is placed in the right ventricle, and a pigtail catheter is placed in the aortic root as described for the TF TAVR procedure. The apex of the left ventricle is identified by palpation, fluoroscopy, and/or echocardiography. An anterolateral thoracotomy is made in the 5th or 6th intercostal space, a rib-spreading retractor is placed, and the pericardium is incised to expose the left ventricular (LV) apex. Two pledgeted 2-0 prolene purse-string sutures are placed into the myocardium just cephalad to the apex lateral to the left anterior descending artery. In patients with previous sternotomy, opening the pericardium may not be necessary as sutures can be placed through the pericardium that are strongly adherent to the myocardium.

Fluoroscopy is used to align all 3 aortic cusps in the same plane. The LV cavity is accessed with an arterial needle, and a 0.035-inch wire is passed into the LV, across the aortic valve and into the ascending aorta. The wire is maintained in the ascending aorta and not allowed to pass into the right carotid artery. A 7-Fr sheath is placed through the LV apex and across the aortic valve. The 0.035-inch wire is manipulated into the descending aorta using a 6-Fr right Judkins 4 catheter. The 0.035-inch wire is exchanged for a stiff wire (Amplatz super stiff; Boston Scientific, Natick, MA) and left in the abdominal aorta. The 7-Fr sheath is exchanged for a TA delivery sheath,
which is positioned 4 cm inside the LV. A valvuloplasty balloon (20-22 mm, Z-med; Numed Inc., Hopkinton, NY) is placed over the wire and across the aortic valve. Under rapid ventricular pacing at 180 to 200 beats per second, BAV is performed. The balloon is removed, and the valve is crimped and placed through the LV delivery sheath and positioned across the valve.

Positioning of the valve uses TEE and fluoroscopic imaging. One-half of the valve is positioned above the aortic annulus, and the valve is aligned to be coaxial to the long axis of the aorta and perpendicular to the aortic annulus by manipulating the super stiff wire.\(^4^{7}\) Once the optimal position is confirmed, the valve is deployed during rapid ventricular pacing. Echocardiography with color Doppler and angiography are employed to evaluate valve position and assess the amount of paravalvular regurgitation.

All catheters and wires are removed, and the apex sutures are tied down during rapid ventricular pacing. Protamine is administered, and additional stitches may be placed in the LV apex to achieve hemostasis. The pericardium is closed over the LV apex surgical site, and a chest tube is placed in the left pleural space. Once hemostasis has been achieved, local anesthetic may be injected into the intercostal bundle, and the chest is closed in multiple layers.

**ALTERNATIVE ACCESS SITES**

In the recent past, operators have investigated more novel routes for delivery of the SAPIEN bioprosthesis. Direct cannulation of the ascending aorta (transaortic) with the delivery sheath has been successfully performed using a mini-sternotomy incision.\(^4^{8}\) A transaortic approach can be considered when there is inadequate iliofemoral anatomy and relative contraindications to TA TAVR (severe LV dysfunction and chronic obstructive pulmonary disease). Additionally, transcarotid and transsubclavian delivery after surgical cutdown has been successfully performed. Venous approaches with revival of the antegrade transseptal approach and transcaval approach (inferior vena cava to abdominal aorta puncture) have been reported. Minimal morbidity and mortality can be achieved when the appropriate alternative access approaches are tailored to the TAVR patient.\(^4^{8}\)
OUTCOMES OF TAVR

Hemodynamic Improvements

By invasive measurements, there is immediate improvement in hemodynamic measurements after TAVR and near-complete resolution of aortic gradients. For the SAPIEN series of valves, mean aortic gradients are reduced to less than 10 mm Hg and tend to be lower with larger prostheses. Aortic valve areas between 1.5 and 2.3 cm$^2$ are expected after implantation by echocardiography.$^{49-51}$

Few comparisons have been made between the hemodynamic performance of the transcatheter bioprosthesis and surgical prosthesis, but results suggest a favorable profile with TAVR. In a retrospective study of patients with AS and low ejection fraction, the Edwards SAPIEN bioprosthesis achieved a 20% larger reduction in mean aortic gradient than with SAVR and a 55% larger aortic valve area. Furthermore, the incidence of prosthesis-patient mismatch favored TAVR (16% with TAVR vs 29% with SAVR), and at 1 year, improvement in LV ejection fraction was significantly greater with TAVR (14% with TAVR vs 7% with SAVR; $P = .01$).$^{52,53}$

Quality of Life

Quality of life outcomes are particularly important in patients undergoing TAVR due to their often advanced age and accumulated comorbidities. Investigators have used several well-validated tests to assess subjective improvements in quality of life, including the Medical Outcomes Study Short Form-36 Item Health Survey, New York Heart Association (NYHA) functional class, Kansas City Quality of Life Questionnaire, Minnesota Living With Heart Failure Questionnaire, and 6-minute walk distance. Significant improvements in NYHA heart failure symptoms have been noted as early as 30 days after TAVR.$^{54}$ The PARTNER study found that NYHA symptoms improved between 30 days and 6 months and were stable at 1 year, such that 75% of surviving patients were in NYHA class I/II compared with only 8% at baseline.$^8$
Mortality

There have been a number of multicenter US, Canadian, and European registries of TAVR using various generations of the Edwards device. The only reported randomized trial comparing balloon-expandable TAVR to either medical therapy or SAVR comes from the PARTNER trial.

The PARTNER trial randomized patients among 2 different cohorts. Cohort A consisted of patients with high surgical risk (STS >10) randomized to TAVR (TF or TA) versus SAVR and was designed to demonstrate the noninferiority of TAVR. Cohort B consisted of inoperable patients randomized to TF TAVR versus medical therapy (including BAV as necessary) and was designed to demonstrate the superiority of TAVR.

The results of cohort B were published first and consisted of 358 randomized patients with an average age of 83 years, STS score >11, and numerous comorbidities including stroke, coronary artery disease, chronic obstructive pulmonary disease, pulmonary hypertension, atrial fibrillation, and frailty. The study demonstrated an impressive 20% absolute mortality reduction (50.7% vs 30.7%; \( P < .001 \)) with TF TAVR at 1 year. More recently, 2-year results demonstrated the continued survival advantage of TF TAVR in this group of patients (mortality, 43.3% vs 68.0%; \( P < .001 \)).

Subsequently, the cohort A findings were published and consisted of 699 patients with an average age of >83 years and STS score >11, and also with a significant prevalence of comorbidities. The TAVR was either aborted or converted to open surgery in 4.6% of patients. The primary end point (death from any cause at 1 year) was realized in 24.2% of the TAVR group and 26.8% of the surgical group (\( P = .44 \)), demonstrating noninferiority of the transcatheter procedure. These results are further substantiated by the recently provided 2-year data, with mortality rates of 35.0% and 33.9% in the SAVR and TAVR groups, respectively.

COMPLICATION MANAGEMENT OF TAVR

A major key to success in performing TAVR is complication prevention (CT scan and appropriate sizing of both annulus and iliofemoral anatomy) and
rapid identification and management if complications occur. Multimodality imaging, particularly echocardiography, has been instrumental in the recognition of complications and is key in guiding therapy. In assessing outcomes from the various published TAVR registries, it is often difficult to make comparisons, because outcome definitions were not standardized until the Valve Academic Research Consortium recently convened and published their criteria.\textsuperscript{56}

**Hypotension**

Acute hypotension during TF TAVR is not uncommon and may be due to acute aortic insufficiency, LV dysfunction (due to “stunning” with rapid pacing, ostial coronary occlusion, or other factors), pericardial effusion (typically from right ventricular perforation by the pacing wire or aortic root trauma), arrhythmia, peripheral vascular injury, a “suicide ventricle” (hyperdynamic intraventricular obstruction after unloading by BAV or TAVR), mitral valve injury, annular or root rupture, and ventricular septal defect.\textsuperscript{58} Treatment of acute hypotension is dictated by its etiology. Intra-aortic, intraventricular, or intravenous boluses of epinephrine or norepinephrine are immediately effective as temporizing measures. The suicide ventricle, while uncommon, is suggested by high residual dynamic gradients (obstruction worse after a premature beat) and can be identified echocardiographically. It is important to differentiate from other causes of acute heart failure as it will be aggravated by diuresis and positive inotropes but can be effectively treated with volume, vasoconstrictors, and negative inotropes. In addition to finding the root cause analysis, additional causes of hypotension are discussed in detail below.

**Vascular Complications**

Assurance of appropriate vascular size and minimal calcification and tortuosity on the preprocedural evaluation is paramount. Major vascular complications are those that cause limb-threatening ischemia or require additional interventions, either surgical or endovascular. The rate of major vascular complications was 14.0% in the PARTNER trial cohort A group and 16.2% in the PARTNER trial cohort B group.\textsuperscript{8} The rate of complications in the PARTNER trial should be tempered by knowledge of the substantial
decline (up to 3-fold) in major vascular complications that has been demonstrated with the smaller, second-generation SAPIEN XT bioprosthesis. The routine use of arterial preclosure with suture-based devices has also resulted in substantial decreases in vascular complications.

Aortoiliac avulsion or perforation may be suspected during arterial dilatation and insertion of the delivery sheath, but it may not be clinically manifest until removal of the delivery sheath. If perforation is identified at sheath removal, the sheath should be immediately reinserted (with dilator in place) to help tamponade the bleeding while preparation for more definitive treatment is made. Depending on the site and severity of injury, an aortic occlusion balloon such as the Coda balloon (Cook Medical) may be inserted from the contralateral arterial access site to the level of the distal abdominal aorta. With control of blood flow to the ruptured vessel, ipsilateral repair can be performed swiftly with either a balloon-expandable (Atrium iCAST; Atrium Medical Corporation, Hudson, NH) or self-expanding (Gore Viabahn; W.L. Gore and Associates, Inc., Flagstaff, AZ) covered stents. If the rupture involves partial or complete avulsion of the internal iliac artery, temporizing measures should be followed by prompt surgical intervention (Fig. 42-12). The internal iliac receives collateral circulation from the contralateral internal iliac, making injury in this vessel difficult to treat percutaneously without preemptive vascular plugging. Iliofemoral dissection is usually retrograde and does not limit flow, but severe dissections may be flow-limiting or even occlusive. Flow-limiting dissections should be treated with endovascular or surgical repair. Suture-mediated, severe stenosis of the common femoral artery at the access site often responds to gentle balloon dilatation, which does not need to completely eliminate the narrowing to be successful; mild to moderate residual narrowing is rarely symptomatic and is often resolved at follow-up.
FIGURE 42-12 Iliac rupture and management. Injecting contrast through the delivery sheath during slow withdrawal is prudent when iliac injury is suspected. If rupture is identified (A), the dilator is immediately reinserted. Sheath and dilator are immediately reinserted (B) to tamponade bleeding while an aortic occlusion balloon is deployed from contralateral access. Covered stents can then be used to seal the perforation percutaneously (C).

Aortic Regurgitation

Acute, moderate or severe native aortic regurgitation after BAV is best treated with implantation of a new valve. For this reason, some operators prefer to prepare the new valve for implantation prior to performing BAV, and some operators prefer to predilate with a small balloon (20 mm). If balloon sizing is needed to determine the size of the newly implanted valve, then pre-BAV preparation of the new valve is not possible. The risk of severe aortic insufficiency in patients with trileaflet AS is uncommon, with higher incidence seen in patients with bicuspid valves of any variety. Bradyarrhythmia should be avoided in the setting of significant aortic regurgitation, and increasing the pacing rate to 95 to 100 beats per minute may be a helpful
Acute, moderate or severe prosthetic aortic regurgitation after TAVR will be paravalvular, transvalvular, or mixed. It should be treated according to its etiology. Acute paravalvular regurgitation in the setting of an undersized or underexpanded valve may respond to postdilatation. Paravalvular regurgitation related primarily to malpositioning of the valve (too aortic or too ventricular) may require implantation of a second valve. Transvalvular regurgitation may occur due to incomplete valve closure when the valve is deployed in the setting of systemic arterial hypotension, and this improves when the blood pressure is increased. The valve also may simply require a brief period of time (minutes) to “warm up” and achieve full leaflet mobility. Transvalvular regurgitation may be severe when due to a “frozen” leaflet, and a pigtail or other catheter may be helpful in pushing the leaflet down so that it can begin to function. This condition may also require a second valve promptly, particularly if the native valve leaflets are overhanging and interfering with prosthetic valve function. This complication has not been reported with the longer S3 valve.

Chronic, moderate or severe paravalvular aortic regurgitation after TAVR may be treated percutaneously by implantation of a second valve or by implantation of 1 or more vascular plugs (Fig. 42-13).
FIGURE 42-13 Percutaneous paravalvular leak closure. Paravalvular leak may be treated by postdilatation, deployment of second valve, and/or implantation of vascular plugs. This patient had a focus of moderate to severe paravalvular leak despite deployment of second valve, and implantation of a vascular plug (seen here while still attached to deployment cable) was curative.

**Stroke**

A major concern for operators and patients is the risk of stroke during TAVR. Stroke in association with TAVR may occur because of atheroembolism, thromboembolism, calcium fragments, cardiogenic shock during the procedure, preexisting cerebral vascular disease, or interaction of these factors. In the PARTNER trial cohort B group, the risk of major stroke at 30 days with TAVR compared with medical management was 5.0% versus 1.1% ($P = .06$), and the combined risk of major and minor stroke was 6.7% versus 1.7% ($P = .03$). Importantly, quality of life metrics still demonstrated
substantial improvements in the TAVR group.\textsuperscript{64} More recent registry data with the second-generation SAPIEN XT device show a stroke rate of 2\%.\textsuperscript{65}

In the PARTNER trial cohort A group, the risk of major stoke at 30 days was 3.8\% with TAVR (TF and TA approaches) and 2.1\% with SAVR ($P = .20$), and at 1 year, the rates were 5.1\% and 2.4\%, respectively ($P = .04$).\textsuperscript{9} It is important to note, however, that while stroke was significantly greater at 30 days in the TAVR group (4.6\% vs 2.4\%), when followed out to 2 years, there was no significant difference between the 2 groups (7.7\% vs 4.9\%; $P = .52$).\textsuperscript{57}

New-generation embolic protection devices, such as the Embrella (Edwards Lifesciences) and the Montage Dual-Filter System (Claret Medical, Santa Rosa, CA), have shown some preliminary feasibility in deflecting or capturing emboli during TAVR, and clinical trials of the devices are eagerly anticipated.\textsuperscript{63} Cerebrovascular events are highest periprocedurally (the first 24 hours after TAVR), and the risk remains for approximately 2 months. These data have implications for potentially discontinuing dual antiplatelet therapy 2 months after TAVR.\textsuperscript{66}

Major ischemic stroke may be treated by catheter-based mechanical embolic retrieval where available. This strategy is particularly helpful in patients who undergo TAVR with conscious sedation because neurologic compromise can be identified rapidly in this patient population and immediate intervention can be performed. Thrombolysis may also be considered, although the expected benefit may be reduced (particularly with atheroembolism); bleeding risk is typically high because of patient age and morbidity as well as the arteriotomies created for TAVR.

Of note, it has recently been demonstrated that up to one-third of patients undergoing TAVR develop new-onset atrial fibrillation, and this was associated with an increased risk of stroke at 30 days and 1 year.\textsuperscript{67} Further study should focus on optimal antiplatelet and anticoagulant strategies to minimize stroke risk.

**Permanent Pacemaker Implantation**

The aortic annulus is in close proximity to the left bundle branch and atrioventricular node. Pressure exerted on this region by a stented valve may cause left bundle branch block and complete heart block either immediately
after implantation or in the days thereafter. The incidence of permanent pacemaker implantation with the Edwards SAPIEN device is 5% (4.5% in the PARTNER trial cohort B group and 5.7% in the PARTNER trial cohort A group; not significantly different than the incidence with medical therapy or SAVR). When compared to self-expanding valves, permanent pacemaker rates with the newer SAPIEN XT valve are significantly lower.\textsuperscript{68} Risk of permanent pacemaker with the SAPIEN valves is between 3% and 10%. Other factors that may contribute to the need for a pacemaker include the presence of a baseline right bundle branch block, extensive leaflet calcification, and an oversized transcatheter valve.\textsuperscript{69}

**Coronary Occlusion**

Obstruction of the coronary ostium by the native aortic leaflets occurs in <1% of patients undergoing TAVR.\textsuperscript{51} A narrow sinus of Valsalva, a short distance between the annulus and the coronary ostium, and the presence of bulky leaflet calcification may all contribute to coronary obstruction. Fortunately, these factors can be assessed on preprocedural imaging, and if concern exists, a pre-TAVR valvuloplasty with root angiography to assess coronary artery patency can be performed.

Acute, aorto-ostial coronary occlusion may be treated effectively with percutaneous coronary intervention, which may be facilitated in high-risk cases by placing a 0.014-inch coronary interventional wire with balloon or stent preemptively into the coronary artery prior to deployment of the new valve. The coronary stent will be placed to create a tunnel that covers the coronary ostium, the transcatheter valve stent, and the native aortic leaflet (Fig. 42-14).\textsuperscript{70}
Coronary occlusion treated with percutaneous intervention. Acute, aorto-ostial coronary occlusion was suspected prior to deployment of a second bioprosthesis, and the left main coronary artery was preemptively cannulated and wired with placement of a balloon (A). Post–transcatheter aortic valve replacement angiography revealed significant narrowing at the ostium of the left main coronary artery (B). Angioplasty of the left main coronary artery was successfully performed with a balloon (C). Final angiography after stent deployment revealed no significant narrowing with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow (D).

Cardiac or Proximal Aorta Trauma
While rare, it is important to consider cardiac trauma during TAVR. Right ventricular perforation may cause pericardial effusion, which can be hemodynamically significant. Large inspiratory drops in systemic arterial pressure (pulsus paradoxus) suggest a hemodynamically significant effusion, and echocardiography may be confirmatory. Treatment with pericardiocentesis is appropriate since the bleeding into the pericardium is often self-limited. If blood loss is substantial, blood may be autotransfused from the pericardium into a systemic vein while preparation is made for surgical exploration. The site of perforation may not be identifiable at surgery.

Aortic root trauma may be immediately catastrophic or may present subtly with thickening of the interatrial septum on echocardiography and subsequent development of pericardial effusion. Effusion may be treated as above, and surgical repair may be considered. Immediate treatment with protamine and blood pressure control is recommended for conservative management. Late presentation of subclinical rupture has been seen at follow-up echocardiography.

**Valve Embolization**

Valve embolization is most commonly due to loss of capture during rapid ventricular pacing (leading to ejection of the incompletely deployed valve from the annulus), but it also may be due to malpositioning. Embolization is best avoided by confirmation of stable pacing, careful valve positioning, and slow, controlled deployment. In the event of aortic movement during deployment, the valve may be immediately pushed back into the annulus if the second operator has maintained pressure on the inflation syringe (to hold the no-longer-crimped valve on the partially inflated balloon) without further inflation or deflation. If the valve cannot be pushed back across the annulus, then it may be pulled into the arch (and ideally into the descending aorta) before being deployed. If the deployment balloon has been deflated, the valve will be loose on the wire and should be recaptured with the balloon and deployed in a safe location, either just distal to the left subclavian artery or immediately proximal to the common iliac bifurcation (Fig. 42-15). Wire position across the valve must be maintained to prevent the valve from turning and obstructing the aorta. After the embolized valve is secured, a second valve may be implanted in the annulus to complete the TAVR. Valve
embolization into the left ventricle is less common and almost always requires surgical intervention.

**FIGURE 42-15** Distal deployment of an embolized valve. Valve embolization may be treated by distal deployment, as in panel A. The valve replacement procedure is completed using a second valve (B). A postoperative computed tomography scan (C) shows the embolized valve deployed in the distal arch and the second valve successfully deployed within the aortic valve annulus.

**FUTURE DIRECTIONS**

The field of TAVR is still young, and there are a number of future directions that show great promise. The initial case series, multiple registries, and the PARTNER I trial were all performed in patients with high or prohibitive surgical risk. Recent experience in Europe has demonstrated efficacy and safety of the procedure in lower surgical risk patients, and the PARTNER II trial aims to study patients with moderate surgical risk (STS score, 3%-8%). It will be interesting to determine whether the procedure is safe.
and effective enough to be extended to lower risk groups. In lower risk patients, more data can be acquired to assess long-term valve performance.

**Newer Devices**

While the early experience with the SAPIEN bioprosthetic devices have shown that TAVR is feasible, newer devices aim to make delivery simpler and more suitable for broader commercial use. Most new devices currently undergoing clinical testing are self-expanding and include the Lotus valve (Boston Scientific), St. Jude Medical Portico valve (St. Jude Medical, Saint Paul, MN), and the Direct Flow valve (Direct Flow Medical Inc., Santa Rosa, CA). The advantage of a self-expanding valve is that it offers the potential for retrievability. The S3 valve recently acquired approval in Europe (CE mark, or Community European) and is a lower profile, balloon-expandable valve that is designed to further reduce paravalvular regurgitation. It is the only commercial valve available that can be delivered through a 14-Fr expandable sheath (eSheath). In 2013, the JenaValve (JenaValve Technology Inc., Munich, Germany) received the CE mark approval for the treatment of high-risk and inoperable patients with aortic insufficiency. This device has a unique anchoring and clipping mechanism (JenaClip), allowing the patient’s native valve leaflets to be clipped onto the valve and enabling the device to be firmly anchored in the correct anatomic position.

**Expanded Indications**

Bicuspid aortic valves occur in nearly 1% of the population and are the most common congenital cardiac abnormality. AS is common, affecting nearly 75% of patients.\(^7\) Calcification, which tends to be severe and asymmetric in bicuspid valves, may affect the circularity of a transcatheter heart valve in the annulus, thereby increasing the risk of severe paravalvular regurgitation or embolization. For self-expanding systems, there is concern that the nitinol frame may not generate sufficient radial force, leading to underexpansion. For these reasons, patients with bicuspid valves have been excluded from TAVR trials and registries. However, the success of TAVR for patients with AS, including those with functional bicuspid valves, has prompted investigation of its feasibility in congenitally bicuspid valves. Recent data suggest that TAVR can be performed with good clinical outcomes with
stenotic bicuspid valves. Additional applications for TAVR may also include patients with a degenerated bioprosthetic SAVR. Surgeons are increasingly likely to use bioprosthetic valves that have the advantage of not requiring anticoagulation. The consequence is that more people will have degeneration of their surgical valves as the bioprosthesis ages. In an effort to avoid further surgery, implantation of transcatheter heart valves within degenerated bioprosthetic devices at all valvular positions has been attempted and has been successful. Bioprosthetic valves are sized according to the outer diameter, and information about the inner diameter can be obtained from the manufacturer. Recently, a commercially available computer application has been developed that assists in identifying the correct size SAPIEN valve and correct position of implant for different surgical valves and homografts. Because the inner diameter of the surgical valve is often small and rigid, transcatheter devices are often underdeployed. Although the hemodynamic performance of the valve-in-valve implants reported was similar to reports of surgical valves, it remains to be seen if underdeployment will accelerate the degradation of the transcatheter heart valves and lead to earlier valve failure. Early data have shown that valve-in-valve therapy is a safe and feasible alternative to treat high-risk patients for failing bioprosthesis with improvement seen in hemodynamics (Fig. 42-16).
FIGURE 42-16 Valve-in-valve transcatheter aortic valve replacement (TAVR) for failing surgical aortic valve replacement. Valve-in-valve application by Dr. Vinayak Bapat providing specifications for a Perimount 2700 25-mm surgical bioprosthetic (A) in a patient with severe valvular regurgitation. Success of valve-in-valve therapy is based on the correct identification of the surgical valve and choosing the correct size of the TAVR valve. The valve-in-valve application provides gross and fluoroscopic images to guide TAVR (B). Panel C shows final deployment of a 26-mm SAPIEN transcatheter bioprosthesis inside a Perimount 2700 25-mm valve with no residual valvular regurgitation.

CONCLUSION

The number of patients with severe symptomatic AS is steadily on the rise, and historically, a large percentage of these patients were unfit for SAVR. In
the current era, however, TAVR has emerged as the standard of care for inoperable patients and is a valid alternative to surgery for selected high-risk patients with symptomatic AS. When performed for appropriate patients and with attention to procedural detail, TAVR can be an elegant procedure leading to improved quality of life and survival. Pre- and postoperative management are as important as intraprocedural management. As technology, techniques, and patient selection improve in the future, TAVR may be an alternative to surgery in lower risk patients.

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188.


**MULTIPLE CHOICE QUESTIONS**

1. What are the current indications for transcatheter aortic valve replacement (TAVR)?
   A. Patients with severe symptomatic aortic stenosis (AS) who are at
prohibitive/high surgical risk
B. Patients with severe symptomatic AS who are at intermediate surgical risk
C. “Valve-in-valve” therapy for patients with bioprosthetic aortic valve failure
D. Patients with severe symptomatic aortic regurgitation who are at prohibitive surgical risk
E. A, B, and C

2. What is the preferred access site for TAVR?
   A. Transfemoral
   B. Transapical
   C. Transaortic
   D. Transsubclavian
   E. Transcarotid
   F. Transcaval

3. True or false? TF TAVR under conscious sedation can be performed with minimal morbidity and mortality compared to TF TAVR under general anesthesia.

4. Which modality allows for the most accurate assessment for aortic annular sizing and transcatheter heart valve selection?
   A. Transthoracic echocardiography (TTE)
   B. Transesophageal echocardiography (TEE)
   C. Multidetector computed tomography (MDCT)
   D. Balloon sizing

5. What are the risk factors for coronary occlusion in patients undergoing TAVR?
   A. Low coronary ostial heights
   B. Shallow sinuses of Valsalva
   C. Bulky native leaflet calcification
   D. All of the above

**ANSWERS**
1. E

Results from the PARTNER trial have allowed TAVR to become the standard of care for prohibitive risk patients with severe AS and to be seen as a valid alternative to surgery for high surgical risk patients. In 2016, TAVR received US Food and Drug Administration (FDA) approval for patients with severe AS who are at intermediate risk for death or complications associated with open-heart surgery (Society of Thoracic Surgeons [STS] risk score of 4%-8%). In 2015, the FDA approved an expanded indication to include “valve-in-valve” repair of failed surgical bioprosthetic aortic valves. Currently, there are no transcatheter valves that have been FDA approved for the treatment of severe symptomatic aortic regurgitation. In Europe, a TAVR system (JenaValve) is an option to treat severe native aortic valve regurgitation in patients with high or greater risk for open surgical valve replacement or repair.

2. A

The transfemoral (TF) method is the most commonly used approach, with the majority of TAVR devices being deployed by this technique. TF procedures are now performed using a fully percutaneous “preclosure” technique as described. Advantages of the TF technique include the fact that it is the least invasive approach and can be performed in most patients with lower profile delivery systems (14 and 16 Fr). Most local vascular complications, including dissection, can be managed with endovascular techniques.

3. True

Babaliaros and colleagues reported in a series of 142 patients that TF TAVR under conscious sedation using a “minimalist approach” could be performed with minimal morbidity and mortality compared to TF TAVR under general anesthesia. Minimalist approach TAVR under conscious sedation allowed for a shorter length of stay and lower resource use than standard TF TAVR under general anesthesia. Minimalist approach TAVR resulted in significantly lower hospital costs.

4. C

TTE is the initial imaging modality of choice due to its ease and safety. TTE tends to underestimate true open surgical sizing, and TEE may be useful to
help provide a more accurate assessment of the aortic annulus. Balloon sizing of the annulus during balloon aortic valvuloplasty may be particularly helpful when the annulus is questionably too large for a given valve. MDCT allows for the reconstruction of the annulus in its true axis in a reproducible fashion. MDCT allows for careful evaluation of the aortic root and left ventricular outflow tract and an in-depth understanding of the potential risk of annular rupture. Computed tomography (CT) measurements of the annulus and root are also invaluable for the identification of patients at increased risk of coronary occlusion during TAVR. MDCT also provides information on the aortobifemoral anatomy and details of arterial diameter and calcification, which are invaluable for procedural access planning. Another application of CT is to establish a fluoroscopic projection that defines the precise aortic valve plane that is perpendicular to the axis of implantation and allows optimal deployment of the valve prosthesis. By using CT to determine the “deployment angle,” operators can avoid performing multiple aortic root angiograms.

5. D

Obstruction of the coronary ostium by the native aortic leaflets occurs in <1% of patients undergoing TAVR. Patients with low coronary ostial heights as determined by MDCT (<12 mm for a male and <11 mm for a female) are at increased risk of coronary occlusion. In addition, shallow sinuses of Valsalva (SOV) <30 mm and, more significantly, a ratio of SOV/annulus diameter <1.25 have been associated with the highest risk of coronary occlusion. The severity of valve calcification, especially the presence of bulky calcium nodules on the left or right aortic leaflets, may contribute to coronary occlusion after TAVR. Fortunately, information derived from CT has become incredibly useful to improve the safety profile of TAVR and reduce the risk of coronary occlusion.
Balloon-Expandable Transcatheter Aortic Valve Replacement

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been shown to improve mortality and quality of life in patients with severe aortic stenosis who are designated inoperable or high risk for surgical aortic valve replacement (SAVR).\textsuperscript{1-5} The first implantation of a transcatheter heart valve (THV) in the aortic position was performed by Cribier et al\textsuperscript{6} to treat an inoperable patient with severe symptomatic aortic stenosis. From the development of the porcine model to the first clinical implantation in the aortic position, the makeup of a THV was a foldable biological cardiac valve sewn inside an expandable stent frame. This device would be crimped onto a balloon in order to deploy the THV via inflation. With this concept, the technology has emerged as one of the most transformative in the field of interventional cardiology. Given the initial focus on development of a balloon-expandable THV to facilitate TAVR, the largest experiences with TAVR are with balloon-expandable THVs. The main objectives of this chapter are to review the available devices, methods of implantation, clinical outcomes, valve hemodynamics, and durability associated with these systems.
THE BALLOON-EXPANDABLE TRANSSCATHETER HEART VALVE

The initial large-scale clinical experience with the balloon-expandable THV was with the Cribier-Edwards balloon-expandable aortic stent valve (Edwards Lifesciences, Irvine, CA). This consisted of a trileaflet tissue valve composed of equine pericardium mounted on a stainless steel frame.\textsuperscript{6}

Subsequent improvements to this system led to the development of the second-generation Edwards SAPIEN THV (Edwards Lifesciences). Major differences between the first- and second-generation devices were the incorporation of pretreated bovine pericardium as the material for the valve leaflets, which had been demonstrated to decrease valve calcification, in addition to a polyethylene terephthalate skirt, which extended to a larger expanse of the stent frame, thus improving sealing and potentially reducing paravalvular regurgitation (PVR).\textsuperscript{7} The 2 sizes of this device, the 23- and 26-mm diameter THVs, could be inserted via 22- and 24-Fr delivery systems for transfemoral (TF) TAVR and through a 29-Fr sheath via transapical access for patients without vascular adequate for the TF approach.

The third-generation of the balloon-expandable Edwards THVs is the SAPIEN XT THV (Edwards Lifesciences). This also consists of a trileaflet pericardial bovine valve, but the leaflets have a scallop shape to improved leaflet durability and the valve is mounted on a cobalt chromium stent frame.\textsuperscript{7} The latter decreases the profile of the THV, given the thinner struts and fewer rows between commissures. The SAPIEN XT THV is available in 23-, 26-, and 29-mm sizes in the United States, with a 20-mm size available internationally. The sheath sizes are smaller than those of the previous generation Edwards THVs because of the lower profile characteristics, as described earlier. The NovaFlex+ delivery system replaced the original RetroFlex3 sheath used for the previous generation device (Edwards Lifesciences). Through this system, the 20- and 23-, 26-, and 29-mm SAPIEN XT can be advanced through 16-, 18-, and 20-Fr expandable TF delivery sheaths, respectively. The clinical manifestations of these reduced catheter profiles are discussed later.

The latest generation of Edwards THVs is the SAPIEN 3 THV, recently approved by the US Food and Drug Administration (FDA); it improves upon
the previous generation by the addition of an outer skirt, which is used to further fill paravalvular gaps and reduce paravalvular leak. The crimped cobalt chromium stent frame shortens significantly (up to 8 mm depending on valve size used) when deployed. This foreshortening is a critical component of the sleek delivery profile. Through the latest generation TF delivery system, the Commander (Edwards Lifesciences), 20- and 23-mm and 26- and 29-mm THVs can be deployed through 14- and 16-Fr expandable sheath systems, respectively. The Commander system also has increased flex properties and a fine-tuning dial, which may facilitate less traumatic and more precise valve deployments. The SAPIEN 3 THV is currently in use internationally and has recently been approved based on data from the Placement of Aortic Transcatheter Valves (PARTNER) II Trial, as described later.

OVERVIEW OF CLINICAL TRIALS AND OUTCOMES

After the first 4 TAVR cases, Cribier and colleagues petitioned the French government to start a feasibility trial, which was restricted to compassionate use. The first study was the Initial Registry of Endovascular Implantation of Valves in Europe (I-REVIVE) trial, which involved 7 patients receiving antegrade or retrograde approach for implantation. Twenty additional patients were recruited into the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) trial, involving only antegrade access. There was an 80% procedural success rate in these initial small studies, and although many of these critically ill patients died of their comorbidities, some survived years, and all had no prosthesis dysfunction. Future feasibility analyses supported the use of TAVR in at least inoperable patients, with demonstrated survival extending well beyond that of patients without TAVR.

The PARTNER trial was the world’s first prospective randomized TAVR trial and analyzed inoperable patients (cohort B), who had an estimated mortality or major morbidity from SAVR of >50%. This trial demonstrated that TF TAVR is superior compared to standard medical therapy and resulted in a 20% absolute reduction in mortality at 12 months. This trial also included a high-risk operable arm (cohort A) that included patients with
estimated mortality from SAVR of at least 15%. The results from this analysis showed that transapical (TA) and TF TAVR have similar 1-year survival compared to SAVR. As a result of these impressive results, the FDA approved TF TAVR using the Edwards SAPIEN THV in November 2011 for treatment of aortic stenosis in inoperable patients. In 2012, this approval was extended for the TF and TA access routes to high-risk patients who are eligible for surgery but face high risk of serious complications or death.

Long-term data for balloon-expandable THVs are currently limited and will become available with further follow-up of existing trials and registries. Toggweiler et al\(^{12}\) published the first 5-year outcome data, following 88 patients who received the second-generation Edwards SAPIEN THV. Survival rates at 1, 2, 3, 4, and 5 years were 83%, 74%, 53%, 42%, and 35%, respectively. Interpretation of mortality per year is limited by the small patient numbers and also from the learning curve given the early experience of the center. However, no patient developed severe transvalvular regurgitation or prosthetic stenosis. Recently presented data for PARTNER I cohort B showed 5-year mortality of 93.6% in the standard therapy arm versus 71.8% in the TF TAVR arm (\( P < .01 \)). Longer term follow-up of the surgical arm (cohort A) demonstrated equivalent survival between TAVR and SAVR at 5 years with high mortalities in both arms (~70%).\(^{13}\) Importantly, valve durability was demonstrated with no increase in transvalvular gradient or significant attrition of valve area during the 5-year follow-up of both arms.\(^{13,14}\)

The second randomized PARTNER trial (PARTNER II) has also completed recruitment. Cohort B of this trial was designed to investigate the performance and outcomes with the third-generation SAPIEN XT THV and the NovaFlex+ delivery catheter in patients deemed inoperable. In comparison to the Edwards SAPIEN THV, the SAPIEN XT demonstrated similar survival at 30 days but lower rates of important complications including bleeding and vascular complications. The surgical arm of the trial (cohort A) was designed to investigate outcomes related to TAVR versus SAVR in patients at intermediate surgical risk. Enrollment has been completed in this arm, and results will be forthcoming in 2016.

The PARTNER II trial also incorporated the use of the latest generation SAPIEN 3 THV in an attached registry of high-risk and intermediate-risk patients, completed in 2014. The results of the SAPIEN 3 registry showed
excellent early results. All-cause and cardiovascular mortality rates at 30 days were 2.2% and 1.4% for the high-risk/inoperable registry and only 1.1% and 0.9% for the intermediate-risk registry, respectively. The frequencies of stroke and disabling stroke were 1.5% and 0.9% for the high-risk/inoperable registry and 2.6% and 1.0% for the intermediate-risk registry, respectively. Finally, rates of moderate or severe PVR were 2.9% and 4.2% in the high-risk/inoperable and intermediate-risk registries, respectively. These outcomes will markedly influence TAVR indications as well as the landscape of available balloon-expandable THV technologies.

PREPROCEDURE PLANNING

Hallmarks of planning prior to performing TAVR with a balloon-expandable THV include assessments of the aortic valve annulus and vascular access. Multimodality imaging is essential for patient screening and procedural guidance during TAVR and has been incorporated into consensus statements, reviews, and guidelines. Correct valve sizing for a balloon-expandable THV requires meticulous attention to 3-dimensional imaging, including multislice computed tomography (CT) and transesophageal echocardiography (TEE). A multislice CT is also a gold standard assessment in determining the adequacy of peripheral access, in addition to evaluating anatomy relevant to the alternative access options discussed in the following section. Optimal TAVR implantation requires: (1) determining anatomic features that would preclude or make advantageous the use of a particular access route; (2) valve sizing based on established criteria for measuring the annulus dimensions matched to the specific valve type; and (3) accurate valve positioning (axial height and alignment) within the annular valve plane. The challenge of valve sizing and positioning cannot be underestimated and requires an intimate understanding of the anatomy of the aortic valve complex. Correct sizing and placement of transcatheter aortic valves will result in excellent valve hemodynamics, no or trace PVR, low requirements for new pacemakers due to conduction abnormalities, and no evidence of coronary obstruction or annulus injury.

ACCESS ALTERNATIVES
The first TAVR with a balloon-expandable THV was performed via an antegrade approach through the femoral vein, incorporating a transseptal puncture through which the THV crossed the mitral valve and led to final positioning in the aortic valve annulus. Because of the difficulty and complexity inherent in these approaches, the contemporary TF and TA approaches were developed after improvements in valve design and delivery systems as mentioned earlier.

Factors that may determine preferred TAVR vascular access include peripheral arterial disease (inadequate vessel diameter, severe calcification, or extreme tortuosity of the iliofemoral vessels), the presence of extensive calcification of the ascending aorta (ie, porcelain aorta), hostile chest wall anatomy (due to either orthovoltage radiation exposure or chest wall deformities), previous coronary bypass graft surgery with mammary conduits adherent to the chest wall, and severe lung disease. The 4 most common techniques for TAVR access with the balloon-expandable THV are the retrograde TF, antegrade TA, and the more recently developed direct or transaortic (TAo) approach. In the PARTNER trial, using the larger profile SAPIEN RetroFlex3 introducer sheath (outer sheath diameter of 9.2 mm for the 26-mm valve), there were frequent major vascular complications associated with TF TAVR procedures. In the PARTNER II trial, the previous-generation SAPIEN system was compared to the lower profile SAPIEN XT system and its NovaFlex+ introducer sheath (33% lower cross-sectional area), and major vascular complications were reduced from 15.5% to 9.6% ($P = .04$). This highlights the importance of lower profile delivery systems in maximally using safe fully percutaneous TF TAVR as a primary default access strategy. The SAPIEN XT system was approved by the FDA in 2014 for commercial use in high-risk and inoperable patients and uses the NovaFlex+ introducer sheath replacing the larger profile SAPIEN RetroFlex3 introducer sheath.

The TA approach has also become lower profile with the SAPIEN 3 THV, which uses the Certitude delivery system (Edwards Lifesciences), an 18-Fr system. This is much lower in profile than the previous generation Edwards SAPIEN and SAPIEN XT systems, requiring at least 24-Fr, and therefore potentially reduces the occurrence of bleeding due to myocardial tears and the incidence of myocardial injury. The TA approach avoids peripheral access issues, but also has limitations, including increased length of hospitalization and increased risk of 30-day and 1-year all-cause
mortality. These adverse TA outcomes may have been influenced by differences in underlying baseline comorbidities between the 2 populations, given the “TF first” approach often adopted by clinicians, which relegated only patients with significant peripheral vascular disease to TA TAVR. Recently, a propensity matched analysis from the PARTNER I trial comparing TF and TA approaches demonstrated higher 30-day mortality and increased length of stay with the TA approach. Other adverse outcomes associated with the TA approach include a higher likelihood of periprocedural bleeding, increased risk of hemodynamic instability, and greater patient discomfort, due to pain related to the anterolateral thoracotomy. In an analysis of PARTNER cohort A health-related quality of life (HRQoL) outcomes, Reynolds et al showed short-term differences in favor of TF TAVR when compared to SAVR. However, in patients deemed unsuitable for a TF approach and thus meriting TA TAVR, HRQoL was not significantly different from that of SAVR across all studied follow-up time points. This was further validated in an analysis of the PARTNER TA TAVR nonrandomized continued access registry.

The TAo access site for balloon-expandable TAVR has been introduced more recently. In the largest series of TAo cases, when compared with a contemporary group of TA patients, there was a lower combined bleeding and vascular event rate (27% vs 46%; \( P = .05 \)), shorter median intensive care unit length of stay (3 vs 6 days; \( P = .01 \)), and a favorable learning curve. Transcarotid access and antegrade transseptal access via the femoral vein have also been described, but like TAo, these approaches have not been studied in a randomized controlled trial. Access alternatives present themselves as individual to each patient, taking into account several variables such as caliber, atherosclerotic disease, and calcification of the vasculature, in addition to various patient comorbidities. While the TF approach is currently preferred, there remains a somewhat undefined niche for each access method, given the lack of data comparing TAVR access alternatives.

PRE- AND POSTDILATION

Balloon aortic valvuloplasty (BAV) has traditionally been performed before balloon-expandable THV deployment. This provides better transition of the valve through the annulus and potentially avoids mechanical complications
related to the force and contour of the delivery system. However, BAV carries independent risks of atrioventricular block requiring permanent pacemaker (PPM), aortic insufficiency, and cerebrovascular accident (CVA). Garcia et al\textsuperscript{29} more recently studied forgoing pre-TAVR BAV with the SAPIEN XT THV. In this small study, 10 patients with moderate calcification, homogenous distribution of calcium, symmetric opening of the valve, and some degree of aortic insufficiency as defined by TEE underwent SAPIEN XT valve placement without antecedent BAV. No patients were found to merit need for postdilation, and PVR was classified as none or trivial in all patients.\textsuperscript{29} TAVR without predilation thus appears to be a feasible technique with potential benefits but has not yet been investigated comprehensively.

Undersizing of the valve, which may be unavoidable given limited size availability of current platforms, or valve underexpansion can result in PVR or device migration. The impetus to avoid PVR after valve deployment needs to be balanced with the risk of annular rupture with postdilation. Barbanti et al\textsuperscript{30} studied 31 patients receiving balloon-expandable valves who experienced rupture and compared them to a group of matched controls to define predictors of rupture. These included subannular/left ventricular outflow tract calcification, annular area oversizing ≥20\%, and balloon postdilation. Figure 43-1, adapted from Barbanti et al,\textsuperscript{30} shows case examples of 2 patients demonstrating the interplay of these variables on clinical outcome. As a potential modification, a routine strategy of initial underexpansion of the valve and subsequent postdilation when deemed necessary showed potential in reducing the risk of annular injury and PVR in selected patients.\textsuperscript{31}
FIGURE 43-1 Annular area oversizing and left ventricular outflow tract (LVOT) calcification and the risk of annular rupture. Case examples of 2 patients who underwent transcatheter aortic valve replacement (TAVR) with a 26-mm (A, B) and a 23-mm (C, D) SAPIEN XT valve. In these cases, significant annular area oversizing (27.9% and 38.5%, respectively) resulted in different outcomes. The case shown in panels A and B (multidetector computed tomography double-oblique transverse and coronal projections, respectively) with severe LVOT calcification (white arrow) experienced annular rupture during TAVR complicated by procedural death. The second case (C and D) displays an absence of LVOT calcification, and despite comparable prosthesis oversizing, this patient underwent an uneventful TAVR. (Reproduced from Barbanti M, Yang TH, Rodes Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. Circulation. 2013;128:244-253. Copyright © American Heart Association, Inc. All rights reserved.)

With pre- and postdilation, as well as dilation during deployment, the
importance of rapid ventricular pacing, most frequently with a temporary ventricular pacemaker advanced via the internal jugular or femoral veins, cannot be understated. To provide the least amount of movement during valve deployment and the most reliable positioning of a pre- or postdilation balloon, rapid ventricular pacing provides, in effect, ventricular standstill and prevents unnecessary and unpredictable movement during these critical maneuvers.

**MULTIMODALITY IMAGING**

Multimodality imaging appears essential for procedural guidance during TAVR and has been incorporated in consensus statements, reviews, and guidelines. The goals of imaging during implantation incorporate achieving the best prosthesis-patient match, assessing valve position and function before and after deployment, and identifying immediate complications. The annular plane can be identified by preimplantation CT scan or angiography, but can also be assessed via intraprocedural rotational angiography with rapid pacing and subsequent CT reconstruction. This latter technique involves contrast opacification and is thus riskier in patients with advanced renal disease. Assessment of the annular plane is essential to appropriate valve positioning because “off-axis” annulus determinations may increase the risk of malaposition and PVR. Intraprocedural TEE can provide a real-time biplane assessment of the annulus during deployment, thus fostering precise valve positioning and prediction as well as detection of PVR and other complications, including coronary artery obstruction, annular rupture, pericardial tamponade, severe mitral regurgitation, aortic dissection, and left ventricular pseudoaneurysm. This form of imaging becomes even more valuable in the setting of lower profile balloon-expandable delivery systems, which incorporate a significant element of foreshortening on valve deployment, meriting judicious positioning and repositioning. TEE also provides an assessment of coaxiality and shows the tips of the native leaflets to ensure stent coverage of the native aortic valve. TEE likely mandates general sedation and endotracheal intubation, which may introduce risk in patients who are hemodynamically unstable or have underlying severe lung disease.

The motivation to eliminate the need for general anesthesia has led to an
increasing interest in intracardiac echocardiography (ICE) imaging. However, single-plane ICE imaging cannot accurately visualize the oval annulus, and a single-plane annular dimension, such as that provided by transthoracic echocardiography, does not provide comprehensive assessment of annular size. Coronary heights cannot be reliably measured due to the limited intracardiac planes of imaging and atrial catheter position. Because of significant acoustic shadowing of the valve after deployment, PVR may not be reliably assessed with ICE. This form of imaging holds further promise to ascertain valve positioning once newer 3-dimensional ICE catheters are developed, although acoustic shadowing may still be a limitation to this modality. Appropriate valve positioning is best performed with multimodality assessment, although considerations inherent to the clinical context may limit use of certain imaging modalities.

**DIAGNOSING AND MANAGING COMPLICATIONS**

**Paravalvular Regurgitation**

The 2-year follow-up to PARTNER cohort A showed that TAVR resulted in significantly worse PVR than SAVR, with >50% of TAVR patients having at least mild PVR after the procedure. Moreover, even mild PVR after TAVR was associated with a 10% to 15% higher mortality at 2 years than procedures resulting in trace or less PVR (Fig. 43-2). This finding was confirmed in an analysis of 2270 patients from the PARTNER trial and its registries, which demonstrated a stepwise increase in mortality with none to trace, mild, and moderate to severe PVR. What remains unknown is whether PVR is causative or simply associated with higher mortality due to unidentified confounding variables. This study demonstrated that moderate or severe PVR resulted in hemodynamic effects on the left ventricle with increases in left ventricle volume size compared to those without significant PVR. This same effect was not seen with mild PVR, suggesting that the increase in mortality may not be causative. Also, it is uncertain whether PVR as a prognostic entity and its associated adverse outcomes are particular to balloon-expandable systems because trials with self-expanding systems have
not demonstrated the same effects of mild PVR.\textsuperscript{2,37} However, there are many factors that make the assessment of PVR and its impact challenging, including the variable echocardiographic grading of PVR across studies. Trial data from newer generations of existing devices, including their expansion into lower risk profiles, and the implementation of other device systems should further elucidate the significance of PVR. The SAPIEN 3 THV employs the use of an external sealing cuff at the bottom of the stent frame to reduce the incidence of PVR. A small study of 27 patients compared the incidence of PVR between the SAPIEN 3 THV and the previous generation SAPIEN XT THV. Although the mean residual gradient and effective orifice area were similar in both groups, the need for postdilation and the incidence of PVR were greater with the SAPIEN XT THV (≥mild: 42%; moderate: 8%) than with the SAPIEN 3 THV (≥mild: 7%; moderate: 0%; \(P = .002\) for ≥mild vs SAPIEN XT THV). A prospective multicenter study involving 150 patients with severe symptomatic AS of intermediate or high risk who underwent TAVR with the SAPIEN 3 THV demonstrated low rates of significant PVR (moderate PVR 3.5%, severe PVR 0%) at 30 days.\textsuperscript{38} Rates of moderate or severe PVR were very low for both high-risk and intermediate-risk patients in the 30-day outcomes of the PARTNER II SAPIEN 3 THV registries (2.9% and 4.2%, respectively).\textsuperscript{15} Further study will elaborate the clinical significance of PVR. In the interim, expertise in multimodality imaging to achieve the best valve size and position is essential to minimize PVR.
FIGURE 43-2 Relation of aortic regurgitation to all-cause mortality in the transcatheter aortic valve replacement (TAVR) as-treated population of the Placement of Aortic Transcatheter Valves (PARTNER) trial. In this analysis by Kodali et al,\textsuperscript{35} paravalvular leak of mild or greater severity (A, B) and total aortic regurgitation (C, D) were related to higher all-cause mortality. (Reproduced from Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. \textit{N Engl J Med}. 2012;366:1686-1695. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission.)

Cerebrovascular Accident

CVA in the setting of TAVR remains a major peri- and postprocedural complication manifesting in a significant quality of life detriment and increased mortality. About half of these events following TAVR occur within
the first 24 hours after the procedure, and mechanical factors such as valve embolization, multiple valve positioning attempts, and balloon postdilation have been identified as predictors of these acute events, whereas other factors such as atrial fibrillation have been associated with a higher rate of subacute (>24 hours) events. In an analysis by Kahlert et al, high-intensity transient signals on transcranial Doppler evaluation, deemed to be a surrogate for microembolization, were more frequent during positioning of the balloon-expandable THV when compared with other aspects of the procedure.

Several magnetic resonance imaging studies have shown that the rate of silent cerebral embolism may approach 80% in patients after TAVR. Van Mieghem et al confirmed the hypothesis of procedure-related embolism, noting 75% of TAVR procedures resulted in capture of debris when a filter-based embolic protection device was used. However, a meta-analysis of >10,000 patients in 53 studies confirmed that TAVR results in an acceptable periprocedural stroke rate of 1.5% and a 30-day CVA/transient ischemic attack rate of 3.3%. Thus, whether capturing periprocedural debris translates into a clinical benefit remains uncertain at this time.

Risk stratification for CVA based on patient characteristics is essential in defining who would likely benefit from cerebral embolic protection devices, as well as for tailoring postprocedural management (eg, surveillance for postprocedural atrial fibrillation). No study to date has identified any effect of valve type (balloon-expandable vs self-expandable) on TAVR stroke rate. Although initially rates of stroke with TAVR were noted to be higher when compared with SAVR, subsequent randomized trials have noted no difference in 30-day stroke rates. In fact, the emergence of TAVR and the rigorous clinical trials associated with its development have highlighted the importance of neurologic oversight when assessing stroke risk after any procedure. A recent study demonstrated that stroke rates following SAVR might be more than doubled when assessed by a neurologist.

Vascular Events and Bleeding

In an analysis performed from PARTNER data, Genereux et al reported that 15.3% of PARTNER high-risk and inoperable patients experiencing Valve Academic Research Consortium (VARC) major vascular complications had significantly higher rates of 30-day and 1-year mortality.
In this analysis, the only identifiable independent predictor of major vascular complications was female sex (hazard ratio, 2.31; \( P = .03 \)). Major vascular complications are an independent predictor of major bleeds, which were found to be the strongest independent predictor of 1-year mortality in PARTNER cohort A, although there was a much more significant prognostic impact in the SAVR arm. In an analysis by Hayashida et al, VARC major vascular complications increased 30-day mortality and were predicted by low procedural experience, femoral calcification, and sheath-to-femoral artery ratio greater than 1.05. As mentioned previously, 1-year data from PARTNER IIB showed a reduction in major vascular complications, from 15.5% to 9.6% \( (P = .04) \), with the lower profile SAPIEN XT delivery system. As it pertains to the TF approach, reduction in vascular and bleeding events is dependent on appropriate radiographic and angiographic screening of access and development of lower profile valve delivery systems, in addition to implementation of advanced percutaneous closure techniques. With newer generation valve delivery systems, using 14- to 18-Fr sheaths, the risk of vascular complications has been shown to drop below 5%.

**Conduction Abnormalities**

The difference in the PPM implantation rate between the balloon-expandable SAPIEN valve and self-expanding CoreValve (Medtronic, Dublin, Ireland), quantified as 6.5% with SAPIEN versus 25.8% with CoreValve \( (P < .001) \) in a large meta-analysis, was confirmed in the US CoreValve Pivotal Trial Extreme Risk cohort results. In this trial, CoreValve was associated with a rate of PPM implantation of 22.2% at 30 days and 27.1% at 1 year. In an analysis of PARTNER outcomes, Nazif and colleagues showed predictors of PPM implantation with balloon-expandable valves to include preexisting right bundle branch block, the ratio of prosthesis diameter to left ventricular outflow tract diameter, and left ventricular end-diastolic dimension. In this study, at 1 year, PPM implantation was associated with significantly higher mortality or repeat hospitalization \( (42.0\% \text{ vs } 32.6\%; \ P = .007) \).

In a separate analysis of PARTNER outcomes, Nazif et al reported that persistent, new-onset left bundle branch block occurred in 10.5% of TAVR patients with normal baseline conduction. This finding did not increase all-cause mortality, as it had in a retrospective study, but was associated with a
higher rate of PPM implantation and failure of improvement in left ventricular ejection fraction (Fig. 43-3). Device-related factors, such as the depth of the device implant in the left ventricular outflow tract and the continuous radial force exerted by self-expanding valves upon deployment, appear to predispose TAVR patients to conduction abnormalities. Use of real-time multimodality imaging is warranted in order to curtail the frequency of this adverse outcome, although device modification is necessary given the health and economic ramifications of high PPM incidence after TAVR.

**FIGURE 43-3** Post–transcatheter aortic valve replacement (TAVR) left bundle branch block (LBBB) and evolution of left ventricular ejection fraction (LVEF). In this analysis of patients undergoing TAVR in the Placement of Aortic Transcatheter Valves (PARTNER) trial and continued access registry, Nazif et al. studied the impact of a new LBBB on clinical outcomes. The evolution of LVEF over time is shown for (A) the overall population and stratified by baseline left ventricular function: (B) LVEF < 35%, (C) LVEF 35% to 50%, and (D) LVEF 50%. This demonstrates a lack of improvement in LVEF with development of LBBB after TAVR and is most marked in patients with the lowest baseline LVEF (B). (Adapted
Other post-TAVR conduction abnormalities, such as atrial tachycardia and atrial fibrillation, have also been associated with increased morbidity. In an analysis by Urena et al.,\textsuperscript{58} in patients without known atrial fibrillation or atrial tachycardia before the procedure, the occurrence of these arrhythmias during a 24-hour electrocardiogram recording after TAVR was associated with a significantly higher rate of 30-day cerebrovascular events (7.1% vs 0.4%; \( P = .03 \)).

\textbf{Coronary Occlusion}

A rare, but potentially fatal, consequence of balloon-expandable THV implantation is coronary occlusion. The risk of this particular complication is usually adequately assessed with preprocedural multidetector CT or TEE, which would evaluate the height of the coronary ostia from the annular plane and the width of the sinus of Valsalva. In a large multicenter registry of over 6000 patients, of whom 44 had symptomatic coronary occlusion after TAVR, mean coronary ostial heights (10.6 ± 2.1 mm vs 13.4 ± 2.1 mm; \( P < .001 \)) and sinus of Valsalva diameters (28.1 ± 3.8 mm vs 31.9 ± 4.1 mm; \( P < .001 \)) were lower in patients with obstruction than in control subjects.\textsuperscript{59} In this analysis, 30-day mortality with coronary occlusion during TAVR was 40.9%. In borderline cases, morbidity may decrease with preemptive wiring of a susceptible coronary artery and potentially positioning of an undeployed stent in the coronary artery at risk, which could then be deployed against the stent frame of the balloon-expandable THV to ensure adequate coronary flow. Finally, predilation under TEE guidance may also add to the risk assessment of coronary occlusion, through visualization of calcium in the annular apparatus or native leaflet moving close to the ostium of a susceptible coronary artery upon balloon inflation.

\textbf{OTHER BALLOON-EXPANDABLE THV SYSTEMS}
The Innovare balloon-expandable system (Braile Biomedica, Sao Jose do Rio Preto, Brazil) consists of a trileaflet bovine pericardial valve mounted in a cobalt-chromium stent frame, is implanted transapically, and is available in 4 sizes: 20, 22, 24, and 26 mm. A feasibility study of 33 patients showed an implantation success rate of 91%. The 30-day and 1-year mortality rates were 18.2% and 39.5%, respectively. The valve hemodynamics at hospital discharge showed some degree of aortic insufficiency in 10 patients, and the peak and mean gradients at 1-year follow-up were 21.3 ± 12.4 mm Hg and 10.5 ± 6.9 mm Hg, respectively.

Another balloon-expandable THV anticipated to undergo feasibility study is the Colibri THV (Colibri Heart Valve, Broomfield, CO). This is a 14-Fr premounted, precrimped, and prepackaged ready-for-use TAVR system. The valve is made of 3 independent pieces of porcine pericardium, which are created using a unique folding method and then sewn into a stainless steel laser-cut frame. Besides the low profile of this system, the unique feature of this valve is that it is stored dry in a crimped state and the valve can be used directly off the shelf in a manner similar to coronary stents.

**CONCLUSIONS**

Since the inception of TAVR, balloon-expandable THVs have been at the forefront of technological development and large-scale clinical trials impacting the field. The PARTNER trial has shown the superiority and noninferiority of TAVR with the balloon-expandable Edwards SAPIEN THV compared to medical treatment in inoperable patients and SAVR in high-risk patients, respectively. There have been excellent long-term hemodynamic results after implantation of balloon-expandable THVs, although residual PVR may be a poor prognostic sign and merits modification of the technology. Identification of these adverse clinical events, made apparent through large randomized clinical trials, has led to the development of the SAPIEN 3 THV, which has been designed to reduce PVR and has a lower profile delivery system than its predecessors, facilitating TF access for a larger portion of TAVR patients. The improved safety and efficacy of balloon-expandable systems will allow their incorporation into the treatment of lower risk populations and through less invasive means.
REFERENCES


Clinical Outcomes With Self-Expanding Transcatheter Aortic Valve Bioprostheses

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Since the introduction of the 18-Fr CoreValve self-expanding transcatheter aortic valve replacement (TAVR), over 70,000 implants have been performed worldwide. The use of this self-expanding bioprosthesis has provided an alternative to surgery in patients who are suboptimal for conventional surgical aortic valve replacement and has resulted in improved survival and quality of life for thousands of patients worldwide. There are a number of potential advantages of a self-expanding bioprosthesis over alternative transcatheter designs, including the progressive self-expansion of the inflow frame reducing the degree of paravalvular regurgitation (PVR) over time; supra-annular location of the porcine pericardial valve, which improves hemodynamics and potentially improves long-term durability; and large cell diameter, which provides access to coronary arteries after implantation.

The purposes of this chapter are to review the CoreValve self-expanding frame design and newer iterations of the self-expanding prosthesis, discuss the clinical evidence for use of the self-expanding devices in an expanding population, and outline the risks and benefits of this device in patients with aortic stenosis.
COREVALVE SELF-EXPANDING BIOPROSTHESIS

The CoreValve System consists of 3 components: a transcatheter bioprosthesis, the delivery catheter system, and the compression loading system. The transcatheter bioprosthesis is composed of a self-expanding nitinol frame that supports a trileaflet porcine pericardial valve available in 23-, 26-, 29-, and 31-mm diameters that treat an annulus range from 18 to 29 mm (Fig. 44-1). The inflow portion of the frame is designed to conform to the annulus and to stabilize the frame at the annular location. The lowest 12 mm of the frame contains a porcine pericardial skirt to seal the annulus. The valve is located in a supra-annular position at the waist (constrained portion) of the valve frame. The outflow portion of the valve frame is constructed to support the valve commissures and orient the frame to facilitate laminar flow. All valve sizes are delivered using an 18-Fr catheter delivery system. The valve is deployed without rapid pacing and is partially repositionable until annular contact with the transcatheter heart valve (THV) is made. The CoreValve bioprosthesis has now been replaced commercially with the Evolut R transcatheter system (see below), which allows repositioning of the valve if the initial deployment is suboptimal.
EARLY COREVALVE REGISTRIES

Early European registries between 2007 and 2010 demonstrated the value of self-expanding transcatheter replacement in patients who were not optimal candidates for surgical valve replacement, but transcatheter replacement was limited by 2-dimensional echocardiographic-based valve sizing, the availability of only 26- and 29-mm sizes, and delivery systems that had high friction, resulting in forward movement into the ventricle of the device with deployment. In the initial CE Mark series, 126 patients (mean age, 82 years; 42.9% male; mean logistic European System for Cardiac Operative Risk Evaluation score [EuroSCORE], 23.4%) with severe aortic valve stenosis underwent treatment with the CoreValve self-expanding bioprosthesis. The
Overall technical success rate was 83.1%, and the 30-day mortality rate was 15.2%, without significant differences in the subgroups. All-cause mortality at 2 years was 38.1%, and the mean aortic valve gradients remained unchanged from 30 days (8.5 ± 2.5 mm Hg) to 2 years (9.0 ± 3.4 mm Hg). There was no incidence of structural valve deterioration in this early series. The major limitations of these early series were postprocedural PVR (10%-15%) and high rates of conduction system disorders resulting in relatively high permanent pacemaker implantation rates (20%-40%).

The European Advance Registry included 1015 patients at high risk for surgical aortic valve replacement with an age of 81 ± 6 years and mean logistic EuroSCORE of 19.4% ± 12.3%. Self-expanding TAVR resulted in a 30-day all-cause mortality of 4.5%, rate of stroke of 3.0%, and life-threatening or disabling bleeding rate of 4.0%. The 12-month rates of all-cause mortality were 11.1%, 16.5%, and 23.6% among patients with a logistic EuroSCORE ≤ 10%, EuroSCORE of 10% to 20%, and EuroSCORE > 20% (P < .05), respectively. At 3 years, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) ≤7% group had a lower rate of all-cause mortality (28.6% compared with 45.9% in patients with an STS >7%; P < .01). In patients with STS PROM ≤7%, mortality at 3 years was higher in those with moderate or severe aortic regurgitation at discharge than in those with mild or less aortic regurgitation (39.9% vs 22.9%, respectively; P < .01).

The Italian CoreValve Registry reported the 5-year outcomes after self-expanding TAVR. The all-cause mortality rate was 55.0% at 5 years, and the overall neurologic event rate was 7.5%. Rehospitalization occurred in 46% patients, most of which (42.7%) were due to acute heart failure. Importantly, mean transaortic gradients remained low 5 years later (12.8 ± 10.9 mm Hg). Late prosthesis failure occurred in 5 cases (1.4%); among these, redo TAVR was successfully carried out in 2 patients (0.6%). The remaining 3 cases of prosthesis failure did not undergo additional invasive interventions. Ten patients (2.8%) showed late mild stenosis with a mean transaortic gradient ranging from 20 to 40 mm Hg. No other cases of structural or nonstructural valvular deterioration were observed.
The US CoreValve Extreme Risk and High Risk Pivotal Trial and Registries were performed to evaluate the safety and efficacy of the CoreValve bioprosthesis in patients with severe aortic stenosis. This portfolio of studies evaluated patients who were deemed extreme risk or high risk for surgery by a local heart team and included both pivotal trials and continued access and expanded use registries.

**CoreValve US Extreme Risk Study**

Given the lack of clinical equipoise for subsequent randomized study in patients without surgical options, the CoreValve US Pivotal Study was a prospective, multicenter, nonrandomized investigation that included 489 patients with severe aortic stenosis who were deemed at extreme risk for surgery, defined as a ≥50% predicted 30-day mortality or irreversible morbidity at 30 days. The primary end point was a composite of all-cause mortality or major stroke at 12 months and was compared with a prespecified objective performance goal. The rate of all-cause mortality or major stroke at 12 months was 26.0%, compared with a 43.0% performance goal ($P < .0001$). Individual 30-day and 12-month events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively). The frequency of moderate or severe PVR was lower 12 months after self-expanding TAVR (4.2%) than at discharge (10.7%; $P = .004$ for paired analysis).

The benefits of self-expanding TAVR in extreme-risk patients were sustained at 2 years; the rate of all-cause mortality or major stroke was 38.0% (all-cause mortality, 36.5%; major stroke, 5.1%). Multivariable predictors of all-cause mortality at 2 years included the presence of coronary artery disease and admission from an assisted living center (Fig. 44-2). An STS PROM >15% was also predictive of 2-year all-cause mortality. The frequency of moderate or severe PVR (4.3% at 1 year; 4.4% at 2 years) was unchanged between the first and second years. These findings further reinforce that 2-year clinical outcomes are determined by comorbid conditions rather than
valve performance in these complex patients.\textsuperscript{9}


Clinical outcomes after self-expanding TAVR using an alternative access approach were also evaluated in the CoreValve US Extreme Risk Study. Reardon et al\textsuperscript{10} evaluated 150 patients with prohibitive iliofemoral anatomy who were treated with the CoreValve THV delivered by way of the subclavian artery (n = 70) or a direct aortic approach (n = 80). The preoperative aortic valve area was 0.72 ± 0.27 cm\textsuperscript{2}, and mean aortic valve gradient was 49.5 ± 17.0 mm Hg.\textsuperscript{10} After the TAVR, the effective aortic valve area was 1.82 ± 0.64 cm\textsuperscript{2} at 1 month and 1.85 ± 0.51 cm\textsuperscript{2} at 12 months.\textsuperscript{10} The mean aortic valve gradient was 9.7 ± 5.8 mm Hg at 30 days and 9.5 ± 5.7 mm Hg at 12 months.\textsuperscript{10} The primary end point was all-cause mortality or major stroke at 12 months and occurred in 15.3% of patients at 30 days and 39.4% at 12 months.\textsuperscript{10} The individual rates of all-cause mortality and major stroke were 11.3% and 7.5% at 30 days and 36.0% and 9.1% at 12 months, respectively.\textsuperscript{10} These data show that the CoreValve THV delivered by an alternative access provides a suitable alternative for treatment of extreme-risk patients with symptomatic severe aortic stenosis who have prohibitive iliofemoral anatomy and no surgical options. Three-dimensional access planning and real-time image guidance for direct aortic access TAVR may be facilitated using co-registration of multidetector computed tomography (CT) and noncontrast DynaCT image co-registration.\textsuperscript{11}

TAVR with a self-expanding bioprosthesis resulted in substantial
improvements in both disease-specific and generic health-related quality of life in extreme-risk patients, but there remained a large minority of patients who died or had very poor quality of life despite TAVR. In a detail health status analysis that evaluated 436 patient who were extreme risk for surgery, there was substantial improvement in both disease-specific and generic health status measures, with an increase in the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) of 23.9 points at 1 month, 27.4 points at 6 months, and 27.4 points at 12 months (P < .003 compared with baseline). A large minority of patients (39%) had a poor outcome after TAVR that was predicted by the presence of being wheelchair dependent or having a lower mean aortic valve gradient, prior coronary artery bypass grafting, oxygen dependency, or very high predicted mortality with surgical aortic valve replacement, and low serum albumin.

**CoreValve US High-Risk Pivotal Trial**

The CoreValve High-Risk Pivotal Trial enrolled patients deemed to be at elevated surgical risk. Two cardiac surgeons and 1 interventional cardiologist at each site needs to confirm the estimated 30 days surgical mortality or irreversible morbidity to be >15%. Because of the limitations of the standard STS PROM, additional non-STS factors, such as severe comorbidity, frailty, and disability, were also considered in the assessment of surgery risk. A total of 795 patients were randomly assigned in a 1:1 fashion to self-expanding TAVR or surgical aortic valve replacement. The primary end point, the rate of death from any cause at 1 year in the as-treated population, was significantly lower in TAVR patients than in surgery patient (14.2% vs 19.1%, respectively), with an absolute reduction in risk of 4.9 percentage points (upper boundary of the 95% confidence interval [CI], –0.4; P < .001 for noninferiority; P = .04 for superiority).

Hemodynamic differences between self-expanding transcatheter and surgical bioprostheses were found in the CoreValve US High-Risk Clinical Study. Compared with surgery patients, TAVR patients had a lower mean aortic valve gradient, larger valve area, and less patient-prosthesis mismatch (all P < .001), but more PVR at discharge, which decreased at 1 year. Surgery patients experienced a significant right ventricular systolic dysfunction at discharge and 1 month, with normal right ventricular function
Preimplantation aortic regurgitation rated as mild or worse was associated with reduced mortality hazard for both the TAVR patients (hazard ratio [HR], 0.48; 95% CI, 0.27-0.85; \( P = .01 \)) and the surgery patients. Aortic regurgitation rated as mild or worse after TAVR was associated with increased risk for all-cause mortality (HR, 1.95; 95% CI, 1.08-3.53; \( P = .03 \)). This benefit was consistent along a broad array of patient subsets (Fig. 44-3).

![FIGURE 44-3 Outcomes of patient subsets with self-expanding transcatheter aortic valve replacement (TAVR) and surgery. Subgroup analysis for the rate of death from any cause at 1 year: The survival benefit with TAVR was consistent across 9 clinical subgroups. The percentage of patients with an event represents the Kaplan-Meier event rate at 1 year. Horizontal lines indicate 95% confidence intervals (CIs). The body mass index is the weight in kilograms divided by the square of the height in meters. The Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) provides an estimate of the rate of death at 30 days among patients undergoing surgical aortic valve replacement on the basis of a number of demographic and procedural variables. CABG, coronary artery bypass grafting.](From Adams DH,)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>TAVR no. of patients with event/total no. of patients (%)</th>
<th>Surgical replacement no. of patients with event/total no. of patients (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>26/204 (12.9)</td>
<td>33/194 (17.2)</td>
<td>0.72 (0.43-1.20)</td>
<td>0.97</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>29/186 (15.7)</td>
<td>34/163 (21.4)</td>
<td>0.71 (0.43-1.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32/207 (15.5)</td>
<td>31/187 (16.7)</td>
<td>0.89 (0.55-1.47)</td>
<td>0.21</td>
</tr>
<tr>
<td>Female</td>
<td>23/183 (12.7)</td>
<td>36/170 (21.8)</td>
<td>0.56 (0.33-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Body-mass index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤30</td>
<td>44/283 (15.7)</td>
<td>50/245 (20.6)</td>
<td>0.73 (0.48-1.09)</td>
<td>0.79</td>
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<tr>
<td>&gt;30</td>
<td>11/107 (10.3)</td>
<td>17/112 (15.8)</td>
<td>0.64 (0.30-1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>STS PROM estimate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7%</td>
<td>21/202 (10.5)</td>
<td>25/180 (14.2)</td>
<td>0.72 (0.40-1.29)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>&gt;7%</td>
<td>34/188 (18.2)</td>
<td>42/177 (24.1)</td>
<td>0.72 (0.46-1.13)</td>
<td></td>
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<tr>
<td><strong>Left ventricular ejection fraction</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60%</td>
<td>38/243 (15.6)</td>
<td>46/236 (19.9)</td>
<td>0.76 (0.49-1.16)</td>
<td>0.68</td>
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<tr>
<td>&gt;60%</td>
<td>17/147 (11.6)</td>
<td>21/126 (17.8)</td>
<td>0.64 (0.34-1.22)</td>
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<td><strong>Hypertension</strong></td>
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<td></td>
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<tr>
<td>No</td>
<td>3/19 (15.8)</td>
<td>5/14 (36.5)</td>
<td>0.37 (0.09-1.54)</td>
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<tr>
<td>Yes</td>
<td>52/371 (14.1)</td>
<td>62/343 (18.4)</td>
<td>0.74 (0.51-1.07)</td>
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<tr>
<td><strong>Previous CABG</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>No</td>
<td>44/275 (16.2)</td>
<td>47/246 (19.6)</td>
<td>0.80 (0.53-1.21)</td>
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<tr>
<td>Yes</td>
<td>11/115 (9.6)</td>
<td>20/111 (18.1)</td>
<td>0.50 (0.24-1.04)</td>
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</tr>
<tr>
<td><strong>Peripheral vascular disease</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>No</td>
<td>29/228 (12.8)</td>
<td>36/207 (17.8)</td>
<td>0.68 (0.42-1.11)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>24/159 (15.3)</td>
<td>31/148 (21.2)</td>
<td>0.70 (0.41-1.19)</td>
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</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>No</td>
<td>40/254 (15.8)</td>
<td>43/195 (22.3)</td>
<td>0.67 (0.44-1.03)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15/136 (11.3)</td>
<td>24/162 (15.3)</td>
<td>0.72 (0.38-1.37)</td>
<td></td>
</tr>
</tbody>
</table>
Kaul\textsuperscript{17} provided an overview of the benefit-risk analysis of the CoreValve US Pivotal Trial suggesting an overall net benefit of self-expanding TAVR in these patients (Fig. 44-4).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure44-4.png}
\end{figure}

Reardon et al\textsuperscript{18} reported the 2-year results of the CoreValve US High-Risk Pivotal Trial and found that the rate of 2-year all-cause mortality was significantly lower in the TAVR group (22.2\% vs 28.6\% in the surgery group; log-rank $P < .05$), with an absolute reduction in risk of 6.5 percentage points. Importantly, the rate of death or major stroke at 2 years was significantly lower in the TAVR patients (24.2\% vs 32.5\% in surgery patients; log-rank $P = .01$).\textsuperscript{18} The hemodynamic (Fig. 44-5) and clinical
beneficial effect of TAVR over surgery was maintained at 3 years after the procedure.\textsuperscript{19}

![Diagram showing hemodynamic of self-expanding transcatheter aortic valve replacement (TAVR) versus surgery at 3 years. Reduction in aortic valve (AV) mean gradient and increased AV area are maintained through 3 years. Data reported on the basis of site-reported echocardiographic findings in patients with echocardiographic measurements at all time points reported. Paired sets of mean AV gradient data were available for 174 TAVR and 113 surgical aortic valve replacement (SAVR) patients; AV area was available for 126 TAVR and 85 SAVR patients. TAVR was associated with significantly lower gradients and larger aortic valve areas at each time point (all $P < .05$). (Reprinted from Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. \textit{J Am Coll Cardiol.} 2016;67:2565-2574, Copyright © 2016, with permission from American College of Cardiology Foundation.)

Overall stroke rates are lower in patients undergoing TAVR than patients undergoing surgery.\textsuperscript{20} The 30-day, 1-year, and 2-year stroke rates were 4.9%, 8.7%, and 10.9%, respectively, for TAVR and 6.2%, 12.5%, and 16.6%, respectively, for surgical aortic valve replacement ($P = .46$, .11, and .05, respectively).\textsuperscript{20} The impact of stroke was profound, with an all-cause mortality in TAVR patients with a major stroke of 83.3% and in surgery patients of 54.5% ($P = .29$).\textsuperscript{20} Late major stroke was disproportionately
higher (23.8% at 2 years) among patients with poor iliofemoral access randomized to surgery. Predictors of early stroke included peripheral vascular disease and falls within 6 months, and late strokes were predicted by severe aortic calcification and high Charlson scores. Lack of dual antiplatelet therapy use during and after TAVR was associated with early stroke.

**Prosthesis-Patient Mismatch**

Another potential reason for the benefit of TAVR over surgery is superior hemodynamics in the TAVR group, understanding that the frequency of patient-prosthesis mismatch (PPM) is higher in patients undergoing surgery than TAVR. In an analysis of patients enrolled in the US High-Risk Pivotal Trial randomized to TAVR or surgery, patients were characterized as having severe PPM, defined as an effective orifice area index (EOAi) ≤0.65 cm²/m², or no PPM, defined as an EOAi >0.65 cm²/m². The incidence of severe PPM in the surgery group at 1 year was 25.7% compared with 6.2% in the TAVR group (P <.0001). At 1 year, the rates of all-cause mortality and acute kidney injury were significantly greater in patients with severe PPM compared with no severe PPM (20.6% vs 12.0% [P = .0145] for death; Fig. 44-6; and 19.2% vs 8.5% [P = .0008] for acute kidney injury, respectively). These findings demonstrate that severe PPM is more common in patients treated with surgery than those treated with TAVR and that patients with severe PPM are a greater risk for death and acute kidney injury than patients without severe PPM.

**Cost-Effectiveness Analysis**

A health status evaluation in patients enrolled in the CoreValve US Pivotal Trial found that health status improved substantially in surviving patients who were treated with either self-expanding TAVR or surgery.\(^{22}\) TAVR via the iliofemoral route was associated with better early health status compared with surgery.\(^ {22}\) In this analysis, among surviving patients eligible for iliofemoral access, there was a clinically relevant early benefit with self-expanding TAVR across all disease-specific and generic health status measures.\(^ {22}\) Among the alternative access cohort, however, most health status measures were similar for TAVR and surgery.\(^ {22}\) There were no consistent differences in health status between TAVR and surgery at the later time points.\(^ {22}\)

Reynolds et al\(^ {23}\) performed a formal economic analysis in patients enrolled in the CoreValve US High-Risk Pivotal Trial using empirical data
regarding survival and quality of life and medical resource use and hospital costs through 12 months. Relative to surgery, TAVR reduced initial length of stay an average of 4.4 days, decreased the need for rehabilitation services at discharge, and resulted in superior 1-month quality of life. In contrast, index admission and projected lifetime costs were higher with TAVR than with surgery ($Δ$ $11,260 and $17,849 per patient, respectively). TAVR provided a lifetime gain of 0.32 quality-adjusted life-years. Lifetime incremental cost-effectiveness ratios were $55,090 per quality-adjusted life-year gained and $43,114 per life-year gained. Sensitivity analyses indicated that a reduction in the initial cost of TAVR by approximately $1650 would lead to an incremental cost-effectiveness ratio <$50,000 per quality-adjusted life-year gained.

SPECIFIC PATIENT AND ANATOMIC SUBSETS

The benefits of self-expanding TAVR were examined in a number of patient subsets.

Female Sex

Despite a higher cardiovascular risk profile in men, studies have not shown differences in outcomes after self-expanding TAVR between men and women. Forrest et al compared the clinical outcomes in women and men in 3687 patients (1708 women and 1979 men) enrolled in the CoreValve US Pivotal Trials and Registries. Women tended to be slightly older and to have more frailty, but fewer cardiac comorbidities, higher left ventricular systolic function, less coronary artery disease, and fewer previous strokes. All-cause mortality was 5.9% for women and 5.8% for men at 30 days ($P = .87$) and 24.1% and 21.3%, respectively, at 1 year ($P = .08$). Similarly, the incidence of stroke was 5.7% in women and 4.0% in men at 30 days ($P = .02$) and 9.3% and 7.7%, respectively, at 1 year ($P = .05$). Women had a higher incidence of bleeding, including more life-threatening bleeds, and a greater incidence of major vascular complications than men at 30 days.

In women at increased risk for surgery, women treated with self-
expanding TAVR had better outcomes than women treated with surgery. Baseline characteristics and predicted risk were comparable in the 2 groups, although the frequency of diabetes mellitus was lower in patients undergoing TAVR (33.3% vs 45.3% in the surgery group; \( P = .02 \)) in the US High-Risk Pivotal Trial.\(^\text{26}\) One-year mortality was lower in TAVR patients (12.7% vs 21.8% in surgery patients; \( P = .03 \)).\(^\text{26}\) The composite all-cause mortality or major stroke rate was also lower in TAVR patients (14.9% vs 24.2% in surgery patients; \( P = .04 \); Fig. 44-7).\(^\text{26}\)


**Prior Coronary Artery Bypass Graft**

Patient with prior coronary artery bypass graft may benefit from self-expanding TAVR compared with repeat surgery. In an analysis of 226 patients with prior coronary artery bypass graft surgery enrolled in the CoreValve US High-Risk Trial, 1-year all-cause mortality was 9.6% for
TAVR versus 18.1% for surgical aortic valve replacement ($P = .06$); cardiovascular mortality was 7.0% for TAVR versus 13.8% for surgical aortic valve replacement ($P = .09$).$^{27}$ A combination of STS PROM risk score >7 and age >80 years was a significant predictor of mortality, with TAVR demonstrating a survival advantage ($P = .03$).$^{27}$ No differences were seen for stroke.$^{27}$ The surgical aortic valve replacement group had longer intensive care unit and hospital stays and increased incidence of acute kidney injury, life-threatening or disabling bleeding, and major adverse cardiac and cerebrovascular events ($P < .05$).$^{27}$

**Reduced Left Ventricular Function**

It is estimated that one-third of patients with symptomatic aortic stenosis have reduced left ventricular ejection fraction (LVEF) before TAVR. In an analysis by Dauerman et al,$^{28}$ 156 patients from the CoreValve US Extreme and High-Risk trials with LVEF ≤40% were evaluated. Early LVEF recovery was defined as an absolute increase of ≥10% in ejection fraction at 30 days.$^{28}$ One-year outcomes were compared between patients with and without early recovery.$^{28}$ Early LVEF recovery occurred in 62% of patients, generally before discharge. By 30 days, LVEF increased >17% compared with baseline in the early recovery group with minimal increase in the no early recovery group (48.9% ± 8.8% vs 31.5% ± 6.9%, respectively; $P < .001$).$^{28}$ One-year all-cause mortality was numerically (but not statistically) higher in the no early recovery group (24% vs 12%; $P = .07$). Absence of previous myocardial infarction and baseline mean gradient ≥40 mm Hg were identified as predictors of early LVEF recovery.$^{28}$

**High-Risk Surgical Patients With STS PROM <7%**

The CoreValve US Pivotal High-Risk Trial evaluated patients with an STS PROM of 7% or less who had nontraditional risk factors, including indices of frailty, disability, and comorbidities.$^{29}$ Two-year all-cause mortality was lower in patients treated with self-expanding TAVR (15%) than in patients treated with surgery (26.3%; log-rank $P = .01$). The 2-year rate of stroke was numerically but not statistically lower with self-expanding TAVR (11.3% vs 15.1% in surgery patients; log-rank $P = .50$).$^{29}$ Quality of life by the KCCQ-
OS showed significant and equivalent increases in both groups at 2 years.\textsuperscript{29} These findings suggest that self-expanding TAVR compares favorably with surgery in high-risk patients who were previously considered intermediate risk using traditionally risk scores.\textsuperscript{29}

**Self-Expanding TAVR for Surgical Valve Failure**

Proper positioning of the self-expanding bioprosthesis improves the hemodynamic result in patients undergoing TAVR in surgical valve failure.\textsuperscript{30} In an analysis of 292 consecutive patients, of whom 157 were treated to CoreValve Evolut, optimal implantation depth was defined as a depth of 0 to 5 mm. A high implantation was associated with a significantly lower rate of elevated gradients in comparison with low implantation (15% vs 34.2%, respectively; $P = .03$). Lower gradients were seen in patients treated with the CoreValve Evolut (vs balloon-expandable prostheses; $P = .02$) and regurgitation as the failure mode (vs stenosis/mixed etiologies; $P = .002$). There may be particular advantages of a supra-annular, self-expanding TAVR device in the subset of patients with surgical valve failure.

**Angulated or “Horizontal” Aortas**

An aortoventricular angle $>70^\circ$ has been an exclusion criterion for treatment with the CoreValve self-expanding TAVR. An analysis of 3578 patients with less severe angulation found no significant correlation in the frequencies of device success or procedural success, frequencies of moderate or greater aortic regurgitation at 30 days, number of valves implanted, or need for balloon after dilation or new pacemakers with increasing degrees of aortoventricular angulation (Fig. 44-8).\textsuperscript{31} These results have been attributed to the use of “best practice” techniques, such as use of co-planar aortography, alignment of the delivery catheter along the greater curvature of the aorta using stiffer guidelines (eg, SuperStiff Amplatz or Lunderquist 0.035-inch guide wires), stabilization of the delivery catheter using gentle forward force on the delivery catheter guide wire positioned in the left ventricular apex, alignment of the delivery catheter marker to allow visualization of the inflow of the prosthesis in a co-axial alignment, slow deployment and controlled annular contact to stabilize the valve frame, avoidance of deeper implantation by forward tension on the delivery guide wire and retraction on the catheter,
and careful assessment of the hemodynamic and echocardiographic results after deployment.\textsuperscript{31}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Effect of aortoventricular angle and outcomes with self-expanding transcatheter aortic valve replacement (TAVR). A. A horizontal line is drawn in the coronal plane at the level of the annulus, and a second line is drawn along the axis of the aortic annulus. The 50° angle in this case is defined by the intersection of these 2 lines. B. Relationship of aortoventricular angulation and residual aortic regurgitation after TAVR. (Adapted from Zorn GL 3rd, Little SH, Tadros P, et al. Prosthesis-patient mismatch in high-risk patients with severe aortic stenosis: a randomized trial of a self-expanding prosthesis. \textit{J Thorac Cardiovasc Surg}. 2016;151:1014-1022, Copyright © 2016, with permission from The American Association for Thoracic Surgery.)}
\end{figure}

**Bicuspid Aortic Valve Disease**

Bicuspid aortic valve disease is a common cause of aortic stenosis in younger patients, and a number of classification systems have been proposed.\textsuperscript{32,33} Selection of the appropriate transcatheter size has been challenging in these patients.\textsuperscript{34} In a series of 139 patients with bicuspid valve disease, patients were treated with self-expanding and balloon-expandable TAVR.\textsuperscript{34} The patients had Sievers type 0 bicuspid disease in 26.7%, Sievers type 1 bicuspid disease in 68.3%, and Sievers Type 2 bicuspid disease in 5.0%.\textsuperscript{34}

Postimplantation aortic regurgitation grade >2 occurred in 28.4% of patients (19.6% balloon-expandable THV vs 32.2% self-expandable THV; \(P = .11\)) but was prevalent in only 17.4% when multislice CT (MSCT)-based transcatheter aortic valve sizing was performed (16.7% balloon-expandable THV vs 17.6% self-expandable THV; \(P = .99\)).\textsuperscript{34} MSCT sizing was
associated with reduced aortic regurgitation on multivariate analysis (odds ratio [OR], 0.19; 95% CI, 0.08-0.45; \( P < .0001 \)). \(^{34}\) Thirty-day device safety, success, and efficacy were noted in 79.1%, 89.9%, and 84.9% of patients, respectively, and 1-year mortality was 17.5%. \(^{34}\) Unique sizing algorithms may be useful in this subset of patients that incorporate a supra-annular measurement of sinus dimensions that allows appropriate sizing of the prosthesis in patients with bicuspid aortic valve disease.

### Aortic Regurgitation

A number of series have evaluated the outcome of patients undergoing TAVR of severe aortic regurgitation. \(^{35,36}\) In a series of 43 patients who underwent self-expanding TAVR for native valve aortic regurgitation, eight patients (18.6%) required a second valve during the index procedure for residual aortic regurgitation; notably, all second valves were required in patients without valvular calcification. \(^{36}\) Postprocedure aortic regurgitation grade 1 or lower was present in 34 patients (79.1%). At 30 days, the major stroke incidence was 4.7%, and the all-cause mortality rate was 9.3%. \(^{36}\) At 12 months, the all-cause mortality rate was 21.4% (6 of 28 patients). \(^{36}\) In another series of 26 patients (1.6%) who presented with aortic regurgitation, patients with aortic regurgitation were significantly younger, more frequently had New York Heart Association Class III/IV heart failure, and had a higher incidence of severe pulmonary hypertension compared with patients with aortic stenosis. Valve Academic Research Consortium-2 (VARC-2)–defined device success was lower in the aortic regurgitation group (79% vs 96%; \( P = .006 \)). \(^{37}\) At 1 month, patients treated for aortic regurgitation had a higher overall mortality (23% vs 5.9%; OR, 4.22; 95% CI, 3.03-8.28; \( P < .001 \)) and cardiac mortality (15.3% vs 4%; OR, 4.01; 95% CI, 2.40-7.66; \( P < .001 \)). Results were consistent at 12 months (overall mortality: 31% vs 19%; HR, 2.1; 95% CI, 1.5-4.41; \( P < .001 \); and cardiac mortality: 19.2% vs 6%; HR, 3.1; 95% CI, 2.09-8.22; \( P < .001 \)). \(^{37}\) Self-expanding TAVR in patient with aortic regurgitation may be considered when there are limited surgical options.

**PREDICTING OUTCOMES WITH SELF-**
EXPANDING TAVR

Due to the limitations of conventional risk scores in predicting outcome with TAVR, the CoreValve US Pivotal Trial and Registries examined the importance of nonconventional risk factors, including frailty, disabilities, and comorbidities. In an analysis of 3687 patients treated with self-expanding TAVR, patients were divided 2:1 into derivation and validation cohorts. The overall mortality rate was 5.8% at 30 days and 22.8% at 1 year. Thirty-day mortality was predicted by home oxygen use, assisted living, albumin levels <3.3 g/dL, and age >85 years, and 1-year mortality was predicted by home oxygen use, albumin levels <3.3 g/dL, falls in the past 6 months, STS PROM score >7%, and severe (≥5) Charlson comorbidity. A simple scoring system created on the basis of these multivariable predictors effectively stratified risk at 30 days and 1 year into low-risk, moderate-risk, and high-risk subsets and showed a 3-fold difference in mortality rates for the low-risk and high-risk subsets at 30 days (3.6% and 10.9%, respectively) and 1 year (12.3% and 36.6%, respectively). The 1-year mortality model was more stable than the 30-day model (C-statistics: 0.79 vs 0.75).

BEST PRACTICE SELF-EXPANDING BIOPROSTHESIS IMPLANTATION

The positive results of the US CoreValve Clinical Trials were due to a number of important contributing factors, detailed in the following sections.

Preprocedural CT Angiography

Multidetector CT is useful for determining the appropriate THV size in patients undergoing self-expanding TAVR. In an analysis of 1023 patients with severe aortic stenosis deemed high or extreme risk for surgery and treated with the CoreValve bioprosthesis, a sizing algorithm was evaluated and used based on the perimeter-derived diameter (Table 44-1). A device annular sizing ratio (DAR) was also calculated based on the native annulus perimeter and perimeter of the selected THV. Higher DARs were associated with lower rates of moderate or severe aortic PVR (DAR ≤10%, 17.6%; DAR
10% to 15%, 9.9%; DAR 15% to 20%, 6.3%; and DAR >20%, 4.9%; \( P < .001 \). There was no increase in clinical events associated with higher DARs.

### Table 44-1 Sizing Algorithm for Self-Expanding Bioprostheses

<table>
<thead>
<tr>
<th>Valve Size</th>
<th>Diameter, mm</th>
<th>Perimeter, mm</th>
<th>SOV, mm</th>
<th>Leaflet to STJ, mm</th>
<th>Ascending Aorta, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 mm</td>
<td>18-20</td>
<td>56.5-62.8</td>
<td>≥25</td>
<td>≥15</td>
<td>≤34</td>
</tr>
<tr>
<td>26 mm</td>
<td>20-23</td>
<td>62.8-72.3</td>
<td>≥27</td>
<td>≥15</td>
<td>≤40</td>
</tr>
<tr>
<td>29 mm</td>
<td>23-26</td>
<td>72.3-8.16</td>
<td>≥29</td>
<td>≥15</td>
<td>≤43</td>
</tr>
<tr>
<td>31 mm</td>
<td>26-29</td>
<td>81.6-91.1</td>
<td>≥29</td>
<td>≥15</td>
<td>≤43</td>
</tr>
<tr>
<td>34 mm</td>
<td>26-30</td>
<td>81.6-94.2</td>
<td>≥31</td>
<td>≥16</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Vascular Access

Multidetector CT imaging of the vascular access for self-expanding TAVR has been invaluable for determination of minimal lumen diameters, vessel calcification, and tortuosity. Historically, an 18-Fr sheath was comparable to the CoreValve bioprostheses requiring iliofemoral diameters >6.0 mm in the absence of calcification and 6.5 to 7.0 mm in the presence of severe calcification in the iliofemoral vessels. A balloon-expandable sheath has also been used with iliofemoral diameters <5.5 mm with the larger CoreValve devices.\(^{39}\) The newer generation of Evolut R with its 14-Fr Enveo delivery system has allowed treatment of iliofemoral diameters of 5.0 mm or larger.

### Optimal Implantation

Self-expanding bioprosthesis positioning requires a precise knowledge of the aortovalvular complex at the time of implantation. Traditionally “best practice” recommendations are reviewed during a preprocedural planning meeting that includes the selection of a co-planer view that aligns the basal planes of the 3 coronary sinuses (Fig. 44-9). The co-planar view can be estimated with the use of a multidetector noncontrast CT scan and confirmed with aortography at the time of the procedure. The co-planar view is then used to identify the noncoronary sinus for placement of the injection pigtail catheter for contrast injection during implantation. The noncoronary sinus is critical at it represents the most inferior position of the valve leaflets that are used for proper implantation.
Establishment of co-planar view. Alignment of the 3 coronary sinuses is performed to identify the noncoronary sinus (arrow) and left coronary sinus for self-expanding transcatheter aortic valve replacement.

**Wire Positioning**

With the early CoreValve bioprosthesis, there was a tendency for downward migration into the left ventricular during implantation. This force can be countered by using the left ventricular guide wire to provide a counterforce but required optimal position and shaping to avoid left ventricular perforation (Fig. 44-10A). In the initial CoreValve series, 0.035 Extra Support or Lunderquest wires were preferred but have now largely been replaced by preshaped left ventricular guide wires such as the Confida (Fig. 44-10B) or Safari wires.
**FIGURE 44-10** Optimal position of left ventricular guideline during CoreValve deployment.  

**A.** Hand-shaped 0.035” extra support guide wire with a 1-cm floppy tip. The guide wire is shaped such that there are no transition zones that would result in left ventricular perforation with forward force on the guide wire. This forward force on the ventricular guide wire stabilizes the position of the CoreValve device during deployment.  

**B.** The Confida preshaped left ventricular guide wire with a transition zone remote from the tip that lessens right of left ventricular perforation.

<table>
<thead>
<tr>
<th><strong>Shaft diameter</strong></th>
<th>0.035”/0.89 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shaft material</strong></td>
<td>Stainless steel</td>
</tr>
<tr>
<td><strong>Shaft color</strong></td>
<td>Green</td>
</tr>
<tr>
<td><strong>Tip material</strong></td>
<td>Stainless steel</td>
</tr>
<tr>
<td><strong>Flexible tip length</strong></td>
<td>20 cm</td>
</tr>
<tr>
<td><strong>Coating</strong></td>
<td>PTFE</td>
</tr>
<tr>
<td><strong>Guide wire length</strong></td>
<td>260 cm</td>
</tr>
</tbody>
</table>
**Predilatation**

Based on the extent of annular and valvular calcification, balloon valvuloplasty may be useful in fracturing the restrictive annulus and allowing full bioprosthesis expansion. However, the avoidance of rapid ventricular pacing may be of particular use in patients with reduced LVEF and patients who have lesser degrees of calcification.\(^{40}\)

Another important component of self-expanding implantation is the lining up of the marker at the distal delivery catheter tip to allow co-axial biosprothesis release (Fig. 44-11). In the co-planar aortography projection, this is generally a caudal angulation that elevates the right coronary sinus to ensure coverage.

![Alignment of the delivery catheter marker. Left Panel: The CoreValve delivery catheter is positioned along the lesser curvature, and the delivery catheter marker is not in plane. Right Panel: The catheter is now located along the greater curvature of the aorta by forward pressure on the left ventricular guide wire, and the gantry has been rotated caudal to provide a “co-axial” alignment of the delivery catheter marker.](image)

**Depth of Implantation**

A key component to optimal self-expanding TAVR is a slow and gentle deployment with incremental rotation of the microknob to secure the position of the CoreValve. Once there has been annular contact with the inflow
portion of the frame, there is generally a drop in the systolic arterial pressure. Fast (up to 110 bpm) ventricular pacing during deployment may help stabilize the valve in the setting of systolic hypertension. Once the sheath has been fully retracted, the tension on the wire is removed and the valve is released or repositioned. In addition, the angle of the CoreValve frame can be determined to understand whether forward or withdrawal pressure is needed at the end of the procedure. The optimal implantation depth is 3 to 5 mm with the Evolut R bioprosthesis and 4 to 6 mm with the CoreValve bioprosthesis (Fig. 44-12).\textsuperscript{41}


\textbf{Recapture and Positioning}

An advantage of the Evolut R system is that it can be recaptured and repositioned if it is not in optimal position (Fig. 44-13).
**FIGURE 44-13** Placement of an Evolut R with recapturing and repositioning. A. Positioning of the Evolut R 4 mm below the noncoronary sinus. B. Annular contact of the Evolut R. C. Retraction of the delivery catheter sheath to the prerelease position. D. The inflow is now located at 2 mm below the annular plane. E. Because the prerelease position is deemed to be too close to the sinus of Valsalva, the Evolut R is recaptured. F. The Evolut R is appropriately positioned at 4 mm below the noncoronary sinus. G. Final aortography showed the Evolut R at 4 mm below the noncoronary sinus without paravalvular regurgitation.

**Concordance of Postprocedural Imaging**

Multiple modality imagining is performed at end of the procedure, with an assessment of hemodynamics, aortography, and echocardiography. Hemodynamic evaluation is a critical component of the postprocedural assessment. Optimal implantation demonstrates a wide separation between the aortic and left ventricular end-diastolic pressures (Fig. 44-14).  

**FIGURE 44-14** Hemodynamics after self-expanding valve placement. Simultaneous determination of left ventricular end-diastolic pressure (*blue line*) and diastolic blood pressure in the aorta (*red line*) in a patient without paravalvular regurgitation (PVR) (A) and a patient with moderate PVR (B). (Adapted from Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59:1134-1141, Copyright © 2012, with permission from American College of Cardiology Foundation.)

**Balloon Postdilation**

Balloon postdilation is performed in approximately 20% to 25% of cases of self-expanding TAVR, most commonly for residual PVR and less commonly...
for residual transaortic gradients. In an analysis of 3532 patients treated with self-expanding TAVR, 22% of patients underwent postdilation. Male sex ($P < .0001$), larger aortic annular diameters ($P < .0001$), lower device-to-annular ratios ($P < .0001$), and higher grades of baseline aortic regurgitation ($P < .05$) were more common in the patients who underwent balloon postdilation. Thirty-day and 1-year clinical event rates, including stroke, were similar in the 2 groups. One case of valve migration and 3 cases of fatal annular rupture occurred following balloon postdilation likely due to balloon oversizing. As a result, in the setting of significant left ventricular outflow tract (LVOT) calcification, the minimal lumen diameter is used to select a compliant balloon, and 1 mm less than the LVOT minimal lumen diameter is selected for a noncompliant balloon. In the absence of LVOT calcification, a balloon sized to the mean diameter of the annular is selected for a compliant balloon, and 1 mm less than the mean diameter is used for a noncompliant balloon. Care must be taken to avoid crossing the guide wire through the self-expanding frame cells prior to postdilation.

**COMPLICATIONS WITH SELF-EXPANDING TAVR**

**Stroke**

Neurologic events are uncommon after self-expanding TAVR. In patients enrolled in the CoreValve US Extreme Risk and High-Risk Pivotal Trials or Continued Access Studies, the 1-year stroke rate after TAVR was 8.4%. Analysis of the stroke hazard rate identified an early phase (0-10 days; 4.1% of strokes) and a late phase (11-365 days; 4.3% of strokes). Baseline predictors of early stroke included National Institutes of Health stroke scale score $>0$, prior stroke, prior transient ischemic attack, peripheral vascular disease, absence of prior coronary artery bypass surgery, angina, low body mass index ($<21$ kg/m$^2$), and falls within the past 6 months. Significant procedural predictors were total time in the catheterization laboratory or operating room, delivery catheter in the body time, rapid pacing used during valvuloplasty, and repositioning of the prosthesis. Predictors of stroke
between 11 and 365 days were small body surface area, severe aortic calcification, and falls within the past 6 months. There were no significant imaging predictors of early or late stroke.

**Paravalvular Regurgitation**

There are a number of potential mechanisms for PVR after TAVR (Fig. 44-15). Appropriate self-expanding bioprosthetic sizing using multidetector CT imaging is the most important factor in reducing the frequency of significant post procedural PVR. Occasional, incomplete frame expansion occurs due to excess calcification of the LVOT (Fig. 44-16). Ventricular and aortic placement can be managed with recapturing and repositioning.
aortic valve implantation. Paravalvular leaks with consecutive periprosthetic aortic regurgitation result from underexpansion of the prosthesis stent frame, which might be caused by calcifications of the annulus or the cusps of the native valve (A), valve malposition with too shallow (B) or too deep (C) implantation depth of the prosthesis, and/or annulus-prosthesis size mismatch (D). (Adapted from Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol. 2012;59:1134-1141, Copyright © 2012, with permission from American College of Cardiology Foundation.)

**FIGURE 44-16** Extensive calcification of the left ventricular outflow tract. **Upper Left Panel:** Extensive calcification of the aortic valve in cross-section. **Lower Left Panel:** Volume rendering shows the calcification extending into the mitral annulus. **Right Panel:** Extensive left ventricular outflow tract calcium.

A smaller randomized study of 120 patients who received a balloon-expandable TAVR and 120 patients assigned to a self-expandable TAVR found that device success, defined as successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only 1 valve implanted in the proper anatomic location, was higher in the balloon-expandable valve group (95.9%) than the self-expanding group (77.5%; \( P < .001 \)).\(^{49}\) This was primarily due to
a significantly lower frequency of residual more-than-mild aortic regurgitation in the balloon-expandable TAVR group (4.1% vs 18.3% in the self-expanding TAVR group; \( P < .001 \)) and the less frequent need for implanting more than 1 valve with balloon-expandable TAVR (0.8% vs 5.8% with self-expanding TAVR; \( P = .03 \)). Despite these findings, there were no differences in clinical outcomes between the 2 devices.

One unique feature of the self-expanding bioprosthesis is that an improvement in aortic valve hemodynamics and a reduction in PVR may occur in some patients over time. The US CoreValve Extreme Risk Study showed an improvement in the rate of moderate or severe PVR in over 80% of patients between 30 days and 1 year. Serial analysis of echocardiograms in this study showed that aortic valve velocity, mean gradient, and effective orifice area further improved significantly from discharge to 1 month and that this improvement was sustained to 1 year. PVR was moderate or severe in 9.9% of patients, and 83% of patients improved by at least 1 grade of regurgitation by 1 year. Oversizing was associated with an improvement in PVR over time (Fig. 44-17). PVR can also be treated with transcatheter closure devices.

![Regression of paravalvular regurgitation over time. A. The proportion of patients with varying degrees of paravalvular aortic regurgitation (PVAR) in 383 patients with paired echocardiography studies available. B. Mean annular sizing ratio (100 × [valve perimeter – aortic annulus perimeter]/aortic annulus perimeter) for patients without PVAR, with PVAR that regressed by 1 year, and with residual PVAR that remained at 1 year. Error bars represent standard deviation. AR, aortic regurgitation.](image-url)

(Adapted from Oh JK, Little SH, Abdelmoneim SS,

Significant PVR has been associated with high rates of early\(^5,53,54\) and late mortality\(^5,54,55\) after self-expanding TAVR. Predictors of PVR after self-expanding TAVR are the degree of calcification and undersizing of the self-expanding prosthesis.\(^56\) Although the VARC-2 Working Group has classified residual PVR[CD2] as none, mild, moderate, and severe, a more granular classification including trace, mild-moderate, and moderate-severe may provide more incremental prognostic valve.\(^57,58\)

**Conduction Abnormalities**

Due to the proximity of the origin of the left bundle branch in the LVOT at the location of the noncoronary and right coronary sinuses, implantation of a self-expanding bioprosthesis has been associated with the development conduction abnormalities,\(^59\) including new left bundle branch block (33%-38%)\(^59,60\) and atrioventricular block or bradycardia (20%). Conduction abnormalities have been associated with presence of preexisting conduction disorders and depth of implantation.\(^60\) The frequency of the need for a new permanent conduction system disturbance was lower in the US Pivotal Trials (20%) than in prior studies. Baseline conduction system disturbances such as right bundle branch block and left anterior fascicular hemiblock were predictors of the need for a permanent pacemaker. Although intermediate-term mortality has not been affected by the use of permanent pacemaker placement,\(^51\) longer term studies with larger numbers of patients are needed.

The ADVANCE-II Registry was designed to evaluate “best practice” implantation technique on the occurrence of conduction disturbances in 194 patients after self-expanding TAVR.\(^62\) Optimal implantation was defined as an implant at an optimal depth ≤6 mm below the aortic annulus.\(^62\) An optimal implantation depth was achieved in 43.2% of patients, and the overall rate of permanent pacemaker implantation was 18.2%.\(^62\) The rate of permanent pacemaker placement was nonsignificantly lower in patients with depths ≤6 mm versus depths >6 mm (13.3% vs 21.1%, respectively; \(P = .14\)).\(^62\) New-onset left bundle branch block and first-degree atrioventricular block occurred in 45.4% and 39.0% of patients, respectively, and resolved
spontaneously within 30 days in 43.2% and 73.9% of patients, respectively.\textsuperscript{62} In patients with new proton pump inhibitor, the rate of intrinsic sinus rhythm increased from 25.9% at 7 days to 59.3% at 30 days ($P = .004$).\textsuperscript{62}

**Leaflet Thickening and Valve Thrombosis**

Serial imaging using multidetector CT imaging has shown that a minority of patients treated with both transcatheter and surgical bioprostheses may show leaflet thickening and valve thrombosis.\textsuperscript{63-65} In rare circumstances,\textsuperscript{65} these may result in elevated gradients that can be treated with oral anticoagulation.\textsuperscript{63,64} The clinical implications are uncertain,\textsuperscript{66} and a 400-patient multidetector CT substudy including 200 patients treated with transcatheter and surgical aortic valve replacement will be part of the Evolut R low-risk randomized clinical trial.

**Other Complications**

Coronary occlusion is a rare complication after self-expanding TAVR\textsuperscript{67} and can be mitigated by careful preprocedural assessment of the sinus of Valsalva width and coronary heights. Annular ruptures are also rare\textsuperscript{68} and are most often due to oversizing balloons used for postdilation. Vascular complications are infrequent due to the smaller vascular access diameters (6 mm) needed for the 18-Fr CoreValve system that will accommodate all sizes of THV up to 31 mm. The vascular access diameter is further reduced with the Evolut R to a true 14 Fr (not expandable 14 Fr), and access diameter is reduced to 5 mm in the iliofemoral vessels. Endocarditis is a rare complication.\textsuperscript{69}

**EVOLUT R SELF-EXPANDING BIOPROSTHESIS**

Design improvements of transcatheter bioprostheses have focused on reducing procedural complications by decreasing delivery catheter profile, improving annular sealing, and providing the ability to reposition the transcatheter valve during deployment (Fig. 44-18). The fourth-generation
Evolut R self-expanding bioprosthesis addresses these issues; it includes a 14-Fr equivalent EnVeo R Deliver Catheter System (Medtronic, Minneapolis, MN) (Fig. 44-19), a modified nitinol design at the annulus that optimizes radial expansive force, a longer porcine pericardial sealing skirt, and a nitinol delivery catheter capsule that allows resheathing and recapturing during deployment. A recent modification of the Evolut R 34XL includes annular diameters of 30 mm and the EnVeo Delivery catheter of 16 Fr equivalent, which was approved for commercial use in the United States.

**FIGURE 44-18 Evolut R bioprosthesis.**
The Evolut R was first evaluated in a single-arm, multicenter pivotal study in 60 high- or extreme-risk patients with symptomatic aortic valve stenosis. Patients were older (mean age, 82.8 ± 6.1 years; STS PROM, 7.0% ± 3.7%) and underwent self-expanding TAVR via the transfemoral route in 98.3%, using a 29-mm valve in 68.3% of patients. No death or stroke was observed up to 30 days. The VARC-2 overall device success rate was 78.6%. PVR after TAVR was mild or less in 96.6%, moderate in 3.4%, and severe in 0% of patients at 30 days.

The Evolut R US Study included 241 patients who were at high or extreme risk for surgery. Patients were elderly (mean age, 83.3 ± 7.2 years) and had high surgical risk (STS PROM, 7.4%). Resheathing or recapturing was performed in 22.6% of patients; more than 1 valve was required in 3 patients (1.3%). Thirty-day outcomes included all-cause mortality (2.5%), disabling stroke (3.3%), major vascular complications (7.5%), life-threatening or disabling bleeding (7.1%), and new permanent pacemaker (16.4%). Aortic valve hemodynamics were markedly improved at 30 days: the mean aortic valve gradient was reduced from 48.2 ± 13.0 mm Hg to 7.8 ±
3.1 mm Hg (\(P < .001\)), and aortic valve area was increased from 0.6 ± 0.2 cm\(^2\) to 1.9 ± 0.5 cm\(^2\) (\(P < .001\)).\(^{41}\) Moderate residual paravalvular leak was identified in 5.3% of patients and was related to the degree of oversizing (Fig. 44-20).

**FIGURE 44-20 Relationship of oversizing to paravalvular regurgitation.**

**FUTURE PERSPECTIVES**

Additional design iterations are ongoing with the Evolut 2.0 (Pro), which will contain a thin pericardial skirt on the outside of the frame that will increase the surface area contact with the annulus to reduce PVR. The 1200-patient Evolut R Low-Risk Study will randomly assign patients with severe aortic stenosis and an estimated 30-day surgical risk of <3% to either self-expanding TAVR or surgery. The primary end point for the study is all-cause mortality or major stroke at 2 years. These studies and others will further expand the spectrum of patients who will benefit from the use of self-expanding bioprostheses in the future.

**REFERENCES**


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Pulmonary Balloon Valvuloplasty and Percutaneous Pulmonary Valve Implantation

Mike Saji
D. Scott Lim

INTRODUCTION

Since percutaneous balloon pulmonary valvuloplasty (BPV) for pulmonary valve stenosis (PS) was first successfully performed by Rubio-Alverez and Limon-Lason\(^1\) using a ureteral catheter in 1950s, it has become the standard of care for treatment of isolated PS over surgical valvotomy.\(^2,3\) In 2000, based on these experiences, the percutaneous pulmonary valve implantation (PPVI) was first performed by Bonhoeffer et al\(^4\) in a patient with a dysfunctional of right ventricle–to–pulmonary artery conduit. In 2010, the Melody valve (Medtronic, Minneapolis, MN) became commercially available in the United States under a humanitarian device exemption protocol and, more recently, was awarded postmarket approval by the US Food and Drug Administration. Since then, PPVI has been performed in over 4500 patients in more than 30 countries worldwide. In this chapter, we will review BPV and PPVI with particular focus on the indication, technical aspect, clinical outcomes, and potential complications.
Isolated PS is a relatively common disorder, accounting for approximately 10% of all congenital heart defects, and it varies in regard to severity of obstruction to the pulmonary orifice size, leaflet morphology (eg, dome-shaped, unicommissural, bicuspid, or dysplastic tricuspid valve), and annulus (eg, hypoplastic or enlarged annulus). Other congenital cardiac defects that may be associated with PS include atrial septal defect, ventricular septal defect, tetralogy of Fallot, transposition of the great arteries, double-outlet right ventricle, and ventricular inversion. Significant obstruction may lead to an inability to augment pulmonary blood flow during exertion, resulting in exercise-induced fatigue, syncope, or chest pain. Physical examination reveals a systolic ejection murmur with maximal intensity at the left upper sternal border, and transthoracic echocardiography is key to determining the severity and morphologic diagnosis. Once a severe PS is diagnosed, cardiac catheterization is performed in order to provide appropriate therapy.

Given the relative low risk and high likelihood of a long-standing good result, the generally accepted indication of BPV is more than moderate degree of PS (echocardiographic peak instantaneous pressure gradients ≥50 mm Hg or mean Doppler pressure gradients ≥30 mm Hg for symptomatic patients and peak Doppler pressure gradients ≥60 mm Hg or mean pressure gradients ≥40 mm Hg for asymptomatic patients) with less than moderate pulmonary valve regurgitation. BPV provides an immediate reduction of pulmonary valvular gradients and modest increase of pulmonary pressure and cardiac index. Improvement in right ventricular dysfunction frequently results in reduction of tricuspid regurgitation and right-to-left shunt if it exists. Patients with mild (gradient <30 mm Hg) stenosis are contraindicated for intervention, as natural history studies have demonstrated the benign natural history of mild PS at follow-up. Even in the asymptomatic patient, severe PS should be treated to prevent myocardial damage associated with long-term right ventricular pressure overload. Exercise testing may induce abnormal hemodynamic response due to low cardiac output in these patients.
Technique

BPV is performed most commonly under local anesthesia with procedural sedation, with continuous noninvasive heart rate, pressure, and oxygen saturation monitoring. Although transfemoral venous access is commonly preferred, transaxillary, transjugular, or transhepatic venous access can be successfully performed as well.\textsuperscript{13-15}

A balloon wedge catheter (Arrow International Inc., Reading, PA) is usually used for right-sided pressure measurements, obtaining right ventricular and then pulmonary artery pressures. If a simultaneous gradient is required, a dual lumen catheter can demonstrate simultaneous gradient across the pulmonary valve. Simultaneous recording of the right ventricular pressure and femoral arterial pressure also helps in assessing the severity of the pulmonary valve; right ventricular peak systolic pressure $\geq 75\%$ of peak systolic systemic pressure is considered significant as well, particularly in younger patients. After gradient evaluation, right ventriculogram is performed in the right ventricle with left lateral projection (Fig. 45-1A). A straight anteroposterior view helps to assess the right ventricular size and ejection fraction, whereas the left lateral view, which is perpendicular to the pulmonary valve annulus, helps to determine the single plane assessment of valvular annular dimension. Left-sided catheterization and angiography are usually not warranted. After crossing the catheter through the pulmonary valve, 0.035-inch exchange length wire is passed to the pulmonary artery (left pulmonary artery is preferable) through the catheter already in place, and then the catheter is removed. If the size of the femoral venous sheath does not accommodate the selected balloon catheter, the sheath may be upsized to an appropriate size at this point. The selected balloon angioplasty catheter is advanced and positioned at the pulmonary valve. Tyshak II balloons (NuMed, Inc., Hopkinton, NY) are usually preferred due to their low-profile cross-sectional area for introduction. Landmarks from the previous ventriculogram or balloon indentation on fluoroscopy may help in positioning the balloon during inflation. The balloon is inflated with diluted contrast material ($\sim 15\%$) using a syringe and hand inflation. The balloon is rapidly inflated until the disappearance of the sharp part of the balloon waist and no greater than the burst pressure of the balloon (Fig. 45-1B-C). Conservative balloon sizing is important to avoid the creation of significant pulmonary regurgitation and rupture of pulmonary annulus. The current recommendation
is to use a balloon diameter 1.2 to 1.3 times the pulmonary annulus based on follow-up data,\textsuperscript{16,17} except for pediatric patients with a dysplastic pulmonary valve, in whom it is recommended to use a diameter 1.4 to 1.5 times the pulmonary annulus.\textsuperscript{18} Use of balloon diameters more than 1.5 times the pulmonary annulus may result in annular injury.

**FIGURE 45-1** A. Right ventriculogram is performed to evaluate the pulmonary valve stenosis. B. The balloon is inflated slowly until the waist is seen (arrow) to adjust the positioning of the balloon. C. If the waist is seen at the center of the balloon, the balloon is fully inflated until that waist is eliminated.

For larger annuli, the double-balloon technique may be considered if the largest single balloon is inadequate. The following formula is used to calculate the effective balloon size:\textsuperscript{17} \[\text{effective balloon diameter} = \frac{D_1 + D_2 + \pi (D_1/2 + D_2/2)}{\pi}.\] \(D_1\) and \(D_2\) are the diameters of each balloon used. This formula has been further simplified,\textsuperscript{19} as follows: \[\text{effective balloon diameter} = 0.82 (D_1 + D_2).\] The double-balloon technique produces less hypotension during the procedure because it allows right ventricular output in between the balloons during inflation. However, single-balloon valvuloplasty is currently preferred due to its ease and simplicity, with usually excellent outcomes compared to the double-balloon technique.\textsuperscript{20}

Following balloon valvuloplasty, repeat hemodynamic measurements are undertaken to assess the results of the valvuloplasty. If the result is not satisfactory (gradient in excess of 30 mm Hg), a repeat dilatation with a larger balloon is considered. Once the catheter and guide wire are removed, a right ventriculogram is performed to evaluate for any complication, such as tricuspid regurgitation or pulmonary annular injury.
The patient is observed overnight with heart rate, blood pressure, and pulse oximetry monitoring for any late complications. Clinical reevaluation at least once using echocardiography is generally recommended for follow-up.

**Clinical Outcomes and Potential Complications**

The Valvuloplasty and Angioplasty of Congenital Anomalies Registry reported mortality of 0.24% (mostly neonate and young infant) and major complication of 0.35% from 822 BPV procedures from 26 sites. Major acute complications were inversely related to age and mostly associated with cardiac catheterization as follows.

Injury of the right ventricular outflow tract occurs in 0.1% of patients undergoing BPV. Because the right ventricular infundibulum is lacking in elastic fibers as compared with the pulmonary trunk, it is susceptible to tearing and dissection. An oversized balloon, especially in neonatal patients with a narrowed infundibulum, may result in myocardial injury and thereby increase the risk of right ventricular perforation. The uncommon but feared complication of “suicidal right ventricle” may result after BPV in which muscular spasm after relief of valvar PS occurs. Patients with significant infundibular gradients that develop after valvuloplasty may benefit by acute administration of fluids to expand the right ventricle or administration of β-blocker medications to slow the heart rate.

Pulmonary regurgitation is less common and less severe following balloon valvuloplasty than following open surgical valvotomy. However, if one includes milder degrees of pulmonary regurgitation, it has been reported in approximately 60% to 90% of cases, and the degree of pulmonary regurgitation may increase with time. Although most patients do not require surgical intervention for increased pulmonary regurgitation, clinical follow-up is recommended in patients with more than mild pulmonary regurgitation to identify the small number of patient with late development of severe pulmonary regurgitation and right ventricular dysfunction in whom pulmonary valve replacement would be warranted. This cohort may now be considered for PPVI as well, and this will be discussed later in this chapter. See also the section titled “Percutaneous pulmonary valve implantation.”

The complication of severe tricuspid regurgitation has been demonstrated to occur in 0.2% of patients, although it is primarily confined to neonatal
patients due to the tricuspid papillary muscle rupture being caused by the proximal part of the inflated balloon.\textsuperscript{22}

Other potential complications are arrhythmia (eg, complete heart block, right bundle branch block, ventricular tachycardia), pulmonary thromboembolic events, and acute pulmonary edema. In the younger patient with severe PS, the pulmonary vascular bed may have been exposed to long-standing hypoperfusion and remodeling. As such, it may not be able to adapt to acute increases in pulmonary blood flow after resolution of the valvar stenosis, which can result in acute pulmonary edema. Fortunately, such acute pulmonary edema is frequently transient in nature.

Late complications at follow-up include femoral vein stenosis or occlusion, which occurs in approximately 7% to 19% of patients (more likely in infants) but is mainly asymptomatic. Restenosis of the pulmonary valve is uncommon but can be detected by follow-up echocardiography in about 8% to 10% of patients.\textsuperscript{21,28} Repeat BPV is first considered; however, subsequent surgical intervention is reported in 10% to 16% of cases at 10 years.\textsuperscript{28,29} The risk factors of recurrence identified in previous studies are primarily a balloon–to–pulmonary valve annulus ratio $<1.2$ and immediate postvalvuloplasty gradient $>30$ mm Hg.\textsuperscript{26,30} A small annulus due to dysplasia and postsurgical or complex PS were also found to be a predictive factors for restenosis,\textsuperscript{28} and surgery may be generally recommended in these patients.

**Comparison With Surgery**

In surgical series for open approaches to PS, mortality rates vary from 3% to 14%, and recurrence rate range from 0% to 8%.\textsuperscript{28} Due to baseline differences between patient populations, it is difficult to compare directly the effectiveness of BPV and surgical valvotomy. However, in the present era, BPV has become the initial standard of care due to the far less invasive nature with less mortality and comparable relief of obstruction with less regurgitation compared to open surgery.\textsuperscript{31}

**Aneurysmal Poststenotic Dilation**

Poststenotic dilation of the pulmonary artery is relatively common in congenital PS, but the natural history remains unclear, although it is likely
benign in most cases. Typical poststenotic dilation diameter involves the main and left pulmonary arteries. BPV serves to relieve the stenosis and may prevent further poststenotic dilation. Rarely, the left pulmonary artery dilatation after BPV may be due to traumatic injury from a long and large balloon. Recommended modifications include using a smaller initial balloon ratio and using shorter balloons to minimize risk of injury to the left pulmonary artery.

PERCUTANEOUS PULMONARY VALVE IMPLANTATION

Clinical Indications and Patient Selection

Dysfunction of a surgically placed pulmonary valve, manifesting as some combination of stenosis or regurgitation, is a common problem after surgical repair of right-sided congenital heart disease. Surgical pulmonary valve replacement using a valved conduit or tissue valve has been a long-standing therapy that has been performed with low mortality. However, dysfunction of the bioprosthetic valve occurs in more than half of the patients by 10 years postoperatively. As a result, the majority of such patients have been faced with the prospect of multiple repeat open-heart surgeries during their life. Therefore, patient management strategy has been based on delaying surgical intervention for as long as possible, so that the number of open-heart surgeries performed on any individual patient is kept to a minimum. However, this approach bears the risk of delaying surgery beyond a theoretical point of limited return when right ventricular dysfunction and impaired exercise capacity might be irreversible.

Previous studies have shown that late surgical pulmonary valve replacement did not lead to normalization of right ventricular dimensions as assessed by magnetic resonance imaging (MRI). The impact of timing of pulmonary valve replacement on right ventricular function, exercise performance, and long-term survival remain undefined, and the clinical decision making regarding timing of intervention in these patients is still complicated. However, the less invasive therapy of PPVI has led to a shift toward earlier pulmonary valve replacement, although the optimal timing has
still yet to be clearly determined. The following are the criteria commonly used in recent years in the United States for patients with right ventricle–to–pulmonary artery conduit, native right ventricular outflow tract (RVOT) obstruction, and failing bioprosthetic valve:

1. Symptomatic patients with severe RVOT obstruction and exercise intolerance related to symptoms with continuous wave Doppler velocity >3.5 m/s by echocardiography
2. Asymptomatic patients with severe RVOT obstruction, peak continuous wave Doppler velocity >4.0 m/s, or RVOT obstruction with right ventricular systolic pressure greater than two-thirds of systemic systolic pressure
3. Patients with severe pulmonary regurgitation and right ventricular end-diastolic volume index >150 cm/m² by cardiac MRI

On the other hand, the European Society of Cardiology/Association for European Pediatric Cardiology guidelines for the management of adults with congenital heart disease include the following indications in patients with right ventricular–to–pulmonary artery conduits:

1. Symptomatic patients with right ventricular systolic pressure >60 mm Hg (tricuspid regurgitation [TR] velocity >3.5 m/s; may be lower in cases with reduced flow) and/or moderate to severe pulmonic regurgitation
2. Asymptomatic patients with severe right ventricular outflow tract obstruction and/or severe pulmonic regurgitation when at least 1 of the following criteria is present:
   • Decrease in exercise capacity on cardiopulmonary exercise testing
   • Progressive right ventricular dilation
   • Progressive right ventricular systolic dysfunction
   • Progressive TR (at least moderate)
   • Right ventricular systolic pressure >80 mm Hg (TR velocity >4.3 m/s)
   • Sustained atrial/ventricular arrhythmias

In addition to the clinical indication, patients have to fulfill the anatomic criteria in regard to 2 crucial factors: coronary position relative to the
intended landing zone for the PPVI and a suitable landing zone for the intended pulmonary valve implant.

Interventions on the RVOT and pulmonary trunk expose the risk for coronary artery compression due to expansion of the RVOT. The ostium of the left coronary artery usually runs close to the pulmonary artery in patients with tetralogy of Fallot. Postoperatively, the right ventricle–to–pulmonary artery conduit may run in close proximity and directly over the left main coronary artery. It is essential to assess the course of the coronary artery in relation to the RVOT/pulmonary trunk prior to PPVI. Tomographic imaging (computed tomography [CT] or MRI) allows the determination of coronary proximity to the intended landing zone of the PPVI. Alternatively, selective coronary angiography during balloon dilation of the patient’s conduit can determine the risk for functional compression prior to stented valve implantation (Fig. 45-2). Contrast-gated CT (Fig. 45-3) allows a multiplanar reformatting of the image to determine the distance from the coronary to the landing zone in the pulmonary outflow. Cardiac MRI can also be helpful. CT scanning also allows for accurate measurement of the pulmonary annular size. Of the 2 available transcatheter valves for pulmonary implantation, the Melody valve has a potential diameter of 18 to 22 mm to replace the dysfunctional RVOT. The SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) comes in diameters of 23, 26, and 29 mm and covers ranges from 18 to 28 mm (annular areas of 340-680 mm²). Certain patients, particularly those with a transannular patch after tetralogy of Fallot repair, may have quite large RVOT diameters, potentially exceeding the currently available transcatheter valve sizes. Older patients with failing bioprosthetic valves in the pulmonary position also are potential candidates for either a Melody or SAPIEN valve implanted valve-in-valve.
In complex congenital heart disease, it is essential to assess the course of proximal coronary arteries in relation to the right ventricular outflow tract/pulmonary trunk prior to percutaneous pulmonary valve implantation. Coronary angiography is performed with the pulmonary balloon inflated. A. Right anterior oblique. B. Left anterior oblique. There is no evidence of coronary artery compression (arrow) in either view.
FIGURE 45-3 Multidetector computed tomography shows that the left coronary artery runs in close to the pulmonary artery (PA; arrow) in a patient considered for percutaneous pulmonary valve implantation.

**Device Design and Technique**

PPVI may be performed under procedural sedation or general anesthesia. Femoral access is preferred because it allows for an easy working position in the catheterization laboratory. Transjugular access can also be performed safely, particularly if the angles for delivery from the inferior vena cava are suboptimal.

The commercially available valves for PPVI are the Melody valve and the SAPIEN series valves (SAPIEN, SAPIEN XT, and SAPIEN 3 valves; Edwards Lifesciences). The Melody valve is composed of a balloon-expandable stent and valved bovine jugular venous conduit (Fig. 45-4A). The stent comprises 6 rows of circumferential struts, each of which is fashioned
from a length of platinum-iridium wire that is welded at the ends and formed to have 8 crown “zigs.” Each strut is welded together at the crowns with gold-brazed to increase their strength. The stent measures 34 mm in length when in expanded configuration and 28 mm in length when expanded to 18 mm in diameter. The most important design characteristics that make this stent appropriate for use in the Melody valve platform are its relative malleability, which is felt to be important for facilitating conformation to irregular RVOT conduits; easy crimping on a balloon delivery catheter; and its ability to expand well beyond the expected working diameter of the valve without shortening to a degree that would distort the valve leaflets. However, this is also a potential disadvantage because the low radial strength of the stent materials can lead to stent fracture as the valve is compressed between the sternal table and the water-hammer effect of the aorta. Stent fracture has been associated with early valve failure, necessitating prestenting of the landing zone to protect the subsequently implanted Melody valve. Another advantage of the Melody’s venous valve is its relatively deep commissures, which allow for valve competence in a range of sizes, thereby providing for a single valve that can be dilated up to approximately 24 mm. The valve sheath tissue is sutured to the frame at each stent node with a separate interrupted suture between the stent and venous conduit. Blue suture is used at the distal end of the valve to ensure proper orientation of the valve on the Ensemble transcatheter delivery system (Medtronic), which has a blue nose cone on the end.
The Ensemble delivery system (Fig. 45-4B-C) consists of a balloon-in-balloon system and is mounted within a Teflon sheath that is 22-Fr in outer dimension at its distal portion, where it covers the valve, and 16-Fr along most of its length. The delivery system is manufactured with outer balloon diameters of 18, 20, or 22 mm, and the inner balloon is half the outer balloon diameter and shorter than the outer balloon. The tip of the balloon catheter is equipped with a blue nose cone, which tapers distally to act as a vascular introducer, and has a proximal end that engages within the distal end of the sheath to create a smooth contour. The delivery system is identical among the different balloon sizes.

The Melody valve is crimped manually onto the balloon of the appropriate-sized Ensemble delivery system, and the covering portion of the capsule is advanced over the mounted Melody valve. Once the valve is covered, the system is introduced into the vein over a stiff guide wire and advanced to a proper position in the RVOT (Fig. 45-5). After withdrawing the sheath to expose the valve, the inner and outer balloons of the balloon-in-balloon system are inflated in succession to deploy the valve. Once the valve is implanted successfully, the balloons are deflated and the entire delivery system is removed over the guide wire. As mentioned, it is important to prestent the landing zone prior to the Melody valve implantation to prevent the stent fracture. Stent fracture occurs due to the pulmonary conduit valve being compressed by the water-hammer effect of the aorta posteriorly and the sternal table anteriorly. Stent fracture has been linked to early valve failure. 39,42
FIGURE 45-5 A. Angiogram (left anterior oblique projection) demonstrates the recoil of the stent implanted 3 months ago in 16-mm homograft that showed significant stenosis. B. Angiogram shows distance between main pulmonary artery and left main coronary artery (*asterisk*). C and D. Additional stent was implanted to open the recoil. E. Additional inflation was performed to gain the inner diameter. F. Acceptable opening of the homograft was achieved. G and H. Melody valve was positioned and implanted in the double stent. I. The final angiogram demonstrates good valvular competence and good acceptable opening of the homograft.
The SAPIEN series valves are made of bovine pericardium and affixed within a short stent frame (stainless steel in the SAPIEN and cobalt-chromium in the SAPIEN XT and SAPIEN 3 valves). The stent frame is of relatively high radial strength and has not been found to date to develop stent fractures when implanted in the pulmonary position. The SAPIEN series valves come in 20-, 23-, 26-, and 29-mm diameters and, therefore, have been used in pulmonary landing zones of 18 to 28 mm in diameter. The first-generation SAPIEN valves are mounted on the delivery balloon and have delivery system sheath requirements of 22- and 24-Fr inner diameters. The second- and third-generation SAPIEN valves are mounted on the shaft of the delivery catheter and then advanced up onto the balloon once inside the vasculature. This has allowed downsizing of the delivery system to facilitate its introduction via 16- to 20-Fr expandable sheaths. The third-generation SAPIEN valve has an outer skirt of polyethylene terephthalate designed to minimize paravalvular leak.

The actual procedure to implant the SAPIEN series valves in the pulmonary position is similar to that for the Melody valve. Although prestenting may not be as needed to protect the SAPIEN valve from stent fractures, it does provide a longer landing zone as well as prevent inflow and outflow obstruction when the shorter valve is implanted in longer narrowed conduit segments.

**Outcomes and Follow-Up**

PPVI results in significant reduction in right ventricular systolic pressure in previous studies, and pulmonary systolic pressure has also been shown to increase after deployment, indicating restoration of valvular competence. Systemic systolic pressures increase significantly after PPVI, which is a reflection of increased cardiac output. Significant paravalvular leak is rare. Patients have been demonstrated to have a significant improvement in New York Heart Association functional class after PPVI as well, regardless the pathology. However, there is a different functional response after PPVI between patients with predominantly stenotic versus predominantly regurgitant pathology in terms of ventricular remodeling as assessed by MRI and exercise capacity data. In patients with PS, an improvement in peak oxygen uptake after PPVI is seen, with the reduction in RVOT gradient being the only predictor of improved exercise capacity. As assessed by MRI, the
relief in right ventricular afterload by the RVOT gradient reduction leads to a reduced right ventricular end-systolic volume and increased right ventricular ejection fraction. In contrast, in patients with primarily pulmonary regurgitation, excise capacity remains unchanged, and PPVI does not improve the right ventricular ejection on MRI findings. The hypothesis is that pulmonary regurgitation is reduced to a minimum at peak exercise and therefore is not a limiting factor for cardiac output augmentation during exercise due to increased systemic venous return, shortening of diastole, and a reduction in pulmonary vascular resistance.

**Potential Complications**

Mortality and major complications have been reported in 0% to 5% and 3% to 11% of cases, respectively, predominantly due to intraprocedural complications.

Significant blood loss due to RVOT/conduit rupture occurs in 2% of cases. Bleeding generally drains into the pleural space rather than pericardium. Acutely, fluoroscopy can identify the pleural location of bleeding and provide for rapid drainage to reestablish the hemodynamic stability. Conduit or RVOT rupture can often be treated by placement of the Melody valve or another covered stent, and small ruptures can self-seal. Emergent surgical intervention for catastrophic rupture is rarely required.

Significant damage to the tricuspid valve occurs in less than 1% and, in most cases, it can be prevented by localizing the stiff guide wire to the center of the valve as it crosses the tricuspid annulus. Balloon-tipped floating catheters may minimize the risk of entrapment of the delivery system in either the chord or subvalvular apparatus of the tricuspid valve.

Cardiac and vascular injury due to the stiff guide wire occurs in 1% of cases. Although a stiff guide wire is required to provide sufficient support for advancement of the delivery system, the distal end may lead to injury of a branch pulmonary artery. The operator has to make sure that the guide wire is in the stable position in one of the distal pulmonary artery branches. Additionally, if the stiff guide wire is shaped by hand, care should be taken to create a smooth curve along its length, because acute bends can be traumatic to the right ventricle.

Other complications reported are uncommon and include device dislodgement, acute pulmonary edema, compression of the left coronary
artery, arrhythmia (ventricular tachycardia, complete heart block), and endocarditis.

**Stent Fracture**

The most commonly noted problem following PPVI with the Melody valve is stent fracture that can lead to loss of the functional integrity of the valve. Although it may occur with the Melody valve, it has not yet been reported following implantation with the SAPIEN series valves. It is classified into 3 types: type I, in which there are 1 or more strut fractures without loss of structural integrity; type II, in which there are strut fractures with loss of integrity; and type III, in which there is fragmentation or embolization of stent fragment.\(^4\) Data from the initial US trial on the Melody valve demonstrated a stent fracture rate of 28% in patients in whom prestenting of the RVOT was not performed,\(^47\) whereas the stent fracture rate with prestenting was 5% to 20%.\(^38,48,49\) Non-prestented status is the strongest predictor for stent fracture and restenosis, which is the most common reason for reintervention. The freedom from valve dysfunction rate was 87% and freedom of reintervention rate was 92% to 95% at 1 year.\(^39,48\) Other risk factors for stent fracture are chest wall contact, higher early Doppler gradient in the RVOT, absence of conduit calcification, and asymmetry of the Melody valve following implantation.

**SAPIEN SERIES VALVES IMPLANTED IN THE PULMONARY POSITION**

Since the first reports of using the SAPIEN series valves in the aortic position, investigators have reported small numbers implanted in the pulmonary position, which is in contrast to the tens of thousands reported for aortic applications. Although all reported patients underwent prestenting prior to SAPIEN valve implantation, there have been no reports of SAPIEN valve stent fracture.\(^50-53\) SAPIEN valves were implanted in conduits of diameters from 16 to 30 mm, with acute complication rates of 0% to 21%. These same reports characterized high acute implant success rates (95%-100% in case series of 72 total reported patients), with <5% reintervention rates at short-
and intermediate-term follow-up.

**SUMMARY**

Since the first percutaneous pulmonary valve was approved for commercial use in 2010, a significant number of patients have benefited from this therapeutic approach. Factors limiting its early success have included early valve failure due to stent fracture as well as size and deliverability of the valve to the pulmonary position. Both of these issues have been significantly improved upon with procedural as well as device modifications, such that the procedure has become generally accepted as first-line therapy in the field. Indications for PPVI have been set out in multispecialty guidelines, although issues related to functional assessment of pulmonary valve dysfunction remain, as do correlation with long-term outcomes. However, it appears that transcatheter pulmonary valve implantation will undergo further maturation and remain the primary therapeutic modality in pulmonary valve conduit dysfunction.

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INTRODUCTION

The MitraClip (Abbott Laboratories, Chicago, IL) device offers a novel, percutaneous, transvenous, transcatheter approach for patients suffering from severe mitral regurgitation, despite maximal medical therapy, in whom surgery is not an option. This chapter serves to describe mitral valve anatomy in the context of regurgitant pathology, provide a detailed description of the MitraClip procedure along with practical “pearls” to optimize deployment, and finally outline the current evidence base for MitraClip through a brief review of published literature.

MITRAL VALVE ANATOMY

The mitral valve apparatus is an elegantly complex structure that is comprised of the mitral valve leaflets, annulus, annular attachment at the atrioventricular junction, chordae tendineae, and the papillary muscles, all of
which work synchronously throughout the cardiac cycle to deliver blood to the left ventricle.

The valve itself is composed of the aortic and mural leaflets, more often clinically referred to as the anterior and posterior leaflet, respectively.\textsuperscript{1,2} The anterior leaflet of the mitral valve is broader than the posterior leaflet and comprises one-third of the annular circumference. This semicircular anterior leaflet shares a fibrous continuity with the left and noncoronary cusps of the aortic valve and between the aortic cusps adjacent to the membranous septum. This region of continuity is referred to as the intervalvular fibrosa or aortic-mitral curtain. The motion of the leaflet defines an important boundary between the inflow (during diastole) and outflow (during systole) tracts of the left ventricle. In contrast to the anterior leaflet, the posterior leaflet is narrower and extends two-thirds around the left atrioventricular junction within the inlet portion of the ventricle. The posterior leaflet is commonly described as having 2 clefts that separate the leaflet into 3 scallops along the free edge. The Carpentier nomenclature describes the most lateral scallop as P1, adjacent to the anterolateral commissure; the central scallop as P2; and the most medial as P3, adjacent to the posteromedial commissure.\textsuperscript{1,2} The anterior leaflet is divided into 3 regions, named A1, A2, and A3, which correspond to the opposing scallops of the posterior leaflet (Fig. 46-1). Often, the free edge of the anterior leaflet is continuous and without indentation, making the distinction between different regions of the anterior leaflet somewhat challenging.
The primary purpose of the MitraClip procedure is to perform a percutaneous edge-to-edge repair and effectively create a double mitral orifice, based on the original “Alfieri stitch” surgical approach. Accordingly, due to the central location within the valvular complex, A2 and P2 pathology generally provides the ideal anatomy for procedural success. Commissural regurgitant jets pose a technical challenge, due to difficulty delivering the clip and grasping tissue at the ends of the free edge of each leaflet.

The mitral annulus gives a point of attachment for the mitral valve and separates the left atrium from the left ventricle (LV). The anterior, or aortic, aspect of the annulus is fibrous and less prone to dilatation. The posterior aspect...
annulus is a dynamic, nonrigid, oval-shaped structure that alters shape throughout the cardiac cycle. The posterior, or mural, aspect of the annulus is muscular and therefore often subject to dilatation and calcification.

**MitraClip Implantation Pearl**

Following grasping, care must be taken to ensure that adequate tissue from both leaflets has been captured and there is not excessive tension placed on 1 or both leaflets that may lead to leaflet tear or, worse, clip detachment.

The chordae tendineae are fan-shaped chords that arise from the papillary muscles (PM) and insert into the mitral leaflets. The anterolateral and posteromedial PM arise from the mid to apical segments of the LV at the anterolateral and posterior walls, respectively. The posteromedial PM gives chords to the medial aspect of both leaflets (A3, P3, and half of A2 and P2), while the anterolateral PM chords attach to the lateral aspect of the leaflets (A1, P2, and half of A2 and P2).

**MitraClip Implantation Pearl**

Awareness of the chordal structures is important as the clip passes below the valve as entanglement may occur. This risk increases when additional clips are used, as these are passed through the mitral valve in a closed position and opened below the valve in the LV. Risk of chordal entanglement can be minimized by ensuring a coaxial advancement of the clip into the LV.

**PATHOPHYSIOLOGY**

Mitral regurgitation (MR) is the ejection of blood from the LV back into the left atrium during ventricular systole. This is due to failure of the leaflets to adequately coapt (close/seal) or appose (come together and overlap). There are numerous classification systems that describe the etiology of the
regurgitation, which has relevant implications for therapeutic intervention. One such classification divides the etiologies into either primary or functional, also known as secondary, MR (Fig. 46-2). Primary MR is a consequence of valvular pathology, while secondary MR is due to anatomic distortions or functional impairment of the LV. In primary MR, the standard treatment is repair or replacement of the affected valve. In functional MR, therapy involves management of the underlying LV dysfunction or attempted restoration of normal annular size and shape. For select patients in whom optimized medical therapy is unsuccessful, surgical or percutaneous intervention may be pursued.

**FIGURE 46-2** Primary mitral regurgitation (MR) versus functional MR. A. Normal mitral valve function. B. and C. Primary (degenerative) mitral regurgitation. D. Functional (secondary) mitral regurgitation.

**Primary Mitral Regurgitation**

The most prevalent etiology of primary MR is valvular degeneration that causes morphologic changes to the valve, including leaflet thickening and stretching of leaflet tissue. This accounts for approximately 60% of MR cases. The severity of these changes can be limited to focal involvement of 1 leaflet or can range to severe involvement of both leaflets in their entirety. For example, fibroelastic deficiency may account for the single, localized prolapsing segment, which is often normal in appearance. This prolapse is due to focal chordal elongation with or without rupture. Barlow disease, on the other hand, occurs in the setting of extensive myxomatous changes to both leaflets and is associated with chordal thinning and elongation.
Accordingly, segments of both leaflets prolapse into the left atrium. A more severe manifestation is a flail leaflet, characterized by complete eversion of the leaflet edge into the left atrium. A flail may be present in the event of primary chordal rupture and may result in severe mitral regurgitation.

**MitraClip Implantation Pearl**

Actions that may increase the success rate of adequate leaflet grasp include the following:

1. Control heart rate. The more bradycardic, the easier it is to time the clip positioning to ensure optimal grasp into the MitraClip arms.
2. MitraClip arm angle. Usually the clip arm angle is decreased to a 120° angle and pulled back in order to grasp the leaflets. Occasionally, a more obtuse angle may be needed to ensure adequate leaflet capture if the leaflet separation is too wide for capture.

Other less common causes of primary mitral valve disease include infective endocarditis, deep clefts, congenital mitral cleft, and rheumatic mitral disease. As a result of earlier and more effective treatments for rheumatic fever in the developed world, this disease process is decreasing in prevalence and accounts for approximately 12% of MR. This acquired valvulopathy often leads to commissural fusion of the leaflets and results primarily in mitral stenosis with associated regurgitation. Progressive inflammation leads to leaflet and chordal thickening. Over time, the leaflets may calcify and restrict leaflet motion, with subsequent malcoaptation during systole resulting in regurgitation.

**Secondary (Functional) Mitral Regurgitation**

Functional MR occurs in the context of morphologically normal leaflets and subvalvular apparatus, on a background of an underlying dilated cardiomyopathy or ischemic cardiomyopathy secondary to coronary artery disease. This accounts for approximately 25% of MR. The regurgitation is due to geometric perturbations of the LV, which may or may not be associated with dilatation. Regional or generalized wall motion abnormalities
of the LV can distort the position of the papillary PMs during systole, resulting in chordal tension and leaflet restriction. Ventricular dilatation causes subsequent annular dilatation, resulting in failure of leaflet coaptation or inadequate apposition.

**MitraClip Implantation Pearl**

There are currently no commercial indications for the MitraClip in secondary MR.

In functional MR, there are 2 important elements to consider during the MitraClip procedure.

1. Patients with severe LV dilatation will have a larger coaptation gap.
2. The zone of coaptation is lower in functional MR patients than in primary MR patients. Thus, the site of transseptal puncture must be slightly lower in the functional MR cohort.

**NATURAL HISTORY AND PROCEDURAL INDICATIONS FOR MITRAL REGURGITATION**

The clinical course of MR is usually indolent and progressive, except for the rare perimyocardial infarction complication of acute MR due to PM rupture. The posteromedial PM is more prone to rupture compared to the anterolateral PM due to single versus dual blood supply, respectively. The insidious nature of the disease in the majority of patients is a consequence of cardiac compensation for increasing regurgitant volume, initially through enlargement of the left atrium and by increasing LV systolic function as a measure to increase stroke volume and maintain cardiac output. As the valvular regurgitation progresses, the heart loses its ability to compensate for the increased regurgitant volumes and cannot maintain physiologic demands. The LV eventually dilates, with evidence of diastolic dysfunction, elevated pulmonary artery pressures, and ultimately systolic dysfunction, which may
progress to decompensated heart failure. The presence of LV dilatation and attenuated systolic function, particularly in the context of symptoms or functional impairment, heralds a very poor prognosis if left untreated. Annual mortality rates with optimal medical therapy in patients age 50 years or older are approximately 3% for moderate MR and approximately 6% for severe MR.\textsuperscript{4,5}

Until recently, surgical valve repair and replacement were the only treatments proven to improve symptoms and prevent heart failure. Current American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend surgical intervention in symptomatic patients with chronic severe primary MR and in asymptomatic patients with chronic severe primary MR with evidence of systolic dysfunction or LV dilatation.\textsuperscript{6,7} MV repair is the preferred method of surgical correction and has been shown to be superior to MV replacement in terms of morbidity and mortality.\textsuperscript{8-10} Mortality has been shown to decrease by approximately 70% in such patients. As expected, the best outcomes are obtained in asymptomatic patients treated in high-volume advanced repair centers with low operative mortality (<1%) and high repair rates (>80%). These results highlight the importance of early detection, assessment, and management of MR by experienced physicians and surgeons.

Patients with secondary MR carry higher preoperative mortality compared to their primary MR counterparts, attributable to severe comorbidities of the latter patient population.\textsuperscript{9,10} Accordingly, the ACC/AHA and ESC guidelines recommend surgery for patients with severe secondary MR and preserved systolic function only when undergoing coronary artery bypass grafting or aortic valve replacement.\textsuperscript{6,7}

Although surgery is the gold standard for treatment, there remains a cohort of patients who are either at prohibitively high risk for surgery or who may not benefit from a valve surgery, particularly those with functional MR. There is scant clinical evidence to demonstrate reduction in mortality following surgical repair in patients with systolic dysfunction and ventricular dilatation. Accordingly, treatment of such patients is debatable. The application of the MitraClip in such patients is the subject of an ongoing clinical trial.
THE MITRACLIP DEVICE

The complete device apparatus is composed of (1) a steerable guide handle attached to the steerable sleeve and the clip delivery system, (2) the clip, (3) the delivery catheter handle, and (4) the delivery catheter (Fig. 46-3).

![MitraClip device](image)

**FIGURE 46-3 MitraClip device.**

The MitraClip device is delivered using a 24-Fr catheter guide with a mobile steerable tip to precisely position the clip. The clip is a 4-mm wide and 8-mm long chrome-cobalt clip with 2 articulated arms that open from 0° (closed position) to 240° (open position), which facilitates grasping and drawing together the anterior and posterior leaflets. The inner parts of the clip’s arms are grippers, lined with small frictional elements that promote more effective grasping of the leaflets once the device has been deployed and is ultimately closed. The outer aspect of the clip is covered in a polyester mesh to promote epithelialization and tissue growth to facilitate a fibrous tissue bridge between the leaflets (Fig. 46-4). The clip delivery system has 2 knobs that control the anterior-posterior and medial-lateral steering of the catheter tip. The delivery catheter handle is composed of: (1) 2 levers to lock/unlock the clip and to lift/depress the gripper lines, respectively; (2) a knob to facilitate the opening and closing of the clips; and (3) a screw to enable release of the clip from the shaft of the delivery catheter.
Procedure

The MitraClip procedure is performed under general anesthesia, primarily to enable pauses in ventilation, which facilitates precise clip positioning and deployment. The additional advantage of general anesthesia is comfort to the patient, particularly in the context of a potentially lengthy procedure (which is contingent on operator experience and valvular anatomy) as well as extended periods of transesophageal echocardiography (TEE) evaluation.

One of the key advantages of the MitraClip procedure is that it is performed via venous access. It is recommended to use a micropuncture needle for veinotomy, in order to minimize vascular complications and ensure optimal sheath placement. Two sites of venous access are required. The first site is the jugular or femoral vein for right heart catheterization at the commencement of the procedure and immediately following release of the clip, which provides some indication of the efficacy of the intervention. A second venous sheath is placed in the femoral vein for eventual passage of the 24-Fr MitraClip apparatus. A Perclose ProGlide suture can be placed in a “pre-close” fashion to achieve hemostasis at the conclusion of the case. Alternatively, a figure of 8 suture can be applied at the end of the case to provide local external hemostasis.
MitraClip Implantation Pearl

As opposed to arterial closure, deployment of the Perclose suture may be performed with much less tension on the sutures and still result in adequate venous stasis. Avoidance of overtightening may decrease risk of venous stenosis.

Cardiac imaging with visualization of the interatrial septum (IAS) and the mitral valve apparatus is vital to the success of the MitraClip procedure. Operators should be able to obtain and interpret echocardiographic views to guide transseptal puncture, device positioning, and clip deployment. Furthermore, operators should be aware of the parameters used to assess the success of clip deployment based on echocardiographic interrogation, including but not limited to an immediate decrease in 2-dimensional color Doppler regurgitant jet, decrease in proximal isovelocity surface area, reduction in regurgitant volume, and improvement of pulmonary venous flow. Repeat hemodynamic assessment should demonstrate improvement of pulmonary pressures with decrease of V wave and reduction in left atrial pressure. At our institution, TEE is performed by a cardiac anesthesiologist or cardiologist experienced in MitraClip procedures, with an understanding of the expectations and requirements of the operator. Effective communication between the echocardiogram operator and the interventional cardiologist is imperative to facilitate an efficient and effective procedure.

MitraClip Implantation Pearl

Periprocedural planning is imperative to the success of the MitraClip deployment. A multidisciplinary heart team approach is recommended to confirm the etiology of the MR, assess for presence of significant baseline stenosis, and determine the most effective site of clip placement to ensure resolution of the regurgitation.

Arguably, the transseptal puncture is the most critical step of the procedure. If the puncture is inaccurate, subsequent device maneuverability
and clip positioning are made difficult, often resulting in failed or, at best, unsatisfactory clip deployment position reflected by minimal or no improvement in MR. Furthermore, poor clip position may actually worsen the degree of MR or create a mitral stenosis gradient. Accordingly, great care must be taken to ensure precise transseptal puncture, repeating the process if necessary to ensure an optimal starting position. The transseptal puncture is performed under both fluoroscopic and TEE guidance using standard equipment and technique.

To perform transseptal puncture, simultaneous viewing of a short-axis biatrial image for anteroposterior positioning and a bicaval image for superoinferior positioning is recommended. The optimal site for puncture is located slightly inferior and posterior on the septum (Fig. 46-5). Once this position is located, obtain a 0°, midesophageal, 4-chamber view to measure the “device distance,” defined as the distance of the septal puncture from the mitral annulus. Ideally, this distance should be 4.0 to 4.5 cm above the mitral annulus as measured perpendicular to the plane of mitral valve coaptation during systole (Fig. 46-6).

**FIGURE 46-5** Transseptal puncture.
MitraClip Implantation Pearl

Transseptal puncture may be facilitated by placing a bend on the BRK needle. With left atrial enlargement, a BRK-1 needle should be considered. If difficulty is encountered puncturing the septum, such as in the case in a thickened or fibrotic septum, focal cautery orization of the septum may be used to facilitate entry.

Once the needle is across the septum, the entire system is advanced into the left atrium and heparin is administered for anticoagulation with a target activated clotting time of >250 seconds. The 24-Fr Abbott MitraClip delivery steerable system is then advanced over a superstiff wire into the left atrium. The superstiff wire is then removed and the baseline left atrial pressure recorded. Next, the MitraClip device is carefully advanced into the left atrium through the device deployment sheath under fluoroscopy and TEE guidance. From the plane of entry into the left atrium, parallel to the mitral annulus, the clip delivery system should first be steered toward the valve using the
medial-lateral steering knob to turn the device 90°. By turning the guide clockwise, the clip is aligned perpendicular to the annulus. Once the device reaches just above the leaflets, an assessment of the position of the clip in a mediolateral and anteroposterior plane is made, using bicommissural (midesophageal view, approximately 50-75°) and LV outflow tract (midesophageal, approximately 115-145°) echocardiographic views, respectively (Fig. 46-7).

FIGURE 46-7 Bicommissural and left ventricular outflow tract views.

The trajectory of the clip is optimized by moving the delivery catheter handle up and down while assessing the direction of the delivery shaft. Adjustments in the medial or lateral direction are made in the bicommissural view either by moving the entire system or by adjusting the M knob. Adjustments in the anterior or posterior direction are made in the LVOT view by rotating the guide handle counterclockwise or clockwise, respectively. Once an ideal position is achieved, the clip is opened to 180°, and a 3-dimensional enface “surgeon’s view” of the mitral valve is obtained to assess for orientation of the clip arms relative to the leaflets (Fig. 46-8). Any adjustments are made by rotating the delivery catheter handle in the desired direction and then transmitting the torque by moving the handle up and down.
rapidly. Once the clip is perpendicular to the leaflets, the clip is advanced in the open position through the valve. The orientation of the clip is then reconfirmed, followed by closure of the clip to 120°. Next, the delivery catheter handle is retracted slowly to grasp both leaflets into the semi-opened clip. Once leaflet capture is confirmed, the grippers are pushed down, and the clip is completely closed. TEE interrogation is then performed in multiple views to ensure leaflet capture with adequate tissue grasp, reduction in MR (assessed by regurgitant volume, size of MR proximal isovelocity surface area, and pulmonary vein Doppler), and absence of a significant stenosis gradient (Fig. 46-9). If these procedural goals have been met, the clip is released. If these goals are not met, and significant MR persists without significant stenotic gradient (<6 mm Hg), the clip can be opened and repositioned or additional clips can be positioned and deployed. These are deployed in the previously described manner with 1 key difference: subsequent clips are passed through the valve in a closed position "then opened below" the valve in the ventricle. Placement of additional clips carries a risk of worsening MR due to deformation of the leaflets, clip interaction with potential instability, and/or significant stenosis. An inherent advantage of the MitraClip device is the ability to remove a clip following closure and subsequent assessment. If the operator is dissatisfied with the result of an additional clip, this can simply be opened, detached from the leaflet, brought back into the guide, and removed from the body.

**FIGURE 46-8** A. Checking orientation in 3-dimensional (3D) enface view. B. Correcting orientation in 3D enface view.
FIGURE 46-9 Predeployment check. A. Leaflet insertion. B. Reduction in regurgitation (i) preprocedure and (ii) postprocedure. C. Pulmonary vein assessment (i) preprocedure and (ii) postprocedure. D. Mitral stenosis (i) preprocedure and (ii) postprocedure.

**MitraClip Implantation Pearl**

It is technically more challenging to place multiple clips. Due to a lack of adequate clearance between the septum and the valve plane, if there is any expectation or consideration for multiple clips, it may be helpful to place the first clip in the more medial position with all subsequent clips placed laterally.

The MitraClip procedure is generally safe and well tolerated. Aside from the risks associated with general anesthesia, those specific to the procedure
include femoral venous complications; transseptal trauma resulting in an atrial septal defect (significant shunts may require closure) or left atrial perforation (care must be taken to manipulate the guide catheter away from the posterior wall of the left atrium prior to removal); clip detachment and embolization (clip stability must be assessed fluoroscopically and via echocardiography prior to final release of the clip); and endocarditis. The overall rate of such adverse events in experienced centers is less than 1%.

**CLINICAL OUTCOMES FOR THE MITRACLIP**

Table 46-1 summarizes the relevant clinical studies. Procedural success was achieved in the majority of patients with reduction of MR from 4+ to <2+ in all of the listed studies. Additionally, these results were attained with an excellent safety profile without significant rates of adverse procedural outcomes.

Table 46-1 *Summary of Relevant Clinical Studies Involving the MitraClip Procedure*

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Etiology of MR</th>
<th>Age, years</th>
<th>STS Score</th>
<th>EuroScore</th>
<th>MR ≤2+, %</th>
<th>30-Day Mortality, %</th>
<th>1-Year Mortality, %</th>
<th>MR ≥3+ at 1 Year, %</th>
<th>Need for Surgery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franzén et al11</td>
<td>51</td>
<td>DMR 31% FMR 69%</td>
<td>73 ± 10</td>
<td>15 ± 11</td>
<td>29 ± 22</td>
<td>94</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tamburino et al12</td>
<td>31</td>
<td>DMR 42% FMR 58%</td>
<td>71 (62-70)</td>
<td>10 ± 9</td>
<td>14 ± 12</td>
<td>97</td>
<td>3.2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PERMIT-CARE13</td>
<td>51</td>
<td>FMR</td>
<td>70 ± 9</td>
<td>14 ± 14</td>
<td>30 ± 19</td>
<td>82</td>
<td>4.2</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rudolph et al14</td>
<td>104</td>
<td>DMR 34% FMR 66%</td>
<td>74 ± 9</td>
<td>NA</td>
<td>36 (21-54)</td>
<td>94</td>
<td>3.8</td>
<td>25</td>
<td>18</td>
<td>6.7</td>
</tr>
<tr>
<td>TRAMI*</td>
<td>470</td>
<td>DMR 33% FMR 67%</td>
<td>75 ± 5</td>
<td>11 (4-19)</td>
<td>23 (12-38)</td>
<td>94</td>
<td>2.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EVEREST I*15</td>
<td>107</td>
<td>DMR 79% FMR 21%</td>
<td>71 (26-80)</td>
<td>NA</td>
<td>NA</td>
<td>74</td>
<td>0.9</td>
<td>4.1</td>
<td>NA</td>
<td>29.9</td>
</tr>
<tr>
<td>EVEREST High-Risk Registry</td>
<td>78</td>
<td>DMR 41% FMR 59%</td>
<td>77 ± 10</td>
<td>14 ± 8</td>
<td>NA</td>
<td>80</td>
<td>7.7</td>
<td>24.4</td>
<td>20</td>
<td>0</td>
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<tr>
<td>ACCESS-EUROPE15</td>
<td>567</td>
<td>DMR 23% FMR 77%</td>
<td>74 ± 10</td>
<td>NA</td>
<td>NA</td>
<td>79</td>
<td>3.4</td>
<td>17.3</td>
<td>21</td>
<td>6.3</td>
</tr>
<tr>
<td>EVEREST II*</td>
<td>385</td>
<td>DMR 74% FMR 26%</td>
<td>67 ± 13</td>
<td>5 ± 4</td>
<td>NA</td>
<td>78</td>
<td>1</td>
<td>6</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>EVEREST II/REALISM High-Risk Registry*</td>
<td>351</td>
<td>DMR 30% FMR 70%</td>
<td>76 ± 11</td>
<td>11.3 ± 7.7</td>
<td>NA</td>
<td>86</td>
<td>4.8</td>
<td>22.8</td>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td>COAPT (enrolling)</td>
<td>430</td>
<td>FMR</td>
<td></td>
<td></td>
<td></td>
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Abbreviations: DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MR, mitral regurgitation; NA, not applicable; STS, Society of Thoracic Surgeons.

The EVEREST trial16 early cohort investigated the MitraClip, and 1-year clinical outcomes were published in 2009. This was a prospective, multicenter study evaluating the feasibility, safety, and efficacy of MitraClip in patients with moderate-to-severe (3+) or severe (4+) MR with a class I
surgical indication. In total, 107 patients were enrolled, which included 55 from the EVEREST I cohort and 52 from the prerandomization phase of EVEREST II, with a mean follow-up of nearly 2 years. This very early experience demonstrated the feasibility and safety of the MitraClip device. There was a very low periprocedural complication rate, with 30-day and 1-year mortality rates of 0.9% and 4.1%, respectively. In addition, this study demonstrated a meaningful reduction of MR in up to two-thirds of a carefully selected group of patients.

The subsequent landmark study was EVEREST II in 2012. This was a multicenter randomized clinical trial designed to compare the efficacy and safety of percutaneous treatment with MitraClip as compared to conventional surgical MV repair or replacement. From a total of 279 patients, ultimately 170 were assigned to the MitraClip group and 80 to the control group. Compared to surgery, the MitraClip had a lower 30-day complication rate. At 1 year of follow-up, surgery was more effective in reduction of MR, but there was equivalent improvement of symptoms, functional class, and favorable LV remodeling in both groups. Furthermore, these symptomatic improvements were sustained after 4 years, as evidenced by persistent reductions in New York Heart Association (NYHA) functional class. The 4-year follow-up results reported no mortality difference between the MitraClip and surgical cohorts, a low rate of subsequent MV surgery in the MitraClip repaired group beyond the first 6 months of therapy, and a low rate of adverse events from 1 to 4 years in both groups.

The EVEREST II High-Risk Registry (HRR) was a substudy from the EVEREST II cohort that included patients with moderate-severe or severe MR with an estimated surgical risk of 12% or greater, based on the Society of Thoracic Surgeons risk score or as estimated by the surgical team. Enrollment of patients has continued as part of the REALISM Registry, which has 2 arms: high-risk patients and non–high-risk patients. The combined REALISM and EVEREST II HRR demonstrated an impressive 30-day mortality of less than 5% with significant improvement in patient-reported symptoms, reduced rate of hospitalization, and improved LV remodeling at 1 year. These trials also support that after the learning curve is overcome with more procedural experience, better outcomes are to be expected as compared to the statistics reported in the initial trials.

Based on the outcomes from EVEREST II, the AHA/ACC guidelines state
that the MitraClip intervention should only be considered for high-risk or nonoperable patients with chronic primary MR who remain severely symptomatic with NYHA class III to IV heart failure symptoms despite optimal heart failure therapy. Similarly, the ESC guidelines recommend that MitraClip may be considered in patients with symptomatic severe primary MR who fulfill the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by a heart team, and have a life expectancy greater than 1 year. Uniquely, however, based on experience from the EVEREST trials and observational studies, ESC guidelines suggest that MitraClip is feasible at low procedural risk in patients with secondary MR in the absence of severe tethering and may provide short-term improvement in functional condition and LV function. In 2013, the ACCESS-EU trial supported this recommendation as this patient cohort was comprised of a predominantly functional MR “real-world” population, yet had favorable results showing the effectiveness and safety of the procedure. While the AHA/ACC guidelines acknowledge that MitraClip provides a safe, less invasive, effective alternative to surgery, the procedure is not yet approved for clinical use for secondary MR in the United States.

The currently enrolling COAPT trial is a randomized, parallel-controlled, multicenter clinical evaluation of the MitraClip device for the treatment of clinically significant secondary (functional) MR in symptomatic heart failure subjects who are treated per standard of care with optimal medical therapy but have been deemed ineligible for MV surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device or to no MitraClip device (control group). The primary outcome measures include the primary safety end point (composite of single leaflet device attachment, device embolizations, endocarditis requiring surgery, mitral stenosis requiring surgery, and any device-related complications requiring nonelective cardiovascular surgery) and the primary effectiveness end point (recurrent heart failure hospitalizations). The conclusion and results of this investigation are eagerly anticipated and will likely frame the guidelines for the safety and efficacy of MitraClip in patients with functional MR.

**CONCLUSION**

The mitral valve apparatus is a complex anatomic structure with numerous
components that must work in concert for the valve to function. The most common cause of MR is primary MR, which has traditionally been remedied with surgical valve repair or replacement. Recently, the MitraClip device has emerged as a safe and effective alternative approach to treat high-risk patients with severe MR with proven durability and clinical improvement. The excellent safety profile for the procedure can be attributed to 2 key elements. First, this percutaneous repair is completed via transvenous access, which limits the significance of vascular complications compared to an open surgical approach. Second, the transseptal approach is a far less invasive method of accessing the mitral valve compared to surgical access via the left atrium whether by sternotomy or with minimally invasive or robotic surgery. In the United States, current US Food and Drug Administration approval for the MitraClip device is only for treatment of high-risk, nonoperable patients with primary MR. The currently enrolling randomized COAPT study is expected to address the additional information of the safety and utility of this device in the setting of secondary, or functional, MR compared with medical therapy alone. Short- and intermediate-term follow-up have further supported the use of the MitraClip as a safe minimally invasive therapy for severe MR, but additional investigations must be pursued to evaluate the long-term risks and benefits of this intervention.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. Which of the following is NOT a characteristic of the anterior leaflet?
   A. It is broader than the posterior leaflet.
   B. It is also known as the mural leaflet.
   C. It comprises one-third of the annular circumference.
   D. It shares a fibrous continuity with the left and noncoronary cusps of the aortic valve.

2. The MitraClip is based off of what surgical technique?
   A. Mitral valve annuloplasty
   B. David’s technique
C. Feikes technique  
D. Alfieri stitch

3. How can you minimize risk of chordal entanglement with the MitraClip?  
A. By using multiple clips  
B. By making the majority of positioning adjustments after the clip is advanced into the ventricle  
C. By making the majority of positioning adjustments when the clip is within the valve leaflets  
D. By ensuring coaxial advancement of the clip prior to moving into the left ventricle

4. Which of the following statements is true regarding strategies to minimize complications with transseptal puncture?  
A. Adjunctive imaging techniques rarely provide additional information or utility compared to fluoroscopy alone.  
B. After transseptal puncture, slight counterclockwise rotation of the transseptal needle may be helpful to avoid puncturing the posterior wall of the left atrium (LA).  
C. After transseptal puncture, slight counterclockwise rotation of the transseptal needle may be helpful to avoid puncturing the aorta.  
D. The optimal site for puncture is located anterior and superior on the septum.

5. Which of the following conclusions about the EVEREST II trial are correct?  
A. There was a lower 30-day complication rate compared to surgery.  
B. At 1 year, surgery was more effective in reducing mitral regurgitation with no clinical differences in terms of symptoms, functional class, and LV remodeling.  
C. Four-year follow-up showed no mortality difference between MitraClip and surgery.  
D. A and B  
E. B and C  
F. A and C  
G. All of the above
ANSWERS

1. B

The valve is also known as the aortic leaflets, which share a continuity with the aortic valve (left and noncoronary cusps) that is often referred to the intervalvular fibrosa or aortic-mitral curtain. All the other answers are characteristics of the anterior leaflet.

2. D

The Alfieri stitch is an edge-to-edge repair/plication. Percutaneous mitral annuloplasties are currently under investigation but use a different technique for valvular intervention. David’s technique is a surgical technique that preserves the anterior leaflets and its chordal attachments by excising a central trapezoidal segment of the anterior leaflet and resuspending the residual leaflet to the anterior annulus. In the Feikes technique, the anterior leaflet is incised in the midline and the incision is extended sideways, then the 2 segments of the anterior leaflet are turned backward and sutured to the posterior mitral annulus.

3. D

Multiple clips and positional changes when in the left ventricle (LV) increase the risk of entanglement. The manipulation of the valve at the level of the valve does not increase entanglement into the chords; however, it is not advisable. The best way to minimize risk of entanglement is to perform the majority of the positioning adjustments when the clip is in atria, prior to inserting into the LV. Minor changes and fine adjustments can be made in the ventricle with caution and visualization on transesophageal echocardiography (TEE) and fluoroscopy to ensure the clip does not tangle.

4. B

TEE is essential to the MitraClip procedure; without it, the procedure would not be possible. TEE accurately and reliably identifies the inferior-posterior location that is usually the optimal site of puncture. B is correct; slight counterclockwise rotation of the transseptal needle may be helpful to avoid
puncturing the posterior wall of the LA. Clockwise rotation is needed if the needle is pointed toward the aorta.

5. G

All of the above are true statements.
Percutaneous Left Atrial Appendage Closure

Jacqueline Saw
Maurice Buchbinder

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults with a current prevalence estimated at 1.5% to 2% of the general population. With the aging population in the United States, AF prevalence is projected to increase steadily from approximately 6 million cases in 2010 to 15.9 million by 2050. AF is a major cause of stroke, being responsible for 15% of all strokes and 30% of strokes in patients over age 80. Unfortunately, stroke is the leading cause of long-term disability and the fourth leading cause of death in the United States. The presence of AF is associated with a 4- to 5-fold risk of ischemic stroke, and the incidence increases significantly with advancing age. Moreover, strokes associated with AF are more severe; AF-related stroke victims have a 50% greater likelihood of becoming disabled or handicapped and a >50% likelihood of death. Accordingly, stroke prevention with anticoagulation is one of the main pillars of AF management, and guidelines for anticoagulation have become more stringent recently. The Canadian Cardiovascular Society had lowered their threshold for recommending oral anticoagulation (OAC) for CHADS\textsubscript{2} (congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke) score $\geq$1, the
European Society of Cardiology (ESC) for CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category) score $\geq$1, and the American College of Cardiology (ACC) for CHA$_2$DS$_2$-VASc score $\geq$2.$^{1,8-10}$

**Anticoagulation for AF and Limitations**

Several randomized placebo-controlled trials have demonstrated that OAC is highly effective in preventing thromboembolism with AF, and landmark meta-analysis with warfarin demonstrated a 64% relative stroke reduction and 26% relative mortality reduction.$^{11,12}$ Although OAC is the current gold standard for AF stroke prevention, a significant proportion (30%-50%) of eligible patients do not receive therapy due to absolute contraindications or perceived risks of bleeding.$^{13,14}$ Furthermore, OAC increases the incidence of major bleeding despite the use of novel OAC (NOAC); a recent meta-analysis of all 4 NOAC trials showed major bleeding rates of 6.2% with warfarin and 5.3% with NOAC.$^{15}$ Even though the risk of intracranial hemorrhage is consistently lower with NOAC, overall major bleeding is not diminished with dabigatran or rivaroxaban compared with warfarin.$^{16,17}$ Apixaban and edoxaban were the only 2 agents that lowered major bleeding compared to warfarin.$^{18,19}$

There are also other concerns with OAC therapy, including patients with renal and liver dysfunction (excluding use with NOAC), high risk of falls, noncompliance, and patients requiring dual antiplatelet therapy after stent placement. For warfarin, there are additional issues with drug and diet interaction, the need for anticoagulation monitoring, and narrow therapeutic window, with time in therapeutic range of only 50% to 60% in community practices.$^{20,21}$ There are also high discontinuation rates with OAC even in the setting of clinical trials, with discontinuation rates of 16% to 34% for warfarin and 21% to 37% with NOAC at the end of study follow-up.$^{16-19}$

Therefore, even though OAC is effective for thromboembolic prevention, there remains a large proportion of eligible patients not on therapy for a multitude of reasons. Moreover, there is a residual stroke risk of 2% to 5% annually despite optimal OAC.$^{22}$ These challenges have led to the investigations of device-based therapies for nonvalvular AF. In fact, the ESC
recently gave a Class IIB recommendation for percutaneous left atrial appendage (LAA) closure for patients with high stroke risk and contraindications to long-term OAC.\textsuperscript{9}

**Rationale for LAA Occlusion**

In the presence of AF, the left atrium loses active contraction, leading to decreased blood velocity in the LAA, which results in stasis and increased risk of thrombus formation.\textsuperscript{23} Abnormalities in the thrombosis cascade in overloaded LAA may additionally increase the risk of thrombus formation with AF.\textsuperscript{24} Transesophageal echocardiography (TEE), autopsy, and surgical reports confirmed that >90% of nonrheumatic AF-related left atrial thrombi were isolated to or originated from the LAA.\textsuperscript{25} Atrial thrombi are detected on TEE in approximately 15% of AF patients not receiving long-term OAC.\textsuperscript{26} The presence of LA thrombus, spontaneous echo contrast, and low LAA velocities (≤20 cm/s) are independent predictors of stroke and thromboembolism on TEE.\textsuperscript{27-29} Thus, local mechanical approaches to exclude the LAA from systemic circulation to limit embolization in nonvalvular AF patients have been developed. Early attempts of surgical removal or ligation of LAA developed over 60 years ago were limited by the invasiveness of major cardiac surgery and by significant rates of incomplete exclusion that were associated with increased risks (~2.5-fold) of stroke.\textsuperscript{30,31} Minimally invasive percutaneous approaches have since been developed over the past 2 decades and can be broadly divided into endocardial and epicardial devices (Table 47-1). This chapter reviews contemporary percutaneous LAA closure, with in-depth discussions of the available leading devices with regard to procedural techniques and clinical outcomes.

<table>
<thead>
<tr>
<th>Table 47-1 Left Atrial Appendage (LAA) Closure Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Name</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Endocardial Devices</strong></td>
</tr>
<tr>
<td>PLAATO</td>
</tr>
<tr>
<td>WATCHMAN</td>
</tr>
<tr>
<td>ACP</td>
</tr>
<tr>
<td>Amulet</td>
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<tr>
<td>WaveCrest</td>
</tr>
<tr>
<td>Occlutech LAA Occluder</td>
</tr>
<tr>
<td>Sideris Transcatheter Patch</td>
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<tr>
<td>LAmble</td>
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<tr>
<td>Pfm</td>
</tr>
<tr>
<td>Cardia</td>
</tr>
<tr>
<td><strong>Epicardial Devices</strong></td>
</tr>
<tr>
<td>LARIAT</td>
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<tr>
<td>AtriClip</td>
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<tr>
<td>AEGIS</td>
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<td>Cardioblate Closure System</td>
</tr>
</tbody>
</table>

Abbreviations: CE, Conformité Européene; ePTFE, expanded polytetrafluoroethylene; FDA, US Food and Drug Administration; PET, polyethylene terephthalate.

**INDICATIONS FOR PERCUTANEOUS LAA CLOSURE**
The current most commonly adopted indication for percutaneous LAA closure is for patients ineligible for long-term OAC, although this practice varies geographically. In Europe, the majority of LAA closures are done according to the ESC recommendation for patients with high stroke risk and contraindications to long-term OAC. However, there are high-volume centers (eg, in Switzerland and Germany) where LAA closures may be performed for anticoagulation-eligible patients, and this is likely related to the full reimbursement of this procedure in these countries. In Canada, LAA closure is generally restricted to patients with high stroke risk and contraindications to long-term OAC. In the United States, LARIAT (SentreHEART, Redwood City, CA) and WATCHMAN [Boston Scientific, Natick, MA] received approval by the US Food and Drug Administration [FDA]) and may be performed for patients with high stroke risk with or without contraindications to OAC.

**CURRENTLY AVAILABLE DEVICES FOR PERCUTANEOUS LAA OCCLUSION**

**WATCHMAN**

The WATCHMAN device was the second dedicated LAA device manufactured after PLAATO (Appriva Medical, Sunnyvale, CA), which was the first device manufactured but was subsequently removed from the market for commercial reasons. WATCHMAN was originally designed and manufactured by Atritech (Plymouth, MN) and was acquired by Boston Scientific in 2011. The current second-generation WATCHMAN LAA Closure Technology is constructed of a self-expanding nitinol frame covered by a permeable 160-μm polyethylene terephthalate (PET) membrane (Fig. 47-1). There are 10 fixation anchors at the perimeter of the nitinol frame that are designed to engage the LAA tissue for device stability. The PET membrane covers approximately 50% of the proximal outer aspect of the nitinol frame, which blocks thrombus embolization from the LAA and promotes endothelialization. The spherical contour of WATCHMAN can
accommodate most LAA anatomy. There are 5 device sizes available (21, 24, 27, 30, and 33 mm), and all are delivered through dedicated 14-Fr sheaths (double curve, single curve, and anterior curve). The fourth-generation device was evaluated in a European registry, and the fifth-generation (WATCHMAN-FLEX) device is awaiting first-in-man evaluation. The WATCHMAN received Conformité Européene (CE) mark in 2005 and FDA approval in March 2015. To date, >10,000 WATCHMAN devices have been implanted worldwide.
FIGURE 47-1 A. The WATCHMAN device. B. The double-curve and single-curve 14-Fr access sheaths. There are 3 radiopaque marker bands (33, 27, and 21 mm) on the distal sheath, which should be aligned to the left atrial appendage (LAA) “ostium” according to the size of the device used.

Amplatzer Cardiac Plug and Amulet

The Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Plymouth, MN) is the third dedicated LAA device to be manufactured and is specifically designed to occlude the proximal segment of the LAA. In Europe, operators initially used nondedicated Amplatzer devices for LAA closures in a small series of patients. However, the incidence of embolization was high (12% in the 32-patient series in Bern), and these nondedicated devices are no longer used for this indication.

This device consists of a self-expanding nitinol mesh, which forms a lobe and a disc connected by a central articulating waist (Fig. 47-2). The lobe is intended to be implanted at 10 mm inside the orifice (proximal neck of LAA) and, along with the 6 pairs of stabilizing wires at the distal lobe, serves as the key anchoring mechanism. The disc is intended to be deployed in the left atrium and pulled in under traction against the LAA orifice by the central waist, which helps seal the orifice. Both the lobe and disc have polyester mesh sewn in manually. The ACP comes in 8 different sizes according to the lobe dimension accommodating LAA diameters of 12.6 to 28.5 mm (Fig. 47-3). The second-generation ACP device, Amulet, is similar in design but has a wider lobe, longer waist, recessed proximal end screw, and more stabilizing wires. These features improve device stability and may theoretically reduce the risk of thrombus formation on the atrial side of the device. Amulet comes in 8 different sizes and can accommodate larger LAA (up to 32 mm diameter). The ACP device has to be manually loaded onto the delivery cable, but Amulet comes preloaded on the delivery cable for ease of setup. ACP/Amulet is delivered through the TorqueVue 45 × 45 sheath (see Fig. 47-2), which has a 3-dimensional distal tip allowing anterior and superior angulation for coaxial positioning at the landing zone. The TVLA1 and TVLA2 sheaths are no longer being manufactured. The access sheath size varies according to device size (see Fig. 47-3).
FIGURE 47-2 Amplatzer Cardiac Plug device showing the 2 key components of the lobe and disc and the recommended TorqueVue 45 × 45 sheath.

FIGURE 47-3 Device characteristics of Amplatzer Cardiac Plug (left) and Amulet (right).
The ACP received CE mark approval in December 2008, and the Amulet was approved in January 2013. The delivery system of Amulet has been redesigned, and the updated system will be relaunched in the latter half of 2014. To date, >10,000 ACP/Amulet devices have been implanted worldwide.

**LARIAT**

The LARIAT LAA closure system requires both an endocardial and epicardial approach for implantation. LARIAT has FDA and CE mark approvals for suture and knot tying during surgical applications but is not approved specifically for stroke reduction with AF. There was a prior surge in interest and procedural volume in the United States before the approval of WATCHMAN, due to the availability of this device for patients who were not candidates for anticoagulation. LARIAT consists of a snare with a pretied suture that is magnetically guided over the LAA in the epicardium. The device consists of 3 components: (1) 15-mm compliant occlusion balloon catheter (EndoCATH), (2) 0.025- and 0.035-inch magnet-tipped guide wires (FindrWIRZ), and (3) 12-Fr LARIAT suture delivery device.\(^{34}\)

**WaveCrest**

The WaveCrest occluder by Coherex Medical (Salt Lake City, UT) is made of a nitinol frame with retractable anchors to enable optimal device positioning. The occluder is covered by a polytetrafluoroethylene (PTFE) membrane on the left atrial side of the device and a foam substrate on the inside surface to minimize peridevice leak. In contrast to other devices, the anchoring system can be operated independently of the lobe, allowing repositioning before anchoring. Contrast can be injected through the delivery sheath or on the appendage side of the occluder to evaluate occlusion. It comes in 3 sizes (22, 27, and 32 mm) and can be implanted through 4 different 15-Fr delivery sheaths. The device was first implanted in June 2012, and CE mark was obtained in 2013.

**IMPLANTATION TECHNIQUES FOR**
WATCHMAN, ACP/AMULET, AND WAVECREST

**Preprocedural Imaging**

Baseline TEE is important to exclude preexisting LAA thrombus and to assess LAA anatomy for device closure suitability. A full 0° to 180° sweep of the LAA is useful to appreciate the anatomy and for accurate widest and deepest dimension measurements. For WATCHMAN, the widest LAA ostium (from the level of the circumflex artery to ~2 cm within the pulmonary vein ridge) is measured at 0°, 45°, 90°, and 135°, and the available depth (from ostium to apex of LAA) is also measured at the same angles (Fig. 47-4). For ACP, measurements at both the short-axis (30-60°) and long-axis (120-150°) angles of the landing zone and orifice are performed. The LAA orifice for ACP/Amulet is measured from the pulmonary vein ridge to the circumflex artery. The landing zone is measured at 10 mm inside the orifice for ACP (~13-18 mm for Amulet), at an angle that is perpendicular to the neck axis. The LAA depth is measured from the orifice to the back wall along the axis of the neck. The LAA measurements are usually wider at the long axis (corresponding to caudal projection on fluoroscopy) compared to the short axis (corresponding to right anterior oblique [RAO] cranial).
Preprocedural cardiac computed tomography angiography (CCTA) is also useful given its superior spatial resolution and 3-dimensionality as a noninvasive alternative to or in addition to TEE. CCTA has excellent sensitivity for ruling out LAA thrombus. Although the specificity and negative predictive value for LAA thrombus have traditionally been suboptimal with CCTA due to difficulty differentiating thrombus from inadequate contrast mixing (eg, spontaneous echo contrast), additional protocols using double contrast injections, delayed imaging, dual energy, and prone positioning have optimized the results.\textsuperscript{35} CCTA also offers superior anatomic visualization and measurements of the LAA compared to TEE. Patients do not need to be fasting prior to CCTA; furthermore, saline infusion is typically administered before scans, providing more accurate measurements at euvoletic states. Thus, CCTA may become a preferred alternative to TEE in experienced CCTA centers and is increasingly being used.
performed routinely prior to LAA closures.

**Procedural Imaging**

Procedural TEE is the routine standard in the majority of centers and is typically accompanied by general anesthesia. There are a few centers adept at procedural intracardiac echocardiography (ICE) to guide LAA closure, obviating the need for general anesthesia. However, obtaining adequate ICE LAA images can be challenging, and proceduralists may overcome this problem by advancing the ICE probe into the left atrium through another transseptal puncture. Although a few centers rely on fluoroscopy alone during LAA closure, this is not advised for the average operator.

**Transseptal Puncture**

Venous access is preferred through the right femoral vein for more direct transseptal access. Access site subcutaneous tissues should be well prepared and separated with scalpel and forceps to ease advancement of large 13- to 14-Fr sheaths. Manual compression, “figure-of-8” suture, and preclosing with 6-Fr Perclose (Abbott Vascular, Chicago, IL) are commonly used for venous hemostasis.

The preferred location for transseptal puncture is inferior and posterior at the fossa ovalis for all endocardial LAA devices. This position is gauged well with the bicaval and short-axis TEE view, respectively. ICE is a good alternative to guide transseptal puncture. It is generally advised not to use a patent foramen ovale as the access, but instead to perform a separate transseptal puncture inferoposteriorly to provide more direct vector orientation to access the LAA, which arises anteriorly and superiorly. Intravenous heparin is administered before or immediately following transseptal puncture to maintain an activated clotting time (ACT) >250 seconds. Adequate mean left atrial pressure (10-15 mm Hg) should be attained with fluid bolus for accurate LAA measurements.

**Fluoroscopic LAA Measurements**

Following transseptal access, a 5-Fr marker pigtail may be advanced into the LAA and cineangiograms taken in multiple projections to ascertain the LAA
anatomy and measurements. RAO caudal projections usually provide better visualization of the mid-distal LAA for WATCHMAN, whereas RAO cranial projections better visualize the ostium and proximal LAA for ACP/Amulet. Multiple angiographic views are often taken and can be predicted by baseline CCTA for angle selection. For WATCHMAN, it is common to start with RAO (20-30°) caudal (20-30°), posteroanterior (PA) caudal (20-30°), and RAO (20-30°) cranial (10-20°) projections. For ACP, we usually start with RAO (30°) cranial (10°), RAO (30°) cranial (30°), and PA caudal (20-30°) projections.

**Access Sheath Advancement**

To cross the interatrial septum with the access sheath safely, a long (260-cm) J-tipped stiff 0.035-inch wire (eg, Amplatz Super Stiff J-tip 3-mm curve) should be advanced into the left upper pulmonary vein (LUPV) as a rail support. The appropriately sized access sheath can then be safely advanced to the LUPV ostium on the stiff wire. To ease sheath access, the venous access and subcutaneous tissue should be dilated well, and the sheath should be gently rotated during advancement to achieve coaxial approach when crossing the septum. To advance the sheath into the LAA, it is best to use a pigtail (5-6 Fr) to seek the LAA orifice and then use it as a rail to safely navigate the sheath into the LAA.

For WATCHMAN, the 14-Fr access sheath is advanced deep into the LAA until the corresponding radiopaque marker band for the device size (see Fig. 47-1B) is aligned with the LAA ostium. Once in position, the pigtail is removed, and often some catheter torque is required to maintain sheath position in the distal lobe.

For ACP/Amulet, the appropriately sized sheath/dilator is usually advanced to the LUPV orifice over the stiff J-wire, and then the sheath is withdrawn slightly and counterclocked to fall into the LAA ostium. Alternatively, a J-wire or pigtail may be used to facilitate engaging the LAA to minimize traumatizing the thin left atrium.

**WATCHMAN Sizing and Implantation Steps**

WATCHMAN sizing is based on the widest LAA ostium diameter, which should be 17 to 31 mm to accommodate available devices. The instructions
for use recommend oversizing by 9% to 25%, which generally corresponds to 2 to 4 mm oversizing based on widest dimension. The depth of the LAA should be roughly as deep as the device diameter chosen. The delivery system containing the compressed device should be prepped and de-aired and then introduced into the access sheath. The delivery system is advanced until both distal marker bands of the delivery system and access sheath are aligned; the sheath unit is then “locked” in place. The device is then unsheathed slowly by withdrawal of the access sheath, preferably inducing apnea in intubated patients to allow stable deployment. Once the device is fully unsheathed, it may still be partially recaptured if the device is implanted too distally and then redeployed more proximally by withdrawal of the sheath. If the device is too proximal or if the sizing or position is suboptimal, the device can be fully recaptured and removed. A new device and delivery system can then be reintroduced through the existing 14-Fr access sheath.

The PASS criteria should be met before device release: position (device distal to or at LAA ostium; small protrusion of shoulder by <5-7 mm is acceptable), anchor (a tug test to assess stability by retracting the deployment knob and letting go), size (widest device shoulder should be compressed 8%-20% of original size on TEE), and seal (assess for any residual flow on TEE; must be <5 mm before release). When these criteria are met, the device may be released by counterclockwise rotation of the cable for 3 to 5 turns. Final angiography and TEE assessment are then performed.

**ACP/Amulet Sizing and Implantation Steps**

ACP sizing is based on the widest landing zone diameter on fluoroscopy or TEE. A standard recommendation is to upsize the device by 3 to 5 mm for ACP and 2 to 4 mm for Amulet. This degree of oversizing improves stability of the device; however, caution should be exercised if the landing zone is very elliptical to avoid dramatic oversizing in the narrowest dimension, which often results in the lobe jumping out of the LAA.

The prepped device is advanced to the tip of the access sheath, which is positioned at the landing zone of the LAA (10 mm from the orifice for ACP and 13-18 mm for Amulet). The first step of device deployment is unsheathing by withdrawal of the delivery sheath to deploy the “ball.” Once the “ball” is formed, the system can be relatively safely advanced or withdrawn within the LAA to achieve optimal position. The remainder of the
lobe is then deployed by a “push-pull” maneuver, which often requires counterclockwise rotation of the sheath to allow coaxial expansion of the lobe for full contact against the LAA neck. Adequate positioning of the lobe is assessed on cineangiogram and TEE before deploying the disc. This step requires slight traction of the delivery cable during unsheathing of the disc to separate the lobe from the disc and to ensure that the disc is deployed in the left atrium. If the position is unsatisfactory at any point prior to release, the disc and lobe can be resheathed into the “ball” configuration, ensuring that the 2 platinum markers on the lobe do not enter the radiopaque band on the sheath (which marks the location of the stabilizing wires at the tip of the sheath). If a different device size is required, the device can be completely withdrawn, but the sheath would need to be replaced before introducing the new device.

Five criteria should be met before releasing the ACP/Amulet device: (1) tire-shaped lobe (which ensures adequate compression of the lobe and engagement of stabilizing wires); (2) separation of the lobe and disc (ensuring that the disc is pulled in against the LAA orifice with good seal); (3) concavity of the disc (indicating traction of the disc from the lobe with good seal); (4) axis of the lobe (should be perpendicular to the neck axis at the landing zone, which ensures proper contact of lobe and stabilizing wires against the LAA); and (5) lobe is adequately within the circumflex artery on TEE (the width of the lobe should be two-thirds or greater within the circumflex). If there is uncertainty about device stability, a gentle tug test by slight pulling of the disc may be performed, but vigorous wiggle testing should be avoided. Alternatively, the device can be observed for several minutes to assess for any device movement prior to release. The presence of residual leak is assessed on TEE, and contrast injection is performed through the delivery sheath to assess optimal positioning. If satisfactory position is achieved, the device is released with counterclockwise rotation of the delivery cable.

IMPLANTATION TECHNIQUES FOR LARIAT

For the LARIAT procedure, a preoperative CCTA is necessary to exclude
large (>40 mm) appendages and other anatomic contraindications (eg, posteriorly rotated LAA under the pulmonary artery, pericardial adhesions), which may occur in up to 20% of cases. TEE is also performed before the procedure to exclude LAA thrombus and during the procedure to verify the anatomic position of the EndoCATH (SentreHEART) balloon at the LAA ostium.

The procedure requires pericardial and transseptal access, advancement of the endocardial magnet-tipped guide wire to the apex of the LAA, connection of the epicardial and endocardial magnet-tipped guide wires, and snare capture of the LAA with closure confirmation before release of the pretied suture for LAA ligation. Pericardial access requires an anterior approach through the subxiphoid area with a 17-gauge epidural needle. A 0.035-inch guide wire is then advanced and left in the pericardial space while the transseptal puncture is performed. The EndoCATH with the magnet-tipped 0.025-inch endocardial guide wire is advanced to the LAA apex through the transseptal catheter. The epicardial access is then sequentially dilated to insert the 14-Fr guide-cannula, and the epicardial magnet-tipped guide wire is then directed toward the LAA to connect with the endocardial magnet. With the EndoCATH balloon inflated at the LAA ostium, the LARIAT suture is then looped over the LAA to snare it along the epicardial magnet. The snare is closed and cut after confirmation on TEE and left atrial angiogram. A pigtail catheter is usually left in the pericardial space for several hours or overnight after procedure. Colchicine has been routinely used to reduce pericarditis related to this procedure.

**CLINICAL TRIALS EVALUATING SAFETY AND EFFICACY OF LAA OCCLUSION**

Only 2 randomized trials on percutaneous LAA closure have been published to date. There are several registries that have evaluated the efficacy and safety of various LAA occlusion devices, although the majority are early experience registries.
WATCHMAN

WATCHMAN was evaluated in the multicenter PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study. In this study, 707 patients with nonvalvular AF and CHADS\textsubscript{2} score $\geq$ 1 were randomized to WATCHMAN (n = 463) or warfarin (n = 244) in a 2:1 ratio. Technical success was 90.9\% with WATCHMAN. Warfarin was continued for 45 days with WATCHMAN in 86\% of patients, and switched to clopidogrel (until 6 months) if there was no leak $>5$ mm on TEE at 45 days. At 6 months, 92\% of patients were off warfarin. Aspirin was continued lifelong after implant. WATCHMAN was noninferior to warfarin for the composite primary efficacy end point of stroke, systemic embolism, and cardiovascular death event rates at 1065 and 1588 patient-years of follow-up. The primary procedure-related adverse event and major bleeding rate was higher with WATCHMAN (5.5\% vs 3.6\% annually; relative risk [RR] 1.53; 95\% confidence interval [CI], 0.95-2.70; Table 47-2). At the 45-month (2621 patient-years) follow-up, the primary efficacy end point was significantly lower with WATCHMAN (2.3 vs 3.8 events per 100 patient-years; RR, 0.6), meeting both the noninferiority and superiority criteria (presented at the Heart Rhythm Society meeting in 2013). Hemorrhagic stroke (RR, 0.15), cardiovascular death (RR, 0.4), and all-cause mortality (HR, 0.66) were also significantly lower with WATCHMAN.

Table 47-2 WATCHMAN Studies
Due to early safety concerns in PROTECT-AF, the FDA mandated a second randomized trial to confirm the late PROTECT-AF and CAP (Continued Access Protocol) registry safety results of WATCHMAN. Thus, the PREVAIL study (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs Long-Term Warfarin Therapy) was conducted, which randomized 407 patients to WATCHMAN or warfarin in a 2:1 ratio (see Table 47-2). Technical success improved to 95.1%. The safety end point met the prespecified noninferiority criterion and had significantly improved compared to PROTECT-AF. At 18 months, the first primary efficacy event rate (composite of stroke, systemic embolism, and cardiovascular/unexplained death) was 0.064 with WATCHMAN versus 0.063 with warfarin (rate ratio, 1.07; 95% CI, 0.57-1.89), which did not achieve the prespecified noninferiority criteria. The rate for the second primary efficacy end point (stroke or systemic embolism >7 days after randomization) was 0.0253 versus 0.0200 (risk difference, 0.0053; 95% CI, –0.0190 to 0.0273), achieving noninferiority. Overall, the efficacy event rates were low and numerically comparable in both arms. In the warfarin arm, the incidence of ischemic stroke was surprisingly low at 0.7 per 100 patient-years, which was much lower than comparative contemporary NOAC trials.
and probably contributed to the failure of meeting the first noninferiority end point.

The ASAP (Aspirin Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study evaluated 150 patients with nonvalvular AF and CHADS\textsubscript{2} score $\geq 1$ who were ineligible for warfarin.\textsuperscript{40} Patients underwent WATCHMAN implantation and were treated with thienopyridine for 6 months and lifelong aspirin thereafter. The mean duration of follow-up was 14 months, and the all-cause stroke and systemic embolism rate was 2.3% per year. The observed ischemic stroke rate was 77% lower than expected based on the CHADS\textsubscript{2} score of 2.8. The ASAP-TOO study will be a large multicenter randomized controlled trial comparing WATCHMAN to single antiplatelet therapy in patients who are ineligible for OAC; this study is anticipated to launch toward the end of 2016.

The CAP registry showed lower procedure-related events compared to PROTECT-AF, with a procedural stroke rate of 0% and serious pericardial effusion rate of 2.2% with WATCHMAN.\textsuperscript{37} The subsequent CAP2 registry stopped enrolling patients in the United States in early 2014.

There is a definite learning curve with WATCHMEN implantation, with improvement in technical success and procedural safety with increasing experience. The implant success rate improved from 90.9% in PROTECT-AF to 94.3% in the CAP registry and to 95.1% in PREVAIL.\textsuperscript{39} There was a significant reduction in procedural time (56 vs 50 minutes; $P < .001$) from PROTECT-AF to the CAP registry. There was also a significant decline in procedural safety event rates when comparing the first and second halves of PROTECT-AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events within 7 days of procedure ($P = .006$).\textsuperscript{37}

**Amplatzer Cardiac Plug**

The ACP was evaluated in several small retrospective registries (Table 47-3), mostly involving single-center experience worldwide.\textsuperscript{33,41-50} In aggregate, >1100 patients were included in these registries, showing good safety profile (serious pericardial effusion, $\sim 1.7$%; device embolization, $\sim 1.1$%; ischemic stroke, $\sim 0.4$%) and procedural success ($\sim 96.4$%).

Table 47-3 **Procedural Success and Complications in ACP Registries**
Recently, Tzikas et al\(^{51}\) published a pooled ACP retrospective registry of 22 European and Canadian centers including 1047 patients. The mean age was 75 years, the CHA\(_2\)DS\(_2\)-VASc score was 4.5, and the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score was 3.1. Twenty-nine percent of patients were on OAC prior to implant. Technical success rate was 97.3%, and in 93.3% of patients, the first device selected was implanted. With follow-up TEE, the closure rate (<3 mm residual flow) was 97.6%. The rate of periprocedural major adverse events of 7-day death, ischemic stroke, systemic embolism, and procedure- or device-related complications requiring major cardiovascular or endovascular intervention was 4.97%. Mortality was 0.76%, pericardial tamponade 1.2%, device embolization 0.8%, and stroke 0.9%. The observed annual stroke rate was 2.3%, which was 59% lower than the expected 5.6% stroke rate based on CHA\(_2\)DS\(_2\)-VASc score. This reduction was similar to that observed in other smaller registries.\(^{33,46,48}\)

The US pivotal ACP trial was initiated in early 2013 and randomized nonvalvular AF patients with CHADS\(_2\) score ≥2 to ACP versus anticoagulation (warfarin or dabigatran) in a 2:1 ratio. However, due to slow enrollment and anticipated FDA approval of WATCHMAN, this study was discontinued in December 2013 after enrollment of approximately 80 patients. A new randomized Amulet study is being planned and will involve noninferiority comparison to WATCHMAN.

**LARIAT**
The first published study with LARIAT was a single-center experience of 89 patients in Poland.\textsuperscript{34} The mean age was 62 years, CHADS\textsubscript{2} score was 1.9, and CHA\textsubscript{2}DS\textsubscript{2}-VASc score was 2.8. Technical success was 96%. There were a few procedural complications (1 right ventricular puncture, 1 superficial epigastric artery laceration, 1 hemopericardium) and postprocedural adverse events (2 cases of severe pericarditis, 1 late pericardial effusion, 2 unexplained sudden deaths, and 2 late strokes). Of the 65 patients who underwent TEE at 1 year, complete LAA closure was observed in 98%.

More recently, Price et al\textsuperscript{52} reported the multicenter retrospective US LARIAT experience of 151 patients. The procedure duration was 76.6 minutes, technical success was 93%, but procedural success (without procedural complication) was only 86%. Major adverse in-hospital events were relatively high, including significant pericardial effusion (requiring intervention) in 10%, major bleeding requiring transfusion in 4.6%, and emergency cardiac surgery in 1.3%. At median 133 days of follow-up, there were 3 deaths (2.3%), 3 strokes or transient ischemic attacks (2.3%), and 3 pericardial effusions (2.3%). TEE follow-up was performed in 60 patients and showed residual leak $\geq$5 mm in 7%, <5 mm in 15%, and no leak in 78%; thrombus was seen in 5% of patients after LARIAT. This study brought to light the potential high complications with LARIAT and the need for prospective randomized studies with this device.

**COMPLICATIONS WITH PERCUTANEOUS LAA CLOSURE**

The acute complications with the WATCHMAN and ACP devices appear comparable. With increased operator experience, the procedure can be performed with a low periprocedural ischemic stroke risk of $<0.5\%$, serious pericardial effusion of 1\% to 2\%, and device embolization of 0.5\% to 1\%. Ischemic strokes may occur due to procedural air embolism from inadequate device preparation or poor technique, or from thrombus in the LAA or on equipment. Baseline imaging to exclude preexisting LAA thrombus, adequate procedural anticoagulation (keeping ACT $>250$ seconds), and meticulous techniques are important to minimize thromboembolism. The risk of pericardial effusion can be minimized by careful wire, sheath, and device
manipulations in the left atrium and LAA. Using a relatively atraumatic pigtail to guide sheath advancement into the LAA can minimize such risks. Pericardial tamponade requires emergent pericardiocentesis and possibly even pericardial window or surgical intervention for cardiac perforation. Pericarditis related to LARIAT is often managed with nonsteroidal anti-inflammatory drugs, colchicine, or steroids. Device embolization can usually be managed by percutaneous retrieval if feasible. A large arterial sheath that is ≥2-Fr larger than the implanting access sheath is often required to retrieve the embolized device, in conjunction with loop snares and even bioptome. Embolized devices trapped in the left ventricle, left atrium, and aorta have been successfully retrieved. However, surgical removal may be required if the device is trapped by tissues (eg, papillary muscles or trabeculations) or if the device cannot be fully retracted into the large sheath.

Longer term issues with percutaneous LAA closures include thrombus formation on the atrial side of devices and residual leaks. Follow-up TEE or CCTA at approximately 3 to 6 months after procedure should be routinely performed, and sometimes, it should be repeated at 1 year. Device thrombus formation may occur in 2% to 5% of cases with these devices, which tends to occur on nonendothelialized device protrusions such as the threaded insert with WATCHMAN and the proximal end screw with ACP, especially if implants are too deep. Thus, deep implantations resulting in uncovered trabeculations and recesses should be avoided. Newer device designs may also be less thrombogenic; for example, Amulet has a recessed proximal end screw that allows faster and/or more complete endothelialization. Although there is no consensus on management, device thrombus is usually managed with anticoagulation (OAC or low-molecular-weight heparin) for 8 to 12 weeks, with repeat TEE to assess for thrombus resolution before discontinuing anticoagulation. Reported thromboembolic stroke event rates related to device thrombus are low at 0.3% to 0.7%.37,40

Residual leak may occur with a significant proportion of WATCHMAN implants. In the PROTECT-AF study, some degree of leak was seen in 32% of cases at 12-month follow-up (36.8% >3 mm and 63.2% ≤3 mm). However, residual leak was not associated with higher risk of thromboembolism,53 although the number of events was low, and this finding was inconclusive. Residual leak with ACP has been reported to be lower; leak >5 mm has not been documented, leak of 3 to 5 mm occurs in 0% to 1% of cases,48 and leak <3 mm occurs in 0% to 16% of cases.42,44,46 The ACP’s low incidence of
leak is presumably related to the lobe-disc design, with fabric in both components. Residual leak has also been demonstrated with LARIAT, with variable reported incidence of 2% to 22% on follow-up TEE. With any of these devices, if there are residual leaks >5 mm, patients should probably be continued on long-term OAC, or alternatively, repeat LAA closure with a different device may be attempted.\textsuperscript{54}

CONCLUSION

In summary, several devices for percutaneous LAA closure are CE marked and available in many countries. The WATCHMAN device has the most supportive data and received FDA approval in early 2015 for warfarin-eligible patients. Data from PROTECT-AF, PREVAIL, and CAP have shown good procedural safety after the initial learning curve. Furthermore, superiority of primary efficacy end points with WATCHMAN was demonstrated at long-term follow-up in the PROTECT-AF study, together with reduction in cardiovascular and all-cause mortality. The large randomized controlled ASAP-TOO study with WATCHMAN for warfarin-ineligible patients will be launched imminently. For ACP, there has also been a good deal of real-world experience to date, and a recent large multicenter registry of almost 1000 patients revealed a good safety profile. A randomized trial comparing the ACP to WATCHMAN is being launched. LARIAT has also gained interest lately; however, early studies were concerning for relatively high complication rates of serious pericardial effusion and major bleeding. Further prospective studies are necessary to evaluate the safety and efficacy of LARIAT. There are also several other percutaneous LAA devices under clinical investigation, and future randomized trials comparing them to WATCHMAN are anticipated.

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Percutaneous Closure of Atrial Septal Defect and Patent Foramen Ovale

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Over the course of the past decade, there has been a burgeoning interest in closing septal defects percutaneously. To date, there are now percutaneous closure devices available for the intended closure of ostium secundum atrial septal defects (ASDs) as well as patent foramen ovale (PFO). With the increased interest in these percutaneous procedures, the interventional cardiologist now has an additional set of procedures to master outside the coronary vasculature. This chapter will review the current techniques and devices employed during these specialized procedures.

ATRIAL SEPTAL DEFECT

ASDs are the most common adult congenital cardiac abnormality, occurring in about 8% of the adult congenital heart disease population with a slight female predominance (3:2). They are classified by the anatomic location as well as their associations with other local anatomic structures. ASDs can be classified as follows: (1) ostium primum, in which the defect is located inferiorly and is often associated with tricuspid and or mitral valve abnormalities as well as a ventricular septal defect; (2) ostium secundum, in which the defect is related to persistent separation at the midatrial level due to failed fusion during cardiac development; and (3) sinus venosus, in which
there is partial anomalous pulmonary venous return due to the septal defect extending superiorly along the atrial septum to include the incoming pulmonary veins. Of these 3 types of ASDs, transcatheter repair is tenable at this time only with the secundum-type defect.

In general, the threshold for closure is dictated by hemodynamic findings. Historical data, largely from the surgical literature, suggest that ASD closure is warranted in patients with a pulmonary/systemic flow ratio (Qp/Qs) of 1.5 or greater. Closure may also be warranted if pulmonary hypertension or early echocardiographic evidence of right ventricular enlargement and/or failure is present. A paradoxical embolus may also be considered to be an indication for closure. Clinically, patients often present with dyspnea on exertion or evidence of right-sided heart failure. It is generally rare to see a cryptogenic neurologic event with an ASD, given that most of the flow early in the process involves left-to-right shunting; as the right heart fails, however, the shunting becomes mixed and even reversed in late-stage disease, with predominantly right-to-left shunting. An electrocardiogram showing incomplete right bundle branch block is common in patients with secundum ASD.

A transesophageal echocardiogram (TEE) is critical in defining the anatomy of the ASD and is useful in determining the potential success of percutaneous closure of a secundum-type defect. An adequate (≥1 mm) anterosuperior aortic rim is important to allow adequate anchoring of the ASD closure device. In addition, the size of the defect and an estimate of the shunt fraction may be helpful in determining the eligibility for closure as well as appropriate balloon sizing. Right ventricular enlargement of at least a mild degree is usually observed. Other important features revolve around the definition of the type of defect and the relationship of the mitral valve annulus to the ASD. An investigation of the left atrial appendage to rule out thrombus and a bicaval view to assess inflow into the atrium are important to exclude a sinus venosus–type defect. A multifenestrated secundum ASD is noted in about 10% of all secundum ASDs, and imaging to assess for this is important because it could have an influence on planning for device closure. Finally, other defects such as anomalous pulmonary venous return should also be excluded with TEE or computed tomography (CT).

**Percutaneous ASD Closure**
Percutaneous closure of a secundum ASD has been performed for many years in both pediatric and adult populations. The first attempt at transcatheter ASD closure was in 1974 by King and Mills. The techniques have been refined over time, and there are now a number of commercially available devices outside the United States. Within the United States, one device, the Amplatzer Septal Occluder (AGA Medical, Golden Valley, MN), has received approval from the US Food and Drug Administration for secundum ASD closures (Fig. 48-1).

**FIGURE 48-1** The Amplatzer Septal Occluder (AGA Medical, Golden Valley, MN) is composed of 2 nitinol disks covered by polyester. It is approved for use in the United States for appropriate secundum-type atrial septal defects.

The Amplatzer Septal Occluder (ASO) consists of 2 attached circular disks—a larger left atrial disk separated by a small space on top of a smaller right atrial disk. These disks are made of polyester fabric encasing a wire
mesh made of a nitinol. The device is screwed onto a delivery cable and delivered via a long sheath. In the typical ASO, the left atrial disk is 6 to 8 mm larger than the right atrial disk, and a central space (“waist”) consists of a small mesh tube, which also promotes self-centering. The device is sized per the right atrial disk.

Screening for potential percutaneous closure candidates consists of the tests noted earlier to diagnose and confirm a secundum-type ASD. In addition, tests to exclude concurrent infection, pregnancy, and a hypercoagulable state should be performed prior to closure. It is important to also administer intravenous (IV) antibiotics at the time of closure to prevent any potential infectious risk. This is performed usually just prior to obtaining venous access. The procedure in the catheterization laboratory is relatively straightforward and has recently been reviewed.3

Two venous sheaths are placed in the right femoral vein. Unfractionated heparin (100 U/kg) is then administered IV with an aim to keep an activated clotting time of greater than 200 seconds. To confirm the hemodynamic significance of the ASD, a saturation run with pressure measurements should be performed prior to the planned closure. Once the shunting has been confirmed, one of the sheaths can be replaced with an 8- or 10-Fr sheath to allow the passage of a 10-MHz intracardiac echocardiography (ICE) probe (AcuNav; Siemens Medical Solutions, Malvern, PA; Fig. 48-2), which allows direct visualization of the atrial chambers and atrioventricular valves during closure. An alternative is to use TEE during the procedure, but studies have suggested a greater benefit for using ICE over TEE.4,5 Once the probe has been guided into the right atrium at the level of the ASD, a 6-Fr multipurpose diagnostic coronary catheter is directed over a 260-cm J-tipped (Rosen) wire to the right atrium. Alternative choices of catheter include an Amplatzer Left-1, but this may direct the wire toward the coronary sinus. Some operators prefer an Amplatzer (stiff) guide wire. The catheter is then manipulated toward the ASD, and the wire is guided across the ASD into the left atrium and anchored within the pulmonary veins, preferably the left superior pulmonary vein. Once the wire is anchored, the catheter is removed. Using the ICE and previous TEE data as a guide, a 24- or 34-mm sizing balloon (St. Jude Medical, Saint Paul, MN) can be guided across the ASD and its position confirmed by ICE and/or fluoroscopy. Typically, the stretched diameter of the ASD is 30% larger than the unstretched diameter. The sizing balloon is then inflated with a 1:4 mixture of contrast and saline, and a balloon “waist”
appears fluoroscopically as well as on the ICE. This “waist” is then measured as the stretched diameter of the ASD using predefined markers on the balloon catheter for calibration (Fig. 48-3). To avoid oversizing, a “stop-flow” technique has been developed in which the balloon is gently inflated while color Doppler echo visualizing the shunt flow is used on ICE or TEE. The “stop-flow” measurement is the point at which flow across the shunt is fully occluded by the balloon. Once the stop-flow ASD size is confirmed, the balloon is then deflated and removed.

**FIGURE 48-2** AcuNav intracardiac echocardiographic catheter. It images at 10 MHz and is 10-Fr sheath compatible. (Siemens Medical Solutions. Used with permission from Siemens Healthineers.)
FIGURE 48-3 Sizing balloon used in the measurement of septal defect size. In this photograph, the sizing balloon has been inflated to reveal the atrial septal defect size when stretched, allowing appropriate sizing for a septal occluder device. Markers on the sizing balloon allow accurate estimation of defect size.

Typically, the chosen ASD closure device size with the ASO is 1 to 4 mm larger than the stretched diameter. Because of the variety of ASD closure device sizes (4-40 mm), the delivery sheath size may vary. For example, for a 22-mm ASO, a 9-Fr delivery sheath is adequate, whereas a 36-mm ASO requires at least a 12-Fr delivery sheath. Once the proper delivery sheath size is chosen, the femoral sheath is exchanged for a long (80 cm) curved delivery sheath. The introducer should be placed into the pulmonary vein and then removed along with the wire once the sheath has been anchored within the pulmonary vein. Great care should be taken to expunge any air from the
sheath by carefully removing fluid and potential air from the sheath and then gently flushing with saline.

The ASO is screwed in a clockwise fashion until tight onto the delivery cable. A 180-degree counterclockwise turn is then used to slightly loosen the device and prevent locking of the ASO onto the delivery cable. A small introducer sheath included in the packaging should then be used to expunge any air from the delivery cable and device while pulling back in a pool of saline. This short sheath with the ASO on the distal end of the delivery cable is then connected onto the proximal end of the delivery sheath and pushed into the delivery sheath with care taken to avoid kinking of the cable or sheath. It is common to experience some mild initial resistance with the introduction of the ASO into the delivery sheath.

Fluoroscopy can then be used to visualize the delivery cable and ASO within the sheath as it approaches the tip of the delivery sheath. When the device is at the tip of the sheath, the entire system is then retracted back into the upper portion of the left atrium. When this is accomplished, the sheath is gently retracted from the delivery cable, and the left atrial disk should be deployed (Fig. 48-4). Under ICE and fluoroscopic guidance, the left atrial disk, delivery cable, and sheath are then retracted as a unit until the left atrial disk is flush against the left atrial side of the ASD. Once this is established, the sheath is then further retracted to allow deployment of the right atrial disk (Fig. 48-5). The device should be well-seated across the atrium with both respective atrial disks fully expanded on either side of the septum. A gentle but firm to-and-fro motion ("Minnesota wiggle"\(^6\)) can be used to gauge the positional stability of the ASO while using ICE or TEE. This can be confirmed with ICE and Doppler imaging of the ASD on either side of the device. Contrast or bubbles may be injected through the delivery sheath to image the right atrium and detect contrast across the ASD with the device, still held in place by the delivery cable, in the defect. If these methods detect minimal or no leakage, the device is then detached from the delivery cable by attaching the rotator knob on the back end of the delivery cable and using a counterclockwise rotation of the knob. It is imperative to maintain a very slight and gentle constant traction on the device as the knob is rotated until the device is released. The device may “jump” or slightly reorient/recenter itself as the device is released (Fig. 48-6).
FIGURE 48-4 Fluoroscopy (top panels) showing the left atrial disk of an Amplatzer Septal Occluder being used. Intracardiac echocardiography (bottom) shows the left atrial disk used within the left atrium.
FIGURE 48-5 Deployment of the right atrial disk under fluoroscopy and intracardiac echocardiographic (ICE) guidance. The ICE imaging also shows the Doppler signal at the aortosuperior rim of the device.
FIGURE 48-6 (A) Immediate result of device release (left) compared with the final result (right). Please note the orientation change of the Amplatzer Septal Occluder after it has settled into position. This is considered normal and can be further investigated with intracardiac echocardiography, seen in panel B, which shows excellent device placement and apposition.

Prior to release, if positioning is unsatisfactory, the sheath can be readvanced into the left or right atrium to recover the right and/or left atrial disk, and the deployment process can begin again. If the deployments remain unsatisfactory, some operators have advanced a second catheter to help better align the device as it is deployed by using a constant upward pressure on the device and/or sheath as it is deployed across the ASD. This obviously requires another venous sheath to be placed. For larger ASDs, a novel
technique has recently been described in 14 patients using the sizing balloon inflated within the right atrium to help support large ASOs as they are deployed.

Once the device has been released, ICE should be used to scan along the atrium from the superior vena cava (SVC) to the inferior aortic border to confirm the positioning of the device as well as the elimination of the shunt itself by Doppler (Fig. 48-7). In addition, a scan of the atrioventricular valves should be performed to exclude impingement on either of these structures. Alternatively, some operators inject bubbles through the now empty venous delivery sheath and image as the bubbles are in the right atrium to see if any bubbles are able to cross the ASD. Residual shunting through the device is not uncommon immediately after release. Significant residual shunting is rare and usually suggests device malposition or a second defect. A second device can be used depending on the size and location of the defect. If there are significant bubbles or Doppler-detected flow across the ASD on either side of the device, a second device can be placed by recrossing the ASD with a multipurpose catheter and stiff J-wire and eventual deployment of a smaller second ASO without the use of a sizing balloon. Alternatively, some operators who have noted moderate persistent defects on one end of the device have used coronary catheters to “adjust” the positioning along the end of the device with a persistent residual shunt. Once the final result has been deemed to be satisfactory, the sheaths are removed.
Before the availability of a large device designed to cover fenestrated defects, the general approach was to use multiple devices if the defects were 7 mm or further apart along the atrial septum, with the first device used to cover the largest defect. Currently, the preferred method is to use 1 device, and the Amplatzer Multifenestrated Septal Occluder, also known as the cribriform device, is the most common device used in the United States for these types of defects. This device differs from the ASO by harboring 2 fixed-distance polyester-covered nitinol circular disks with a central space (“waist”) of 4 mm. The right atrial disk is thicker than the left atrial disk, but both have the same diameter. Available sizes in the United States are 18, 25, 30, and 35 mm, measured as a diameter of the disks.

Device deployment for the cribriform device is similar to the ASO but with a few differences: the device should be delivered through the largest defect, with calculation of the distance from the main defect to the aortic rim measured on TEE or ICE used as the basis for device sizing.

Another device, the Gore Helex device (W. L. Gore & Associates, Inc., Flagstaff, AZ), is also available in the United States for secundum ASD closure. This device consists of a single nitinol wire acting as a looped frame.
with an ePTFE covering, which allows for acute mechanical closure and eventual endothelialization. The device comes in 15- to 35-mm diameter sizes with 5-mm increments. The device sizing choice is based on at least a 2:1 ratio of device-to-defect size per stop-flow ultrasound imaging. The device has islets to allow for fluoroscopic visualization and device alignment with the defect. It may also be used for multifenestrated defects.

The Helex delivery sheath with the premounted device may be directed into the left atrium either alone or with a guide wire used as a monorail system. The left atrial disk is then released at the end of the catheter and slowly pulled back toward the septum with a pull-stabilize-pull technique; as the device approaches the septum, the second loop is released, covering the left side of the atrium and SVC. The right atrial loop is then opened with gentle tension and fully released to allow the device to settle along the defect on both sides. The radiopaque islets are visualized to make sure the device is aligned and centered both by fluoroscopy and ultrasound imaging, and the device may then be released (unlocked) with final detachment of the release cord.

In addition, clopidogrel is administered after device closure, with a loading dose of 300 to 600 mg in the laboratory, with plans for a maintenance dose of 75 mg once a day for at least 1 month with concomitant aspirin. The aspirin should be continued for 6 months after closure. Currently, no data have been published, but ticagrelor or prasugrel may be used as an alternative for patients who are sensitive to clopidogrel. A small study has suggested that platelet activity is enhanced in the presence of ASD and largely reversible after defect closure.

The issue of thrombus formation and its significance is interesting and controversial. The devices are thought to acutely close septal defects by mechanical obstruction of the defect as well as thrombosis with long-term closure secondary to endothelialization.

**Postprocedural Care**

In addition to the postprocedure administration of aspirin and clopidogrel for 3 to 6 months, our standard of practice in the hospital has been to continue IV antibiotics (cefazolin 1 g IV every 8 hours; for penicillin-sensitive patients, vancomycin 1 g IV every 12 hours) through the course of the hospitalization after the procedure.
The patient is usually discharged on the following morning after a transthoracic echocardiogram (TTE) with contrast. This is done for 2 reasons: (1) to reconfirm proper device positioning (Fig. 48-8), and (2) to establish the degree of shunting, if any, across the device. In addition, an anteroposterior and lateral chest x-ray is taken. The ultrasound imaging studies are repeated at 1, 6, and 12 months, and then as needed. The use of contrast during the TTE follow-up studies is reserved for patients with persistent residual shunts. Chest x-rays are performed only as indicated.

**FIGURE 48-8** Transthoracic echocardiogram image of a large Amplatzer Septal Occluder 1 day after placement across a secundum defect.

The patient should allow at least 4 weeks for complete endothelialization of the device. In our program, no lifting of objects that weigh more than 20 pounds is recommended for the first month after procedure. Gentle walking is allowed immediately after procedure and until the patient returns for follow-up at 1 month. An important reminder involves the prevention of device infection: the patient should follow American College of Cardiology/American Heart Association guidelines for bacterial endocarditis prophylaxis for 6 months after procedure.

**Complications**
The delivery of a septal defect closure device has a particular set of complications of which every operator should be aware. Beyond the rare complication of vascular access issues, there are a number of unique potential complications related to these devices. These include transient bradyarrhythmias and tachyarrhythmias, ST-segment elevation, device embolization, device erosion, thrombosis and embolism, and pericardial effusion.

The incidence of bradyarrhythmias, such as complete heart block, is rare. In a review, 10 patients underwent percutaneous ASD closure. Periprocedural atrioventricular (AV) block was noted in 3 patients (1.9%). During the postprocedure follow-up at 1 week, an additional 7 patients developed AV block. Four of these 10 patients had first-degree AV block. All had no symptoms or hemodynamic compromise. All patients with higher degree AV block completely recovered within 6 months. Two patients had residual first-degree block at 12 and 33 months after the procedure. Interestingly, patients with a larger defect and hence larger shunt fraction and ASO (>19 mm) had a much higher incidence of AV block. In a series from Italy, 11 the incidence of AV block was 1 of 417 patients (0.2%). In this patient, complete heart block developed, and the operators then removed the device with complete cessation of the AV block. One year later, the patient underwent an uneventful percutaneous ASD closure. In another study, 9 of 41 patients (22%) exhibited nonsustained supraventricular tachycardia; no patients had atrial fibrillation or other atrial tachycardias. Five of 199 patients (2.5%) in the study by Wang et al 14 experienced supraventricular tachycardia, but all of these events were terminated with administration of IV adenosine.

Tachyarrhythmias, such as atrial tachycardia and atrial fibrillation, have also been reported. In a recent series from the Mayo Clinic 13 using ICE-directed ASD or PFO closure, the incidence of atrial tachyarrhythmia was 4.3% (4 of 94 patients). Three of these patients had atrial fibrillation, whereas 1 had a supraventricular tachycardia. Two of these 4 patients recovered spontaneously, whereas the other 2 were cardioverted without incidence. There were no cases of ventricular arrhythmias. In another study, 9 of 41 patients (22%) exhibited nonsustained supraventricular tachycardia; no patients had atrial fibrillation or other atrial tachycardias. Five of 199 patients (2.5%) in the study by Wang et al 14 experienced supraventricular tachycardia, but all of these events were terminated with administration of IV adenosine.

ST-segment elevation is an interesting development during and after ASD
closure. This usually occurs in the inferior leads, and the mechanism postulated has been inadvertent air embolism during device deployment. It is usually transient and resolves spontaneously within 20 minutes. Clinically, the patient may complain of chest discomfort and nausea, but this usually subsides in a short period.

Device dislodgement and embolization is a known complication of ASD closure. This is an operator-driven error and can be the result of many possible errors, most commonly incomplete attachment to the delivery cable, sizing and device error, malpositioning, and premature device release. In an Italian series of ASD closure\textsuperscript{11} with a variety of devices, 1 patient (0.2\%) had device embolization. In a more generalized survey of ASO operators by Levi and Moore,\textsuperscript{15} a 0.6\% incidence of device embolization was noted. In general, larger devices are thought to be associated with a higher incidence of device embolization because of the inadequacy of a rim to anchor the device in a large defect. Indeed, in several series,\textsuperscript{11,14-16} larger (or undersized) devices were shown to be more prone to malpositioning and dislodgement/embolization. Device embolization was noted in 7 of 417 Italian patients (1.7\%) and 1 of 191 patients (0.5\%) in the Taiwanese experience.

Techniques to retrieve the ASO vary, but all involve a gooseneck snare and the use of an oversized venous sheath. The review by Levi and Moore\textsuperscript{15} in which they surveyed a number of experienced ASO operators suggests that a stiffer sheath with a beveled tip may be advantageous when recapturing a dislodged ASO. The technique to retrieve a device involves snaring the right atrial disk screw and pulling the device back into a sheath (Fig. 48-9). A bioptome generally cannot sufficiently “grab” a device by its right atrial screw for removal. In some cases, however, a bioptome may be used to pull the device into the inferior vena cava (IVC) with the snare holding the right atrial disk screw. Once there, a stiff J-wire can be advanced across the device in the IVC to stabilize its position.\textsuperscript{17} The ASO can then be pulled more easily into the retrieval sheath and removed. In their survey, 15 of 21 (71\%) device embolizations were successfully retrieved via a percutaneous route from a total cohort of 3824 patients. The other 6 patients underwent surgical removal. Chessa et al\textsuperscript{11} successfully retrieved 4 of 11 embolized or malpositioned devices. The other 7 patients underwent successful surgical retrieval and closure.
FIGURE 48-9 Retrieval of an Amplatzer Septal Occluder after embolization into the right atrium. The arrow shows the location of the snare around the screw-type interface between the original delivery catheter and device. The snare is used to grab (A) and retract the device back into the capture sheath. Note that the right atrial disk is first collapsed (B) and withdrawn into the sheath (C), followed by the left atrial disk. Eventually, the entire device is captured within the sheath (D) and removed.

There is a growing interest in the thrombosis rate for any septal defect closure device. In the case of the ASO, this has been examined in a small
study by Anzai et al.\textsuperscript{18} In their study, 66 patients underwent septal defect closure with either a CardioSeal, an Amplatzer PFO occluder, or an ASO. TEE was performed in 50 patients 1 month after closure, and the incidence of detectable thrombus in the 27 patients with the Amplatzer devices was 0%. A recent review by Krumsdorf et al.\textsuperscript{19} of the incidence of thrombosis induced by septal closure devices (including both ASD and PFO devices) in 1000 patients undergoing septal defect closure suggested that the mean incidence of thrombosis in the 407 ASD closure cases, using a variety of devices, was 1.2% (5 of 407 patients). The incidence of thrombosis in those receiving an Amplatzer device was 0%. These thrombi were detected at the planned 30-day and/or 6-month follow-up, which included a TEE. Interestingly, 14 of 221 ASD patients (6.3%) had a coagulation disorder; in these patients, there was a higher incidence of a precedent embolic event prior to closure. In addition, of the 326 Amplatzer devices used in this study, there were no cases of detected thrombus by echocardiographic imaging. This reduced incidence of detectable thrombosis in the Amplatzer patients may be due to the covering of the nitinol mesh with polyester. Other devices, because of a difference in the covering, may be more prone to thrombus formation. However, a recent review and meta-analysis of 17 reports found 54 patients with device thrombosis, and no device was spared from this complication.\textsuperscript{20} Predictors of thrombus formation include hypercoagulability, presence of atrial fibrillation, and presence of a persistent atrial septal aneurysm in PFO patients. The presence or absence of a residual shunt does not appear to predict thrombus formation, nor does diabetes, hypertension, or concomitant coronary heart disease.\textsuperscript{19}

Overt cardiac rupture is heretofore unheard of, but the development of significant pericardial effusion leading to pericardial tamponade has been reported in a number of studies. The report by Chessa et al.\textsuperscript{11} included 2 pericardial effusions (0.5%), 1 of which required emergent surgical drainage in the catheterization laboratory because of a guide wire perforation. The other effusion resolved with medical therapy after 20 days. Four (2.0%) of the 199 patients in the series described by Wang et al.\textsuperscript{14} developed pericardial effusions, 1 of which required pericardiocentesis for relief of tamponade. In a recent registry review of ASO erosions, 28 cases (14 in the United States) were examined. All erosions were near the aortic root, and the large majority of these patients had a deficient aortic rim (89%) or superior rim. In addition,
oversizing of the defect with aggressive balloon sizing and a subsequent oversized device may have played a role in these perforations. Early recognition is the key to avoid any poor outcome. Serial echocardiograms are recommended for those patients who develop a pericardial effusion at the time of the procedure and early after the procedure.

**Results**

The results of percutaneous ASD closure\textsuperscript{6,11,14,21-24} are very encouraging. The earliest report of using the Amplatzer device for secundum ASD closure\textsuperscript{22} was a small pediatric study of 16 patients, and these procedures were performed without complication. An acute closure without residual shunting was achieved in 13 of the 16 patients (81%), and 2 of these 3 patients had no TEE-detectable shunt at 3 months, for an overall success rate of 94%. In another study of ASD closure,\textsuperscript{23} 200 patients were closed using the ASO device. At 3 months postprocedure, 98.1% of patients had no detectable shunt, with only trivial residual shunting noted in the remaining patients. In a review of 3580 ASD closures in 3535 patients, Omeish and Hijazi\textsuperscript{24} reported a 97.4% acute success rate for closure based on TEE findings of minimal or no shunt at the time of closure. At 3 months, the closure rate per the TTE was 99.2%, and at 3 years, it was 100%. There were no device-related deaths, and there was a serious complication rate of 0.3%. In a recent study from Taiwan,\textsuperscript{14} 197 patients underwent ASD closure with the Amplatzer device and the use of TEE. A deficient rim, defined as less than 5 mm, was noted in 114 patients, 113 of which were noted on the superior-anterior (aortic) portion of the atrial septum. Interestingly, the presence of a deficient rim was not associated with an increase in procedural failure. A total of 191 procedures were successful; repositioning (redeployment) of the device was needed in 28 patients. Of the 6 failures, 4 were in adults with an ASD stretched diameter of greater than 34 mm and 2 were in young children younger than 4 years of age with stretched ASDs of greater than 20 mm. Complications were noted in 3 patients; 1 had complete AV block that eventually resolved after 3 days, 1 experienced cardiac tamponade requiring pericardiocentesis, and 1 had embolization of the device and required emergent surgery after failed attempts to retrieve the device. The follow-up on these patients included TEE, and residual shunts were seen in 4% of patients at 2 years.
Summary

The development of a percutaneous device to close secundum ASDs has advanced the use of these devices in the adult cardiac catheterization laboratory. Experience with these devices is growing, and these devices have become common in many centers in the United States and around the world as a true alternative to surgical closure. The acute and medium-term (<10 years) experience has been very positive, and percutaneous ASD closure will continue to grow as the devices and operators improve. Early recognition of problems in ASD closure is important and may obviate the need for surgical intervention in a large number of complicated cases.

PATENT FORAMEN OVALE

PFO is a common congenital heart finding that can be an incidental finding in 10% to 30% of autopsies but can have a much higher incidence in patients with a neurologic event unascribed to another cause (“cryptogenic”). A PFO is a residual of a failed closure of the fossa ovalis, a remnant of the fetal circulation. In most people, the foramen ovale closes shortly after birth. In patients with a PFO, this closure fails to occur, and the heart is left with a persistent potential shunt between the right and left atrium (Fig. 48-10). In the large majority of patients with PFO, no neurologic events ensue. This is likely due to the adequacy of atrial flow and turbulence, which prevent thrombi from forming, and to the small chance of passage of embolic material through a small shunt.
Patients foramen ovale from a cadaver shows the probe patency from the right atrial (top) and left atrial (bottom) sides of the defect.

**Relationship of the PFO to Neurologic Events**

As noted earlier, a large percentage of the general population harbors a PFO. An evolving interest in PFO has been driven by the finding that 40% of ischemic stroke patients have no defined cause (“cryptogenic”). In many of
these patients, especially young patients, a PFO is discovered. The mechanisms postulated for the development of a cryptogenic stroke with PFO are (1) passage of thromboemboli from the right heart circulation across a PFO into the left atrium and thus into the cerebral circulation, and (2) in situ thrombosis across the PFO and thromboembolism from the PFO itself into the left atrium and subsequently into the cerebral circulation. Although there is no absolute proof that a PFO is a cause of cryptogenic neurologic events, there are several series suggesting that there is a higher incidence of PFOs in patients with cryptogenic stroke.\textsuperscript{25-28}

Mas et al\textsuperscript{29} performed a retrospective study of 132 patients with a cryptogenic neurologic event and a PFO and/or atrial septal aneurysm (ASA). The findings suggested that the annual rate of recurrent stroke was 1.2%, with a 3.4% annual rate for any neurologic event. The risk was highest for patients with both a PFO and ASA with an annual stroke recurrence rate of 4.4%. Another study by Nedeltchev et al\textsuperscript{30} examined 318 patients with a cryptogenic neurologic event (stroke or transient ischemic attack [TIA]) and PFO. A total of 159 patients underwent medical therapy; this consisted of vitamin K antagonists with a targeted international normalized ratio of 2.0 to 3.0 in 79 patients and platelet inhibitors (aspirin or clopidogrel) in 80 patients. At a mean follow-up period of 29 months, 21 patients (13.4%) had had a recurrent neurologic event (7 strokes, 14 TIAs). Based on this, the mean annual rate of stroke recurrence was 1.8% (5.5% for recurrent stroke or TIA). The Patent Foramen Ovale in Cryptogenic Stroke Study\textsuperscript{31} (PICSS) was a substudy of the 630-patient Warfarin-Aspirin Recurrent Stroke Study (WARSS), in which 203 patients had a documented PFO. In this medical therapy comparison, there was no difference in outcomes of recurrent stroke or death between warfarin or aspirin treatment, and the presence of a PFO did not affect outcomes. In addition, the size of the PFO or the presence of an ASA also did not affect outcomes. A meta-analysis of several studies\textsuperscript{32} in secondary prevention of recurrent neurologic events in PFO patients, however, suggested that warfarin is superior to aspirin and may be equivalent to surgical closure of a PFO.\textsuperscript{33}

Standard medical therapy has thus not been concretely defined but generally consists of warfarin with or without concomitant antiplatelet therapy. Within the neurology community, the actual “best practice” regarding medical therapy remains controversial\textsuperscript{34}; thus, patients may be
taking aspirin, aspirin and dipyridamole, clopidogrel with or without aspirin, or warfarin for secondary prevention of a cryptogenic stroke. With the development of devices for mechanical closure of a PFO, this has generated a great interest in mechanical closure of PFOs in patients with cryptogenic stroke.

**Special Interest: PFO and Migraine Headaches**

An interesting relationship, albeit not a proven causal one, has suggested that PFOs may be implicated in migraine headaches. From observational studies, it appears that patients with migraine headaches have about twice the incidence of PFOs, especially with ASA, than the general population. PFO closure may help alleviate the frequency of migraine headaches, as suggested by a study of migraine headache attacks in a population undergoing PFO closure for cryptogenic neurologic events. Based on these findings, a randomized clinical trial in the United Kingdom studying the role of PFO closure with the StarFlex device (NMT Medical, Boston, MA) in patients with migraine headaches (Migraine Intervention With StarFlex Technology [MIST]) without cryptogenic neurologic events was reported at the 2006 American College of Cardiology Scientific Sessions and published. In this important study, 147 patients were randomized to either device closure of their PFO or medical management with a sham procedure. The primary end point of the trial, complete cessation of migraine headaches, was achieved in 3 of 74 patients in the device group and 3 of 73 patients in the medical treatment (sham procedure) group. The device group had an improvement in their headache burden score (frequency × duration) and experienced a 50% or greater reduction in headache days, but neither of the predefined secondary end points were met. Controversy about MIST revolved around the echocardiographic data, and 1 of the co-primary investigators eventually was sued for libel by NMT, the company that made the StarFlex and sponsored the trial.

The PRIMA-PFO study using the Amplatzer PFO device was presented at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in 2014. In this small study, 83 patients were randomized to device or best medical therapy and followed for 1 year with a primary end point of number of reduced migraine days. There was no significant difference between the 2 groups.

The PREMIUM PFO trial was also recently presented at the TCT 2015
meeting. The results of this trial suggested a small but nonsignificant statistical benefit regarding responders to therapy in patients receiving an Amplatzer device versus a sham procedure. A reduction in number of headache days per month was noted ($P = .03$) as part of a subgroup analysis, and there was a greater benefit in patients who experience an aura with their migraines, as shown by a treatment response in 49% of patients with the device versus 23% of patients in the sham group ($P = .015$) and complete remission in 10.8% of patients in the device group versus 1.5% of patients in the sham group ($P = .02$).

Based on these results, there has been diminished enthusiasm for PFO device–based treatment in migraneurs.

**Special Interest: PFO and Diving and High-Altitude Pulmonary Edema**

The interest in diving and PFO has persisted since the early 1960s when American naval physicians examined the incidence of decompression sickness (DCS) and relationship to the patient’s PFO status. Although the current indications do not include decreasing the risk of DCS, many operators believe that this is a valid medical indication for closure. The theory is that decompressive nitrogen gas bubbles forming in the venous circulation could cross the PFO and thus cause symptoms of DCS. There have been no randomized trial data to suggest benefit of PFO closure to prevent DCS, and there remains a debate as to whether divers should even be screened for a PFO in the absence of previous episodes of DCS. A recent guidance document suggests no need for screening, with a recommendation that if a PFO closure is undertaken, screening with a follow-up shunt study and completion of antiplatelet medications after closure should be done before allowing the diver to resume activities. In small studies, there is some evidence of a benefit in patients with PFO closure.

Similar concerns have been raised for mountain climbers and the incidence of high-altitude pulmonary edema. There has been a paucity of data regarding the role of closure in this situation, but some interesting physiologic studies show no difference in the incidence of PFO in high-altitude dwellers versus sea-level dwellers but some differences in physiologic response.
Finally, platypnea-orthodeoxia syndrome has also been linked to PFO in some patients in the generally postoperative condition in which positional changes can augment right-to-left blood flow across the PFO, leading to desaturation when sitting upright. Few anecdotal data have suggested benefit of closure.\textsuperscript{49, 50}

**The Decision to Close a PFO**

The decision to percutaneously close a PFO is often a difficult one. Currently, in the United States, there are no available devices specifically indicated for PFO closure. Outside the United States, there are a number of commercially available devices (Fig. 48-11). At present, the Gore Helex and Amplatzer PFO occluder (APO) are retrained by a Humanitarian Device Exemption (HDE) from the Food and Drug Administration (FDA). The HDE is specific in the indication for mechanical closure; it states that the device may be used under the HDE only for patients who have suffered a cryptogenic stroke and who have failed warfarin therapy. This has led to a difficult decision-making tree for many physicians, in part because of the widely held belief that mechanical closure is superior and in many cases preferable to medical therapy. In addition, patients may believe that they are at risk for a recurrent cryptogenic event while on warfarin therapy, which by itself may be objectionable because of the required monitoring. As a result, a number of closures are performed outside of the HDE ("off-label"), driven both by physician and patient preferences regarding mechanical closure and avoiding warfarin or other medical therapy. This is occurring despite the lack of concrete data suggesting that mechanical closure confers any advantage over medical therapy.
A variety of devices are available outside the United States for percutaneous closure of a patent foramen ovale. Within the United States, only the CardioSeal and Amplatzer Patent Foramen Ovale (PFO) Occluder have humanitarian device exemption from the US Food and Drug Administration for secondary prevention of cryptogenic stroke. (Images of Cardioform Septal Occluder © 2015 W. L. Gore & Associates, Inc. Used with permission.)

**Percutaneous PFO Closure**

Percutaneous PFO closure can be accomplished easily with either of the 2 previously approved devices in the United States. The APO differs from the ASO in that the APO has a larger right atrial disk than left atrial disk—
opposite that of the ASO—and the APO has a very thin, 3-mm long “waist” compared to the ASO (Fig. 48-12). The APO size is reported by the right atrial disk size, and the APO comes only in 18-, 25-, and 35-mm sizes. The 18-mm device is compatible with an 8-Fr sheath, whereas the 35-mm device requires a 9-Fr sheath. Similar to the ASO, the APO is retrievable while still on the delivery cable and may be redeployed to achieve a satisfactory closure.

![Image](image.png)

**FIGURE 48-12** The differences between the Amplatzer Septal Occluder (ASO; left) for secundum-type atrial septal defects and Amplatzer Patent Foramen Ovale Occluder (right) are evident with both devices oriented with the left atrial disk at the top: the ASO has a larger left atrial disk and a larger “waist” in the middle.

The technique for deploying the APO is very similar to the previously described technique using the ASO, with the exception that no right-sided heart catheterization is necessary and there is no need for a “stop-flow” technique. Instead, the sizing for PFO closure is based not on the stretched PFO diameter but rather on anatomic measurements. The proper APO size for PFO closure is based on the shortest distance of (1) the distance between the aortic root to the defect or (2) the distance between the defect and the SVC. In addition, the ASA length should be considered. For instance, a 9-mm PFO with a distance of 12 mm from the farther edge of the PFO to the aortic root and 14-mm SVC-PFO length would dictate an 18-mm device. For a 6-mm PFO, an aortic root–PFO distance of 15 mm, and SVC-PFO distance of 20 mm, the size should be 25 mm. If any of the measured distances are less than 6 mm, the device should not be used. In many US centers, the Amplatzer multifenestrated device has been used for “off-label” PFO closure given its mechanical similarity to the APO.

To be a candidate for closure, all cryptogenic stroke patients should have a thorough workup, including hypercoagulability studies, carotid and magnetic resonance imaging studies, and a TEE to diagnose and characterize the PFO.
and its surrounding anatomy. Once the decision to close the PFO has been reached, the patient should cease taking warfarin at least 3 days prior to the procedure. Just prior to starting the procedure, antibiotics should be administered.

In the catheterization laboratory, the sizing of the defect is identical to the procedure described in the earlier APO section. No right-sided heart catheterization is necessary, and ICE may be employed for imaging. Once the size of the PFO has been established, the choice of device size ensues, and this is dictated by the size of the defect.

**Postprocedure Care**

The postprocedure care does not differ from that of ASD closures (see above).

**Complications**

Complications associated with PFO closure are similar to those of ASD closure. In an earlier study, Windecker et al\(^5\)\(^1\) reported their experience in 80 patients, of whom 8 (10%) experienced a periprocedural complication. Air embolization occurred in 2 patients, resulting in a transient neurologic deficit in 1 patient and inferior ST-segment elevation in the other. An intraprocedural cerebrovascular accident (CVA) occurred in 1 patient, also presumed due to air embolism. Cardiac tamponade requiring pericardiocentesis after puncture of the right atrium by the delivery sheath was seen in 1 patient. Three device embolization events occurred, 2 of which were successfully retrieved by percutaneous method, and in 1, the device used was a reversed button device in which the occluder portion remained in the proper position in the PFO. In another report, Hung et al\(^5\)\(^2\) closed 63 PFOs using the Clamshell, CardioSeal, or Buttoned devices. The only periprocedural complication was 4 episodes of periprocedural or postprocedural new-onset atrial fibrillation, all of which resolved within the 2.6-year mean follow-up. In another series of 152 patients with PFO and cryptogenic neurologic events,\(^5\)\(^3\) 1 patient had a femoral artery laceration that necessitated surgery and eventual surgical PFO closure. Ten procedural complications were seen: device embolization in 4 patients, cardiac tamponade requiring pericardiocentesis in 1 patient, symptomatic air
embolism in 3 patients, and arteriovenous fistula at the puncture site in 1 patient. None of these 10 patients had any permanent disability due to the complications. Braun et al\textsuperscript{54} reported their findings in 276 patients, with 11 patients (4\%) suffering a periprocedural complication. Transient atrial fibrillation was seen in 2 patients, TIAs in 2 patients, reversible ST-segment elevation in 4 patients, and transient third-degree heart block in 1 patient. Device embolization occurred in 2 patients. The experience at the Massachusetts General Hospital\textsuperscript{55} in 110 patients revealed a periprocedural complication in 2 patients: pericardiocentesis was necessary in 1 case, and a device embolism occurred in another. A significant shunt or device malposition requiring a repeat procedure was needed by 4 patients (3.6\%) in this study. In a phase I trial with the APO in 50 patients,\textsuperscript{56} an arteriovenous fistula that required surgical treatment occurred in 1 patient. There were no APO-related complications.

Data from the large randomized CLOSURE-I (Evaluation of the Starflex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale)\textsuperscript{57} and RESPECT-PFO (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)\textsuperscript{58} trials showed a relatively low rate of procedural complications, mostly clustered around vascular access. For instance, in the CLOSURE-I study, there was a 3.2\% major vascular complication rate (13 of 402 patients), which included 4 patients with a hematoma, 3 patients who received a transfusion, 1 patient who underwent a surgical vascular repair, 1 patient with left atrial perforation, 1 patient with peripheral nerve damage, and 3 patients retroperitoneal hematomas.

In RESPECT-PFO,\textsuperscript{58} there were a total of 22 adverse events in the 499 device-treated patients; among these events, there were 3 vascular events (2 bleeding and 1 hematoma), 2 cases of pericardial tamponade, and 1 cardiac perforation. There was also 1 patient with a right-sided thrombus noted periprocedurally, which led to procedure abandonment and no device deployment. Other adverse events were generally noted later in follow-up.

Taken together, the acute safety of the procedure remains very good, especially in the hands of well-experienced operators.

**Results**
PFO closure for the secondary prevention of neurologic events in patients with cryptogenic stroke has been generally positive. The incidence of an acute residual shunt after closure ranges from 17% to 55%\(^\text{51-56,59}\), a large majority of these are trivial or mild in grade. Larger shunts (moderate or greater in degree) had an incidence of 3% to 12%, with the general experience that most will close fully by 6 months. It is currently a topic of debate whether a residual shunt is related to a higher risk of recurrent neurologic events.

Windecker et al\(^\text{51}\) reported the 5-year follow-up on patients and found an annual risk of a recurrent TIA of 2.5%, 0% for CVA, and 0.9% for peripheral embolism. They also found that a residual shunt was a predictor for an event. The experience of Hung et al\(^\text{52}\) in Boston revealed 3 TIAs and 1 CVA in 63 patients at the mean follow-up of 2.6 years, for a 3.2% calculated annual risk of TIA or stroke after device placement.

In the study by Wahl et al,\(^\text{53}\) 9 patients (6%) in the 150-patient series had a neurologic event within a mean follow-up of 1.7 years after device placement. The risk of a neurologic event was significantly higher \((P = .02)\) in the 21% of patients with a residual shunt. In the United States, the small 18-patient study by Du et al\(^\text{59}\) showed acute complete closure in 12 patients (67%) and complete closure by 2 years. No neurologic events were seen within the mean follow-up of 2.2 years. In the study by Braun et al,\(^\text{54}\) 276 patients were followed for a mean of 15 months after PFO closure, and the annual risk of thromboembolic events was 1.7% for TIA, 0% for stroke, and 0% for peripheral emboli. There was no significant difference between patients with and without a residual shunt. Interestingly, 8 patients (2.9%) were noted to have thrombus adhering to the device; this prompted warfarin treatment, and follow-up TEE showed no thrombus in any of these patients. In yet another study\(^\text{53}\) involving 110 patients at a mean follow-up of 2.3 years, there was an annual neurologic event rate after PFO closure of 0.9%. The initial experience of Hong et al\(^\text{56}\) with the APO in 50 patients revealed no neurologic events after closure at a mean follow-up of 16.5 months.

The major weakness of the data generated had been the lack of a prospective randomized controlled trial of device versus medical therapy. A meta-analysis of several reports of closure or medical therapy\(^\text{60}\) included 10 studies of transcatheter closure and 6 studies of medical therapy, with 1355 patients undergoing device therapy and 895 patients treated medically for the
secondary prevention of cryptogenic neurologic events. The findings included an annual rate of recurrent neurologic events in the device group of 0% to 4.9%, whereas the medical group had an annual rate of 3.8% to 13.0%. The conclusion from this study was that transcatheter closure was safe and provided a benefit in the prevention of secondary neurologic events but that a firm recommendation about therapy could not be made in the absence of randomized controlled clinical trials comparing device and medical therapy. Indeed, a report from the American Academy of Neurology made the same recommendation regarding clinical trials to investigate the benefits of medical versus device therapy. This report noted that medical therapy itself was inconclusive as to whether warfarin or aspirin should be the recommended therapy for secondary prevention. In addition, the findings noted that PFO by itself did not increase the risk of a subsequent event in patients treated medically but that patients with a PFO and an ASA were possibly at a higher risk of subsequent events in patients treated medically.

As a result of the above recommendations and the desire to move beyond HDE status, 2 large randomized trials in the United States have examined outcomes after PFO closure for cryptogenic neurologic events. The first of these, the CLOSURE-I study, had planned to enroll 1600 patients in a randomized trial comparing device closure using the StarFlex device versus best medical therapy. In the end, 909 patients were enrolled, and there was no significant difference in events between the 2 groups in the 2-year composite end point of subsequent stroke, TIA, death at 30 days, or neurologic death between 31 days and 2 years. There were a number of interesting findings within this trial: (1) a large majority of neurologic events in both groups had no relation to the device or PFO; (2) atrial fibrillation was much more common in the device group (5.7%) versus medical therapy (0.7%); and (3) effective closure with the NMT device was 86%. The failed trial eventually led to a downfall of the company.

Results with the Amplatzer PFO device were reported in a similar randomized trial called RESPECT-PFO; the trial compared the APO against best medical therapy (antiplatelet or warfarin). In this important trial, 980 patients were enrolled and randomized to device or medical therapy with a primary efficacy end point that was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. The trial took 8 years to complete enrollment and was stopped after 25 primary end point events (9 in the device group and 16 in the medical therapy group).
In the intent-to-treat analysis, this difference was not statistically significant ($P = .08$), but the prespecified per protocol ($P = .03$) and as-treated analysis ($P = .007$) did show an advantage for the device group. There was no statistical difference in the incidence of atrial fibrillation (3.0% vs 1.5%). Five-year follow-up of the intent-to-treat analysis was recently presented in San Francisco at the TCT meeting and showed continued safety of the device and perhaps efficacy when compared to medical therapy ($P = .042$).

Subsequent large trials, such as a trial in Europe using the APO, again showed no significant advantage in PFO closure for cryptogenic neurologic events. As a result of these trials, there remains no FDA indication for percutaneous closure of PFO in the setting of a cryptogenic neurologic event.

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**MULTIPLE CHOICE QUESTIONS**

1. A 32-year-old woman is referred to you because of an abnormal electrocardiogram (ECG) showing an incomplete right bundle branch block. She has mild exertional dyspnea, and an echocardiogram is ordered because you hear a widely split S₂ on examination and she reports a history of a “hole in her heart” when she was young. A transesophageal echocardiogram reveals a 12-mm secundum atrial septal defect (ASD) and mildly dilated right ventricle (RV), with an RV systolic
pressure estimated at 44 mm Hg. What do you tell her?
A. Her ASD is not clinically significant.
B. Her ASD should be closed percutaneously.
C. Her ASD should be closed surgically.
D. You need further review of the transesophageal echocardiogram (TEE) to determine the likelihood of success for percutaneous closure.

2. Recent data from trials involving patent foramen ovale (PFO) closure devices suggest which of the following?
A. For cryptogenic stroke or transient ischemic attack (TIA), closure is statistically superior to medical therapy.
B. Migraine headaches are easily treated with PFO closure.
C. There is no statistical benefit for PFO closure in cryptogenic stroke or TIA.
D. PFO closure is dangerous and should be avoided in all cases.

3. Which type of ASD can be safely and reliably closed using a percutaneous device?
A. Ostium primum with good rim
B. Ostium secundum with multiple fenestrations but with adequate rim
C. Ostium secundum with inferior rim of <1 mm
D. Sinus venosus with adequate rim

4. You are in the catheterization laboratory and in the midst of an ASD closure. You have crossed the defect, and you notice that the patient now has inferior ST-segment elevation on her ECG and is complaining of chest pain. What do you do next?
A. Obtain arterial access and perform a coronary angiogram
B. Withdraw the venous sheath from the pulmonary vein
C. Give oxygen and supportive care
D. Give a bolus of tissue plasminogen activator (tPA)

5. A scuba diver comes to see you because his friend recently went with him for a dive and developed decompression sickness (DCS). His friend was told he had a PFO and is in the midst of a decision with his physician regarding PFO closure. Your patient has never had DCS but is alarmed by
his friend’s recent events. What do you do?
A. Reassure him that his risk is low for DCS
B. Obtain a transesophageal echocardiogram with bubbles to rule out PFO
C. Obtain a screening transthoracic echocardiogram with bubbles
D. Obtain an ECG

ANSWERS

1. D
It is likely that her shunt is clinically significant, given her symptoms as well as the RV findings. Safe and successful percutaneous closure would require adequate rims to secure a device, and the TEE would need to be reviewed more closely. It could be closed surgically, but there are no data suggesting that surgical closure would be any better than percutaneous closure pending the anatomic review.

2. C
Data from several PFO closure trials (CLOSURE-I, RESPECT-PFO, PC) showed no statistical improvement in outcomes with PFO closure versus best medical therapy as dictated by a neurologist. Data regarding migraine headaches and PFO closure are mixed at best. PFO closure has been demonstrated to be relatively safe in these large trials.

3. B
Secundum ASD is the only defect that can be safely closed as long as there is an adequate rim.

4. C
This is a classic case of air embolus. Supportive care, including oxygen, will help with resolution of the ECG findings and symptoms. Answers A and D only add risk to the procedure and are unnecessary; answer B does not help and will only add extra effort to the eventual closure of the defect because you will have to recross the defect again.
5. A

In patients who scuba dive with no prior history of DCS, there is no indication to do testing for a PFO. Answer D does not address the suspicion of a PFO.
Alcohol Septal Ablation in Drug-Refractory Obstructive Hypertrophic Cardiomyopathy

John S. Douglas Jr.

SCOPE OF THE PROBLEM

Hypertrophic cardiomyopathy (HCM), defined clinically by the presence of hypertrophy of a nondilated left ventricle without loading conditions or other recognized causes of hypertrophy, occurs in 1 per 500 individuals in the general population, with approximately 700,000 cases in the US population. HCM, inherited with an autosomal dominant Mendelian pattern, is the most common familial heart disease and the most common cause of sudden death in athletes and adolescents. HCM is caused by 1 of more than 1500 different mutations of genes encoding sarcomeric proteins. This genetic heterogeneity and the diverse and unpredictable phenotypic expressions, clinical manifestations, and prognosis limit the value of genetic testing or projections based on affected family members. The vast majority of individuals who are genotype positive/phenotype positive are asymptomatic or minimally symptomatic and are undiagnosed. Heart failure is the most common clinical presentation of HCM in adults. Diagnosis may be difficult due to compensating adjustments in lifestyle that minimize symptoms and nonspecific physical and electrocardiogram (ECG) findings. Elevation of left atrial pressure results from diastolic dysfunction and mitral regurgitation.
Limitations of cardiac output in HCM resulting in fatigue, dyspnea, presyncope, and syncope are commonly related to left ventricular outflow tract (LVOT) obstruction and low end-diastolic volume because of diastolic dysfunction. LVOT obstruction (LVOT pressure gradient ≥30 mm Hg) is present in one-third of HCM patients at rest and in an additional one-third with provocation with Valsalva maneuver, nitroglycerin, post-extrasystolic potentiation, or exercise echocardiography, a preferred method of evaluating patients with no resting LVOT gradient but marked exercise tolerance. The presence of LVOT obstruction is a predictor of HCM-related progressive heart failure and heart failure death, and relief of obstruction surgically results in better survival than achieved by patients without this treatment. Relief of LVOT obstruction is a principle goal of both medical and septal reduction therapies.

PATHOPHYSIOLOGY: A 60-YEAR ADVENTURE

The cardiac surgeons Drs. Brock and Morrow coined the term functional aortic stenosis in the 1950s to describe the absence of expected LVOT obstruction in the cardioplegia-arrested heart during open heart surgery, and in the 1960s, Braunwald et al used the newly developed techniques of left heart catheterization to investigate the pathophysiology of obstructive HCM. These hemodynamic studies demonstrated highly variable LVOT obstruction depending on physiologic and pharmacologic maneuvers, which altered loading conditions and contractility (Fig. 49-1). The advent of echocardiography in the early 1970s introduced a powerful new tool for understanding the pathophysiology, diagnosis, and prognosis of HCM and for monitoring treatment of HCM (Figs. 49-2 and 49-3). LVOT obstruction results from several mechanisms, including narrowing of the LVOT by septal hypertrophy, anterior location of the mitral valve encroaching on the LVOT, and systolic anterior motion (SAM) of the anterior mitral valve leaflet leading to SAM-septal contact (see Figs. 49-2 and 49-3). The anterior leaflet of the mitral valve is longer in patients with HCM, and this favors its sail-like movement into the LVOT resulting in (1) a pressure gradient between the left ventricle (LV) and aorta and (2) a posteriorly directed jet of mitral
regurgitation (see Fig. 49-3C). In symptomatic patients without a resting LVOT pressure gradient, provocation with Valsalva maneuver (see Fig. 49-1B) or exercise echocardiography must be considered. LVOT obstruction adversely impacts long-term outcomes with respect to morbidity and mortality. Recently, cardiac magnetic resonance imaging (MRI) has become a valuable adjunctive imaging strategy, offering greater spatial resolution and detection of hard-to-see structures by echocardiography, including LVOT membranes, anomalies of the mitral subvalvular apparatus, focal segmental LV hypertrophy, and apical abnormalities. Contrast-induced MRI hyperenhancement techniques provide an estimate of myocardial fibrosis, with absence of hyperenhancement being associated with lower risk of sudden death (SD) and hyperenhancement of ≥15% of LV mass being associated with a doubling of risk of SD.¹
FIGURE 49-1 A. Simultaneous aorta–left ventricular pressure tracings show a bifid arterial waveform typical of obstructive hypertrophic cardiomyopathy (HCM) and a large left ventricular outflow tract (LVOT) pressure gradient of over 100 mm Hg. After a premature ventricular contraction, there is an augmentation of left ventricular pressure due to increased contractility and LVOT obstruction. Although subtle, there is also a decrease in aortic pulse pressure, the Brockenbrough sign. B. In a 65-year-old man with marked exercise intolerance, there was no LVOT gradient at rest but a >100-mm Hg gradient with Valsalva maneuver. Changes in contractility (A) and loading (B) can lead to marked changes in LVOT obstruction.

FIGURE 49-2 An M-mode echocardiogram (circa 1972) of the first obstructive hypertrophic cardiomyopathy patient seen by the author. A. At rest; note marked septal hypertrophy and minimal systolic anterior motion (SAM). B. After amyl nitrite, there was marked SAM-septal contact. C. Left anterior oblique–cranial view of the left ventriculogram showing SAM-septal contact.
FIGURE 49-3 Alcohol septal ablation procedure in a 65-year-old woman with obstructive hypertrophic cardiomyopathy (HCM), disabling angina, and effort dyspnea on optimal medical therapy. Basal septal thickness was 2.3 cm, and there was systolic anterior motion (SAM) with septal contact during systole (A). Left ventricular outflow tract (LVOT) gradient at rest was 67 mm Hg (B) and 110 mm Hg with Valsalva. LVOT turbulence was present, along with an eccentric posteriorly directed jet of moderate to severe mitral regurgitation (C). The first septal perforating artery was selected (D), and a 2.5 × 9 mm balloon catheter was introduced and inflated (E) through which agitated contrast solution was injected producing brightening of the basal septum at the SAM-septal contact point. With confirmation that the correct
septal artery had been selected and that there was no contrast solution reaching the LAD or other distant sites, 3 mL of alcohol was slowly injected over 10 minutes and allowed to “dwell” for 5 additional minutes. Following alcohol injection, there was no SAM (F), and the LVOT pressure gradient was reduced to 10 mm Hg at rest and 19 mm Hg with 100 μg of nitroglycerin plus Valsalva maneuver (G). There was also no LVOT turbulence and no mitral regurgitation (H). Coronary angiography revealed an occluded septal artery (I). The patient experienced relief of symptoms and, at last follow-up 3 years later, was asymptomatic. This patient had a left anterior descending artery stent placed several years earlier that bridged across the septal artery so entry into the septal artery was through stent struts.

TREATMENT OF OBSTRUCTIVE HCM

Treatment of patients with obstructive HCM is aimed at relief of symptoms and preventing SD (Table 49-1). Strategies to achieve the latter include abstaining from intense competitive sports and implantable cardioverter-defibrillator (ICD) implantation in high-risk patients,\(^5,6\) as well as treatment strategies to reduce LVOT obstruction. The 2011 American College of Cardiology (ACC)/American Heart Association (AHA) guideline statement “stand alone” Class I indications for ICD are prior cardiac arrest and sustained ventricular arrhythmias (ventricular fibrillation [VF] or ventricular tachycardia [VT]); Class II indications are SD in a first-degree relative, LV wall thickness ≥30 mm, and unexplained syncope.\(^5\) Other SD risk factors to be considered include nonsustained VT and abnormal blood pressure response to exercise. In a 2-center longitudinal study of 1000 patients with HCM presenting at 30 to 59 years of age, 5- and 10-year survival rates (confined to HCM death) were 98% and 94%, respectively, and were not different from the expected all-cause mortality in the general US population.\(^7\) This 0.5% per year mortality rate achieved by contemporary management strategies compares favorably to the 3% to 6% per year mortality rate reported in early HCM referral cohorts and the 1.5% per year mortality rate in the 1990s prior to utilization of current strategies. Although not included in the 2011 guideline statement,\(^5\) MRI-assessed myocardial fibrosis has begun to assume importance in risk stratifying patients.\(^7\) Late gadolinium enhancement was also a notable omission from the European Society of Cardiology (ESC) risk prediction model,\(^6\) which when applied to 35 incurred SD events in one study found that 21 (60%) failed to qualify for an ICD.\(^8\)
This and the absence of other potentially high-risk clinical entities (eg, apical aneurysm) suggested that the available guideline statements\(^5,6\) are outdated with respect to SD prevention by ICDs.

**Table 49-1 Management Goals and Strategies in Obstructive Hypertrophic Cardiomyopathy**

<table>
<thead>
<tr>
<th>Relieve symptoms</th>
<th>Prevent sudden death</th>
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<tr>
<td>• Lifestyle changes</td>
<td>• Lifestyle changes</td>
</tr>
<tr>
<td>• Medications</td>
<td>• Implantable cardioverter-defibrillator</td>
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<td>• Septal reduction</td>
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<td>° Myectomy</td>
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<td>° Septal Ablation</td>
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<tr>
<td>• Dual-chamber pacemaker</td>
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Relief of symptoms in patients with obstructive HCM is primarily accomplished by reducing LVOT obstruction by lifestyle changes and pharmacotherapy. Dehydration, the splanchnic pooling that accompanies a large meal, and alcohol consumption increase LVOT obstruction and should be avoided. β-Blockers are the drug of choice for treatment of symptomatic obstructive HCM and act by favorable negative inotropic and chronotropic effects. β-Blockers reduce LVOT gradient and are particularly effective in reducing provoked gradients such as those associated with exertion and have a class I indication in the 2011 guideline statement, which recommends titrating the dose to a resting heart rate of 60 to 65 bpm.\(^5\) Verapamil also has a Class I indication for symptomatic patients with HCM who do not respond to β-blockers or have contraindications to these drugs. Caution has been recommended in the use of verapamil in symptomatic patients with very large resting LVOT gradients because sudden hemodynamic collapse has been reported. Verapamil has negative inotropic and chronotropic effects similar to β-blockers. Patients with LVOT obstruction who remain symptomatic despite treatment with β-blockers and/or verapamil can be considered for treatment with disopyramide, a Class IA antiarrhythmic drug with negative inotropic
effects as well as anticholinergic side effects that hinder widespread usage. In addition, initiation of disopyramide therapy requires in-hospital cardiac monitoring for QT prolongation and arrhythmias (torsades de pointes). Disopyramide has a Class IIa indication in the 2011 guidelines.⁵

MANAGEMENT OF DRUG-REFRACTORY OBSTRUCTIVE HCM

For patients whose symptoms and LVOT obstruction prove refractory to optimal pharmacologic therapy, septal reduction therapies with myectomy or alcohol septal ablation are the currently recommended strategies.⁵,⁹ Dual-chamber pacing, which was widely used 20 years ago, was shown in 3 randomized crossover trials to produce a significant improvement in symptoms and exercise tolerance along with a decrease in LVOT gradients in <50% of patients. This led to a Class III indication for pacing as first-line therapy in drug-refractory patients.⁵ The observation that older patients were a subgroup that benefited most led to a 2011 guideline class IIb recommendation for pacing in patients with obstructive HCM who were poor candidates for septal reduction therapy.⁵ The choice of septal reduction strategy (myectomy or alcohol septal ablation) requires a comprehensive evaluation of clinical symptoms, comorbidities, and hemodynamic, echocardiographic, and angiographic features and should incorporate the wishes of a well-informed patient.¹⁰

ROLE OF SURGICAL MYECTOMY

The Morrow procedure, a transaortic approach to septal myectomy, was initially adopted as safe and effective after presentation of the outcomes of 83 patients in 1975.¹¹ Failure of this procedure in selected patients and a greater appreciation of the diversity of mitral valve structural abnormalities in HCM by Klues and colleagues¹²,¹³ led to alternative surgical techniques to include a more extensive myectomy,¹⁴ as well as approaches to abnormalities of the mitral valve and papillary muscles¹⁵,¹⁶ using intraoperative transesophageal echocardiography monitoring. In patients with other cardiac issues such as
atrial fibrillation or obstructive coronary disease, additional procedures may be carried out (maze procedure or coronary bypass). In the current era, the risk of surgery in HCM centers of excellence has decreased significantly, with reported mortality for isolated myectomy ranging from 0.0% to 1.5%,\(^{17-20}\) with some reports of the additional procedures increasing risk to 2% to 3.4%.\(^ {17,21}\) Although long-term outcomes after myectomy have not been evaluated in a randomized controlled trial, observational studies have almost uniformly reported significant improvements in heart failure symptoms, functional capacity, and survival similar to that of the general population.\(^ {2,3,7}\)

Surgical myectomy results in permanent reductions in LVOT obstruction, reduces or abolishes mitral regurgitation, and is associated with long-term survival exceeding that of a comparable group of unoperated patients with LVOT obstruction.\(^ {3}\) Surgical myectomy results in excellent long-term outcomes and has a Class IIa indication in the 2011 guideline statement.\(^ {5}\) However, it is an invasive procedure that requires well-honed surgical skills not widely dispersed, and this has resulted in underutilization, particularly in Europe where its demise was inaccurately reported.\(^ {20}\)

**ROLE OF ALCOHOL SEPTAL ABLATION**

Alcohol septal ablation (ASA) is a percutaneous catheter-based procedure that was first reported by Sigwart\(^ {22}\) in 1995. He had previously noted that balloon occlusion of the first septal perforator artery temporarily reduced the LVOT pressure gradient and correctly surmised that delivery of alcohol would produce infarction of the hypertrophied septum and permanent reduction in LVOT gradient. When performed by skilled operators,\(^ {23-27}\) ASA leads to reductions in peak resting or provoked LVOT gradient in >80% of patients. Treatment of the portion of the hypertrophied septum producing the obstruction, that is, the SAM-septal contact area, leads to immediate at least partial relief of obstruction with further decrease over time as thinning of the septum occurs. Reductions in mitral regurgitation parallel the reduction in LVOT obstruction such that patients with severe obstruction and significant SAM-related mitral regurgitation do well with ASA (see Fig. 49-3). Long-term benefits include reduction in LV end-diastolic pressure, regression of
LV hypertrophy, reduced size of the left atrium, less atrial fibrillation, and relief of pulmonary hypertension.\textsuperscript{23,26-30} ASA results in significant improvement of heart failure symptoms, peak oxygen consumption, and exercise capacity. Similar to the experience with surgical septal reduction, patients after successful ASA also appear to have long-term survival rates comparable to the non-HCM population.\textsuperscript{27} The less invasive nature of ASA with prompt return to active lifestyle with continued improvement over time has led to a dramatic increase in ASA worldwide, far exceeding the number of surgical myectomy procedures. ASA limitations include the following: (1) less precise targeting of the anterior basal septum, the SAM-septal contact area removed by the surgeon; (2) the need for permanent pacing in a significant minority of patients; and (3) a septal scar with, as yet, uncertain long-term consequences.

**Patient Selection for ASA**

Patients selected for ASA must qualify based on clinical, hemodynamic, and anatomic criteria. The 2011 ACC/AHA guideline statement and the European guidelines recommend that ASA be offered only to patients with severe symptoms despite optimal medical therapy (usually New York Heart Association (NYHA) functional class III or IV or other exertional symptoms that interfere with everyday activity or quality of life)\textsuperscript{5,9} (Table 49-2). The physician should be convinced that relief of obstruction and subsequent favorable changes in mitral regurgitation, diastolic compliance, and LV hypertrophy will result in significant improvement in symptoms. This assessment may be difficult in the patient with severe obstructive HCM and severe chronic pulmonary disease and/or other comorbidities. Hemodynamic criteria required include dynamic LVOT gradient at rest or with physiologic provocation $\geq 50$ mm Hg associated with SAM of the mitral valve. Dynamic outflow obstruction produces a characteristic “spike and dome” arterial waveform, post-extrasystolic potentiation, and the Brockenbrough sign (see Fig. 49-1). Anatomic features that must be present include basal septal hypertrophy $\geq 15$ mm. ASA is discouraged in patients with septal thickness $\geq 30$ mm due to uncertain effectiveness of ASA and in patients with septal thickness $<1.5$ mm due to the risk of creating a ventricular septal defect.\textsuperscript{5} Patients with midventricular obstruction, subvalvular membrane, intrinsic mitral valve or subvalvular abnormalities, and malpositioned papillary
muscles are not good candidates for ASA. Because ASA induces a right bundle branch block in a majority of patients, a preexisting left bundle branch block results in a high probability of complete heart block. The 2011 guideline statement gives a Class IIa indication for surgical myectomy and class IIa for ASA when surgery is contraindicated or high risk (see Table 49-2). ASA may be selected over myectomy by a well-informed patient, and this is a Class IIb indication. The most recent European guideline statement gave ASA and myectomy equal status as therapeutic options in drug-refractory obstructive HCM. The 2011 guideline statement indicates that ASA should not be done in patients less than 21 years of age and discouraged in those younger than 40. This recommendation to avoid ASA in younger patients is a result of the more complete relief of obstruction with myectomy, concern regarding the arrhythmic potential of the septal scar produced by ASA, and the paucity of a long-term data at the time the guideline statement was drafted. Since then, longer term follow-up has been completed, and although there remain some concerns, several studies have reported favorable outcomes in younger patients after ASA, with survival similar to the age-matched general population and to age-matched HCM patients without obstruction.

Table 49-2 Indications for Septal Reduction Strategies

<table>
<thead>
<tr>
<th>Class I: Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive hypertrophic cardiomyopathy (HCM) clinical program and only for severe drug-refractory symptoms and left ventricular outflow tract (LVOT) obstruction.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIa</td>
</tr>
<tr>
<td>1. Surgical myectomy is the first consideration for the majority of patients with HCM with severe drug-refractory symptoms and LVOT obstruction.</td>
</tr>
<tr>
<td>2. When surgery is contraindicated or high risk, alcohol septal ablation can be beneficial in eligible adult patients with severe drug-refractory symptoms and LVOT obstruction.</td>
</tr>
<tr>
<td>Class IIb</td>
</tr>
<tr>
<td>1. Alcohol septal ablation may be considered as an alternative to surgical myectomy when a well-informed patient expresses a preference for septal ablation.</td>
</tr>
</tbody>
</table>
2. Septal ablation is discouraged in patients with marked septal hypertrophy (>30 mm).

Class III: Alcohol septal ablation should not be done in patients less than 21 years of age and discouraged in adults less than 40 years of age if myectomy is a viable option.

Performance of ASA

Although some have suggested omitting medications for 24 hours prior to ASA (to ensure a LVOT gradient that can be monitored during the procedure), it is the author’s practice to continue medication. A temporary pacemaker is inserted via the right internal jugular vein, which is left in place for 48 hours. Some have preferred screw-in temporary leads, but a balloon-tip pacing lead is adequate if carefully managed. Dual arterial access is obtained in order to monitor the LVOT gradient during the procedure. Unfractionated heparin is administered to achieve an activated clotting time >250 seconds. The degree of baseline LVOT obstruction is determined by measurement of resting and provoked pressure gradient using the Valsalva maneuver and/or nitroglycerin or post–premature ventricular contraction gradient. Patency of the right coronary artery is confirmed, and angiographic views of the left coronary artery are taken to highlight the arterial supply to the basal septum (30° right anterior oblique with cranial angulation and 30° left anterior oblique with caudal angulation are frequently the best angles to display the anatomy without overlap). The basal septum is most frequently supplied by septal perforating branches from the left anterior descending artery (LAD); however, there may be branches supplying the septum that arise from the diagonal, ramus intermedias, circumflex, left main, or right coronary arteries. Based on the location of the septal hypertrophy and SAM-septal contact, the most likely feeding septal artery is selected to be tested by myocardial contract echocardiography from a transthoracic approach. A short over-the-wire balloon catheter is chosen to approximate the septal artery diameter (frequently a 1.5 × 6 mm balloon) (see Fig. 49-3). A steerable coronary guide wire, preferably with hydrophilic coating, is introduced into the septal branch followed by the balloon catheter. If the septal artery is difficult to enter with the guide wire, reshaping of the guide wire may be necessary. The coronary arteries in HCM patients are frequently large, and it may be difficult to direct the guide wire tip, which is tracking along the roof of the artery, into the
small septal artery arising from the “floor” of the artery. The author avoids use of redirecting strategies such as the Venture catheter or “blocking balloon” and prefers to pass an extra-support “buddy wire” into the distal LAD, which straightens the artery slightly, permitting entry into the septal branch. In the presence of a very large septal perforating artery, it may be desirable to isolate a branch for treatment to limit the size of septal infraction and reduce the risk of complete heart block (Fig. 49-4). It is not essential that the septal artery meet any size requirements. Tiny, almost invisible, septal branches that supply the targeted septal region can often be entered with hydrophilic guide wires and small (1.25-mm) balloon catheters (Fig. 49-5). Once placed in the proximal portion of the septal artery, the balloon catheter is inflated to 4 to 5 atm. The coronary guide wire is removed, and contrast solution is injected through the balloon to ensure that it is occlusive and that no contrast enters the parent vessel. Oversizing of the balloon is avoided because it may lead to “melon seeding” of the inflated balloon back into the parent vessel with escape of alcohol, with potentially catastrophic consequences. After stability of the inflated balloon in the septal artery is assured, a 50/50 mixture of contrast and saline is agitated with air and injected. The myocardial segment receiving the “bubbles” appears bright on echocardiography (see Figs. 49-3 to 49-5; Figs. 49-6 and 49-7). If brightening of the SAM-septal contact zone occurs with no brightening elsewhere, 1 to 2.5 mL of alcohol is delivered over 8 to 10 minutes, after adequate analgesia is assured. If “brightening” of the right side of the septum occurs (see Fig. 49-6) or if brightening of papillary muscle (see Fig. 49-7) or other nonseptal areas is noted, another septal artery must be sought. In the author’s experience, septal arteries arising from a diagonal branch are more likely to supply the left side of the septum, as illustrated in Figure 49-6. The optimal amount of alcohol to administer is uncertain, but lower amounts of alcohol have been associated with lower rates of complete heart block. Careful monitoring of balloon stability, echocardiographic findings, and LVOT pressure gradient are carried out during alcohol injection. After administration of 1 to 2 mL of alcohol, reassessment of the LVOT pressure gradient is carried out (either resting or provoked gradient based on the initial assessment) with a goal of achieving a gradient <20 mm Hg if possible. Because adequate gradient reduction is highly correlated with long-term outcomes, residual gradient >20 mm Hg should lead to consideration of treating a second septal artery. If satisfactory LVOT gradient reduction is
achieved, the procedure is ended after testing the pacemaker and ensuring that it is well protected because there may be no escape rhythm if complete heart block occurs (see discussion of complications in the following section).
FIGURE 49-4 Subselecting a septal artery branch due to very large septal artery distribution: A. Coronary angiogram showing unusually large first septal perforating artery. B. Resting left ventricular outflow tract (LVOT) gradient of 100 mm Hg. C. Balloon inflation in the posterior branch of the septal artery and injection of 2 mL of alcohol after confirming appropriate basal septal brightening D. Postprocedure LVOT gradient was 11 mm Hg (E).

FIGURE 49-5 Use of a small, almost invisible, septal artery to deliver alcohol to the basal septum. A. Right anterior oblique coronary angiogram (arrow showing tiny septal artery). B. Balloon catheter inflated in the small septal artery. C. Septal brightening following contrast mixture injection. D. Resting left ventricular outflow
tract pressure gradient was reduced from 75 to 8 mm Hg with excellent subsequent clinical outcome.

**FIGURE 49-6** Seeking a septal artery supplying the left side of the basal septum. A. Left ventricular outflow tract (LVOT) gradient at rest of 100 mm Hg. B. Right anterior oblique cranial coronary angiogram showing septal branches arising from left anterior descending artery (LAD) and also from the first diagonal artery. C. Brightened right side of septum (arrow) when contrast bubbles were injected into balloon placed into the septal artery arising from the LAD. D. Balloon in septal artery arising from diagonal artery. E. Left side of septum brightened appropriately after contrast was injected into the septal artery from the diagonal artery. F. Resolution of LVOT gradient after alcohol injection in the septal artery arising from the diagonal artery.
FIGURE 49-7 Contrast myocardial imaging showing inappropriate myocardial brightening remote from basal septum. A. Left anterior oblique–caudal view showing septal artery arising from ramus intermedius artery. B. Arrow shows guide wire in this septal artery. C. Following injection of agitated contrast mixture, brightening occurred remote from the septum in what appears to be a papillary muscle. D. Right anterior oblique view of left coronary artery showing septal artery from left anterior descending artery (LAD). E. A balloon catheter is placed in a septal artery arising from the LAD. F. Brightening of the basal septum occurred after injection of contrast mixture. G. Left ventricular outflow tract gradient that was 100 mm Hg before ablation fell to zero and was 13 mm Hg during a Valsalva maneuver.

Complications of ASA

The most common complications of ASA involve the conduction system. Approximately 60% of patients develop right bundle branch block with left anterior hemiblock in 20%; 10% develop left bundle branch block, and transient complete atrioventricular (AV) block occurs in 25% to 55% of patients.\textsuperscript{24-27,38-40} Recently reported need for permanent pacemaker implantation ranged from 3%\textsuperscript{38} to 20%.\textsuperscript{26} Reinhard et al\textsuperscript{38} reported that 55% of patients experienced brief AV block during the procedure with persisting AV block in 23% at 14 hours, 18% after 3 days, 7% at 1 week, and only 3% at 13 days, leading the investigators to recommend waiting ≥7 days before permanent pacemaker implantation is performed. This length of time is unacceptable to many US physicians. Perhaps some form of temporary pacing that permits outpatient observation can be applied in the future. Also, a move to use lower alcohol dosing has reduced the rate of AV block, although less complete relief of LVOT obstruction has been associated with lower alcohol doses.\textsuperscript{41,42} Procedural complications reported among 874 ASAs performed in 9 US centers were LAD dissection in 8 patients, cardiac tamponade in 4, retroperitoneal bleed in 1, ventricular septal defect in 1, VT/VF in 14, high-grade AV block in 78, and death in 6.\textsuperscript{42} Among 459 ASA procedures reported from 9 European centers, there was only 1 in-hospital death; 18% of patients developed complete heart block and 9% had permanent pacemaker implantation.\textsuperscript{43} The volume of alcohol injected in the US cohort (2.9 ± 1.5 mL) was greater than in the European experience (median dose, 1.5 mL; 87% of patients received ≤2 mL). Although use of intraprocedural myocardial contrast echocardiography (MCE) is thought to reduce myocardial necrosis distant from the septal target area,\textsuperscript{44} inferior
myocardial infarction has been reported in 2 patients in whom MCE was used.45 The potential for collateral transport of alcohol suggests that ASA should not be attempted in patients with right or dominant circumflex coronary artery obstruction.

**Clinical Outcome After ASA**

Using a definition of procedural success as ≥50% reduction in peak resting or provoked LVOT gradient and final resting gradient ≤20 mm Hg without death or need for surgery, ASA was successful in 80% to 85% of patients.23-27 Procedural failure may occur due to absence of or inability to access an appropriate septal perforating artery or significant procedural complications. Failure to achieve a sustained LVOT gradient reduction after an apparently successful procedure may occur because of transient septal stunning due to balloon-induced septal ischemia or changing ventricular loading resulting in gradient reduction (intravascular volume increase due to angiographic contrast medium and/or saline infusion). A need for right ventricular pacing may also contribute to intraprocedural LVOT gradient reduction. Finally, administration of “extremely low-dose” alcohol (<1 mL) has been associated with higher LVOT gradients and persisting symptoms.43

In long-term follow-up, clinical efficacy of ASA has been demonstrated with improvements in NYHA classification from class III to I, improvements in exercise time and maximal oxygen consumption, and favorable LV remodeling. Fernandes et al46 showed progressive reductions in LVOT gradients and septal thickness out to 10 years. However, lack of precision inherent in ASA leaves a significant minority of patients (~15%) with disabling symptoms following the procedure due to residual LVOT obstruction and/or diastolic dysfunction. A repeat septal reduction procedure was needed in 10% of ASA-treated patients reported by Sorajja et al27 and in 18% by Fernandes et al46 (14% had repeat ASA; 4% had myectomy). In 94% of repeat ASA procedures, there was successful reduction in LVOT obstruction and long-term relief of symptoms.46 Among 874 ASA patients reported in a North American registry, 15.6% required at least 1 additional repeat septal reduction procedure (ASA in 12.8%; myectomy in 2.8%).42

**Survival After ASA**
Two small longitudinal studies raised concerns regarding a possible arrhythmogenic effect of septal ablation scar. Among 89 ASA-treated patients, there was no mortality attributed to sudden cardiac death during a 5-year follow-up period. However, among 42 patients with ICD or pacemaker, 9 had documented VT/VF, for an annual event rate of 4.9%. Among 91 ASA patients followed for 5.4 years, 19 (21%) experienced cardiac death or ICD-aborted cardiac death, with an estimated annual event rate of 4.4%. Whether the relatively large volume of alcohol administered (mean, 3.5 mL) contributed is uncertain. Several studies compared survival following ASA to that in the general population or to medically treated HCM patients. Sorajja et al found the 8-year survival of ASA-treated patients to be the same (79%) as the expected survival of a similar US population. Vriesendorp et al reported that 10-year survival was similar in medically treated obstructive HCM patients (84%), ASA-treated patients (82%), and nonobstructive HCM patients (85%). In a North American registry of 874 ASA patients, the 1-, 5-, and 9-year survival rates were 97%, 86%, and 74%, compared to 98%, 95%, and 88%, in a disease-free US population. In a Scandinavian 4-center study of 279 ASA-treated patients, the 10-year survival rate was comparable to the age- and sex-matched general population.

**COMPARISON OF ASA AND MYECTOMY**

Since the development of ASA more than 2 decades ago, there has been considerable debate as to the comparative efficacy and safety of the 2 septal reduction strategies of ASA and myectomy. Because there are no randomized comparisons and none are anticipated, consideration of observational studies of these very different therapies is necessary. MRI performed before and after ASA (n = 24) and myectomy (n = 24) showed that the site of septal reduction differed substantially with respect to location and extent. With myectomy, the surgeon consistently removed about 6 g of anterior basal septum, producing left bundle branch block in one-half of patients. ASA performed in patients 12 years older resulted in right bundle branch block in 60% and transmural septal infarction (involving 16 g of myocardium) in 75% of patients. Necrosis confined to the right side of the septum sparing the basal
septum occurred in 25%, accounting for failure to relieve obstruction in a substantial minority of patients. This observation highlights the importance of identifying septal arteries that supply the left side of the basal septum (see Fig. 49-6; Fig. 49-8). The comparative imprecision of ASA results in a need for repeat procedures, as has been noted, but yields long-term symptomatic benefit and survival similar to myectomy in published meta-analyses. Myectomy has a predictable track record, but the less invasive and repeatable ASA has considerable appeal to both patients and their physicians, and the favorable long-term (8-10 years) results currently being reported from multicenter and multinational registries are reassuring. The place of ASA in younger patients and in those with septal thickness ≥30 mm is less clear. Sorajja et al reported that younger patients (<65 years old) obtained better symptom relief with myectomy. However, among 110 younger patients (<45 years old; mean age, 35 years), Leonardi et al reported that, despite greater septal thickness in younger patients (2.2 vs 2.0 mm; \(P = .02\)), equally good relief of LVOT obstruction and symptoms was obtained with ASA with fewer procedural complications. Similarly, among 75 patients ≤50 years old (mean age, 42 years) treated with ASA in the Czech Republic and followed a median of 5.1 years, favorable relief of symptoms (NYHA class 2.8 to 1.6, \(P < .01\)), LVOT gradient reduction (73 to 16 mm Hg; \(P < .01\)), and reduced septal thickness (2.3 to 1.4 mm; \(P < .01\)) were reported with only 1 case of SD (annual risk, 0.2%). In a European multinational registry, 26 patients had basal septal thickness ≥30 mm (median, 32 mm; maximum, 54 mm) and underwent ASA, which was equally effective compared with patients without massive septal hypertrophy. These studies suggest that ASA results in similar hemodynamic and symptom improvements in adult patients independent of age and may be effective in selected patients with massive septal hypertrophy.
FIGURE 49-8 Pathologic specimen of the heart of an 84-year-old woman who died several days following an otherwise successful alcohol ablation procedure because of retroperitoneal bleeding while on intravenous heparin bridge to warfarin anticoagulation for stroke prevention. There was necrosis of the left side of the thickened basal septum, which had resulted in complete relief of left ventricular outflow tract obstruction and mitral regurgitation. Bleeding is one of the complications of alcohol septal ablation. Contrary to the report of Valeti et al in which magnetic resonance imaging studies following alcohol ablation showed either transmural necrosis or necrosis of the right side of the septum, this patient appears to have had necrosis primarily of the left side of the septum involving the systolic anterior motion (SAM)–septal contact point (note the presence of a septal callus as the result of repeated contact with the anterior mitral valve leaflet).

REFERENCES


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**MULTIPLE CHOICE QUESTIONS**

1. What are the prevalence of hypertrophic cardiomyopathy (HCM) in the general population and the number of Americans affected?
   A. 1 in 10,000; 35,000 Americans affected
2. Which statement most accurately characterizes the occurrence of left ventricular outflow tract (LVOT) obstruction (gradient >30 mm Hg) in patients with HCM?
   A. 9 in 10 have resting or provoked obstruction
   B. 6 in 10 have resting or provoked obstruction
   C. 3 in 10 have resting or provoked obstruction
   D. 1 in 10 have resting or provoked obstruction

3. What is the most useful method of confirming a diagnosis of HCM?
   A. History
   B. Physical examination
   C. Electrocardiogram
   D. Echocardiogram
   E. Magnetic resonance imaging

4. Which statement most accurately characterizes the comparison of surgical myectomy and alcohol septal ablation (ASA) in treatment of patients with drug-refractory symptoms and obstruction?
   A. Higher in-hospital mortality with myectomy; similar 1-year mortality
   B. Similar in-hospital and 1-year mortality
   C. Higher in-hospital and 1-year mortality with ASA
   D. Higher in-hospital and 1-year mortality with myectomy

5. Which of the following most accurately describes outcomes of ASA?
   A. Right bundle branch block in a majority
   B. Left bundle branch block in one-third of patients
   C. Transient complete heart block in 70%
   D. Transient complete heart block in 20%

**ANSWERS**

1. D
2. B

3. D

4. B

5. A
Device Retrieval Systems

Kirk N. Garratt

BACKGROUND

Unintended loss of material during catheter-based cardiovascular procedures is uncommon but may have serious consequences. Occasionally, a lost or embolized item ends up in a small peripheral vessel, where it can be left in place safely. More often, retrieval of the lost material is desired to reduce risks of thrombosis, infection, and perforation.

The problem of lost foreign bodies in blood vessels is long-standing; early reports of percutaneous vascular foreign body removal first appeared 50 years ago.\textsuperscript{1,2} A review of the published literature in 1991 found nearly 200 reported cases with a percutaneous retrieval success rate of 90%.\textsuperscript{3} A more recent review concluded that percutaneous retrieval of peripheral intravascular foreign bodies has a high success rate and minimal morbidity and is preferable to open vascular surgical removal.\textsuperscript{4} All manner of gear has been liberated into blood vessels (filters, plugs, coils, torn balloon fragments, rotational atherectomy burrs, fractured catheters, percutaneous heart valves), but in the adult catheterization laboratory, losses most often involve retention of fractured coronary guide wire fragments or unexpanded coronary stents that have been stripped free of their delivery balloon catheters. Stent loss and attempts at their retrieval are associated with increased rates of complications, including need for coronary artery bypass grafting surgery, myocardial infarction, and death.\textsuperscript{5} Loss of foreign bodies in the coronary arteries has been reported to occur in slightly less than 1\% of cases,\textsuperscript{6} but
retention and embolization events are likely to be significantly underreported. As radial artery access gains in popularity, retrieval of lost foreign bodies may prove more difficult, although the techniques described herein have proven useful in this setting. Optimal management of lost interventional products requires (1) judgment about when to leave retained components in place and when to remove them; (2) knowledge of those techniques proven to be effective and efficient at foreign body removal; and (3) competency with a few specialty devices designed to assist in component removal.

AGGRESSIVE OR CONSERVATIVE MANAGEMENT

Significant harm can befall a patient with a retained component. Although late infection, perforation, and even material toxicity are concerns, the principal anxiety is thrombosis; occurring in a coronary artery or similar sensitive vessel, thrombosis around a foreign body can be fatal. However, extraction of foreign bodies from the vascular system carries risk. Thus, before attempting to retrieve a misplaced or embolized component, it is reasonable to ask, “Can I just leave the foreign body where it is?”

Several factors must be considered in the decision process:

1. **Is the retained component in a location that is highly sensitive to the impact of thrombosis?** A sudden thrombotic event in any blood vessel is unwanted but is more easily tolerated in noncritical locations. Fragments left in the left main coronary artery; the proximal portions of the left anterior descending arteries or dominant left circumflex or right coronary arteries; the profunda femoralis; or any cranial artery represent very high risk of harm in the event of thrombosis. Those in arterial or venous structures serving somatic tissue (not organs) are least sensitive to thrombosis.

2. **Is the retained component deformed in such a manner that it disturbs blood flow significantly?** A study of coronary stent design found that increasing stent thickness from approximately 81 to approximately 161 μm increased thrombus development by approximately 150% in animals and ex vivo flow chambers. Lost components typically intrude into the
vessel lumen to a much greater extent. Venous structures may be more prone to thrombosis related to flow perturbation than arteries even when antiplatelet therapies are used. The more adherent a component is to the vessel wall, the less blood flow is disturbed, and clot risk is reduced. In general, smaller fragments that lay close to the vessel surface are better candidates for conservative management.

3. **Can the component be compressed?** In view of the above, reducing the profile of an offending component may significantly reduce the risk it poses. This is especially attractive for coronary stents, which are meant to be compressed into the vessel wall, but compressing other materials into vessels (especially benign peripheral arterial locations) may be safer than attempting component retrieval. If conservative management is under consideration, an attempt to reduce the profile of the retained fragment through balloon angioplasty should be considered.

4. **Does the retained fragment extend from one vascular area to another?** A fractured guide wire may be unspooled over a distance of several feet, resulting in a trail of thin wire that may extend from a coronary artery to the descending aorta. This imbues risk to multiple vascular segments simultaneously and favors fragment retrieval. The thin filaments of wire, when adjacent to coronary stents or other vascular objects, appear to create an environment of high risk for thrombosis.

5. **Is the approach to the retained component with a retrieval device complicated?** The simpler the approach, the greater the likelihood that the component will be extracted safely. Excessive tortuosity, diffuse vascular disease, calcification, thrombosis, and (especially) small vessel caliber make component retrieval more difficult. Although these characteristics likely contribute to thrombosis risk also, the risk of causing additional harm during attempted retrieval may be prohibitive. Note that retained foreign bodies that are entrapped pose greater risk than those that are simply embolized.

### DEVICES

**Snares**
Snaring devices remain the most useful and ubiquitous commercial retrieval devices available. Before the widespread availability of commercial vascular snares, loop snares were fashioned by doubling over a long coronary guide wire, feeding both ends of the wire into the distal end of a vascular catheter, and pulling the wire ends simultaneously at the proximal end of the catheter to collapse the loop of wire formed at the distal catheter tip (Fig. 50-1). Creating a kink in the mid-portion of the guide wire before it is inserted can be helpful, since this facilitates formation of a rounder loop. Unfortunately, these crude loops lack maneuverability: the plane of the loop runs parallel to the catheter, limiting utility. Attempting to angle the loop before insertion can be somewhat helpful, but creating a loop that deviates from the axis of the delivery catheter by more than 20° to 30° is difficult.

**FIGURE 50-1** Forming a loop snare using a coronary guide wire and a simple hollow catheter. Advancing both ends of the wire into the distal catheter tip forms a loop. Pinching the wire to create a bend increases the circularity of the formed loop.
Commercial loop snares are now widely available in a variety of sizes and shapes, including loops with angles (relative to the delivery catheter) ranging from 0° to 90° and snare diameters ranging from 2 to 35 mm (Fig. 50-2). Snares with loops less than 10 mm in diameter are generally referred to as “micro-snares,” Commercial snares are made of complex alloys, like braided nitinol, that hold their shape much better than steel-based wires. The snare portion may be coated in gold or other radio-opaque material to enhance fluoroscopic visualization. Closure of the snare is affected by retracting a lever or a single wire, which can usually be locked into place with a turnscrew device, freeing hands for other purposes. The catheter portion ranges in length from 65 to 120 cm (micro-snares may be up to 175 cm) and are typically 4 to 6 Fr in diameter.
Variants on the single-loop snare theme include the EN snare (Merit Medical, Jordan, UT), which incorporates 3 interlaced nitinol loops angled 120° from one another that form a tulip-shaped device when opened (Fig. 50-3). Seven different snare configurations and sizes ranging from 2 to 45 mm provide broad applicability; the delivery catheter is 6 Fr. A 4-loop device that forms a clover-shaped snare is appropriately called a CloverSnare 4-Loop Retrieval System (Cook Medical, Bloomington, IN) (Fig. 50-4). Designed chiefly for use in the peripheral arterial system, this 6-Fr system uses a telescoping guide delivery system; the outer sheath is 80 cm, the inner sheath is 85 cm, and the snare catheter length is 90 cm.
FIGURE 50-3 EN snare. This unique snaring device assumes a tulip shape with 3 petal-like nitinol loops that expand outward when the inner wire is advanced and retract inward as the wire is retracted. (Merit Medical, reprinted by permission.)

FIGURE 50-4 CloverSnare 4-loop Retrieval System. This 4-wire device resembles a 4-leaf clover when fully expanded. Retracting the loops into the delivery catheter forms an effective trap. (Permission for use granted by Cook Medical, Bloomington, Indiana.)

An innovative snare device is the LoopMaster-Sochman snare (Andramed Medical Devices), available in Europe. This somewhat more complex device is designed to help when a closed loop snare cannot be advanced around the free end of a lost component (Fig. 50-5). Instead, a closed loop with a preformed “cobra head” shape is advanced along one side of a lost
component. A second straight wire is then advanced along the opposite side of the lost component and through the loop snare. When the loop snare is closed, it captures the second wire, forming a new snare around the lost component.

![LoopMaster-Sochman snare](image)

**FIGURE 50-5** LoopMaster-Sochman snare (Andramed Medical Devices, Reutlingen, Germany). When a loop snare cannot be passed around the end of a foreign body, the curved portion of this snare can be advanced alongside the retained item and manipulated around it. Then, the straight wire component is advanced, creating a loop around the item. (Used with permission from Andramed GmbH, Germany.)

The ExPro (Radius Medical, Maynard, MA) straddles the boundary between loop snares and basket retrievers. This device is essentially a loop snare with a twist—literally. The snare portion is twisted such that the snare makes a 180° turn as it exits its delivery catheter, which may facilitate entrapment of a foreign body.

**Baskets**

Basket retrievers are somewhat more complex variants of loop snare retrieval devices. Basket retrievers were developed to aid in management of ureteral or gastrointestinal stones, but many have been used successfully in the vasculature. Some have leading flexible wire tips, although most do not (Fig. 50-6). These are generally larger tools suitable for use in the aorta or larger
arteries and veins, but not in the coronary arteries or bypass grafts. Although elegant in design, their use in product retrieval is generally crude: the basket is brought close to the lost component; the system is manipulated to grab, snag, or entangle the component; and the system is withdrawn.

![Gemini Paired Wire Helical Basket Retrieval devices](image)

**FIGURE 50-6** Gemini Paired Wire Helical Basket Retrieval devices. Double wires increase flexibility and grip. Some versions have an incorporated flexible wire at the tip. (Image provided courtesy of Boston Scientific. Copyright © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.)

The prototypical vascular basket retrieval system is the Dotter Intravascular Retrieval Set (Cook Medical). The system consists of a relatively stiff activation wire used to extend the basket out the distal tip of the delivery catheter. The system is advanced through a guide catheter until near the object of interest; the delivery catheter is gently advanced into the vascular space and the activation wire pushed forward to open the basket. Retraction on the activation wire closes the basket, hopefully entrapping the sought component. Baskets have many shapes, most of interest to physicians working outside the vasculature. Some have multiple strands of wire for each arm of the basket (improves entanglement), and some have complicated contours to create a wider opening on one side of the basket (facilitates grabbing stones and other large items).

*Forceps*
Open-mouthed grapping tools that replicate the grabbing function of forceps have been developed for intravascular use. Low-profile, high-tension cable systems are used to activate the forceps. These include the following:

1. **Side-biting vascular forceps.** These catheters are designed for use in the peripheral arterial tree (Fig. 50-7). A formable guide wire may be attached to the distal tip for use without a delivery catheter, producing a streamlined 3-Fr device.

![FIGURE 50-7 Vascular forceps. Designed for use in the peripheral vasculature, a flexible guide wire at the tip improves the safety of passage through vessels outside of a guide catheter. (Permission for use granted by Cook Medical, Bloomington, Indiana.)](image)

2. **Forward-biting forceps.** Most such devices are intended for nonvascular medical applications, such as urology or gastrointestinal procedures, but they may be of use in some vascular situations. Most are relatively small caliber (3-4 Fr) but are intended to be used through endoscopes; no guide wire can be placed at the catheter tip, so advancing the device through a vessel can be hazardous. The forward-facing “teeth” of the forceps can be used to grip lost gear. Some forward-biting forceps have 2 or more operational arms (double-jaw), whereas others have 1 operational arm set against a stationary base (single jaw). Such systems have limited or no
safeguards to prevent inadvertent seizure of vascular tissue, which is an obvious safety concern.

3. Neuro-interventional forceps. Percutaneous intervention in the cerebrovasculature has increased the risk of component loss or embolization into the neck and brain. This space is uniquely unforgiving and requires small-caliber, atraumatic, highly flexible systems. Engineers have responded with a 4-arm preshaped grasping forceps that is compressed and delivered inside any soft, flexible cerebrovascular catheter; retraction of the catheter expands the forceps arms, and advancing the catheter closes them (Fig. 50-8). Despite an aggressive-appearing grasping tip configuration, the hooked portions of this system are fairly soft and designed to open fully when the delivery catheter is retracted, allowing a “catch and release” approach when needed.

**FIGURE 50-8** Alligator Retrieval Device. Designed for use in the small, delicate intracranial vessels, the aggressive appearance of the forceps arms belies a relatively soft material. (Image courtesy of Medtronic. Copyright © Medtronic. All rights reserved.)
The simplest retrieval tools may be coronary guide wires. As described below, they may be used to entangle a component and extract it. Occasionally, standard catheterization laboratory tools may be used to effect retrieval of lost components. Simple aspiration through a diagnostic or guide catheter, or a dedicated aspiration thrombectomy catheter, may capture smaller fragments and debris. Fractured angioplasty balloons or other devices being advanced over a guide wire can be more easily recovered if approached while still attached to the guide wire; in such cases, recovery is usually successful if approached through guide wire entanglement or by advancing a loop snare coaxially over the original guide wire. Catheters, including over-bent designs such as pigtail and Grollman catheters, can be useful for dislodging stuck material, making a component easier to approach with a proper retrieval device. Angioplasty balloon catheters can also be very helpful. Balloons may be used to hold a fragment in place during snare or basket manipulations, or if a lost object is attached to a guide wire and an angioplasty balloon can be passed over the wire and beyond the object (eg, a partially expanded coronary stent), then inflating the balloon may permit retrieval. A balloon inflated alongside a foreign body might be used to drag it from a distal to a more proximal vascular location. Balloons are also helpful for fixing components in place while other equipment is brought into the field and can also be used to reduce blood loss when an arteriotomy or venotomy is needed to extract a foreign body.

**TECHNIQUES**

**Entanglement**

Entanglement is a crude but effective method that involves largely uncontrolled and unpredictable but relatively secure engagement between components. This technique can be used for large and small vascular foreign bodies.

Entanglement to retrieve fractured coronary guide wires has been very successful. This long-standing technique has proven to be quick and effective in recovery of fractured guide wire fragments. Coronary guide wires have historically been constructed with a shapeable, flattened steel alloy ribbon (optimizes for shaping and visualization) wound with a length of high-tensile
strength steel or other material; the ribbon is welded to a steel shaft. The weld is a weak point in the wire and will fracture if stressed excessively. The metal wire wound around the ribbon has a separate weld and will unravel when the wire body is retracted. Newer guide wires are constructed differently, some having a continuous length of nitinol or other modern alloy extend from the body of the wire to the distal tip, and may be less prone to fracture.

Simply advancing 1 or more other wires alongside a fractured wire fragment and twisting repeatedly can entangle the wires. Note that a few simple turns may not suffice; dozens of 360° turns may be needed. Entangling also distributes the tension of retraction along a long portion of a retained wire rather than at one point as occurs with snaring. Figure 50-9 displays a series of images illustrating use of wire entanglement to distribute the tension along a length of fractured guide wire to improve odds of successful retraction, even when a wire has been snared. Placing multiple additional wires and twisting in different directions is helpful.
FIGURE 50-9 Retrieving a fractured guide wire through wire entanglement. A. During a retrograde approach to a right coronary artery (RCA) chronic total occlusion, a guide wire was advanced (through a Corsair catheter; Asahi Kasei, Sakai, Osaka, Japan) successfully through a septal perforator, into the distal RCA, through the occlusion, and into the right coronary guide catheter. The wire was trapped with a loop snare (hollow arrow), but fractured when an attempt was made to exteriorize the
wire tip (solid arrow denotes the thin strand of wire connecting the radio-opaque wire tip with the body of the wire). B. The distal wire tip was released, and new coronary guide wires were advanced alongside the damaged tip. C. The wires were rotated vigorously to entangle the fractured wire component and distribute the retraction stress. D. The wire was retracted and exteriorized successfully.

Entanglement of larger components can be achieved in a similar fashion using a braiding technique, described below.

**Snaring**

Snares are most easily employed when a free edge of a retained foreign body is accessible. The prototypical example would be the proximal limit of a fractured guide wire; encircling the proximal end with a snare, cinching it tight, and retracting should effect successful retrieval. However, snares today are more likely used to retrieve lost stents.

A stent is likely to be lost by being stripped free of its delivery balloon. This is most easily managed when the stent is at the coronary ostium or, better yet, dangling on the guide wire within the aorta. In this case, removing the delivery balloon and passing a snare over the guide wire, then negotiating the stent loop beyond the stent, effectively traps it. Occasionally, catching the proximal end of a stent with a snare allows it to be removed without grossly deforming the stent, such that it can be withdrawn through a guide catheter (Fig. 50-10).
FIGURE 50-10 Loop snare gripping a damaged stent. This coronary stent would not pass through the target lesion, and the proximal edge of the stent caught on the tip of the guide catheter when an attempt was made to remove the stent. A loop snare was advanced coaxially over the guide wire to which the stent was still attached. The proximal edge of the stent was distorted, creating a convenient feature to grip with the snare. After successful removal and release of the snare tension, the stent was still entangled with the snare loop.

As mentioned, cleverly designed 2-component snares can facilitate snaring a foreign body even when a free end is not accessible (see Snares section).
When no commercially available snare is suitable, advancing a coronary guide wire around a foreign body and gripping the free end of the guide wire with a standard loop snare can facilitate component removal.

Snares are also invaluable for retrieving components from the venous system. Figure 50-11 illustrates recovery of the distal portion of an infusion catheter fractured as a consequence of a “pinch off” complication.\textsuperscript{15}
FIGURE 50-11 Retrieval of foreign body from venous system. A. Chest x-ray of patient with infusion port catheter indicates catheter is pinched at the junction of the clavicle and first rib (solid arrow). B. Subsequent chest x-ray indicates fracture of catheter, with distal portion embolized into the right atrium and ventricle. C. A loop snare advanced through a sheath in the right jugular vein captures the fragment, which was extracted successfully.

**Braiding**

Similar to wire entanglement, catheter braiding\(^1^6\) can be used to entrap a large foreign body. This involves advancing a catheter adjacent to the foreign body and rotating it until it “braids” with the foreign body. In Figure 50-12, a portion of catheter that has embolized to the pulmonary artery is braided with a Grollman catheter to entangle it. While the grip is not usually strong enough to allow full retrieval, this technique can be helpful in dislodging a trapped foreign body and moving it to a location from which it can be more easily gripped with a snare or forceps device.
FIGURE 50-12 Braiding technique. A portion of a Hickman infusion catheter had fractured and embolized to the pulmonary artery. The fragment could not be accessed with a snare or basket device. A Grollman pulmonary catheter was advanced alongside the fragment and twirled until the Hickman fragment and Grollman catheter were entangled. The materials were retracted out of the pulmonary artery and right heart, and the fragment removed successfully.

CONCLUSIONS

Lost components are inevitable in an interventional practice. Some sterile foreign bodies may be left in place without harm. Most are best removed, and familiarity with commercially available devices to aid in foreign body extraction is valuable. Wire entanglement, gripping forceps, and loop snares are of greatest value in extracting components lost in a vascular space.

REFERENCES


Percutaneous Treatment of Coronary Artery Fistula

Sanford Zeigler
Michael D. Dake

INTRODUCTION

Coronary artery fistula is defined as any abnormal luminal connection between 1 or both coronary arteries and the cardiac chambers or great vessels. Coronary artery fistulae (CAFs) are a rare entity, found in 1 out of 50,000 live births and in 1 of 500 patients undergoing coronary angiography. They may be congenital or acquired and, clinically, can range from completely asymptomatic to florid congestive heart failure and ischemia with electrocardiogram (ECG) changes and other typical presenting complaints.

In the majority of cases, CAFs are isolated, but they can be associated with other anomalies in 20% to 45% of cases. Common associated anomalies include tetralogy of Fallot, atrial septal defect, patent ductus arteriosus, and ventricular septal defect. CAFs are an important component of pulmonary atresia with intact ventricular septum, as they can provide the only blood supply to areas of the left ventricle.

Acquired CAFs can be a consequence of surgical or percutaneous intervention, trauma, or infection. Most cases are congenital malformations, although an increased incidence of CAF to the right ventricle has been observed in the heart transplant population due to repeated endomyocardial biopsy. The presence of a CAF places the patient at increased risk of
Coronary artery fistulas are classified according to the Congenital Heart Surgery Nomenclature and Database Project completed in 2000, which incorporates the prior angiographic classification schema of Sakakibara et al.\(^6\) along with the etiology of the lesion (acquired vs congenital), vessel of origin, and site of drainage.\(^2\) In the era of percutaneous treatment, the morphology of the fistulous connection is also important to recognize. The condition was first treated in 1947 with surgical ligation, and in 1990, 2 separate groups first described transcatheter embolization of large coronary fistulas using both coils and detachable balloons.\(^7,8\) There is a paucity of clinical data supporting any particular treatment modality, although outcomes are favorable with both percutaneous and open surgical techniques.\(^9\)-\(^12\) Current management favors catheter-based closure of these anomalies unless open fistula closure is to be performed as an adjunct to surgical correction of associated anomalies.

**SELECTION**

There are no clear guidelines regarding patient selection for fistula closure. Most authors agree that all symptomatic patients should be treated. There is no clear consensus regarding the management of asymptomatic patients. Criteria for closure of asymptomatic fistulae include presence of a systolic murmur, presence of a continuous murmur, and Qp/Qs >2.0 as a cutoff for significance, whereas others propose a shunt fraction greater than 1.5. Some groups recommend closure of fistulas >1.5 mm.\(^13\) Other authors have endorsed closure of all large fistulas to prevent future endocarditis\(^14\) or atherosclerosis.\(^13\) Some small fistulas in young patients will spontaneously close, and in low-risk cases, follow-up angiography could be considered.

In any case, anatomic considerations must inform the decision to pursue percutaneous fistula closure. The fistula should be accessible and safe to embolize. No large branches that could be inadvertently embolized should be near the fistula, and the neck should be narrow enough to be closed by available devices. Major contraindications to catheter-based closure include

- bacterial endocarditis
- myocardial ischemia
- arrhythmias
- coronary aneurysm with or without rupture
- coronary atherosclerosis
- hypervolemic chamber overload.\(^5\)
very young age or coronary arteries too small to catheterize, a large and wide-based fistula, multiple fistulas, a distal fistula, adjacent myocardial branches, and the need for other surgical repairs. 

**DEVICES**

Devices include the following:

A. Coils (0.010-, 0.012-, 0.014-, 0.018-, 0.021-, and 0.035-inch diameters)
   1. Pushable
   2. Detachable
B. Vascular plugs
C. Septal occluders (atrial septal defect, ventricular septal defect)
D. Duct occluders (patent ductus arteriosus)

**TECHNIQUE**

Wang et al\textsuperscript{10} recently published a review of percutaneous treatment of CAF in 54 patients, including their technical approach. After selective coronary angiography, they selected a site within the fistula that was favorable to device occlusion. Optimal sites for occlusion include acute vessel curves or sites where the vessel narrows but that are far from normal coronary artery branches. Arterial side access to the fistula was attempted first in all cases, using a 2.5-Fr microcatheter in some cases to help navigate through difficult tortuositites.

In cases that had a more favorable occlusion site on the venous side or in which the device delivery catheter could not reach the occlusion site from the arterial side, an atrioventricular (AV) loop technique was used. After arterial catheterization, the guide wire was threaded through the fistula to the superior vena cava or pulmonary artery. The wire was then snared and exteriorized. The venous end of the wire then was used to place a 6- or 7-Fr delivery sheath into position. This technique was used in 21 of 32 patients, of whom 2 patients developed moderate or severe tricuspid regurgitation. When the AV loop technique was not used, no tricuspid regurgitation was reported. Other cases were approached from a more straightforward transvenous or
The Boston Children’s Hospital group used an AV loop method in all patients, and reported no resulting tricuspid regurgitation. Distal angiography should then be performed to identify any distal coronary side branches near the site of occlusion. If present, a detachable device should be used. In these cases, the authors deployed the device for 10 to 15 minutes under 12-lead ECG surveillance prior to releasing the device. Completion angiography was performed, followed by placement of additional devices if needed. Only 3 of 32 patients needed an additional device.

Acute myocardial infarction due to extension of thrombosis from the fistula has been reported following surgical and transcatheter coronary fistula closure. In cases with a large residual cul-de-sac or a giant coronary artery aneurysm that has not been excluded from the arterial circulation, Wang et al recommend attempting to close the inflow to fistula or aneurysm, followed by dual antiplatelet therapy or therapeutic anticoagulation to prevent subsequent myocardial infarction due to progression of fistula thrombosis, again paying close attention to nearby normal coronary branch vessels.

The choice of a specific transcatheter device for the endovascular management of a CAF is traditionally predicated on considerations of both anatomic and physiologic characteristics of the individual lesion.

Relevant anatomic features that are commonly factored into device selection include the length, diameter, and morphology of the aberrant fistulous tract between the afferent and efferent vessels and the size of the parent vessel supplying the lesion and the vessel draining the fistula. In terms of the physiologic variables that warrant evaluation when planning therapy, flow through the fistula, perfusion of tissue by the feeding artery and its branches distal to the shunt, and perfusion of the tissue subtended by the vessel draining the fistula are all important to assess.

**Coils**

A variety of transcatheter agents have been used successfully to occlude coronary fistulas. Embolization coils are clearly the most traditional and versatile type of device employed. Their transcatheter placement is the most common embolization technique reported in the medical literature. Coils are
available in multiple different configurations from simple cylindrical forms to a variety of preformed geometric shapes to amorphous strands ideal for packing. They are manufactured in multiple different coil diameters and lengths out of a wide variety of metallic (e.g., platinum, nitinol, stainless steel) and nonmetallic (polymeric) materials of different diameters (0.010, 0.012, 0.014, 0.018, 0.021, and 0.035 inches).

The method of transcatheter deployment is typically classified as either pushable or detachable. Pushable coils are loaded into the delivery catheter from a cartridge and then advanced by means of a guide wire, usually of the same gauge, or a dedicated coil pusher. Once the coil segment is introduced to the target position at the catheter tip, it is either deployed by further guide wire advancement or injected using a syringe. In either case, the coil is not able to be repositioned or retrieved once it is outside the delivery catheter. Of course, a dedicated coil retriever, snare, or forceps can be subsequently used to retrieve a malpositioned coil, but this requires skill and time.

Detachable coils are a more recent advancement and allow the coil to be test placed before it is finally deployed. The coil and pushing “wire” are essentially one until a detach mechanism is activated and the distal coil becomes disconnected from the proximal delivery segment. Until the coil is detached, it may be advanced and withdrawn from the catheter multiple times until the desired morphology is achieved. There are many proprietary methods to allow detachment when the interventionalist is satisfied with the coil’s appearance. These include mechanical (e.g., ball and claw, screw), electrical, radiofrequency, and other methods.

Irrespective of the particular type of delivery mechanism, coils are also selected based on a variety of anatomic factors, including the diameter and shape of the vessel tract and parking space or length available to deposit a coil pack.

The size of the coil is chosen to allow for an oversize of 15% to 30% depending on the target vessel diameter. This allows for some margin of tolerance in providing the necessary friction and interference fit between the coil and vessel wall. Ideally, this will prevent coil migration while providing a stable coil configuration to the coil matrix. A tight coil nest or pack promotes an accelerated tempo of vessel occlusion. If the coil is too oversized, it cannot reach its preformed shape and elongates into a sinusoidal strand that is not as effective.

The fundamental coil element may be supplemented with attached fibers
or other supplemental agents to promote thrombus formation. Recently, coils with hydrogel polymeric jackets have been introduced. Once deployed, the polymeric coating swells to effectively enlarge the coil diameter so it occupies more space, filling in gaps in the coil matrix to facilitate vessel occlusion. Predictably, technologic developments will continue to contribute to coil use by providing new adjunctive features that will increase the efficiency of vessel occlusion.

The coil length is another variable to consider before selecting a devise. The labeled nominal length on coil package is the length of the device measured in its unconstrained or reconfigured shape. Depending on the diameter of the target vessel or fistula tract and the degree of coil oversizing based on the flow and critical importance of downstream tissue at risk from coil migration, the length of the deployed coil can be reasonably estimated. This calculus, however, takes operator experience to anticipate any elongation beyond the nominal length secondary to variable degrees of oversizing. Suffice it to say, this is not an exact science, and one should factor in a generous margin of error when selecting a coil length to match the available parking space.

**Vascular Plugs**

Vascular plugs are typically self-expanding nitinol mesh devices with or without a fabric covering that are placed via a catheter to occlude a blood vessel. Similar to embolization coils, vascular plugs come in a variety of sizes and designs depending on the target anatomy and the manufacturer.

The Amplatzer Vascular Plug (St. Jude Medical Inc., Saint Paul, MN) is the modern day prototype of the vascular plug. It was specifically designed for occlusion of arteries or veins within the peripheral vasculature. More recently, the original design has been modified to address specific anatomic challenges, and currently, there are 2 other devices in addition to the initial Amplatzer Vascular Plug—the Amplatzer Vascular Plug II and Amplatzer Vascular Plug 4. The plugs should be distinguished from the Amplatzer occluders, which are a family of devices comprised of 2 nitinol disks with or without a polyester fabric cover that are used to permanently occlude septal defects within the heart.

The original Amplatzer Vascular Plug is a cylindrical nitinol mesh with proximal and distal radiopaque markers. The proximal marker has a
microscrew that attaches the plug to a 135-cm nitinol delivery wire. The plug comes in 7 sizes from 4 to 16 mm in diameter in 2-mm intervals.

The Amplatzer Vascular Plug is advanced through a catheter or sheath with an appropriately sized inner lumen to the target. The device selected should be 30% to 50% larger than the diameter of the vessel to ensure good apposition to the wall and optimal occlusion. Once in proper position, the plug is expanded by advancing the delivery wire and withdrawing the constraining catheter. After the device is deployed to the satisfaction of the operator, it is detached by unwinding the microscrew. Prior to final actuation of the microscrew and device detachment, the plug may be withdrawn back into the delivery catheter and repositioned to achieve a desired position.

Subsequent iterations of the device produced the Amplatzer Vascular Plug II and Amplatzer Vascular Plug 4. The Amplatzer Vascular Plug II incorporates a central cylindrical plug (like the original plug) with occlusion disks at each end. The central lobe and 2 disks provide 3 zones of apposition and 6 planes of occlusion. This is intended to enhance effectiveness of plug occlusion. It is available in 11 sizes from 3 to 22 mm in diameter. The delivery system varies from a 5- to 8-Fr sheath depending on the size of the plug, and the deployment steps are identical to the original device.

The most recent addition to the family of Amplatzer Vascular Plugs and the most procedurally relevant for the management of coronary artery fistulas is the Amplatzer Vascular Plug 4. This smaller device is composed of 2 fine-meshed tapered lobes. The advantage of this device is the size of the catheter system necessary for delivery. The Amplatzer Vascular Plug 4 can be deployed through any 4- or 5-Fr angiographic catheters with a minimum 0.038-inch inner lumen diameter.

The plug is attached to a 155-cm nitinol wire with a 20-cm floppy distal segment to aid in delivery through tortuous vascular anatomy and distal vessels. It is available in diameter sizes of 4 to 8 mm, and the device selected should be 30% to 50% larger than the vessel to be occluded. Given the size of most coronary artery fistulous tracts and the anatomic challenges facing catheterization of the channels, the Amplatzer Vascular Plug 4 represents the most logistically feasible option of the Amplatzer family of plugs.

Over the past few years, there has been a growing interest in microcatheter design and development of compatible microdevices to treat neurovascular lesions and superselective distal anatomic challenges within abdominal and peripheral vascular beds. As a result, microvascular plugs and occluders are
now emerging into the market place. These smaller devices are attractive additions to our catheter armamentarium for accessing and occluding CAFs and other lesions.

An example of this new technology is the MVP (Microvascular Plug System; Covidien, Dublin, Ireland). This device incorporates a 12-mm long nitinol basket with a partial polytetrafluoroethylene (PTFE) covering over its distal aspect. The device is available in 2 sizes to occlude vessels of 1.5 to 3.0 mm (MVP-3) and 3.0 to 5.0 mm (MVP-5). It is delivered on a 180-cm delivery wire, and the plug is detached electrolytically using a separate detachment system and cable set. The MVP-3 can be delivered through a microcatheter with a 0.021-inch inner diameter and the MVP-5 via a catheter with a 0.027-inch inner lumen. These new devices may prove particularly well suited to catheter occlusion of CAFs; however, experience with their use in this application is limited.

**Septal Occluders**

Intracardiac septal defect closure devices for occlusion of atrial or ventricular septal lesions have a proven track record, and in many situations involving atrial pathology (especially secundum atrial septal defects), they are currently the primary treatment option. Not all septal defects are the same; however, the designs of most septal occluders incorporate a double disk configuration with or without a fabric cover of polyester (St. Jude Inc.) or PTFE (W. L. Gore and Associates Inc., Flagstaff, AZ).

Without going into specific details, the main difference between atria and ventricular septal devices concerns the length of the waist between the 2 occluding disks. The more muscular ventricular septum requires a device with a longer interdisk waist to accommodate anchoring of the disks on either side of the thicker wall between the cardiac chambers. Other differences between atrial and ventricular devices exist in terms of symmetry of design and size of the 2 disks. Both atrial and ventricular septal defect occluding devices can be easily recaptured into the delivery catheter and redeployed to secure optimal placement.

A range of devices with a large variety of dimensions is available. In terms of an atrial septal occlude (St. Jude Inc.), the minimum disk diameter is 12 mm with an interdisk waist diameter of 4 mm and a waist length of 3 mm. These dimensions increase to disk diameters of 54 mm with a waist diameter
of 38 mm and a length of 4 mm. The smallest disk diameter of a ventricular septal occluder (St. Jude Inc.) is 9 mm with a waist diameter of 4 mm and a length of 7 mm.

The use of these devices to treat a CAF requires a specific anatomic configuration amenable to the unique design of these double-disk devices. In practical terms, they may be used if the communication to a cardiac chamber can be catheterized and an appropriately sized disk can be positioned at the intracardiac orifice of the fistula. In this regard, authors have advocated that when using a septal occluder to straddle the drainage site into a cardiac chamber, the device should be twice the size of the orifice.12

**Duct Occluders**

One additional specific structural heart closure device warrants description because it is relatively well suited to the endovascular management of coronary artery fistula. The Amplatzer Duct Occluder (St. Jude Inc.) is a mushroom-shaped nitinol mesh device with a polyester graft covering. The leading end of the occluder has a skirt to secure positioning and prevent embolization. The trailing end is a slightly tapered stalk that conforms to tapering anatomy.

The smallest device has a length of 5 mm and a 9-mm skirt, and the largest occluder is 8 mm long with an 18-mm skirt. There are 3 intervening sizes available. In the setting of coronary artery fistula, the plug would be placed with the skirt end inside the cardiac chamber immediately adjacent to the orifice of the fistula and the stem extending into the fistulous tract.

**Figures 51-1, 51-2, 51-3, and 51-4** are radiographic images showing the clinical findings in patients who presented with coronary artery fistulas.
FIGURE 51-1 A 15-year-old girl with fistula between left anterior descending (LAD) coronary artery and the pulmonary artery with 1 large and 1 tiny entrance just above the pulmonary valve. A. Axial computed tomography image displays a large left coronary artery measuring 4.2 mm. B. The LAD is also large (4.0 mm), and 2 circular enhancing densities are noted between the LAD and the main pulmonary artery just at the level of the pulmonic valve. C. A small serpentine vessel is evident entering the main pulmonary artery just above the valve (arrow). This is the largest of the fistulous tracts from the LAD. D. Approximately 2 cm proximal to the trifurcation of the LAD, the origin of a bizarre fistula is evident. The vessel has both dilated and narrowed segments as it courses toward the pulmonary artery.
FIGURE 51-2 Axial computed tomography images of a 49-year-old man with complex coronary artery fistula with multiple feeders emanating from a left coronary artery branch and a right conal branch and draining into the main pulmonary artery. 

A. Large left coronary artery and multiple adjacent circular densities representing tortuous fistulous channels. Also, similar findings are evident in the region just cephalad to right coronary artery. 

B. A complex network of small vessels courses anteriorly along both sides of the pulmonary artery. 

C. At the level of the pulmonary valve, a tangle of channels is adjacent to the left wall of the main pulmonary artery. 

D. The multiple fistulous vessels course anteriorly to communicate with the anterior aspect of the main pulmonary artery. 

E. A complicated array of vessels is noted just above the site of communications with the pulmonary artery.
FIGURE 51-3 Three-dimensional reconstructions of a computed tomography data set from a 49-year-old man with a complicated coronary artery fistula network first noted on echocardiography. A. Tangled mass of coronary artery branches originating predominantly from the left anterior descending artery, but also with contribution from a right coronary artery conal branch. B. The fistulous channels course anteriorly along the lateral aspect of the main pulmonary artery (not shown) and coalesce to drain into the anterior aspect of the pulmonary artery just above the valve.
FIGURE 51-4 Images from a computed tomography (CT) scan performed after coil embolization of the coronary artery fistula network. A and B. Axial views show metallic artifacts from coils placed in feeding branches of both the left and right coronary arteries. Most of the communications between the right coronary artery and left anterior descending (LAD) branches to the main pulmonary artery have been obliterated, and only a few small
abnormal channels persist. **C and D.** Multiplanar CT reformations through the course of the LAD display metallic embolization coils in branches of the vessel, as well as in a branch of the right coronary artery (C). The majority of fistulous vessels are occluded and only 1 or 2 small residual channels are identified.

**CONCLUSION**

The successful endovascular management of a symptomatic CAF requires experience and judgment on the part of the interventionalist. These lesions are rare, and a prudent evaluation or risks and benefits is important to ensure patient safety and procedural effectiveness.

The use of a spectrum of transcatheter endovascular devices has been described in the medical literature. Reports of experience with embolization coils, vascular plugs, and septal and duct occluders have all been detailed. Currently, the most commonly employed technique to promote occlusion of a fistula involves direct catheterization of the fistula and deployment of metallic coils through either a diagnostic angiographic catheter or a microcatheter. In the future, the role of a microvascular plug as a single device to occlude a fistulous tract may expand.

**REFERENCES**

18. Mesko ZG, Damus PS. Myocardial infarction in a 14-year-old girl, ten years after surgical correction of congenital coronary artery fistula.
MULTIPLE CHOICE QUESTIONS

1. Which of the following statements regarding coronary artery fistulae (CAF) is true?
   A. A coronary-cameral fistula is a type of CAF between a coronary artery and a chamber of the heart.
   B. A CAF may close and resolve spontaneously.
   C. Most CAFs are small and do not cause any symptoms or complications.
   D. A and B.
   E. All of the above.

2. All of the following techniques are currently used to treat CAF except:
   A. Open surgical ligation with suture
   B. Transcatheter coil embolization
   C. Hyperbaric oxygen therapy
   D. Transcatheter placement of patent ductus arteriosus, atrial septal defect, or ventricular septal defect occluder devices

3. Which of the following statements is true regarding CAF and children?
   A. Children with CAF usually show no symptoms other than a heart murmur.
   B. The size and significance of a CAF cannot usually be determined by echocardiography.
   C. After diagnosis, closure of the CAF is often performed because of the danger of complications, such as rupture of the fistula, myocardial ischemia, or endocarditis.
   D. A and B.
   E. A and C.
   F. All of the above.

4. All of the following statements regarding CAF and concerns about exercise are true except:
   A. There are no exercise restrictions for patients with small CAF with
negligible symptoms.
B. Patients with CAF are at a slightly higher than normal risk for arrhythmias or sudden death during extreme exertion, such as athletic competition.
C. Stress testing is not recommended for patients with CAF before participating in sports requiring extreme exertion.
D. Patients with CAF should be monitored regularly by a cardiologist to guard against the late development of arrhythmias, ischemia, or heart failure that may limit safe levels of exercise.

5. Which of the following general statements regarding patients with CAF is true?
A. In the absence of significant associated symptoms such as arrhythmias, ischemia, or heart failure, a woman with CAF should experience no difficulty bearing children.
B. Infants who are born with CAF are more likely than normal infants to have other heart defects.
C. In nearly all series of patients with CAF, the vast majority (>90%) of the defects drain to the right side of the circulation.
D. Small, asymptomatic fistulae arise much more commonly (>85%) from the left coronary system.
E. A and C.
F. B and D.
G. All of the above.

ANSWERS

1. E
All of the statements are correct.

2. C
Hyperbaric oxygen therapy has no effect on CAF and is not recognized as a standard treatment. The other techniques are commonly performed in clinical practice for treatment of CAF.
3. E
Echocardiography is often used to determine the size and importance of CAF. Typical echocardiographic features that indicate a significant CAF include cardiac chamber dilation, narrowest color Doppler flow jet ≥4 mm, or reversal of flow in the descending aorta. Both answers A and C are correct.

4. C
It is recommended that adults with CAF undergo stress testing prior to participating in strenuous physical activities or athletic competition. The other statements are correct.

5. G
All of the statements are correct.
INTRODUCTION

Clinical benefit from any revascularization procedure will be the net gain due to reperfusion of the ischemic organ balanced against the risk of a procedural complication. The same is true for renal artery ischemia caused by atherosclerotic or, less commonly, fibromuscular dysplasia (FMD) lesions (Fig. 52-1). Recent clinical trials have attempted to determine the benefit of revascularization but have been seriously hampered by difficulty in defining a threshold for an ischemia producing renal artery stenosis (RAS).
Renal ischemia due to an obstruction of the renal artery causes 3 well-described clinical scenarios: (1) renovascular hypertension, (2) ischemic nephropathy, and (3) cardiac destabilization syndromes such as sudden-onset pulmonary edema, decompensated heart failure, and acute coronary syndromes. Helping to identify patients with these clinical manifestations of renal ischemia who also have anatomically suitable lesions for treatment is the purpose of this chapter. The primary method of revascularization for renal artery stenosis is endovascular, not open surgery. Open surgery is rarely performed today and usually accompanies another related open surgical procedure on the abdominal aorta, for example.

**PREVALENCE OF RENAL ARTERY STENOSIS**
The prevalence of renal artery stenosis (RAS) depends on the population examined. In a Medicare population (mean age, 77 years), screening renal ultrasound duplex studies demonstrated greater than 60% RAS in 6.8% of patients.\(^1\) There were almost twice as many males (9.1%) as females (5.5%; \(P = .053\)), and there were no racial differences (Caucasian, 6.9%; African American, 6.7%) in the prevalence of RAS. Among the general hypertensive population, RAS is the most common (2%-5%) secondary cause of hypertension. An autopsy series of patients older than 50 years found RAS (≥50%) in 27% of patients, and this rate increased to 53% if there was a history of diastolic hypertension >100 mm Hg. Among patients entering dialysis treatment, 10% to 15% have RAS as the cause of end-stage renal disease.\(^2\) Approximately 25% of elderly patients with renal insufficiency have unsuspected RAS.

RAS is predominantly due to atherosclerosis in the adult population, with FMD being more common in younger females.\(^3\) RAS is more common in patients who have atherosclerosis involving any other vascular bed. In patients undergoing cardiac catheterization for suspected coronary artery disease, the prevalence of RAS ranges from 25% to 30%, whereas peripheral arterial disease or abdominal aortic aneurysm is associated with RAS in 30% to 40% of cases.

**NATURAL HISTORY**

Atherosclerotic RAS generally progresses over time and is often associated with loss of renal mass and worsening renal function. Lesion progression in serial angiographic studies ranges from 39% to 49%. RAS lesion progression is directly related to the underlying severity of the stenosis. The more severe the narrowing (≥60%), the more likely it is to progress to occlusion.\(^4\) Worsening of “asymptomatic” RAS is associated with a progressive loss of renal function.\(^5\) Control of blood pressure with medical therapy does not prevent progression of RAS.\(^6,7\) Renal artery occlusion occurred in 16% of the medically treated arm over a 1-year period in a randomized trial.\(^8\)

Atherosclerotic RAS remains a major cause of end-stage renal disease. In a serial angiographic study of RAS patients compared to normal controls, renal function significantly declined and was related to the severity of the
RAS. RAS is estimated to be responsible for renal failure in 10% to 15% of patients entering dialysis programs. In patients starting dialysis secondary to atherosclerotic RAS, the mean survival was 25 months, and the 2-, 5-, and 10-year survival rates were 56%, 18%, and 5%, respectively.

RAS is an independent predictor of adverse cardiovascular events such as myocardial infarction, stroke, and cardiovascular death. Patients with significant RAS are more likely to have renal insufficiency, coronary artery disease, peripheral arterial disease, hypertension, and cerebrovascular disease. In patients identified as having greater than 75% RAS at the time of cardiac catheterization, the 4-year survival was 57% compared to 89% in patients without RAS ($P < .001$). Patients with greater severity of RAS have worse survival than those with milder or no RAS. Patients with bilateral RAS exhibit a lower 4-year survival (47%) when compared to patients with unilateral RAS (59%; $P < .001$), independent of prior myocardial revascularization procedures.9

**DIAGNOSIS**

**Screening for RAS**

Screening for RAS is appropriate in patients at increased risk for RAS (Table 52-1). Whenever possible, screening tests for RAS should be performed noninvasively using direct imaging tests (Doppler ultrasound, computed tomographic angiography [CTA], or magnetic resonance angiography [MRA]) (Fig. 52-2). Noninvasive imaging has become so sophisticated and accurate that it is seldom necessary to perform catheter-based angiography for the diagnosis of renal artery disease.

**Table 52-1 Increased Prevalence of Renal Artery Stenosis**

- Onset of hypertension ≤30 y or ≥55 y
- Malignant, accelerated, or resistant hypertension
- Unexplained renal dysfunction
- Development of azotemia with an ACE inhibitor or ARB medication
- Unexplained pole-to-pole diameter discrepancy of ≥1.5 cm between
Kidneys

- Cardiac disturbance syndrome (flash pulmonary edema)
- Peripheral arterial disease (abdominal aortic aneurysm or ankle-brachial index <0.9)
- Multivessel (≥2) coronary artery disease

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

FIGURE 52-2 Magnetic resonance angiography showing a right accessory renal artery with a suspicious narrowing of the right main renal artery. RAS, renal artery stenosis.

It may be appropriate to perform screening angiography for RAS at the time of cardiac or peripheral vascular angiography of other vascular beds. For patients who are candidates for revascularization with risk factors as outlined in Table 52-1 or clinical syndromes suggestive of RAS, aortography is given a Class I indication for screening at the time of angiography performed for other clinical indications. There is good evidence that nonselective, diagnostic, screening renal angiography is safe and is not associated with incremental risk when performed at the time of cardiac catheterization.

**Duplex Ultrasonography**
Duplex ultrasonography (DUS) is an excellent noninvasive imaging test to detect RAS but is highly dependent on the skills of the technician performing the test. It is the least expensive of the imaging modalities and provides useful information about the degree of stenosis, the kidney size, and other associated disease processes such as obstruction. The location and degree of stenosis can accurately be determined by duplex ultrasound of the renal artery.

Overall, when compared to angiography, DUS has a sensitivity and specificity of 84% to 98% and 62% to 99%, respectively, when used to diagnose RAS. Renal artery duplex is an excellent test for the follow-up after renal stenting to confirm patency. Following endovascular therapy, a renal artery duplex should be obtained within the first few weeks to establish a baseline, and then at 6 months, 12 months, and yearly thereafter to ensure patency.

One drawback of DUS is that it may not identify RAS in accessory renal arteries (67%) compared to main renal arteries (98%). Therefore, if the patient has hypertension that cannot be adequately controlled with a good regimen, and the DUS fails to demonstrate RAS, another imaging modality may be considered to identify stenosis of an accessory renal artery.

**Resistance Index**

The intrarenal resistance index (RI) is the ratio of the peak systolic to end-diastolic velocity within the renal parenchyma at the level of the cortical blood vessels.\(^{13}\) The RI is a representation of small vessel glomerulosclerosis. There have been conflicting reports regarding the usefulness of RI to predict individual patient response to revascularization. One retrospective study demonstrated that an elevated RI greater than 0.80 predicted a lack of improvement in blood pressure and renal function after revascularization; however, it included balloon angioplasty without stent procedures, a strategy that is now recognized as less optimal compared to stenting (see below).\(^{14}\) A prospective study of renal stenting in 241 patients with an elevated RI (>0.70) showed improvement in blood pressure and renal function after intervention.\(^{15}\) Patients with a higher RI (>0.8) actually benefitted more from revascularization than did those with milder elevations.
Noninvasive Angiography

CTA uses ionizing radiation and iodinated contrast to produce excellent images of the abdominal vasculature (Fig. 52-3). CTA has a sensitivity and specificity for detecting RAS of 89% to 100% and 82% to 100%, respectively. Excellent 3-dimensional image quality with enhanced resolution can be obtained with multidetector-row CTA technology. The advantages of CTA over MRA include greater spatial resolution, an absence of flow-related phenomena that may overestimate the degree of stenosis, and the capability to visualize calcification and metallic implants such as endovascular stents and stent grafts. CTA is well tolerated with an open gantry, and thus, claustrophobia is not as limiting a factor as it is for MRA. The disadvantages of CTA compared to MRA are exposure to ionizing radiation and the need to administer potentially nephrotoxic iodinated contrast agents.

FIGURE 52-3 Computed tomography angiogram showing a patent left renal artery
MRA also provides excellent imaging of the abdominal vasculature and associated anatomic structures (see Fig. 52-2). When compared with angiography, MRA has demonstrated a sensitivity of 91% to 100% and a specificity of 71% to 100%. Contrast-enhanced MRA using gadolinium improves image quality when compared with noncontrast studies and shortens imaging time, thereby eliminating some of the artifact created by gross patient movement. However, MRA does not have the same sensitivity and specificity in patients with FMD and is generally not a good screening test if FMD is suspected.

MRA should not be used in patients with a glomerular filtration rate less than 30 mL/min/1.73 m\(^2\) because of the increased likelihood of developing nephrogenic systemic fibrosis. MRA may not be used in patients with metallic (ferromagnetic) implants such as some mechanical heart valves, cerebral aneurysm clips, and electrically activated implants (pacemakers, spinal cord stimulators). At present, MRA is not very helpful in following patients after stent implantation due to imaging artifact produced by the metallic stent.

**Invasive Angiography**

The traditional “gold” standard for determining the severity of RAS has been invasive angiography. The Achilles heel of renal stenting is the inaccuracy of the angiographic determination of the severity of the ostial renal stenoses. Even with quantitative measurement, angiography may be unable to discriminate between nonobstructive stenoses and clinically significant ones (Fig. 52-4).\(^\text{16}\) Most would agree that interventionalists are able to identify “critical” stenoses in renal arteries, but for mild to moderately severe lesions, physiologic confirmation is necessary.
Translesional Pressure Gradients

Hemodynamic measurement of the severity of RAS assures that there is a physiologic reason to expect benefit with revascularization. Confirmation of a hemodynamic gradient is evidence of physiologic RAS with renin release and has been documented by De Bruyne and colleagues.\textsuperscript{17} Hemodynamic parameters of significant RAS (peak systolic gradient $>21$ mm Hg,\textsuperscript{18} renal fractional flow reserve [FFR] of $\leq 0.8$,\textsuperscript{19} and a dopamine-induced mean translesional gradient $\geq 20$ mm Hg\textsuperscript{20}) are associated with clinical improvement after renal stenting in patients with mild to moderate renal artery stenoses.

Renal FFR is measured after induction of maximum hyperemia. This hemodynamic assessment of flow, which is widely used in the coronary
circulation, is based on the principle that flow across a conduit artery is proportional to pressure across the vascular bed and inversely proportional to the resistance of the vascular bed. Under conditions of maximum hyperemia, the flow through the conduit artery is maximal, while the resistance of the vascular bed is at a minimum and constant. Any reduction in flow under these conditions is caused by the stenosis and is proportional to the ratio of pressure distal to the stenosis (Pd) and the pressure proximal to the stenosis (Pa). Renal hyperemia can be achieved with papaverine, dopamine, or acetylcholine. Translesional pressure gradients are measured, and FFR (Pd/Pa) is calculated using a 0.014-inch pressure guide wire. Renal artery FFR correlates well with other hemodynamic parameters of lesion severity and, in some series, has been proven to be a better predictor of clinical response. In one study, renal FFR was measured after renal stent placement in 17 patients with refractory hypertension and moderate to severe (50%-90% stenosis) unilateral RAS. Ten patients had normal baseline renal FFR (defined as FFR ≥0.80), whereas an abnormal baseline renal FFR (<0.80) was recorded in 7 patients. At 3 months after intervention, 86% of patients with an abnormal renal FFR experienced improvement in their blood pressure, compared with only 30% of those with normal renal FFR (P = .04). In this small series, baseline systolic, mean, or hyperemic translesional pressure gradients were not different between patients whose blood pressure improved and those in whom it did not.

**Renal Frame Count**

Angiographic measurements of renal blood flow by using renal frame counts (RFC) and renal blush grades (RBG) for microvascular flow can differentiate normal patients from patients with FMD. RFC is the number of cine frames required for the contrast to reach the smallest visible distal branch in the renal parenchyma. As in Thrombolysis in Myocardial Infarction (TIMI) frame counting, the first frame used for the RFC is the frame in which the contrast first fills the main renal artery. The last frame is when contrast enters the smallest visible branch of the distal renal parenchyma along the axis of the main renal artery. The measurements are done with 30-frames-per-second angiography.

RFC was initially described in patients with FMD of the renal arteries (15 kidneys), who were compared to subjects with normal renal arteries (50
kidneys) and had a significantly higher (prolonged) mean RFC (26.9 vs 20.4; 
\( P = .0001 \)). Hypertensive patients with renal artery stenoses have also been 
shown to have decreased renal perfusion as measured by RFC. Clinical 
responders tended to have higher baseline RFCs than nonresponders and had 
greater improvement in their RFC values following renal stenting. Three-
quarters of the hypertensive patients who responded to renal stenting had a 
baseline RFC ≥25, and if the RFC improved by >4, then 79% were 
responders to renal stenting.

RENOVASCULAR HYPERTENSION

**Clinical Characteristics**

It has been shown that patients with the highest systolic blood pressures have 
the greatest decrease in systolic pressure, but there is no correlation 
between blood pressure improvement after renal stent placement and the 
variables of age, sex, race, severity of stenosis, number of vessels treated, 
baseline diastolic pressure, or baseline serum creatinine. Two variables, 
bilateral RAS (odds ratio [OR], 4.6; \( P = .009 \)) and mean arterial pressure 
>110 mm Hg (OR, 2.9; \( P = .003 \)), are associated with improved blood 
pressure response following renal artery stent placement. Studies comparing 
the results in elderly (≥75 years) versus younger (<75 years) patients or in 
females versus males have failed to show any difference in response to renal 
stent placement.

**Evidence-Based Treatment**

An analysis of 527 renal stent patients enrolled in 5 modern prospective, 
multicenter (117 centers) studies demonstrated that systolic blood pressure 
(SBP) and diastolic blood pressure (DBP) were significantly decreased at 9 
months. An SBP reduction >10 mm Hg occurred in 61% of patients. A 
baseline SBP >150 mm Hg was strongly associated with blood pressure 
response, but other clinical characteristics were not. In hypertensive patients 
in whom RAS is identified, the best predictor of RAS benefit was a baseline 
SBP >150 mm Hg.
The current American Heart Association (AHA)/American College of Cardiology (ACC) guideline indications for RAS in hypertensive patients with hemodynamically significant RAS and a viable kidney (linear length >7 cm) include: (1) accelerated hypertension, (2) refractory hypertension (failure of 3 appropriate drugs, 1 of which should be a diuretic\(^{29}\)), (3) hypertension with a small kidney, and (4) hypertension with intolerance to medications (Class IIa, Level of Evidence B).\(^{30}\) By convention, a hemodynamically significant lesion requires demonstration of a ≥70% RAS by visual estimation, ≥70% RAS by intravascular ultrasound measurement, or a 50% to 70% RAS with a systolic gradient of ≥20 mm Hg or a mean translesional gradient of ≥10 mm Hg.\(^{30}\)

The recently published Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial compared the initial treatment strategy for renovascular hypertension patients; patients received either multifactorial medical therapy (eg, an angiotensin receptor blocking agent, a thiazide-type diuretic, amlodipine, atorvastatin, antiplatelet therapy, and diabetes managed according to clinical practice guidelines) or medical therapy plus renal stenting consistent with the guidelines.\(^{31}\) The CORAL study found that the primary composite end point (death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive failure, progressive renal insufficiency, or the need for renal replacement therapy) in patients with RAS (>60% diameter stenosis) and poorly controlled hypertension on at least 2 medications did not differ between groups. The number of blood pressure medications was not different between the groups (medical vs stent: 3.5 ± 1.4 vs 3.3 ± 1.5 medications) at the completion of the trial, and both groups had a similar decrease in SBP (15.6 ± 25.8 mm Hg in the medical therapy group vs 16.6 ± 21.2 mm Hg in the stent group). The CORAL recommendations for an initial trial of multifactorial medical therapy are consistent with the current AHA/ACC guidelines, which require that patients fail medical therapy for renovascular hypertension prior to revascularization.

**ISCHEMIC NEPHROPATHY**

Treatment of ischemic nephropathy continues to be a source of debate among experts. Opponents of revascularization of RAS patients with renal
insufficiency contend that the kidney is supplied with an excess of nutrient blood flow, and therefore, few kidneys will benefit from revascularization. This does not explain the 10% of patients beginning dialysis for end-stage renal disease due to renal artery occlusion.

Evidence-Based Treatment

The literature is replete with patient series in which RAS improves renal function, as well as counterbalancing reports of worsening of renal failure after successful RAS. However, there are no large randomized studies demonstrating benefit of revascularization over medical therapy alone for improving renal function.

Unfortunately, there are several poorly done studies, such as the recently completed STAR (Stent Placement and Blood Pressure and Lipid Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery) trial and the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial, comparing renal stenting plus medical therapy to medical therapy alone. Unfortunately, methodologic problems, such as enrolling study patients with mild (<50%) or nonobstructive RAS, invalidated these “intent-to-treat” trials. The clinical evidence does not support the sweeping negative statements regarding revascularization for ischemic RAS.

Dramatic benefit for RAS versus medical therapy in patients with the most severe renal disease was demonstrated in a large cohort study. One center offered patients (n = 182) medical therapy only, and the other center offered RAS plus medical therapy (n = 348). Patients were matched for the degree of renal dysfunction, and outcomes were compared over 5 years. Patients who underwent RAS had a marked reduction in mortality (relative risk, 0.55; 95% CI, 0.34-0.88; P = .013) by multivariate Cox regression analysis. When analyzed according to the degree of renal impairment, there were striking improvements in renal function after RAS for the patients with moderate to severe renal impairment. Patients with RAS and advanced chronic kidney disease (stages 4 and 5) benefited from renal stenting with improved renal function and also enjoyed a survival advantage.

Currently, there are several parameters that suggest that a patient is likely to experience improved renal function after revascularization. First, there
must be a hemodynamically obstructive RAS causing hypoperfusion of the kidney. The more renal tissue at risk, the more likely there will be a response or improvement in renal function with RAS. Patients with bilateral renal stenosis and solitary kidney stenosis are traditionally thought to be most likely to improve. Patients with small kidneys (<7 cm) and those with significant proteinuria are less likely to benefit.\textsuperscript{44}

Patients with rapidly declining renal function, as opposed to those with stable renal failure, have the most to gain from revascularization.\textsuperscript{36,45} The rate of decline in renal function, determined as the slope of the regression line of serum creatinine over time, is a very strong predictor of benefit with RAS.\textsuperscript{36} A multivariate analysis demonstrated that the only significant predictor of benefit following RAS was the rate of decline of renal function that preceded the procedure. Baseline creatinine, the presence of proteinuria, renal size, and diabetes were not significant predictors of improvement in this study.

The current AHA/ACC guideline recommendation\textsuperscript{11} for catheter-based therapy to preserve renal function concludes that RAS is reasonable for patients with RAS and progressive chronic kidney disease with bilateral or a solitary functioning kidney with stenosis (Class IIa, Level of Evidence B). RAS may also be considered on an individual basis for patients with hemodynamically significant stenosis and chronic renal insufficiency with unilateral RAS (Class IIb, Level of Evidence C).

**CARDIAC DESTABILIZATION SYNDROMES**

Cardiac destabilization syndromes attributable to RAS include exacerbations of coronary ischemia and congestive heart failure due to peripheral arterial vasoconstriction and/or volume overload.\textsuperscript{46} Renovascular disease may also complicate the management heart failure patients by preventing administration of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB).

The importance of renal artery stent placement in the treatment of cardiac disturbance has been described in a series of patients presenting with either congestive heart failure or an acute coronary syndrome.\textsuperscript{47} Successful renal
stent placement resulted in a significant decrease in blood pressure and control of symptoms in 88% (42 of 48) of all patients. Assessments of the acute treatment effects and effects at 8 months using the Canadian Cardiovascular Society (CCS) angina classification and the New York Heart Association (NYHA) functional classification (see Fig. 52-4) were not different between the combined coronary and renal revascularization group and those who had only renal stent placement, suggesting that renal revascularization was the most significant intervention.47

Another case series of 39 patients treated with RAS for control of congestive heart failure demonstrated that blood pressure improved in 72% of patients and renal function improved in 51% and was stable in 26% of patients.48 The mean number of hospitalizations for congestive heart failure prior to stenting was 2.37 ± 1.42 (range, 1-6), and after renal stenting, the number of hospitalizations was 0.30 ± 0.065 (range, 0-3; P < .001). Seventy-seven percent of patients had no further hospitalizations after RAS over a mean follow-up period of 21.3 months. RAS can relieve the renal ischemia and result in marked improvement in both heart failure and angina symptoms.47 The ACC/AHA guidelines make percutaneous revascularization for hemodynamically significant RAS and recurrent unexplained congestive heart failure or sudden unexplained pulmonary edema a Class I, Level of Evidence B indication. RAS for renal artery stenosis and refractory unstable angina earned a Class IIa, Level of Evidence B indication.11

**ASYMPTOMATIC RAS**

There is no evidence to support beneficial outcomes for revascularization of an asymptomatic RAS, regardless of the severity of the stenosis. The current ACC/AHA guidelines make renal intervention for unilateral asymptomatic, bilateral asymptomatic, or solitary asymptomatic RAS a Class IIb, Level of Evidence C recommendation, which suggests there is an uncertain risk-to-benefit ratio for this treatment. Patients with compelling anatomic lesions threatening global renal function may be considered for treatment on a case-by-case basis.11

**RENAAL ARTERY INTERVENTION**
Balloon angioplasty is much less effective than stent placement for treating atherosclerotic aorto-ostial plaque (Fig. 52-5). Renal stents significantly lowered the translesional pressure gradient reduction when compared with balloon dilation alone. The superiority of renal stents compared to balloon angioplasty alone was confirmed in a randomized trial and in 2 meta-analyses. This evidence led to a Class I ACC/AHA guideline recommendation for primary stent placement in atherosclerotic RAS.

![FIGURE 52-5 A. Baseline significant ostial renal artery stenosis (arrow). B. Poststent deployment.](image)

**Patient Selection**

Optimal patient selection for renal revascularization is more complex than a visual estimation of stenosis or a measurement of a translesional pressure gradient. This is because patients with RAS have multifactorial reasons for hypertension and renal insufficiency that may or may not improve as renal blood flow improves. Perhaps the most common reason for failure to improve after renal revascularization is overestimation of the severity of the RAS by angiography. The ostial segment of the renal artery has a complex 3-dimensional geometry that can be very difficult to appreciate by 2-dimensional angiographic imaging. Performing angioplasty or stent placement in mildly narrowed renal arteries would not be expected to be of clinical benefit and may be the reason why no more than 70% of hypertensive patients fail to improve after renal revascularization. In addition, the presence of anatomic RAS does not necessarily establish that the
hypertension or renal failure is caused by the RAS. Many patients have had essential (primary) hypertension for years and then develop atherosclerotic RAS later in life. The mere presence of RAS does not imply that the RAS per se is causing the high blood pressure.

The pathophysiology of renovascular hypertension has been well understood since the experiments of Goldblatt and others. De Bruyne and colleagues\textsuperscript{17} demonstrated this cause-and-effect relationship by performing an in vivo experiment that showed a threshold gradient for the release of renin following graded renal artery obstruction.

Restenosis after renal artery stent placement is related to both acute gain and late loss, similar to coronary artery restenosis. In the largest single series of renal stent implantation, a larger reference vessel diameter (RVD) and larger acute gain (ie, poststent minimum luminal diameter [MLD]) after stent deployment were strongly associated with a lower incidence of restenosis. For example, restenosis in a vessel with an RVD of <4.5 mm was 36% compared to only 6.5% for an artery with a RVD of >6.0 mm in diameter.\textsuperscript{51} Renal stenting has been shown to be a durable treatment, with 1-year patency rates $\geq$85% (Table 52-2)\textsuperscript{49,52-55} and 5-year primary patency approaching 80%.\textsuperscript{52,54}

Table 52-2 Renal Stent Patency at 12 Months

<table>
<thead>
<tr>
<th>Author</th>
<th>Arteries Treated (No.)</th>
<th>Restenosis Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al\textsuperscript{52}</td>
<td>74</td>
<td>11.0</td>
</tr>
<tr>
<td>Tuttle et al\textsuperscript{53}</td>
<td>148</td>
<td>14.0</td>
</tr>
<tr>
<td>Henry et al\textsuperscript{54}</td>
<td>209</td>
<td>11.4</td>
</tr>
<tr>
<td>Van de Ven et al\textsuperscript{49}</td>
<td>43</td>
<td>14.0</td>
</tr>
<tr>
<td>Rocha-Singh et al\textsuperscript{55}</td>
<td>180</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Percutaneous catheter-based therapy with primary stent placement has replaced open surgery as the treatment of choice for atherosclerotic RAS.\textsuperscript{11} However, despite a technical success rate exceeding 95% for renal artery stent placement, there remains wide variation in the reported success rates in improving hypertension. While at least some of the variability in outcomes is
attributable to a lack of standard reporting criteria, the dominant factor appears to be poor patient and nonobstructive lesion selection for treatment. Variability in the angiographic assessment of the hemodynamic severity of renal artery stenoses has undermined the predictability of a treatment response with successful stenting. Although the majority of hypertensive patients with atherosclerotic RAS and hypertension will experience improved blood pressure control and/or the need for fewer medications, few patients will be cured of hypertension.

**Procedural Complications**

Complications associated with catheter-based renal intervention are related to vascular access, catheter trauma, or systemic complications related to contrast reactions or renal toxicity. Vascular access complications are the most common complications in renal artery intervention. They include access site bleeding and hematoma (1.5%-5%), access site vessel injury (1%-2%), retroperitoneal hematoma (<1%), pseudoaneurysm (0.5%-1%), arteriovenous fistula (<1%), and nerve injury (<1%). Major complications of peripheral vascular angiography range from 1.9% to 2.9% (Table 52-3). One solution to reducing vascular access complications is to perform RAS from radial artery access (see Fig. 52-1A).

| Table 52-3 Complications of Renal Stent Placement |
|----------------|----------------|----------------|----------------|
| Author         | Patients (No.) | Death (%)      | Dialysis (%)   | Major Complications (%) |
| Tuttle et al   | 148            | 0              | 0              | 4.1                        |
| Rocha-Singh et al | 180          | 0.6            | 0              | 2.6                        |
| Burket et al   | 171            | 0              | 0.7            | 0.7                        |
| White et al    | 133            | 0              | 0              | 0.75                       |
| Dorros et al   | 163            | 0.6            | 0              | 1.8                        |
| Total/Mean     | 795            | <1             | <1             | 2                          |

Catheter-related renal artery complications include atheroembolism, vessel dissection, or arterial perforation; these are rare (<1%) but often devastating events. Anaphylactic contrast reactions occur in fewer than 3% of patients, and fewer than 1% of these patients require hospitalization. The risk of contrast-induced nephropathy (CIN) is increased in patients with baseline chronic renal insufficiency, diabetes mellitus, and multiple myeloma and
those who are receiving other nephrotoxic drugs such as aminoglycosides. Prevention of CIN requires vigorous hydration and the use of as little iso-osmolar contrast as possible.\textsuperscript{60}

**Radial Artery Access**

Vascular access complications account for the majority of clinical complications of renal stenting. One way to minimize access site bleeding is to use the radial artery (Fig. 52-6). The coronary interventional literature has demonstrated a marked reduction in vascular access complications with radial artery access compared to both brachial and femoral artery access. Low-profile radial sheaths and the ability to use a “sheathless” technique with 6-Fr guiding catheters make the radial artery approach a viable option. In addition to minimizing vascular access complications, the radial artery approach has other advantages, including increased patient acceptance and improved guiding catheter engagement due to the downward or caudal orientation of most renal arteries. The radial approach may require longer (125-cm) guide catheters and longer shaft length balloons and stents (140-150 cm). The undeniable benefit of the radial access approach, however, is a major reduction in the vascular access–related bleeding complications with same-day discharge and increased patient satisfaction.\textsuperscript{61}

**FIGURE 52-6** A. Baseline right renal artery stenosis via the radial approach. B. Poststent deployment.

*Embolic Protection Devices*
Atheroembolism has been associated with an increase in surgical morbidity and a dramatic reduction in 5-year survival compared with patients who had no evidence on biopsy of renal atheroembolization (54% vs 85%; \( P = .011 \)). Because atheroembolism is a potential complication of renal artery stenting, investigators have looked for a role of embolic protection devices (EPDs) in optimizing outcomes after renal intervention (Fig. 52-7). However, distal protection is technically difficult given the early bifurcation of renal arteries. In a small randomized trial, 100 patients undergoing renal artery stenting were randomly assigned to an open-label EPD or use of abciximab in a 2 × 2 factorial design. A positive interaction was observed between treatment with abciximab and embolic protection. Renal artery stenting alone, stenting with EPD, and stenting with abciximab were associated with similar and modest declines in estimated glomerular filtration rate (eGFR) at 1-month follow-up (–10, –12, and –10 mL/min/1.73 m\(^2\) eGFR change, respectively); however, the group treated with both EPD and abciximab was protected from a decline in eGFR and was superior to the other 3 groups (+9 mL/min/1.73 m\(^2\) eGFR change; \( P < .01 \)).
In an uncontrolled retrospective trial, RFC were measured in 66 patients undergoing renal artery intervention with and without EPD. EPD was associated with improved renal blood flow measured by RFC compared with the control group following RAS (mean reduction in RFC, 14.2 vs. 6.7; \( P = .03 \)).\(^{64}\) EPDs may be effective in preventing renal atheroembolic injury, and a controlled trial measuring the impact of EPDs on renal blood flow following RAS should be performed.

**In-Stent Restenosis**

The optimal treatment of renal artery in-stent restenosis (ISR) is uncertain. Primary renal artery stent placement compared to successful balloon angioplasty of ISR lesions demonstrated improved patency for the stent
group with a 58% reduction in recurrent ISR (29.4% vs 71.4%; \( P = .02 \)) and a 30% reduction in follow-up diameter stenosis (41% vs 58.2%; \( P = .03 \)). The repeat stent group also had better secondary patency (\( P = .05 \)) and a greater freedom from repeat ISR (\( P = .01 \)) when compared with balloon angioplasty alone. Other methodologies such as coronary drug-eluting stents, covered stents, cutting balloons, and brachytherapy have been reported, but no systemic studies or any comparative data are available to support any strategy other than optimal repeat bare metal stenting.\(^{65-68}\)

**CONCLUSION**

Patients with presumed atherosclerotic renovascular hypertension should initially be given a trial of multifactorial medical therapy to treat their blood pressure as suggested by the results of CORAL. For patients whose blood pressure is not controlled with medical therapy, the recommendation of the ACC/AHA guidelines document states that it is reasonable to offer renal artery stenting to patients with an atherosclerotic severe RAS (>70% angiographic diameter RAS or 50%-70% stenosis with hemodynamic confirmation of lesion severity) associated with resistant hypertension and failure of 3 drugs, 1 of which is a diuretic, or in patients with hypertension and intolerance to medication.\(^{11}\)

Catheter-based therapy for symptomatic (hypertension, ischemic nephropathy, or cardiac destabilization syndromes), hemodynamically significant, atherosclerotic RAS is the preferred method of revascularization. The discordance between the high (>95%) procedural success and the moderate (60%-70%) clinical response is most likely due to 3 major factors: poor patient selection, poor discrimination of lesion severity by angiography, and the presence of severe parenchymal renal disease. Encouraging data suggest that the use of physiologic lesion assessment can enhance selection for revascularization and improve clinical response rates.\(^{17-19}\) In addition to maximizing the clinical benefit by better patient and lesion selection for renal stenting, the broader use of radial artery access for renal stenting decreases vascular access complications, improves patient satisfaction, and enables same-day discharge in a subset of patients.
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the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary


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**MULTIPLE CHOICE QUESTIONS**

1. A 52-year-old woman undergoes magnetic resonance angiography (MRA) of the abdomen for abdominal pain, which identifies a unilateral
80% left renal artery stenosis. She is referred to you for an opinion regarding treatment. The patient has normal renal function and a diagnosis of hypertension, which is well controlled on 2 medications. Which of the following is appropriate?
A. Perform a renal ultrasound to obtain a baseline image and velocity.
B. Perform an angiogram to confirm the MRA stenosis.
C. Perform an angiogram with renal stenting.
D. There is no need for renal stenting unless her blood pressure becomes uncontrolled.

2. A 72-year-old man with a known unilateral 70% renal artery stenosis and normal renal function is referred for further evaluation by his primary care physician. His blood pressure has ranged from 150/92 mm Hg to 165/88 mm Hg on his home blood pressure cuff over the past several weeks. He is taking a diuretic and an angiotensin-converting enzyme (ACE) inhibitor for his hypertension. In the office today, you measure his blood pressure at 138/86 mm Hg in both arms after 5 minutes of resting. Which of the following is appropriate?
A. Add a β-blocker to his regimen.
B. Add a calcium antagonist to his regimen.
C. Repeat the ultrasound to look for progression of the lesion.
D. Ask him to bring his home cuff into the clinic so that it can be checked against the clinic blood pressure cuffs.

3. An 82-year-old woman presents to the emergency department in acute heart failure manifested by pulmonary edema. She is managed with diuretics. Her blood pressure is 142/90 mm Hg on diuretics and a β-blocker. During her hospital stay, an abdominal ultrasound reveals a 60% to 99% unilateral right renal artery stenosis. Her renal function is mildly impaired with an estimated creatinine clearance of 62 mL/min. Which of the following is most appropriate?
A. Perform an angiogram, and if an ischemic renal artery stenosis is confirmed, perform renal stenting.
B. Add an ACE inhibitor.
C. Add a calcium antagonist.
D. Discuss minimizing sodium in her diet.
4. You follow a 65-year-old man with well-controlled hypertension on 3 medicines and stable coronary disease in your clinic. You notice that his estimated glomerular filtration rate has fallen from 64 mL/min to 48 mL/min over the past year. An ultrasound shows a unilateral severe (>80%) renal artery stenosis with a small kidney (pole to pole is 6 cm). Which of the following is most appropriate?
   A. Perform renal stenting to improve his renal function.
   B. Perform a computed tomography angiogram or MRA to confirm the stenosis severity.
   C. Refer him to nephrology for a consultation regarding his declining renal function.
   D. Discontinue his diuretic and repeat his renal function tests.

5. A patient is admitted and stabilized following a non–ST-segment elevation myocardial infarction on Saturday night. His blood pressure is uncontrolled (~160/90 mm Hg) on 3 medications (diuretic, ACE inhibitor, and β-blocker), and his estimated creatinine clearance is 45 mL/min. You are scheduled to perform a coronary angiogram on Monday morning. Which of the following is most appropriate?
   A. Delay the coronary angiogram several hours until he can get a renal duplex ultrasound performed.
   B. Perform a nonselective aortogram to image the renal arteries during the cardiac catheterization.
   C. Perform selective renal angiography to rule out significant renal artery stenosis during the catheterization.
   D. Add a fourth antihypertensive drug (eg, a calcium channel blocker).

**ANSWERS**

1. D
   There is no indication for revascularization of asymptomatic renal artery stenosis.

2. D
   There is no indication for intervention. It is important to resolve any
systematic measurement differences on home equipment.

3. A
This is a level I indication for renal revascularization.

4. C
There is no benefit from revascularizing a shrunken kidney (<7 cm). He has nephrosclerosis and should be introduced to a nephrologist who can help preserve his renal health.

5. B
This patient is at high risk for renovascular disease and should have a nonselective aortogram performed in conjunction with his cardiac catheterization.
INTRODUCTION

Hypertension is a common, modifiable risk factor of cardiovascular mortality. At present, 30% to 40% of adults in developed countries suffer from hypertension.\(^1\) When hypertension was first recognized, control was difficult due to limited treatment options and often regarded as a fruitless endeavor. In 1931, Dr. Paul Dudley White wrote, “Hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control it.”\(^2\) Starting in the 1930s, surgical sympathectomy to reduce sympathetic tone was observed to significantly lower blood pressure at the expense of significant procedural morbidity and long-term disability. It was not until the late 1960s that pharmacotherapy for hypertension became available and widespread. Pharmacologic treatment for hypertension has proven generally effective, spurred development of many classes of medications, and assisted in the reduction in mortality from cardiovascular disease. Despite this success, many patients have hypertension that remains uncontrolled. Many cases of uncontrolled hypertension may be attributed to inaction or lack of awareness on the part of patient or provider, but the prevalence of true treatment-resistant hypertension is increasing. In recent years, interest in modifying the sympathetic nervous system has
reemerged with the advent of novel minimally invasive methods such as catheter-based renal artery denervation that can potentially restore more balanced autonomic nervous system physiology and offer alternative treatment options for systemic conditions such as hypertension. In this chapter, we will review what is known about the efficacy of catheter-directed autonomic modulation as a novel treatment of hypertension, discuss best practices to achieve desired results, and outline what the future may hold for this controversial area of endovascular medicine.

BACKGROUND

Pathophysiology

Although the pathophysiology of hypertension is complex and incompletely characterized, the sympathetic nervous system is known to play an important role. In essential hypertension, prior studies have demonstrated increased systemic sympathetic nerve firing as well as excessive sympathetic drive to the kidneys. In the 1850s, French physiologist Claude Bernard discovered that disrupting innervation of the greater splanchnic nerve resulted in diuresis and that electrical stimulation resulted in antidiuresis. Early work on the pressor nerves built the foundation for describing the sympathetic nervous system’s effect on regulation of blood pressure. In animal studies, stimulation of chemosensitive renal afferent nerves has been shown to increase systemic efferent sympathetic nerve activity and increase blood pressure. Renal efferent nerves increase systemic blood pressure by stimulating renin production, tubular reabsorption of sodium, and renal arterial vasoconstriction. Furthermore, dense sympathetic innervation of the renal tubules helps regulate pressure natriuresis and sodium excretion in the setting of hypertension, although this process is impaired in long-standing hypertension.

Direct measurement of renal sympathetic activation by sampling renal norepinephrine spillover confirms increased sympathetic drive to the kidneys in the setting of long-standing hypertension. Norepinephrine spillover is defined as the amount of norepinephrine escaping neuronal uptake and local metabolism and “spilling over” into the venous outflow of an organ. By
infusing radiolabeled norepinephrine, the outward flow of norepinephrine can then be measured by renal vein sampling. Measurements of renal norepinephrine spillover suggest elevated spillover in hypertensives compared to the normotensive population. Resistant hypertensives have even higher norepinephrine spillover than the general hypertensive population likely due to excessive underlying sympathetic stimulation and concurrent medications (eg, vasodilators, diuretics) that stimulate sympathetic activation.

**Surgical Sympathectomy and Rise of Modern Pharmacotherapy**

Surgical sympathectomy was the first intervention investigated for treatment of uncontrolled hypertension. In the 1930s to 1940s, several surgeons described different methods of sympathectomy resulting in significant and sustained reductions in systolic and diastolic pressure.\(^8\),\(^9\) Splanchnicectomy and lumbar sympathectomy were 2 more common procedures for malignant hypertension. Studies of surgical sympathectomy demonstrated a high risk of morbidity such as prolonged hospitalization, orthostatic hypotension, impotence, and gait disturbances.\(^10\) Despite associated morbidities, these trials showed a mortality benefit in selected subjects with malignant hypertension.\(^11\),\(^12\) These results were not generalizable to all who suffered from hypertension, and many clinicians remained skeptical of surgical therapeutics to reduce blood pressure.\(^2\) The first effective pharmacologic antihypertensives were ganglionic blockers (eg, tetraethylammonium) modeled after the initial surgical experience, although these too carried a high risk of side effects similar to surgical therapy.\(^13\)

The next stage of antihypertensive development produced centrally acting sympathetic inhibitors as well as \(\alpha\)- and \(\beta\)-adrenergic antagonists. Shortly afterward, diuretics and directly acting vasodilators like hydralazine became available. It was not until the Veterans Administration Cooperative Studies in the 1970s that pharmacologic therapy for hypertension became widely accepted.\(^14\),\(^15\) Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as well as dihydropyridine calcium channel blocking agents became commonly used in the 1990s as these medications were more tolerable and provided longer lasting blood pressure reduction. Current
guidelines from the Eighth Joint National Committee (JNC-8) recommend combination therapy with the following specific blood pressure targets: <150/90 mm Hg for patients >60 years old and <140/90 mm Hg for patients <60 years old or with chronic kidney disease or diabetes. Recently, new evidence suggests more aggressive antihypertensive control may provide further benefit in selected patients. The Systolic Blood Pressure Intervention Trial (SPRINT) showed a reduction in major adverse cardiovascular events compared to usual practice at 1 year with more aggressive antihypertensive therapy targeting systolic blood pressure <120 mm Hg in patients >50 years old with high-risk features for cardiovascular events. Existing guidelines and recent studies highlight the importance of antihypertensive therapy and the need for additional therapies.

**Resistant and Uncontrolled Hypertension**

Despite advances in our understanding of resistant hypertension and in pharmacologic treatment, the prevalence of true treatment-resistant hypertension is as high as 15% to 30% of treated hypertensive patients. Patients with resistant hypertension, according to an American Heart Association consensus document, are defined as patients whose blood pressure remains above goal despite adequate treatment with 3 or more different classes of antihypertensive agents, ideally including a diuretic. Physician inertia, medication noncompliance, and nonadherence to lifelong pharmacologic therapy are all attributed to hypertensive pharmacologic pseudoresistance, but a sizable proportion of remaining patients can be classified as true treatment-resistant hypertensives. Resistant hypertensives are at higher risk for cardiovascular events. In patients with hypertension and coronary artery disease, the prevalence of resistant hypertension is greater than 30% and is associated with a higher risk of all-cause death and a higher risk of cardiovascular mortality. An analysis of the Reduction of Atherothrombosis for Chronic Health (REACH) registry, a multinational database of patients with 3 or more atherosclerotic risk factors or with known coronary, cerebrovascular, or peripheral vascular disease, identified a resistant hypertension prevalence of 12.7%. These patients suffered an 11% higher hazard of a combined primary end point of cardiovascular death, myocardial infarction, and stroke at 4 years. A dose-response relationship was noted, with patients on more antihypertensive medications experiencing
a significantly higher incidence of cardiovascular outcomes.\textsuperscript{21}

The resistant hypertensive population can be difficult to separate from uncontrolled hypertensives as a whole. The spectrum of uncontrolled hypertension ranges from patients with high blood pressure due to inadequate medical regimens or nonadherence to true treatment resistance.\textsuperscript{19} In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) cohort, nearly half the patients required 1 to 2 medications, whereas the rest needed 3 or more antihypertensives. At 5 years, approximately one-third of patients remained uncontrolled despite 2 medications.\textsuperscript{22} The ALLHAT study demonstrates that resistant hypertension remains prevalent despite close monitoring and protocol-directed medication titration. Due to the limitations of current pharmacotherapy and the long-term morbidity associated with resistant hypertension, novel catheter-directed and device-based therapies for hypertension are of great interest in their potential to achieve guideline-defined blood pressure targets in patients struggling to respond.

**RETURN OF INTEREST IN THE SYMPATHETIC NERVOUS SYSTEM AS A THERAPEUTIC TARGET**

Given the prevalence of resistant hypertension, there is intense academic and commercial interest in developing therapies that can predictably modulate autonomic tone for promotion of health. Ablating renal sympathetic innervation was originally thought to provide an antihypertensive effect by reducing tubular reabsorption of sodium and downregulating the renin-angiotensin-aldosterone system (RAAS) via interruption of signaling from the central nervous system (CNS) to the kidneys via renal efferent nerves. More recently, it has been recognized that disruption of renal afferent nerves also alters the feedback loop of sympathetic signaling from the kidneys back to the CNS, which may reduce central systemic sympathetic outflow as well. Studying the effects of total nephrectomy and sympathetic tone in patients with end-stage renal disease, Converse et al\textsuperscript{23} demonstrated increased postganglionic sympathetic nerve discharge in those who had not undergone
nephrectomy. Thus, excess sympathetic nervous activity in the setting of chronic renal insufficiency is associated with renal afferent innervation. The concept of a feedback loop of efferent and afferent signaling between the kidneys and brain may have far-reaching influence on other disease and metabolic activity.

From the initial surgical experience in the 1930s to 1940s, sympathetic denervation was established as a means to reduce blood pressure and mortality. However, how to selectively target renal sympathetic nerves for blood pressure reduction while avoiding the morbidity of disrupting neighboring abdominal, pelvic, and lower extremity innervation remained a challenge. The anatomy of postganglionic renal sympathetic nerves is favorable for catheter-directed therapy as neuronal fibers extending from the sympathetic chain reside in the adventitia along the length of the renal arteries in route to the kidneys. The first patented minimally invasive method to disrupt renal innervation emerged in the early 2000s with development of a single-lead endovascular radiofrequency ablation catheter that could be navigated along the length of the renal artery (Fig. 53-1). With electrode wall contact on the intimal side, externally directed radiofrequency energy could thermally ablate neighboring sympathetic nerves residing in the adventitia.

Initial studies applied radiofrequency energy every 5 mm along the length of bilateral main renal artery trunks. Early swine catheter studies demonstrated a reduction in norepinephrine content in renal outflow greater than 85%, which was comparable to direct surgical renal denervation. A subsequent first-in-human report described successful renal denervation in a 59-year-old man with a history of 2 transient ischemic attacks, obstructive sleep apnea, and long-standing hypertension despite 7 antihypertensive agents. His mean blood pressure prior to invasive treatment was 161/107 mm Hg. At 30 days, his blood pressure was reduced to 141/90 mm Hg and then to 127/81 mm Hg at 1 year. Total-body norepinephrine spillover was reduced by 42% along with reductions in other measures of sympathetic excess.
The initial open-label, proof-of-concept pilot study, SYMPPLICITY HTN-1,24 enrolled 153 patients at 19 investigational sites in Australia, Europe, and the United States (Table 53-1). Patients with systolic office blood pressure (OBP) ≥160 mm Hg despite taking at least 3 antihypertensive drugs, including a diuretic, were eligible. Investigators performed catheter-directed radiofrequency ablation of the renal sympathetic nerves with the Symplicity Flex catheter (Medtronic, Santa Rosa, CA). The study achieved systolic and diastolic OBP reductions of 20 and 10 mm Hg at 1 month, respectively. The study investigators have reported data on 88 subjects out to 3 years with sustained OBP reduction (–32/–14 mm Hg).26,27 A follow-up phase II study, SYMPPLICITY HTN-2, enrolled 106 patients at 24 centers in Australia, New Zealand, and Europe in a multicenter, prospective, randomized controlled trial (see Table 53-1).28 Patients with baseline systolic OBP ≥160 mm Hg (or ≥150 mm Hg in patients with type 2 diabetes mellitus) despite at least 3 antihypertensive drugs (diuretic was not mandated) were eligible for 1:1 randomization between catheter-based renal denervation (RDN) and control. The control arm of the trial was not blinded as patients continued preexisting antihypertensive therapy. The mean change in systolic and diastolic OBP at 6 months was –32/–12 mm Hg in the RDN group compared to an insignificant
change from baseline (mean, 1/0 mm Hg) in the control group. Further follow-up data of 70 of the 89 patients in SYMPPLICITY HTN-2 who received RDN demonstrated a mean 36-month (treatment) and 30-month (crossover) systolic and diastolic OBP reduction of –34 and –14 mm Hg, respectively.29

Table 53-1 Trials of Catheter-Based Renal Denervation (RDN) for Resistant Hypertension Using Simplicity Flex Catheter System

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPPLICITY HTN-1</td>
<td>153 patients with systolic OBP ≥160 mm Hg despite ≥3 drugs (including a diuretic)</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean medications: 4.7 Mean BP 177/101 mm Hg</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Open-label pilot study</td>
</tr>
<tr>
<td>Randomization</td>
<td>No control</td>
</tr>
<tr>
<td>Catheter</td>
<td>Symplicity Flex catheter system</td>
</tr>
<tr>
<td>Safety End Points</td>
<td>97% performed without complication (1 renal artery dissection)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>OBP –22/-10 mm Hg at 6 months</td>
</tr>
<tr>
<td></td>
<td>OBP –32/-14 mm Hg at 3 years in 88 patients</td>
</tr>
</tbody>
</table>

| SYMPPLICITY HTN-2 | 106 patients with systolic OBP ≥160 mm Hg for ≥3.50 mm Hg in T2DM despite ≥3 drugs |
| Baseline       | Mean medications: 5.2 vs 5.3 Mean OBP (mm Hg): 178/97 vs 178/98               |
| Trial Design    | Randomized controlled trial RDN + medical therapy vs continued medical therapy |
| Randomization  | Phase II study 1:1 randomization                                            |
| Catheter       | Symplicity Flex catheter system                                            |
| Safety End Points | No serious adverse events No difference in renal function at 6 months between the groups |
| Outcomes       | Mean change in OBP at 6 months: RDN: –42/-12 mm Hg vs control: 1/0 mm Hg (P < .001) |

| SYMPPLICITY HTN-3 | 535 patients with systolic OBP ≥160 mm Hg despite ≥3 drugs (including a diuretic) |
| Baseline       | Mean medications: 5.1 vs 5.2 Mean OBP (mm Hg): 180/97 vs 180/99 Mean ABP (mm Hg): 159/98 vs 160/91 |
| Trial Design    | Sham-controlled randomized trial RDN + medical therapy vs sham procedure + medical therapy |
| Randomization  | Sham-controlled 2:1 randomization                                           |
| Catheter       | Symplicity Flex catheter system                                            |
| Safety End Points | Few major adverse events: 5 in RDN group (1.4%) and 1 in sham group (0.6%) |
| Outcomes       | Nonsignificant differences at 6 months Systolic OBP: –14 vs –12 mm Hg (P = .26) Systolic ABP: –7 vs –5 mm Hg (P = .98) |

| DENER-HTN      | 106 patients with BP ≥140/90 mm Hg despite ≥3 drugs Resistant hypertensive confirmed with 4-week SSAHT prior to randomization |
| Baseline       | Enrollment: mean daytime OBP 163/95 mm Hg Randomization: daytime ABP (mm Hg): 150/93 vs 152/91 24-Hour ABP (mm Hg): 152/90 vs 147/88 |
| Trial Design    | Open-label randomized controlled trial SSAHT + RDN vs SSAHT alone           |
| Randomization  | 1:1 randomization after 4 weeks of SSAHT for all patients                   |
| Catheter       | Symplicity Flex catheter system RDN: 2-4 weeks after randomization          |
| Safety End Points | Few minor RDN-related adverse events                                       |
| Outcomes       | Daytime systolic ABP: –16 vs –10 mm Hg, P = .03 Nighttime systolic ABP: –14 vs –8 mm Hg, P = .03 24-hour systolic ABP: –15 vs –10 mm Hg, P = .02 |

*All comparisons presented an RDN group vs. medical therapy group.

Abbreviations: ABP: ambulatory blood pressure; SSAHT, standardised stepped-care antihypertensive treatment; T2DM, type 2 diabetes mellitus.


Importantly, neither SYMPPLICITY HTN-1 nor HTN-2 reported any significant differences in adverse events or measures of safety between denervation treatment and control groups. At long-term follow-up, renal function was preserved in each study, and initial imaging substudy analysis showed no incidence of renal artery stenosis at the site of ablation. Postural hypotension was not observed, suggesting that venoconstriction remains intact after RDN. Finally, given persistent blood pressure reduction data and signs of an increasing responder rate over time, the Symplicity Flex catheter received CE (Conformité Européenne) market approval as a treatment for resistant hypertension in Europe and subsequent similar approval in several areas around the globe.
SYMPLICITY HTN-3

The success of SYMPLICITY HTN-1 and HTN-2 generated great enthusiasm for RDN as a novel treatment for resistant hypertension. In order to pursue US Food and Drug Administration (FDA) approval, SYMPLICITY HTN-3, a prospective, single-blind, randomized, sham-controlled phase III trial, was conceived with hopes to definitively demonstrate clinical efficacy and safety of RDN (see Table 53-1).\(^3\) A total of 535 patients with resistant hypertension taking maximally tolerated doses of at least 3 antihypertensive medications, including a diuretic, were randomized in 2:1 fashion, with 364 patients in the RDN group and 171 in the control group. The defined end points were as follows: a primary efficacy end point of change in OBP at 6 months, a secondary efficacy end point of change in 24-hour ambulatory blood pressure monitoring (ABPM) at 6 months, and a primary composite safety end point. All patients underwent baseline renal angiography, but after randomization, those in the control group remained on the table as a sham procedure with all randomized patients blinded to their treatment assignment. The intention was to identify patients with severe manifestations of resistant hypertension and to eliminate the bias of study subjects’ awareness of treatment assignment.

At baseline, patients in HTN-3 were taking an average of 5 antihypertensive medications, 4 of which were at maximal dosing. All patients enrolled were on diuretics, primarily of the thiazide class. Despite this aggressive medication regimen, the average baseline systolic OBP was 180 mm Hg. All patients enrolled in HTN-3 also underwent 24-hour ABPM with a mean baseline of 160 mm Hg. At 6 months, the adverse event rate was low and no different from control, demonstrating that RDN, as implemented in HTN-3, can be performed safely. Although OBP and 24-hour ABPM decreased by 14.13 mm Hg and 6.89 mm Hg, respectively, after RDN, similar declines were also seen in the control group. The mean difference in office-based systolic blood pressure was –2.4 mm Hg, and mean difference in 24-hour ABPM was –1.96 mm Hg. Both of these differences failed to meet predefined superiority margins and were statistically insignificant. After completing 6 months of follow-up, control group patients who qualified to crossover to RDN were treated and followed but failed to demonstrate any significant superiority in blood pressure lowering 6 months after RDN. Given
prior data suggesting a long-term responder effect, 12-month OBP and 24-hour ABPM measures of patients initially randomized to denervation were examined but also failed to demonstrate any significant long-term difference from those in the control arm on medications alone.\textsuperscript{31}

The results of SYMPLICITY HTN-3 greatly tempered prior enthusiasm that had developed around the concept of RDN. HTN-3 also launched a debate regarding the validity of all prior studies of RDN that had demonstrated such a stark difference in efficacy of blood pressure lowering while excluding sham procedure in a blinded control group. Questions surfaced as to whether previous demonstrations of blood pressure reduction after RDN were merely a manifestation of placebo effect. Given the many physiologic components driving elevated blood pressure in hypertensive patients, many also question whether denervation trial participants manifested the Hawthorne effect of behavior modification by virtue of being observed in a trial, thereby leading to blood pressure declines in both treatment and control groups. Another concern raised in the design of these RDN trials is the likelihood of regression to the mean given that qualifying patients were included primarily based on isolated OBP measurements above 160 mm Hg, and not 24-hour ABPM.\textsuperscript{32} Proponents of RDN have challenged that the design of HTN-3 underestimated the potential benefits of RDN. The following section will explore these questions.

\textbf{Technologic Limitations of the Symplicity Flex Catheter: Was Denervation Underdosed?}

The catheter tested in the SYMPLICITY trials was a first-generation device with a single-lead electrode. Precise electrode positioning within the renal artery, proper wall apposition, and successful circumferential denervation are extremely operator dependent with this device. Further refinements and engineering advances have created “second-generation” catheter platforms that may better ensure adequate denervation and optimization of results. These catheters can deliver multidirectional circumferential nerve ablation, which is more efficient and reproducible in achieving complete denervation by maximizing “4-quadrant” renal arterial denervation. Ideally, the procedure should achieve a full 360° ablation by applying energy at the superior, inferior, anterior, and posterior arterial walls. A substudy analysis of HTN-3
suggested the number of successful renal arterial quadrants ablated is an independent predictor of blood pressure reduction after RDN. Of note, less than 25% of patients received circumferential 4-quadrant denervation in both right and left renal arteries. A dose effect trend was also documented between the number of full 4-quadrant ablations achieved during RDN and blood pressure lowering. Although HTN-1 tested regional norepinephrine spillover after denervation to confirm the sympathetic modulation, HTN-3 did not include norepinephrine spillover measurements, rendering it difficult to compare the concept of dose effect between trials. The concept of a denervation dose effect requires further study for validation. Leaders in the field now debate that HTN-3’s failure to achieve its prespecified end points was attributable to inadequate denervation due to protocol limitations and overall operator inexperience. A wide range of operator volume was seen. Most operators had not previously performed RDN.7

**How Generalizable and Homogeneous Was the SYMPLICITY HTN-3 Patient Population?**

The severity of hypertension required to qualify for randomization was so extreme that it is difficult to generalize the HTN-3 study population to uncontrolled hypertensive patients typically seeking assistance in lowering their blood pressure. In one single-center study, only 0.8% of the entire hypertensive population of an academic cardiology patient practice would have met the general inclusion criteria of HTN-3. Some have speculated that the underlying pathophysiology of resistant hypertension in many patients enrolled in HTN-3 may have been beyond alteration, even if adequate circumferential denervation had been achieved.

Ideally, in testing the efficacy of blood pressure lowering of a novel therapy, a trial would include patients with similar acuity of illness and minimize any confounding factors that would cloud the true treatment effect of the tested intervention. Although only patients thought to have severe true treatment-resistant hypertension were enrolled, there was large variance between patients in the number and type of medications taken. After enrollment, a substudy analysis of HTN-3 revealed that 38.2% and 42.1% of patients in the RDN and sham control groups, respectively, changed either the number of medications or dosing during the 6-month study period.33 Such
common medication changes confound the testing of a treatment effect. It is impossible to retrospectively determine the underlying nature of resistant hypertension in patients who qualified for randomization. Compliance with pharmaceutical regimens was confirmed only by patient interview and without an objective measure of drug ingestion.

The measurement of blood pressure in these and other antihypertensive efficacy trials has come under criticism in that almost all have historically used OBP for qualification and as a primary outcome measurement. Increasingly, however, the use of OBP limits assessment of blood pressure to a small window of time that is prone to confounders in the office setting such as white coat hypertension. Twenty-four–hour ABPM, with interventions such as witnessed medication ingestion prior to recording, has been suggested as a potentially more valid method to measure blood pressure in such trials.

Differences in treatment efficacy between African Americans and non–African Americans were also noted. Assessing outcomes by ethnicity, systolic OBP response in the control (sham) arm showed a significant and larger reduction in African Americans than in non–African Americans. Assessing prescribed medications, African Americans were prescribed aldosterone antagonists and vasodilators more often than non–African American participants. Furthermore, African Americans had significantly higher baseline diastolic blood pressure and more complex antihypertensive regimens (eg, at least 1 medication prescribed 3 times daily). Through interaction analysis, some experts hypothesize that improved medication adherence after randomization contributed to greater blood pressure reduction in the control (sham) arm, especially in the African American cohort. In subgroup analysis, blood pressure response to RDN in non–African Americans was similar to that which has been described in prior RDN trials and global registries. These differences will need to be studied further to better understand what distinguishes RDN responders from nonresponders.

**DENER-HTN**

SYMPLICITY HTN-3 was praised for its sham design but criticized due to possible inadequate denervation and subgroup differences. DENER-HTN (Renal Denervation in Patients With Resistant Hypertension) was a randomized controlled trial designed to examine efficacy and cost-
effectiveness of RDN added to standardized antihypertensive therapy (see Table 53-1).\textsuperscript{36} Fifteen French centers recruited 106 patients with 24-hour ABPM systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg despite 3 or more antihypertensives at maximally tolerated doses, including a diuretic. To confirm resistant hypertension, each patient was switched to a standardized 3-drug regimen for 4 weeks including maximally tolerated doses of indapamide, amlodipine, and ramipril or irbesartan. Patients were then randomized 1:1 to RDN with the Medtronic Symplicity Flex catheter or standardized oral antihypertensive therapy. Preselected antihypertensives from other classes could be added during follow-up (spironolactone, bisoprolol, prazosin, or rilmenidine, sequentially in this order) if 24-hour ABPM remained above the goal of 135/85 mm Hg. At 6 months, the average reduction in 24-hour ABPM systolic blood pressure was significantly greater in the RDN group than the control group in all 3 monitoring settings: daytime ambulatory monitoring (–15.8 mm Hg vs –9.9 mm Hg; \(P = .03\)), nighttime ambulatory monitoring (–13.9 mm Hg vs –7.6 mm Hg; \(P = .03\)), and 24-hour ABPM (–15.4 mm Hg vs –9.5 mm Hg; \(P = .02\)). A similar proportion of patients in each group received add-on treatment from other medication classes, reaching a median of 5 drugs in each group. Medication adherence was strictly followed using the Morisky Medication Adherence Scale questionnaire.\textsuperscript{36}

DENER-HTN was a smaller trial but possibly implemented a more relevant protocol and design than SYMPLICITY HTN-3. Patient selection was more homogenous by design with a 4-week period of medication standardization. DENER-HTN used 24-hour ABPM as the desired end point, providing a more complete understanding of hypertensive burden at baseline and overall change in blood pressure over time. Further, patients in both groups required additional therapy after randomization (mean, 5 medications). The continued addition of medical therapy in a stepwise fashion, with sympatholytic drugs after other classes, has led some to hypothesize that antiadrenergic agents may enhance the effects of RDN. From the DENER-HTN trial, patients with evidence of sympathetic dysregulation and hypertension may be more suited targets for RDN. Some investigators have even suggested that detecting excess sympathetic activity when diagnosing hypertension may be useful for selecting previously untreated patients who may benefit from RDN.\textsuperscript{37} The DENER-HTN study has reinvigorated interest in RDN’s therapeutic potential based on a stricter
trial design than HTN-3 and its thought-provoking results.

RENAL DENERVATION PROCEDURAL CONSIDERATIONS TO OPTIMIZE RESULTS

The renal afferent and efferent sympathetic nerves, as described earlier, reside along the adventitia of the renal arteries. Coursing from the sympathetic trunk, the nerves travel from the aorta to the main renal arteries. The limited histologic studies available at the time suggested that the distribution of nerves were most concentrated around the proximal segments of the renal arteries. For this reason, initial radiofrequency ablation techniques emphasized targeting RDN in the mid-to-proximal segments of the renal arteries.25

The Symplicity Flex catheter system, as used in the SYMPPLICITY HTN studies, is a single-electrode system designed to apply focal radiofrequency ablation to the renal nerves through precise operator manipulation. The catheter shaft allows the operator to rotate the tip and to partially flex the distal end to allow maneuverability. The catheter is connected to a generator console, which provides real-time data regarding treatment time, impedance changes, energy delivery in watts, and temperature. A renal angiogram is initially performed to assess for exclusions such as significant renal artery stenosis, vessel diameter <4 mm or target length <20 mm, and the presence of large accessory renal arteries. Using a 6-Fr guiding system via transfemoral access, the Symplicity Flex system is advanced directly from a selective guiding catheter into the renal arteries without the need for a guide wire. The HTN-1 and HTN-2 trials aimed for at least 4 radiofrequency ablations lasting 120 seconds at 8 watts or less applied to the lumen of the renal artery. As practiced in these studies, the initial ablation is performed 5 mm proximal to the distal bifurcation. The catheter is then retracted 5 mm and rotated to the next radiofrequency ablation site. Retracting the catheter toward the proximal renal artery, the goal is to provide 360° of circumferential ablation in superior, inferior, anterior, and posterior quadrants. During ablation, temperature and impedance are monitored and energy delivery is altered according to the generator’s proprietary algorithm. Patients generally require
dense conscious sedation and careful monitoring for associated visceral pain during catheter activation. Angiographically, operators may see denervation “notches,” or areas of focal spasm marking sites of applied thermal injury. These are typically self-limited, with severe cases resolving with intra-arterial nitroglycerin. Postprocedural monitoring is typically straightforward including standard of care for vascular hemostasis, supportive care for any residual visceral pain, and routine postprocedural monitoring per usual conscious sedation guidelines. Report has been made of platelet activation and possible luminal microthrombi where denervation was applied. For this reason, antiplatelet therapy may be considered periprocedurally, although this practice has not been formally studied.\textsuperscript{10,24,38}

A recent histologic analysis at autopsy demonstrates that the maximal number of nerves are present in the proximal and ventral segments of the renal arteries.\textsuperscript{39} As the paravertebral aorticorenal ganglia receives many branches from the greater, lesser, and least splanchnic nerves, which then form the renal plexus, the absolute number of sympathetic nerves near the ostia of the renal arteries is likely to be greatest. However, nerves are spatially closer to the luminal surface moving more distally along the length of the renal artery and at the bifurcation (mean, 2.84 mm in proximal segments vs 1.81 mm in the distal segments).\textsuperscript{39} A swine study of radiofrequency denervation in the main renal trunk versus main trunk plus vessels distal to the bifurcation suggests that more consistent denervation is produced by including suitable vessels distal to the bifurcation.\textsuperscript{40} Our enhanced understanding of variations in sympathetic fiber proximity to the renal artery luminal surface has influenced much of the newer technology for RDN, which we discuss later in the chapter.

STATE OF THE ART RENAL DENERVATION CATHETERS

\textit{Symplicity Spyral}

Given the lessons learned from the SYMPPLICITY trials outlined earlier, technical improvements in catheter design have been implemented with the newer Symplicity Spyral catheter (Medtronic). As opposed to a manually
directed single-lead electrode system, Spyral is a self-expanding helical 4-electrode design delivered over an 0.014-inch wire that conforms to various vessel diameters ranging from 3 to 8 mm (Figs. 53-2 and 53-3). The electrodes are positioned circumferentially to deliver a 4-quadrant pattern of radiofrequency-induced denervation with 1 simultaneous treatment cycle that lasts only 60 seconds. A newer generator console system allows simultaneous monitoring of performance of each electrode and the option to selectively power each on or off individually. Spyral is undergoing phase II testing through the SPYRAL HTN global clinical trial program.

FIGURE 53-2 Symplicity Spyral Catheter (Medtronic, Santa Rosa, CA). Spyral is a self-expanding helical 4-electrode design delivered over an 0.014-inch wire that conforms to vessel diameter. (Copyright © Medtronic 2016.)
**Vessix**

The Vessix catheter (Boston Scientific, Maple Grove, MN) is a balloon catheter that inflates to only 3 atm pressure placing 4 helical offset electrodes in contact with the renal artery to deliver treatment (Fig. 53-4). These electrodes are bipolar and can deliver radiofrequency energy with lower wattage than comparable unipolar systems and for shorter treatment time in as little as 30 seconds. Given the lack of a grounding pad, visceral discomfort may not be as severe as unipolar systems. Each electrode can be individually monitored and activated via a generator console. The catheter profile is 7 Fr, and different balloon sizes are available from 4 to 7 mm in diameter. Initial clinical studies have been promising but have yet to include published randomized data with a sham control group. Vessix is currently undergoing phase II testing in the REDUCE HTN: REINFORCE study.
The Vessix catheter (Boston Scientific, Maple Grove, MN) is a balloon catheter that inflates to only 3 atm pressure placing 4 helical offset electrodes in contact with the renal artery to deliver treatment. (Image provided courtesy of Boston Scientific. © 2016 Boston Scientific Corporation or its affiliates. All rights reserved.)

EnligHTN

The EnligHTN catheter (St. Jude Medical, Saint Paul, MN) delivers circumferential radiofrequency denervation through an 8-Fr multielectrode basket design expanded by the operator (Fig. 53-5). When fully expanded, the 4 electrodes of the basket are spaced circumferentially to target all 4 quadrants. Each electrode is individually monitored and activated through a generator console. The electrode systems are unipolar, and treatment time is 90 seconds for simultaneous electrode firing. Initial clinical trials have been encouraging but also lack randomized data compared to a sham procedure.
FIGURE 53-5 The EnligHTN catheter (St. Jude Medical, Saint Paul, MN) delivers circumferential radiofrequency denervation through an 8-Fr multielectrode basket design via 4 electrodes spaced circumferentially to target all 4 quadrants. (EnligHTN and St. Jude Medical are trademarks of St. Jude Medical, Inc. or its related companies. Reproduced with permission of St. Jude Medical, © 2016. All rights reserved.)

PARADISE

The PARADISE catheter (ReCor Medical, Palo Alto, CA) is a 6-Fr low-pressure balloon system that delivers rotational therapeutic ultrasound energy instead of radiofrequency energy (Fig. 53-6). Via a fluid-cooled balloon, the self-centered rotational ultrasonic source delivers energy that theoretically allows full circumferential denervation in a 360° donut pattern. Energy intensity can be adjusted by the operator via a generator console that can change the depth of desired thermal injury. Phase II trial enrollment has begun via the RADIANCE-HTN global clinical trial.

FIGURE 53-6 The PARADISE catheter (ReCor Medical, Palo Alto, CA) is a 6-Fr
low-pressure balloon system that delivers rotational therapeutic ultrasound energy instead of radiofrequency energy.

**Peregrine**

Since thermal denervation achieves its effect via tissue injury, alcohol has been explored as an alternative neurolytic therapeutic option. Alcohol has been safely used as a therapeutic tool in diseases such as hypertrophic cardiomyopathy septal ablation. The Peregrine catheter (Ablative Solutions, Kalamazoo, MI) delivers dehydrated alcohol to the periadventitial space of the renal arteries (Fig. 53-7). The Peregrine catheter is navigated into the renal arteries with deployment of 3 guide tubes from the catheter tip. These engage the intimal surface with subsequent penetration of the vessel with 220-μm needles. The guide tubes are spaced 120° apart and allow for 360° circumferential spread of the injected alcohol, which extravasates throughout the periadventitial space. First-in-man experience has been promising but will require further clinical investigation to confirm safety and efficacy.41
**FIGURE 53-7** The Peregrine catheter (Ablative Solutions, Kalamazoo, MI) delivers dehydrated alcohol to the periadventitial space of the renal arteries by deploying 3 guide tubes from the catheter tip that penetrate the intimal surface with 220-μm needles. The guide tubes are spaced 120° apart and allow for 360° circumferential spread of the injected alcohol, which extravasates throughout the periadventitial space.

**FUTURE TRIAL DESIGN TO EVALUATE RENAL DENERVATION**

As described earlier, the available evidence base of clinical trials that have tested the efficacy of RDN has been met with skepticism due to methodologic limitations. SYMPPLICITY HTN-1 and HTN-2 lacked adequate control arms to test for placebo effect and lacked sufficient 24-hour ABPM measurements to demonstrate true treatment-resistant hypertension in their population. SYMPPLICITY HTN-3, as discussed earlier, has raised more
questions than answers as uncertainty remains as to whether the RDN hypothesis for lowering blood pressure in a relevant population was adequately tested. The best way to study whether or not a specific population benefits from this therapeutic concept is still unclear. Many ideas have been proposed in how to design future trials of RDN.

Separating the treatment effect of RDN in patients on vastly different medication regimens with varying degrees of compliance who also manifest differing levels of disease severity or underlying pathophysiology remains a challenge. Ideally, an operator would be able to measure a marker of sympathetic tone or of renal nerve signaling before and after RDN to determine treatment success. Unfortunately, no such tool has yet been devised. In order to eliminate confounding, randomizing hypertensive patients off medications or hypertensive patients receiving an identical standardized drug regimen to RDN versus a sham procedure has been suggested as an alternative pathway in trial design. Such studies would be more sensitive to the treatment effect of RDN itself. Identifying patients who are more generalizable for potential treatment response then those enrolled in SYMPLICITY HTN-3 has also been suggested, given that patients enrolled in SYMPLICITY HTN-3 were supposedly uncontrolled on an average of 5 medications. Limiting the importance of OBP readings and relying, instead, on 24-hour ABPM and home blood pressure readings for study end points may ensure enrollment of patients with true treatment-resistant hypertension. Improved methods to screen for patient medication compliance (eg, monitoring of medication refills or pill counts, or testing for metabolites of medication) have also been suggested. In regard to catheter technology, currently available radiofrequency RDN systems, as described earlier, have improved from that which was tested in the SYMPLICITY trials. New-generation catheter designs offer improvements such as multiple electrodes, balloon-inflatable or expansive catheter designs to better ensure wall apposition, and circumferential treatment delivery to optimize adequate radial denervation. Hopefully, ongoing and future studies of novel denervation technology with modified trial designs can definitively answer the question of whether denervation alters pathophysiology for the potential benefit of patients.

Currently, the Symplicity Spyral, Vessix, and Paradise catheters are being evaluated via FDA-approved phase II trials in the United States through the SPYRAL HTN-ON MED and HTN-OFF MED studies, REDUCE HTN:
REINFORCE study, and the RADIANCE study, respectively. Proponents of RDN await the results of these trials to determine if RDN will prove to be a valuable addition to the armamentarium of antihypertensive therapies.

RENAL DENERVATION AS TREATMENT FOR OTHER DISEASE STATES

**Obstructive Sleep Apnea**

Patients suffering from obstructive sleep apnea (OSA) have an increased risk for cardiovascular morbidity and an increased prevalence of resistant hypertension. During airway obstruction and cumulative nocturnal hypoxia, OSA patients experience excessive upregulation of sympathetic tone, which is thought to increase susceptibility to cardiovascular morbidity. Whether sympathetic nerve activity drives the pathogenesis of OSA or whether persistent hypoxia from apnea and hypopnea drives an increase in sympathetic tone is incompletely understood. A few small observational studies have described physiologic effects of RDN in patients with OSA. A limited meta-analysis suggests that RDN may improve both blood pressure as well as the apnea-hypopnea index.\(^{42}\) The potential role of RDN in ameliorating the pathophysiology and consequences of OSA will need to be explored further in randomized trials.

**Cardiac Arrhythmia**

Multiple pathophysiologic perturbations influence the pathogenesis of atrial and ventricular arrhythmia including sympathetic nervous overactivity. Pharmacologic \(\beta\)-receptor blockade is a mainstay of treatment but with limited efficacy. For hypertensive patients with atrial fibrillation, limited trial data have demonstrated a reduction in recurrent atrial fibrillation after pulmonary vein isolation (PVI) treatment combined with RDN compared to PVI alone.\(^{43}\) This suggests a role of autonomic imbalance in the initiation or propagation of atrial arrhythmogenicity. Larger randomized trials are under
way to further validate this hypothesis.

Ventricular arrhythmogenesis is another similar target for modulation of autonomic activity with hope that RDN may reduce ventricular tachycardia in at-risk patients. Randomized trials are lacking, but ongoing trial results will determine whether there is merit in this approach.

**Insulin Resistance**

Alterations in glucose metabolism in patients with insulin resistance are driven by a complex interplay between different physiologic mechanisms, of which the sympathetic nervous system plays a role. RDN, primarily through disruption of afferent sympathetic nervous signaling, has generated interest as a therapeutic tool to potentiate sensitivity to insulin. When RDN was performed in a study of hypertensive patients, 40% of whom had type 2 diabetes, improved glucose metabolism was seen as measured by changes in fasting glucose, insulin, and C-peptide levels as well as by insulin sensitivity index and oral glucose tolerance test measurements. This study and subsequent reports have spurred interest in larger randomized controlled trials to further test the benefit of restoring autonomic balance to improve glucose metabolism.

**Chronic Congestive Heart Failure**

Heart failure is a complex pathophysiologic state in which multiple neurohormonal systems including the renin-angiotensin-aldosterone, arginine vasopressin, and sympathetic nervous systems are activated to maintain cardiac output. Increased sympathetic activity leads to enhanced vasoconstriction and increased systemic and pulmonary vascular resistance, which maintains left ventricular preload. Increased tubular sodium reabsorption from renal sympathetic stimulation and overall excess renal and cardiac sympathetic stimulation have been demonstrated in patients with chronic heart failure. Suppression of sympathetic input with β-blockade is now a mainstay of therapy by virtue of its clear mortality benefit. As an alternate means to reestablish autonomic balance, there is interest in therapeutic RDN in the setting of chronic heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). The pilot study for REACH (Renal Artery Denervation in Chronic Heart failure)
demonstrated that RDN via the Symplicity system may be safe in 7 patients with chronic HFrEF (New York Heart Association [NYHA] class III-IV) on maximally tolerated medical therapy including β-blockers. Six months after RDN, renal function remained stable and there were no reported episodes of syncope, hypotension, or other hemodynamic disturbances. Additionally, the pilot study suggested an improvement in exercise capacity with significantly increased 6-minute walk distances at 6 months.

REACH (NCT01639378) is now ongoing with plans to randomize 100 patients to RDN plus maximal medical therapy versus a sham procedure plus maximal medical therapy with change in symptoms as the primary outcome. SYMPPLICITY-HF (NCT01392196) has completed enrollment of 40 patients with chronic HFrEF (NYHA class II-VI) in a phase II clinical trial evaluating physiologic response and safety of RDN in this population. Targeting the HFrEF population, the DIASTOLE (Denervation of the Renal Sympathetic Nerves in Heart Failure With Normal Left Ventricular Ejection Fraction; NCT01583881) study has enrolled 60 patients with HFpEF to RDN with the Symplicity system plus medical therapy versus medical therapy alone. The primary outcome is change in diastolic function as measured by the E/E’ ratio at 12 months. In coming years, a greater understanding of RDN effects in the setting of HFrEF and HFpEF will guide decisions to pursue more ambitious clinical trial evaluation.

**Chronic Kidney Disease**

Hypertension is a major risk factor for chronic kidney disease (CKD), and control of hypertension is known to reduce progression to end-stage renal disease. Excessive sympathetic activity in renal failure has been well described and is elevated in patients with end-stage renal disease compared to patients with end-stage renal disease who have undergone nephrectomy. In patients with CKD, resistant hypertension is common, and sympathetic overactivity has been shown to contribute to progression. In the SYMPPLICITY-HTN studies, patients with estimated glomerular filtration rates (GFR) ≤45 mL/min/1.73 m² were excluded. RDN trials have demonstrated no renal injury in patients randomized to denervation.

Given difficulties achieving control of blood pressure and in slowing the progression of nephropathy, alternative therapies in the CKD population that
can reduce cardiovascular risk and progression of CKD would be very valuable. Fifteen Australian patients with stage 3 to 4 CKD and resistant hypertension underwent RDN with minimal contrast exposure including 6 patients by carbon dioxide angiography. Estimated GFR was not adversely affected, but OBP significantly improved from an average 174/91 mm Hg at enrollment to 144/73 mm Hg after 1 year. With this suggestion of safety in the CKD population, a German group investigated rates of GFR change before and after RDN. Twenty-seven patients with stage 3 or 4 CKD and resistant hypertension confirmed by 24-hour ABPM underwent RDN. Renal function was analyzed for 3 years retrospectively and then for 1 year prospectively after RDN. The rate of estimated GFR decline prior to RDN was 4.8 mL/min/1.73 m² per year. After RDN, estimated GFR improved on average 1.5 mL/min/1.73 m² per year. Additionally, mean 24-hour ambulatory blood pressure improved from 151/80 mm Hg to 143/76 mm Hg at 1 year. If future studies are favorable, patients with CKD may prove to be a high-risk population that would benefit from the physiologic modification of RDN.

ALTERNATIVE CATHETER SOLUTIONS FOR BLOOD PRESSURE REDUCTION

Carotid Baroreceptor Modulation

Baroreceptor reflex function has long been appreciated as a potent mediator of homeostatic balance in blood pressure regulation. Baroreceptors in the carotid bodies, located in the wall of the carotid artery bilaterally, are easily accessible for therapeutic manipulation as has long been described during carotid artery massage. Pulsatile signaling from the baroreceptors delivers continuous feedback through the carotid sinus nerve to the CNS modulating sympathetic and parasympathetic feedback. Blood pressure lowering after carotid artery stenting is well recognized but typically short lived due to baroreceptor reset from the CNS. The MobiusHD device (Vascular Dynamics, Mountain View, CA) is a self-expanding stent-like device
deployed similar to comparable carotid stent technology that increases carotid artery wall strain to increase carotid sinus nerve feedback (Figs. 53-8A and B). Unlike carotid stents, however, the MobiusHD maintains pulsatility to theoretically prevent baroreceptor reset and to maintain blood pressure lowering. First-in-man trial results are promising thus far but await study completion and further investigation.51

FIGURE 53-8 The MobiusHD device (Vascular Dynamics, Mountain View, CA) is a self-expanding stent-like device (A) that increases carotid artery wall strain to increase carotid sinus nerve feedback (B).

Arteriovenous Shunting

The ROX Coupler (ROX Medical, San Clemente, CA) approaches catheter-based intervention for blood pressure lowering in a completely different way without any need to modulate the autonomic nervous system. Through a catheter-based sidewall puncture from the central iliac artery to the vein, the ROX arteriovenous coupler device is implanted, creating a fixed shunt to offload arterial pressure (Fig. 53-9). The procedure is technically reversible by placement of a covered endovascular prosthesis over the device to disable the shunt. The initial ROX CONTROL HTN study was an open label randomized study that demonstrated promising reduction in 24-hour ABPM (−13.5 mm Hg vs −0.5 mm Hg; P < .0001). Substudy analysis suggests that
patients with isolated systolic hypertension, whose hypertension may be due to excessive vascular stiffness as opposed to sympathetic overactivity, may derive benefit from this approach. Further studies will need to determine which patients may benefit the most and whether there are any long-term adverse physiologic sequelae from the coupler.52

FIGURE 53-9 The ROX Coupler (ROX Medical, San Clemente, CA) creates a fixed shunt to offload arterial pressure via a sidewall puncture from the central iliac artery to the vein.

POTENTIAL LIMITATIONS OF CATHETER-INDUCED AUTONOMIC MODULATION

Although there is great promise to the techniques described earlier, it must be noted that there is also great uncertainty. In addition to the debate regarding actual therapeutic benefit, it is unknown whether alteration of this physiologic system could provoke long-term risk for untoward effects such as postural hypotension or altered vagal responses. Long-term effects on renal physiology after RDN are also unknown, although the benefits of a sustained reduction in hypertensive severity are thought to outweigh any theoretical disadvantage. Whether sympathetic imbalance can relapse either through physiologic escape mechanisms, reinnervation, or altered CNS or postganglionic signaling is also unknown. All of these possibilities will need to be kept in mind as this exciting area of medical science continues to unfold.
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**MULTIPLE CHOICE QUESTIONS**

1. According the US Preventive Services Task Force (USPSTF), 15% to 30% of the population may have lower blood pressure outside of the office setting. The USPSTF recommends which of the following as the most evidence-based method of diagnosing hypertension?
   
   A. Ambulatory blood pressure monitoring (AMBP)
   
   B. Mean of 3 office-based blood pressure (OPB) measurements on different days
   
   C. Home blood pressure monitoring (HBPM)
   
   D. The mean of 2 OPB measurements taken while the patient was seated with at least 5 minutes between entry into the office and blood pressure measurement

2. Patients with resistant hypertension are defined as which of the
following?
A. Patients with systolic blood pressure ≥160 mm Hg for >1 year despite antihypertensive therapy
B. Patients whose blood pressure remains above goal despite adequate treatment with ≥3 different classes of antihypertensive agents, ideally including a diuretic
C. Patients with systolic and diastolic blood pressure ≥180/100 mm Hg for 1 year after secondary causes have been excluded
D. Patients with systolic and diastolic blood pressure ≥160/100 mm Hg for 1 year despite treatment with ≥2 different classes of antihypertensive agents

3. Among hypertensives, what is the estimated prevalence of resistant hypertension?
   A. 5% or less
   B. 5%-15%
   C. 15%-30%
   D. 30%-40%

4. Renal sympathetic denervation is thought to provide an antihypertensive effect by which of the following mechanisms?
   A. Reducing tubular reabsorption of sodium and downregulating the renin-angiotensin-aldosterone system (RAAS) via interruption of signaling from the central nervous system (CNS) to the kidneys via renal efferent nerves
   B. Disrupting the feedback loop of sympathetic signaling from the kidneys back to the CNS, which may reduce central systemic sympathetic outflow
   C. Both

5. In SYMPLICITY HTN-3, the Simplicity catheter system delivered radiofrequency energy circumferentially to thermally ablate the sympathetic renal nerve fibers. The device was intended to provide full 360° ablation by applying energy at different points in the renal arteries along the superior, inferior, anterior, and posterior arterial walls. In a substudy analysis, which percentage of patients enrolled in HTN-3 received circumferential 4-quadrant ablation of both the left and right
renal arteries?
A. 10%
B. 25%
C. 50%
D. 75%

ANSWERS

1. A
The USPSTF recommends OBP as an initial screening. However, further evaluation with ABPM or HBPM is recommended to diagnose hypertension. According to the USPSTF, there is convincing evidence that AMBP is the best method for diagnosing hypertension and considers it the gold standard. Comparisons between OBP and HBPM have been less well studied.

2. B
Patients with resistant hypertension, according to an American Heart Association consensus document, are defined as patients whose blood pressure remains above goal despite adequate treatment with 3 or more different classes of antihypertensive agents, ideally including a diuretic.

3. C
Despite advances in our understanding of resistant hypertension and in pharmacologic treatment, the prevalence of true treatment-resistant hypertension is as high as 15% to 30% of treated hypertensive patients. In patients with hypertension and coronary artery disease, however, the prevalence of resistant hypertension is more than 30% and is associated with a higher risk of all-cause death and a higher risk of cardiovascular mortality.

4. C
Ablating renal sympathetic innervation was originally thought to provide an antihypertensive effect by reducing tubular reabsorption of sodium and downregulating the RAAS via interruption of signaling from the CNS to the kidneys via renal efferent nerves. More recently, it has been recognized that
disruption of renal afferent nerves also alters the feedback loop of sympathetic signaling from the kidneys back to the CNS, which may reduce central systemic sympathetic outflow as well.

5. B

Ideally, the renal denervation procedure should achieve full 360° ablation of the renal arteries. A substudy analysis of HTN-3 suggested only up to 25% of patients received circumferential 4-quadrant denervation in both right and left renal arteries. A dose effect trend was also documented between the number of full 4-quadrant ablations achieved during renal denervation and blood pressure lowering. Although HTN-3 has been widely cited as a neutral study, many consider that HTN-3’s results were attributable to inadequate denervation due to protocol limitations and overall operator inexperience. This criticism has led to further research, development of multiple new technologies, and new randomized trials.
Peripheral Arterial Disease

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INTRODUCTION

Since the time of the first edition of this book by Yeung and King in 2006, the practice of peripheral vascular medicine has evolved into a more effective and well-organized discipline. Most would agree that practice guidelines for the management of patients with peripheral arterial disease (PAD) first published in 2006, with updates in 2011 and 2013, and 2016, coupled with the rapid innovation in technology (Table 54-1), clinical research, and continuing educational programs, have provided the backbone for the remarkable progress in this field.

Table 54-1 Advances in Technology for Management of Peripheral Arterial Disease

- Drug-coated ballons and stents
- Crossing devices for occluded vessels
- Reentry devices
- Scoring balloon catheter
- Retrograde recanalization using collaterals
- CTO crossing using external ultrasound guidance
- Peripheral orbital atherectomy
- Directional atherectomy
• Phoenix atherectomy device
• Laser atherectomy
• Jetstream atherectomy

Abbreviation: CTO, chronic total occlusion.

Vascular physicians representing a variety of medical, surgical, and imaging societies continue to work tirelessly to improve the quality of care, such as by writing guidelines for the management of patients with PAD and defining medical competence in the diagnosis and treatment of PAD. Since 2005, several thousands of physicians, mostly cardiologists and vascular surgeons, have become credentialed in vascular imaging interpretation after passing the Registered Physician in Vascular Interpretation examination. The American Board of Vascular Medicine also offers certification that recognizes expertise in both general vascular medicine and endovascular specialty.

In addition, hospitals have implemented plans to protect patients and health care personnel from the frequently prolonged radiation exposure in the catheterization laboratory at the time of treatment. The PVI Registry of the American College of Cardiology further demonstrates ongoing efforts to improve care by voluntarily tracking the outcomes of peripheral vascular procedures. The ultimate common goal is to deliver a safe, effective, sustained, and valuable service to the increasing number of PAD patients.

This chapter provides interventional cardiology specialists with practical information and general guidance for the evaluation and treatment of patients with PAD of the lower extremities. In part, this chapter replicates what the Emory interventional cardiology trainees are expected to learn during their years of training and represents a compilation of knowledge extracted from practice guidelines, relevant publications, and our personal experience.

As in other areas of medicine, treatment recommendations can be controversial and open to revision informed by research. Most controversy lies in the choice of treatment and the effectiveness of a variety of stents, balloons, and medical devices currently used in patients with symptomatic PAD.

For example, perhaps the most exemplary case of practice variation among vascular specialists is the treatment of a totally occluded, 15-cm-long, moderately calcified superficial femoral artery (SFA). The SFA is one the
most commonly affected vessels in patients with PAD, and surgery is the
gold standard therapy for these long calcified lesions when symptoms persist
despite risk factor modification, supervised exercise, and drug therapy with
cilostazol. Complex SFA lesions are increasingly treated with endovascular
techniques that, although less invasive, nonetheless carry the risk of
reintervention due to restenosis of the index vessel (Fig. 54-1).

**FIGURE 54-1** A. Angiogram of a patient with critical limb ischemia and an open
wound in the right foot from a long total occlusion of the right superficial femoral
artery (SFA). B. Complex endovascular revascularization of the right SFA using a Pioneer reentry device, atherectomy, balloons, and distal filter protection. C. Suboptimal angiographic results of the right SFA from unexpected thrombotic complication. Thrombus extending into the profunda artery, treated with Angiojet and systemic anticoagulation. D. Good blood flow to the right popliteal and trifurcation vessels, with subsequent healing of the ulcer in the right foot, despite suboptimal angiographic results shown in C. E. Restenosis of the right SFA 4 months later, diagnosed by surveillance arterial duplex ultrasound and confirmed by angiogram. F and G. Right SFA restenosis treated with repeat atherectomy. H. Patent popliteal artery and trifurcation vessels (not shown). The patient remains asymptomatic with a healed ulcer in the right foot 15 months after the initial procedure. The patient undergoes periodic surveillance arterial duplex ultrasound examinations to monitor for patency and to monitor the mild SFA vessel wall dilatation after atherectomy.

If an endovascular approach is preferred over surgery, several questions remain: Should the vascular obstruction undergo debulking with atherectomy first after using a reentry device, or be treated with a drug-coated balloon or stent instead, assuming no procedure-related complications? If the decision is made to place a stent, should it be a self-expanding nitinol stent, drug-eluting stent, or a flexible stent graft?

While the AHA/ACC guidelines from 2013 indicate that endovascular intervention is recommended as the preferred revascularization option for focal femoropopliteal arterial lesions (Transatlantic Intersociety Consensus [TASC] type A),4 the 2016 guidelines do not restrict lesion characteristics.

Future editions of this chapter and the management of PAD will benefit from innovation in endovascular procedures and medical devices and the availability of new drugs and outcome data from comparative effectiveness research, but until then, we must do what we believe is best, safest, and most effective for each patient.

**INITIAL PATIENT EVALUATION**

Patients seen in a cardiology practice should be asked about symptoms of PAD and examined for the consequences of this prevalent disease, especially those who are age 50 years and older and have risk factors for atherosclerosis, such as tobacco use, diabetes, hypertension, chronic kidney disease, and hyperlipidemia. Elevated plasma homocysteine and C-reactive
protein levels are also considered risk factors for developing PAD. In addition, all adults 70 years of age and older should be evaluated for PAD (Class I recommendation from American College of Cardiology [ACC]/American Heart Association [AHA] guidelines). Since the vast majority of patients with PAD have atypical symptoms, clinicians and health care personnel caring for these patients must have a high level of suspicion for vascular disease. Lower extremity claudication with typical effort-related limb pain occurs in only 11% of patients. Observing the patient’s gait and asking family members about the patient’s walking limitations may help diagnose PAD.

The physical examination should include a detailed assessment of the femoral, popliteal, dorsalis pedis, and posterior tibial pulses as absent (0), diminished (1), normal (2), or bounding (3), keeping in mind that about 10% of the population has congenital absence of the dorsalis pedis or posterior tibial pulses. If unable to palpate pulses, find them using a handheld Doppler device. However, the presence of pulses does not exclude PAD. Document the presence or absence of bruits in the carotids, subclavian, abdominal, and femoral artery territories. Be sure to obtain blood pressure in both arms to exclude subclavian artery stenosis; a >10 mm Hg systolic pressure difference between arms should be considered abnormal and suspicious for arterial stenosis in the upper extremities.

Examine the feet for tissue loss and previous amputations, which could indicate critical limb ischemia. Patients with critical limb ischemia often have rest pain and ischemic ulcers in the toes and forefoot. On physical exam, they may also have calf atrophy, thickening of the toenails, scaly/shiny skin from loss of subcutaneous tissue, loss of hair, pallor of the affected limb, diminished or loss of pulse, and skin that is cold to the touch.

If an ischemic ulcer is present, document the location, size in centimeters, presence of infection, and severity of tissue loss. The Wagner grade of the wound/gangrene provides an in-depth description of the affected limb with critical ischemia:

- Grade 0: pre- or postulcerative lesion
- Grade 1: partial-/full-thickness ulcer
- Grade 2: probing to tendon or joint capsule or fascia
- Grade 3: deep ulcer with abscess or osteomyelitis
- Grade 4: partial foot gangrene
• Grade 5: whole foot gangrene

Serial pictures of the wound are often helpful to monitor treatment progress.

Once the clinical diagnosis of limb ischemia is established, findings in the physical examination, such as the presence or absence of sensory loss and muscle weakness, and results of the Doppler signal in the arterial and venous systems will help determine if the limb is viable, threatened, or irreversibly damaged. Reviewing all operative notes from any previous surgical or endovascular revascularization procedures will also guide management decisions.

Critical limb ischemia with chronic rest pain, nonhealing ulcer, and gangrene requires a catheter angiogram and often revascularization procedures to minimize the risk of short-term amputation. These patients can be easily identified by physical examination, and the diagnosis can be confirmed with simple physiologic studies. The ankle pressure is likely to be <50 mm Hg, and the toe pressure is likely to be <30 mm Hg.

Acute limb ischemia with sudden-onset pain in the lower extremity accompanied by paresthesia and loss of motor function constitutes a vascular emergency. Patients require intravenous heparin and immediate evaluation and treatment to determine the level of vessel obstruction and restore the blood flow to the affected limb. Endovascular treatment using catheter-based thrombolysis and thrombectomy is preferred over open surgery (Fig. 54-2).
Acute simultaneous thrombosis of the right superficial femoral artery (A) and the left popliteal artery (B) with ischemic pain in both legs after a brief interruption of warfarin given for atrial fibrillation. Blood flow was restored in both legs (C and D) after urgent endovascular treatment using distal filter protection, Angiojet, atherectomy, balloons, and systemic anticoagulation.

**BASIC TESTING**

**Ankle-Brachial Index**

Ankle-brachial index (ABI) is a simple, cost-effective, noninvasive method for diagnosing PAD in the office setting. There is no formal contraindication for this test, but some patients may have intolerable pain in their legs and arms during cuff inflation. A detailed description of equipment preparation, procedure, calculation, and interpretation has been published. Although it is standard to calculate the ABI by dividing the highest systolic tibial artery pressure by the highest systolic brachial pressure, we find it clinically helpful to calculate and report the ABI for both the dorsalis pedis and the posterior tibial arteries. The normal ABI range is 1.0 to 1.4, borderline range is 0.91 to 0.99, and abnormal range is 0.90 or less. ABI <0.50 at rest suggests multilevel PAD, whereas ABI <0.30 defines critical limb ischemia.

Current ACC/AHA guidelines recommend ABI testing in patients with
exertional leg symptoms, nonhealing wounds, age 65 years and older, or age 50 years and older with a history of smoking or diabetes. Individuals with suspected lower extremity PAD who have effort-related symptoms, diminished pulses, femoral bruit, nonhealing wounds, gangrene, or sudden-onset ischemic leg symptoms or signs of acute limb ischemia should also undergo a resting ABI measurement. According to the Appropriate Use Criteria for lower extremity testing published by the ACC/AHA in 2012, repeat ABIs in patients with known PAD is justified for new or worsening symptoms of claudication, but surveillance ABIs every 12 months or greater were deemed to have uncertain benefit.

**Postexercise Ankle Pressure and/or ABI**

Postexercise ABI using a treadmill should be considered in patients with typical or atypical claudication to diagnose PAD when the resting ABI is normal (0.91-1.4). Abnormal treadmill response is defined as a drop of the postexercise ankle pressure >20 mm Hg compared with the resting pressure. Toe-tip exercise testing with pre- and postexercise ABI could be offered as an alternative to a motorized treadmill test if the patient cannot walk or if a treadmill is not available. Unfortunately, toe-tip exercise may not provoke symptoms in patients with significant PAD, and this alternative mode of exercise test is not accepted as a Current Procedural Terminology substitute code to the standard motorized treadmill by the Centers for Medicare and Medicaid Services.

**Toe Pressure**

Toe pressure measures digital perfusion and is the numerator of the toe-brachial index (TBI) calculation, which is the ratio of toe systolic pressure to brachial systolic pressure. The normal TBI range is 0.80 to 0.90; TBI <0.7 is abnormal, and TBI <0.2 is generally associated with ischemic rest pain or ischemic ulceration. TBI measurement is most helpful in patients with ABIs greater than 1.4 due to arterial wall calcification. Toe pressures provide valuable information in patients with small vessel arterial disease and give an estimate of the wound healing potential of the feet. Toe pressure <40 mm Hg suggests low perfusion pressure insufficient for wound healing, while toe pressure >60 mm Hg makes wound healing more likely. An absolute
variation of greater than 0.15 in the ABI and/or TBI is considered significant when done serially.

**Pulse Volume Recording and Arterial Duplex Ultrasound**

Analysis of the segmental pressures and pulse volume recording (PVR) establish both the physiologic significance of PAD obstruction and the segment of disease. PVR is often used to monitor primary and secondary vessel patency after revascularization, whereas PVR and TBI are used to diagnose and assess the severity of PAD in patients with noncompressible pedal pulses. Noncompressible vessels due to calcification generally have ABIs greater than 1.4 and are frequently encountered in patients with diabetes and chronic renal disease and the elderly. If ankle pressure is elevated due to vessel calcification, the amplitude of the resting waveform PVR should be compared with the PVR after exercise; the severity of the amplitude reduction provides valuable information regarding the significance of the PAD. However, in our opinion, analysis of the pulsed wave Doppler waveforms is more reliable than the PVR.

In addition to ABI, toe pressures, and TBI, interventional cardiologists who perform endovascular peripheral procedures should become proficient in the indication for and interpretation of duplex ultrasound technology. This portable, noninvasive imaging technology provides both anatomic and physiologic information about the arterial and venous vasculature. Duplex ultrasound is used in the initial diagnosis of PAD and is the preferred surveillance imaging modality for patency after revascularization procedures. Advantages of duplex ultrasound compared with magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) for initial diagnosis and postrevascularization follow-up include the convenience and lower cost for the patient and the ease of the examination with no need for contrast. However, the quality of the duplex ultrasound examination is highly operator dependent.

**Postrevascularization Surveillance**

Patients undergoing lower extremity revascularization with endovascular techniques require a baseline ABI and a duplex ultrasound examination of the treated vascular segment within 1 month of the procedure. In addition to the
baseline study, we routinely repeat the ABIs and duplex ultrasound examinations at 3 and 6 months after the endovascular intervention to monitor for patency of the target vessel site. Patients are at highest risk for restenosis during the first 6 months following the procedure, and symptoms of recurrent disabling claudication may occur too late, after (re)occlusion of the index lesion. Repeat revascularization of a totally occluded artery from restenosis is expected to be difficult and time consuming, while also exposing both the patient and the operators to excessive direct radiation. Early detection of physiologic (ABI/PVR) or anatomic (duplex ultrasound) signs of significant restenosis will permit planning for reintervention, before progression to a total occlusion.

Patients previously treated for critical limb ischemia are especially vulnerable for restenosis and atherosclerosis progression. Therefore, this high-risk cohort requires periodic, at least semiannual, clinical and physiologic/imaging evaluation by an integrated team of vascular care professionals, including podiatrists, with the ultimate goal of preventing recurrent ischemic pain, skin ulceration, and amputation.

**ADVANCED TESTING**

**CTA and MRA**

New multidetector technology has made CTA a reasonable alternative to catheter angiography in detecting the location and severity of stenosis in PAD patients. However, MRA with gadolinium, which provides pristine angiographic-like images without radiation and without the need for iodine contrast, received a stronger recommendation as a diagnostic method in the 2013 ACC/AHA guidelines (Class I vs Class IIb). The 2016 guidelines give Duplex ultrasound, CTA, and MRA the same Class I recommendation for the detection of the location and severity of PAD stenosis. Table 54-2 lists the advantages and disadvantages of both imaging tests.

Table 54-2 **Advantages and Disadvantages of Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA) in the Diagnosis of Peripheral Arterial Disease**
<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>MRA</td>
<td>No iodine contrast, no radiation</td>
<td>Inability to detect calcium, metal artifact, rarely allergic reaction to gadolinium, very rarely nephrogenic systemic fibrosis caused by the gadolinium (less common with the newer agents)</td>
</tr>
<tr>
<td>CTA</td>
<td>Detection of calcium</td>
<td>Need for iodine contrast and radiation exposure</td>
</tr>
</tbody>
</table>

An underrecognized benefit of both is the ease with which these images can be shown and explained to the patient as well as the practicality of discussing angiographic findings and treatment options at the time of the outpatient follow-up office visit. With the development of these 2 technologies, the need for conventional diagnostic lower extremity angiograms has decreased, thus lessening the risk associated with invasive procedures. In our practice, we prefer MRA over a diagnostic catheter angiogram as the initial diagnostic procedure (Fig. 54-3).
Symptomatic patients with poor arterial perfusion who experience lifestyle-limiting or disabling claudication, ischemic pain at rest, or ischemic tissue loss benefit from a digital subtraction catheter angiogram, with an aim of correcting the vascular obstruction. Not all symptomatic patients with PAD need a complete aortogram with bilateral lower extremity runoff, and some require a more selective angiogram to limit the amount of contrast administered.

The choice of arteries imaged (abdominal aorta, right/left iliac, femoral,
popliteal, tibioperoneal trunk, anterior tibial, posterior tibial, and peroneal arteries) and the vascular access site (femoral, brachial, and radial) depend not only on findings from the history and physical examination but also on the patient’s comorbidities and previous revascularization procedures. Variables such as renal function, the intended treatment (endovascular vs open surgical revascularization), and heart failure are a few of the many factors that influence planning the catheter angiogram in patients with symptomatic PAD. A diagnostic abdominal aortogram with a bilateral lower extremity runoff generally requires the use of approximately 100 to 150 mL of contrast—20 mL administered for the abdominal angiogram, 30 mL for the iliac angiograms in 2 views, and 70 to 100 mL for the lower extremity runoff. A selective single lower extremity angiogram can be done with less than 50 mL of diluted contrast.

**Catheter Angiogram and Renal Disease**

Renal function must be assessed with a serum creatinine in all patients undergoing contrast exposure before scheduling an angiogram. Renal insufficiency should alert the interventionalist to carefully reevaluate the need for a test using contrast and to review and adjust the patient’s medications before the catheter angiogram. Administer intravenous fluids before contrast exposure to minimize risk of renal injury, and monitor renal function after the endovascular procedure. A duplex ultrasound of the abdominal aorta, iliac arteries, and arteries of the lower extremities before the angiogram could help better plan the diagnostic and endovascular revascularization procedures, such as limiting diluted contrast exclusively to the symptomatic vascular segment. A reliable, high-quality, noninvasive vascular laboratory with both imaging and physiologic testing is of utmost importance for the optimal management of patients with PAD and especially those affected with renal disease (Figs. 54-4 and 54-5).
The arterial duplex ultrasound of this patient with disabling claudication and severe chronic kidney disease predicted the angiographic findings and facilitated the revascularization procedure. The arterial duplex ultrasound shows a totally occluded proximal superficial femoral artery (SFA) with a “nubbin” at the ostium and a low echogenicity plaque in the most proximal SFA segment (A and B). The low echogenicity suggests a soft plaque with a high lipid content at the proximal end of the SFA occlusion. Poor Doppler signal in the proximal right SFA confirms absence of flow (B). The mid SFA is reconstituted by a collateral vessel (C). The distal end of the occluded SFA at the site of the collateral vessel has strong echogenicity, likely from a calcified and dense “hard” fibrous plaque (C and D). The result of the arterial duplex ultrasound facilitated the planning and performance of the right SFA revascularization procedure, as seen in Figure 54-5. CFA, common femoral artery.
FIGURE 54-5 The occluded right superficial femoral artery (SFA) by duplex ultrasound, with a “nubbin” and a proximal soft and hard distal plaque of the patient in Figure 54-4 was confirmed by angiogram (A). The soft plaque in the proximal end of the occluded right SFA was easily crossed with a Viance catheter without dissection (B), and the “hard” fibrous plaque at the distal end of the SFA occlusion was crossed with a 0.035-inch stiff Terumo straight glide wire, advanced through an angled KMP catheter (C), with excellent angiographic results and no complications (D). The crossing wire used with the Viance catheter first entered the collateral vessel in the mid SFA. This reference point in the mid SFA, also seen in the arterial duplex ultrasound (Fig. 54-4, C and D), facilitated the reentry into the distal SFA through the dense fibrous cap by simply pointing the KMP catheter and wire away from the collateral vessel and into the true SFA lumen.

Catheter Angiogram and Heart Disease

The presence of heart failure could also influence the angiographic technique, because left ventricular dysfunction limits hydration with intravenous fluids before and after contrast exposure and also because the patient may not be able to lay flat during and after the procedure. If feasible, a radial or brachial artery access approach may be preferable in patients with heart failure.

Heart disease is prevalent in patients with PAD and should not be
overlooked. It is good practice to exclude ischemic heart disease and heart failure before performing a diagnostic angiogram and treatment of the lower extremities. There is high coexistence of coronary artery disease and cerebrovascular disease with PAD. Knowing the left ventricular function and anticipating the tolerance to intravenous fluids can prevent heart failure decompensation. Knowledge of left ventricular function is also needed before prescribing cilostazol for symptomatic arterial disease, because heart failure with reduced ventricular systolic function is a contraindication for cilostazol use.

Catheter Angiogram and Chronic Anticoagulation

Patients with PAD who are on anticoagulation medications for chronic atrial fibrillation or for mechanical heart valves with a vitamin K antagonist are specially challenging candidates for catheter angiogram, mainly due to the potential risk of hemorrhage and arterial thromboembolism, even during heparin bridging. A careful discussion with the patient during the consent process, weighing the risks and benefits of the procedure, is needed, and an effort must be made to do the angiogram and the endovascular treatment during the same session. Noninvasive imaging studies, preferably with MRA, are of great value for planning the vascular treatment in patients with preserved renal function and no metal devices other than the mechanical valve, although new metal cardiac devices such as implantable cardioverter-defibrillators and pacemakers are now felt to be safe for magnetic resonance imaging (MRI).\textsuperscript{15} Duplex arterial ultrasound performed before the angiogram is a very good alternative to other imaging modalities, since it has the advantages of no contrast, no radiation, no contraindication with metal hardware, and lower cost.

Staged Catheter Angiogram

A limited catheter angiogram and endovascular revascularization are likely to be scheduled on the same day for symptomatic patients with focal disease localized to 1 extremity as indicated by the clinical and noninvasive vascular examination. This same combined approach, but on different days, is common in staged procedures, with the angiogram and endovascular revascularization performed first to correct the inflow disease (ie, iliac
stenosis), followed by treatment of the outflow (femoropopliteal artery stenosis) on a separate day. Treatment of the outflow segment may not be needed if the patient has complete or near-complete resolution of the symptoms of vascular insufficiency after treatment of the inflow vascular segment.

Staged interventions have the advantage of limiting the amount of contrast and radiation exposure to the patient. New hand-held injection devices, such as the AVERT system (Osprey Medical, Minnetonka, MN), reduce the amount of contrast injected during angiographic procedures without sacrificing the quality of the image and may help protect patients from contrast-induced nephropathy. At Emory University, we routinely use an 8-mL syringe with a manifold and use diluted (50:50) contrast to minimize the risk of kidney injury.

**Catheter Angiogram and Choice of Arterial Access**

The angiographic technique is also determined by the presence or absence of femoral arterial access and by prior vascular interventions with stents and surgical grafts. The radial or brachial artery approach is often used in patients with severely stenosed or occluded common femoral or iliac arteries (Fig. 54-6), severe disease, or total occlusion of the distal abdominal aorta as well as in patients who have undergone prior vascular bypasses. Radial artery access is also convenient when patients are unable to lay flat or use the urinal during strict postprocedure bed rest, since this access allows patients to get up sooner than the femoral access approach and with lower risk of bleeding complications. However, arm access should be avoided in patients with arteriovenous shunts for hemodialysis.
Successful endovascular intervention of a 100% ostial left common iliac artery (CIA) using the left radial artery access approach for treatment of rest foot pain and abnormal physiologic studies with ankle-brachial index (ABI) in the critical limb ischemia range at 0.17 and ankle pressure of 32 mm Hg (A-D). Aortoiliac angiogram from the right common femoral artery (CFA) shows stents in both CIAs with occluded left iliac artery at the ostium (B). Crossing of the 100% left iliac artery with a 4-Fr vertebral catheter along with an exchanged length 0.035-inch straight stiff Terumo glide wire, advanced from the left radial artery (C). The occluded left CIA stents were treated with balloon angioplasty and a new self-expanding stent in the left external iliac artery (not shown). Repeat physiologic studies 2 weeks after treatment.
of the inflow segment revealed significant improvement of the ABI from 0.17 to 0.55; however, the patient continued to have disabling pain in the left foot and the decision was made to treat the outflow stenosis in the left superficial femoral artery (SFA) using the right CFA and the contralateral access approach (F and G). Staged endovascular revascularization of the left SFA with directional atherectomy and adjunctive balloon angioplasty resulted in resolution of the pain in the left leg and further improvement of the physiologic studies (H). Notice the improvement of the pulse volume recording (PVR) waveforms and photoplethysmography (PPG) of the left toe as well (H).

The left radial artery side is a better option than the right side due to the closer proximity to the distal abdominal aorta. A 4 Fr × 135 cm long pigtail catheter is available for a diagnostic lower extremity catheter angiogram from the left radial artery. The radial access allows not only a complete diagnostic angiogram, from the abdominal aorta down into the distal vessels, but also allows moving ahead with the endovascular treatment on the same day, as long as the equipment used is compatible with a 6-Fr sheath system and the needed equipment reaches the arterial site to be treated. If a 7-Fr sheath is needed, brachial or femoral artery access is preferable.

VESEL CHARACTERISTICS AND LESION DEFINITIONS

The descriptions and classifications of lesion and vessel characteristics that we will use for the remainder of the chapter are as follows.

**Stenosis Severity**

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Occluded</th>
</tr>
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<tbody>
<tr>
<td>&lt;50%</td>
<td>50%-69%</td>
<td>70%-99%</td>
<td>100%</td>
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**Translesional Gradient** (pullback gradient performed with a ≤4-Fr small lumen catheter for ambiguous 50%-70% range artery stenosis)
Significant $>$15 mm Hg
Nonsignificant $\leq$15 mm Hg

**Degree of Lesion Calcification** (criteria used at Emory University based on fluoroscopy at the lesion site)

Focal $\leq$1 cm in length, on 1 side of vessel wall
Mild 1-3 cm in length present on 1 or both sides of the vessel wall and not continuous
Moderate 3-5 cm on 1 or both sides and not continuous
Severe Continuous on both sides of vessel wall and/or $>$5 cm in length

**Lesion Length**

Focal $\leq$1 cm
Short $>$1 to $\leq$5 cm
Intermediate $>$5 to $\leq$10 cm
Long $>$10 cm

**Angiographic Outcome After Endovascular Intervention**

Primary patency: patent target lesion with no restenosis after intervention
Primary assisted patency: patent target lesion following reintervention for restenosis
Secondary patency: patent target lesion following reintervention of reocclusion

(In our opinion, this division is confusing, and lesions that restenose or occlude should be considered as restenosis.)
DECISION FOR REVASCULARIZATION

Endovascular or open surgical revascularization is justified for patients who experience lifestyle-limiting or disabling claudication despite adequate medical treatment with supervised exercise program and medications, as long as there is a reasonable likelihood of symptomatic improvement with a favorable risk-benefit ratio. Intervention is mandatory in patients with acute limb ischemia and critical limb ischemia for limb salvage.

An exemption to the symptom-driven rule should be considered in patients with severe but asymptomatic (or minimally symptomatic) iliac artery stenosis, because revascularization with a stent has a favorable risk-benefit ratio and progression to total occlusion could complicate treatment. Revascularization for asymptomatic but severe PAD below the inguinal ligament is currently debatable and should be individualized for each patient.

Patients with symptomatic PAD in the critical limb ischemia group (Rutherford categories 4, 5, and 6) should undergo prompt revascularization to avoid amputation or to convert a possible major amputation to a limited amputation. In acute limb ischemia, revascularization treatment should be immediate.

We believe that the majority of patients with symptomatic occlusive disease of the arteries of the lower extremities can be successfully treated with endovascular techniques. Table 54-3 denotes a few exceptions for which open surgical revascularization could be considered as the first line of treatment. However, none of these situations constitute an absolute contraindication to endovascular therapy, and the final decision is based on operator expertise and patient preference. It is always a good practice for the interventional cardiologist to review the patient’s clinical history and angiographic findings with a vascular surgeon, especially in difficult cases, with the aim of achieving consensus on the best revascularization treatment approach.

Table 54-3 Possible Indications for Open Surgical Revascularization as the First Line of Treatment

- 100% bilateral common iliac artery occlusion with severe calcification, nonfocal, and acceptable surgical risk
• Severe unilateral or bilateral common iliac artery stenosis with infrarenal AAA
• 100% occlusion of the CFA with at least moderate to severe calcification
• 100% occlusion of the SFA more than 15 cm long and severe calcification
• 100% occlusion of the popliteal artery greater than 5 cm in length with severe calcification

Abbreviations: AAA, abdominal aortic aneurysm; CFA, common femoral artery; SFA, superficial femoral artery.

GENERAL PROTOCOL

The protocol used to treat any vascular territory should always start with detailed advance planning, including a thorough review of the clinical history and physical examination, results of previous imaging studies, and laboratory data. Next, the equipment likely to be needed must be procured before initiating the case. There is no excuse for discovering during the diagnostic or endovascular procedure that the equipment needed is not available. The interventionalist should also be familiar with the different sheath sizes and lengths and the compatibility with the various balloons and stents. Sheath length depends on the location of the lesion: a longer sheath (25-30 cm) is needed for common iliac artery intervention from the groin, and a shorter sheath (6 cm) for proximal external iliac artery intervention also from the groin. Sheath size is chosen according to the balloon or stent diameter being used. For example, a 7 mm diameter × 22 mm long iCast-covered stent (Atrium Medical, Hudson, NH) requires a 7-Fr sheath, whereas a 5 mm diameter × 22 mm long iCast-covered stent requires a 6-Fr sheath. The 5-mm stent advanced through a 6-Fr sheath could be postdilated to any size up to 12 mm, but with some foreshortening, so understanding the compatibility of different balloons, stents, and devices with the different sheath sizes is of utmost importance.

At the conclusion of any procedure, dictate a complete report including the date of procedure, referring physician, operator(s), indications, description of procedure, complexity, complications, findings, recommendations, and type and amount of contrast used and radiation exposure. One format that we follow is shown in Figure 54-7.
COMMON AND EXTERNAL ILIAC ARTERY STENOSIS: INFLOW DISEASE

Clinical Presentation

Obstructive disease in the vascular segment between the distal abdominal aorta and the common femoral artery (CFA) results in buttock, hip, thigh, calf, and/or foot pain. This anatomic segment of obstruction is also called inflow disease. Inflow PAD is confirmed by diminished or absent pulses in the femoral arteries and suspected by the presence of bruits. Buttock and thigh claudication often progress to calf claudication upon ambulation in patients with inflow disease. PAD with inflow stenosis could be misdiagnosed as osteoarthritis of the spine or hip. Vasculogenic erectile dysfunction may occur in cases of inflow stenosis, especially when the disease is bilateral and proximal to the origins of the internal iliac arteries.

Vascular Testing

- Abnormal resting or postexercise ABIs.
- Abnormal PVR with amplitude reduction and monophasic waveform
morphology in the entire side of the affected leg.

- Duplex ultrasound with occlusive plaque in the iliac artery and color aliasing, monophasic waveform with spectral broadening, and increased peak systolic velocity >100% relative to the adjacent proximal segment. Increased acceleration time of the spectral Doppler flow velocity waveform in the CFA.

### 2013 ACC/AHA Practice Guidelines (Class I)

- Endovascular procedures are indicated for individuals with a vocational or lifestyle-limiting disability due to intermittent claudication when clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and (1) there has been an inadequate response to exercise or pharmacologic therapy and/or (2) there is a very favorable risk-benefit ratio (eg, focal aortoiliac occlusive disease). (Class I, Level of Evidence: A)
- Endovascular intervention is preferred for TASC type A iliac single stenosis ≤3 cm. (Class I, Level of Evidence: B)
- Provisional stent placement in the iliac arteries can be used as salvage therapy for suboptimal or failed result from balloon dilatation (eg, persistent translesional gradient, residual diameter stenosis >50%, or flow-limiting dissection). (Class I, Level of Evidence: B)
- Stenting is effective as primary therapy for common iliac artery stenosis and occlusions (Class I, Level of Evidence B) and also for external iliac artery stenosis or occlusions (Class I, Level of Evidence: C).

### Emory Protocols for Endovascular Treatment

Most patients with symptomatic common and external iliac artery stenosis are treated using endovascular techniques unless: (1) there is an infrarenal abdominal aortic aneurysm requiring repair; (2) there is a 100% flush occlusion with no “beak” or “nubbin” at the ostium of the common iliac artery and with severe calcification and intermediate-length (>5 cm) occlusion; or (3) there is a long occlusion (>10 cm) with severe calcification.

The decision to use endovascular techniques versus open surgery should be made according to operator expertise and patient characteristics and preference after a detailed discussion of the indications, benefits and
limitations, alternative treatment, and potential complications related to each procedure. **Figure 54-8** shows a long, moderately calcified, left common iliac artery flush occlusion at the ostium treated successfully with contemporary endovascular techniques, including a reentry device. This complex lesion would have normally required open surgery with a right-to-left, femoral-to-femoral bypass graft and a stent to the ostium of the right common iliac artery.

**FIGURE 54-8** Angiogram of a long, symptomatic, moderately calcified left common iliac artery occlusion with a flush occlusion at the ostium (A), successfully treated with contemporary endovascular technique, including a Pioneer reentry device (B and C).

**Protocol for Iliac Arteries**

Once the equipment is chosen and readily available to the catheterization laboratory team, the protocol continues by accessing the CFA ipsilateral to the lesion, using a micropuncture 21G needle with a 30-cm-long micropuncture sheath from Vascular Solutions (Minneapolis, MN). The micropuncture wire is used to cross the stenosis in the ipsilateral common iliac artery and/or proximal external iliac artery. After the micropuncture sheath is passed over the wire, the micropuncture wire and dilator are removed, and a 0.035-inch preferably stiff wire (eg, Supracore, Abbott Vascular, Temecula, CA) is passed through the sheath into the abdominal
aorta. The micropuncture sheath is then replaced by a 6- or 7-Fr, 25- to 30-cm-long sheath that crosses the lesion. The 0.035-inch wire is then removed and replaced with a 0.018 inch × 300 cm long Steelcore wire (Abbott). The sheath is retrieved back into the distal ipsilateral iliac artery below the lesion. The treatment of a mid to distal external iliac artery requires a different approach, which is discussed in the protocol variation section below. Intervention in the ipsilateral mid to distal external iliac artery is not advisable, because the sheath, once repositioned at the distal external iliac artery, cannot be too close to the lesion. The indication for using alternative sheath sizes is also discussed in the protocol variations section.

Use of sheath with radiopaque markers allows the tip to be visualized with fluoroscopy, although the metal marker is a few millimeters proximal to the true tip of the sheath. This is of utmost relevance when positioning the balloon or stent at the stenosis site and reinforces the need to leave the metal marker at least 2 cm proximal to the device edge to prevent deploying part of the balloon/stent inside the sheath.

The standard anticoagulation regimen used in peripheral intervention is heparin. The activated clotting time (ACT) should be monitored at regular intervals to keep it within the 200- to 250-second range. A digital subtraction angiogram of the iliac artery stenosis in 2 views must be obtained before the intervention, after which the digital roadmap, bony landmarks, or measuring tape can be used for precise balloon and stent placement.

After sheath placement and wire positioning, proceed with balloon predilation of the common or external iliac artery stenosis to a near-nominal pressure with a balloon size 1 mm in diameter smaller than the reference vessel diameter. Next, exchange the predilation balloon for a balloon-expanded stent with a 1:1 stent-to-vessel size ratio if the stenosis is at the ostium of the common iliac artery, while monitoring for lower abdominal pain. Stop the balloon inflation if abdominal or flank pain occurs to minimize the risk of vessel dissection or rupture. Precise placement of the balloon-expandable stent at the ostium of the common iliac artery, without any prolapse of the stent into the aorta, may allow the future use of the contralateral access approach. During treatment of the ostium of a unilateral common iliac artery, it is good practice to have readily available access on the contralateral femoral side in case there is need for simultaneous “kissing” balloon inflations to prevent plaque shift to the opposite common iliac artery.

A self-expanding nitinol stent is recommended after a balloon predilation
if the iliac stenosis is 2 cm away from the aortoiliac ostium or if it involves the external iliac artery, since these vascular segments require greater flexibility; the size of the self-expanding stent should be 1 mm in diameter larger than the reference iliac vessel diameter. Always do a poststent balloon dilatation with a 1:1 balloon-to-vessel size, at a nominal or slightly above nominal pressure as tolerated, monitoring for lower abdominal pain. For poststent dilatation, always position the balloon inside the self-expanding stent to avoid edge dissections.

After the destination therapy with balloons, stents, or both has been completed, repeat the angiogram of the iliac arteries using the digital subtraction angiography technique with diluted contrast and low magnification. Before moving the patient out of the catheterization laboratory, obtain a final ACT and record the amount of contrast used and the radiation exposure to the patient.

**Protocol Variations**

**Vascular Access Site**

- Use left brachial access if needed for a 7-Fr sheath, or left radial artery access if a 6-Fr sheath can be used, to treat severe obstructive disease of the CFA ipsilateral to the common iliac artery stenosis or if the “nubbin” of the occluded side of the common iliac artery is in the cephalic (proximal) end.
- Use left brachial or left radial access if simultaneous balloon inflation is needed in a nonsignificant contralateral ostial common iliac artery to avoid plaque shift at the time of the stent placement, especially if there is significant stenosis of the contralateral external iliac artery severe enough to require stenting. If no significant disease exists in the contralateral external iliac, use a bilateral femoral access approach to do simultaneous balloon inflation in the nonsignificant ostial common iliac artery.
- Use left brachial or, preferably, radial access if there is a need to intervene in the common or external iliac artery of a patient with a patent femoral-to-femoral bypass.
- Use left brachial or radial access when intervening in the proximal external iliac or common iliac arteries, and when extreme tortuosity distal
to the iliac artery stenosis is present.

- Right brachial artery access is rarely used for lower extremity vascular interventions and only if the left side brachial access is not possible. The right arm is a longer distance to the aortoiliac bifurcation and has a more tortuous trajectory. Access from the right arm could also increase the risk of transient ischemic attack and CVA due to excessive manipulation in the innominate artery segment with the equipment required for lower extremity intervention. In our opinion, right arm access should be avoided.

- Radial or brachial artery access may be needed when distal external iliac artery stenosis coexists with severe stenosis in the path to the contralateral approach, unless the decision is to perform bilateral iliac artery revascularization.

- For brachial or radial approach, give the radial “cocktail” (see below) after inserting a 4 Fr × 10 cm long sheath, and then advance a 4 Fr × 100 cm long JR4 diagnostic catheter (or internal mammary artery) over a stiff 0.035 inch × 300 cm long wire (Supracore) into the descending abdominal aorta and leave the tip of the diagnostic catheter just above the aortic bifurcation. Next, exchange the 4-Fr diagnostic catheter for a 6 Fr × 90 cm long sheath over a 0.035 inch × 300 cm long stiff (Supracore) wire. The tip of the flexor sheath can be manually shaped 1 to 3 cm away from the end to a 45° bend, with the purpose of aiming to the affected iliac artery. Cross the common or external iliac artery stenosis with the same Supracore (or 0.035-inch standard angled glide wire) and a 4 Fr × 100 cm or 125 cm multipurpose (MP) catheter, advanced through the flexor sheath. Then, remove the wire and inject contrast through the MP past the stenosis to confirm the intraluminal placement of the catheter. Balloon angioplasty and stenting with self-expanding stent can proceed once intraluminal placement of the wire has been confirmed.

- Administer the radial “cocktail” consisting of 3000 U of intravenous heparin mixed with 200 μg of nitroglycerin and 2.5 mg of verapamil intra-arterially, immediately after placing the 4-Fr sheath in the brachial or radial artery, to minimize the risk of arterial spasm and thrombosis.

- Use the contralateral femoral approach when the common iliac artery stenosis is in the distal segment and/or extends into the external iliac. The common iliac artery stenosis must be at least 5 cm away from the aortoiliac bifurcation to avoid prolapse of the sheath and wire back into the aorta during the intervention. The radiopaque marker of the sheath
should be more than 3 cm away from the aortoiliac bifurcation to minimize the risk of sheath prolapse. Remember to keep the marker of the sheath several millimeters proximal to the stenotic segment, as the tip of the sheath is a few millimeters distal to the marker. If there is any doubt about sheath stability, use the radial or ipsilateral access.

**Vascular Access Side: Bilateral Versus Unilateral Femoral Access**

- Use bilateral femoral access with a 6 or 7 Fr × 25 to 30 cm long sheath with radiopaque markers at the tip when placing kissing balloon-expandable stents in both ostial common iliac arteries. Place one 0.018 inch × 300 cm long Steelcore wire (or 0.035-inch wire) across each iliac artery, and leave the tip of the wires in the thoracic aorta when doing intervention from the common femoral approach. Balloon-expandable stents must protrude approximately 1 to 2 mm into the aorta when using the kissing technique in patients with severe bilateral aortoiliac disease. Unfortunately, kissing common iliac stents will likely preclude the use of the contralateral approach if needed in the future.
- Use bilateral femoral arterial access for treatment of an ostial/proximal common iliac artery stenosis with a stent when anticipating the need for simultaneous contralateral balloon inflation to prevent plaque shift to the nondiseased opposite iliac side. Combination of ipsilateral femoral and left radial access would be another option.

**Larger Sheath/Wires Sizes**

- Use a 7 Fr × 25 to 30 cm sheath with a radiopaque marker tip and preferably 0.035-inch wires if iCast stents will be used in a calcified tortuous vessel, if Viabahn (Gore Medical, Flagstaff, AZ) stents will be used to treat iliac artery aneurysms, or if there is an increased risk of vessel perforation. Avoid covering the take-off of the internal iliac artery, unless performing bailout for vessel perforation.
- Use a 7-Fr sheath from the brachial artery if balloon-expandable stents ≥7 mm in diameter are needed and the left brachial artery is at least 3 mm in diameter by ultrasound. All self-expandable stents up to 10 mm in
diameter go through a 6-Fr sheath. Some manufacturers even make self expanding stents (up to) size 12 (mm) and 14 mm diameter for 6-Fr sheath. As of 2017, several medical device companies have self-expanding stents up to 10 mm that go through 5-Fr sheath (Zilver, Cook Medical, among others).

• If unable to deliver a stent due to heavy calcification and/or tortuosity, use a 0.035 inch × 300 cm long stiff Supracore wire instead of the 0.018-inch Steelcore wire to straighten the iliac artery.

Covered Stents

• Use balloon-expandable iCast-covered stents in the ostial, proximal, and mid common iliac artery locations when there is an increased risk for vessel perforation, such as calcification and increased tortuosity of the diseased segment. iCast-covered stents can also be used as a bailout in the case of vessel perforation.

• Use a Viabahn self-expanding covered stent in the common iliac artery location as long as the lesion is not ostial and the take-off of the internal iliac artery is not covered by the Viabahn stent. This covered stent can also be used in the external iliac artery above the inguinal ligament.

Balloon Angioplasty Alone (No Stenting)

• Use balloon angioplasty as a destination therapy if good angiographic results are shown at the aortoiliac segment after simultaneous bilateral balloon inflations using the kissing technique or after unilateral iliac balloon dilatation. Measure the pressure gradient across the balloon-treated area; a good angiographic result with ≤15 mm Hg translesional pressure gradient after balloon dilatation could eliminate the need for stents.

• Consider using a Chocolate balloon (QT Vascular, Singapore) if the intention is to treat with balloon-only therapy and if the vessel diameter is 5 mm or smaller, since the largest balloon diameter available as of 2017 is 6 mm, and our own experience indicates that these balloons should be sized 1 mm larger than the reference vessel diameter. Chocolate balloons may have the advantage of decreasing the risk of vessel dissection compared with regular balloons.
**Total Occlusion of the Common or External Iliac**

- Use the ipsilateral CFA approach using a 6 or 7 Fr × 25 cm sheath with a radiopaque marker if there is a favorable “beak” at the distal iliac artery occlusion site.
- Use the left brachial access with the antegrade approach and a 6 or 7 Fr × 90 cm sheath if the beak of the iliac occlusion is at the proximal occlusion site and if there are no signs of significant left subclavian artery stenosis. Puncture the brachial artery under ultrasound visualization. Alternatively, use the left radial access with the 6 Fr × 90 cm long sheath in patients less than 5 feet, 8 inches tall.
- Advance the Viance catheter (Medtronic, Dublin, Ireland) through the 6- or 7-Fr sheath with a 0.014-inch Grand Slam wire (Abbott) that has been given a 45° bend 1 cm away from the tip; advance the wire to engage the “beak.”
- Carefully advance the Viance catheter over the wire until it engages the iliac artery occlusion. Pull the Grand Slam wire back 1 cm into the Viance and rapidly spin the Viance catheter in different directions with simultaneous gentle forward pressure. When the Viance crosses the occlusion, stop spinning to see if the 0.014-inch Grand Slam wire comes out without any resistance and its tip moves freely. The free motion of the wire tip suggests an intraluminal position. Keep advancing the wire into the distal aorta or into the femoral artery if access is from the arm, twisting the wire and confirming free motion of the tip. Advance the Viance over the wire, and then remove the wire. Inject diluted 50% contrast using a 3-mL syringe through the Viance catheter to confirm the intraluminal position. Once confirmed, pass the Grand Slam wire back in again and position it distal to the lesion. Remove the Viance and dilate the occlusion with an undersized balloon. If the tip of the Viance catheter does not enter the true lumen, pull the Viance back approximately 1 to 2 cm into the occlusion; then take a 0.014-inch Confianza Pro (Abbott) 300-cm wire, make a 30° bend 2 to 3 mm away from the tip, and use this wire to probe the occlusion to see if it can reenter the true lumen.
- Use the Viance Crossing catheter inside a 0.035 inch × 135 cm angled Quick Cross catheter (Spectranetics, Colorado Springs, CO) when more support is needed to cross the iliac artery. Usually, the Viance Crossing catheter is used without extra support from the Quick Cross catheter.
Always confirm the intravascular location of the wire by injecting contrast before dilating or passing larger devices. Then, proceed with predilation of the stenosis with a balloon, followed by stenting. Remember to avoid kissing stents if possible and to deploy the balloon-expandable stent precisely at the site of the stenosis. The extra effort at achieving a precise stent deployment may allow future use of the contralateral access if needed.

As an alternative approach to the Viance catheter at crossing total occlusions, a 0.035 inch × 135 cm Quick Cross, Navicross (Terumo, Somerset, NJ), CX1 (Cook Medical), or Slip (Cook Medical) catheter along with a 0.035-inch angled or straight glide wire can be used.

**Use of Reentry Devices in the Common Iliac Artery**

Consider using a Pioneer catheter (Volcano, San Diego, CA) with direct intravascular ultrasound visualization if, during the attempt to cross the occluded common iliac artery from the femoral approach, the wire and crossing catheter remain in the subintimal vascular space.

Before using the Pioneer catheter, a 0.014 inch × 180 cm Thunder wire (Medtronic) must be located in the subintimal space and the wire tip positioned a few millimeters beyond the occlusion.

The entire subintimal track of the wire should first be predilated using a 3-mm balloon to allow the passage of the 6-Fr Pioneer catheter (see Fig. 54-8). The monorail segment of the Pioneer catheter will then be loaded onto the Thunder wire. A 0.014-inch Cougar wire (Medtronic) will be loaded in the needle port of the Pioneer catheter after giving a 45° bend to its tip. After entry of the needle into the true lumen, the 0.014-inch Cougar wire is passed through the needle into the distal vessel while visualizing the free movement of the tip.

Following reentry of the 0.014-inch Cougar wire with the Pioneer catheter, the intraluminal position of the wire must be confirmed with contrast (mandatory). Then, predilate with a 0.014-inch wire compatible with 3.0 × 20 mm coronary balloon at the Pioneer needle reentry site. Do a second balloon dilatation at the same distal reentry site using a 0.018- or 0.035-inch balloon, but with a diameter 1 mm smaller than the reference vessel size, and cover the entire lesion length. The second balloon dilatation across the lesion in the subintimal space is always needed to facilitate the
passage and deployment of the stent(s). Exchange the 0.014-inch wire for a 0.018 inch × 300 cm long Steelcore wire before stenting the diseased iliac artery segment.

**Surveillance After Endovascular Revascularization of the Iliac Arteries (Including Aortoiliac Segment)**

All patients who have undergone revascularization of the iliac arteries with balloon angioplasty, stent, or both should undergo periodic outpatient visits to monitor for symptoms of PAD, presence of femoral pulses, ABIs, and surveillance duplex ultrasound as follows:

- Duplex ultrasound of the treated vascular segment and ABI within 1 month of the initial procedure (baseline surveillance study) and with any subsequent new or worsening lower extremity symptoms.\(^\text{12}\)
- Duplex ultrasound and ABI annually thereafter. During the first year, a 6-month study is also advisable.

**COMMON FEMORAL ARTERY STENOSIS: OUTFLOW DISEASE**

**Clinical Presentation**

Since claudication is generally manifested in the segment distal to the site of the vascular stenosis or occlusion, it is expected that hemodynamically significant CFA disease will result in symptoms felt in the thigh and calf. Claudication is often accompanied with femoral bruits and diminished or absent pulses in the femoral, popliteal, and infrapopliteal arteries (trifurcation vessels). Severe CFA disease may present with critical limb ischemia due to compromised flow in the SFA and the profunda arteries.

Outflow disease is PAD in the vascular territory beginning at the CFA below the inguinal ligament and extending down into the popliteal arteries. Occasionally, revascularization of the inflow segment is sufficient to ameliorate claudication and critical limb ischemia (CLI). Patients with CLI often need additional revascularization procedures more distally, in the
arteries of the outflow segment, to improve blood flow to the foot and correct the low-perfusion state.\textsuperscript{17}

**Vascular Testing**

- Abnormal resting or postexercise ABIs.
- Abnormal PVR with amplitude reduction and monophasic waveform morphology in the affected leg.
- Duplex ultrasound with findings similar to those for the iliac/CFA stenosis.

**2013 ACC/AHA Practice Guidelines (Class II)**

- Stents (and other adjunctive techniques, such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for suboptimal or failed results from balloon dilatation (eg, persistent translesional gradient, residual diameter stenosis >50%, or flow-limiting dissection). (Class IIa, Level of Evidence: C)
- The effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoropopliteal arterial lesions (except to salvage a suboptimal result from balloon dilatation) is not well established. (Class IIb, Level of Evidence: A)

**Emory Protocols for Endovascular Treatment**

Surgical endarterectomy with patch angioplasty of the CFA is reserved for totally occluded, severely calcified, bulky plaques, especially if they extend into the deep profunda and ostial SFA. Surgery is also recommended when there is more extensive disease in the SFA/popliteal segments that requires a bypass graft, or when an endovascular revascularization attempt fails. Figure 54-9 shows the angiographic result of a nontotal but severely calcified CFA stenosis treated with orbital atherectomy and adjunctive balloon angioplasty, with excellent clinical and hemodynamic results. There was no translesional pressure gradient after the procedure, and the patient had complete resolution of the leg claudication.
Endovascular treatment of the CFA almost always involves the use of debulking devices, such as directional atherectomy and/or orbital atherectomy, to increase the lumen diameter and to minimize the risk of vessel dissection from balloon angioplasty. Stenting of the CFA should be avoided and used only as a bailout procedure.

The access for patients with symptomatic stenosis of the CFA is preferentially the contralateral approach, using a 7 Fr × 45 cm long Pinnacle destination sheath (Terumo) advanced into the distal external iliac artery and left approximately 5 cm proximal to the CFA lesion. This distance is important to avoid performing the atherectomy inside the sheath and also to allow more effective cuts by permitting good apposition of the debulking device.

The CFA stenosis is generally crossed with a 0.014 inch × 180 cm long wire, but a Progreat (Terumo) catheter with the included 0.018-inch wire is sometimes needed as an alternative to cross the most difficult CFA lesions. Distal filter protection is frequently used to minimize the risk of distal
atheromatous plaque embolization. Use the Spider filter (Medtronic) for directional atherectomy, and the Emboshield filter (Abbott) mounted on a 0.014-inch Viper wire (Cardiovascular Systems, St. Paul, MN) for orbital atherectomy; choose a filter size 1 mm in diameter larger than the reference vessel diameter when the Spider filter is used. Place the filter in the mid SFA when intervening in the CFA. Use a Hawk 1 LS (Medtronic) atherectomy if the CFA is >5 mm when no calcium or mild to moderate plaque calcification is present, and do four 90° segmental cuts to reduce plaque to <30% angiographic stenosis. If needed, do additional cuts to reduce to <30%. If the CFA is <5 mm in diameter, do more frequent angiographic evaluations after each cut to reduce the risk of device-related perforation. After debulking the CFA lesion, use Chocolate or VascuTrak (Bard Peripheral Vascular, Tempe, AZ) balloons for residual stenosis >30%.

Use drug-coated balloons when the residual stenosis is <30% and when it is a restenotic lesion. For critical stenosis and if the intention is to intervene with atherectomy, first predilate with a 3-mm balloon. For severe calcified plaque affecting both sides of the wall, cross the CFA with a 0.014-inch Viper wire and perform orbital atherectomy. If the Viper wire does not cross the CFA stenosis, use a Progreat catheter with its wire, and once crossed, change to the Viper wire. Alternatively, use a 0.014-inch coronary wire with or without a supportive 0.014-inch catheter. Once the 0.014-inch non-Viper wire has crossed the CFA lesion, exchange for the Viper wire using the same supportive catheter.

Perform orbital atherectomy with a 2-mm solid crown for 4- to 7-mm diameter CFA vessels; a 1.5-mm solid crown may be needed in the case of critical calcific stenosis. If >30% residual stenosis exists after debulking and without flow-limiting dissection, use Chocolate or VascuTrak balloons to achieve a larger final lumen diameter. Size the Chocolate balloon 1 mm larger than the vessel diameter, with expansion to 3 to 5 atm, increasing 1 atm every 30 seconds until the balloon is uniformly expanded for a total of 5 to 8 minutes. Perform gradual balloon inflation under direct fluoroscopic visualization. If >50% residual stenosis remains after orbital atherectomy, use a Hawk 1 LS atherectomy device, keeping in mind the increased procedure-related cost.

Alternatively, >30% residual stenosis can be treated with a VascuTrak balloon using 2- to 4-atm pressure inflations, increasing 1 atm every 30 seconds, for at least 5 to 8 minutes; size the VascuTrak balloon diameter 1:1
to the vessel diameter. We have found consistent good angiographic results when doing prolonged low-pressure inflations for 5 to 8 minutes.

**Protocol Variations**

**Vascular Access Site**

- Use the left brachial artery when the contralateral approach is not possible. Lesions in the CFA can generally be reached with directional atherectomy and orbital atherectomy from the left brachial artery in patients shorter than 5 feet, 8 inches tall. Use a 6 Fr or 7Fr × 90 cm long flexor sheath for directional atherectomy and a 6 Fr × 90 cm length sheath for orbital atherectomy. The orbital atherectomy device will go through a 6-Fr sheath, but if balloon inflation is needed with a 7-mm diameter VascuTrak balloon, a 7-Fr sheath will be required. The distance of the CFA from left brachial puncture site can be estimated using a peripheral balloon with a known 150-cm shaft if needed.

**Total Occlusion**

- Use the standard Viance catheter procedure protocol to cross total ostial CFA occlusions as a first option, as described in the earlier total iliac artery section.
- As a second option, especially if the angiographic “nubbin” at the proximal side of the occlusion is present, cross the occluded CFA using the contralateral approach with a 4-Fr 0.035 inch × 135 cm Navicross, CX1, or Quick Cross catheter with a straight Terumo regular glide wire through a 7-Fr sheath; use the angiogram roadmap for better visualization. Switch to a stiff glide wire if the total occlusion cannot be crossed with a regular 0.035-inch glide wire. Avoid buckling the wire so as not to go subintimal into the ostial SFA and clip off the profunda artery.
- A straight catheter (Navicross, CX1, or Quick Cross catheter) can be used if there is a funnel shape angiographic “nubbin.”
- If there is no angiographic “nubbin” with flush occlusion, probe a straight 0.035-inch regular or stiff 180-cm-long glide wire against the CFA by pointing straight or medially away from the profunda artery.
If the occluded CFA tract cannot be located by angiogram, consider using duplex ultrasound of the groin. Pedal access can also be considered if the occlusion cannot be crossed using the antegrade approach.

SUPERFICIAL FEMORAL-POPLITEAL ARTERY STENOSIS: OUTFLOW DISEASE

Clinical Presentation

The superficial femoropopliteal artery is the most common vascular segment affected in PAD, and the stenosis is often diffuse with a variable degree of calcification. Typical calf claudication with ambulation relieved by rest occurs in less than 15% of patients. More commonly, patients present with atypical or no symptoms, but they may alter their lifestyle and become more sedentary. Since the deep femoral artery ipsilateral to the SFA/popliteal lesion often provides collateral circulation for the reconstitution of the distal flow, preservation of this vessel should be maintained.

Vascular Testing

- Abnormal resting or postexercise ABIs.
- Abnormal PVR with reduced amplitude and monophasic waveform morphology in the affected leg.
- Duplex ultrasound with diffuse, often calcified atherosclerotic plaque with monophasic waveform, spectral broadening, and peak systolic velocity >100% relative to the adjacent proximal segment at the site of the stenosis with distal tardus parvus flow.
- Velocity ratio >2.0 between the stenotic and the proximal adjacent segment.

2013 ACC/AHA Practice Guidelines (Class I-II)

- Endovascular intervention is recommended for disabling claudication
despite maximal medical treatment, including supervised exercise program, and as long as the invasive option has a very favorable risk-benefit ratio. (Class I, Level of Evidence: A)

- Endovascular intervention is preferred for TASC type A. (Class I, Level of Evidence: B)
- Stents (and other adjunctive techniques, such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for suboptimal or failed results from balloon dilatation (eg, persistent translesional gradient, residual diameter stenosis >50%, or flow-limiting dissection). (Class IIa, Level of Evidence: C)
- The effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoropopliteal arterial lesions (except to salvage a suboptimal result from balloon dilatation) is not well established. (Class IIb, Level of Evidence: A)
- For individuals with combined inflow and outflow disease in whom symptoms of critical limb ischemia or infection persist after endovascular inflow revascularization, an outflow revascularization procedure should be performed. (Class I, Level of Evidence: B)

**Emory Protocol for Endovascular Treatment**

The contralateral access approach is used in virtually every case of intervention in the SFA, with the exception of a technically impossible crossover, such as kissing aortoiliac stents, previous aortoiliac bypass, and other anatomic difficulties discussed in the protocol variations below. Debubking with atherectomy and adjunctive balloon angioplasty is our favored mode of SFA and popliteal artery revascularization.

Once the selected equipment, based on review of clinical history, imaging studies, and laboratory data, is available in the catheterization laboratory, the procedural protocol begins by accessing the CFA opposite the side of the SFA/popliteal stenosis. Needle entry, using a 21-guage needle and 30-cm-long micropuncture kit from Vascular Solutions, should be in the midline head of the femur, below the inferior epigastric artery and above the distal CFA bifurcation.

We recommend doing the crossover either with a 4 Fr × 65 cm Rim or 4 Fr VCF catheter (Cook Medical) and using a 0.035 inch × 180 cm Bentson
(Cook Medical) or an angled glide wire advanced through a 4 Fr × 10 cm long sheath. If the VCF does not allow engagement of the contralateral common iliac artery, a 4 Fr × 65 cm Rim or, rarely, a Sim 1 (Terumo) catheter may facilitate the contralateral common iliac artery engagement. After performing the digital subtraction angiogram of the contralateral limb, the Rim or VCF catheter is exchanged for a 7 Fr × 45 cm long Pinnacle Destination sheath using a 0.035 inch × 180 cm Supracore wire. Intravenous heparin should be administered after completing the crossover, and the ACT should be kept in the 200- to 250-second range throughout the endovascular intervention.

Distal filter protection is strongly recommended when planning atherectomy in the SFA/popliteal arteries with: (1) single-vessel runoff, (2) more than mild calcification of the vessel being treated, (3) intermediate to long lesion length, or (4) total occlusion. A Spider filter is favored when doing directional atherectomy, and the Emboshield filter is favored in severe calcified lesions treated with orbital atherectomy. Choose a filter 1 mm in size above the reference vessel diameter to where the filter is being deployed, and place the filter not less than 10 cm distal to the lesion to avoid disturbing the filter with the endovascular device (ie, nose cone of the atherectomy catheter). The Spider filter can also be deployed through a 0.035-inch (5-Fr) Quick Cross or Trailblazer (Medtronic) catheter. This alternative mode of deployment is most useful when crossing a total occlusion with a catheter, which allows the filter to be deployed immediately after injection of contrast distal to the total occlusion to confirm the intraluminal position of the catheter. The most common location used to deploy the filter in the SFA/popliteal intervention is in the popliteal artery, but it can also be deployed in the distal SFA, in the largest caliber size trifurcation vessel, or in the single runoff vessel present. If the lesion is <10 cm from the take-off of the anterior tibial artery and distal protection is needed, the filter can be deployed in the dominant tibial vessel or in the vessel in the distribution of the ischemic ulcer.

**Treatment of Ostial <100% SFA Stenosis**

When treating severe but less than totally occluded ostial SFA/popliteal artery stenosis, the tip of the 7 Fr × 45 cm sheath should be left in the proximal CFA, approximately 5 cm or more proximal to the lesion, to avoid
doing atherectomy cuts inside the sheath and to allow proper apposition of the atherectomy device. The SFA/popliteal artery is then crossed with a 0.014 inch Spartacore wire (Abbott Vascular), advanced inside a 0.035-inch Quick Cross catheter. If filter protection is used, as noted earlier, deploy the Spider filter in the distal segment of the artery and keep it not less than 10 cm away from the distal edge of the lesion to prevent contact with the nose cone of the atherectomy device.

The cutter is chosen according to vessel size. We prefer to use directional atherectomy to reduce the obstructive plaque to <50% residual stenosis. The Silver Hawk MS cutter is recommended for SFA/popliteal arteries sizes up to 5 mm in diameter, while the SX-C cutter is recommended for vessel diameter <4 mm. The LX cutter with a long-nose cone stores the largest amount of plaque and requires less cleaning. Drug-coated balloons are recommended after debulking with atherectomy in restenotic lesions. Chocolate or VascuTrak balloons are preferred in de novo SFA/popliteal artery lesions. VascuTrak balloons are used in 6- to 7-mm diameter vessels and selected with a 1:1 balloon-to-vessel ratio. For vessel sizes less than 6 mm, we recommend using Chocolate balloons at 1-mm size greater than the reference vessel diameter. For critical stenosis, predilate with a 3-mm balloon before performing directional atherectomy to facilitate passage of the device. The use of drug-coated balloons is evolving and, in the future, may be the norm for even de novo lesions.

**Treatment of 100% Ostial SFA Stenosis**

For treatment of a total ostial SFA occlusion, leave the tip of the sheath in the proximal CFA. If there is a “nubbin” at the site of the occlusion, use the Viance catheter to cross the total ostial SFA as described under the iliac artery occlusion. Alternatively, use a 4-Fr 0.035 inch × 135 cm angled stiff catheter, such as the Navicross, CX1, or angled Quick Cross catheter with a straight Terumo regular glide wire under angiographic roadmap visualization. Abandon the Viance procedure and switch to a 0.035-inch stiff glide wire if there is no success in crossing the total occlusion. Consider using a straight catheter (Terumo Navicross or Cook CX1 catheter) if there is a funnel shape “nubbin.” If there is no “nubbin” with flush occlusion, probe a straight 0.035-inch regular or stiff 300-cm-long glide wire on an angled 4-Fr catheter against the distal CFA by pointing medially, away from the profunda artery.
If unable to find the occluded SFA tract by angiogram, consider using duplex ultrasound of the groin, which may aid in finding the occluded path. Consider pedal access if unable to cross using the antegrade approach.

**Treatment of Severe <100% SFA/Popliteal Stenosis 1 cm Away from the Ostium**

In the presence of severe stenosis 1 cm away from the ostium of the SFA, leave the tip of the sheath in the distal CFA or proximal SFA at a distance not less than 5 cm proximal to the lesion. This distance will avoid doing atherectomy inside the sheath and also will allow more effective cuts by obtaining good apposition of the debulking device. We prefer doing directional atherectomy to remove noncalcified, mild, or moderately calcified plaque, although balloons, lasers, and stents may also be considered as a destination therapy.

Use a Turbo LX (Medtronic) long nosecone atherectomy catheter for SFA lesions longer than 10 cm of length (long lesions) and 10 cm above the take-off of the anterior tibial artery. We use the Hawk 1 short nose cone for SFA lesions <10 cm and when the lesion is located 7 cm or more away from the take-off of the anterior tibial artery. Use an MS cutter if the lesion is in the mid or distal popliteal artery, if the lesion is within 7 cm of the take-off of the anterior tibial, or if vessel diameter is less than 5 mm.

Make 2 to 3 cuts around the circumference and then retrieve the atherectomy catheter to confirm the absence of perforation, as debulking in the popliteal artery carries a higher risk of this complication. Consider doing Chocolate balloon angioplasty in the SFA or popliteal area if >30% residual stenosis remains after debulking with atherectomy. The balloon size must be 1 mm larger than the reference vessel diameter. When treating restenotic lesions or when concerned about increased risk of restenosis (eg, long lesions, total occlusions, complex calcified plaque, small diameter vessels), use drug-coated balloons after debulking to at least 30% or less residual stenosis.

**Treatment of 100% SFA/Popliteal Stenosis 1 cm Away from the Ostium**
After leaving the tip of the 7-Fr sheath in the proximal CFA or proximal SFA, attempt to cross the total occlusion using the Viance crossing catheter first. An alternative approach is to cross with a 4-Fr 0.035 inch × 135 cm angled stiff catheter (Navicross, angled CX1, or Quick Cross) with a straight regular glide wire (Terumo) through a 7-Fr sheath using the contralateral approach under angiographic roadmap visualization. If there is no success in crossing the total occlusion, switch the straight Terumo regular glide wire to a stiff straight 300-cm-long glide wire. If there is a “nubbin” at the site of the occlusion, come with the straight stiff glide wire and CX1 or Navicross angled glide catheters to the “nubbin.” Probe the Terumo glide wire against the proximal occlusion by pointing in the direction of the vessel trajectory. If unable to find the occluded tract of the SFA, consider using duplex ultrasound with or without fluoroscopy to cross the SFA.

Following treatment of the SFA/popliteal artery stenosis, always perform a repeat angiogram of the entire lower extremity, from distal to proximal, using low magnification, digital subtraction technique, and diluted contrast. Next, pull back the sheath gradually from distal to proximal and observe for pressure gradients and for angiographic stenosis, dissections, or any other abnormalities. Treat inflow lesion(s) if stenosis >70% and translesional pressure gradient >15 mm Hg prior to complete withdrawal of the sheath. Confirm gradient with a 4-Fr catheter, such as a Slip catheter, when possible. Exchange the Pinnacle Destination sheath for the same-size French, 10-cm-length sheath. Finish by obtaining an ACT and recording the amount of contrast used and radiation exposure.

**Protocol Variations**

**Vascular Access Site**

- Use an antegrade ipsilateral arterial access approach with 7 Fr × 65 cm Pinnacle Destination sheath if there is a difficult acute angle between the 2 common iliac arteries and the distal abdominal aorta, previous kissing stents or aorto-iliac-femoral bypass, or heavily calcified and tortuous iliac arteries; leave at least 5 cm of the sheath inside the femoral artery. Do not use this access if the SFA lesion is ostial or too proximal, because the tip of the 7-Fr sheath must be left not less than 3 cm proximal to the SFA.
stenosis. Make a “C” shape bend on the sheath and leave it over the abdomen of the patient, bringing the proximal end of the sheath into the opposite side of the femoral artery puncture site, so the endovascular procedure can be done simulating the contralateral approach. Keep the sheath secure with a large Tegaderm (3M, Maplewood, MN) taped onto the abdominal wall.

• Use the left brachial arterial access with a 6 Fr × 90 cm Pinnacle Destination sheath when the contralateral or ipsilateral antegrade approach is not technically feasible due to previous kissing stents or surgical grafts or simply because the iliac crossover is too difficult and the lesion is ostial or within 3 cm of the ostium. Most balloon shafts are 150 cm, although some tall patients may require a special 175-cm shaft balloon. The LX and LS atherectomy catheters have a working length of 113 cm and 110 cm, respectively, and the SXC is even longer at 135 cm, whereas the orbital atherectomy catheter is 150 cm long.

• Use the retrograde pedal and, less commonly, the retrograde popliteal access to cross flush occlusions or occlusions that cannot be crossed using the antegrade approach. Locate a patent pedal artery (posterior or anterior tibial) or popliteal artery by angiogram and puncture it under direct ultrasound visualization using a short micropuncture kit. Insert a 4 Fr × 12 cm sheath into the pedal or popliteal artery and advance a 4-Fr angled stiff catheter (Navicross, CX1) and a 0.035 inch × 135 cm angled regular Terumo glide wire to navigate the tibial or popliteal artery in a retrograde manner, toward the total SFA occlusion. Once at the occlusion site, follow the technique of crossing antegrade 100% occlusions described previously.

• On rare occasions, the profunda artery collaterals may be used to enter the distal SFA and then come retrograde into the occlusion using the coronary chronic total occlusion equipment and technique.

Severe Stenosis in the Path of the Contralateral Approach (Native or Stent) for SFA/Popliteal Intervention

• Treatment of the (iliac) inflow stenosis may be sufficient in patients with claudication or critical limb ischemia, even with untreated occlusive
disease left in the outflow vascular segment. If concomitant total SFA/popliteal segment occlusion is present at the same side of the iliac artery or stent restenosis, the intended outflow revascularization procedure should be staged because limb ischemia may improve significantly after treatment of the inflow segment.

- When ostial common iliac artery stenosis coexists with outflow SFA disease, the inflow stenosis must be treated first, with the treatment of the SFA generally deferred. If the decision is made to proceed with treatment of the SFA/popliteal artery, and there is an iliac stenosis in the path of the contralateral access approach, treatment must begin with balloon angioplasty of the iliac artery stenosis before placing a sheath across the stenosis to avoid ischemia on the access site limb; consider stenting the residual iliac stenosis at the end of the intended SFA/popliteal artery revascularization procedure, if angiographically significant, with a translesional gradient >15 mm Hg. An alternative approach is to balloon and stent the iliac stenosis first and to defer the revascularization of the outflow segment for 30 to 60 days.

- If there is an unplanned need to reconstruct the aortoiliac bifurcation after intervention on the outflow segment, keep the 0.035-inch contralateral Supracore wire in the contralateral proximal SFA and pull the Pinnacle Destination sheath back in the ipsilateral iliac artery. Then puncture the contralateral CFA and cross the iliac artery using the retrograde approach with a 0.018 inch × 300 cm long Steelcore wire. Use the 0.035-inch wire in the CFA as a reference for the puncture site, and leave the tip of the Steelcore wire in the thoracic aorta. Once the contralateral common iliac artery has been crossed with the Steelcore wire, exchange the contralateral 0.035-inch wire for a 0.018-inch Steelcore wire and place it in the thoracic aorta. After both common iliac arteries have been secured with wires, proceed with kissing balloons and stents.

- Restenosis of an iliac stent in the path of the contralateral approach must also be treated first, before any attempt to revascularize the outflow segment, unless the decision is made to do open surgery with an ipsilateral aortoiliac graft. If a femoral-to-femoral bypass is needed, the inflow limb of the iliac arteries must be treated with stents first.

- For totally occluded native iliac or stents, follow instructions detailed in the iliac artery disease section.
Severe Calcified Plaque Affecting Both Sides of the Wall of the SFA/Popliteal Artery Stenosis

- Perform orbital atherectomy with a 2.00-mm solid crown to modify severe calcified plaque that affects both sides of the vascular wall. Start with a 1.50-mm solid crown for tight calcified lesions. Use Emboshield filter for SFA/popliteal lesion length >3 cm.
- If there is more than 30% residual stenosis after debulking with 2.00-mm Solid Crown diamondback, use a Chocolate balloon or VascuTrak balloon at low-pressure inflations for 5 to 10 minutes. Use of a Hawk 1 could be considered before using the previously mentioned balloons.
- For restenotic lesions, use drug-coated balloons after debulking to <30% residual stenosis.
- Use a Hawk 1 for calcified lesions <10 cm long, or LX-C for calcified lesions >10 cm long, always with distal filter protection.
- Consider using a Hawk 1 if >50% residual stenosis remains after debulking with orbital atherectomy. The cost of using 2 different debulking devices should be weighed against the benefits.
- Our practice is to use orbital atherectomy first in severe vessel calcification and, if unable to reach <50% residual stenosis, to use Hawk 1 for stenosis reduction.

Thrombosis of the SFA/Popliteal Arteries

- Cross the thrombosed vascular segment with a 0.035 inch × 135 cm Quick Cross or Trailblazer catheter and a 0.035-inch exchange length glide wire, and place a filter distally to protect the trifurcation vessels.
- Perform mechanical thrombectomy with an Angiojet (Boston Scientific, Marlborough, MA) aspiration catheter or laser atherectomy, followed by treatment of the stenotic segment, if present.
- Keep the patient well anticoagulated and correct underlying thrombotic state.

Surveillance After Endovascular Revascularization of the SFA/Popliteal Artery Segment
All patients who have undergone revascularization of the SFA/popliteal arteries should have periodic outpatient visits with the treating physician to monitor for symptoms of PAD progression; the presence of femoral, popliteal, posterior tibial, and dorsalis pedis pulses; ABIs; and surveillance duplex, as follows:

- Perform duplex ultrasound of the common femoral, SFA, popliteal, and trifurcation vessels and ABI within 1 month of the procedure (baseline surveillance) and thereafter upon any subsequent new or worsening lower extremity symptoms.¹²
- Perform duplex ultrasound and ABI at 3, 6, and 12 months and annually thereafter to monitor for restenosis.

**STENOSIS OF THE TRIFURCATION VESSELS: RUNOFF DISEASE**

**Clinical Presentation**

Individually, stenosis of the tibioperoneal, anterior tibial, peroneal, or posterior tibial artery (trifurcation vessels) is not likely to cause claudication. However, when all 3 tibial vessels are severely diseased, symptoms such as numbness, foot aching, and cold feet may develop before the onset of critical limb ischemia. Disease of the trifurcation vessels is more commonly associated with chronic limb ischemia, in part due to poor compensatory collateral circulation. Critical limb ischemia is defined as PAD that results in ischemic rest pain, ischemic tissue loss, or gangrene.¹⁸ Endovascular revascularization of the trifurcation vessels is indicated when the patient has signs and symptoms of CLI or when any foot surgery is being planned and severe trifurcation disease is present.

**Vascular Testing**

- TBI <0.70 and toe pressures <40 mm Hg.
- Abnormal resting or postexercise ABIs.
- Abnormal PVR with decreased amplitude and monophasic waveform
morphology below the knee.

- Duplex ultrasound with diffuse, often calcified atherosclerotic plaque of the trifurcation vessels with monophasic waveform, spectral broadening, and elevated peak systolic velocity >100% relative to adjacent proximal segment at the site of the stenosis; may have distal tardus parvus flow.

2013 ACC/AHA Practice Guidelines (Class II)

- Stents (and other adjunctive techniques, such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilatation (e.g., persistent translesional gradient, residual diameter stenosis >50%, or flow-limiting dissection). (Class IIa, Level of Evidence: C)

- The effectiveness of uncoated/uncovered stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of infrapopliteal lesions (except to salvage a suboptimal result from balloon dilatation) is not well established. (Class IIb, Level of Evidence: C)

Emory Protocols for Endovascular Treatment

Treatment of Severe Nontotal Tibial/Peroneal Artery Stenosis

Endovascular intervention of the arteries below the knee is done using a 6-Fr sheath. However, if a combined SFA/popliteal revascularization is planned, a 7-Fr sheath is generally needed.

Choose a 65-cm-long Pinnacle Destination sheath, and leave the tip in the mid or distal SFA, if no disease is in this segment, when using the contralateral approach for below-the-knee intervention; this sheath length and position allow better angiographic images of the distal vessels with less contrast use. Cross the tibial artery stenosis using a 0.014 inch × 300 cm Spartacore wire (or your favorite wire) under angiographic roadmap visualization. Advance the 0.014-inch wire over a 0.018 inch × 135 cm long Quick Cross with either a 45° angled tip or straight tip as needed to navigate the trifurcation vessels. For patients 6 feet tall or taller, use a 150-cm Quick
Cross catheter. If the tibial artery lesion is in the distal segment, consider using the antegrade approach to avoid running out of device length.

Once the tibial artery stenosis is crossed with the 0.014 inch × 300 cm wire, advanced the Quick Cross catheter distal to the stenosis and confirm the intraluminal location of the catheter by injecting diluted contrast before exchanging the Quick Cross catheter for a balloon. Next, perform a balloon angioplasty with a Chocolate or VascuTrak balloon.

There is no need for distal filter protection in the tibial arteries unless the lesion is >5 cm and has a proximal or mid location in a vessel with a diameter >2 mm.

Consider directional atherectomy with an SXC cutter if the vessel size is 3 mm or larger, the lesion length is ≥3 cm, and the ostium of the anterior tibial artery (ATA) is not involved. Conversely, consider directional atherectomy with an SS cutter if the lesion is not ostial ATA, the vessel size is 2 to 3 mm, and the lesion is <3 cm in length. Less commonly, ostial ATA disease is encountered, which is extremely challenging. We cannot overemphasize the complexity of this lesion. If not calcified, an SS cutter may be used, and after every cut, assess the lesion with an angiogram. Once ≤50% residual is obtained, switch to Chocolate balloon. If there is any calcification, perform orbital atherectomy with a 1.5-mm standard crown with frequent lesion assessment with contrast angiography. Switch to Chocolate balloon when ≤50% stenosis is achieved. For vessels around the ankle and in the foot, consider a solid micro crown, which only comes in 1.25 mm.

If any calcium is identified, consider orbital atherectomy with 1.5-mm standard crown. Slow runoff or no reflow may develop during the procedure, especially if treating lesion lengths >5 cm with moderate to severe calcification. Shorter runs of less than 20 seconds, increased flushing between runs, and slow passes are some of the precautions to mitigate procedure-related complications.

Per standard postintervention routine for any vascular procedure, the operator should repeat the angiogram of the affected tibial artery, and, if angiographic results are good, complete the interventional procedure with an angiogram of the entire lower extremity and aortoiliac vessels with diluted contrast.

**Treatment of a 100% Tibial/Peroneal Artery Stenosis**
Use the Viance catheter and a 0.014-inch wire system as the first choice to cross 100% vessel stenosis, with the second choice being a 0.035-inch Quick Cross, CX1, or Navicross catheter with either straight or angled 0.035 inch × 300 cm glide wires. Once the artery has been crossed and the intraluminal placement of the wire confirmed, complete the steps described earlier for treatment of severe, nontotal tibial/peroneal stenosis. The option of pedal access is our preferred choice if antegrade access fails. Finally, for operators proficient in coronary chronic total occlusions, Finecross (Terumo) or similar catheters and chronic total occlusion wires (eg, Fielder [Abbott], Gya) may be tried.

Protocol Variations

Vessel Wall Calcification

• If severe calcified plaque is present in the trifurcation vessel affecting both sides of the wall, cross with the Viance, Quick Cross, or CX1 technique, and exchange the wire used for the Viper 0.014-inch wire to prepare for orbital atherectomy.
• Always confirm the intraluminal location of the wire before treatment with either balloon or debulking devices.
• Perform orbital atherectomy with 1.25-mm solid crown for ≤4-mm-diameter vessels. Alternatively, use a 1.50-mm classic crown if the vessel diameter is <3 mm, and a 1.25-mm solid micro crown if the vessel diameter is closer to 2 mm or less or if the intervention is in the plantar arch.
• If <50% residual stenosis exists without flow-limiting dissection, use a Chocolate balloon for controlled plaque modification. Size the balloon diameter 1.5:1 to vessel diameter, with expansion up to 3 to 4 atm, under direct fluoroscopic visualization. Every 30 seconds, expand the Chocolate balloon by 1 atm and keep the balloon inflated at 3 to 4 atm for a total of 5 to 8 minutes. Alternatively, a VascuTrak balloon using low-pressure inflations, increasing by 1 atm every 30 seconds, can be used for at least 5 to 8 minutes, sizing the balloon diameter 1:1 to vessel diameter and inflation pressure 3 to 4 atm.
• Drug-coated balloon sizes <4 mm are not available as of 2017.
Consider using coronary drug-eluting stents for critical limb ischemia in the tibial vessels if angiographic results from balloon angioplasty or atherectomy are suboptimal and the disease is localized.

**Ostial Anterior Tibial Artery Stenosis**

- Atherectomy to treat ostial anterior tibial artery stenosis increases the risk of vessel perforation. Downsizing the device and repeating angiograms after each pass is strongly recommended.
- Use a Chocolate or VascuTrak balloon for ostial anterior tibial or any other trifurcation vessels.

**Surveillance After Endovascular Revascularization of the Trifurcation Vessels**

Patients who have undergone revascularization of the trifurcation arteries often have nonhealing ulcers in the feet and must undergo regular follow-up appointments with wound care specialists. The interventional cardiologist should see these complex patients regularly to monitor progress with regard to limb pain and wound healing and, if gangrene occurs, make a prompt referral to the vascular surgeon for open surgery or amputation. The regular surveillance should include a thorough examination of the skin, pulses using Doppler ultrasound, ABIs, TBI, toe pressures, and duplex ultrasound of the entire limb. The treating physician should stay in close communication with the wound care specialist and be ready to reintervene if there is no improvement in wound healing or if there are worsening symptoms with signs of CLI. The vascular surveillance is summarized as follows:

- Duplex ultrasound of the trifurcation vessels and the entire limb with ABI within 1 month of the procedure (baseline surveillance) and upon any subsequent new or worsening symptoms or recurrent signs of critical limb ischemia.
- Duplex ultrasound and ABI at 3, 6, and 12 months and annually thereafter to monitor for restenosis of the trifurcation vessels. It is important to note that often foot ulcers heal even when the treated trifurcation vessel reoccludes. However, unless a nonhealing ulcer recurs or any other symptoms of critical limb ischemia arise, there is generally no need to
reintervene in the trifurcation vessels. A lower threshold for revascularization should be considered in Rutherford classification Stage 3 patients who remain symptomatic despite guideline-directed management therapy and are at high risk of progressing to CLI. Prevention of future ischemic complications in the limbs, coronary arteries, and extracerebral/intracerebral arteries is the main goal for the PAD patient.

ACKNOWLEDGMENTS

The authors acknowledge the years of advice and feedback from mentors, colleagues, and trainees who contributed their recommendations throughout this chapter. The authors also thank Bob Todd, RVT, for his technical assistance; Denise Daniels for her technical support; Drew Imhulse from Emory Media Services for his assistance with the figures and tables; and Michelle Kienholz for her editorial assistance.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. According to the authors, which of the following statements regarding duplex ultrasound uses for surveillance after endovascular revascularization of the femoropopliteal territory is true?
   A. Duplex ultrasound examination is warranted when claudication or signs of critical limb ischemia recur.
   B. Duplex ultrasound examination is recommended to monitor for restenosis 6 and 12 months after revascularization.
   C. Duplex ultrasound examination is recommended to monitor restenosis within 1 month after the procedure, at 3 and 6 months, and then once a year after revascularization.
   D. Concomitant ankle-brachial index (ABI) is recommended 6 and 12 months after procedure.

2. Surgical treatment of symptomatic common and external iliac artery stenosis should be considered in all of the following conditions, EXCEPT:
   A. 100% flush occlusion of the ostium of the common iliac artery with severe calcification and no “beak” at the origin of the diseased segment
   B. 6.5-cm concomitant abdominal aortic aneurysm (AAA)
   C. 100% occlusion of the distal abdominal aorta
   D. Lack of contralateral or ipsilateral femoral access

3. Distal filter protection is recommended with which of the following?
   A. Spider filter in a difficult case of calcified diffuse distal superficial femoral artery (SFA) treated with orbital atherectomy and 1-vessel runoff
B. Emboshield filter in a moderately calcified mid SFA stenosis with no vessel runoff
C. De novo and restenotic focal lesions
D. Spider filter in 100% occlusion of the SFA with 1-vessel runoff

4. Which of the following statements regarding lower extremity revascularization is true?
   A. Revascularization for asymptomatic but severe peripheral arterial disease (PAD) below the inguinal ligament has a Class IIa indication.
   B. Patients with symptomatic PAD in the critical ischemia range and Rutherford category 3 should undergo prompt revascularization to avoid amputation or to convert to limited amputation.
   C. Treatment of the inflow vascular segment may suffice if the patient with critical limb ischemia has a complete or near-complete resolution of the symptoms and signs of vascular insufficiency.
   D. An absolute variation of greater than 0.15 in the ABI and/or toe-brachial index (TBI) is considered an indication for angiogram and revascularization of the lower extremity.

5. Effort-related claudication is found in most patients with PAD.
   A. True
   B. False

**ANSWERS**

1. C

Patients undergoing lower extremity revascularization with endovascular techniques require a baseline ABI and a duplex ultrasound examination of the treated vascular segment within 1 month of the procedure. In addition to the baseline study, the authors routinely repeat the ABIs and duplex ultrasound examinations at 3 and 6 months after the endovascular intervention to monitor for patency of the target vessel site. Patients are at highest risk for restenosis during the first 6 months after the procedure, and symptoms of recurrent disabling claudication may occur too late, after (re)occlusion of the index lesion. Repeat revascularization of a completely occluded artery from restenosis is expected to be difficult and time consuming, while also exposing
both the patient and the operators to excessive direct radiation; therefore, early detection of physiologic (ABI/pulse volume recording [PVR]) or anatomic (duplex ultrasound) signs of significant restenosis will permit planning for re-intervention, before progression to a total occlusion.

2. D

Most patients with symptomatic common and external iliac artery stenosis are treated using endovascular techniques unless: (1) there is an infrarenal AAA requiring repair; (2) there is a 100% flush occlusion with no “beak” or “nubbin” at the ostium of the common iliac artery and there is severe calcification and intermediate (>5 cm) length occlusion; or (3) there is a long occlusion (>10 cm) with severe calcification.

The decision to use endovascular techniques versus open surgery should be made according to operator expertise and patient characteristics and preference after a detailed discussion of the indications, benefits and limitations, alternative treatment, and potential complications related to each procedure. Endovascular revascularization of the common and external iliac arteries can be performed using the left radial or brachial approach, generally using a 5 or 6 Fr × 90 cm long sheath.

3. D

Distal filter protection is strongly recommended when planning atherectomy in the SFA/popliteal arteries with single-vessel runoff, more than mild calcification of the vessel being treated, intermediate to long lesion length, or total occlusion. A Spider filter is used when doing directional atherectomy, and the Emboshield filter can be used in severe calcified lesions treated with orbital atherectomy. Orbital atherectomy with CSI is performed using a 0.014-inch Viper wire only and cannot be replaced by the Spider wire. Restenotic tissue is commonly soft without calcification and less likely to embolize.

4. C

An absolute variation of greater than 0.15 in the ABI/TBI is considered significant when done serially but does not mandate angiogram or revascularization. Symptoms generally mandate further testing and revascularization. Management of patients with the condition described in
answer choice A is currently debatable and should be individualized for each situation. Rutherford category 4 and above describes patients with critical limb ischemia, so answer choice B is wrong. Patients could experience resolution of the symptoms and signs of critical limb ischemia after treatment of the inflow (iliac arteries), especially if a total iliac stenosis is successfully opened; therefore, treatment of the outflow segment is not necessarily required, which is the correct answer.

5. B

Lower extremity claudication with typical effort-related limb pain occurs in only 11% of patients with PAD.
INTRODUCTION

History

The treatment of venous disease has changed dramatically in recent years with the advent of duplex ultrasound evaluation, minimally invasive treatments, and new thrombolytic drugs. For more than 100 years, the treatment of superficial disease had been limited to high ligation and stripping with limited innovation. Attempts at chemical ablation (sclerotherapy) had, historically, been hampered by serious complications and a high rate of recurrence. Deep venous treatment had been largely limited to the use of compression stockings, with occasional attempts to perform venous bypasses, valve reconstruction, or the radical Linton procedure (subfascial ligation of perforator veins), but all of these interventions had high rates of morbidity and low rates of success.

The first big step was the duplex evaluation, which greatly improved the sensitivity and specificity for the diagnosis of deep vein thrombosis (DVT), as well as reduced costs. The progress continued with improved diagnosis of superficial reflux and the mapping of incompetent veins. This greatly improved the results of high ligations and stripping and helped considerably
with the results of ultrasound-guided sclerotherapy for the chemical ablation of incompetent superficial veins. Newer techniques that use thermal ablation and improved methods of chemical ablation have furthered the improvement.

Deep venous disease treatment has also undergone a renaissance with the use of similar minimally invasive techniques, such as angioplasty, stenting, and intravascular ultrasound (IVUS).

**Epidemiology**

The prevalence of varicose veins in the Western population is greater than 20%, with about 5% of patients having the sequelae of venous edema, skin changes, or ulceration. Approximately 0.5% of patients have active ulceration. The incidence is higher in women than in men.

**ANATOMY**

**Superficial Veins**

The superficial system is defined as the portion of veins that lie between the skin and deep fascia that covers the muscles. The main veins of the superficial system are the great saphenous vein (GSV) and the small saphenous vein (SSV) (Figs. 55-1 and 55-2). The GSV starts in the foot, anterior to the medial malleolus, and courses up the medial leg to the saphenofemoral junction in the groin. The GSV runs in the saphenous sheath, which is formed from the deep fascia. In the calf, major tributaries of the GSV are the anterior and posterior arch veins. In the thigh, major tributaries of the GSV are the anterior and posterior accessory saphenous veins. The anterior accessory saphenous vein (AASV) typically joins the GSV at the saphenofemoral junction (SFJ). The SSV starts posterior to the lateral malleolus and runs in the saphenous sheath to the popliteal fossa. The termination point for the SSV is highly variable. It sometimes ends in the popliteal fossa joining the popliteal vein, or through thigh extensions ending in the thigh underneath the gluteus maximus muscle, or it courses medially and joins the GSV, also called the vein of Giacomini.
FIGURE 55-1 Schematic of the superficial veins, anterior view, which depicts the great saphenous vein. Ant, anterior; Post, posterior.
Deep Veins

The deep system includes all the veins beneath the deep fascia (Fig. 55-3). The peroneal, anterior, and posterior tibial veins are usually paired veins that course along the arteries of the same name. The posterior tibial vein joins the peroneal vein to form the tibioperoneal trunk, which joins the anterior tibial vein to form the popliteal vein in the popliteal fossa. This is paired with the popliteal artery. As the popliteal vein courses through the hunterian canal, it becomes the femoral vein (formerly known by the somewhat confusing term of “superficial” femoral vein), which is paired with the superficial femoral artery. This is one of the few times the corresponding vein and artery have different names. The femoral vein joins the profunda femoral vein to form the common femoral vein in the groin. Once the common femoral vein passes under the inguinal ligament, it becomes the external iliac vein, which joins the internal iliac vein to form the common iliac vein. The right and left common iliac veins join to form the inferior vena cava.
Perforators and Pelvic Connections

Perforating veins connect the superficial and deep systems and penetrate through the deep fascia. There are estimated to be over 150 such connections. The important perforators connect along the medial calf and thigh. Some perforating veins connect directly to the GSV and others to the posterior arch vein. There are additional important connections between the pelvic veins and the superficial venous system that sometimes lead to leg vein symptoms. These connections come from the round ligament, obturator, gluteal, and hemorrhoidal veins.

Venous Valves

Valves are critical to the healthy functioning of the venous system. Through normal opening and closing of the valves, blood is directed back to the heart.
In diseased veins, valves may not close properly, resulting in backward blood flow and pooling.

**DIAGNOSTIC EVALUATION**

**History**

The presenting complaints from patients with venous disease can range from concerns that are strictly cosmetic, with underlying psychological impact, to many vague symptoms such as pain, aching, tingling, fatigue, and heaviness, to more severe symptoms such as edema, inflammation, and ulceration (*Table 55-1*). In general, symptoms improve with rest and leg elevation and are worsened by heat and long periods of standing or sitting.

*Table 55-1 Spectrum of Chronic Venous Insufficiency*

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Leg pain, aching, or heaviness</td>
</tr>
<tr>
<td>Leg cramps or tingling</td>
</tr>
<tr>
<td>Leg swelling or feeling of swelling</td>
</tr>
<tr>
<td>Itching</td>
</tr>
<tr>
<td>Restless legs</td>
</tr>
<tr>
<td>Varicose veins</td>
</tr>
<tr>
<td>Spider veins</td>
</tr>
<tr>
<td>Blood clots</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Ulcers</td>
</tr>
</tbody>
</table>

Obtaining a thorough past history of thromboembolic events and thrombophilia as well as family history of the same is important (*Table 55-2*). Medications, particularly birth control and hormone replacement, can also increase risks of thromboembolic events. Past treatment of venous problems should be elicited.

*Table 55-2 Risk Factors*
**Physical Exam**

The physical exam should focus on signs and symptoms of venous insufficiency. The patient should be standing while being carefully examined visually and by palpation for evidence of bulging veins. Any evidence of scars from previous procedures, edema, inflammation, pigmentation, and past or present ulceration should be noted.

**Duplex Scanning**

**Deep Vein**

Duplex examination has been a major advancement in venous disease, particularly in examination for DVT. The exam can be done with the patient supine. Careful B-mode imaging with visualization of the entire vein and wall-to-wall opposition along the entire deep venous system can rule out the presence of DVT, with a very low false-negative rate. The superficial system can be examined similarly or during the standing portion of the exam.

**Iliac Inferior Vena Cava Obstruction**

If imaging of the iliac veins or inferior vena cava (IVC) is to be done, the patient should be instructed to have nothing by mouth (npo) for approximately 8 hours before the exam. Compression is not available, so careful visualization and good color flow are required to make the diagnosis.

**Reflux**
The exam to look for reflux should be done with the patient standing. The exam is conducted using a pulsed wave Doppler and 4- to 7-MHz probe. This provides enough pressure to close the valves. The superficial and deep systems are analyzed for spontaneous flow and augmented flow. In the measurement of any retrograde flow, incompetence is defined as retrograde flow greater than 500 milliseconds.

**Perforator and Pelvic Connections**

Occasionally, pathologic connections between the pelvic veins and leg veins occur. In particular, round ligament, pudendal, obturator foramen, abdominal wall, sciatic foramen, and gluteal veins can connect to the leg. These can lead to pathology in the leg. Patients may present with varicosities of the vulva or scrotum. In men, testicular varicosities can lead to infertility, and in women, ovarian varicosities can lead to pelvic congestion syndrome. Patients with these symptoms may need pelvic sonography with measurements of the gonadal veins. Veins larger than 5 mm are considered to be abnormal.

**Plethysmography**

The clinical practice guidelines of the Society for Vascular Surgery and American Venous Forum suggest that venous plethysmography be used selectively for the evaluation of patients with simple varicose veins (CEAP [clinical, etiologic, anatomic, pathophysiologic] class C₂) or advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C₃ to C₆).³

**Other Imaging**

The utility of duplex imaging of the iliac veins and the IVC can be somewhat limited. Bowel gas and body habitus can obstruct views. Occasionally, additional types of imaging may be required to identify obstruction in the iliac veins and IVC. Great strides have been made in computed tomography (CT) and magnetic resonance (MR) venography, resulting in the capability of identifying obstruction in these vessels. Traditional venography is still in use, especially when the likelihood of intervention is high. One of the major new
advances in deep venous evaluation is IVUS. This provides an ultrasound image from inside the vein that allows accurate calculation of the area and visualization of vein wall thickness and any trabeculations, frozen valves, and external compression.

**Laboratory Tests**

Routine laboratory tests are not usually required for cardiovascular disease (CVD) patients. If thrombophilia is suspected, a workup should be done to identify possible causes. A history of recurrent DVT, DVT in otherwise young healthy patients, or multiple miscarriages or strong family history should raise suspicion. Biopsy of recalcitrant ulcers may uncover an unusual etiology such as neoplasia, pyoderma gangrenosum, hydroxyurea, rheumatoid arthritis, or vasculitis.

**CEAP CLASSIFICATION**

The American Venous Forum developed the CEAP classification system for venous disease, with the name referring to clinical signs of venous disease (C), etiology (E), anatomy (A), and pathophysiology (P).

**Clinical Score**

The clinical score is determined based on the highest level of symptoms:

- \( C_0 \): no symptoms
- \( C_1 \): telangiectasias
- \( C_2 \): varicose veins
- \( C_3 \): edema from the venous insufficiency
- \( C_4 \): skin changes related to venous insufficiency
  - \( C_{4a} \): skin changes limited to inflammation
  - \( C_{4b} \): presence of lipodermatosclerosis
- \( C_5 \): history of venous ulceration but no active ulceration
C₆: active ulceration

**Etiologic Score**

The cause of the venous insufficiency is classified as congenital (Eₖ), primary (Eₚ), or secondary (Eₛ). Secondary generally refers to postthrombotic.

**Anatomic Score**

The anatomic classification identifies the type of veins affected by disease: superficial (Aₛ), perforator (Aₚ), or deep (Aₐ) veins. The anatomic score can further reflect which segment of each system is affected by disease, for example, the GSV above or below the knee (superficial veins), the internal iliac vein, the femoral vein, or the popliteal vein (deep veins), or the thigh or calf perforator veins.

**Pathophysiology Score**

The pathophysiology of venous disease can be labeled as reflux (Pᵣ), obstruction (Pₒ), or both.

**OUTCOME ASSESSMENT**

**Venous Clinical Severity Score**

The Venous Clinical Severity Score (VCSS) system was developed as an outcome assessment instrument for evaluating changes in a person’s disease severity over time and response to treatment. The score is based on the presence of pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, active ulcers (number, duration, and size), and use of compression therapy. As noted by Vasquez et al, the revised VCSS, together with the CEAP, “provides a standard clinical language to report and compare differing approaches to CVD management.”
Quality-of-Life Assessment Tools

As noted in the practice guidelines of the American Venous Forum, there are several quality-of-life assessment tools designed specifically for use with venous diseases. Frequently used validated instruments include the Venous Insufficiency Epidemiologic and Economic Study of Quality of Life (VEINES-QOL/Sym) questionnaire scale, the Chronic Venous Insufficiency Questionnaire (CIVIQ), the Aberdeen Varicose Vein Questionnaire (AVVQ), and the Charing Cross Venous Ulceration Questionnaire.  

TREATMENT

Indications

The decision to treat involves a thorough discussion with the patient on the goals of treatment and realistic expectations of the results. Many patients present primarily with cosmetic concerns, while some may complain of symptoms and complications of venous disease. These symptoms include leg heaviness and fatigue, swelling, pain along the bulging veins, pruritus, and restlessness. Because these symptoms are very nonspecific, other possible causes of these symptoms should be discussed. Patients also should be advised that some of these symptoms may not improve with treatment. Patients also may exhibit other symptoms that are more obviously related to venous disease, such as superficial phlebitis, stasis dermatitis, lipodermatosclerosis, atrophie blanche, and venous ulceration.

Medical Treatment

There are a few drugs that show some promise in the treatment of symptoms related to venous insufficiency, including horse chestnut seed extract; flavonoids such as rutosides, diosmin, and hesperidin; micronized purified flavonoid fraction (MPFF); and other plant extracts, such as French maritime pine bark extract. Synthetic products such as calcium dobesilate, naftazone, and benzarone have shown some promise in treatment as well. These are venoactive drugs that improve venous tone and capillary permeability. Flavonoids appear to reduce inflammation and edema.
Pentoxifylline and MPFF have been shown in several studies to help with healing ulcers. In the clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum, Gloviczki et al\textsuperscript{3} discuss the available evidence for these various therapies.

**Compression**

Compression therapy has been a mainstay of treatment for venous insufficiency. For $C_1$ and $C_2$ disease, support hosiery ($<20\text{ mm Hg}$) has been shown to provide adequate treatment and possibly better compliance in comparison to compression stockings ($>20\text{ mm Hg}$). For more advanced disease ($C_3$-$C_6$), heavier compression ($20\text{ mm Hg}$ or greater) may be needed. Venous ulcers heal just as well with compression therapy alone as with surgery. Recurrence is reduced with corrective surgery. For intractable edema and/or ulceration, compression pumps may be necessary.

**Superficial Disease**

The treatment of superficial venous disease has changed dramatically during the past decade. High ligation and stripping (HL/stripping) was considered the gold standard but now has been replaced by endovenous thermal ablation either by radiofrequency (RF) or laser (EVLT). These can be done on the GSV, SSV, or an accessory vein as long as the veins are straight enough and not too close to the skin as to risk a burn. RF and EVLT have shown equivalent results to HL/stripping with quicker recovery and better quality-of-life scores.\textsuperscript{3,11} The difference between the thermal techniques of RF and EVLT has been minimal when comparing results, with slightly higher occlusion rates for EVLT and slightly better pain scores with RF. These numbers may have improved with both techniques because RF results have improved with the newer catheter designs and pain scores have improved with EVLT using longer wavelength lasers.

Superficial varicosities that are tortuous or too close to the skin can be treated by either stab phlebectomy or chemical ablation with sclerotherapy. Chemical ablation has also gone through dramatic improvements with the use of foam sclerotherapy. This is done by mixing a gas with a detergent sclerosant and agitating between 2 syringes, usually with a 3-way stopcock,
forming a foam solution. Most physicians use room air for the gas, but some prefer the use of carbon dioxide or a combination of carbon dioxide and oxygen. This has been shown in some studies to reduce the risk of neurologic events that have been reported with the use of foam. Studies comparing the difference between the 2 methods show slightly improved results early with phlebectomy and equivalency at 1 year. Longer term studies show a tendency toward more recurrences with sclerotherapy than phlebectomy.

Newer techniques have come to market that are allowing saphenous ablation without heat so that there is less discomfort for the patient and thus tumescent anesthesia is not required. The first technique is mechanical chemical ablation (MOCA or Clarivein). This uses a combination of a mechanical injury using a wire to damage the endothelium of the vein combined with sclerotherapy. This technique has shown comparable results to the thermal techniques in studies limiting the size of the vein generally to less than 12 mm. Recently, the US Food and Drug Administration (FDA) approved and released in the United States the polidocanol microfoam (PEM or Varithena). This is used as a chemical ablation similar to sclerotherapy introduced through a catheter. Patient-reported results have been equivalent to the thermal techniques, with ultrasound imaging showing slightly lower closures. The newest technique to get FDA approval is cyanoacrylate (glue or VenaSeal). The results from glue showed noninferiority to RF.12

Whether these new “nontumescent” techniques replace the thermal methods will depend on the long-term results and, of course, costs.13

**Perforators**

Treatment of perforator veins has also come a long way from the old Linton subfascial perforator ligation and subfascial endoscopic perforator ligation. Now with the use of ultrasound guidance, less invasive methods are available using sclerotherapy and thermal and ligation techniques to treat incompetent veins.14 Ultrasound-guided sclerotherapy using liquid solutions had the limitation of requiring direct injection into the perforator to assure treatment. This carried risks of arterial injection, since all perforators are accompanied by an artery, and a greater risk of DVT, because perforators sometimes empty directly into smaller deep veins such as the tibial veins. The use of foam has allowed remote injection and following of the sclerosant due to the visualization of foam with ultrasonography. This has led to greater use of
ultrasound-guided foam sclerotherapy for the treatment of incompetent perforator veins.

Ultrasound has also allowed thermal methods to be used for the treatment of incompetent perforators (IP). By directly accessing the perforator vein, either a laser fiber or RF device can be placed into the vein, and after tumescent anesthesia is placed around the vein, heat can be applied that ablates the vein. The FDA has only approved the RF Seps device (Medtronic, Dublin, Ireland) for this procedure, and it is primarily used in intractable venous ulceration.

Ligation can also be done by marking with an ultrasound to limit the size of the incision and cut directly down on the IP and ligate divide between ligatures. This maybe more difficult in advanced disease because of the skin changes.

**Deep Vein Reflux**

Deep venous valve failure can be a primary disorder, but much more commonly, it is secondary to DVT. Treatment has been primarily supportive with compression. Attempts at valve reconstructive surgery have been largely ineffective with a high morbidity.

**Deep Venous Obstruction**

Deep venous obstruction has been shown to be an underdiagnosed problem leading to symptoms of venous insufficiency. Risk factors include female gender, history of DVT, particularly proximal, and deep venous reflux on ultrasound examination. Diagnosis can be obtained by ultrasound, CT venography, MR venography, or standard venography, but the highest sensitivity is with IVUS. Pathologic venous occlusive disease is determined by the area calculation for the IVC, common iliac vein, and external iliac vein. An area stenosis of 50% in a symptomatic patient is considered to be pathologic and in need of angioplasty and stent. The treatment of the femoral vein and below is more controversial. The collaterals through the profunda femoral vein usually provide enough blood flow to keep the patient asymptomatic. However, now some think opening the occluded femoral and popliteal vein segments with angioplasty will increase flow and help maintain the stented iliacs and further decongest the calf.
Pelvic Varicosities

Varicosities involving the pelvic area can also extend down on the leg. Connections between the pelvis can be treated with ultrasound-guided sclerotherapy. If the patient has pelvic symptoms, then treatment of incompetent pelvic veins with embolization therapy can be considered. Gonadal vein contrast venography followed by coil embolization and/or sclerotherapy of the pelvic varicosities can be carried out.

ACKNOWLEDGMENT

The authors thank Victoria J. White for editorial assistance with this chapter.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. The prevalence of varicose veins in the West is:
   A. <1%
   B. 1%-5%
   C. 5%-10%
   D. >20%

2. Which of the following statements is correct?
   A. The great saphenous vein (GSV) joins the popliteal vein to form the femoral vein.
   B. The small saphenous vein (SSV) is called the GSV above the knee.
   C. The GSV joins the femoral vein to form the common femoral vein.
   D. The GSV and SSV are deep veins of the lower extremities.
3. What is the best initial diagnostic test for chronic venous insufficiency (CVI)?
   A. Magnetic resonance venogram
   B. Duplex ultrasound
   C. Computed tomography venogram
   D. Plethysmography

4. To diagnose CVI with duplex ultrasound, the patient should be lying down.
   A. True
   B. False

5. Thermal ablation (radiofrequency or endovenous laser therapy) is best for which of the following?
   A. Deep veins
   B. Tortuous tributaries
   C. GSV or SSV
   D. For veins close to the skin

ANSWERS

1. D
2. C
3. B
4. B
5. C
Endovascular Therapies for Abdominal Aortic Aneurysm

Ehrin J. Armstrong
John R. Laird

INTRODUCTION

Rupture of abdominal aortic aneurysms (AAAs) accounts for over 15,000 deaths per year in the United States and is the 10th leading cause of death in men older than 55 years of age (Fig. 56-1). Out-of-hospital AAA rupture is associated with a mortality of 80% to 90%. Most deaths are preventable by the early diagnosis and treatment of AAA, and as a result, more than 60,000 surgical or endovascular procedures for AAA are performed annually in the United States. Despite the excellent results of open surgical repair for the prevention of aneurysm rupture, this procedure is associated with significant morbidity and mortality, especially in high-risk patients. Endovascular aneurysm repair (EVAR), which was developed as a less invasive alternative to open surgical repair, is gaining widespread acceptance and is now performed in approximately 80% of elective aneurysm repairs. This chapter reviews the epidemiology, technical aspects, outcomes, and complications of EVAR for the treatment asymptomatic and symptomatic AAA.
FIGURE 56-1 Ruptured abdominal aortic aneurysm. Noncontrast computed tomography scan of a ruptured abdominal aortic aneurysm with extensive retroperitoneal hemorrhage.

EPIDEMIOLOGY AND NATURAL HISTORY OF ABDOMINAL AORTIC ANEURYSM

The incidence of AAA increases with age. Approximately 2.6% of men and 0.5% of women between 45 and 54 years of age have an AAA, and by 75 to 84 years of age, 19.8% of men and 5.2% of women have an AAA.\(^1\) Men are affected 4 to 6 times more frequently than women.\(^2\) AAA is also more common in Caucasian patients than in black, Hispanic, or Asian patients.\(^3\)

Approximately 15% of patients with AAA have a family history of AAA.\(^4\) Because the pathogenesis of AAA is thought to be multifactorial, including disorders of enzymes regulating connective tissue homeostasis, approximately 5% of patients with an AAA have a concomitant thoracic aneurysm and approximately 15% have either a femoral artery aneurysm or a popliteal aneurysm.\(^5\) Synchronous peripheral aneurysms are more common in
men, while synchronous thoracic aneurysms may be more common in women.\textsuperscript{6} Approximately 10\% of AAAs are juxtarenal, and iliac artery involvement occurs in up to 22\% of AAAs.

Patients with AAAs often have significant medical and cardiac comorbidities. Coronary artery disease is found in 40\% to 70\% of patients with AAAs, with evidence of prior myocardial infarction in up to 46\% of patients.\textsuperscript{7} Cerebrovascular disease is present in 25\% of patients, claudication is present in 28\%,\textsuperscript{7} hypertension is present in 55\%, and chronic obstructive lung disease is present in approximately 20\% to 25\%. A history of blunt abdominal trauma is occasionally found; this can lead to both true aneurysms and pseudoaneurysms of the abdominal aorta. Most studies have shown that AAAs are approximately 6 to 7 times more common in smokers, whereas elevated high-density lipoprotein cholesterol (HDL-C) may be protective.\textsuperscript{1} Furthermore, 23\% of patients with a AAA have some form of cancer.\textsuperscript{7} Consistent with these broad comorbidities, approximately 67\% of patients with AAAs die of a cardiovascular etiology.

The aneurysm growth rate, wall tension, and risk of rupture are dependent on aneurysm diameter. Aneurysms less than 5.5 cm in diameter grow at a median rate of 0.2 to 0.3 cm per year, whereas those greater than 5 to 6 cm expand at rates up to 3 cm per year.\textsuperscript{8} The strongest predictor of AAA rupture is aneurysm size. Aneurysms between 5.5 and 5.9 cm in diameter have an estimated annual risk of rupture of 9.4\%, those between 6.0 and 6.9 cm in diameter have an estimated annual risk of rupture of 10.2\%, and those greater than 7 cm have an estimated annual rate of rupture of 32.5\%.\textsuperscript{9} Eccentric or saccular aneurysms have considerably increased wall stress and are thought to have greater rupture risk than fusiform AAA. Patients with chronic obstructive pulmonary disease or asthma may also have a higher risk of rupture, possibly related to allergic inflammation and/or the concomitant use of bronchodilators and steroids.\textsuperscript{10} Patient age and family history of AAA are not consistent independent predictors of rupture.

**TYPES OF ABDOMINAL AORTIC ANEURYSMS**

True aortic aneurysms result from the dilation of the intima, media, and
adventitial layers of the aorta. Relatively uniform and concentric enlargement results in fusiform aneurysm formation. Saccular aneurysms result from eccentric enlargement of the aorta. As previously noted, saccular aneurysms have less uniform wall stress distribution and thus an increased risk of rupture.

Although traditionally attributed to atherosclerosis, AAAs more accurately can be attributed to a degenerative process in the arterial wall. Most AAAs result from the imbalance of connective tissue formation and degradation. Some congenital disorders such as Marfan syndrome and Ehlers-Danlos syndrome predispose to aneurysm development. Inflammatory aortitis is a rare cause of AAA formation. Pseudoaneurysms generally result from abdominal trauma or may occur at a graft anastomosis following previous aortic surgery.

Inflammatory AAAs are a subset (5%-10%) of AAAs, which commonly present as abdominal or flank pain, fever, and constitutional symptoms. On computed tomography (CT), these AAAs usually have a “halo” sign with inflammatory adventitial tissue predominately anterior and lateral to the AAA. Due to the extensive inflammation and fibrosis of surrounding structures, including the duodenum, vena cava, left renal vein, and ureters, an endovascular approach may be preferred.

Mycotic AAAs are fortunately rare. Most commonly, *Salmonella* species or *Staphylococcus aureus* are the etiologic bacteria, although fungal species or other bacteria are sometimes causative. Infected AAAs pose a significant risk to the patient and present many therapeutic challenges. The traditional surgical approach is ligation of the aorta, resection of the infected aneurysm, and extra-anatomic bypass. Antibiotic-soaked grafts or homografts may play a role. There have been case reports and small series involving the endovascular treatment of mycotic thoracic and AAAs. Although successful outcomes have been demonstrated in a few cases, the potential for infection of the endoprosthesis raises significant concerns regarding this treatment approach. Aortoenteric fistulae from AAAs have also been successfully excluded using an endograft.

**MEDICAL THERAPY OF ABDOMINAL AORTIC ANEURYSMS**
Although the basic understanding of the inflammatory and dynamic nature of AAAs has significantly advanced, there is as of yet no effective medical treatment for limiting the expansion of AAA. Based on the premise that aneurysmal growth is dependent in part on the $\delta P/\delta t$ of the aortic pulsation, $\beta$-blockers have been studied in randomized trials but have not shown any reduction in AAA growth rate or mortality.\textsuperscript{15} Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce the rate of aneurysm expansion in animal models. Some observational studies have suggested an association between ACE inhibitors and a reduced risk of aneurysm rupture,\textsuperscript{16} whereas other studies have suggested accelerated aneurysm expansion with ACE inhibitors.\textsuperscript{17} Two randomized trials of ACE inhibitors or angiotensin receptor blockers in small aneurysms are currently examining this question.\textsuperscript{18,19}

Efforts to reduce the activity of the matrix metalloproteinase (MMP) enzymes with doxycycline in patients with AAA have provided mixed results. Small pilot studies demonstrated that doxycycline reduces the levels of MMP-9 and C-reactive protein (CRP).\textsuperscript{20,21} However, a large clinical trial of doxycycline did not show any benefit in reduction of aneurysm expansion.\textsuperscript{22} Similarly, statin medications have been studied for a possible benefit in stabilization of aneurysm size by pleiotropic effects on reduction of MMP activity. Although observational studies have suggested a possible benefit of statin therapy in reducing aneurysm expansion, meta-analyses have not found a consistent benefit.\textsuperscript{23}

Despite the current lack of an adequate medical treatment for slowing the rate of AAA expansion, all patients with AAA should receive appropriate medical therapy for cardiovascular risk reduction, including smoking cessation, statin therapy, and antiplatelet therapy. Smoking cessation is associated with improved mortality after AAA repair, and smoking cessation may slow the expansion of a preexisting aneurysm.\textsuperscript{24} Treatment with a statin is associated with improved long-term survival after AAA repair, likely due to a reduction in cardiovascular mortality.\textsuperscript{25,26} Antiplatelet therapy may limit thrombus formation within the aneurysm sac, and aspirin therapy is recommended for all patients with AAA for reduction of other cardiovascular events.
REPAIR

The only proven therapy for reduction in mortality from AAA rupture is mechanical aneurysm exclusion or sealing. Elective open AAA repair is associated with a mortality of 2.7% to 7% and may be higher depending on patient comorbidities. Thus, the clinician is faced with balancing the interventional risk of AAA repair with that of continued observation and threat of rupture.

Several trials have been performed to determine the size of an AAA that optimizes the trade-off between risk of AAA rupture and perioperative mortality. These studies have suggested that aneurysms less than 5.5 cm that grow at rates of less than 0.7 cm per 6 months or 1 cm per 12 months may be safely observed. Based on the results of the United Kingdom Small Aneurysm Trial and the Aneurysm Detection and Management Trial, surgery can be reserved for aneurysms larger than 5.5 cm without increasing overall mortality or operative risk.27,28 However, these studies are prefaced on routine AAA surveillance and close patient follow-up and were performed with open surgical repair rather than widespread availability of endovascular techniques for exclusion of the aneurysm. However, one trial (the Positive Impact of Endovascular Options for Treating Aneurysms Early [PIVOTAL]) found no difference in outcomes between endovascular repair and ultrasound surveillance among patients with aneurysms measuring 4 to 5 cm.29

Despite the equivalent overall survival between surveillance and early repair for aneurysms less than 5.5 cm, caution must be used in extending these criteria to underrepresented study groups. Because women have smaller abdominal aortas than men, the criteria for diagnosis of an AAA as well as for intervention for an AAA may not be accurately applied to both genders. Some studies have suggested that a 5.0-cm diameter AAA in women has an equivalent rupture risk to that of a 6.0-cm diameter AAA in men.30 Therefore, the application of a single measurement that is not gender specific or referenced to the patient’s height may not be entirely valid.

Patients with symptomatic AAAs usually present with abdominal pain that may radiate to the flank or groin, abdominal tenderness to palpation, low back pain, or hemodynamic instability related to the retroperitoneal hemorrhage. In addition to the risk of rupture, aneurysms can be associated with a significant risk of embolic complications. Due to the presence of
thrombus or atherosclerotic material within the aneurysm sac, patients may present with evidence of atheroemboli (ie, livedo reticularis), acute renal failure, “blue toe syndrome,” or symptoms of lower extremity arterial insufficiency. Enlargement of the AAA can also cause a mass effect and obstructive symptoms. Obstructive uropathy can occur and is thought to be more common in inflammatory AAAs.

Contained or frank rupture of an AAA demands emergency intervention. Classically, there is severe pain, abdominal tenderness, and shock. The pain is generally sudden in onset and constant, and it may diffusely involve the abdomen or radiate to the flanks, groin, or legs. Occasionally, a ruptured AAA presents as a gastrointestinal hemorrhage or aortocaval fistula. Expeditious diagnosis with an imaging study (usually CT) or direct transfer to the interventional suite or operating room is necessary to reduce the attendant morbidity and mortality of a ruptured AAA.

In summary, the criteria for intervention on an AAA include an aneurysm diameter greater than 5.5 cm in men (perhaps 5.0 cm in women), rapid expansion of an aneurysm (>0.5-0.7 cm/6 months or 1 cm/12 months), or symptomatic aneurysm with either distal embolization from an AAA, aneurysmal mass effect, threatened rupture, or frank rupture.

### OUTCOMES OF ENDOVASCULAR ANEURYSM REPAIR FOR ASYMPTOMATIC ANEURYSMS

The goal of EVAR is to prevent aneurysm rupture and reduce the morbidity and mortality associated with exclusion of the AAA. Successful EVAR exclusion is associated with a progressive reduction in aneurysmal volume at a rate of approximately 3 mL per month and reduction in aneurysm diameter of 4 to 6 mm per year.\(^\text{31}\)

Four randomized trials have compared the outcomes of EVAR to open AAA repair (Table 56-1).\(^\text{32-35}\) Each of these trials enrolled patients with asymptomatic AAA who were candidates for endovascular or open repair. All 4 studies reported lower 30-day mortality with EVAR, with 30-day mortality rates ranging from 0.5% to 1.2% for EVAR and 1.3% to 4.7% for
open surgery. A subsequent meta-analysis found that EVAR is associated with significantly lower perioperative mortality compared with open surgical repair. The long-term mortality in each of the studies did not demonstrate a benefit of EVAR over open AAA repair. These findings may be a result of several factors, most significantly the competing risk of other comorbidities. However, concern has also been raised regarding the long-term implications of placing an endograft, as studies with longer-term follow-up have demonstrated an increased rate of late (>5 years) need for re-intervention and late graft failure. As a result, longer-term surveillance studies remain necessary to confirm the safety and long-term effectiveness of new devices.

Table 56-1 Randomized Trials of Endovascular Aneurysm Repair (EVAR) Versus Open Surgery for Asymptomatic Abdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Year</th>
<th>No. of Patients</th>
<th>30-Day Mortality</th>
<th>Long-Term Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DREAM</td>
<td>2004</td>
<td>345</td>
<td>1.2% EVAR 4.6% open</td>
<td>31.1% EVAR 30.1% open (6 years)</td>
</tr>
<tr>
<td>EVAR-1</td>
<td>2004</td>
<td>1082</td>
<td>1.7% EVAR 4.7% open</td>
<td>26% EVAR 29% open (4 years)</td>
</tr>
<tr>
<td>OVER</td>
<td>2009</td>
<td>881</td>
<td>0.5% EVAR 3.0% open</td>
<td>No difference at mean of 5.2 years</td>
</tr>
<tr>
<td>ACE</td>
<td>2009</td>
<td>316</td>
<td>0.6% EVAR 1.3% open (in-hospital)</td>
<td>4.1% EVAR 6.8% open (1 year)</td>
</tr>
</tbody>
</table>

Approximately 20% to 40% of patients (approximately 10%-15% per year) undergoing EVAR require subsequent re-intervention for a variety of indications, including endoleak, stent migration, graft limb occlusion, or infection. Late conversion of EVAR to open repair is necessary in approximately 2% to 3% of cases, although the frequency of late conversion may be higher in patients with larger AAAs. Open conversion often requires a more extensive operation in a higher risk patient population and thus carries a 10% to 20% mortality rate. The incidence of late rupture of an AAA after EVAR is thought to be 0.5% at 3 to 4 years and is perhaps more frequent after use of a tube graft. Rupture after EVAR carries a mortality rate similar to native AAA rupture.
ANEURYSM REPAIR FOR RUPTURED ABDOMINAL AORTIC ANEURYSMS

Despite improvements in identification and protocols for immediate treatment, ruptured AAA remains associated with an in-hospital mortality rate of 30% to 50%. Because EVAR is less invasive and may be performed using local anesthesia, the application of EVAR to acutely ill patients with ruptured AAA may reduce in-hospital mortality and minimize complications. A frequently used technique that may also improve outcomes is the immediate percutaneous placement of an aortic occlusion balloon; placement of such a balloon provides time for resuscitation efforts while a definitive decision can be made regarding EVAR versus open surgical repair.\(^4^1\)

A number of observational studies have suggested a mortality benefit of EVAR over open surgery for patients with ruptured AAA. These studies have estimated mortality rates with EVAR of 16% to 30% and of 34% to 44% for open surgery.\(^4^2\) However, criticisms of such studies include the inherent selection bias of EVAR for less critically ill patients and patients with anatomically favorable characteristics.

Compared to the observational literature, randomized studies have not demonstrated a benefit of EVAR over open surgery for ruptured AAA. The largest of these studies was the multicenter IMPROVE trial, which was conducted in the United Kingdom and Canada.\(^4^3\),\(^4^4\) In that study, 613 patients with a presumed ruptured AAA were randomized to a strategy of EVAR versus open surgical repair. At 30 days and 1 year, there was no difference in mortality between the 2 groups. However, several aspects of the study design should be considered. Most importantly, randomization was performed prior to imaging, and as a result, only 64% of patients were felt to have anatomy suitable for EVAR. Additionally, 8.9% of patients were found based on imaging and other evaluation to have a diagnosis other than ruptured AAA. In an as-treated analysis, patients treated with EVAR had numerically lower mortality (25% vs 38%). An additional analysis found that patients treated with local anesthesia had significantly lower 30-day mortality.\(^4^5\)

Based on the available data, rapid imaging can help identify patients with ruptured AAA who are anatomically appropriate for EVAR, and such patients should be approached with an “endovascular first” strategy using
local anesthesia whenever feasible. This approach may help minimize the hemodynamic stress associated with anesthesia and also minimize the postoperative complications of open surgical repair. Recent analyses using large registry data have suggested that the majority of benefit for EVAR in ruptured AAA is in low- to moderate-risk patients, whereas open surgery and EVAR have a similar benefit in high-risk ruptures. However, several barriers remain to implementation of such a strategy outside of specialized centers, including the ability to have EVAR available for unexpected anatomy and rapid availability of an endovascular suite.

ANATOMIC DEFINITIONS AND CONSIDERATIONS FOR ENDOVASCULAR ANEURYSM REPAIR

Aneurysm morphology and the status of the iliac and femoral access vessels dictate whether a patient is a candidate for EVAR. Historically, only 50% to 60% of patients with infrarenal AAAs had suitable anatomy for an endograft. Limitations of EVAR include the length of the infrarenal aortic neck; the diameter of the aneurysm neck; the location of the mesenteric arteries, particularly the celiac axis and superior mesenteric artery; and the proximal neck angulation. Distally, anatomic concerns include the size of the iliofemoral arteries, the presence or absence of calcification, the tortuosity of these arteries, and whether there is aneurysmal dilation of the iliac arteries. Successful exclusion of a common iliac artery aneurysm may require embolization of the internal iliac artery and extension of the endograft into the external iliac artery. In recent years, the development of newer endografts and branched and fenestrated endografts has addressed many of these technical limitations in the endovascular treatment of AAA, and as a result, approximately 80% of AAAs are treated with EVAR.

Aneurysm Neck

The aneurysm neck is the length from the most inferior (main) renal artery to the onset of the aneurysm. Most endografts that are commercially available in the United States are designed for suprarenal fixation, but an adequate seal
zone is necessary to exclude the aneurysm below the renal arteries. The maximal diameter of the nonaneurysmal aortic neck that can be sealed is endograft dependent. The device should be oversized by 10% to 20%. The minimal neck length tolerated is also device specific, although generally for infrarenal fixation, the neck length should ideally be at least 15 mm, especially if angulated (Fig. 56-2). An exception to this is the Ovation device from TriVascular (Santa Rosa, CA), which, due to its novel sealing mechanism, is indicated for EVAR regardless of aneurysm neck length. The angle between the suprarenal aorta and the infrarenal neck (α) and the angle of the flow axis between the infrarenal neck and the body of the aneurysm (β), in which the flow axis is the axis (line) between the distal neck/proximal aneurysm to the aortic bifurcation, should also be measured, because extreme neck angulation may limit successful aneurysm exclusion (Fig. 56-3). Calcification and thrombus of the proximal neck should also be noted, because both of these incrementally add to the morphologic complexity of EVAR.

**FIGURE 56-2** Short aneurysm neck. Left panel: Abdominal aortic aneurysm with short infrarenal aortic neck and diminished flow in the right iliac artery due to iliac
In summary, the neck length should ideally be greater than 15 mm, the neck diameter should be less than 32 mm, α or β should be greater than 150°, and the degree of calcification or thrombus greater than 2 mm thick should be less than 25% of the neck circumference. The risk of adverse outcome after EVAR is directly related to the proximal aortic neck angulation. While modern endografts have in large part addressed the anatomic limitations, studies investigating the on-label versus off-label use of endografts have found that off-label use is associated with a higher risk of long-term complications and need for re-intervention.\textsuperscript{47}

\textbf{Arterial Branches of the Abdominal Aorta}
To anticipate and prevent type II endoleak, it is also important to assess for branch arteries off the aneurysm. The lack of patent lumbar arteries, inferior mesenteric artery, or accessory renal artery off the aneurysm sac should reduce the chance of type II endoleak. However, in current practice, these branches are excluded even if patent, and pre-intervention embolization is not generally considered necessary.

**Iliac Arteries**

The anatomy of the iliac arteries is important with regard to the deliverability and proper sealing of endografts. Preoperative assessment should include measurements of the diameter of the common and external iliac arteries and length of the iliac landing zone. The external iliac artery generally needs to be at least 6 to 6.5 mm in diameter to allow passage of the majority of commercially available devices. The iliac arteries should also be evaluated for the presence of ectasia, stenosis, calcification, and tortuosity. Aortoiliac tortuosity and calcification affect device deliverability and are associated with a more complex EVAR procedure. Maintenance of patency of at least 1 of the internal iliac (hypogastric) arteries is important to preserve pelvic blood flow and to prevent buttock claudication and intestinal ischemia (see below).

**CURRENT ENDOVASCULAR ABDOMINAL AORTIC ANEURYSM DEVICES**

In 1999, the AneuRx device (Medtronic, Santa Rosa, CA) and the AnCure device (Guidant Endovascular Solutions, Menlo Park, CA) were approved by the US Food and Drug Administration (FDA) for clinical use and harkened in the era of endovascular aortic aneurysm repair. The AneuRx device was a modular, bifurcated stent graft with thin, polyester graft material fully supported by a nitinol stent framework. This device was later supplanted by newer stent graft designs from Medtronic (Talent, Endurant) and is no longer in clinical use in the United States. The AnCure stent graft was a unibody, bifurcated polyester graft that was not fully supported by stent.
More closely approximating the traditional surgical bifurcated graft, the AnCure device had a nitinol stent ring at the proximal and distal attachment sites with active fixation barbs.\textsuperscript{50} While early studies demonstrated efficacy of this device, excessive perioperative complications with AnCure led to its withdrawal from the market in 2003.

Several EVAR devices have since been approved by the FDA for the treatment of infrarenal AAA. Each device has unique features that may provide benefit in certain anatomic substrates (Table 56-2). Many of these devices incorporate a suprarenal bare stent (with or without attachment hooks/barbs) to provide secure proximal fixation and to reduce the risk of device migration. A wide array of device diameters and lengths along with aortic and iliac extender cuffs are available to customize these devices for complex and varied patient anatomy. Over the years, devices with larger aortic and iliac diameters have been approved to expand the percentage of patients who can be treated with EVAR. More recently, a fenestrated stent graft was FDA approved to facilitate treatment of patients with juxtarenal aneurysms.\textsuperscript{51} Branch grafts have also become available to help maintain patency of the internal iliac artery when there is extension of aneurysm to the iliac bifurcation.\textsuperscript{52} Continued evolution of device design has allowed for lower profile, more flexible delivery systems that can be delivered through the iliac arteries more easily, thereby reducing the risk of iliac rupture or dissection. Due to the advent of these lower profile devices, EVAR can now be performed percutaneously in a large percentage of cases.

\textbf{Table 56-2} \textbf{FDA-Approved EVAR Devices}
The Excluder stent graft (Gore and Associates, Flagstaff, AZ) was FDA approved in 2002. The Excluder device is a modular, bifurcated endoprosthesis with expanded polytetrafluoroethylene (ePTFE) graft material fully supported by nitinol stent rings. This device does not have suprarenal fixation but has an ePTFE sealing cuff and proximal nitinol anchors. A lower permeability graft material was introduced in 2004. The C3 delivery system was introduced in 2010 for more precise and controlled deployment of the device. The latest version of the Excluder is available in aortic diameters up to 35 mm and iliac limb diameters up to 27 mm. The 23- and 26-mm devices can be delivered through a 16-Fr sheath.

The Zenith stent graft (Cook Medical, Bloomington, IN) was approved by
The Zenith device is a modular, 3-piece, bifurcated endoprosthesis with woven polyester graft material fully supported by stainless steel stents. This device is distinguished by bare metal stent suprarenal fixation and proximal retention hooks. The newest version (Zenith Flex) incorporates a hydrophilic delivery sheath with trigger-wire release mechanism for precise placement. Main body diameters up to 36 mm and iliac diameters up to 24 mm are available. Smaller devices (up to 26 mm) can be delivered via an 18-Fr delivery system. An aorto-uni-iliac version of this device (Renu Ancillary Graft Converter) is available and may facilitate secondary endovascular intervention in patients who have received prior endovascular repair. The Zenith Fenestrated EVAR device was more recently approved by the FDA for treatment of challenging neck anatomy that is unsuitable for a conventional, nonfenestrated graft. The Zenith Fenestrated device incorporates up to 3 holes (fenestrations) and cutouts from the proximal margin of the graft material to maintain patency of the renal arteries and superior mesenteric artery when sealing with the stent graft across the juxtarenal segment of the aorta.

The Powerlink stent graft (Endologix, Irvine, CA) was approved by the FDA in 2004. This is a unibody, bifurcated endoprosthesis with ePTFE graft material fully supported by a cobalt-chromium stent. The most recent iteration of this device is the AFX endovascular system. The AFX device is differentiated from other EVAR devices by its unique delivery mechanism, unibody design, and method of fixation. Fixation is not achieved by the usual mechanism of suprarenal bare metal stent and attachment hooks but rather is achieved by buttressing the bifurcation of the AFX device at the native aortoiliac bifurcation. Maintaining the native aortoiliac bifurcation has the advantage of preserving options for future contralateral access for the treatment of lower extremity occlusive disease. The AFX device is available in aortic diameters up to 32 mm and iliac diameters up to 20 mm. The main body can be delivered via a 17-Fr delivery sheath.

The Talent stent graft (Medtronic) was approved by the FDA in 2008. The Talent device is a modular, bifurcated design consisting of polyester graft material fully supported by nitinol stent rings and full-length connecting bar. There is a bare metal proximal stent for suprarenal fixation. This device was supplanted by the next-generation stent graft from Medtronic, the Endurant, which was FDA approved in 2010. The Endurant is also a 2-piece, modular, bifurcation stent graft with proximal bare metal stent and
anchor pins from suprarenal fixation. The most recent iteration of this platform is the Endurant II stent graft system, which is available in 2-piece and 3-piece modular configurations (Endurant IIs). The Endurant II device is available in aortic diameters up to 36 mm and iliac diameters up to 28 mm. Main body diameters up to 28 mm can be delivered via an 18-Fr delivery system. An aorto-uni-iliaic version of the device is also available.

The Ovation stent graft (Trivascular, Santa Rosa, CA) was approved by the FDA in 2012. The Ovation device has a unique modular, bifurcated design with ePTFE graft material and polymer sealing rings in the main body along with proximal bare metal stent with attachment hooks for suprarenal fixation. The iliac limbs are fully supported by nitinol stent rings. The main body O-rings fill with a conformable polymer and are designed to achieve a watertight proximal seal without chronic outward force on the infrarenal aortic neck. Another unique feature of the Ovation device is the low-profile, flexible delivery system. The majority of sizes can be delivered via a 14-Fr delivery system. The Ovation device is available in aortic diameters up to 34 mm and iliac diameters up to 28 mm.

The Aorfix endovascular stent (Lombard Medical, Oxfordshire, United Kingdom) was approved by the FDA in 2013. The Aorfix is a modular, bifurcated endoprosthesis with polyester graft material and a unique nitinol framework that combines circular and helical structures to provide added flexibility and conformability in tortuous anatomy. The Aorfix has a unique approval from the FDA for treatment of aneurysms with up to 90° of neck angulation. The Aorfix device is available in aortic diameters up to 34 mm and iliac diameters up to 20 mm. The main body is delivered via a 22-Fr delivery system.

Investigational Devices

Continued device development and technologic advances will lead to lower profile versions of the current EVAR devices (eg, Zenith LP) as well as newer low-profile stent graft systems. The Incraft device (Cordis, Freemont, CA) is a low-profile stent graft that is currently undergoing clinical investigation in the United States. Incraft is a modular, bifurcated stent graft that is delivered via a low-profile, 14-Fr integrated sheath. In addition to incremental improvements in device profile, efforts will continue to be directed toward expanding the reach of endovascular AAA repair to patients.
with suboptimal or inadequate infrarenal aortic neck anatomy. There will be alternative branched graft and fenestrated technologies to allow noncustomized, simpler, off-the-shelf solutions for patients who are not candidates for traditional infrarenal fixation.

Current and future approaches to the endovascular treatment of AAA may shift the focus to treating the aneurysm sac. The Nellix system (Endologix, Irvine, CA) is the first such device that focuses on filling the aneurysm sac rather than the traditional approach of relying on proximal neck fixation with subsequent aneurysm sac exclusion and depressurization. This system incorporates 2 balloon-expandable ePTFE-covered cobalt-chromium alloy stents surrounded by a set of 2 thin-walled polyester polymer–filled endobags that are designed to completely fill the aneurysm sac and freeze the sac in a definitive and permanent manner. Such an approach has the potential to reduce or eliminate the possibility of type II endoleak and reduce the need for secondary interventions. Initial experience with this device has been promising, and it is currently undergoing clinical investigation in the United States.

Parallel Grafts, Chimneys, Periscopes, and Snorkels

A variety of innovative techniques have been developed in order to expand the patient population with AAA that can be successfully treated by an endovascular approach. It has been estimated that roughly 60% of patients with AAA can be treated with commercially available EVAR devices according to the FDA-approved indications in the instructions for use (IFU). A common limitation for traditional EVAR devices is the lack of an adequate infrarenal neck for proximal fixation. Although fenestrated and branched devices have been developed to overcome the limitations of currently available devices, fenestrated devices may not be practical or possible to use in many cases. In particular, customized fenestrated grafts cannot be used in urgent or emergent settings, as they require time for manufacture. Greenberg and colleagues were the first to describe a “chimney” or “snorkel” graft technique to preserve renal artery flow when a proximal seal zone above the renal artery origin was required (Fig. 56-4). Subsequent publications have documented the safety and efficacy of this approach for a wide variety of clinical scenarios and anatomic substrates. A chimney or snorkel procedure involves deployment of stent grafts into 1 or more aortic visceral
branches and deployment of an aortic endograft such that the proximal parts of the visceral stents are placed parallel to the main aortic endoprosthesis (between the wall of the aorta and the aortic stent) and extend above or beyond it to ensure perfusion of the visceral organs. This technique is also commonly referred to as the “parallel graft” technique. The parallel graft technique is possible using a variety of off-the-shelf technologies, including commercially available EVAR devices and either balloon-expandable (Atrium iCAST; Atrium Medical, Hudson, NH) or self-expanding (Viabahn; WL Gore, Flagstaff, AZ) covered stents.

Moulakakis and colleagues published a review of the early experience with the chimney graft technique in 2012. They reviewed 15 reports that included 93 patients, of whom 24.7% were treated in an urgent setting. A total of 134 chimney grafts were implanted. Primary technical success was
achieved in all cases. A total of 13 patients (14.0%) developed a type I endoleak. Three were detected and treated during the index procedure. Four additional patients required a secondary intervention in the postoperative period. The 30-day in-hospital mortality rate was 4.3%. During a mean follow-up of 9.0 months, 97.8% of the chimney grafts remained patent.

A larger, multicenter registry (PERICLES Registry) provided additional insight regarding the safety and effectiveness of this approach. A total of 517 patients treated over a 6-year period at centers in the United States and Europe met the criteria for enrollment in the registry. The most common endografts employed were the Endurant and Zenith devices. Overall, 898 chimney grafts were placed in 694 renal arteries, 156 superior mesenteric arteries, and 50 celiac arteries. A mix of 49.2% covered balloon-expandable stents, 39.6% self-expanding covered stents, and 11.2% balloon-expandable bare metal stents were deployed. A type I endoleak was noted intraoperatively in 7.9% of cases. In 2.9% of cases, there was persistence of the type I endoleak despite corrective measures, resulting in a technical success rate of 97.1%. The 30-day mortality rate was 4.9%. At a mean follow-up of 17.1 months, primary patency of the grafts was 94%, and secondary patency (patency following reintervention) was 95.3%. Overall survival in this high-risk patient population at latest follow-up was 79%.

These reports suggest that a parallel graft or chimney EVAR approach is a reasonable option for patients presenting with a juxtarenal or pararenal aneurysm, particularly in urgent or emergent situations where a customized fenestrated graft is not an option. This strategy provides an off-the-shelf solution that is reasonably safe and effective, with satisfactory mid-term patency rates for the parallel grafts. Although the frequency of type I endoleak appears acceptably low, the potential for “gutter leaks” around the parallel graft and questions about the long-term durability of this approach lead many to favor a fenestrated graft solution when feasible.

**Fenestrated Grafts**

There is currently 1 fenestrated stent graft available in the United States for clinical use (Zenith Fenestrated Graft; Cook Medical), with numerous other fenestrated devices in various stages of clinical investigation (Fig. 56-5). As previously noted, the Zenith Fenestrated device incorporates up to 3 holes (fenestrations) and cutouts from the proximal margin of the graft material to
maintain patency of the renal arteries and superior mesenteric artery when sealing with the stent graft across the juxtarenal segment of the aorta. This device received FDA approval in 2012 based on results from a multicenter prospective clinical trial.\textsuperscript{51} A total of 67 patients were enrolled at 14 centers in the United States from 2005 to 2012. A total of 178 visceral arteries required incorporation with 118 small fenestrations, scallops in 51, and large fenestrations in 9. All were aligned by stents. Technical success was achieved in 100\% of cases. The 30-day mortality rate was 1.5\%. No aneurysm ruptures or conversions occurred during a mean follow-up of 37 ± 17 months. At 5 years, patient survival was 91\% ± 4\%, and primary and secondary patency of targeted renal arteries was 81\% ± 5\% and 97\% ± 2\%, respectively.

\textbf{FIGURE 56-5} Fenestrated endovascular aneurysm repair graft. A. The Zenith fenestrated graft with 2 fenestrations for the renal arteries and scallop for the superior mesenteric artery. B. Schematic showing deployment of the fenestrated graft across the renal arteries with renal stents implanted through the fenestrations.

The remarkably good results from this early experience with fenestrated grafts (high technical success, low 30-day mortality, no conversion or rupture, and high secondary renal artery patency) provide support for this approach to the treatment of patients with juxtarenal aneurysms and stand in stark contrast to results with traditional open surgical repair. Comparisons between the 2 approaches have shown that endovascular repair with fenestrated grafts is associated with significantly reduced mortality,
morbidity, and renal dysfunction compared to open repair.\textsuperscript{68,69} Tsilimparis and colleagues\textsuperscript{69} reported that open repair was associated with a 5-fold increase in mortality (5% vs 1%) and 2-fold increase in complications (40% vs 20%) compared to fenestrated EVAR. Current limitations to a fenestrated graft approach include the need to customize the fenestrated graft based on precise measurements from the CT scan with resultant delays in treatment pending manufacture of the device. Current fenestrated graft approaches are not feasible in the setting of ruptured aneurysm or other acute aortic syndromes. In addition, technical expertise is required for these cases, and fenestrated EVAR procedures are often long, difficult, and associated with significant radiation exposure for the operator and the patient.

**PROCEDURAL OUTLINE**

**Preintervention Imaging**

Preintervention imaging with contrast-enhanced CT with CT angiography is crucial for preoperative planning. To adequately visualize the aneurysm and make the appropriate measurements, 1- to 2-mm cuts are required. CT angiography can rapidly acquire high-resolution images, which can be postprocessed, producing 3-dimensional reconstructions. Other valuable procedural data, including aneurysm dimensions, angles, thrombus content, extent of calcification, and iliofemoral artery dimensions, can be obtained. Propriety software programs provide very accurate measurements of vessel diameter by reformatting raw data to create slices perpendicular to blood flow. Accurate length measurements are obtained via a computer-generated centerline. Vessel angulation is also easily calculated. With modern reconstruction techniques, it is often possible to plan the specific device sizes and lengths prior to starting the procedure. This detailed preprocedural planning also allows for consideration of alternative strategies or treatment approaches in the event of an intraprocedural complication.

Other methods for imaging AAAs include magnetic resonance (MR) imaging/angiography, digital subtraction angiography (DSA), and intravascular ultrasound (IVUS). MR imaging/angiography has the advantage of using the less nephrotoxic contrast agent gadolinium. However, MR imaging/angiography does not adequately visualize calcification of the
aneurysm wall, and image acquisition time is much longer. IVUS has also been used as an alternative or adjunct to other imaging modalities. IVUS allows precise diameter measurements, accurate assessment of the quality of the aortic neck (eg, thrombus, calcification, confirmatory length measurements), and precise evaluation of the degree of calcification in the iliac arteries. Angiography (or DSA) can define the aneurysm length and side branches but cannot adequately define the aneurysm size, extent of thrombus, or calcification. Duplex examination has a very limited role in endovascular planning. Before intervention, ultrasound is best used for diagnosis, whereas after intervention, it has a role in identification of endoleaks and measurement of aneurysm size and pulsatility.

The Endovascular Suite

Depending on the capabilities of a given institution, EVAR may be performed in an interventional radiology suite, cardiac catheterization laboratory, or operating room. An endovascular suite should have the capabilities of a standard operating theater, including utilization of special air filtration systems and laminar flow. An anesthesiologist and equipment should also be available to provide patient sedation for the procedure and in the event of emergent conversion to an open repair. Nurses and technologists capable of functioning as scrub nurses and circulators must be available for operative assistance.

The endovascular suite also needs to provide optimal radiographic imaging. The image intensifier should provide at least a 12-inch field of view; in cases of complex anatomy, a more magnified view may be desirable. The image-processing equipment should be capable of DSA and road mapping, and a power injector needs to be available for aortography. Whether the endovascular suite is in the cardiac catheterization laboratory, radiology department, or operating room, catheters, guide wires, balloons, stents, and other equipment necessary for successful EVAR should be readily available. In particular, an aortic occlusion balloon should be available in the event of vessel perforation or aneurysm rupture. These balloons are elastomeric and capable of rapidly and relatively atraumatically occluding distal aortic flow, providing temporary control of the situation.
Preintervention Hypogastric Artery Exclusion Procedures

A significant percentage (20%-30%) of AAAs extend beyond the aortic bifurcation to involve the iliac arteries. To minimize the chances of type II endoleak at the distal attachment site in the iliac artery, it is occasionally necessary to extend the graft into the external iliac artery. To provide for complete exclusion of the iliac/aortic aneurysm, it is necessary to occlude the ipsilateral hypogastric artery prior to doing so. Some practitioners have taken the approach of occluding (coils or plug) the internal iliac artery prior to the endograft deployment procedure. Such a staged approach may allow collaterals to develop and gives the interventionist the chance to observe the patient’s response to the hypogastric artery embolization. For those cases in which bilateral common iliac artery aneurysms are present and the patient is clearly not a candidate for open surgical repair, staged occlusion of both hypogastric arteries has been performed. Alternative techniques for hypogastric preservation include use of an additional self-expanding stent to “snorkel” the internal iliac inflow, as discussed earlier. A branched iliac device was also recently approved by the FDA and will have an important role in the treatment of AAA with concomitant iliac aneurysm.

With unilateral hypogastric artery occlusion, there is a 13% reduction in the penile brachial index, up to a 38% incidence of erectile dysfunction, and a 39% to 50% chance of hip or buttock claudication. The occlusion of bilateral hypogastric arteries is associated with a 28% to 55% incidence of pelvic ischemia. Bilateral hypogastric artery embolization results in a 39% reduction in the penile brachial index, a 50% incidence of erectile dysfunction, and an approximately 50% chance of hip or buttock claudication. Most patients have improvement or resolution of these symptoms over time, but this may occur over several months (mean, 14 months). Other reported complications after bilateral internal iliac artery embolization include scrotal skin sloughing, sacral decubitus ulceration, and intestinal ischemia. Having a diseased profunda femoris artery with a stenosis greater than 50% is associated with a higher rate of complications.

If the hypogastric artery cannot be spared, and buttock claudication or pelvic ischemia develops, several steps can be taken to help mitigate the symptoms. As noted earlier, it is possible that if the profunda femoris artery is diseased, profundoplasty may improve symptoms. Regular exercise should be a mainstay of therapy. Cilostazol has not been adequately studied in this

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setting but may be of benefit. Finally, treatment of a diseased contralateral hypogastric artery may be necessary. Surgical hypogastric artery reimplantation via a retroperitoneal incision may also become necessary in recalcitrant settings. In the event that both hypogastric arteries need to be occluded, sufficient staging should be performed, with at least 3 weeks between each embolization.

Covering the hypogastric artery with the endograft limb without coil embolization is another option if there is no aneurysmal involvement of the distal common and proximal external iliac arteries. By covering but not coiling the hypogastric artery, the chances of distal embolization into the small branches of the hypogastric artery are reduced and the likelihood of maintaining collaterals is enhanced. There is a trend toward both a reduced rate and severity of complications with this approach. Adequate sealing zones both in the distal common iliac artery and the proximal external iliac artery are necessary. In suitable patients, type II endoleak is similar between covering and embolizing the hypogastric artery. Other procedures such as surgical bypass and proximal ligation of the internal iliac artery, using an aorto-uni-iliac endograft, and occlusion of the contralateral common iliac artery in conjunction with a femoral-femoral bypass (allowing for retrograde perfusion of the internal iliac artery) are also considerations.

**Arterial Access**

For the vast majority of endografting procedures for AAA, a bilateral femoral approach is used. Depending on the common femoral access and the size of the device being used, a surgical cutdown may be necessary. There are 2 basic types of incisions for the femoral cutdown—vertical and oblique. Small oblique incisions can be used in the great majority of cases and are associated with a lower risk of wound complications. The wound complication rate has been reported to be as high as 7% to 18% for vertical incisions and 0% to 2.8% for oblique incisions. In addition, subsequent femoral access or reoperation is more easily achieved following an oblique incision.

Fully percutaneous EVAR is increasingly performed in many centers. In the majority of cases, the “preclose” technique is used with the Perclose closure device (ProGlide or Prostar XL; Abbott Vascular, Santa Clara, CA). Either the ProGlide or Prostar XL devices may be used for percutaneous large-bore sheath closure. The ProGlide closure device is a 8.6-Fr device with
2 needles and a single monofilament suture with a pretied knot. It is FDA approved for closure of up to 21-Fr sheaths. Two ProGlide devices are generally required for each large-bore sheath closure. The Prostar XL is a 12-Fr device that has 4 needles and 2 braided sutures. The operator ties the knot (usually a fisherman’s knot). The Prostar XL is approved for closure of 10-Fr sheaths in the United States and 24-Fr sheaths in Europe. When percutaneous EVAR is planned, anterior wall puncture of a nondiseased segment of the common femoral artery is essential. This is best performed with ultrasound guidance, but can be performed using fluoroscopic or angiographic landmarks. Using the double ProGlide technique, initial access is gained to the common femoral artery using a smaller 6-Fr sheath. The first ProGlide device is deployed, and then a second device is inserted 45° to 90° to the first to avoid duplicate suture entry sites. The arteriotomy is then progressively dilated, and the endograft delivery sheath is finally inserted. The contralateral limb is generally deployed through a smaller sheath, which can be closed with either 1 or 2 sutures depending on the sheath size. At the time of removal of the large sheath, closure can initially be performed over a 0.035-inch guide wire. If adequate hemostasis is not achieved, a third ProGlide device can be used. If the Prostar XL technique is employed, usually only 1 device is required for each access site. The Prostar XL is more cumbersome and challenging to use, but has been associated with high technical success rates and a low rate of conversion to surgical closure. A large prospective multicenter study and a smaller randomized trial have evaluated both percutaneous closure techniques and found them to have success and complication rates comparable to surgical cutdown.\textsuperscript{74,75} Advantages to a fully percutaneous procedure include less bleeding, earlier recovery, no incision, and perhaps earlier ambulation.\textsuperscript{76,77} This approach requires proper patient selection, with particular attention paid to femoral artery size and the degree of calcification of the femoral artery. Failure of the percutaneous closure mandates prolonged manual compression and possible surgical exploration.

\textbf{Intraoperative Imaging}

Good-quality intraoperative fluoroscopy and angiographic technique is required for precise endograft deployment. Accurate localization of the mesenteric and renal arteries is necessary to avoid inadvertent occlusion of these vessels and to document the proximal extent of the aneurysm. This is
generally accomplished by placement of an angiographic catheter via the contralateral femoral artery or radial/brachial artery. A pigtail or similar multihole angiographic catheter is inserted and advanced to a juxtarenal position. From this position, angiograms are taken during the deployment process to guide precise endograft positioning just below the renal arteries. Use of an angiographic “road map” or bony landmarks may be helpful, but neither method is sufficient for precise deployment. Another useful technique is to trace on the monitor with a marker the outline of the aorta and its major branches to serve as a guide. As long as the patient and image intensifier do not move, this method can assist in positioning of the endograft.

Postdeployment imaging is important to establish if the aneurysm is successfully excluded, to evaluate the patency of the renal and hypogastric arteries, and to evaluate for evidence of dissection of the external iliac arteries. Because the delivery sheaths are large relative to the common femoral artery, they may impede antegrade flow to the lower extremities, and adequate visualization of the iliac and femoral arteries may prove difficult. A retrograde sheath injection may be helpful. Another technique to allow for adequate opacification of the iliac arteries is to attach a 50-mL syringe to both sheath side ports. During aortography, as the contrast is injected, 2 operators manually aspirate from the syringes. This creates enough antegrade flow in the iliac arteries to allow for adequate visualization. The aspirated blood can then be returned to the patient.

Inadvertent renal artery occlusion is a rare complication of EVAR. Covering the renal artery during endograft deployment or as a result of subsequent endograft migration across a renal artery can lead to azotemia and ischemic nephropathy. Partial obstruction of the renal artery can be treated by insertion of a balloon-expandable stent into the renal artery. If complete renal artery occlusion occurs following endograft deployment, the options for salvage of the kidney are limited. If the endograft is not completely deployed, either resheathing or manually pulling the graft caudally may be sufficient to uncover the renal artery. Once the endograft is fully deployed, one option is to use the “dental floss” technique to displace the graft caudally. This will not be a good option if there is suprarenal fixation with attachment hooks/barbs. With the dental floss technique, a guide wire is advanced across the bifurcation of the endograft, snared from the contralateral iliac artery, and then externalized through the contralateral sheath. Traction on both ends of the wire may be sufficient to pull the endograft down and thus uncover the
renal artery. Placing a catheter over the wire across the bifurcation of the graft and pulling on the catheter may reduce the potential for damage to the graft by the guide wire.

**Postprocedure Surveillance Imaging**

Long-term endograft surveillance is required to document continued exclusion of the aneurysm by the endograft (Fig. 56-6). Imaging protocols vary depending on the institution. Following an uncomplicated EVAR, imaging is usually performed at 1 month, 6 months, and 12 months after procedure, and annually thereafter. If an endoleak is detected, immediate intervention may be required (as in the case of a type I or III endoleak), or the surveillance protocol may need to be modified. If a type II endoleak is identified or there is an endoleak of undetermined type, imaging every 6 months or sooner may be necessary.
FIGURE 56-6 Aneurysm regression after endovascular exclusion. A and B. Baseline computed tomography of large abdominal aortic aneurysm with minimal mural thrombus. C. Successful result following endovascular aneurysm repair with flow in main body and iliac limbs without evidence of endoleak. D. Follow-up abdominal ultrasound shows evidence of sac shrinkage.

Helical CT with intravenous contrast and thin slices is the preferred method of post-EVAR imaging. The techniques for CT in this setting are well established and standardized. The equipment is readily available in almost all centers, and extensive literature supports its use. Delayed imaging may be necessary to detect endoleaks in some cases.

Color Doppler ultrasound (CDU) has the advantage of being less expensive than CT and avoids radiation exposure and the use of nephrotoxic contrast agents. The sensitivity of CDU for detecting endoleak ranges from
77% to 97% and may be increased by the use of ultrasound contrast agents. Furthermore, CDU can assess physiologic parameters of the aneurysm such as pulsatility and can provide accurate measurements of the aneurysm sac dimensions and circumference. However, CDU is operator and patient dependent, and its major limitation is the inability to consistently provide adequate diagnostic images.

With the increasing use of EVAR and the need for long-term surveillance, one problem is a lack of necessary patient and physician follow-up. In a recent study, 50% of patients who had undergone EVAR were lost to follow-up after 5 years and were therefore not undergoing necessary surveillance imaging.  

**COMPLICATIONS OF ENDOVASCULAR ANEURYSM REPAIR**

*Endoleak*

Endoleak is the persistent flow of blood into the aneurysm sac after EVAR. There are 4 types of endoleak.  

1. Type I endoleak results from flow into the sac due to inadequate seal at either the proximal (type IA) or distal (type IB) attachment sites.
2. Type II endoleak occurs as a result of retrograde flow into the sac through a branch vessel (eg, accessory renal artery, lumbar artery, internal iliac artery, median sacral artery, gonadal artery, or inferior mesenteric artery).
3. Type III endoleak refers to a leak through the graft itself—either at the junction of modular components or because of a defect in the graft material.
4. Type IV endoleak is not truly an endoleak at all. This instead refers to the tendency of some grafts to be porous for a short period of time after insertion in the body. CT scans in the early postoperative period may demonstrate contrast in the aneurysm sac due to extravasation of contrast through the interstices of the stent-graft.

Endoleaks can be further categorized as primary or secondary. Primary
Endoleaks occur in the first 30 days after EVAR, whereas secondary endoleaks are detected more than 30 days after EVAR.

Endoleak results in continued pressurization of the aneurysm sac and may increase the risk of rupture following an otherwise successful EVAR. Between 20% and 40% of patients develop endoleaks after EVAR. The rate of endoleaks for aorto-uni-iliac endografts may be as high as 52.3%. Type I and III endoleaks are thought to result in the highest sac pressures and thus necessitate immediate intervention. Type II endoleaks are generally more benign and can be observed. Many type II endoleaks resolve spontaneously. Close attention must be paid to the size of the type II endoleak as well as the diameter and volume of the aneurysm sac. If there is growth of the aneurysm sac, consideration should be given to treatment of the type II endoleak. In rare cases, type II endoleaks can result in continued aneurysm pressurization, growth, and ultimate rupture.

**Type I Endoleak**

Type I endoleak can occur early after EVAR due to failure to achieve an adequate proximal or distal seal at the time of the procedure. Delayed type I endoleak may occur due to morphologic changes in the aorta or iliac arteries. Over time, there may be continued dilation of the proximal aortic neck or iliac arteries such that stent graft apposition to the vessel wall may be lost. In addition, as the aneurysm sac diameter and volume decrease, the resultant morphologic changes may lead to endograft migration.

Failure of stent-graft apposition at the proximal or distal attachment sites leads to repressurization of the aneurysm sac, with aneurysmal enlargement and possible rupture. Risk factors for the development of type I endoleak include a short proximal neck (<15 mm), the use of proximal extender cuffs, AAA diameter greater than 5.5 cm, severe neck angulation (<120°), and proximal neck calcification. Oversizing of the proximal endograft by at least 10% to 20% is thought to reduce the rate of type I endoleak.

There may be differences in the significance of proximal attachment endoleaks (type IA) depending on whether the endograft is supported or unsupported. Type IA endoleaks in fully supported endografts are unlikely to spontaneously resolve and should be treated if present at the time of endograft implantation. Treatment of type IA endoleak can be initially attempted with balloon dilation of the proximal attachment site. If this fails,
then deployment of a proximal extension cuff or balloon-expandable stent is necessary. There are reports of selectively coiling the gap between endograft and the arterial wall for type I endoleak. This technique should be reserved for cases in which there is an inadequate landing zone for an extension cuff and use of an uncovered stent is not appropriate.

Distal attachment site endoleaks (type IB) occur more commonly in the setting of iliac tortuosity, iliac artery ectasia, or iliac artery calcification. Regardless of the type of endograft (supported or unsupported), type IB endoleaks should be treated at the time of their discovery. Treatment of type IB endoleaks is generally accomplished with either the placement of an uncovered stent or endograft extension.

The use of devices with suprarenal fixation has been recommended for patients with short or angulated infrarenal aortic necks. Such devices do not appear to confer a lower type I endoleak rate if the aortic neck anatomy is favorable. For those with inadequate neck length, however, suprarenal fixation may be preferred to minimize the risk of late graft migration. Proximal aneurysm neck dilation (>3 mm) occurs in up to 28% of EVAR in the midterm (2 years), although only 20% of these require intervention. An increased risk of proximal aneurysm neck dilation is related to circumferential thrombus within the neck, pre-EVAR neck diameter, and pre-EVAR AAA diameter.\(^3\) Treatment for neck enlargement includes continued observation unless there is endoleak or suspicion of endotension. In such cases, either proximal extension cuffs are used or the patient may need to undergo conversion to open repair. The initial oversizing of the proximal endograft by 10% to 20% is perhaps the most important preventive strategy to reduce the chances of type I endoleak if aneurysm neck dilation does occur.

**Type II Endoleak**

As previously described, if there is stabilization or reduction in aneurysm volume, then intervention for type II endoleak is usually not required. In cases where a higher likelihood of type II endoleak is anticipated, some experts have advocated pre-EVAR embolization of branch arteries, use of thrombogenic AAA sac packing at the time of EVAR, or laparoscopically assisted side branch ligation. When prophylactically or primarily treating type II endoleak, it should be kept in mind that type II endoleak is generally
benign; its treatment should not be at an excessive risk of morbidity and mortality to the patient.

The diagnosis of type II endoleak can sometimes be challenging. If contrast-enhanced CT imaging is used to identify type II endoleak, it is important to recognize that branch flow into the aneurysm sac can be slow, necessitating delayed enhancement images. Contrast-enhanced ultrasound scanning is accurate in detecting endoleak and identifying the source artery. Spontaneous sealing often occurs within 12 months. Type II endoleak can be treated with selective arterial coiling, laparoscopic ligation, or translumbar embolization (Fig. 56-7). Successful treatment of type II endoleak is associated with a reduction in aneurysm surface area.

**FIGURE 56-7** Type II endoleak. Left panel: Type II endoleak caused by retrograde flow through the inferior mesenteric artery (arrow). Right panel: The endoleak is resolved following coil embolization of the inferior mesenteric artery near its origin (arrow).

**Type III Endoleak**

Type III endoleak can occur after EVAR due to separation of the modular components (IIIA) or late failure of the graft material (IIIB). Treatment of type IIIA endoleak at the junction of endograft components often requires
insertion of an iliac limb or extension cuff within the original graft (Fig. 56-8). Similarly, a hole in the endograft material can be patched from the inside with another iliac limb or cuff. If there is complete separation of the endograft limb from the main body, the endograft limb may be pushed into the aneurysm sac and a new limb inserted. More commonly, the disjointed endograft limb is recannulated and extension cuffs are placed to connect the limb and main body.

**FIGURE 56-8** Type III endoleak. A type III endoleak occurs due to late failure of the graft material.

During the procedure of placing new endograft extension cuffs, it is critical to confirm intraluminal placement.

**Type IV Endoleak**

Until the graft becomes impregnated and coated with platelets and fibrin, there may be some contrast “blush” seen in the AAA sac on aortography or contrast CT scan. Type IV endoleak from graft porosity generally resolves within a few weeks after EVAR. It is essential to distinguish graft porosity (type IV endoleak) from type III microleak. The presence of even very small
holes (type III endoleak) in the graft material results in systemic pressurization of the aneurysm sac. The use of color flow duplex imaging can help differentiate these microleaks (type III endoleak) from graft porosity (type IV endoleak).

**ENDOGRAFT LIMB OCCLUSION**

Any endograft deformity, kinking, or stenosis at the time of implantation requires a thorough investigation. Balloon angioplasty of graft limbs, either with standard angioplasty balloons or compliant balloon catheters should be utilized to minimize the risk of subsequent limb occlusion. IVUS may be helpful to evaluate the adequacy of iliac limb expansion. Intraoperative evaluation of endograft limbs by IVUS may result in significantly higher utilization of additional interventions but potentially fewer long-term complications.

Limb thrombosis most commonly (but not always) occurs within 2 months of endograft implantation. Patients can present with atypical leg discomfort, new-onset claudication, or acute limb ischemia. The decision to intervene on the limb depends on the patient’s limitations and the acuity of symptoms. Acutely thrombosed endograft limbs may be treated with open surgical embolectomy (care must be taken to avoid dislocation of modular components during passage of the Fogarty balloon), catheter-directed thrombolysis, or percutaneous thrombectomy with a device such as the Angiojet Rheolytic Thrombectomy catheter (Boston Scientific, Marlborough, MA). After reestablishing flow through the endograft limb, careful evaluation and treatment of predisposing factors such as limb kink, stenosis, or distal dissection are necessary. Risk factors for developing iliac limb occlusions include smaller limb diameter, limb stenosis, unsupported endografts, and the extension of the graft into the external iliac artery.

A cautionary note to the use of aorto-uni-iliac endografts with femoral-femoral bypass is the dependence of the entire lower extremity arterial circulation on the inflow from the endograft. Acute occlusion of this graft results in bilateral lower extremity ischemia with its attendant morbidity, risk of reperfusion syndrome, and mortality.
ENDOGRAFT MIGRATION

Endograft migration occurs in up to 15% to 45% of patients depending on the time frame of evaluation and the definition used for endograft migration (usually, 5-10 mm). The likelihood of endograft migration increases with time, with most occurring at a mean of 20 months after EVAR. Nearly 50% of patients with endograft migration require repeat interventions, including the placement of proximal extension cuffs. Risk factors for endograft migration include neck dilation of 10% or more and pre-EVAR AAA diameter greater than 5.5 cm. The potential for endograft migration emphasizes the need for routine imaging follow-up in patients after EVAR.

CONCLUSION

The endovascular treatment of AAAs has been shown to reduce the morbidity and early mortality associated with aneurysm repair compared with a traditional open surgical approach. EVAR has become the most common method for treatment of AAA, despite the recognition that the long-term outcomes of EVAR are similar to those of open surgery. There has been continuous evolution of devices and techniques for EVAR, and EVAR outcomes will likely continue to improve. Percutaneous EVAR can now be performed in the majority of cases, further reducing the morbidity associated with aneurysm repair. Novel techniques such as chimney, snorkel, and parallel grafts have made it possible to treat juxta- or pararenal aneurysms with an endovascular approach. The development of fenestrated and branched graft devices will further expand the patient population that can be treated successfully with EVAR. Future innovations will include alternative techniques for sac management to reduce the rate of endoleak and the need for late reintervention. Despite the successes of EVAR, it must be kept in mind that lifelong surveillance is required to reduce the risk of late complications such as endoleak or late aneurysm rupture.

REFERENCES


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Clouse WD, Brewster FC, Marone LK, et al. Durability of aortouniiliac


**MULTIPLE CHOICE QUESTIONS**

1. What have randomized trials of open surgery versus endovascular aneurysm repair (EVAR) shown for the treatment of patients with asymptomatic abdominal aortic aneurysms (AAAs)?
   A. Similar operative mortality and long-term outcomes for both open surgery and EVAR
   B. Decreased operative mortality for EVAR, but similar long-term mortality for both open surgery and EVAR
   C. Decreased operative and long-term mortality with EVAR
   D. Increased operative mortality and long-term mortality with EVAR

2. A 67-year-old man with a past medical history of smoking undergoes abdominal aortic ultrasound. The ultrasound demonstrates a 5.1-cm aneurysm with a clear infrarenal neck. One year ago, the patient’s aneurysm was 3.5 cm. What is the recommended treatment at this time?
A. Endovascular or open surgical repair of the aneurysm
B. Repeat ultrasound in 6 months
C. Repeat ultrasound in 1 year
D. Reassurance that his aneurysm is not yet large enough to treat and unlikely to grow further

3. A 72-year-old man undergoes endovascular aortic repair for a 5.6-cm infrarenal aortic aneurysm. During follow-up, computed tomography imaging reveals a type II endoleak originating from an inferior mesenteric artery, but the aneurysm sac has shrunk to 4.7 cm. What is the most appropriate management of the endoleak?
   A. Coil embolization of the inferior mesenteric artery via collaterals
   B. Conservative management; no intervention indicated at this time
   C. Surgical explant of the endovascular graft with open surgical repair of the aneurysm
   D. Placement of additional stent graft material in the main body of the graft to exclude possible concomitant type III endoleak

4. A patient who underwent endovascular aortic aneurysm repair 4 years ago undergoes a surveillance computed tomography (CT) scan. This scan demonstrates dislodgement of the left iliac limb relative to the main body component. What type of endoleak is this considered?
   A. Type I endoleak
   B. Type II endoleak
   C. Type III endoleak
   D. Type IV endoleak

5. A 69-year-old man is diagnosed with a 4.1-cm AAA. Which of the following medical interventions has been shown to reduce aneurysm sac expansion among patients with moderate-size aneurysms?
   A. Doxycycline
   B. Angiotensin-converting enzyme inhibitors
   C. β-Blockers
   D. There is no definite benefit of medical therapy in reducing aneurysm expansion.
ANSWERS

1. B
Four randomized trials have compared the outcomes of EVAR to open AAA repair. Each of these trials enrolled patients with asymptomatic AAA who were candidates for endovascular or open repair. All 4 studies reported lower 30-day mortality with EVAR, with 30-day mortality rates ranging from 0.5% to 1.2% for EVAR and 1.3% to 4.7% for open surgery. The long-term mortality in each of the studies did not demonstrate a benefit of EVAR over open AAA repair, likely due to death from other comorbidities.

2. A
The patient has rapid expansion of his aneurysm and should undergo aneurysm repair. The criteria for intervention on an AAA include an aneurysm diameter greater than 5.5 cm in men (perhaps 5.0 cm in women), rapid expansion of an aneurysm (>0.5-0.7 cm/6 months or 1 cm/12 months), or symptomatic aneurysm with either distal embolization from an AAA, aneurysmal mass effect, threatened rupture, or frank rupture.

3. B
If there is stabilization or reduction in aneurysm volume, then intervention for type II endoleak is usually not required. In cases where a higher likelihood of type II endoleak is anticipated, some experts have advocated pre-EVAR embolization of branch arteries, use of thrombogenic AAA sac packing at the time of EVAR, or laparoscopically assisted side branch ligation. When prophylactically or primarily treating type II endoleak, it should be kept in mind that type II endoleak is generally benign; its treatment should not be at an excessive risk of morbidity and mortality to the patient.

4. C
Endoleak is the persistent flow of blood into the aneurysm sac after EVAR. There are 4 types of endoleak. Type I endoleak results from flow into the sac due to inadequate seal at either the proximal (type IA) or distal (type IB) attachment sites. Type II endoleak occurs as a result of retrograde flow into the sac through a branch vessel (eg, accessory renal artery, lumbar artery,
internal iliac artery, median sacral artery, gonadal artery, or inferior mesenteric artery). Type III endoleak refers to a leak through the graft itself—either at the junction of modular components or because of a defect in the graft material. Type IV endoleak is not truly an endoleak at all. This instead refers to the tendency of some grafts to be porous for a short period of time after insertion in the body. CT scans in the early postoperative period may demonstrate contrast in the aneurysm sac due to extravasation of contrast through the interstices of the stent-graft.

5. D

Although the basic understanding of the inflammatory and dynamic nature of AAAs has significantly advanced, there is as of yet no effective medical treatment for limiting the expansion of AAA. Despite the current lack of an adequate medical treatment for slowing the rate of AAA expansion, all patients with AAA should receive appropriate medical therapy for cardiovascular risk reduction, including smoking cessation, statin therapy, and antiplatelet therapy.
CAROTID ARTERY INTERVENTION

The era of percutaneous or endovascular revascularization techniques was ushered in by Dotter in 1964, and then advanced by Gruentzig with the invention of the balloon angioplasty catheter. The technique of percutaneous transluminal angioplasty (PTA) has been used in both peripheral and coronary vessels to great success and, in many circumstances, has largely replaced surgical therapy as the treatment choice. The use of PTA in the extracranial carotid circulation began in Europe. In a worldwide survey of carotid intervention published in 1998, the specialty of cardiology was dominant, responsible for more than 60% of all the reported cases. Cardiologists have continued to lead this field with the development of embolic protection devices (EPDs); initially proven in saphenous vein graft intervention, cardiologists are already comfortable using this technology.

Pathophysiology

The majority of cerebral ischemic events are a focal manifestation of a systemic disease, atherosclerosis. Extracranial atherosclerotic carotid artery disease accounts for slightly more than half of the 731,000 strokes per year in the United States. Stroke is the third leading cause of death after coronary
artery disease and cancer in the United States, and it is the leading cause of
disability. In the Framingham study, 70% of all stroke patients had
hypertension, 70% had coronary artery disease, and 30% had peripheral
vascular disease.

There are 2 main types of stroke: ischemic and hemorrhagic. Ischemic
stroke results from a reduction of blood flow due to emboli, thrombosis, or
hypoperfusion. Hemorrhagic stroke includes primary cerebral hemorrhages
or hemorrhage secondary to an ischemic event. Atherosclerotic carotid artery
stenoses most often cause symptoms due to emboli events. A minority of
ischemic strokes are caused by thrombotic occlusion, which is in contrast to
acute coronary syndromes, which are usually due to thrombotic vessel
occlusion.

Anatomically, the 2 internal carotid arteries and 2 vertebral arteries come
together at the base of the skull to form the circle of Willis (Fig. 57-1), which
is an ideal anastomotic network. In theory, a single vessel could supply the
circulatory needs of the entire brain. However, although a circle of Willis is
present in every brain, there is a huge amount of individual variability, and
fewer than half are complete anastomotic networks.
Stroke Prevalence, Demographics, and Etiology

The third leading cause of death in the United States is stroke, with more than three-quarters of a million strokes per year. Stroke is a leading cause of functional impairment in adults with approximately 20% of survivors requiring institutional care and up to one-third having a permanent disability. More worrisome, however, is the fact that as the population ages, the number of patients experiencing strokes appears to be increasing.

The majority of strokes are ischemic and are caused by atherosclerotic emboli from the carotid artery or the aortic arch; more rarely, they are related to thromboembolism from the heart chambers. The incidence of asymptomatic extracranial carotid stenosis (≥50%) in persons >65 years of age is estimated to be between 5% and 10%, with fewer than 1% of patients having a critical stenosis (>80%). The annual risk of stroke is between 1% and 4.3% for asymptomatic patients with ≥50% stenosis of the carotid artery. The asymptomatic patients at highest risk of stroke are those with severe stenoses or those with progressive carotid narrowing. Unfortunately, the majority (~80%) of strokes have no warning symptoms. Therefore, identifying asymptomatic patients at highest risk for stroke is extremely important.

The current evidence supporting revascularization (carotid endarterectomy [CEA] or carotid artery stenting [CAS]) in asymptomatic patients is dated, with more current evidence creating debate among experts. The strongest evidence favoring revascularization comes from randomized clinical trials (Asymptomatic Carotid Artery Surgery [ACAS] and Asymptomatic Carotid Surgery Trial [ACST]) that were performed prior to the widespread availability of modern multimodality medical therapy, particularly statins. The most conservative estimate is that the current incidence of an asymptomatic carotid stenosis leading to a stroke is <1% per year, which, if true, would make it difficult for revascularization to provide additional benefit for patients. Unfortunately, there is little evidence upon which to base a treatment recommendation for patients with severe asymptomatic carotid stenosis. This has led to a proposal for a second Carotid
Revascularization Endarterectomy Versus Stenting Trial (CREST-2), which will randomize asymptomatic patients with significant carotid lesions to revascularization (CEA or CAS) versus multimodality medical therapy.

Pending the outcome of new trials, there continues to be reasons to consider revascularization of asymptomatic patients with significant carotid artery stenosis (>60%), such as prior to heart surgery to protect the brain from intraoperative hypoperfusion, rapidly progressing stenoses, patients with contralateral carotid occlusions, or patients with ulcerated or other high-risk plaque features that increase the incidence of stroke. Because the majority of strokes occur without warning, patient-centered care demands giving the asymptomatic patient’s preferences for revascularization (CAS or CEA), in the hands of an experienced team with proven quality outcomes, consideration.

Symptomatic patients have a worse prognosis compared to asymptomatic patients. The risk of atheroembolic stroke is directly related to the severity of carotid artery stenosis and the presence of symptoms. A transient ischemic attack (TIA), a neurologic event lasting <24 hours, predicted a 15% risk of stroke at 1 month and a 30% risk of recurrent TIA, stroke, or death within 3 months. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the stroke rate was 16.2% among those with moderate (50%-69%) stenosis and 25.1% with a 70% to 99% carotid stenosis (Table 57-1). Patients with the very tightest lesions, near occlusions, which were defined in the European Carotid Surgery Trial (ECST) as a severe stenosis with evidence of reduced flow in the distal carotid artery and evidence of narrowing of the poststenotic carotid artery, did not benefit from CEA.

Table 57-1 Symptomatic Carotid Endarterectomy (CEA) Trials: Risk of Stroke at 3 Years

<table>
<thead>
<tr>
<th>Trial</th>
<th>Medical Risk of Stroke (%)</th>
<th>CEA Risk of Stroke (%)</th>
<th>Perioperative 30-Day Stroke and Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET, 70%-99%11</td>
<td>25.1</td>
<td>8.9</td>
<td>5.8</td>
</tr>
<tr>
<td>NASCET, 50%-69%4</td>
<td>16.2</td>
<td>11.3</td>
<td>7.1</td>
</tr>
<tr>
<td>ECST, 70%-99%6</td>
<td>16.8</td>
<td>10.3</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Abbreviations: ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

**Cerebrovascular Symptoms**

Symptomatic cerebrovascular events are classified as TIAs, if they
completely resolve within 24 hours, or as strokes, if they leave a permanent
deficit. Patients with minor strokes include those who symptoms resolve
within 7 days or those with minimal disability (National Institute of Health
Stroke Scale [NIHSS] ≤). Symptoms may be “hemispheric,” meaning they
are related to a single carotid distribution, causing contralateral hemiparesis
or hemiparesthesias, aphasia, and/or ipsilateral monocular blindness
(amaurosis fugax), or they may be “nonhemispheric,” with symptoms of
vertebrobasilar insufficiency (VBI) such as dysarthria, diplopia, vertigo,
syncope, and/or transient confusion.

**Noninvasive Imaging**

Doppler ultrasound or duplex imaging of the extracranial carotid arteries is
cost-effective, accurate, and reproducible. Duplex imaging of the carotids
provides information about the location, extent, and severity of disease.
Blood flow velocity measurements are translated into categories that have
clinical relevance. There is controversy regarding the ability of ultrasound
imaging to serve as the sole imaging criterion to determine suitability for
carotid revascularization. A recent trial suggested that although ultrasound is
an excellent screening tool, its accuracy in a community setting was not
sufficient to replace angiography. As the resolution and speed of magnetic
resonance angiography (MRA) and computed tomographic angiography
(CTA) rapidly improve, they are being used to noninvasively image the
extracranial carotid arteries and intracerebral vessels (Fig. 57-2). The cross-
sectional images can be reconstructed into noninvasive angiograms that have
the very important advantage of imaging the circle of Willis with excellent
resolution and clarity.
FIGURE 57-2 A. Computed tomography angiography (CTA) image of an internal carotid artery stenosis (arrow). B. Magnetic resonance angiography (MRA) image of an internal carotid artery stenosis (arrows). MIP, maximum intensity projection; MPR, multiplanar reconstruction.

**Invasive Angiography**

All of the revascularization trials upon which carotid artery treatment decisions have been based have used angiographic criteria for patient selection. Invasive angiography is the “gold standard” for the diagnosis of vascular pathology of the aortic arch, cervical, and cerebral vessels (Fig. 57-3). The major drawback for invasive angiography has been the risk of adverse events associated with the procedure. In the ACAS trial, there was a 1.2% risk of stroke related to angiography performed by radiologists. More
recently, we have reported a much lower stroke rate (0.5%) for experienced interventional cardiologists performing carotid angiography. Clinical volume, technical skills, and patient selection are important elements in minimizing the risk for diagnostic angiography.

FIGURE 57-3 Digital subtraction angiogram of critical internal carotid artery stenosis (arrow). The asterisk denotes an artifact from dental fillings.
**Stroke Prevention with Pharmacologic Therapy**

Both primary and secondary stroke prevention require aggressive risk factor modification, specifically lipid management, blood pressure control, and smoking cessation. Aspirin therapy (81 mg daily) results in a 25% relative risk reduction compared to placebo. There is no evidence that doses of aspirin greater than 75 to 325 mg per day are more effective for stroke prevention. The CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial, comparing clopidogrel to aspirin, demonstrated a significant benefit for clopidogrel for the combined endpoint of ischemic stroke, myocardial infarction, or vascular death, but it did not show a reduction in stroke risk with clopidogrel compared to aspirin alone. The MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) trial showed no stroke reduction benefit for aspirin and clopidogrel compared to clopidogrel alone, although the bleeding risk was increased with combination therapy. Despite isolated data from a single trial regarding secondary prevention, the preponderance of evidence is that the addition of dipyridamole to aspirin alone for primary or secondary stroke prevention is of marginal benefit. With the exception of patients with atrial fibrillation, there are no data to support the role of anticoagulation with warfarin to reduce the risk of stroke.

Primary prevention has consisted of primarily blood pressure control, tobacco cessation, and aspirin therapy, but recently, the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrated significant risk reduction for stroke with statins. Several other lipid-lowering trials in patients at increased risk for stroke due to cardiovascular disease have also shown efficacy for statin therapy to reduce stroke. Both the 4-S (Scandinavian Simvastatin Survival Study) trial with simvastatin and the CARE (Cholesterol and Recurrent Events) trial with pravastatin demonstrated a 30% relative risk reduction for stroke compared to placebo. Of note, the stroke benefit did not appear in these trials until after 3 years of therapy.

**Surgical Treatment**

CEA has been established as the surgical procedure of choice for stroke prevention in patients with extracranial carotid artery disease (see Table 57-1; [Table 57-1](#)).
Table 57-2) to prevent stroke for usual or average surgical risk symptomatic patients with ≥50% carotid stenosis\textsuperscript{6,11,12} and average risk asymptomatic patients with ≥60% carotid stenosis\textsuperscript{7,13,14} compared to medical therapy.

Table 57-2 Asymptomatic Carotid Endarterectomy (CEA) Trials: Risk of Stroke at 5 Years

<table>
<thead>
<tr>
<th>Trial</th>
<th>Medical Risk of Stroke (%)</th>
<th>CEA Risk of Stroke (%)</th>
<th>Perioperative 30-Day Stroke and death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS\textsuperscript{7}</td>
<td>11</td>
<td>5.1</td>
<td>2.3</td>
</tr>
<tr>
<td>ACST\textsuperscript{14}</td>
<td>11</td>
<td>3.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial.

The applicability of clinical trial results to everyday patients has been questioned. Wennberg and colleagues\textsuperscript{15} demonstrated that the perioperative mortality rate for trial hospitals was 1.4% (95% confidence interval [CI], 1.2%-1.7%) and that the perioperative mortality rate was higher in nontrial hospitals (high volume: 1.7%; 95% CI, 1.6%-1.8%; average volume: 1.9%; 95% CI, 1.7%-2.1%; low volume: 2.5%; 95% CI, 2.0%-2.9%; \(P\) for trend <.001; \textbf{Fig. 57-4}). Patients undergoing CEA at trial hospitals had a mortality risk reduction of 15% (95% CI, 0%-31%) compared with high-volume nontrial hospitals, 25% (95% CI, 7%-40%) compared with average-volume hospitals, and 43% (95% CI, 25%-56%) compared with low-volume hospitals (\(P\) for trend <.001). The authors concluded that the perioperative mortality following CEA as practiced in the communities is substantially higher than that reported in the trials, even in those institutions that participated in the randomized studies. Caution is advised in translating the efficacy of carefully controlled studies of CEA to effectiveness in everyday practice.
FIGURE 57-4 Mortality rates for carotid endarterectomy (CEA) in Medicare patients are increased compared to symptomatic (NASCET) and asymptomatic (ACAS) clinical trial patients.15

Variability in the reporting of CEA results makes interpretation and comparison of studies difficult (Table 57-3). In a meta-analysis of CEA in symptomatic patients (n = 51 studies), the strongest predictor of stroke or death was who (neurologist or surgeon) performed the postoperative assessment.16 When a neurologist evaluated postoperative patients, the risk of stroke and death was 7.7%; however, when a single author surgeon performed the evaluation, the risk was reported as 2.3%.

Table 57-3 Carotid Endarterectomy Complication Rate According to Study Authorship16

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>No. of Studies</th>
<th>Mortality (%; 95% CI)</th>
<th>Stroke and/or Death (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologist assessor</td>
<td>9</td>
<td>1.4 (0.2-2.7)</td>
<td>7.7 (5.0-10.2)</td>
</tr>
<tr>
<td>Neurologist author</td>
<td>11</td>
<td>1.8 (1.2-2.5)</td>
<td>6.4 (4.6-8.1)</td>
</tr>
<tr>
<td>Multiple surgeon authors</td>
<td>26</td>
<td>1.7 (1.4-1.9)</td>
<td>5.5 (4.8-6.1)</td>
</tr>
<tr>
<td>Single surgeon author</td>
<td>5</td>
<td>0.7 (0.4-1.0)</td>
<td>2.3 (1.8-2.7)</td>
</tr>
</tbody>
</table>

The clinical benefit of CEA must be balanced against the perioperative risk associated with the procedure. An expert consensus panel suggested that
CEA was beneficial if the perioperative risk of stroke and death did not exceed 3% for asymptomatic patients and 6% for symptomatic patients. However, an increased risk of perioperative stroke and death rates has been reported for repeat CEAs (10.9%) and in patients with contralateral carotid occlusions (14.3%). There is consensus among experts that there is a population of patients who are at increased risk of complications with CEA due to a variety of unfavorable anatomic features and/or medical comorbidities (Table 57-4). The comparative benefit of CEA in patients treated with modern anti-atherosclerotic therapy has not been established.

### Table 57-4 Features Associated with Increased Risk for Carotid Artery Surgery

<table>
<thead>
<tr>
<th>Anatomic Criteria</th>
<th>Medical Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cervical or intrathoracic lesion</td>
<td>Age &gt;80 years</td>
</tr>
<tr>
<td>Prior neck surgery or radiation therapy</td>
<td>Class III/IV congestive heart failure</td>
</tr>
<tr>
<td>Contralateral carotid artery occlusion</td>
<td>Class III/IV angina pectoris</td>
</tr>
<tr>
<td>Prior ipsilateral carotid endarterectomy</td>
<td>Left main coronary disease</td>
</tr>
<tr>
<td>Contralateral laryngeal nerve palsy</td>
<td>2- or 3-vessel coronary artery disease</td>
</tr>
<tr>
<td>Tracheostoma</td>
<td>Need for open heart surgery &lt;1 month</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction ≤30%</td>
</tr>
<tr>
<td></td>
<td>Recent myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Severe chronic obstructive lung disease</td>
</tr>
</tbody>
</table>

### Carotid Artery Stenting

Extracranial CAS placement has evolved over the past 20 years to become an
accepted method for revascularizing patients with selected carotid lesions (Fig. 57-5). Because the extracranial carotid artery is subject to external compression and rotation, self-expanding stents are used to avoid stent deformation. Concern over the potential release of cerebral emboli led to the development of EPDs. These protection systems fall into 3 categories: (1) distal balloon occlusion with aspiration, (2) proximal occlusion with aspiration, and (3) distal filter systems.

FIGURE 57-5 Left panel: Tight internal carotid stenosis (arrow). Right panel: After stent placement (arrow).

CAS is the preferred revascularization strategy in patients at increased risk for surgical complications of CEA if they have suitable anatomy (see Table
The SAPPHIRE trial randomized high surgical risk patients to CEA or CAS in a large multicenter trial. The investigators clearly demonstrated noninferiority (CAS = 12.2%, CEA = 20.1%; \( P = .004 \) for noninferiority) across the entire cohort at 1 year for major adverse events. In patients at increased risk for complications of CEA, randomized trial data (SAPPHIRE\(^{18} \)) and pivotal registry evidence (ARCHer, \(^{19}\) SECuRITY, \(^{20}\) MAVerIC, \(^{21}\) SPIDERX, \(^{22}\) PRIAMUS, \(^{23}\) BEACH, \(^{24}\) CREATE, \(^{25}\) CAPTURE, \(^{26}\) CASES-PMS, \(^{27}\) CABERNET, \(^{28}\) EXACT, \(^{29}\) CAPTURE-2, \(^{29}\) ARMOUR, \(^{30}\) EPIC, \(^{31}\) EMPIRE, \(^{32}\) and PROTECT\(^{33} \)) support CAS as an alternative to CEA (Fig. 57-6). The durability of CAS relative to CEA was maintained out to 3 years of follow-up.\(^{34} \)

**FIGURE 57-6** Outcomes of improvement in carotid artery stenting: results for high surgical risk patients over time.\(^{19-33}\)

The current multisocietal guidelines recommend CAS as an alternative to CEA for treating symptomatic patients at increased risk for complications of CEA, if performed by an experienced operator and an experienced team, with expected 30-day morbidity and mortality outcomes similar to those observed in clinical trials (4% to 6%).\(^{35,36}\) This category of CAS patient (symptomatic
with ≥70% carotid artery stenosis and at high risk of CEA complications) represents the only group eligible for noninvestigational Centers for Medicare and Medicaid Services (CMS) reimbursement.

There have been 3 international randomized controlled trials comparing CEA to CAS (SPACE, EVA-3S, and ICSS), each of which, unfortunately, had seriously flawed trial designs by failing to provide quality control for CAS operators and not requiring the use of an EPD, which is the standard of care in the United States. The single common denominator among these trials was allowing inexperienced operators to participate in order to accelerate enrollment. These inexperienced operators were challenged by the additional complexity of using an EPD with CAS, leading many of them to abandon this important step and sacrificing patient safety.

The largest trial comparing CAS and CEA in average surgical risk patients was CREST, which enrolled 1321 symptomatic patients (53%) and found no difference for the primary end point of stroke, myocardial infarction (MI), or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization between CEA (8.4% ± 1.2%) and CAS (8.6% ± 1.1%). A potentially disabling cranial nerve palsy occurred in 5.5% (n = 36) of the CEA group. After 4 years of follow-up, there was no difference in stroke occurrence for either symptomatic or asymptomatic patients (Fig. 57-7).

**FIGURE 57-7** Data from the 4-year follow-up of any periprocedural stroke or postprocedural ipsilateral stroke showing no statistical difference for carotid artery
stenting (CAS) versus carotid endarterectomy (CEA).

CREST is the only source of modern randomized comparative data for 1181 asymptomatic patients at average risk for complications with CEA.\textsuperscript{41} There was evidence of equipoise between CEA and CAS for the primary end point of stroke, MI, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization (CAS 5.6% ± 1.0% vs CEA 4.9% ± 1.0%; $P = .56$). There was a 1 in 25 risk for a potentially disabling cranial nerve palsy in these asymptomatic patients undergoing CEA. The multisocietal guideline\textsuperscript{36} recommends considering CAS in asymptomatic average-risk patients (Class IIb) but cautions that the benefit of revascularization versus medical therapy is not well established.

**CAS Procedural Risk**

Clinical and anatomic conditions that put patients at increased risk for CEA complications should influence the treatment recommendations given to patients. Factors that place patients at increased risk for complications from CAS should also be considered when recommending CAS.\textsuperscript{42} CAS procedural risk assessment can be based on patient medical comorbidities, such as their symptom status or age; patient anatomic characteristics, such as a type III aortic arch (Fig. 57-8) or severe carotid artery tortuosity; and procedural factors, such as operator and team experience (Table 57-5). Experts agree that patients with anatomic features that prolong catheter manipulation, make crossing a carotid stenosis difficult, or make using an EPD or deploying a stent difficult should be avoided if possible. Other characteristics that make endovascular therapy more difficult or more risky and that should prompt consideration of CEA are compromised vascular access, severe iodinated contrast reactions, and chronic kidney disease, which puts the patient at risk for contrast-induced nephropathy.
Operator and team experience may be the most important factor in determining which patients are better suited for CEA or CAS. A proven track record of good results, with a team that can provide a safe environment during and after the procedure, is very important. One of the unintended
consequences of CMS’s restricted reimbursement policy for CAS has been to severely constrain the volume of CAS in the United States and limit the development of experienced centers outside those performing clinical trials.

There is little overlap among risk factors or patient characteristics that increase the periprocedural risk after CAS or CEA with a few notable exceptions (see Tables 57-4 and 57-5). Some are supported by clinical evidence such as the finding that echolucent plaques are associated with a higher event rate with CAS, whereas others are based on expert consensus such as high bleeding risk.

The risk for a CAS complication increases when catheter/guide wire manipulation is prolonged in the aortic arch, makes lesion crossing more difficult, decreases the successful deployment or retrieval of an EPD, or makes stent placement difficult. The most difficult anatomic features for CAS were a complex aortic (type III) arch (Fig. 57-9), circumferential lesion calcification, severe angulation of the internal carotid artery, severe atherosclerotic disease of the aortic arch, and a tortuous common carotid artery. Other features that may increase the risk of CAS include patients with dementia due to multiple lacunar strokes, cerebral microangiopathy with diminished vascular reserve, increased risk of bleeding or coagulation disorders, difficult vascular access, and kidney disease.
An increased complication rate for CAS in the elderly (≥75/80 years) has been clearly demonstrated. Younger patients (≤69 years old) were shown to have lower event rates with CAS compared to CEA in two large randomized trials. Elderly patients (>80 years) are more likely to have tortuous vessels, unfavorable aortic arches, and more complex carotid lesions. Despite these facts, it has been clearly shown that with experience and careful patient selection, excellent CAS outcomes are attainable even in the very elderly.

The experience of CAS operators and hospital volumes have a direct impact on procedure outcomes. The lead-in patients for the CREST trial
demonstrated that catheter-based subspecialties (radiology and cardiology) experienced half the number of complications as the vascular surgeons, which was statistically significant (Fig. 57-10). After successful completion of lead-in cases, which ensured operator competence, the final CREST results reported that the quality gap for the vascular surgeons had been closed.

**CREST Lead-In Specialty Outcomes**

- IR [OR = 1.66; 95% CI 0.89 – 3.08]
- Vasc Surg [OR = 2.05; 95% CI 1.18 – 3.56] \( P < 0.014 \)
- Neuro Surg [OR = 1.66; 95% CI 0.66 – 4.16]
- INR [OR = 0.39; 95% CI 0.13 – 1.15]

**FIGURE 57-10** CREST lead-in results showing statistically inferior results for the vascular surgeons, the least experienced group. INR, interventional neuroradiology; IR, intervention radiology; OR, odds ratio.

Although EPD use with CAS has never been subjected to a randomized controlled trial, most experienced operators believe that embolic protection is necessary with CAS; in addition, the US Food and Drug Administration approved the devices without randomized evidence, and Medicare will not reimburse for a CAS procedure in which an EPD has not been used. A meta-analysis of 4747 patients in 24 CAS studies found a significant benefit for protected procedures with a relative risk reduction of 0.59 (95% CI, 0.47-0.73). New brain lesions detected by magnetic resonance diffusion-weighted imaging (DWI) correlate with complex aortic arch vessels, more contrast usage, and longer fluoroscopic times during diagnostic cerebral angiography. The appearance of new contralateral-hemisphere DWI lesions is compelling evidence that some cerebral emboli are caused by catheter manipulation in
the aortic arch and explains why 20% of all strokes associated with CAS affect the contralateral hemisphere. Quantitatively, fewer transcranial Doppler (TCD) embolic signals and fewer DWI brain lesions occur with an EPD in place compared to no EPD used with CAS. When comparing a distal balloon occlusion EPD to a filter EPD during CAS, no difference was found between the devices, with new cerebral lesions detected in 40% of both groups; however, TCD has shown fewer embolic signals with a proximal embolic occlusion (PEO) device compared to a filter EPD.

There is continuing debate regarding the effect of stent type (open cell vs closed cell) on the occurrence of CAS complications. Open-cell stents are typically more flexible and conformable in tortuous lesions, whereas closed-cells stents offer better lesion coverage. Several authors have observed an increase in CAS complication rates with open-cell stents, particularly in symptomatic patients and those with echolucent plaques. Complications in these symptomatic patients correlate with the “free cell area” of the stents. However, a large CAS series failed to show any relationship of stent type with CAS complications, with the authors pointing out that without a randomized controlled trial, lesion morphology, which drives stent choice, may confound the observed outcomes. For example, open-cell stents are preferred in more complex angulated lesions, which are more likely to cause complications, whereas closed-cell stents are preferred in straighter lesion segments, introducing a bias in favor of closed-cell stents.

Earlier intervention (≤14 days) after a symptomatic event has become recommended therapy for CEA given the high recurrent event rate for symptomatic patients. It is unclear whether the timing of CAS following a symptomatic event is beneficial or carries an increased risk of complications. In the symptomatic (stroke or TIA) subset of the multicenter CAPTURE (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) trial (n = 482), there was an increase in complications associated with CAS performed within 2 weeks of the symptomatic event (P = .0047; odds ratio, 2.52; 95% CI, 1.33-4.78). However, in 320 symptomatic CAS patients treated at 2 high-volume European centers, early intervention (≤14 days from onset of symptoms) with CAS was not associated with increased complications. Clarification of the risk-to-benefit ratio for early CAS intervention in symptomatic patients with CAS will require better controlled clinical trials.
VERTEBRAL ARTERY INTERVENTION

The vertebrobasilar system (VBS) accounts for approximately 25% of all ischemic strokes. Atherosclerotic occlusion or thrombosis of the VBS carries a poor prognosis, with mortality rates approximating 80%. Symptomatic posterior circulation lesions that are refractory to medical therapy carry a 10% incidence of stroke or death at 1 year. Patients with peripheral vascular disease have a 40% incidence of vertebral artery stenosis (VAS), whereas symptoms of posterior circulation ischemia correlate with a 25% to 40% incidence of VAS.

VBS symptoms (Table 57-6) are frequently unrecognized and underdiagnosed. Noninvasive ultrasound imaging of the proximal portion of the vertebral artery is often difficult. Noninvasive angiography (MRA or CTA) or invasive angiography is the best way to demonstrate the stenosis in this proximal location, which is the most common location for disease to occur in this vessel.

Table 57-6 Symptoms of Vertebrobasilar Insufficiency (VBI)

<table>
<thead>
<tr>
<th>Common VBI Symptoms</th>
<th>Unusual VBI Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>Confusion</td>
</tr>
<tr>
<td>Drop attacks</td>
<td>Global amnesia</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Syncope</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>Occipital headaches</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>Nausea</td>
</tr>
<tr>
<td>Bilateral homonymous hemianopia</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Nystagmus</td>
</tr>
<tr>
<td></td>
<td>Bilateral facial numbness</td>
</tr>
<tr>
<td></td>
<td>Cortical blindness</td>
</tr>
<tr>
<td></td>
<td>Altered mental status</td>
</tr>
</tbody>
</table>
Vertebrobasilar Anatomy

The vertebral artery originates at a 90° angle as the first branch of the subclavian artery and is divided into 4 segments defined by the bony landmarks illustrated in Figure 57-11. These 4 segments are designated V₁ to V₄, and the ostium is designated as V₀. The ostium and V₁ segment are the most frequent locations of disease in this vessel treated with percutaneous intervention (Fig. 57-12).

FIGURE 57-11 Vertebral artery anatomy. (Reproduced with permission from Silva JA, White CJ. Peripheral vascular intervention. In: Kern MJ. The Interventional Cardiac
The $V_1$ segment courses between the longus colli and scalenus anterior muscles until it enters the transverse foramina of either the fifth or sixth cervical vertebra and becomes the $V_2$ segment. The $V_1$ segment can be treated percutaneously with ease provided it is not tortuous or redundant.

The $V_2$ segment begins as it enters the transverse foramina of C5 or C6, courses through the bony canal of the transverse foramina of C6 to C2, and ends when it exits the transverse foramina of C2. The $V_2$ segment is also easily treated with percutaneous intervention due to favorable anatomic features such as its short distance from the subclavian artery and a straight course through the transverse foramina of the cervical vertebra.
The V3 segment begins as it exits the transverse foramina of C2 and ends as the vessel penetrates the dura mater through the foramen magnum and becomes an intracranial vessel. Percutaneous intervention in the V3 segment is more difficult as this segment is extremely tortuous and does not allow mobility of the atlantoaxial and the atlanto-occipital joints. Balloon-expandable stents should be avoided in this flexible joint region. Avoiding extreme tortuosity and use of short self-expanding stents increase success in this segment.

The V4 segment extends along the inferior portion of the pons and joins the contralateral vertebral artery to form the basilar artery. Anterior spinal communicator arteries originate from the V4 segments bilaterally, join in the midline, and perfuse the anterior two-thirds of the spinal cord. Therefore, percutaneous intervention in V4 segment is extremely risky and is rarely attempted except for acute stroke intervention or severe symptoms unresponsive to medical therapy. Occlusion of the anterior spinal communicators can cause major deficits and brainstem infarcts.

There are several anatomic variants to consider when performing selective vertebral artery angiography. The left vertebral artery origin is anomalous in 5% to 10% of the population, arising from the aortic arch just proximal to the left subclavian artery or from the proximal left subclavian artery. The right vertebral artery arises from the aorta distal to the left subclavian artery or from the right carotid artery in 0.18% of the population. Hypoplasia of 1 vertebral artery with congenital absence of the V4 segment and termination in the posterior inferior cerebellar artery occurs in 6% or the population.

**Indications for Intervention**

Patients with VBS symptoms (see Table 57-6) that are refractory to medical therapy should be considered for vertebral artery intervention. Therapy for symptomatic VBI is reasonable in patients with bilateral vertebral stenosis ≥70%, unilateral vertebral stenosis ≥70% in the presence of an occluded or hypoplastic contralateral vertebral artery, or evidence of artery-to-artery embolism even in the presence of a unilateral stenosis and if vertebral angioplasty would increase total cerebral blood flow to patients with diffuse atherosclerotic disease involving occlusions of both carotid arteries. Revascularization of the vertebral artery should not be attempted if the vessel
Clinical Results

Since the first successful treatment of a vertebral artery stenosis with balloon angioplasty in 1980, multiple case reports and case series have been reported describing the successful use of endovascular techniques to treat posterior circulation atherosclerotic disease. Unfortunately, there is no level 1 evidence from multicenter clinical trials to guide clinical decision making. Endovascular treatment of vertebral artery atherosclerosis still remains a major challenge today due to a lack of randomized controlled trials and a nonpayment decision by Medicare in 1984. Despite these challenges, review of previous studies demonstrates that endovascular treatment of the vertebral artery is safe, feasible, and durable with high technical success rates and low clinical complication rates (Table 57-7).

Table 57-7 Results of Endovascular Stenting for Vertebrobasilar Insufficiency

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Technical Success Rate</th>
<th>Procedural Complications</th>
<th>Improvement in Symptoms</th>
<th>Mean Follow-Up (months)</th>
<th>Late Stroke</th>
<th>Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenkins et al^49</td>
<td>32</td>
<td>100%</td>
<td>TIA (1)</td>
<td>31/32</td>
<td>10.6</td>
<td>0/32</td>
<td>1/32</td>
</tr>
<tr>
<td>Albuquerque et al^50</td>
<td>33</td>
<td>97%</td>
<td>CVA (1)</td>
<td>27/33</td>
<td>16.2</td>
<td>1/33</td>
<td>43%</td>
</tr>
<tr>
<td>Chastain et al^51</td>
<td>50</td>
<td>98%</td>
<td>0</td>
<td>48/50</td>
<td>25</td>
<td>1/50</td>
<td>10%</td>
</tr>
<tr>
<td>Lin et al^52</td>
<td>58</td>
<td>100%</td>
<td>CVA (3)</td>
<td>56/58</td>
<td>31.3</td>
<td>0/58</td>
<td>25%</td>
</tr>
<tr>
<td>Weber et al^53</td>
<td>38</td>
<td>95%</td>
<td>TIA (1)</td>
<td>23/26</td>
<td>11</td>
<td>0/26</td>
<td>36%</td>
</tr>
<tr>
<td>Cloud et al^54</td>
<td>14</td>
<td>100%</td>
<td>TIA (1)</td>
<td>13/14</td>
<td>33.6</td>
<td>1/14</td>
<td>36%</td>
</tr>
<tr>
<td>SSYLVIA^55</td>
<td>18</td>
<td>100%</td>
<td>0</td>
<td>N/A</td>
<td>6</td>
<td>2/18</td>
<td>43%</td>
</tr>
<tr>
<td>Jenkins et al^56</td>
<td>112</td>
<td>100%</td>
<td>TIA (1)</td>
<td>95/105</td>
<td>29</td>
<td>5/105</td>
<td>13%</td>
</tr>
<tr>
<td>Hatano et al^57</td>
<td>117</td>
<td>99%</td>
<td>TIA (2)</td>
<td>113/116</td>
<td>6</td>
<td>2/117</td>
<td>10%</td>
</tr>
<tr>
<td>Lin et al^58</td>
<td>80</td>
<td>100%</td>
<td>CVA (3)</td>
<td>78/80</td>
<td>12</td>
<td>0/80</td>
<td>28%</td>
</tr>
<tr>
<td>Karemehev et al^59</td>
<td>10</td>
<td>100%</td>
<td>TIA (1)</td>
<td>10/10</td>
<td>10</td>
<td>0/10</td>
<td>10%</td>
</tr>
<tr>
<td>Lin et al^60</td>
<td>11</td>
<td>100%</td>
<td>0</td>
<td>11/11</td>
<td>8</td>
<td>0/11</td>
<td>0%</td>
</tr>
<tr>
<td>Zhou et al^61</td>
<td>61</td>
<td>100%</td>
<td>0</td>
<td>N/A</td>
<td>12</td>
<td>N/A</td>
<td>27%</td>
</tr>
<tr>
<td>Gupta et al^62</td>
<td>31</td>
<td>100%</td>
<td>0</td>
<td>31/31</td>
<td>4</td>
<td>0/31</td>
<td>7%</td>
</tr>
<tr>
<td>Vajda et al^63</td>
<td>48</td>
<td>100%</td>
<td>0</td>
<td>48/48</td>
<td>7</td>
<td>0/48</td>
<td>12%</td>
</tr>
</tbody>
</table>

Abbreviations: CVA, cerebrovascular accident; N/A, not applicable; SSYLVIA, Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries; TIA, transient ischemic attack.

In a Cochrane Review, 173 cases of VAS stenting were identified out of 313 cases of vertebral artery intervention. Meta-analysis of these 20 studies
found a 30-day major stroke and death rate of 3.2% and a 30-day TIA and nondisabling stroke rate of 3.2%. These data would suggest that VA stenting is comparable to CAS\textsuperscript{47} in selected patients. In a meta-analysis of 300 proximal vertebral artery interventions at a mean follow-up of 14.2 months, the risk of death was 0.3%, the risk of periprocedural neurologic complications was 5.5%, and the risk of posterior stroke was 0.7%. After a mean of 12 months (range, 3-25 months), restenosis occurred in 26% of cases (range, 0%-43%) but did not correlate with recurrent symptoms.

Endovascular treatment of the ostial and proximal portion of the vertebral artery is a safe and effective technique for alleviating symptoms and improving cerebral blood flow to the posterior circulation. Vertebral artery angioplasty can be performed with high technical and clinical success rates, low complication rates, and durable long-term results. The durability of vertebral artery angioplasty is evidenced by low restenosis rates in multiple large series reported in the literature. Endovascular stenting of vertebral artery atherosclerotic disease in patients who fail medical therapy should be considered first-line therapy for this disease despite the absence of randomized trials demonstrating superiority of endovascular therapy due to the major difficulty and high morbidity of open surgical revascularization.

**SUMMARY**

CAS is one of the most studied medical procedures of all time, and in contrast, vertebral artery intervention is one of the least well studied. Surgical options for vertebral revascularization are not available, making endovascular stenting the best option available to patients facing a grim natural history for symptomatic lesions that have failed maximal medical therapy. For both symptomatic and asymptomatic patients, the largest randomized clinical trial to date (CREST\textsuperscript{41}) confirms equipoise for CAS and CEA when these procedures are performed by experienced operators with experienced teams supporting them. In recognition of this extensive evidence base, there is a multisociety expert consensus document\textsuperscript{48} and 2 professional society guidelines endorsed by 14 of the major stakeholder professional societies, including cardiology, vascular surgery, neurology, radiology, nursing, and neurosurgery, recommending that CAS be considered an alternative to CEA in average surgical risk patients.\textsuperscript{35,36}
Patients at risk for stroke from their carotid artery disease should be encouraged to discuss their treatment options, including revascularization with their physician. As of 2014, there remained uncertainty regarding the value proposition for revascularization (either CEA or CAS) in asymptomatic patients as a strategy to prevent stroke, and asymptomatic vertebral lesions should not be intervened upon. Investigation continues in an attempt to identify subsets of patients with carotid plaque at higher risk of causing strokes, but until those data are available, physicians and patients should continue to strive for value-based care—the best outcomes at the lowest cost and fewest complications, with the best information that is currently available. When considering revascularization of an asymptomatic patient, it is important to acknowledge that as the population lives longer, there is a cumulative benefit of freedom from stroke that ensues if the revascularization procedure is uncomplicated. However, the relative benefit of revascularization in asymptomatic patients over the long-term compared to multifactorial medical therapy, including antiplatelet agents, blood pressure control, and lipid-lowering therapy, is not known.

No one can know exactly what the future holds for carotid or vertebral stenting, but there are several reasonably safe bets. The first is that less invasive CAS will eventually replace the more invasive CEA, despite CMS’s intransigence on payment equality for CEA and CAS. This change will be largely driven by the acceptance of CAS by younger, endovascularly trained vascular surgeons, who will replace senior surgeons (not endovascularly trained), who have fought so hard and so effectively to protect their turf and influence Medicare. The second is that far fewer asymptomatic patients will undergo carotid revascularization to prevent stroke, as multimodality medical therapy continues to improve.

At some point, government regulators and third-party payers will realize that percutaneous CAS is a reasonable less morbid option to open surgical CEA and will expand reimbursement to be equal to that of CEA, returning clinical decision making to the patients and their physicians. This expansion of CAS cases, as a percentage of total carotid revascularization procedures, will drive further technical enhancements and procedural evolution that will result in continued improvements in CAS safety and efficacy.

REFERENCES


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**MULTIPLE CHOICE QUESTIONS**

1. What is the most common pathophysiology for acute stroke?
   A. Carotid artery occlusion
   B. Rupture of an intracranial vessel with hemorrhage
   C. Atheroembolic occlusion of a cerebral artery
   D. Thrombotic embolization to a cerebral artery

2. Which of the following is true regarding patients with asymptomatic carotid artery stenosis?
   A. Revascularization is not indicated for <50% stenosis.
   B. The annual risk of stroke is 5% per year.
   C. At the end of 4 years of follow-up in the CREST trial, there were more strokes in the stent group compared to the surgical group.
   D. Ulcerations of atherosclerotic carotid plaque double the risk of stroke.

3. Which of the following statements is true regarding carotid artery disease?
   A. Symptomatic patients are at greater risk than asymptomatic patients.
   B. An asymptomatic patient with a >80% carotid stenosis has a 10% per year risk of stroke.
   C. Dual antiplatelet therapy is more effective in preventing strokes than aspirin therapy.
   D. Aspirin doses of 325 mg/d are more effective than 81 mg/d for stroke prevention.
4. Which of the following characteristics puts a patient with carotid stenosis undergoing carotid stenting at the highest risk?
   A. Age >80 years
   B. Heavily calcified artery
   C. Lesion ulceration
   D. Tortuosity of the aortic arch (type III)

5. In which of the following circumstances is carotid stenting recommended as a superior option over carotid surgery for stroke prevention in a patient with carotid stenosis?
   A. A patient younger than age 60
   B. A patient with restenosis after prior carotid surgery
   C. A patient who had coronary bypass surgery 1 month ago
   D. A patient with moderate aortic stenosis

**ANSWERS**

1. C

   The most cause of acute ischemic stroke is atheroembolism, usually vessel-to-vessel embolization.

2. A

   There is no indication for revascularization of mildly narrow carotid arteries. The annual risk of stroke is estimated at 1% per year. There was no statistical difference between stent or surgery for all strokes at the end of 4 years. Ulcerations increase the risk of stroke by 30%.

3. A

   Symptomatic patients are at much greater risk than asymptomatic patients. The risk of stroke for a >80% stenosis on modern medical therapy is not known. Neither dual antiplatelet therapy nor doses of aspirin higher than 81 mg/d are more effective at stroke prevention.

4. D
The highest risk for stent complications is excessive tortuosity of the aortic arch.

5. B

Patients at increased risk with surgery are preferred for stenting. None of the other options have been identified as placing patients at increased risk with surgery.
Part V  Complications and Management

58  Risk Stratification in Interventional Cardiology
59  Bleeding Risk Scores
60  Stent Thrombosis
61  Coronary Artery Perforation
62  Embolization and No-Reflow During Percutaneous Coronary Intervention
63  Emergency Surgery Following Percutaneous Coronary Intervention
64  Emergency Resuscitation Measures
The field of interventional cardiology has evolved since the introduction of balloon angioplasty by Andreas Gruntzig, with current high procedural success rates and low attendant periprocedural complications. Percutaneous coronary intervention (PCI) and transcatheter aortic valve replacement (TAVR) are now preferred in many high-risk subgroups in whom they were previously contraindicated.

Evaluation of risk-benefit ratios and risk stratification are important elements in optimizing care for an individual undergoing PCI or TAVR. Various models for prediction of risks can help physicians, patients, and their families better comprehend attendant risks and provide an objective basis for the most suitable treatment option. It is paramount for clinicians to become familiar with the available risk scores and apply them in clinical practice. This chapter focuses on the strengths and weaknesses, ease of applicability, and use of risk prediction models to estimate the risk of mortality and major adverse cardiac events (MACE) in the current environment of interventional cardiology.
PREDICTION MODEL: STATISTICAL CONSIDERATIONS

A good predictive model should be accurate and able to discriminate between different levels of risk. An accurate model, on average, is not biased toward over- or underprediction. If the true average risk of an event in a population is 5%, one could achieve accuracy by predicting 5% risk for every patient. Such estimates would lack precision, however, because the same prognosis is given for both low- and high-risk patients. Discriminatory ability is related to precision (distinguishing high- from low-risk patients).

In the context of this chapter, a “prediction” is the probability that an event will occur. A high-risk patient may have a predicted risk of 0.50, but he or she will not suffer a half-event. This may be why assessment of these models tends to focus more on discriminatory ability than accuracy.

Logistic regression is the standard statistical analysis employed for binary outcomes. Harrell and colleagues recommend that the number of explanatory variables considered should not exceed one-tenth of the number of events. This set of variables should be determined without knowledge of their relationship to the outcome in the modeling data set. Clinical expertise is essential at this stage of model development. After candidate explanatory variables are chosen, the final model may be determined using automatic selection or bootstrap methods. These methods are intended not only to simplify the model, but also to avoid overfitting. Overfitting occurs when a model reflects anomalous associations specific only to the model-building data, resulting in suboptimal performance in other data sets.

Once a final model is chosen, the Hosmer-Lemeshow goodness-of-fit test may be used to determine if the model adequately reflects the observed data. A significant test result indicates an inadequate fit. Accuracy may be internally validated using data-splitting, cross-validation, or bootstrap methods. However, external validation is more valuable than these methods. Comparison of the observed number of events in the external data set against the events predicted by the model determines the model accuracy.

The discriminatory ability of a model may be quantified by the c-statistic (c stands for concordance). The c-statistic, or area under the receiver operating characteristic (ROC) curve, is the proportion of times that the
model correctly ranks the risks for a pair of subjects. That is, if 2 patients are selected, only 1 of whom will have an event, it is the rate at which the model assigns a higher level of risk to the patient with the event. Thus, a c-statistic of 0.50 indicates the model performs as well as assigning risk by the toss of a coin. Perfect discrimination results in a c-statistic of 1.00.

The simplification of the statistical model to an additive integer-scoring tool may be useful for patient counseling. The goal is to assign integer coefficients to risk factors significantly associated with an event so that the physician may quickly sum the coefficients for a numerical ranking of the patient’s risk. Once the logistic regression model is finalized, the simplified scoring tool may be defined by selecting integer coefficients roughly proportional to the log-odds ratio coefficients (ie, parameter estimates) of the logistic regression model variables.

RECENT RISK MODELS PREDICTING COMPLICATIONS FOLLOWING PERCUTANEOUS CORONARY INTERVENTIONS

Multiple models have been developed that incorporate demographic features, existing comorbidities, and angiographic characteristics to predict in-hospital and long-term outcomes of patients undergoing PCI. Of these, the Mayo Clinic Risk Score, American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) CathPCI risk score, and SYNTAX (Synergy Between Percutaneous Coronary Interventions With Taxus and Cardiac Surgery) score models are the most commonly applied in practice. These models are usually used in synergy and complement prognostic information; the Mayo Clinic and NCDR CathPCI scores stratify patient risk based on bedside clinical variables and PCI urgency (Table 58-1), while the SYNTAX score can further refine the overall risk and success of PCI based on the angiographic complexity and extent of coronary artery disease (CAD). Nine models that predict the risk of in-hospital and 30-day mortality and MACE have been described in the recent literature. They are listed below and compared in Table 58-1 and Table 58-2.
Table 58-1 Comparison of Available Risk Scores Predicting Complications Following Percutaneous Coronary Interventions in the Current Era

<table>
<thead>
<tr>
<th></th>
<th>ACC-NCDR(^a)</th>
<th>NY State(^{1,2,3})</th>
<th>NNE Model(^{2})</th>
<th>Michigan(^{2})</th>
<th>Beaumont Hospital(^{2})</th>
<th>Cleveland Clinic(^{2})</th>
<th>Mayo Clinic(^{1})</th>
<th>Brigham and Women’s(^{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk(s) studied</td>
<td>Mortality</td>
<td>Mortality</td>
<td>Mortality</td>
<td>Mortality</td>
<td>Mortality</td>
<td>Mortality</td>
<td>Mortality, Q-MI, emergent CABG</td>
<td>Mortality, Q-MI, emergent CABG, stroke</td>
</tr>
<tr>
<td>Study time period</td>
<td>Jan 99-Sep 00</td>
<td>Jan 91-Dec 94</td>
<td>Jan 94-Dec 96</td>
<td>Jul 97-Sep 99</td>
<td>Jan 96-Dec 98</td>
<td>Jul 94-Dec 94</td>
<td>Jan 96-Dec 99</td>
<td>Jan 97-Feb 99</td>
</tr>
<tr>
<td>Sample size (model development)</td>
<td>50,123</td>
<td>62,670</td>
<td>15,331</td>
<td>10,729</td>
<td>9,954</td>
<td>12,985</td>
<td>5,463</td>
<td>1,877</td>
</tr>
<tr>
<td>Event rate (%)</td>
<td>1.4</td>
<td>0.9</td>
<td>1.1</td>
<td>1.6</td>
<td>1.4</td>
<td>4.5</td>
<td>4.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Area under ROC (c)</td>
<td>0.89</td>
<td>0.892</td>
<td>0.88</td>
<td>0.90</td>
<td>0.87</td>
<td>0.648</td>
<td>0.782</td>
<td>0.767</td>
</tr>
<tr>
<td>Internal validation</td>
<td>c = 0.89</td>
<td>c = 0.88 ± 0.02</td>
<td>c = 0.92</td>
<td>c = 0.87</td>
<td>c = 0.635</td>
<td>c = 0.755</td>
<td>0.742</td>
<td></td>
</tr>
<tr>
<td>Simplified scoring</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>tool</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term mortality</td>
<td>No</td>
<td>Yes on external data(^b)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operator volume</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>included in the risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACC-NCDR, American College of Cardiology-National Cardiovascular Data Registry; CABG, coronary artery bypass grafting; Exp, expected; MI, myocardial infarction; NA, not available; NHLBI, National Heart, Lung, and Blood Institute; NNE, Northern New England; NY, New York; Obs, observed; ROC, receiver operating characteristic.

Table 58-2 Commonly Included Variables in the Currently Available Risk Stratification Models\(^a\)
<table>
<thead>
<tr>
<th>Event</th>
<th>ACC-NCDR&lt;sup&gt;22&lt;/sup&gt;</th>
<th>NY State&lt;sup&gt;16,20&lt;/sup&gt;</th>
<th>NNE&lt;sup&gt;23&lt;/sup&gt;</th>
<th>Michigan&lt;sup&gt;24&lt;/sup&gt;</th>
<th>Beaumont&lt;sup&gt;25&lt;/sup&gt;</th>
<th>Cleveland Clinic&lt;sup&gt;26&lt;/sup&gt;</th>
<th>Mayo Clinic&lt;sup&gt;27&lt;/sup&gt;</th>
<th>Brigham and Women’s&lt;sup&gt;31&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By decade</td>
<td>1.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.37</td>
<td></td>
</tr>
<tr>
<td>Logarithm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>&gt;65 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 y</td>
<td>2.61</td>
<td>0.93</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69 y</td>
<td>3.75</td>
<td>1.63</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79 y</td>
<td>6.44</td>
<td>3.32</td>
<td>2.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80 y</td>
<td>11.3</td>
<td>3.72</td>
<td>2.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%-59% (EF)</td>
<td>1.00</td>
<td>1.00</td>
<td>2.53</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%-49%</td>
<td>0.87</td>
<td>1.00</td>
<td>3.32</td>
<td>1.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%-39%</td>
<td>0.99</td>
<td>1.49</td>
<td>5.16</td>
<td>1.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%-29%</td>
<td>2.04</td>
<td>1.49</td>
<td>5.16</td>
<td>1.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%-19%</td>
<td>3.43</td>
<td>3.68</td>
<td>5.16</td>
<td>1.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>3.93</td>
<td>3.68</td>
<td>5.16</td>
<td>1.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>2.38</td>
<td>3.01</td>
<td></td>
<td></td>
<td>2.11</td>
<td>3.76</td>
<td>(NYHA ≥III)</td>
<td>(NYHA ≥III)</td>
</tr>
<tr>
<td>Acuteness of presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>1.78</td>
<td>2.19</td>
<td></td>
<td></td>
<td>2.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergent PCI</td>
<td>5.75</td>
<td>7.71</td>
<td></td>
<td></td>
<td>2.13</td>
<td>1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI 1-7 d</td>
<td>2.10</td>
<td>1.85</td>
<td>2.14</td>
<td></td>
<td>3.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI 6-23 h</td>
<td>1.31</td>
<td>3.67</td>
<td>(primary therapy)</td>
<td>2.80</td>
<td>(&lt;14 d)</td>
<td>4.75</td>
<td>3.15</td>
<td></td>
</tr>
<tr>
<td>AMI &lt;6 h</td>
<td>1.31</td>
<td>5.22</td>
<td>2.80</td>
<td>4.75</td>
<td>3.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>8.49</td>
<td>18.3</td>
<td>6.10</td>
<td>11.5</td>
<td>12.7</td>
<td>4.95</td>
<td>3.47</td>
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</tr>
<tr>
<td>IABP use</td>
<td>1.68</td>
<td>2.39</td>
<td>3.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk angiographic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-VD</td>
<td>1.82</td>
<td>1.54</td>
<td>2.20</td>
<td>1.32</td>
<td>1.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-VD</td>
<td></td>
<td>(multivessel intervention)</td>
<td>2.37</td>
<td>2.20</td>
<td>1.74</td>
<td>1.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM disease</td>
<td>2.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.34</td>
<td>2.40</td>
</tr>
<tr>
<td>Thrombus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.67</td>
<td>1.90</td>
<td>(LM treated)</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA B2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.63</td>
<td>2.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. New York (NY) State model\textsuperscript{19-21}
2. American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR)\textsuperscript{15,22}
3. Northern New England (NNE)\textsuperscript{23}
4. Michigan Consortium\textsuperscript{24}
5. William Beaumont Hospital\textsuperscript{25}
6. Cleveland Clinic\textsuperscript{26}
7. Mayo Clinic\textsuperscript{14,27}
8. Brigham and Women’s Hospital\textsuperscript{21}
9. Toronto Score\textsuperscript{28}

In general, these risk models have good predictive capability (c-statistic, approximately 0.9). Their discrimination ability is reduced in high-risk populations. A recently described enhanced NCDR CathPCI model is effective in determining survival in patient undergoing urgent PCI with high-risk clinical features, such as cardiogenic shock or cardiac arrest. Based on the model, survival to hospital discharge after urgent PCI was 35% for patients with sustained shock and cardiac arrest, whereas patients who had transient shock without cardiac arrest had 85% chance of survival.\textsuperscript{17}

**VARIABLES INCLUDED IN THE RISK SCORES**

<table>
<thead>
<tr>
<th></th>
<th>ACC/AHA C</th>
<th>SCAI II</th>
<th>SCAI III</th>
<th>SCAI IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.94</td>
<td>2.66</td>
<td>2.58</td>
<td></td>
</tr>
</tbody>
</table>

**Other high-risk clinical features**

<table>
<thead>
<tr>
<th></th>
<th>Renal failure</th>
<th>PVD</th>
<th>Diabetes mellitus</th>
<th>Female sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.04</td>
<td>2.12</td>
<td>1.41</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>3.51</td>
<td>1.78</td>
<td>1.41</td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td>2.32</td>
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<td>3.57</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td></td>
<td></td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td>2.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.54</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{*Odds ratio from logistic regression models.}

Abbreviations: ACC-NCDR, American College of Cardiology-National Cardiovascular Data Registry; AML, acute myocardial infarction; CHF, congestive heart failure; EF, ejection fraction; IABP, intra-aortic balloon pump; LM, left main; LVEF, left ventricular ejecion fraction; NNE, Northern New England; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SCAI, Society for Cardiac Angiography and Interventions; VD, vessel disease.
All the models incorporate similar demographic features, existing comorbidities, and lesion variables (with the exception of NY State) (see Table 54-2). In general, the risk factors associated with in-hospital complications can be divided into the following broad categories: age, left ventricular function, acuity of presentation, high-risk angiographic features, and additional high-risk demographics, such as congestive heart failure, New York Heart Association class, renal failure, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, and other variables.

**Age**

Advancing age is an important risk factor for PCI complication and is universally present in the risk models. Possible explanations for increased risk include reduced cardiac reserve, presence of multivessel disease, and increased prevalence of comorbidities. In all the risk scores, there was a graded increase in the mortality risk with advancing age. Thus, an octogenarian has 2.7 times the risk (Michigan model) as compared with patients between 50 and 59 years of age. The Mayo Clinic risk and NY state risk scores extend these observations to composite end points, with an unadjusted odds ratio for these complications of 6.03 and 4.7, respectively, in a person older than 80 years of age who undergoes PCI, as compared with a younger patient. Age was considered a binary variable in a recent simplified scoring system. This dichotomous cutoff of age might underestimate risks from PCI in the very elderly.

**Left Ventricular Function**

Assessment of left ventricular function is an important variable with prognostic implications during PCI. Various models have measured this risk variable differently. Cardiogenic shock resulting from severe left ventricular systolic dysfunction is the single most important predictor of PCI complications. The mortality in patients presenting with shock in various risk scores ranged from 28% (ACC-NCDR) to 33% (Michigan). In the Cleveland and Mayo Clinic models, the odds ratios of in-hospital complications in patients with shock were 12.7 and 4.95, respectively. Moreover, in the enhanced NCDR CathPCI model, sustained shock is associated with higher unadjusted in-hospital mortality than transient shock.
In the NY State model, reduced ejection fraction and congestive heart failure were independent predictors of death during or after angioplasty. Increased risk of death was associated with patients presenting with New York Heart Association (NYHA) class greater than or equal to III in the Mayo model, in the NCDR CathPCI risk model, and in the NNE cardiovascular study group, with an ejection fraction of 40% of less. Similar conclusions were derived from other risk score models. Therefore, it is important to have clinical or objective assessment of left ventricular function at the time PCI is performed.

**Acuity of Presentation**

Acute myocardial infarction (especially within 24 hours), cardiac arrest, hemodynamic instability with cardiac arrhythmia, and cardiogenic shock are important clinical variables that influence the acuity of presentation and adversely affect the outcome of the procedure. In the NCDR CathPCI database, the overall in-hospital mortality after PCI was 1.27%, ranging from 0.65% in nonurgent PCI to 4.81% in ST-segment elevation myocardial infarction (STEMI). Use of intra-aortic balloon pump during an urgent procedure is an important marker for increased mortality risk as seen in the NY State, ACC-NCDR, and NNE models. The odds ratio estimate for complications in urgent or emergent procedures in the Mayo Clinic risk score was 2.13. Similarly, mortality with emergent PCI procedures was high in the other study populations, with rates between 5.8% and 6.35% in the ACC-NCDR and NNE groups, respectively.

**High-Risk Angiographic Features**

Multivessel disease had a higher odds ratio for complications during PCI: 1.54 per extra vessel in the Michigan model, 1.86 in the Mayo Clinic model, and 1.32 per extra vessel in the Cleveland Clinic model. Multivessel angioplasty was a risk factor in the NY State model (odds ratio, 1.82) and can influence the prognosis of the patient. Other angiographic risk factors of importance are presence of thrombus (Mayo Clinic and Michigan models), American College of Cardiology/American Heart Association (ACC/AHA) type C lesion classification (ACC-NCDR, NNE, and Cleveland Clinic models), and left main coronary artery disease (ACC-NCDR and Mayo
Clinic models) or left main intervention (Brigham and Women’s model).

**Additional High-Risk Demographics**

**Renal Failure**

Renal failure has been found to be an important predictor of in-hospital complications following PCI.\(^{33,34}\) The Michigan model had an odds ratio of 5.5 for mortality in patients undergoing PCI who have a creatinine level of more than 1.5 mg/dL. Similar findings were noted in all other models except the Cleveland Clinic model. Despite differences in the definition of renal failure, the presence of renal insufficiency clearly increases the risk of complications during PCI. Assessment of renal function before PCI not only helps in prevention and management of contrast-associated acute kidney injury, but also adds this variable to the profile of the patient.

**Peripheral Vascular Disease**

Peripheral vascular disease is linked to higher mortality with the NNE, Michigan, and Beaumont models. Similar observations were noted in the NY State model (the odds ratio for mortality in patients with femoral popliteal disease was 1.775). This is an important diagnosis and is readily available from history and clinical examination. Peripheral vascular disease is not clearly defined in most of the risk scores; however, femoral popliteal disease (NY State model), claudication, amputation, peripheral bypass surgery, angioplasty, aortic aneurysm, and history of transient ischemic attacks, stroke, or carotid stenosis (Michigan model) add to the risk of the patient undergoing PCI.

**Frailty**

Although not included in the previously mentioned risk models, the role of frailty has recently been recognized because frail patients have poor in-hospital and long-term outcomes. Frailty can help estimate the biological age and clinical vulnerability of elderly patients. Frail patients have an odds ratio for in-hospital mortality of 4.6 after urgent PCI.\(^{35}\) Adding frailty to the Mayo
Clinic Risk Score improved the discriminability for adverse long-term outcomes (mortality and myocardial infarction) following PCI.\textsuperscript{36} Frailty is increasingly recognized as an important variable that determines not only eligibility but also prognosis of elderly subjects evaluated for high-risk percutaneous procedures, such as TAVR. There is still no consensus on the definition; however, uniform evaluation with existing definitions is strongly encouraged, especially as the age of the patients referred to cardiac catheterization laboratory continues to increase. In the PARTNER trial, for example, frailty was assessed using a composite of 4 markers (serum albumin, dominant handgrip strength, gait speed, and Katz activity of daily living survey), which were combined into a frailty score.\textsuperscript{37}

**Other Variables**

Other predictors (eg, diabetes mellitus [NY State and Beaumont models] and female sex [NY State, Cleveland Clinic, Michigan, and Beaumont models]) are not consistent across all the risk models and have a generally lower, weaker relationship with procedural complications.

**AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION LESION AND SYNTAX CLASSIFICATIONS**

Percutaneous angioplasty techniques have evolved rapidly since the original proposal of this classification in 1986 and its subsequent modification in 1990.\textsuperscript{38,39} It is still the most widely used system to scorecard the individual operator and the institution. More recently, in a new classification system, 2 variables (nonchronic total occlusion and degenerated saphenous vein grafts) were significantly correlated with death, non–Q-wave myocardial infarction, and the need for emergency coronary artery bypass grafting (CABG).\textsuperscript{40} The Society for Cardiac Angiography and Interventions (SCAI) proposed a simpler classification, collapsing ACC/AHA lesions A, B1, and B2 lesions into non-C category, and then stratifying the lesion by patency (SCAI I =
non-C/patent; SCAI II = C/patent; SCAI III = non-C/occluded; SCAI IV = C/occluded), resulting in better, but modest, discrimination (c-statistic, 0.665) for prediction of major in-hospital complications as compared with ACC/AHA lesion classification (c-statistic, 0.624). ACC/AHA type A is associated with a 2% risk of complications, whereas the risk of complications increases to 21% with type C lesions.

Investigators compared the Mayo Clinic risk score with ACC/AHA lesion classification for prediction of complications following PCI. The ACC/AHA lesion classification was inferior to the Mayo model in predicting the complications from the procedure. In other studies, procedural success was adversely affected by type C lesions. Among the type C lesions, chronic total occlusion and extreme tortuosity are significant lesion variables affecting procedure outcome. Type C lesion was one of the significant variables predictive of the need for emergency CABG following PCI.

Prior studies that relied on the ACC/AHA classification could not demonstrate value of adding angiographic variables toward assessment of prognosis. More recently, SYNTAX score derived from comprehensive angiographic information of patients enrolled in the SYNTAX trial clearly demonstrated its utility in not only providing prognostic information but also in selecting the mode of revascularization in patients with multivessel disease. SYNTAX score, a score based solely on angiographic extent and complexity of CAD, can predict the risk of complications with PCI based on the extent of CAD (eg, length of segment), complexity of CAD (eg, bifurcation/trifurcation disease, thrombus, calcification), and myocardium at risk (eg, left main disease, CAD dominance; http://www.syntaxscore.com/calc/start.htm; Fig. 58-1). The score divides patients undergoing revascularization into low (score <22), intermediate (23-32), and high (>32) risk, with corresponding 1-year major adverse cardiovascular and cerebrovascular events (MACCE) of 14.7%, 16.7%, and 23.7%, after PCI, respectively. SYNTAX has strong discriminative ability in various clinical presentations including left main and multivessel disease, non-STEMI, STEMI, and elective procedures. The score is frequently used in complex disease (eg, left main/multivessel disease) to assess the most appropriate revascularization strategy (PCI vs coronary artery bypass surgery), where patients with low-intermediate scores can be offered PCI (AHA/ACC class IIa indication). Newer hybrid models integrating
SYNTAX score with clinical variables, such as Global Risk Classification (GRC) and clinical SYNTAX score, can be used to increase the discriminative power in patients with significant comorbidities\textsuperscript{52,53} and underscore the importance of clinical and demographic information in calculating risk.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{syntax_score.png}
\caption{SYNTAX (Synergy Between Percutaneous Coronary Interventions With Taxus and Cardiac Surgery) score. Angiographic complexity and extent of coronary artery disease are computed to calculate SYNTAX score. A higher number of diseased vessels and the presence of each of the listed variables increases the risk of complications after percutaneous coronary intervention. (Based on Sianos G, Morel MA, Kappetein AP, et al. The syntax score: an angiographic tool grading the complexity of coronary artery disease. \textit{Eurointervention}. 2005;1:219-227.)}
\end{figure}

\textbf{PITFALLS IN THE CURRENT RISK SCORE MODELS}

Outcome analysis following PCI is an important tool for quality control. However, benchmarking of outcome data is complicated by variations in the
case mix, referral patterns, procedural techniques, and operator and hospital volume (Table 58-3). The models that address the prediction of complications following PCI have several limitations.\textsuperscript{20,22-27,54} With the exception of the ACC-NCDR Registry and SYNTAX models, the other risk scores are derived from either regional (NNE and Michigan Consortium) or single-institution databases (Mayo Clinic, Beaumont, and Brigham and Women’s), limiting their generalizability. Some data sets antedate current state-of-the-art interventional practice. Important outcome measures, such as myocardial infarction, stroke, or need for emergency CABG, can significantly contribute to morbidity, length of hospital stay, and cost and are not considered in most available models except the hybrid SYNTAX, Mayo Clinic, Cleveland Clinic, and Brigham and Women’s Hospital models. Similarly, operator volume, an important variable predicting outcome following PCI, was not used in most models.\textsuperscript{21,55}

Table 58-3 \textbf{Drawbacks of Available Risk Models for Prediction of Complications Following Percutaneous Coronary Interventions}

- Different definitions of included variables.
- Risk scores derived from single-center, regional databases have reduced generalizability.
- Outcome measures other than mortality (myocardial infarction, stroke, and emergency coronary artery bypass surgery) are ignored.
- Operator and institutional coronary angioplasty volume is not tested.
- Often-used ACC/AHA lesion classification has only modest discriminatory accuracy for prediction of complications.
- A lower incidence of events would require an even larger size of the database from which the model is derived.
- Time elapsed between collection of data and analysis compromises applicability of score to contemporary current practice.
- Newer models, including current definitions of myocardial infarction, are unavailable.
- Influence of referral bias.

Abbreviation: ACC/AHA, American College of Cardiology/American Heart Association.
WHICH MODEL TO CHOOSE FOR PREDICTION OF COMPLICATIONS?

The properties of an “ideal” predictive model are highlighted in Table 58-4. All the models described in this chapter have excellent predictive accuracy, with c-statistics varying from 0.89 in Mayo Clinic score model to 0.93 in NCDR CathPCI. The c-statistic for combined end points for the Cleveland Clinic model was, however, modest (0.648). The prediction is not a crystal ball; the vast majority of high-risk patients would not have any complication from the procedure. However, the aim of the risk score should be to correctly risk-stratify a patient into low-, moderate-, or high-risk categories. Most of the risk scores with the exception of new Mayo Clinic Risk models, NCDR, and NY State use both clinical and angiographic variables and, hence, cannot be used electively for risk stratification at the time of first contact in a patient with unknown angiographic variables. SYNTAX can further tailor procedural success and risk of complications based on the angiographic complexity of revascularization. It can enhance decision making when it comes to optimal revascularization technique (eg, PCI vs CABG) based on the risk of procedural complications. For example, patients with low or intermediate SYNTAX score will have good results with PCI. Also, in patients with unprotected left main disease at ostial and mid-body location, PCI can be recommended if the overall SYNTAX score is low.

Table 58-4 Characteristics of an Ideal Risk Score Model for Prediction of Complications Following Percutaneous Coronary Interventions

<p>| | |</p>
<table>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>It should be derived from simple and easily obtainable variables that are available preprocedure.</td>
</tr>
<tr>
<td>2.</td>
<td>It should predict not only mortality but also all major procedural complications, including mortality, myocardial infarction, stroke, and need for urgent bypass surgery.</td>
</tr>
<tr>
<td>3.</td>
<td>It should be validated internally and externally.</td>
</tr>
<tr>
<td>4.</td>
<td>It should reflect modern practice, which currently includes stent implantation, glycoprotein IIb/IIIa blockers, and poststent thienopyridine administration.</td>
</tr>
</tbody>
</table>
Most of the mortality models have been externally validated. Holmes and colleagues\textsuperscript{57} applied 5 of these risk models—including NY State, Cleveland Clinic, Michigan, NNE, and ACC-NCDR, developed from different data sets—to patients undergoing PCI in the National Heart, Lung, and Blood Institute Dynamic Registry. Three models (NY State, Cleveland Clinic, and NNE) predicted in-hospital mortality rates that were not significantly different than those previously observed. NY State and Mayo Clinic models can be used to predict the 30-day mortality as two-thirds of patients die within 30 days after hospital discharge.\textsuperscript{58} In both high- and low-risk subgroups, however, the Michigan model slightly underpredicted mortality, and the ACC-NCDR Registry predicted significantly higher mortality than that observed. Potential reasons for this discrepancy were misclassification of renal disease and nonavailability of higher-risk variables (eg, cardiac arrest was the strongest prediction in the Michigan model) in the ACC Dynamic Registry. Omission of variables not included in the Dynamic Registry will lead, by default, to underestimation of the mortality risk. Additional limitations are related to clinical definitions, missing data, and how other variables such as renal failure and ejection fraction are handled.

The NCDR CathPCI, Mayo Clinic, Michigan Consortium, Brigham and Women’s, and Beaumont hospital studies\textsuperscript{14,15,17,24,25,31,59} have developed risk scores that are easy for an interventionalist to apply at the bedside for rapid risk scoring of the patient. These scores help the physician to triage the patient for the best treatment option, stratify the risk for the PCI procedure, counsel patient and family, and benchmark the outcomes in a more consistent and uniform fashion (Figs. 58-2 to 58-4 and Table 58-5).
Mayo Clinic risk score for major adverse cardiovascular events after percutaneous coronary intervention. Complication rates rise with increase in the risk score (horizontal axis). Estimated rates of procedural complications for the integer scoring system are depicted. The integers are proportional to the estimated continuous coefficient from the logistic model. Percentages at risk are shown for each of the 5 risk categories: <2% is very low risk for complications with coronary angioplasty; 2% to <4%, low risk; 4% to <10%, moderate risk; 10% to 20%, high risk; and more than 20%, very high risk. If left ventricular ejection fraction (LVEF) is not available, add 1 when patients present with congestive heart failure (CHF); otherwise, enter 0. If creatinine is not available, add 1 for man or patient presenting with CHF; enter 0 for woman without CHF. MI, myocardial infarction. (Reprinted from Singh M, Rihal CS, Lennon RJ, et al. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. Mayo Clin Proc. 2007;82:701-708, Copyright © 2007 with permission from Mayo Foundation for Medical Education and Research.)
FIGURE 58-3 National Cardiovascular Data Registry bedside risk score. This model divides patient into 8 groups (horizontal axis) based on their predicted risk for in-hospital mortality. The percutaneous coronary intervention (PCI) patient can be classified into one of the groups by adding points based on patient’s age, clinical characteristics (eg, prior congestive heart failure, cardiogenic shock, chronic lung disease, New York Heart Association functional class IV, peripheral vascular disease, glomerular filtration rate), and PCI urgency. Group 1 (score 0-0.5) has the lowest probability for in-hospital mortality, while group 8 (score 30+) has the highest probability of in-hospital mortality, approaching 45%. (Reprinted from Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol. 2010;55:1923-1932, Copyright © 2010, with permission from American College of Cardiology Foundation.)
FIGURE 58-4 Michigan risk score. This score is only for in-hospital mortality and is read similar to the Mayo Clinic risk score. To estimate risk, calculate the total score by adding individual scores if comorbidity is present. For number of diseased vessels, add 0.5 for each major epicardial vessel with more than 70% stenosis. Identify the total score on the horizontal axis of the plot and corresponding probability on the vertical axis. Scores of 2.5 or less are associated with risk of death less than 0.8%, whereas scores higher than 7 are associated with risk of death greater than 40%. (Reproduced from Moscucci M, Kline-Rogers E, Share D, et al. Simple bedside additive tool for prediction of in-hospital mortality after percutaneous coronary interventions. Circulation. 2001;104:263-268.)

Table 58-5 Michigan Risk Score
Since the introduction of its use in patients with aortic valve stenosis (AS) who have prohibitive surgical risk, TAVR is now used widely for treatment of severe AS in patients with high surgical risk and has recently been approved for valve-in-valve procedures. The heterogeneity of the population undergoing TAVR, the presence of multiple medical comorbidities, and the rapid advancement in the technical aspects of the procedure hindered the development of TAVR-specific risk models. Nevertheless, previously applied surgical models have been used for initial risk stratification and patient selection for TAVR, including Society of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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<tbody>
<tr>
<td>Acute MI</td>
<td>1</td>
</tr>
<tr>
<td>Shock</td>
<td>2.5</td>
</tr>
<tr>
<td>Creatinine &gt;1.5 mg/dL</td>
<td>1.5</td>
</tr>
<tr>
<td>History of cardiac arrest</td>
<td>1.5</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>0.5</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>1.0</td>
</tr>
<tr>
<td>EF &lt;50%</td>
<td>0.5</td>
</tr>
<tr>
<td>Thrombus</td>
<td>0.5</td>
</tr>
<tr>
<td>PVD</td>
<td>0.5</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.5</td>
</tr>
<tr>
<td>Total Score</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: EF, ejection fraction; MI, myocardial infarction; PVD, peripheral vascular disease.

Thoracic Surgeons (STS) risk estimate and European System for Cardiac Operative Risk Evaluation (EuroSCORE).\cite{6,7,60,61} Despite their wide use, these surgical derived scores have limited discrimination and calibration in the TAVR patient population.\cite{64,65} In addition, assessment of frailty,\cite{66} comorbidities\cite{67} (Charlson Index, CAD index), certain high-risk anatomic features (eg, proximity of coronary arteries ostium to aortic annulus, calcification of left ventricular outflow tract\cite{68}), and baseline echocardiographic variables (eg, low-flow aortic valve stenosis and severe mitral valve regurgitation\cite{69-72}) are essential to determine best access route, treatment approach, and potential outcomes in patients with severe AS (Fig. 58-5).

**FIGURE 58-5** Proposed algorithm for best treatment approach in severe aortic stenosis (AS). Society of Thoracic Surgeons (STS) score can be used as a screening tool and help classify patients into low to high surgical risk. Additional comorbid conditions (eg, frailty, hostile chest, end-stage liver disease) can prevent candidates from surgery. These patients can be offered transcatheter aortic valve replacement.
(TAVR). In patients with significantly elevated STS >15%, significant comorbid conditions (eg, oxygen dependency, wheelchair bound), or reduced life expectancy, balloon valvuloplasty can be offered as part of palliative therapy. COPD, chronic obstructive pulmonary disease; LAA, left atrial appendage; MMSE, mini-mental status exam; SAVR, surgical aortic valve replacement. (Reprinted from Walsh JA III, Teirstein PS, Stinis C, et al. Risk assessment in patient selection for transcatheter aortic valve replacement. *Intervent Cardiol Clin*. 2015;4:12, Copyright © 2015, with permission from Elsevier.)

A recent risk prediction model (OBSERVANT risk score) has been developed that displays improved discrimination and calibration compared with the STS score. Seven variables were combined to predict 30-day mortality in patients undergoing TAVR (glomerular filtration rate <45 mL/min [6 points], critical preoperative state [5 points], NYHA class IV [4 points], pulmonary hypertension [4 points], diabetes mellitus [4 points], previous balloon aortic valvuloplasty [3 points], and left ventricular ejection fraction <40% [3 points]; Figs. 54-6 and 54-7). The model showed good discrimination (c-index, 0.73). However, the model risk score need further validation in other TAVR cohorts.

---

**FIGURE 58-6** OBSERVANT risk scoring system for prediction of 30-day mortality after transcatheter aortic valve replacement (TAVR). Left side: Bedside chart from which a total OBSERVANT risk score is calculated. Right side: Risk score (horizontal axis) with its corresponding estimated 30-day mortality percentage. Scores of 0 to 6 are associated with 2.4% 30-day mortality after TAVR, scores of 7 to 14 are associated with 7.8% 30-day mortality, and scores ≥14 are associated with steep increase in 30-day mortality (28%). Dotted line corresponds to confidence interval (CI). BAV, balloon aortic valvuloplasty; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.
ventricular ejection fraction; NYHA, New York Heart Association. (Reprinted from Capodanno D, Barbanti M, Tamburino C, et al. A simple risk tool (the observant score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *Am J Cardiol*. 2014;113:1851-1858, Copyright © 2014, with permission from Elsevier.)

**FIGURE 58-7** Comparison of observed and predicted 30-day mortality rates by OBSERVANT model and logistic EuroSCORE after stratification by quartiles. OBSERVANT risk score has better discriminative power (c-statistic, 0.71) than logistic EuroSCORE (c-statistic, 0.66), especially in patients in the highest risk quartile for 30-day mortality after transcatheter aortic valve replacement (TAVR). OBSERVANT risk score needs further validation in other TAVR cohorts. (Reprinted from Capodanno D, Barbanti M, Tamburino C, et al. A simple risk tool (the observant score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *Am J Cardiol*. 2014;113:1851-1858, Copyright © 2014, with permission from Elsevier.)

**SUMMARY**

The risk models described in this chapter predict in-hospital and 30-day mortality or MACE following PCI or TAVR. All the models are robust and represent current practice in interventional cardiology. Based on the description of strengths and limitations of the currently available models, physicians should be better able to counsel patients and their families about the risks involved in undergoing interventional procedures.

The focus of future studies should be on the uniformity and consensus
regarding the definitions of variables used, the outcomes measured, inclusion of postprocedure variables (elevation of cardiac enzymes, stroke, emergency CABG) and operator volume, and a strong national effort to streamline these measures.

REFERENCES


32. Chaitman BR, Ryan TJ, Kronmal RA, et al. Coronary artery Surgery Study (CASS): comparability of 10 year survival in randomized and


MULTIPLE CHOICE QUESTIONS

1. Which risk model has the highest discrimination and calibration for 30-day mortality after transcatheter aortic valve replacement (TAVR)?
   A. European System for Cardiac Operative Risk Evaluation (EuroSCORE)
   B. Society of Thoracic Surgeons (STS) risk score
   C. OBSERVANT risk score
   D. PARTNER novel risk score

2. Which of the following variables is not included in all of the clinical risk models?
   A. Age
   B. Acuity of presentation
   C. Cardiogenic shock
   D. Sex

3. Which of the following 2 models can be used to predict 30-day mortality
after PCI?
A. NY State and Mayo Clinic
B. NCDR CathPCI and Mayo Clinic
C. Michigan and NCDR CathPCI
D. NY State and NCDR CathPCI

4. Which of the following statements is true about Synergy Between Percutaneous Coronary Interventions With Taxus and Cardiac Surgery (SYNTAX) and ACC/American Heart Association (AHA) lesion scores?
A. The ACC/AHA lesion classification was superior to the Mayo Clinic risk model in predicting the complications from the procedure.
B. SYNTAX score is frequently used in complex disease intervention to assess the most appropriate revascularization strategy.
C. ACC/AHA type C is associated with 2% risk of complications during PCI.

5. Which of the following is not needed to estimate frailty?
A. Handgrip strength
B. Serum albumin level
C. Gait speed
D. Katz activity
E. Renal function

ANSWERS

1. C

EuroSCORE and STS risk models were developed for risk stratification of surgical procedures and have low discrimination and calibration for outcomes in TAVR (STS risk score c-statistic, 0.58). They are mainly used to decide best interventional approach for severe aortic valve stenosis: surgical aortic valve replacement (SAVR), TAVR, or balloon valvuloplasty. OBSERVANT risk model was shown to have high discrimination and calibration abilities (c-statistic, 0.73) when compared to EuroSCORE. However, this model needs to be validated in other cohorts. The PARTNER novel risk model was developed to predict poor outcome including 6-month mortality and Kansas
City Cardiomyopathy Questionnaire–Overall Summary Scale (KCCQ-OS) score less than 45 after TAVR. This risk model has moderate discrimination (c-statistics, 0.66).

2. D

Most of the clinical risk models are derived from similar variables, including age, acuity of presentation, left ventricular function, and periprocedural shock. Age is a universal risk marker for prediction of complications after percutaneous coronary intervention (PCI). For instance, patients old than 80 years have 6.03 and 4.3 unadjusted odds ratios for mortality in Mayo Clinic and New York (NY) State risk scores. Acuity of presentation, including cardiac arrest at presentation, cardiogenic shock, and ST-segment elevation myocardial infarction (STEMI), is associated with higher complication rates. For example, the overall in-hospital mortality after PCI was 0.65% in nonurgent PCI and 4.81 in STEMI in the National Cardiovascular Data Registry (NCDR) CathPCI model. Other predictors (eg, diabetes mellitus [NY State and Beaumont models] and female sex [NY State, Cleveland Clinic, Michigan, and Beaumont models]) are not consistent across all the risk models and have a generally lower, weaker relationship with procedural complications.

3. A

American College of Cardiology (ACC)-NCDR CathPCI, Michigan, Cleveland Clinic, Northern New England (NNE), and Brigham and Women’s models can predict the in-hospital mortality. NY State and Mayo Clinic risk models can be used to predict 30-day mortality. Both models have high discrimination abilities (NY State c-statistic of 0.89 and Mayo Clinic c-statistic of 0.9 for 30-day mortality).

4. B

ACC/AHA and SYNTAX score are 2 of the most common classifications used to determine lesion complexity during PCI intervention. An ACC/AHA type A lesion is associated with 2%, type B1 with 4%, type B2 with 10%, and type C with 21% risk of in-hospital complications. However, the discrimination ability is modest (c-statistic, 0.624). The Mayo Clinic risk score was superior to ACC/AHA lesion classification in predicting in-
hospital complications from PCI (c-statistic difference 95% confidence interval, 0.05-0.15). SYNTAX score is based solely on angiographic extent, complexity of coronary artery disease, and myocardium at risk. The score is frequently used in left main and multivessel disease intervention to assess the most appropriate revascularization strategy (PCI vs coronary artery bypass surgery). Patients with low-intermediate scores can be offered PCI (AHA/ACC class IIa indication).

5. E

Frailty is an estimate of biological age that can help assess the eligibility and vulnerability of elderly patients in high-risk percutaneous procedures. Frail patients have an odds ratio for in-hospital mortality of 4.6 after urgent PCI. There is no consensus on the definition of frailty. Common markers that have been used to calculate frailty score include serum albumin, dominant handgrip strength, gait speed, and Katz activity of daily living. Renal function is not used to calculate frailty score.
INTRODUCTION

Advances in the catheterizations techniques, stent designs, and pharmacotherapeutics have reduced adverse ischemic event rates such as cardiovascular death, ST (stent thrombosis), recurrent myocardial infarctions, and revascularizations in patients with coronary artery disease undergoing elective or acute percutaneous coronary intervention (PCI). However, the same antithrombotic regimens also increase bleeding risk, and a cornerstone of contemporary cardiovascular interventions is balancing ischemic and bleeding events in order to optimize the net benefit for the individual patient.

Bleeding complications in patients undergoing cardiovascular interventions have previously been underappreciated. Over the decade, however, awareness has gradually raised that adverse bleeding outcome after PCI carries substantial hazard comparable to that of post-PCI myocardial infarction associated with mortality. A growing number of studies showing the impact of bleeding on short- and long-term mortality have promoted bleeding end points to a pivotal metric, increasingly applied as a single and combined primary end point in randomized controlled trials (RCTs). The composite end point of net adverse clinical events (NACE), assessing both ischemia and bleeding in the same outcome measure, was conceived to investigate the balanced effect of novel therapeutic agents or clinical
strategies in antithrombotic treatment regimens.

However, understanding the full impact of bleeding on outcome is still challenging. While ischemic adverse events are mostly narrowly adjudicated by widely accepted consensus definitions such as ST by the academic research consortium or myocardial infarction (MI) by the global definition of MI, bleeding assessment has been based on a large and very heterogeneous palette of definitions, often arbitrarily modeled as per-protocol criteria for specific clinical trials.

In the following, we will summarize the existing bleeding risk scores, their comparability, and their effect on clinical outcomes, as well as highlight their importance in contemporary clinical decision making and clinical trial design.

BLEEDING EPIDEMIOLOGY IN INTERVENTIONAL CARDIOLOGY

Bleeding is the most common noncardiac complication after PCI and leads to incremental increase in costs of health care. Rao et al\(^1\) recently published an updated bleeding model based on the US National Cardiovascular Data Registry (NCDR) in order to predict the risk of postprocedure major bleeding complications among patients undergoing PCI. Bleeding was defined as adverse events occurring within 72 hours after PCI or before hospital discharge, and the criteria are described in Table 59-1. In contemporary clinical practice describing more than 1 million procedures from over 1000 invasive US centers, this report identified over 60,000 PCI procedures, with postprocedure bleeding comprising an incidence of 5.8% in this cohort. Among the bleeding events, 32% related to a specific anatomic location; 44.6% were detected due to a pre- to postprocedure hemoglobin decrease, 21.8% by a blood transfusion, and 1% by cardiac tamponade; and 0.6% were intracranial hemorrhage events.\(^1\) Approximately half of bleeding events occur at the arterial site and may cover a large spectrum of clinical importance from uncomplicated subcutaneous access site hematoma to fatal retroperitoneal bleeding.

Table 59-1 Bleeding Criteria
<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>TIMI Bleeding Definitions</strong>&lt;sup&gt;46&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Major</td>
<td>Intracranial hemorrhage or a 5 g/dL decrease in the hemoglobin concentration or a 15% absolute decrease in the hematocrit</td>
</tr>
<tr>
<td>• Minor</td>
<td>Observed blood loss (including imaging): 3 g/dL decrease in the hemoglobin concentration or 10% decrease in the hematocrit</td>
</tr>
<tr>
<td></td>
<td>No observed blood loss: 4 g/dL decrease in the hemoglobin concentration or 12% decrease in the hematocrit</td>
</tr>
<tr>
<td>• Minimal</td>
<td>Any clinically overt sign of hemorrhage (including imaging) that is associated with a &lt;3 g/dL decrease in the hemoglobin concentration or &lt;9% decrease in the hematocrit</td>
</tr>
<tr>
<td><strong>GUSTO Bleeding Definitions</strong>&lt;sup&gt;67&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>• Severe or life threatening</td>
<td>Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention</td>
</tr>
<tr>
<td>• Moderate</td>
<td>Bleeding that requires blood transfusion but does not result in hemodynamic compromise</td>
</tr>
<tr>
<td>• Mild</td>
<td>Bleeding that does not meet the criteria for severe or moderate</td>
</tr>
<tr>
<td><strong>ACUITY/HORIZONS Bleeding Definitions</strong>&lt;sup&gt;35&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Major bleeding</td>
<td>Intracranial hemorrhage, intraocular hemorrhage, bleeding at the access site, with a hematoma that was 5 cm or larger or that required intervention; a decrease in the hemoglobin level of 4 g/dL or more without an overt bleeding source; a decrease in the hemoglobin level of 3 g/dL or more with an overt bleeding source; reoperation for bleeding; transfusion of any blood products</td>
</tr>
<tr>
<td>• Minor bleeding</td>
<td>Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life threatening, disabling, or major</td>
</tr>
<tr>
<td><strong>CURE</strong>&lt;sup&gt;68&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Major bleeding</td>
<td>Life-threatening (fatal, intracranial, requiring surgical intervention, results in substantial hypotension requiring the use of intravenous inotropic agents), hemoglobin decrease ≥5 g/dL or required ≥4 units of blood, other major bleeding, transfusion of 2-3 units, intraocular</td>
</tr>
<tr>
<td>• Minor bleeding</td>
<td>Led to discontinuation of study drug</td>
</tr>
<tr>
<td><strong>PLATO</strong>&lt;sup&gt;69&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Major life-threatening bleeding</td>
<td>Fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, decline in the hemoglobin level of 5.0 g/dL or more, or the need for transfusion of at least 4 units of red cells</td>
</tr>
<tr>
<td>• Other major bleeding</td>
<td>Bleeding that led to clinically significant disability (eg, intraocular bleeding with permanent vision loss), bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL but less than 5.0 g/dL or requiring transfusion of 2 to 3 units of red cells</td>
</tr>
<tr>
<td>• Any major</td>
<td>Any bleeding requiring medical intervention but not meeting the criteria for major bleeding</td>
</tr>
<tr>
<td>• Minor</td>
<td>Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)</td>
</tr>
<tr>
<td>• Minimal</td>
<td>All others (eg, bruising, bleeding gums, ooze from injection sites) not requiring intervention or treatment</td>
</tr>
</tbody>
</table>
Subherwal et al.² has described the temporal trends of the incidence of bleeding among 1.7 million patients undergoing PCI between 2005 and 2009.
The finding of a nearly 20% reduction in post-PCI bleeding over time was largely due to temporal changes in antithrombotic strategies, as bivalirudin use increased from 17% to 30% and any heparin plus glycoprotein IIb/IIIa inhibitor decreased from 41% to 28%, while PCI by radial access and the use of vascular closure devices remained similar among all-comer PCI.2

Bleeding varies according to the clinical setting of PCI. In ST-segment elevation MI (STEMI) patients, the usage of fibrinolysis and the hectic preprocedural phase with the associated risk of misdosing anticoagulant regimen and a potentially less thorough assessment of individual bleeding risk, as well as the urgent need to gain vascular access, are all likely contributors to the well described increased incidence of major bleeding complications. Several registries have reported elevated bleeding rates in STEMI patients ranging from 6.5% to 11%.3,4 Intensified antiplatelet and antithrombotic pharmacotherapy in non–ST-segment elevation MI (NSTEMI) patients also makes this subset of patients particularly susceptible to bleeding complications, and the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology [ACC]/American Heart Association [AHA] Guidelines) registry has reported major bleeding rates of almost 12%.

However, the reported bleeding incidence and the associated mortality risk are greatly dependent on the circumstance (RCT vs observational registry with either retrospective or prospective data collection), patient risk presentation (eg, elderly, acute coronary syndrome [ACS], vs non-ACS), and the bleeding criteria applied.

BLEEDING DEFINITIONS

A large number of bleeding definitions exist (see Table 59-1). This is a challenge as bleeding end points are given an increasingly pivotal role as safety end points in clinical randomized trials, but the comparability is low because the criteria may be quite different. For instance, The TIMI (Thrombolysis in Myocardial Infarction) bleeding classification is a laboratory-based scale, while the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleeding classification is a clinically based scale that does not
consider clinical chemistry data. More than 15 different bleeding criteria are currently applied to various degrees and originate from datasets highly differing in setting and inclusion period (see Table 59-1). They are based on RCTs or observational registries or defined by consensus in research consortiums (Table 59-2), originate from treatment periods in the early 1990s to present day, and assess highly varying clinical entities (eg, intracranial hemorrhage or hemoglobin drop) in order to define major bleeding. It is well known that variations in bleeding criteria used to define major bleeding have led to differences in reported rates.5

Table 59-2 Bleeding Academic Research Consortium (BARC) Criteria

<table>
<thead>
<tr>
<th>BARC Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of bleeding</td>
</tr>
<tr>
<td>1</td>
<td>Bleeding that is not actionable and patient does not have unscheduled studies, hospitalization, or treatment by a healthcare professional</td>
</tr>
</tbody>
</table>
| 2 | Any clinically overt sign of hemorrhage that is actionable but does not meet criteria for type 3, 4, or 5 bleeding, meeting at least 1 of the following criteria:  
1. Requiring medical or percutaneous intervention guided by a healthcare professional, including (but not limited to) temporary/permanent cessation or reversal of a medication, coiling, compression, or local injection  
2. Leading to hospitalization or an increased level of care  
3. Prompting evaluation defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging) |
| 3 | Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses |
| 3a | Any transfusion with overt bleeding  
Overt bleeding plus hemoglobin (Hb) drop ≥3 to <5 g/dL<sup>4</sup> (provided Hb drop is related to bleeding) |
| 3b | Overt bleeding plus Hb drop ≥5 g/dL<sup>5</sup> (where Hb drop is related to bleed)  
Cardiac tamponade  
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)  
Bleeding requiring intravenous vasoactive drugs |
| 3c | Intracranial hemorrhage (does not include micro bleeds or hemorrhagic transformation; does include intrasinal). Subcategories: confirmed by autopsy, imaging, or lumbar puncture  
Intraocular bleed compromising vision |
| 4 | Coronary artery bypass graft-related bleeding  
Perioperative intracranial bleeding within 48 hours  
Reoperation following closure of sternotomy for the purpose of controlling bleeding  
Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period  
Chest tube output ≥2 L within a 24-hour period |
| 5 | Categorized further as either definite or probable:  
5a: Probable fatal bleeding is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging  
5b: Definite fatal bleeding is bleeding that is directly observed (either by clinical specimen—blood, emesis, stool, etc—or by imaging) or confirmed on autopsy |

<sup>a</sup>Hemoglobin drop should be corrected for intravenous transfusion in which 1 unit of packed red blood cells or whole blood would be expected to increase hemoglobin by 1 g/dL.<br>Adapted from Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;124:2736-2747.

Intuitively, major bleeding criteria such as the GUSTO criteria, which
only consider clinical variables such as intracranial hemorrhage, hemodynamic compromise, or intervention/clinically significant disability, identify much less major bleeding but convey a much higher mortality prediction than the more recent and sensitive per-protocol bleeding criteria, which in some cases adjudicate major bleeding already at a liberal use of any blood transfusion with overt bleeding, such as the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), REPLACE-2 (The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events), or STEEPLE (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation) criteria. Logically, the latter scores will entail higher estimates of major bleeding, but with less associated mortality hazard (see Table 59-1).

Another example of large differences between major bleeding criteria comes from the REPLACE-2 study investigating bivalirudin with provisional glycoprotein IIb/IIIa inhibitor (GPI) versus heparin with planned GPI in patients undergoing elective or urgent PCI. Bleeding complications were evaluated by the TIMI criteria and the per-protocol REPLACE-2 criteria. When the TIMI major bleeding criteria were used, no difference in bleeding was found; however, when the REPLACE-2 major bleeding criteria were applied, significantly less bleeding was seen in the bivalirudin group. A crucial difference between the TIMI bleeding criteria and the REPLACE-2 bleeding criteria is that a drop in hemoglobin concentration ≥3 g/dL is considered major bleeding in the REPLACE-2 bleeding criteria, but only minor bleeding in the TIMI bleeding criteria (see Table 59-1).

A similar example is found in the STEEPLE trial evaluating 2 different doses of enoxaparin with unfractionated heparin in patients undergoing elective PCI. Again, the TIMI major bleeding criteria were used without finding a difference between any of the groups. Conversely, when the per-protocol STEEPLE major bleeding criteria were used, there was significantly more bleeding in the unfractionated heparin group than in any of the enoxaparin groups. Also in this case, the STEEPLE criteria adjudicate major bleeding when a drop in hemoglobin concentration ≥3 g/dL occurs in the presence of overt bleeding, a finding that only qualifies for minor bleeding according to the TIMI criteria. Furthermore, the STEEPLE criteria consider any transfusion of ≥1 unit of packed red blood cells in the scenario of overt bleeding as pathognomonic for major bleeding, which adds additional variability to the bleeding adjudication as transfusion standards vary
considerably across institutions and regions.

An obvious reason for this large number of per-protocol bleeding criteria is that the earliest major bleeding definitions, such as GUSTO and TIMI, only consider clinically major bleeding and are not very sensitive to other bleeding that requires clinical action and increases treatment items for the patient as well as the length of hospital stay and cost and thus constitutes a sensible end point to measure. Less sensitive bleeding criteria decrease statistical power, thereby augmenting the need for large sample sizes in RCTs. This is especially an issue in the constantly improving environment of the pharmacotherapeutic and technical interventional advances in PCI with consequently decreasing adverse event rates. Less sensitive bleeding criteria have therefore become increasingly less attractive to clinical trial investigators.

Adding to the lack of generalizability of bleeding criteria is the circumstance of their origin (ie, whether they were defined or evaluated in clinical trials with rigorous prospective data collection by clinical coordinators and individual event adjudication by clinical event committees, or whether the outcome was evaluated retrospectively by chart review in observational registries, possibly resulting in underreporting of adverse events). In contrast, bleeding criteria and outcomes from clinical trials can be harder to extrapolate to different clinical settings due to the often narrow inclusion criteria of the trial, whereas registries tend to provide a more accurate image of outcomes in real-world clinical practice.

Finally, large differences in concomitant antiplatelet and anticoagulant regimens, as well as highly variable interventional techniques, have been applied over the years and in publications reporting bleeding outcome from the different criteria.

For all of these reasons, in an effort to harmonize bleeding criteria, standardized bleeding definitions for cardiovascular clinical trials were designed and resulted in a consensus report from the Bleeding Academic Research Consortium (BARC), defining the BARC bleeding criteria, which have recently been validated in an independent population (see Table 59-2).\(^8\) Ndrepepa et al\(^8\) found in this patient-level pooled analysis of 12,459 patients recruited in 6 randomized trials of patients undergoing PCI that BARC class ≥3 was associated with a significant and similar adjusted 1-year mortality hazard of 3.19 (95% confidence interval [CI], 2.34-4.35), compared to TIMI (major + minor; 3.64; 95% CI, 2.62-5.07) and REPLACE-2 (major; 3.14;
95% CI, 2.30-4.29). The European Society of Cardiology Working Group on Thrombosis has stated in their latest issued position paper that bleeding should be reported using at least 2 bleeding scales and 1 of these should be the BARC bleeding criteria.9

**BLEEDING AND OUTCOMES**

The best clinical evidence of the association between bleeding and mortality in ACSs comes from 2 prominent examples in large-scale randomized trials, in which the ischemic end points between the treatment groups were very similar but major bleeding differed significantly, resulting in a mortality benefit associated with the reduced bleeding. This effect was evident in the HORIZONS-AMI (The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial at 30 days and 1 year of follow-up in STEMI patients treated with bivalirudin compared to patients treated with unfractionated heparin and GPs.10 Patients undergoing primary PCI and treated with bivalirudin had a significantly reduced primary end point defined by the non–coronary artery bypass graft (CABG)–related major bleeding rate of 4.9% versus 8.3% in patients treated with heparin plus a provisional GPI, resulting in a significant decrease in death as a result of cardiac cause from 2.8% to 1.8%. At the same time, ischemic outcome in terms of reinfarction, revascularization stroke, and all ST (acute and subacute) did not differ, indicating that the survival benefit is attributable to the improved bleeding profile of bivalirudin at 30 days of follow-up. This difference between groups widened even more in the time period between 30 days and 1 year after PCI. Cardiac death and reinfarction occurred less frequently in patients treated with bivalirudin. This long-term reduction might have been attributable to the prevention of iatrogenic hemorrhagic complications. The rates of all-cause mortality, cardiac mortality, and stroke were each 5-fold higher in patients with major bleeding compared to those without major bleeding, while the rate of reinfarction was 2 times higher.11

A similar effect of decreased major bleeding associated with improved survival has also been reported in patients without STEMI. While the rates of death, MI, or refractory ischemia through day 9 after hospitalization were equal between groups, non–ST-segment elevation ACS patients randomized to fondaparinux treatment had a lower rate of major bleeding at 9 days and
significantly improved 6-month survival compared with patients assigned to enoxaparin.\textsuperscript{12} The OASIS-5 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial therefore constitutes another example of a survival benefit attributable to an improved bleeding profile. Since then, several other substudies in cohorts originating from RCTs have confirmed that major bleeding is a powerful independent predictor in ACS populations of 30-day\textsuperscript{13} and 1-year mortality\textsuperscript{14} regardless of the bleeding criteria used. Major bleeding has also been associated with ischemia end points and ST.\textsuperscript{13}

In observational data from over 3 million all-comer procedures in the NCDR CathPCI Registry performed in the United States between 2004 and 2011, a propensity-matched analysis revealed that postprocedural bleeding events were associated with increased risk of in-hospital mortality and that approximately 1 out of 8 deaths was related to bleeding complications. Major bleeding was associated with increased in-hospital mortality with a number needed to harm (NNH) of 29. The association between major bleeding and in-hospital mortality was observed in all strata of preprocedural bleeding risk, although NNH decreased substantially across NCDR bleeding risk strata (high: NNH = 21; intermediate: NNH = 39; and low: NNH = 69). Although both access site (NNH = 117) and non–access site bleeding (NNH = 16) were associated with increased in-hospital mortality, the mortality risk associated with access site bleeding was substantially lower than for non–access site bleeding.\textsuperscript{15} Both access and non–access site bleeding events occurring within 30 days of PCI were also independently associated with an increased long-term risk of mortality at 1-year follow-up. Non–access site bleeding has recently been confirmed to be a stronger correlate of mortality than access site bleeding, and it improves the discriminatory power of models for mortality prediction.\textsuperscript{16}

In patients with MI, nuisance bleeding (BARC 1) is common in the following year, related with ongoing use of dual antiplatelet therapy (DAPT) and independently associated with worse patient perception of quality of life.\textsuperscript{17} Whether or not premature DAPT cessation after PCI due to nuisance bleeding is associated with increased rates of ST or MI is not well described. Improved selection of patients for prolonged DAPT may help minimize the incidence and adverse consequences of nuisance bleeding. Bleeding outcomes in relation to criteria, patient presentation, and circumstance of data collection are summarized in Table 59-3. The clinical variables defining the
various bleeding criteria are summarized in Table 59-4.

### Table 59-3 Incidence of Bleeding and the Association with Short- and Long-Term Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Year</th>
<th>Setting, Design</th>
<th>Primary Definition</th>
<th>Patients</th>
<th>Bleeding Events, No. (%)</th>
<th>Death Rate, %</th>
<th>Adjusted Risk Ratio for Death (95% CI)</th>
<th>Death Rate, %</th>
<th>Adjusted Risk Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlani et al⁹⁶</td>
<td>2010</td>
<td>STEMI, registry</td>
<td>Protocol defined</td>
<td>1389</td>
<td>152 (10.9)</td>
<td>19.7 vs 8.2</td>
<td>2.8 (1.8-4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matic et al⁹⁷</td>
<td>2013</td>
<td>STEMI, registry</td>
<td>BARC</td>
<td>1808</td>
<td>115 (6.4) BARC ≥ 2</td>
<td>10 vs 6.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRACE⁹⁸</td>
<td>2003</td>
<td>ACS, registry</td>
<td>GRACE</td>
<td>24,045</td>
<td>933 (3.9)</td>
<td>18.6 vs 5.1</td>
<td>1.6 (1.2-2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rao et al⁹⁹</td>
<td>2005</td>
<td>NSTE-ACS, RCT</td>
<td>GUSTO</td>
<td>26,452</td>
<td>107 (0.4)</td>
<td>25.7 vs 2.9</td>
<td>10.6 (8.3-13.6)</td>
<td>35.1 vs 4.2</td>
<td>7.5 (6.1-9.3)</td>
</tr>
<tr>
<td>Eikelboom et al⁰⁰</td>
<td>2006</td>
<td>NSTE-ACS, RCT</td>
<td>CURE</td>
<td>34,146</td>
<td>763 (2.3)</td>
<td>12.8 vs 2.5</td>
<td>9.8 (7.5-12.7)</td>
<td>4.6 vs 2.9</td>
<td>1.9 (1.3-2.8)</td>
</tr>
<tr>
<td>ACUITY⁰¹</td>
<td>2007</td>
<td>NSTE-ACS, RCT</td>
<td>ACUITY</td>
<td>13,819</td>
<td>644 (4.7)</td>
<td>7.3 vs 1.2</td>
<td>7.6 (4.7-12.2)</td>
<td>3.5 (2.7-4.4)</td>
<td></td>
</tr>
<tr>
<td>GRACE⁰²</td>
<td>2007</td>
<td>ACS, registry</td>
<td>GRACE</td>
<td>40,087</td>
<td>1140 (2.8)</td>
<td>20.9 vs 5.6</td>
<td>1.9 (1.6-2.2)</td>
<td>7.9 vs 5.2</td>
<td>0.8 (0.6-1.0)</td>
</tr>
<tr>
<td>OASIS-5⁰³</td>
<td>2009</td>
<td>NSTE-ACS, RCT</td>
<td>ESSENCE</td>
<td>20,078</td>
<td>990 (4.9) major 423 (2.1) minor</td>
<td>8.4 vs 2.7</td>
<td>3.5 (2.6-4.6)</td>
<td>14.3 vs 5.4</td>
<td>3.1 (2.6-4.8)</td>
</tr>
<tr>
<td>CRUSADE⁰⁴</td>
<td>2012</td>
<td>NSTEML registry</td>
<td>CRUSADE</td>
<td>32,895</td>
<td>3902 (11.9)</td>
<td>8.4 vs 5.3</td>
<td>1.3 (1.2-1.5)</td>
<td>29.3 vs 21</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>Kinnaird et al⁰⁵</td>
<td>2003</td>
<td>PCI &gt;50% urgent, registry</td>
<td>TIMI</td>
<td>10,974</td>
<td>588 (5.4) major 1394 (12.7) minor</td>
<td>7.5 vs 0.6</td>
<td>3.5 (1.9-6.7)</td>
<td>17.2 vs 5.5</td>
<td>Not significant</td>
</tr>
<tr>
<td>REPLACE-2⁰⁶</td>
<td>2007</td>
<td>PCI &gt;50% elective, RCT</td>
<td>REPLACE-2/ ISAR-REACT 3</td>
<td>6001</td>
<td>195 (3.2) major 5.1 vs 0.2</td>
<td>8.7 vs 1.9</td>
<td>2.7 (1.4-4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ndrepepa et al⁰⁷</td>
<td>2008</td>
<td>PCI &gt;50% elective, RCT meta-analysis</td>
<td>TIMI</td>
<td>5384</td>
<td>59 (1.1) major 156 (2.9) minor</td>
<td>12.2 vs 3.3</td>
<td>4.1 (2.1-4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVENT⁰⁸</td>
<td>2009</td>
<td>PCI &gt;60% elective, nonSTEMI, nonSTEMI registry</td>
<td>TIMI</td>
<td>5961</td>
<td>0.7 major 7.9% minor 174 (3.8) major 381 (6.5) minor</td>
<td>3.9 (1.5-10.5)</td>
<td>21.9 vs 2.4</td>
<td>3.8 (2.5-5.9)</td>
<td></td>
</tr>
<tr>
<td>ISAR-REACT 3⁰⁹</td>
<td>2010</td>
<td>PCI &gt;80% elective, all TIMI negative, RCT</td>
<td>REPLACE-2/ ISAR-REACT 3</td>
<td>4570</td>
<td></td>
<td></td>
<td></td>
<td>5.2 vs 1.3</td>
<td>4.1 (2.6-6.5)</td>
</tr>
<tr>
<td>HORIZONS-AMI, ACUITY, REPLACE-2 ⁻дают</td>
<td>2011</td>
<td>PCI &gt;70% urgent PCI, RCT pooled</td>
<td>TIMI</td>
<td>17,034</td>
<td>267 (1.6) major</td>
<td>21.0 vs 2.2</td>
<td>4.9 (3.6-6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ndrepepa et al, ISAR²⁰</td>
<td>2012</td>
<td>PCI &gt;70% elective, PCI pooled</td>
<td>BARC</td>
<td>12,459</td>
<td>1233 (9.9) 5,4% BARC ≥ 2</td>
<td>3.2 vs 0.3</td>
<td>6.0 vs 2.1</td>
<td>2.7 (2.0-3.6)</td>
<td></td>
</tr>
<tr>
<td>CathPCI Registry, NCDB²¹</td>
<td>2013</td>
<td>PCI &gt;50% urgent, registry</td>
<td>CathPCI Registry Bleeding criteria</td>
<td>3,386,688</td>
<td>57,246 (1.7%)</td>
<td>5.3 vs 1.9</td>
<td>3.4 (3.2-3.59)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACS, acute coronary syndrome; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; BARC, Bleeding Academic Research Consortium; CI, confidence interval; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events Study; CRUSADE, Clopidogrel in Unstable Angina to Prevent Recurrent Events Study; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events Study; EENT, Evaluation of Drug-Eluting Stents and Iberian Events; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Use of Strategies to Open Occluded Arteries; ISAR-REACT 3, Intravenous Thrombolysis and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; NCDR, National Cardiovascular Data Registry; NSTE, non-st-segment elevation; NSTEML, NSTEMI, non-ST-segment elevation myocardial infarction; OASIS-5, Organization for the Assessment of Strategies for Ischemic Syndromes; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; REPLACE-2, Randomized Evaluation in PCI Linking Angioplasty to Reduced Clinical Events; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; Trt, treatment; Trt, treatment.

### Table 59-4 Summary of Clinical Variables Defining the Various Bleeding Criteria
PATHOPHYSIOLOGIC TIES BETWEEN BLEEDING AND MORTALITY

Several possible mechanisms explaining the association between bleeding and mortality exist. First, considerable overlap between bleeding and ischemic risk factors has been described, and bleeding has been suspected to act as a mere marker of increased mortality risk, rather than inferring a causal relationship. Conversely, consequences of bleeding are consistently reported to be independently associated with increased short- and long-term survival and constitute pathologic mechanisms that convey proven and biologically very meaningful risk indices of mortality. These mechanisms are likely to be multifactorial, but obvious consequences of bleeding include the rare cases of truly life-threatening or fatal bleeding, such as intracranial hemorrhage, as well as the consequences of blood loss entailing volume depletion, anemia, and hypotension. These mechanisms might be especially relevant in vulnerable STEMI patients with coronary artery disease susceptible to supply and demand mismatches, leading to possible deterioration with arrhythmias, hypovolemic instability, and shock, which
occur either directly as a result of decreased oxygen delivery to target organs or as part of a vicious circle of hypotension and myocardial ischemia entailing decreasing cardiac output, organ hypoperfusion, and cardiogenic/hypovolemic shock.

Another direct consequence of bleeding is disruption of antiplatelet therapy, which potentially puts the patient at increased risk of adverse ischemic outcomes by allowing aggregation of new thrombus material on uncovered stent struts without neoendothelialization: DAPT disruption in patients treated with drug-eluting stents has been found to convey a 12-fold adjusted hazard for major adverse cardiovascular events within the first 7 days after disruption. In addition, those with major bleeding have longer in-hospital stays and undergo more procedures, which may increase the chances of an adverse outcome, such as nosocomial respiratory, gastrointestinal, or blood infections or procedural complications.

Bleeding is often approached with a common and liberal use of transfusion, even though the effect of transfusions on mortality in many patients with coronary artery disease is at best neutral, as no positive effect could be identified in patients with a hematocrit >30%. Rao et al showed in a pooled analysis of 24,112 patients from clinical trials that even after adjusting for the propensity to receive blood and other confounders, transfusion was associated with a 4-fold hazard for 30-day death. Furthermore, a transfusion hemoglobin threshold of 7 or 8 g/dL, compared with higher hemoglobin thresholds, is associated with fewer red blood cell units transfused without adverse associations with mortality, cardiac morbidity, functional recovery, or length of hospital stay. Many potential mechanisms for the adverse effects of transfusion have been described, including activation of inflammatory cascades, platelet activation and aggregation, impaired delivery of oxygen and nitric oxide, vasoconstriction, and subsequently thrombosis and tissue ischemia. All of these could lead to paradoxical decreases in tissue oxygenation. However, it has to be stated that all of these data connecting transfusion to poorer outcome in patients with coronary artery disease are retrospective and have to be interpreted with caution.

Considerations regarding transfusion thresholds are important for the assessment of bleeding criteria, as the above pathologic considerations related to transfusion create different transfusion strategies in different health care
systems and are subject to change over time as new evidence regarding blood transfusion in coronary artery disease patients emerges. Therefore, bleeding criteria, such as the GUSTO score, that only apply clinical findings and do not incorporate hemoglobin or hematocrit levels will be less generalizable.

**RISK FACTORS PREDICTING BLEEDING**

In clinical practice, balancing the ischemic and bleeding risk is of utmost importance. It has been argued that comorbidity accounts for the excess mortality seen in patients with major bleeding, and that although bleeding may be causally related to adverse outcomes in some patients, it is often merely a marker for patients at higher risk for adverse events. Therefore, balancing ischemic and bleeding risk can seem like an unmanageable task, as both risk realms occur in the same type of patients. Nevertheless, numerous studies report that non–CABG-related bleeding within 30 days is strongly and independently associated with an increased risk of subsequent mortality at 1 year in patients undergoing PCI for all indications. In addition, Pocock et al have demonstrated that prognostic modeling of individual patient risk of ischemic and hemorrhagic complications and their mortality impact within 30 days in the ACUITY trial has identified several independent predictors that differ for MI and major bleeding. Independent predictors of MI were elevated biomarkers, family history of coronary artery disease, age, ST-segment elevation $\geq 1$ mm, and previous MI. Age and ST-segment elevation $\geq 1$ mm were also predictors for bleeding; however, importantly, female sex, anemia, serum creatinine, white blood cell count, previous cerebrovascular accident, previous PCI, bivalirudin plus GPI as opposed to lone bivalirudin treatment, and upstream GPIs as opposed to deferred GPIs all predicted major bleeding, but not ischemic events, on an individual basis. Some of these bleeding predictors were also identified in the CRUSADE bleeding score, namely female sex, anemia, creatinine clearance, and previous vascular disease (others were hypotension, tachycardia, signs of congestive heart failure at presentation, and diabetes mellitus). Mehran and colleagues subsequently built a risk score based on the ACUITY and HORIZONS-AMI trials, with female sex, serum creatinine, and anemia being the central
demographic risk contributors. Despite matching for age, body mass index, and type of antithrombotic therapy, bleeding risk after PCI remains significantly higher in women than in men. Bleeding is associated with increased risk of 1-year mortality with no bleeding-by-sex interaction, which illustrates that bleeding is as detrimental for 1-year survival in women as in men, but occurs more frequently in women. Female sex, low body mass index, and renal insufficiency have been consistent independent predictors of major bleeding, which is important knowledge for bleeding avoidance strategies.

It follows that although considerable overlap exists between risk predictors of bleeding and ischemic outcome, consideration of the individual risk profile for patients undergoing PCI and the relative treatment effects of alternative antithrombotic pharmaceutical regimen permits personalized decision making to optimize therapy of patients with ACS.

The clinical risk factors comprising the 3 most commonly applied bleeding risk scores are summarized in Table 59-5.

Table 59-5 Clinical Risk Factors Comprising the 3 Most Commonly Applied Bleeding Risk Scores

<table>
<thead>
<tr>
<th>Bleeding Predictors</th>
<th>CRUSADE III</th>
<th>NCDR CathPCI Registry</th>
<th>ACUITY/HORIZONS-AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Age</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>White blood cell count</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>ACS presentation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Antithrombotic medication: UFH + GPI vs bivalirudin</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CHF at presentation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prior vascular disease</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>No previous PCI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; CHF, congestive heart failure; GPI, glycoprotein IIIb/IIIa inhibitor; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
PCI-related bleeding may be avoided by different strategies such as the use of bivalirudin, radial access, vascular closure devices, and attention to appropriate dosing.

Compared with unfractionated heparin and provisional GPIs, bivalirudin has been shown to reduce bleeding in the setting of STEMI, both when administered in the prehospital phase\textsuperscript{25} as well as immediately before and during primary PCI.\textsuperscript{10} Bivalirudin also reduced major bleeding after subacute PCI in non–ST-segment elevation ACSs\textsuperscript{26} and after elective PCI in stable coronary artery disease.\textsuperscript{6} However, in both the HORIZONS-AMI and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trials, conducted in the STEMI setting, the use of bivalirudin was associated with an increased risk of acute ST. Balancing bleeding and ischemic risk in these patients should therefore involve rigorous upstream antiplatelet therapy with early loading doses of P2Y\textsubscript{12} inhibitors, which in combination with bivalirudin do not seem to increase bleeding.\textsuperscript{27}

The beneficial bleeding profile of bivalirudin has recently been contested due to the evolution of pharmacoinvasive strategies in PCI. The HEAT-PPCI trial presented at the ACC 2014 meeting in Washington, DC, showed that primary PCI patients treated with weight-adjusted (low-dose) unfractionated heparin had similar outcomes than patients treated with bivalirudin regarding the end point of major bleeding (3.1\% vs 3.5\%), whereas patients treated with unfractionated heparin had significantly better results in terms of the composite of major adverse cardiac events (5.7\% vs 8.7\%) driven by a 4-fold higher rate of definite or probable ST (0.9\% vs 3.4\%), particularly acute ST. Both groups had similar use of bailout GPIs (15.5\% vs 13.5\%). This is the third study indicating an increased risk of acute ST (within hours of the end of primary PCI) in bivalirudin-treated STEMI patients, which has previously been reported in HORIZONS-AMI\textsuperscript{10} and EUROMAX.\textsuperscript{25} Only the HORIZONS-SWITCH protocol has so far indicated a way to mitigate this early ST risk, which occurs if heparin is given at the time of very first patient contact.\textsuperscript{28} Therefore, STEMI patients should be indeed treated with an anticoagulant as early as possible (eg, ambulance, emergency room, hospital floor), regardless of the final anticoagulant strategy and without waiting for sophisticated therapies to get started in the interventional suite.

The BRAVE-4 trial, presented at the same convention, showed that non–CABG-related bleeding was numerically higher in primary PCI patients
treated with prasugrel plus bivalirudin compared with patients treated with clopidogrel plus unfractionated heparin (14.1% vs 12.0%; \( P = .54 \)), while the primary composite end point of death, MI, unplanned revascularization of the infarct-related artery, ST, stroke, or major bleeding did not differ. There was a trend toward higher use of GPIs in the clopidogrel plus unfractionated heparin arm. However, BRAVE-4 was terminated early due to slow recruitment and was thus underpowered to test its primary hypothesis. Both trials have been subject to much controversy as they have given the indication that the beneficial bleeding profile of bivalirudin seen in previous trials is in fact due to the higher use of GPIs in the unfractionated heparin comparator groups.

Both HEAT and BRAVE-4 were conducted using potent oral as opposed to parenteral antiplatelet agents, thereby indicating once again how multidimensional the field of combination pharmacologic therapy has become in the treatment of STEMI PCI. This field will continue to evolve, and new studies will shed light on the new set of questions that has arisen.

The benefit of the radial approach in terms of adverse ischemic and bleeding outcome is controversial. In the RIVAL trial (Radial Versus Femoral Access for Coronary Intervention) in ACS patients, the rate of death, MI, or stroke at 30 days did not differ between patients randomized to PCI by radial or femoral access.\(^{29}\) In addition, the rate of non–CABG-related major bleeding at 30 days was similar in both groups. However, there was an overall significantly lower rate of large hematomas and pseudoaneurysms needing closure in the radial group. In prespecified subgroup analyses, those benefits in vascular complications were observed in all types of centers, whereas a beneficial effect of the radial approach for death, MI, or stroke was found only in high-volume centers and in STEMI patients.

The data regarding a mortality benefit associated with radial access in STEMI patients as found in the RIVAL subanalysis are disputed. In the multicenter randomized STEMI-RADIAL trial, patients treated with primary PCI by radial access by operators experienced in both access sites had a significantly lower incidence of major bleeding, fewer access site complications, shorter intensive care stay, and less contrast utilization; however, no survival benefit with radial access was shown at the 30-day follow-up.\(^ {30}\) Conversely, a recent meta-analysis of RCTs also indicated a significantly decrease mortality hazard associated with radial access in STEMI patients.\(^ {31}\)
The benefits of vascular closure devices (VCD) were investigated in the ACUITY trial. Access site bleeding was defined as requiring interventional or surgical correction, hematoma ≥5 cm at the access site, retroperitoneal bleeding, or hemoglobin drop ≥3 g/dL with ecchymosis or hematoma <5 cm, oozing blood, or prolonged bleeding (>30 minutes) at the access site. Almost 40% of patients received a VCD; rates of major access site bleeding were lower with VCD compared with no VCD and were lowest in patients treated with bivalirudin monotherapy and a VCD.32

Appropriate dosing of antiplatelet and anticoagulant treatment is an obvious strategy to reduce bleeding. The magnitude of misdosing has been highlighted in data from the CRUSADE registry.33 In this observational study, Alexander et al33 showed that more than 40% of the patients who were administered antithrombotic agents received at least 1 dose outside the recommended range and that bleeding increased relative to the degree of excess dose and to the number of agents administered in excess, which in turn translated into higher mortality and longer length of stay among patients administered excess dosing. The authors estimated that 15% of major bleeding in this particular cohort may have been attributable to excess dosing. Elderly patients with ACS33 and women with ACS34 are more likely to be overdosed with antithrombotic agents. Consequently, taking age, gender, body weight, and renal insufficiency into consideration when dosing antithrombotic agents is a crucial step to reduce bleeding in PCI populations.

Finally, appropriate operator techniques for proper arterial puncture at access site and technical developments such as smaller sheath sizes contribute to bleeding reduction. Fluoroscopy will help to locate the middle third of the femoral head as a landmark for identifying an optimal puncture site in the common femoral artery above the bifurcation but below the inferior epigastric artery. Arteriotomy at the appropriate anatomic location will reduce the risk of bleeding and retroperitoneal hematomas.35

Surprisingly, although bleeding avoidance strategies have been associated with significantly lowering bleeding rates, these strategies are paradoxically less often used among higher risk patients.36

Indeed, incorporation of preprocedural routine estimates of individualized bleeding risk affects physicians’ utilization of bivalirudin during PCI and might change the risk-treatment paradox in which patients at highest risk for bleeding are least likely to receive bleeding avoidance strategies. In 6491 PCI
procedures, Rao et al\textsuperscript{37} demonstrated that overall bivalirudin use significantly increased in the postimplementation period in intermediate (27%-35\%) and high bleeding risk patients (25%-43\%), and decreased in low-risk patients (30%-25\%).\textsuperscript{37} As women continue to have an almost 2-fold greater rate of bleeding following PCI compared with men, the use of effective bleeding avoidance strategies is particularly important in women.\textsuperscript{38}

Bleeding avoidance strategies are summarized in Table 59-6.

Table 59-6 **Bleeding Avoidance Strategies for Patients Undergoing Percutaneous Coronary Intervention (PCI)**

<table>
<thead>
<tr>
<th>Preprocedural routine estimates of individualized bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial approach for PCI</td>
</tr>
<tr>
<td>Usage of bivalirudin during PCI</td>
</tr>
<tr>
<td>Usage of vascular closure devices</td>
</tr>
<tr>
<td>Attention to appropriate dosing, based on age, sex, weight, and renal function</td>
</tr>
<tr>
<td>Attention to proper puncture site identification in femoral approach</td>
</tr>
<tr>
<td>Use of smallest possible sheath sizes</td>
</tr>
</tbody>
</table>

**TREATMENT OF BLEEDING**

Symptoms of hypervolemia such as unconsciousness, altered consciousness with confusion, anxiety or agitation, general weakness, cool and clammy skin and pallor, rapid breathing, decreased or no urine output, hypotension, and tachycardia should all evoke an acute diagnostic workup for seeking bleeding sources. In the absence of (or in addition to) overt hematomas and oozing from puncture sites, urgent diagnostic imaging in order to exclude cardiac tamponade (transthoracic echocardiography), intracranial hemorrhage (computed tomography [CT] of brain), or retroperitoneal bleeding (CT angiography) should be performed. In major overt bleeding, PCI-related antithrombotic therapy should be discontinued temporarily, which obviously will increase the risk of acute adverse ischemic events. Bleeding is often approached with a liberal use of transfusion; however, it should be
considered that in absence of overt life-threatening bleeding, the effect of transfusions on mortality is at best neutral in coronary artery disease patients with a hematocrit >30%, and a transfusion hemoglobin threshold of 7 or 8 g/dL appears recommendable. In case of life-threatening bleeding, treatment with inotropes and vasopressors might be needed.

BLEEDING COMPlications AFTER TRANsCATHERETER AORTIC VALVE REPLACEMENT

Bleeding complications are also an important end point measure in other percutaneous interventions. Patients undergoing transcatheter aortic valve replacement (TAVR) are an elderly and high-risk population undergoing femoral access site puncture with a large size French sheath and often lengthy procedures. Criteria for bleeding complications in TAVR have been standardized in the Valve Academic Research Consortium (VARC) Bleeding Definitions (Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials) and are based on the BARC bleeding criteria (Table 59-7).

### Table 59-7 Valve Academic Research Consortium (VARC) Bleeding Definitions

<table>
<thead>
<tr>
<th>Life-threatening or disabling bleeding</th>
<th>Fatal bleeding (BARC type 5) OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR</td>
</tr>
<tr>
<td></td>
<td>Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR</td>
</tr>
<tr>
<td></td>
<td>Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units' (BARC type 3b)</td>
</tr>
<tr>
<td>Major bleeding (BARC type 3a)</td>
<td>Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND</td>
</tr>
<tr>
<td></td>
<td>Does not meet criteria of life-threatening or disabling bleeding</td>
</tr>
<tr>
<td>Minor bleeding (BARC type 2 or 3a, depending on the severity)</td>
<td>Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major</td>
</tr>
</tbody>
</table>

*Given that 1 unit of packed RBCs typically will raise the hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.


Larger sheath sizes are a well-known predictor of bleeding complications.
in percutaneous cardiac interventions. In contrast to the Edwards Sapien Valve, which requires either large 22- or 24-Fr sheaths for delivery, the CoreValve is delivered through an 18-Fr sheath. The newer Edwards Sapien XT Valve can also be delivered through an 18-Fr sheath. Currently, therefore, bleeding complications are a natural element of treating patients with transfemoral TAVR and had a 30-day incidence of 11% in the PARTNER-I trial. Recently, VARC major in-hospital bleeding was described to occur with an in-hospital incidence of 3.5% in observational data from 7710 patients undergoing TAVR, gathered in the US national registry (the Society of Thoracic Surgeons [STS]/ACC Transcatheter Valve Therapy [TVT] Registry).

A purely empirical DAPT strategy is commonly used; however, 2 smaller studies have recently shown that a strategy using aspirin alone has been shown to reduce life-threatening bleeding without increasing the risk of stroke or MI. A trial testing whether a procedural anticoagulant strategy with bivalirudin improves bleeding outcomes compared with unfractionated heparin is currently enrolling.

### BLEEDING IN PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING PCI

Anticoagulation with vitamin K antagonist (VKA) agents has been the standard of care for several decades and has been considered superior to DAPT in preventing stroke and thromboembolism in atrial fibrillation (AF) patients who do not undergo PCI. Conversely, in patients in need of PCI, DAPT with aspirin and a thienopyridine has been shown to be more beneficial in preventing ST than oral anticoagulation alone.

The current AHA guidelines on AF for patients undergoing PCI are nonspecific because they recommend “low-dose aspirin (less than 100 mg per d) and/or clopidogrel (75 mg per d), which may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding. (Class IIB; Level of Evidence: C).” Recently, 1 European and
North American consensus paper stated that triple therapy (TT) with warfarin, aspirin, and thienopyridine should be preferred for AF patients undergoing PCI with stenting and with a CHADS₂ score >1. The length of TT in these patients is dependent on stent type and the assessment of ischemic and bleeding risk. Simultaneously, it is well recognized that the benefits of TT come with a significant 3-fold increase in bleeding risk compared to warfarin monotherapy and a 5-fold increase compared to DAPT, and these hazards increase further with longer durations of TT. For this reason, the guidelines indicate that the choice of discharge therapy should be dependent on balancing the risk of bleeding and thromboembolism in each individual patient.

These consensus statements have recently been challenged by the WOEST trial, which found that in patients undergoing PCI and on an anticoagulant therapy (69% indication AF, 88% CHADS₂ >1), the use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events, as compared to TT. A recent Danish nationwide retrospective study based on dispensed drug prescriptions in real-life AF patients hospitalized with an MI and/or undergoing PCI in the period from 2001 to 2009, oral anticoagulant therapy plus clopidogrel was equal or better than TT regarding both benefit and safety outcomes, essentially confirming the WOEST trial.

Estimating major bleeding risk in patients with AF undergoing PCI is performed with the HAS-BLED score. The HAS-BLED bleeding risk score is an AF-specific score based on hypertension, abnormal renal function (dialysis, renal transplantation, or serum creatinine >200 mmol/L) and liver function (chronic hepatic disease or biochemical evidence of significant hepatic derangement, bilirubin >2 times upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 times upper limit of normal), stroke, bleeding (history or bleeding predisposition), labile international normalized ratio (INR; unstable INR or poor time in the therapeutic range <60%), elderly status (eg, age >65 years), and use of drugs or alcohol (Table 59-8). Major bleeding was defined in the HAS-BLED study as intracranial, requiring hospitalization, involving hemoglobin decrease >2 g/L, and/or requiring transfusion, and major bleeding was assessed at 1 year.
### HAS-BLED Bleeding Risk Score Criteria

<table>
<thead>
<tr>
<th><strong>Hypertension</strong></th>
<th>1 point for uncontrolled high systolic blood pressure (SBP) with a SBP ≥160 mm Hg</th>
</tr>
</thead>
</table>
| **Abnormal kidney and/or liver function** | 1 point for impaired kidney or liver function  
2 points for both |
| **Stroke** | 1 point for previous history of stroke, especially deep brain (lacunar) stroke |
| **Bleeding** | 1 point for previous history of bleeding, anemia, or predisposition to bleeding |
| **Labile international normalized ratio (INR)** | 1 point for unstable or high INRs or <60% of time in therapeutic range |
| **Elderly** | 1 point for age 65 or older |
| **Drugs and/or alcohol** | 1 point for taking antiplatelets agents  
1 point for consuming 8 or more alcoholic drinks per week (or 2 points for both) |

The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) bleeding risk score determines major bleeding risk for patients on warfarin. It is composed of anemia (hemoglobin <13 g/dL in men and <12 g/dL in women), severe renal disease (glomerular filtration rate <30 mL/min or dialysis dependent), age ≥75, any prior hemorrhage diagnosis (eg, gastrointestinal bleed, intracranial hemorrhage), or a history of hypertension. Major hemorrhage was defined from clinical databases by retrospective search of International Classification of Diseases, Ninth Revision, codes for extracranial hemorrhages (ie, gastrointestinal, genitourinary, retroperitoneal) and primary and secondary diagnoses of intracranial hemorrhage, including intracerebral, subarachnoid, or subdural hemorrhages, which were confirmed by chart review and restricted to fatal,
requiring transfusion of ≥2 units of packed blood cells, or hemorrhage into a critical anatomic site (e.g., intracranial, retroperitoneal).

The HEMORR\textsuperscript{2}HAGES risk score\textsuperscript{58} was developed from existing classification schemes, classified into a new scheme, and validated in 3791 AF patients in a combined Medicare inpatient administrative dataset from 7 states.\textsuperscript{58} The score assigns 2 points for a prior bleed and 1 point for each variable shown in Table 59-9. Patients are stratified into low, intermediate, and high risk for major bleeding according to scores of 0 to 1, 2 to 3, and ≥4, respectively. In patients prescribed warfarin, HEMORR\textsuperscript{2}HAGES had a greater predictive accuracy than older bleed prediction schemes. Interestingly, the score performed similarly in subjects prescribed aspirin or no antithrombotic therapy.

Table 59-9 HEMORR\textsuperscript{2}HAGES Bleeding Risk Score Criteria

<table>
<thead>
<tr>
<th><strong>Hepatic or renal disease</strong></th>
<th>1 point for hepatic disease with history of cirrhosis, 2-fold or greater elevation of AST or ALT, or albumin &lt;3.6 g/dL or 1 point for renal insufficiency with creatinine clearance &lt;30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethanol abuse</strong></td>
<td>1 point for ethanol abuse</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>1 point for a current cancer diagnosis</td>
</tr>
<tr>
<td><strong>Older age</strong></td>
<td>1 point for age &gt;75 years</td>
</tr>
<tr>
<td><strong>Reduced platelet count or function</strong></td>
<td>1 point for reduced platelet count or function</td>
</tr>
<tr>
<td><strong>Rebleeding risk</strong></td>
<td>2 points for a prior bleed</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1 point for uncontrolled hypertension</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>1 point for most recent hemoglobin &lt;10 g/dL or hematocrit &lt;30%</td>
</tr>
</tbody>
</table>
Genetic factors
1 point for CYP2C9 single-nucleotide polymorphisms

Excessive fall risk (including neuropsychiatric disease)
1 point for previous history of fall risk

Stroke
1 point for previous stroke or brain infarct detected by brain imaging

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The use of the ATRIA and HEMORR$_2$HAGES risk scores in clinical practice is currently debated because it has been demonstrated that the HAS-BLED score shows significantly better prediction accuracy than the weighted (and more complex) ATRIA and HEMORR$_2$HAGES scores.

Finding the right balance that minimizes bleeding risk and maintains anti-ischemic efficacy remains a complex and controversial clinical dilemma in these unique patients. The arrival of novel antiplatelet agents and anticoagulants on the scene has led to an exponential increase in the combinations that may be employed by clinicians in real-life situations. At present, 4 novel and approved oral anticoagulant options have been studied in AF populations (dabigatran, rivaroxaban, apixaban, and edoxaban), none of which have been tested in connection with PCI or any of the 4 commonly used oral antiplatelet options (aspirin, clopidogrel, ticagrelor, prasugrel). Just the sheer number of combinations means that the best antiplatelet and oral anticoagulant combination based on data from RCTs will not be known for many years. At present, clinical trials for some of the novel oral anticoagulant options have either been announced or started to enrolled AF patients undergoing PCI, but results will not be available for another couple of years.

CONCLUSION

The outcome measure of bleeding in patients undergoing percutaneous cardiovascular interventions has evolved into a central and permanent end point in RCTs, as an increased number of studies rely on the combined end point of ischemic and bleeding adverse events in order to describe net clinical
benefit of a new antiplatelet or anticoagulant drug. In addition, in clinical practice, increased attention is steered toward the avoidance of bleeding complications, with the goal of balancing antithrombotic regimens to the benefit of patients undergoing PCIs and TAVR, with or without AF.

In an effort to produce comparable data, the number of bleeding criteria applied should be limited, and reporting 1 bleeding criterion of choice as well as 1 standardized set of criteria, such as the definitions by BARC or VARC, should become the standard method for reporting bleeding complications in a randomized or observational context.

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clinical risk algorithm from the National Cardiovascular Data Registry. 
Stent Thrombosis

Sorin J. Brener
Gregg W. Stone

INTRODUCTION

Percutaneous coronary intervention (PCI) is one of the most common procedures performed in US and European hospitals. In the United States, 954,000 PCI procedures were performed in 2010, and in over 90% of these procedures, at least 1 coronary stent was implanted. Stent thrombosis (ST) is the most feared complication of coronary stenting and is characterized by rapid accumulation of thrombus within or adjacent to the stent. ST is typically associated with the abrupt onset of an acute coronary syndrome (ACS), manifesting as severe unstable angina, acute myocardial infarction, or sudden cardiac death. ST should be distinguished from progressive in-stent restenosis, resulting in eventual vessel occlusion, typically presenting as progressive exertional angina, but occasionally as ACS.

In this chapter, we will review the classification of ST, the pathophysiology and predictors of ST, its consequences and treatment, and ongoing efforts to prevent this rare but major complication of percutaneous coronary revascularization. Data will be presented separately for bare metal stents (BMS; in aggregate for all types) and for first-generation (G1) and second-generation (G2) drug-eluting stents (DES). The G1-DES data refer specifically to paclitaxel-eluting stents (PES; Boston Scientific, Natick, MA) and sirolimus-eluting stents (SES; Cordis, Miami, FL), whereas G2-DES data reflect the experience accumulated predominantly with everolimus-eluting
stents (EES; Abbott Vascular, Santa Clara, CA; or Boston Scientific), zotarolimus-eluting stents (Endeavor [E-ZES] and Resolute [R-ZES]; Medtronic, Santa Rosa, CA). All these DESs have durable polymers (Table 60-1). A special section is devoted to DESs with bioabsorbable polymers or polymer-free DESs and to bioresorbable vascular scaffolds toward the end of this review.

Table 60-1 Properties of First- and Second-Generation Drug-Eluting Stents

<table>
<thead>
<tr>
<th>Stent Name</th>
<th>Manufacturer</th>
<th>Scaffold</th>
<th>Strut Thickness</th>
<th>Polymer (thickness)</th>
<th>Drug</th>
<th>Elution in 1 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher</td>
<td>Cordis</td>
<td>SS</td>
<td>140 μm</td>
<td>PEVA/PBMA (12.6 μm)</td>
<td>Sirolimus</td>
<td>98%</td>
</tr>
<tr>
<td>Taxus Liberte</td>
<td>Boston Scientific</td>
<td>SS</td>
<td>97 μm</td>
<td>PIB (16.0 μm)</td>
<td>Paclitaxel</td>
<td>7%-10%</td>
</tr>
<tr>
<td>Xience V</td>
<td>Abbott Vascular</td>
<td>CoCr</td>
<td>81 μm</td>
<td>PVDF-HFP/PBMA (7.8 μm)</td>
<td>Everolimus</td>
<td>80%</td>
</tr>
<tr>
<td>Promus Element</td>
<td>Boston Scientific</td>
<td>PtCr</td>
<td>81 μm</td>
<td>PVDF-HFP/PBMA (7.8 μm)</td>
<td>Everolimus</td>
<td>80%</td>
</tr>
<tr>
<td>Endeavor</td>
<td>Medtronic</td>
<td>CoCr</td>
<td>91 μm</td>
<td>PC (4 μm)</td>
<td>Zotarolimus</td>
<td>100%</td>
</tr>
<tr>
<td>Resolute</td>
<td>Medtronic</td>
<td>CoCr</td>
<td>91 μm</td>
<td>BioLinx (5.6 μm)</td>
<td>Zotarolimus</td>
<td>75%</td>
</tr>
</tbody>
</table>

Abbreviations: BioLinx, blend of C10, C19, and PVP; CoCr, cobalt chromium; PBMA, polybutyl metacrylate; PC, phosphocholine; PEVA, polyethylene vinyl acetate; PIB, polysopropylmethylethylene; PtCr, platinum chromium; PVDF-HFP, polyvinylidene fluoride-co-hexafluoropropylene; SS, stainless steel.

CLASSIFICATION OF STENT THROMBOSIS

ST has been defined by the Academic Research Consortium (ARC) with respect to both its timing and certainty of its occurrence, in order to standardize interpretation of clinical trials and registries (Table 60-2). The ARC classification only considers events that occur after PCI is completed (after the patient has left the catheterization suite). More recently, an additional category of ST has been proposed—that which occurs after the stent has been implanted but before the PCI is completed, known as intraprocedural stent thrombosis (IPST). IPST is defined as the new appearance or worsening of preexisting thrombus within or adjacent to the recently implanted stent, with or without associated clinical symptoms. Diagnosis of IPST requires frame-by-frame angiographic analysis, usually in an angiographic core laboratory. The frequency of IPST is increased in patients undergoing stent implantation for ST-segment elevation myocardial
infarction (STEMI), those with high white blood cell count, and patients receiving treatment for thrombotic or bifurcation lesions and with bivalirudin monotherapy (vs heparin plus glycoprotein IIb/IIIa inhibitors).\textsuperscript{4} IPST is an independent predictor of subsequent mortality, reinfarction, and out-of-lab ARC ST. IPST heralds a much worse outcome at both 30 days and 1 year, even when normal epicardial blood flow is achieved at the end of the procedure.\textsuperscript{4,5}

\textbf{Table 60-2 Classification of Stent Thrombosis (Academic Research Consortium)}
Before the introduction of DES in 2003, acute (<24 hours) and subacute (1-30 days) ST was noted in 0.9% of more than 6000 patients treated with BMS, with approximately 50% of the events occurring within the first day of stent implantation.
implantation. The most important parameters associated with early ST were residual dissection, longer stent(s), and smaller minimal in-stent luminal diameter. Thus, most early ST was caused by inadequate deployment, which could be improved by more liberal use of intravascular ultrasound to avoid stent underexpansion and uncovered edge dissections or residual disease. The introduction of G1-DES did not reduce the incidence of early ST, especially if antiplatelet therapy is interrupted within the first 30 days. Similarly, the risk of early ST with G2-DES was reported to be 0.5%, compared with 0.7% for both BMS and G1-DES ($P = .074$), in a large German registry of PCI.

In contrast, incidence of late (1-12 months) and very late (>1 year) ST differs significantly among the different stent types. G1-DES are associated with a significantly higher risk of very late definite ST than either of the other types of stents (BMS or G2-DES), and it appears that this excess risk persists over many years after stent implantation. Among more than 18,000 patients treated in the German Registry, placement of G1-DES increased the risk of ST between years 1 and 3 nearly 5-fold compared with BMS or G2-DES. In fact, the risk of very late ST with G2-DES may be similar to BMS, although more studies are required in this regard to be certain of these observations.

**PATHOPHYSIOLOGY OF STENT THROMBOSIS**

Acute and subacute ST differ significantly from late and very late ST with respect to pathophysiologic mechanisms. For the former, a number of factors contribute, including technical issues such as stent underexpansion, untreated disease at the edges, and residual uncovered dissections; patient- and lesion-related characteristics, such as presentation with ACS, small vessel size, long lesion length, and plaque characteristics such as presence of thrombus; and the inherent thrombogenicity of the implanted stent, determined by its architecture and presence or absence of polymer and antiproliferative drugs. All these variables further interact with the potency and continuity of dual antiplatelet therapy (DAPT), whose premature discontinuation appears to be the most powerful predictor of early ST.

Late and very late ST is characterized by a number of pathologic processes...
and conditions: delayed arterial healing and endothelial coverage after DES; hypersensitivity reactions to the polymer (particularly relevant to SES); vessel toxicity with positive remodeling and fibrin deposition behind the struts (particularly relevant to PES); and bifurcation stenting, neoatherosclerosis, and strut fracture (which affects both BMS and DES). Neoatherosclerosis is a recently described phenomenon that underlies both restenosis and ST (Fig. 60-1). Neoatherosclerosis may be incited by the persistent inflammatory stimulus provided by the permanent presence of the drug-eluting polymer. In vivo studies of patients with ST using optical coherence tomography (OCT) highlighted the role of lipid-laden intima with (explaining clinical presentation as ACS) or without rupture, suggestive of neoatherosclerosis, as the underlying cause. In a series of 15 patients with ST, OCT identified an obstructive thrombus in all subjects, marked stent underexpansion (60% of predicted area), and neoatherosclerosis in one-fourth of cases. In contrast to early ST, interruption of DAPT plays a less important role in late ST (although it may be important if there is an additional trigger to increase platelet reactivity, such as trauma or the need for unplanned surgery). At least for G1-DES, the risk of late and very late ST appears to remain constant over 4 to 5 years from stent implantation, at a rate of 0.3% to 0.6% per year.

**FIGURE 60-1** Neoatherosclerosis and stent thrombosis. A. Cross-sectional histology
of bare metal stent (BMS) implanted in the coronary artery for 7 years antemortem (Movat, ×20). B. High-power image of the box in A (×100). A large necrotic core (NC) containing cholesterol crystals is identified within the neointima. The fibrous cap overlying the NC is infiltrated by numerous foamy macrophages and is markedly thinned (yellow arrowheads point to thinnest portion), which resembles vulnerable plaque encountered in native coronary arteries. The asterisks represent metal struts. C. Cross-sectional histology of paclitaxel-eluting stent (PES) implanted in the coronary artery for 4 years antemortem (Movat, ×40). D. High-power image of the box in C (×200). A relatively small NC containing cholesterol crystals is formed around metal struts (asterisk). The fibrous cap is infiltrated by numerous foamy macrophages and is markedly thinned (yellow arrowheads point to thinnest portion). (Histology images A—D reprinted from Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol. 2012;59:2051-2057, Copyright © 2012, with permission from American College of Cardiology Foundation.)

G2-DESs, particularly EES with durable fluorinated polymer, appear to be less susceptible to late and very late ST. In a pathologic analysis of patients (after excluding those with stent duration of implantation >3 years), morphometric assessment was available in 73 SES, 85 PES, and 46 EES stents, half of which were implanted for off-label indications.19,20 Remarkably, the incidence of uncovered struts in each of these groups was 18.0%, 18.7%, and 2.6%, respectively (P <.0005), despite a similar average implant duration of approximately 9 months in the 3 groups. The 3 groups also had similar rates of restenosis underlying ST (12%-17%). Neoatherosclerosis was observed in 35%, 19%, and 29% of patients in the SES, PES, and EES groups, respectively (P = .91), while hypersensitivity reactions were seen exclusively with SES. The overall inflammation score was significantly lower for EES (0.26 vs 1.00 for each of G1-DES; P <.0005). It is important to emphasize that these data were obtained from autopsies, but only one-third of the deaths were stent related, whereas one-third were a result of noncardiac causes and the remainder were cardiac deaths unrelated to ST. Thus, only one-third of these patients fulfilled the criteria for definite ST according to the ARC definition (see Table 60-2).

PREDICTORS OF STENT THROMBOSIS

Multiple observational series and randomized clinical trials have analyzed the
independent predictors of ARC ST for BMS and DES, with models including demographic and baseline characteristics, procedural variables, and medication regimen and adherence.\textsuperscript{8,12,21-25} Almost invariably, early discontinuation of DAPT—defined as <4 weeks for BMS and <3 to 6 months for G1-DES—was associated with a 5- to 90-fold increase in hazard of ST (Table 60-3). Other important predictors emerging in some of these analyses were chronic kidney disease, diabetes mellitus, bifurcation stenting, stent length, and intracoronary irradiation provided for BMS in-stent restenosis.

Table 60-3 Predictors of Stent Thrombosis (ST) in 1911 Patients Treated with First-Generation Drug-Eluting Stents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
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<th>$P$</th>
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<tr>
<td><strong>Total ST</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Premature interruption of antiplatelet therapy</td>
<td>19.21</td>
<td>5.63-65.51</td>
<td>&lt;.001</td>
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<tr>
<td>Total stent length (mm)</td>
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<td>1.001-1.04</td>
<td>.037</td>
</tr>
<tr>
<td><strong>Acute/Subacute ST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary stenting in acute MI</td>
<td>74.22</td>
<td>5.89-861.45</td>
<td>.001</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
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<td>1.01-1.08</td>
<td>.048</td>
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<tr>
<td><strong>Late Stent Thrombosis</strong></td>
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<td></td>
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<tr>
<td>Premature interruption of antiplatelet therapy</td>
<td>24.79</td>
<td>7.51-81.84</td>
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<td>Renal failure</td>
<td>8.40</td>
<td>1.81-39.09</td>
<td>.007</td>
</tr>
</tbody>
</table>

Abbreviation: MI, myocardial infarction.

A more recent analysis of nearly 19,000 patients stented between 1998 and 2011 demonstrated that, using BMS as reference, G1-DES, diabetes mellitus, current smoking, prior myocardial infarction (MI), presentation with STEMI, complex lesion morphology, and increasing residual stenosis were independently associate with higher rates of definite ST up to 3 years from procedure. More than 50% of all events occurred within the first month.\textsuperscript{10}

Following the first report of 4 cases of late and very late ST occurring after G1-DES,\textsuperscript{26} Stone et al\textsuperscript{27} performed a meta-analysis of 9 randomized clinical trials comparing SES with BMS (n = 1748 patients, 4 trials) or PES with BMS (n = 3513, 5 trials). The rates of protocol-defined ST up to 4 years were 1.2\% versus 0.6\% for SES and BMS, respectively ($P = .20$), and 1.3\% versus 0.9\% for PES and BMS, respectively ($P = .30$). The study highlighted the excess of ST events occurring beyond 1 year from PCI in the DES-treated
patients, corresponding to approximately 1 additional event for approximately 500 patient-years. The majority of patients were not on DAPT at the time of the event. Notably, the incidence of death or MI was similar in DES and BMS patients. In this regard, the beneficial effects of DES in terms of preventing restenosis (which, when severe, may lead to MI) may offset the rare but serious consequences of ST.28

In a consecutive series of nearly 6000 patients treated between 2007 and 2010 and followed for 2 years, definite or probable ST occurred in 1.9%. Three-quarters of the events occurred within 30 days, and only 16% occurred beyond 1 year. Cardiogenic shock, STEMI presentation, lack of DAPT, diabetes mellitus, and stent length and diameter were independent predictors of ST.29

Recent data suggest that G2-DES, particularly EES, have lower rates of ST than G1-DES. In an analysis of 4 randomized trials of EES and PES (n = 6789), ST occurred by 2 years in 0.7% of EES patients and 2.3% of PES patients (P = .0001). The reduction in ST events with EES was apparent in all intervals—early, late, and very late. DAPT discontinuation beyond 6 months was associated with increased risk of ST in PES patients only.30 Supporting these data are the results from the XIENCE V USA postapproval registry of 8061 patients. The incidence of definite or probable ARC ST was 0.8% at 1 year, and the independent predictors for its occurrence were discontinuation of DAPT before 30 days (hazard ratio [HR], 8.63; 95% confidence interval [CI], 2.69-27.73; P = .0003), chronic kidney disease, and total stent length.31 Black race may also be related to higher risk of ST, independent of medication compliance.32

**PLATELET INHIBITION AND STENT THROMBOSIS**

The most comprehensive analysis to date of the relationship between high on-treatment platelet reactivity (HPR) and ST is derived from the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) study. Patients (n = 8583) with uncomplicated DES implantation had platelet function testing at an average of 20 hours after PCI using the VerifyNow device (Accriva, San Diego, CA). Half of the patients had ACS, and one-
third had 3-vessel coronary artery disease (CAD) or left main trunk involvement. An average of 1.8 lesions per patient were treated using 1.7 stents. Nearly two-thirds of the stents used were EES, whereas 30% were G1-DES. At 1 year, the compliance was 84% with DAPT (aspirin and clopidogrel) and 95% with aspirin. Forty-two percent of patients had platelet reactivity units (PRU) >208, consistent with HPR on clopidogrel. Definite or probable ST occurred in 0.84% of patients by 1 year and in 1.07% of patients by 2 years. There was a significant excess of definite or probable ST in those with PRU >208, (HR, 1.98; 95% CI, 1.30-3.01; P < .0001; Fig. 60-2). Eighty percent of the events were definite ST; very late ST accounted for only a fourth of all events. HPR was predictive for 2-year definite or probable ST (HR, 2.08; 95% CI, 1.22-3.17; P = .008) and even more so for definite ST (HR, 2.84; 95% CI, 1.48-5.48; P = .002), but was not an independent predictor of mortality at 1 or 2 years, reflecting possibly the interplay between higher bleeding risk and lower ischemic risk associated with more effective platelet inhibition.

At the clinical level, the PARIS Registry evaluated in detail the compliance of patients to DAPT as well the reasons and timing of its discontinuation. Among 5033 patients enrolled in 5 countries after successful DES or BMS implantation for any clinical indication, the rate of discontinuation of DAPT was 2.6% at 30 days, 11.8% at 6 months, and 19.9% at 1 year. As expected, the rate of physician-recommended discontinuation was different at each time point: 0.3%, 7.6%, and 12.3%, respectively. At 1 year, the rate of death was 2.2%, spontaneous MI 1.9%, ST 1.9%, and revascularization 4.5%. There was no significant difference in protocol-defined ST between patients on and off DAPT (1.9% vs 2.7%, \( P = .14 \)), but the incidence of MI was higher in those off DAPT (4.8% vs 1.4%, \( P < .001 \)). After adjusting for baseline characteristics, patients off DAPT were more likely to experience death (\( P = .002 \)), MI (\( P < .001 \)), and ST (\( P = .009 \)), particularly in the first 7 days after PCI, and only when discontinuation was the result of disruption (interruption due to noncompliance or bleeding), rather than physician-recommended interruption.\(^{34}\) A recent evaluation of DAPT disruption in the R-ZES program found that discontinuation beyond 1 month after PCI is associated with a very low risk of ST.\(^{35}\)

**DURATION OF DUAL ANTIPLATELET THERAPY AFTER STENTING**

The duration of DAPT after stenting is dictated both by clinical presentation and by stent type. European and American professional guidelines concur that ACS patients should receive DAPT for up to 1 year regardless of whether PCI was performed or DES was implanted.\(^{36,37}\) In contrast, for patients undergoing stent implantation for non-ACS indications, the duration of DAPT prescription varies with stent type. Consensus has evolved that BMS does not require more than 1 month of DAPT.\(^{38}\) For DES, considerable uncertainty remains. Concerns of increased ST rates with G1-DES led to the recommendation (not founded on randomized trials) that at least 1 year of DAPT should be used. Furthermore, the ongoing hazard of very late ST with G1-DES has prompted the evaluation of longer DAPT therapy, even up to 36 months from PCI.

Several randomized trials have been performed to determine whether
patients might benefit from DAPT usage after DES for longer than 1 year. The Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Events (DES LATE) trial enrolled 5045 patients free of any complications 12 months after DES implantation and randomized them to aspirin alone or to DAPT for at least an additional year. Two-thirds of the patients received G1-DES, and the same proportion had ACS. The primary end point was a composite of cardiac death, myocardial infarction, or stroke 24 months after randomization. There was no difference in the incidence of the primary end point between the 2 groups (2.4% vs 2.6%, respectively; \( P = .75 \)). Definite ST occurred in 0.5% and 0.3%, respectively (\( P = .34 \)), whereas Thrombolysis In Myocardial Infarction (TIMI) major bleeding was noted in 1.1% and 1.4%, respectively (\( P = .20 \); Fig. 60-3).39

**FIGURE 60-3** Major adverse coronary events according to duration of dual antiplatelet therapy (aspirin alone = red; dual therapy = blue) in 5045 event-free patients 12 months after drug-eluting stent implantation. FU, follow-up; HR, hazard
These results confirmed a previous report from the same group. The Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) randomized 2013 patients to 1 of 4 stents (EES, PES, ZES, or BMS) and to short (6 months) or long (24 months) DAPT. Aspirin was continued indefinitely in all patients. After excluding failed PCI and early complications, 1970 patients were randomized to the 2 DAPT regimens. Three-fourths of patients had PCI for ACS. The primary end point (all cause death, MI, or stroke) occurred in 10.0% and 10.1% of patients in the short and long DAPT groups, respectively ($P = .98$), and there was no interaction between the rate of events and clinical presentation or stent used (BMS vs DES). ST was not different between the groups ($P = .80$; Fig. 60-4). Type 2 or greater Bleeding Academic Research Consortium classification (BARC) bleeding was less common in the short DAPT group (3.5% vs 7.4%; $P = .0002$), with all the difference occurring, as expected, beyond 6 months from randomization. In a more detailed analysis of the event rates according to stent type, the investigators found that E-ZES patients had significantly better outcomes with shorter DAPT ($P_{INT} = .004$).

Similar results were reported from another meta-analysis of more than 8000 patients followed for nearly 1.5 years and comparing DAPT for 16 versus 6 months. The Dual Antiplatelet Therapy Study (DAPT) compared 12 to 30 months of DAPT after BMS or DES and was powered to detect differences in rare events such as ST. Among 9961 patients treated with DES, adherent to DAPT, and free of major ischemic or bleeding complications after 12 months of DAPT, an additional 18 months of DAPT resulted in a significant reduction in definite or probable ST (0.4% vs 1.4% for aspirin monotherapy, \( P < .0001 \); almost all due to fewer instances of definite ST). Importantly, there was also a substantial reduction in MI (2.1% vs 4.1%, \( P < .0001 \)), but no effect on cardiac death (0.9% vs 1.0%, \( P = .98 \)). Both stent-related and non–stent-related MI were lowered by approximately 50% with prolonged DAPT, at the cost of an increased rate of moderate or severe bleeding (2.5% vs 1.6%, \( P = .001 \)).

In contrast to considering longer DAPT, the advent of G2-DES and the frequent need to discontinue DAPT earlier because of intervening surgery or bleeding have spurred studies evaluating DAPT duration shorter than 1 year, even as low as 1 month. The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial randomized 1443 patients to EES or SES (3:1) and 6 or 12 months of DAPT (1:1). The incidence of target vessel failure (TVF, defined as cardiac death, target vessel MI, or target vessel revascularization) was 4.8% and 4.3% for the 6- and 12-month DAPT regimens, respectively (\( P = .001 \) for noninferiority). Interestingly, ST occurred in 0.9% of the short DAPT group and in 0.1% of the long DAPT group (\( P = .10 \)). The Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following E-ZES Implantation (RESET) trial compared 3 months of DAPT in patients receiving E-ZES to 12 months of DAPT in patients receiving other DES. Among 2117 patients followed for 1 year, the incidence of TVF was 4.7% in each group (\( P = .84 \); \( P < .001 \) for noninferiority). Definite ST occurred in 0.2% and 0.3%, respectively (\( P = .65 \)). The OPTIMIZE trial randomized 3119 patients receiving E-ZES for
stable CAD or low-risk ACS to 3 or 12 months of DAPT. All-cause death, MI, stroke, or major bleeding occurred in 6.0% and 5.8% of patients, respectively ($P = .84$; $P = .002$ for noninferiority). There was also no significant difference in outcome in a landmark analysis at 3 months $P = .91$). ARC definite or probable ST occurred in 0.6% and 0.7% of patients, respectively ($P = .64$), until 3 months, and in 0.3% and 0.1%, respectively ($P = .18$), beyond 3 months (Fig. 60-5).^47

![ARC Def./Prob. stent thrombosis](image)


None of these trials have been adequately powered to definitively
determine the optimal duration of DAPT after DES, particularly as the risk-to-benefit ratio of DAPT duration may be stent specific. Nonetheless, data are accumulating that there is little to be gained from extending DAPT beyond 1 year, and in fact, this practice may result in excess major bleeding. Conversely, data are emerging that 3 to 6 months of DAPT may be safe for several G2-DES, although more data are required before firm recommendations can be made to routinely stop DAPT early.

An interesting observation emerged from the review of these 11 trials and the 12 meta-analyses that have been performed to summarize them. For definite or probable ST, there was no interaction between the length of DAPT and stent type ($P = .76$ for SES vs PES vs ZES vs EES), suggesting that longer DAPT is equally beneficial for all stents in preventing ST. In contrast, major adverse cardiac events were predominantly reduced by prolonged DAPT in G2-DES, with little or no effect for ZES and EES ($P = .048$).

For now, a rational proposal would be to continue DAPT for 1 year after DES in patients with ACS and for 3 to 6 months (or possibly 12 months in the absence of side effects) after G2-DES in patients in whom the stent was implanted for stable coronary artery disease. The US Food and Drug Administration (FDA) recently completed a review of all the 11 trials published since Fall 2015 on this topic (n = 33,051 patients) and concluded that shorter DAPT duration is associated with increased risk of ST (odds ratio [OR], 1.63; 95% CI, 1.00-2.66, random effect model, $I^2 = 39\%$) and MI (OR, 1.37; 95% CI, 1.08-1.72; $I^2 = 31\%$), without a significant effect on all-cause mortality.

**COMPARISON OF SPECIFIC STENT TYPES**

Because ST is infrequent, reliable estimation of ST rates and comparison between stents in individual trials are difficult. To overcome this limitation, network meta-analyses have been performed that enable indirect comparison of studies with common comparator groups. Palmerini et al $^{49}$ culled information from 49 randomized clinical trials describing the incidence of definite ST in 50,844 patients followed for up to 2 years. At 30 days and 1 year, fluoropolymer-based EES (both cobalt-chromium [CoCr] and platinum-
chromium [PtCr]) had significantly lower rates of ST than BMS, SES, PES, E-ZES, and R-ZES (Fig. 60-6). At 2 years, only comparisons of EES with BMS and PES were possible and showed continued marked reductions in ST with EES (OR, 0.35 [95% CI, 0.17-0.69] and OR, 0.34 [95% CI, 0.19-0.62], respectively). Direct and indirect estimates provided similar results in favor of CoCr-EES versus BMS, strongly suggesting that the potential hazard for ST associated with EES is reduced not just compared to other DES, but to BMS as well. These data confirmed the experimental observations regarding the passivation and thromboresistance of vascular surfaces afforded by surfaces coated by durable fluoropolymer, as they exist on the CoCr-EES. A smaller meta-analysis of 13 trials comparing EES with SES, PES, or R-ZES in over 17,000 patients followed for nearly 2 years again showed that EES reduced ST by 45% (relative risk [RR], 0.55; 95% CI, 0.38-0.78; \( P = .001 \)). These results were independent of duration of DAPT, duration of follow-up, or the comparator stent. The largest meta-analysis so far, not restricted to ARC definition of ST, in 76 trials with 117,762 patient-years of follow-up found that EES reduced ST compared with BMS by nearly 50% (RR, 0.51; 95% CI, 0.35-0.73; \( P < .001 \); Fig. 60-7).


TREATMENT AND CONSEQUENCES
OF STENT THROMBOSIS

In general, ST results in ACS with or without ST-segment elevation and presents as an acute MI. As with de novo plaque rupture, the preferred therapeutic paradigm is an early invasive strategy with balloon angioplasty and/or stenting, often preceded by thrombus aspiration. Intravascular ultrasound is strongly recommended to exclude stent underexpansion and/or untreated edge disease or dissections. It is obviously important to determine the timing of the event relative to index PCI and the adherence to DAPT on presentation. In the first decade of stenting, ST was associated with considerable mortality and morbidity. In a recent comprehensive analysis from the National Cardiovascular Data Registry (NCDR), ST was noted in 1.8% (n = 7315) of all patients undergoing PCI for ACS. The timing of ST was early in 20%, late in 20%, and very late in 60% of patients. As in other series, the in-hospital mortality in patients with early ST was much higher than in the other groups (7.9% vs 3.8% vs 3.6%, respectively; P < .001) a finding that persisted after multivariable adjustment. It is notable that BMS was involved in one-third of the patients with early and late ST, but in only one-sixth of patients with very late ST. The mortality did not differ in patients with DES or BMS ST, but the treatment received did, particularly for early ST. Patients with ST due to DES were much more likely to receive another DES (37%) than those with BMS (8.6%), probably reflecting the initial reluctance to implant a DES. Balloon angioplasty alone was used in 30% to 50% of all patients, while thrombus aspiration was performed in only 50%. It remains unclear why early ST may be associated with higher mortality. It is possible that early ST is associated with greater thrombus burden in the presence of poorly inhibited platelets, which contributes to inadequate myocardial reperfusion. Similar data were generated from the large HORIZONS AMI trial.

STENT THROMBOSIS AFTER STEMI

Among all patients undergoing PCI and stenting, those with STEMI usually harbor the largest thrombus burden. Intuitively, placing a metallic object in such an environment, even after thrombus aspiration (which is rarely
complete\textsuperscript{56}, is expected to lead to a higher rate of ST. Indeed, ACS in general has been found to be an independent predictor of ST.\textsuperscript{10} The randomized Evaluation of the Xience-V Stent in Acute Myocardial Infarction (EXAMINATION) trial evaluated the efficacy and safety of BMS versus EES in 1498 STEMI patients. At 2 years, the composite of all-cause death, MI, and any revascularization was 17.3\% versus 14.4\%, respectively ($P = .11$). Definite ST occurred in 2.1\% of BMS-treated patients compared to 0.8\% of EES-treated patients ($P = .03$), consistent with the results of the network meta-analysis discussed earlier.\textsuperscript{57} Two meta-analyses of STEMI datasets confirm these observations.\textsuperscript{58,59} In the larger meta-analysis including 28 trials and 34,068 patient-years of follow-up, SES, PES, and EES reduced the need for revascularization compared with BMS and had equivalent rates of death or recurrent MI. Moreover, EES was associated with a statistically significant reduction in the rate of ST, including very late ST when compared with SES ($RR$, 0.38; 95\% CI, 0.21-0.74), PES ($RR$, 0.39; 95\% CI, 0.21-0.73), and even BMS ($RR$, 0.42; 95\% CI, 0.23-0.76). In a recent network meta-analysis of 21 trials (15 of which compared G1-DES with BMS, 4 of which compared G1-DES with G2-DES, and 2 of which compared G2-DES with BMS) including 12,866 patients, G2-DES were associated with a significantly lower incidence of definite ST at 30 days compared with BMS ($OR$, 0.36; 95\% CI, 0.15-0.81) and at 1 year ($OR$, 0.49; 95\% CI, 0.30-0.79). The reduction in ST was accompanied by a significantly lower rate of MI and TVR but not mortality (Fig. 60-8).\textsuperscript{60}

These data, in aggregate, suggest that DES (and in particular EES) may be appropriate in most patients with STEMI, in the absence of a clear need for early discontinuation of DAPT or anticipated noncompliance with medical therapy.

NEW APPROACHES FOR PREVENTION OF STENT THROMBOSIS

Because of the inherent thrombogenicity and inflammatory potential of a permanent implant consisting of metal and polymer, 2 concepts have evolved to resolve the persistent risk of very late ST, observed particularly with G1-DES. The first approach attempts to eliminate the negative effect of a durable
polymer, by using bioabsorbable polymers or creating polymer-free stents with direct drug coating. Bioabsorbable polymers have been developed to resorb after having eluted the antiproliferative agent. Most of the clinical experience stems from studies of the bioabsorbable polymer (BP)-based biolimus-eluting stent (BES). The polymer is polylactic acid applied solely to the abluminal stent surface by a fully automated process. Over a 6- to 9-month period, the polymer is converted into carbon dioxide and water. In a noninferiority trial comparing SES with BES in 1707 patients with stable CAD or ACS (55% of all patients), the primary end point of cardiac death, MI, or TVR at 9 months was 10.5% versus 9.2%, respectively (PNI = .03). Definite ST occurred in 2.0% and 1.9% of patients, respectively.61

A similar approach to BES was tested in the EVOLVE II trial comparing the platinum-chromium EES stent with the SYNERGY stent (Boston Scientific), an EES-eluting stent with bioresorbable PLGA [poly(lactic-co-glycolic acid)] polymer applied only to the abluminal aspect of the vessel. Target lesion failure at 1 year was well within the noninferiority margins at 1 year (6.5% vs 6.7%, respectively). Definite or probable ST was noted in 0.6% and 0.4%, respectively (P = .50).62

In the LEADERS-FREE trial, 2466 patients at high risk for bleeding because of advanced age or need for oral anticoagulation therapy were randomized to a polymer-free biolimus-coated stent or a BMS with DAPT for 1 month only. There was no difference between the groups in incidence of definite or probable ST at 1 year (2.0% vs 2.2%, respectively; P = .70).63 In the ISAR-TEST 3 study, SES was compared with a BP-SES and with a polymer-free (PF) SES. The primary end point of in-stent late loss at 6 to 8 months was significantly higher in the PF-SES arm compared with the other two arms, failing noninferiority criteria. Death or MI was similar at 1 year in the 3 groups (P = .70), whereas the incidence of definite ST was 0%, 0.5%, and 1.0%, respectively (P = .72). Obviously, the study (n = 605) was not powered for any of the clinical events.64

Extending the network meta-analysis described earlier to include studies with BES, Palmerini et al65 concluded that BES is superior to PES and to BMS with respect to cardiac death or MI. BES is equivalent to SES, EES, and ZES with respect to cardiac death or MI, whereas EES is superior to BES with respect to definite ST (OR, 0.41 [95% CI, 0.21-0.77] at 1 year and OR, 0.52 [95% CI, 0.29-0.98]) at longest term follow-up available.65
The second approach to mitigating the consequences of a permanent implant, including the need for long-term DAPT, is that of a fully bioresorbable scaffold that resorbs after eluting the antirestenotic drug, leaving behind a well-healed coronary segment without a permanent implant. The restoration of normal coronary physiology in the stented segment is particularly important because adequate endothelial function may prevent further progression of atherosclerosis. The lack of a permanent implant also obviates concerns of late strut fracture or malapposition and may reduce the development of neoatherosclerosis. Six such devices have reached the stage of clinical trials (Table 60-4), although many more are in various stages of preclinical development. The polylactic acid ABSORB scaffold (Abbott Vascular) was first tested in a small first-in-man trial of 30 patients. At 2 years, the rate of ST was 0% and late loss was 0.48 ± 0.28 mm (compared with 0.33 ± 0.37 mm with CoCr-EES in the SPIRIT II study). There was significant change in lumen diameter at 2 years in response to acetylcholine stimulation in the stented segment, as well as proximal and distal to it, suggesting recovered endothelial function. A structural modification of the scaffold (version 1.1, tested in 101 patients in cohort B) led to reduced late loss (0.27 ± 0.20 mm at 2 years), comparable to that observed with EES. The ABSORB II study randomized (2:1) 501 patients to bioabsorbable vascular stent (BVS) or EES. At 2 years, target lesion failure occurred in 4.8% and 3.0% of patients, respectively (P = .35). Definite or probable ST occurred in 1.5% and 0%, respectively (P = .17). The ABSORB III study was recently presented at the 2015 TransCatheter Therapeutics Meeting. Among 2008 patients randomized 2:1 to BVS versus EES, the primary end point of target lesion failure was recorded at 1 year in 7.8% and 6.1% of patients, respectively, satisfying the prespecified criteria for noninferiority (P = .007). All components of the primary end point were numerically lower in the EES group, whereas angina at 1 year was nearly identical in both groups (18%). Definite or probable ST occurred in 1.54% and 0.74% of patients, respectively (P = .13). Long-term follow-up from these studies is required to determine whether ST rates are at all lower with the bioresorbable scaffold compared to the best-in-class metallic DES. The ABSORB BVS was also tested in the most thrombogenic milieu possible—patients with acute STEMI. In the TROFI II trial, 191 patients were randomized to BVS or EES. The primary end point—healing score by optic coherence tomography—was lower in the ABSORB arm than in the EES arm (1.74 vs 2.80, respectively; P
for noninferiority <.001), and definite ST occurred in 1.1% and 0%, respectively ($P = .70$).  

Table 60-4 Bioresorbable Stents in Various Stages of Development (Presented by S. Windeker, MD, Transcatheter Cardiovascular Therapeutics 2013 Meeting)

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<tr>
<th>Company</th>
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Bioresorbable scaffolds have also been manufactured from magnesium and iron. The paclitaxel-eluting bioresorbable magnesium DREAMS scaffold (Biotronik, Berlin, Germany) was tested in the first-in-man BIOSOLVE I trial. Among 46 patients followed for 1 year, 3 had TVF, and there was no STs. There was improved endothelial function in patients treated with this stent as well. However, the late lumen loss 6 months after the DREAMS stent was 0.68 ± 0.57 mm, higher than with G2-DES. This stent has been reconfigured to elute sirolimus (to further reduce late loss) and is again undergoing human testing.

The next challenges for bioresorbable scaffolds are to determine optimal DAPT duration and confirm the results of ABSORB III and TROFI II in other datasets. An intriguing possibility exists that these bioresorbable scaffolds can be used to “seal” existing coronary lesions that are not yet hemodynamically significant and prevent progression of atherosclerosis and plaque rupture.

**CONCLUSION**
Stents in general and DES in particular have revolutionized PCI. ST is a rare event but continues to be of great importance because of its often devastating consequences. Early ST is typically related to procedural deficiencies or unplanned discontinuation of DAPT. Most studies showed similar rates of early and late ST with DES and BMS, as long as DAPT was not discontinued early. Very late ST, however, was more common with G1-DES than BMS, but appears to have been nearly eliminated with G2-DES, particularly those with a durable fluorinated polymer. Current data do not support the superiority of BP-based DES or polymer-free metallic DES as an alternative to G2-DES, although more data are needed, especially with novel, innovative designs. Completely bioresorbable scaffolds offer the promise of healing the endothelium in the stented area, restoring endothelial function, and potentially, preventing progression of atherosclerosis. Ongoing trials will determine whether these theoretical advantages translate into a reduced risk of very late ST.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. After percutaneous coronary intervention (PCI) with a drug-eluting stent (DES), what is the incidence of acute and subacute stent thrombosis?
   A. Similar to incidence after bare metal stent (BMS)
   B. Higher than incidence after BMS
C. Lower than incidence after BMS  
D. Higher for first-generation DES than for BMS but lower for second-generation DES than for BMS

2. Contributors to late and very late DES thrombosis include which of the following?  
   A. Delayed healing and incomplete endothelialization of stent struts  
   B. Chronic inflammation related to polymer-releasing drug  
   C. Neoatherosclerosis  
   D. All of the above

3. In ADAPT-DES, high platelet reactivity after PCI, defined as platelet reactivity units (PRU) >208:  
   A. Was an independent predictor of mortality at 2 years  
   B. Was an independent predictor of definite ST at 2 years  
   C. Was an independent predictor of death or ST at 2 years  
   D. None of the above

4. In the Dual Antiplatelet Therapy (DAPT) study, powered for ST as an individual end point, prolonged DAPT as compared to aspirin monotherapy led to all of the following changes except:  
   A. Reduced incidence of definite or probable ST by more than 50%  
   B. Reduced cardiac mortality by more than 50%  
   C. Increased moderate and severe bleeding by more than 50%  
   D. Reduced incidence of myocardial infarction by more than 50%

5. ABSORB III is the largest completed trial thus far of bioresorbable vascular scaffolds (BVS) compared with the “best-in-class” metallic everolimus-eluting stent (EES). This trial demonstrated that:  
   A. BVS have a significantly lower rate of target lesion failure at 1 year than EES and a similar rate of residual angina as EES  
   B. BVS have a significantly higher rate of target lesion failure at 1 year than EES and a similar rate of residual angina as EES  
   C. BVS have similar rate of target lesion failure and residual angina at 1 year as EES, fulfilling the criteria for noninferiority  
   D. None of the above
ANSWERS

1. A
Early stent thrombosis (ST) is predominantly dictated by procedural considerations (proper deployment and expansion and lack of residual dissection) and adherence to dual antiplatelet therapy and much less by stent type. With proper technique, all devices have a 0.5% to 0.7% rate of early ST.

2. D
Late and very late ST is a complex process involving the interaction between a diseased, nonhealing endothelium (because of the antiproliferative drug), chronic inflammation from the polymer delivering the drug, and even ensuing stent strut fracture. More recently, neoatherosclerosis was added to the list of contributors. It describes a process of accelerated atherosclerosis occurring in the stented segment and leading to plaque rupture similar to that observed in spontaneous myocardial infarction.

3. B
ST, definite in particular, is the quintessential platelet-derived adverse event. Thus, it is logical that insufficient platelet inhibition, as measured by high residual platelet reactivity (HPR), will be associated with and predictive of ST. The association of HPR with death is complicated by the higher risk of bleeding in patients without HPR, which may counteract the effect of lack of ST on mortality.

4. B
In the DAPT study, prolonged DAPT beyond 12 months lowered the incidence of ST (almost exclusively definite ST) by 70% from 1.4% to 0.4% and reduced the rate of spontaneous myocardial infarction by 50% from 4.1% to 2.1%. Importantly, 50% of the myocardial infarction events were not related to previously stented lesions, fulfilling the description of secondary prevention for patients with coronary artery disease. These important effects were countered by a significant increase in clinically relevant bleeding events, resulting in a neutral effect on cardiac mortality.
The ABSORB III trial, not yet published in a peer-review journal, was the pivotal trial for US Food and Drug Administration approval of BVS in the United States. Numerically, all components of the primary end point, target lesion failure at 1 year, were higher with BVS than EES, but well within the prespecified margins of noninferiority. Rate of residual angina was nearly identical in the 2 groups.
Coronary Artery Perforation

James R. Margolis

In the stent era, coronary artery perforation (CAP) is the most serious complication and a leading cause of death from percutaneous coronary intervention (PCI). Although preventable to a great extent, perforations are inevitable in any high-volume center. Prompt recognition and treatment can make the difference between benign and fatal outcomes. The incidence of CAP varies with the complexity of disease under treatment and with the aggressiveness of individual operators. An operator who never experiences a perforation is probably underdilating lesions and underdeploying stents. The reported incidence varies from 0.2% to 0.6%.\(^1\)\(^-\)\(^5\) It is much higher when atheroablative devices are used.\(^5\) In a meta-analysis of nearly 200,000 PCIs, the pooled incidence was 0.43%.\(^4\) Although there is no good series reporting the effect of stenting on the incidence of perforation, routine stenting most likely increases the perforation rate.

CLASSIFICATION

The classification of Ellis and colleagues\(^1\) is generally accepted. In this classification, a grade I perforation is an extraluminal crater without extravasation (this might also be termed a pseudoaneurysm); a type II perforation is a pericardial or myocardial blush without contrast jet extravasation; and a type III perforation is an extravasation through a 1-mm or larger perforation. This classification correlates with prognosis. A fourth
category is designated cavity spilling, in which the perforation empties into an anatomic cavity: right ventricle, left ventricle, coronary sinus, and so on (Fig. 61-1).
Contrast in RV
Perforation site

Contrast in RV outflow track
Site of perforation

Small leak

Tiny leak

Occlusion site
Original perforation site
Small perforations can usually be solved by prolonged balloon inflations combined with reversal of anticoagulation. Large perforations require more sophisticated treatment. Perforations in vein grafts frequently resolve with simple measures. This is because scarring around vein grafts may be enough to limit extravasation.

Perforations in proximal arteries require treatments that will both resolve the perforation and preserve antegrade flow. Blocking antegrade flow can sometimes solve more distal perforations. The most practical way to treat perforation in previously occluded arteries is to reocclude the artery. Perforations involving bifurcations are much more difficult to solve, because it may be necessary to stop bleeding in 2 branches while preserving flow to both branches. Occluding flow is the best way to solve perforations of small branches.

Perforations caused by balloons are relatively easy to solve, whereas those caused by stents are generally more severe and more difficult to treat. Devices are 2-edged swords in that debulking prior to stenting may prevent perforations, but the devices themselves can cause very severe and sometimes untreatable perforations.5

Guide wire perforations are more frequent, especially when hydrophilic wires are used in complex cases. In the usual scenario, the guide wire migrates distally in a tiny branch and eventually perforates the distal tip of the branch. This complication may not be recognized until after the guide wire has been withdrawn. Although the leaks are generally small, they can lead to cardiac tamponade. In one reported series, 20% of perforations causing cardiac tamponade were the result of guide wire perforations.6 This is especially a problem in the presence of glycoprotein IIb/IIIa inhibition. Because of relatively small and sometimes unrecognized leaks, guide wire perforation can lead to late cardiac tamponade.
Perforations are a significant problem in patients with chronic total occlusions. Guide wire perforations in this setting are seldom a serious problem, unless the perforation is unrecognized and balloon inflation is made over the perforating guide wire. In cases of chronic total occlusion, a guide wire may enter a tiny branch running parallel to the main vessel. If a balloon is inadvertently inflated within this vessel, serious perforation can ensue. Either of the aforementioned circumstances may result in cardiac tamponade and death. This is particularly distressing when the intervention is entirely elective.

**HIGH-RISK SITUATIONS**

Certain anatomic and morphologic conditions predispose to perforation. Recognition of these circumstances and appropriate adjustments in treatment strategies can prevent problems that would otherwise occur.

**Native Arteries**

Certain locations in the native coronary arteries represent a higher than standard risk for perforation.

**Lesions on Bends**

In general, lesions on bends present high risks for dissection with balloons and extreme risks for perforation with atherectomy devices. The curving nature of the right and left circumflex arteries may explain the higher incidence of perforation in these vessels.\(^4\)\(^5\) Excimer laser has the highest perforation risk when used on sharp bends. Excimer laser ablates only in a forward direction. Similar to the headlights on an automobile, laser light points straight when the road turns. Thus, excimer laser invariably causes perforation when used on a sharp bend. Rotablator (Boston Scientific, Marlborough, MA) has some ability to follow bends, but wire bias tends to drive the Rotablator burr toward the outer curvature, thus predisposing to perforation. When using Rotablator on sharp curves, the rule is to undersize the burr by at least 1 and preferably 2 sizes. Directional atherectomy and cutting balloon are less likely to perforate lesions on bends, but the undersize
rule is still operative when these devices are used in the curved portions of arteries.

**Bifurcation Lesions**

Bifurcations are troublesome to treat no matter what the strategy. Because plaque in this location frequently involves both the main artery and the ostium of the branch vessel, debulking strategies are often employed. The problem is that debulking devices may perforate the carina of the bifurcation, thus producing a very large hole that requires emergent treatment. Treatment of this problem with a covered stent invariably sacrifices the side branch and may not solve the problem. The perforation may involve both branches; therefore, collateral filling of the side branch can lead to continuing leak. Worse, once the stent graft covers the side branch ostium, access to the side branch is no longer possible.

The best way to deal with this problem is to avoid it. Theoretically, the bifurcation could be reconstructed with 2 “kissing” covered stents, but this is technically difficult because of the bulky nature of the stent grafts. In the face of a large perforation at the left anterior descending (LAD)/diagonal bifurcation, it may be best to occlude both branches with kissing balloons and send the patient to surgery.

**Lesions in Branches and Distal Vessels**

Because of their tapering nature, branches and distal vessels may be prone to rupture during stenting. Stents of appropriate size for proximal branches may be too large distally. This is particularly a problem in the distal LAD, where diffuse negative remodeling may be present. Figure 61-1 is an example of a long, drug-eluting stent in the LAD with a perforation occurring at the distal one-third of the stent. With the advent of drug-eluting stents, it is more common to stent more distally and to use longer stents. The best way to approach these tapering vessels is to carefully interrogate them with intravascular ultrasound (IVUS) before and after stenting. Stents should be sized appropriately for the distal vessel, and then postdilated proximally with short balloons of larger sizes.
Acute Margin Lesions

Lesions of the right coronary artery (RCA) at the acute margin represent a significant risk for perforation, especially with devices. The problem with this area is that the artery bends more acutely than is generally appreciated in the left anterior oblique projection. Compounding the problem is the bifurcation with the anterior ventricular branch and the propensity for severe stenoses to involve this bifurcation. When devices are used to treat this area, there is a tendency for the device to migrate in the direction of the anterior ventricular branch and thus perforate the artery at the inferior aspect of the bifurcation. This results in extremely large perforations that can become catastrophic if not treated within seconds.

Calcified Vessels

Calcified arteries are noncompliant. When stretched to extreme degrees, they tend to tear, especially at junctures where heavily calcified areas meet relatively normal ones. This is a particular problem when stents are placed in these vessels without proper preparation with Rotablator or cutting balloon. When the stents are deployed, they cannot be expanded fully. High-pressure balloons are then used, and the resulting uneven expansion of noncalcified areas leads to perforation or rupture. The mechanisms are similar to those described under vein grafts and eccentric lesions (vida infra).

Vein Grafts

Vein graft perforations generally occur when a resistant lesion suddenly responds to high-pressure balloon inflation. Pathologically, these are tears or ruptures as opposed to discrete holes. These resistant lesions may be the result of old fibrosis, sometimes outside the wall of the vein graft. The vein graft itself is relatively thin walled. Once resistance of the fibrous tissue is overwhelmed, the graft itself ruptures. Clinically, this is seen as an imprint that persists on an inflated balloon despite high pressure. If the imprint suddenly resolves as, for example, after a single bar increase in pressure, the operator should be concerned that rupture has occurred. In this instance, it is prudent to inject around the deflated balloon before removing it. If perforation has occurred, the balloon can be reinflated at low pressure while
anticoagulation is reversed and preparations are made for stent grafting. Because vein grafts are normally embedded in scar tissue and there is no pericardium, vein graft perforations usually act differently from those in native vessels. Following perforation of a vein graft, extravasation is generally limited by the dense surrounding cicatrix. This is especially true of vein grafts to the lateral left ventricle and posterior surfaces of the heart. These perforations can usually be treated with reversal of anticoagulation and observation. There are exceptions to this rule, especially in the proximal and mid-portions of grafts to the LAD and RCA. Vein graft perforations tend to be large. When they do bleed freely, blood loss is extreme, and early and effective treatment is mandatory. The first treatment must always be to cover the perforation with an inflated balloon.

**Eccentric Lesions**

Plaque eccentricity is the single most important morphologic feature that portends a propensity to perforation. Thick atheroma on one side and thin, frequently normal, arterial walls on the other characterize eccentric plaques. Balloon inflation and stenting tend to preferentially stretch the thin normal wall while barely affecting the noncompliant plaque. This is especially true when the plaque is diffusely fibrotic or heavily calcified. This is one condition in which preparation of the vessel with cutting balloon or a debulking device prior to stenting may actually reduce the risk of perforation. Routine use of IVUS prior to stenting will identify extreme eccentricity that may not be evident on the angiogram. Sumitsuji and colleagues in the Japanese Intervention and Ultrasound Study group have identified 3 ultrasound patterns that may predict perforation: (1) severe eccentric calcified plaque with weak segment on the opposite side; (2) severe eccentric fibrous plaque with weak segment on the opposite side; and (3) severe superficial calcium with weak segment in the opposite side.

**Guide Wire Perforations**

Guide wire perforations are a product of technologic advance (Fig. 61-2). They occur most frequently with hydrophilic wires. The extreme lubricity of these wires allows them to migrate without being noticed distally into and out of the tips of small branches. During difficult cases, involving multiple
balloon exchanges, it is not unusual to find the tip of a hydrophilic wire several centimeters into the pericardial space. Usually, this does not result in a clinical problem. Occasionally, it can result in a minor or major leak into the pericardium that is difficult or impossible to resolve.
FIGURE 61-2 Guide wire perforation treated with thrombin injected through a microcatheter. (A) Guide wire in distal portion of small branch. (B) Faint contrast stain during first post–percutaneous coronary intervention injection. (C) Subsequent injection shows grade II perforation. (D) Balloon inflated at low pressure temporarily stops the leak. (E) After balloon inflation, the perforation is not fully sealed. (F) Grade II leak resumes within a few minutes after balloon inflation. (G) After thrombin administration, the perforation is sealed without interrupting flow to other branches.

The best way to prevent guide wire perforations is to avoid hydrophilic
wires whenever possible, but guide wire perforations can also occur with conventional wires, especially ones with stiffer tips. The guide wire perforation in Figure 61-2 was caused by a conventional wire with intermediate tip stiffness. Unfortunately, hydrophilic wires are most useful in the most difficult cases. In such cases, it is good practice to exchange the hydrophilic wire for a conventional wire at the earliest opportunity. When using hydrophilic wires, it is important to be constantly aware of distal tip position and to guard against distal migration. Problems with guide wire perforation are accentuated in the presence of glycoprotein IIb/IIIa inhibitors. Most guide wire perforations can be easily solved with reversal of anticoagulation. When IIb/IIIa inhibitors are used, anticoagulation reversal is prolonged.²

**Aortic Perforations**

In a single case, I had the experience of a pinhole leak in the aortic root resulting from stenting of the RCA ostium. This occurred in an elderly patient with a calcified aorta. The aortic location of the leak was immediately above the RCA ostium and could not be distinguished angiographically from a proximal RCA perforation. This problem was only identified at surgery after stent grafting of the proximal RCA and its ostium failed to correct the problem. It was possible to suture the small aortic hole without cardiopulmonary bypass and without grafting the coronary artery.

**ROLE OF ANTICOAGULATION**

Effective management of perforations is greatly dependent on the ability to reverse anticoagulation. Different anticoagulants have different levels of reversibility and differing times required to reverse their effects. All anticoagulants can be reversed with large amounts of fresh frozen plasma and platelets. Unfortunately, the time required to obtain these agents from the blood bank and subsequently administer them is at best 1 hour and usually much longer. Although it has been my general practice to fully reverse anticoagulation in the presence of any perforation ≥ grade 2, there is evidence that partial reversal of anticoagulation is safe.²
**Heparin**

Heparin is the anticoagulant most commonly used for PCI. In the case of perforation, it is the anticoagulant that can be most quickly and completely reversed (using protamine). Although protamine reversal should be instantaneous, in reality, it takes almost 30 minutes to achieve a normal activated clotting time (ACT) in the setting of perforation. Because protamine titrations are not generally available in the catheterization laboratory, it is necessary to perform a de facto titration by guessing at the initial protamine dose and giving additional protamine after serial ACT measurements. There is a minimum delay of 10 to 15 minutes between doses. If too much protamine is given initially, the protamine itself acts as an anticoagulant, and the operator does not know what to do in the face of a persistently elevated ACT. There is also the problem of reabsorption of heparin from adipose tissue and release of protein-bound heparin. Thus, the theoretically instantaneous reversal of heparin does not take place under real-world conditions. The heparin problem is further complicated by the concomitant use of glycoprotein IIb/IIIa inhibitors. It is extremely difficult to reverse anticoagulation in the presence of these agents.²,⁸

**Direct Thrombin Inhibition**

Direct thrombin inhibition with bivalirudin in lieu of heparin has become increasingly popular. The advantages of bivalirudin are predictable pharmacokinetics and the ability to avoid concomitant administration of a glycoprotein IIb/IIIa inhibitor. The half-life of bivalirudin is 25 minutes. After 2 half-lives (50 minutes), anticoagulation is essentially finished. Although there is no readily available antagonist to bivalirudin, its effect is dissipated in less time than it takes to obtain and infuse fresh frozen plasma. Because bivalirudin blocks thrombin-induced platelet aggregation, it is unnecessary to give concomitant glycoprotein IIb/IIIa inhibitors, even in the presence of unstable angina.⁷ This is a major advantage of bivalirudin, if perforation occurs.

**Thienopyridines**

Theoretically, the presence of thienopyridines should make it difficult to stop
bleeding after coronary perforation. There is no specific information on this subject either in the literature or in my personal experience. My colleagues and I give thienopyridines during or immediately after stent procedures; pretreatment is the exception. However, an increasing number of patients undergoing PCI are receiving chronic thienopyridine therapy. In these patients, platelet transfusion would be the only way to completely reverse anticoagulation. Newer antiplatelet agents, specifically prasugrel and ticagrelor, have a more rapid onset of action compared to clopidogrel. Theoretically, this could be problematic in the presence of CAP, but there are no reports of problems with these agents in the presence of CAP.

**Glycoprotein IIb/IIIa Inhibitors**

Glycoprotein IIb/IIIa inhibitors present the greatest problem when attempting to reverse anticoagulation after coronary perforation. Despite relatively short half-lives and low blood levels, the effects of these agents generally persist. Although there is no series that documents a poorer prognosis in patients with perforation who have been treated with IIb/IIIa inhibitors, it is generally accepted that that these agents complicate the treatment of perforation. There are only 3 possible solutions: (1) avoid use of IIb/IIIa inhibitors whenever possible; (2) avoid coronary perforation when IIb/IIIa inhibitors must be used; or (3) transfuse platelets when perforation occurs in the presence of IIb/IIIa inhibition. In my opinion, glycoprotein IIb/IIIa inhibition is only indicated in the presence of thrombus (ie, acute coronary syndromes). High-risk situations for perforation occur mostly in chronic settings in which IIb/IIIa inhibition has little rationale. When an operator approaches situations that are high risk for perforation, this risk must be carefully evaluated before administration of these agents.

**ROLE OF DEVICES**

Although devices make it possible to successfully treat otherwise untreatable lesions, the perforation rate with devices is more than double the rate with balloons alone. Devices have been discussed elsewhere in this chapter, especially in relation to lesions on bends, eccentric lesions, and bifurcation lesions. Here, each of the devices is discussed on an individual basis. In
general, when used incorrectly, devices can be a source of massive perforation. When used correctly, they can actually prevent perforation by changing the compliance of diseased arteries and allowing ballooning and stenting at lower pressures.

**Balloons and Stents**

Balloons and stents are responsible for more perforations than all other devices combined. The major causes of perforations with balloons and stents are oversizing and stenting of highly eccentric lesions. In the series by Sumitsuji, the stent-artery ratio was 1.25 or more in 67% of perforations, and 72% of perforations occurred when eccentric lesions were treated. Guidance using IVUS or optical coherence tomography (OCT) is invaluable in accurately sizing vessels and assessing eccentricity.

**Rotablator**

Although Rotablator use has decreased over the past 15 years, this device is invaluable in the presence of heavy calcification. Perforation secondary to Rotablator occurs mostly with larger burr sizes and when treating lesions on sharp bends. In recent years, I have avoided large burr sizes, because complete debulking is no longer my primary goal. Rather, I am trying to merely change lesion and vessel compliance to permit full stent deployment. This goal can usually be accomplished using burr sizes of 1.5 mm or less—never more than 1.75 mm. With lesions on sharp bends, I invariably start with a 1.25 burr, and check compliance with a balloon before going to larger burr sizes. Compliance is evaluated by the ability to fully inflate a 2.5-mm or 3.0-mm balloon. When a larger stent is contemplated, compliance is verified with a larger balloon. If full balloon inflation is possible, then it should also be possible to fully deploy a stent. If an imprint remains on the balloon, even at high pressure, then further rotational ablation is necessary. I never exceed a burr size of 1.5 mm for lesions on sharp bends.

**Excimer Laser**

Much of the preceding commentary on Rotablator use is also true for excimer laser. The goal is not massive debulking, but rather compliance changes that
will permit full stent deployment. Such compliance changes can often be accomplished with very small laser catheters used at higher-than-conventional energies. Excimer laser is absolutely contraindicated for lesions on sharp bends.

**Directional Coronary Atherectomy**

The safety of directional coronary atherectomy (DCA) is highly dependent on operator skill and experience. This method can be extremely useful in preparing arteries for stenting but extremely dangerous when used overaggressively. Perforations secondary to DCA tend to be massive and possibly untreatable. Again, when the final goal is full stent deployment, aggressive debulking is unnecessary. To avoid perforations from DCA, IVUS guidance is essential. Directional atherectomy catheters are no longer available in the United States and are available only by special order elsewhere.

**Cutting Balloon and Angioscore**

Cutting balloon is a hybrid between an angioplasty balloon and an atherectomy device. In terms of perforation, it tends to act more like a balloon in that oversizing is the most important cause of perforation. Similar to the debulking devices, the present role of cutting balloon is to change the arterial wall compliance to allow proper stenting. When used properly in this regard, cutting balloon can change lesions from undilatable to easily dilatable and easily stentable. In my practice, cutting balloon has greatly reduced the need for Rotablator. To avoid perforation from cutting balloon, I tend to slightly undersize the balloon but use relatively high pressures (ie, pressures high enough to fully expand the balloon).

Angioscore is mechanistically similar to cutting balloon, but easier to use and theoretically safer on sharp bends. Like cutting balloon and other atherectomy devices, the goal should be compliance changes allowing full stent expansion. Perforation is best avoided by using high pressure but with undersized balloons.

**Problem With Devices on Bends and at Bifurcations**
As previously noted, cutting and ablating devices must be used with extreme caution when treating lesions on bends and when treating bifurcation lesions. For bifurcation lesions, these devices are especially dangerous when used in the direction of side branches, especially when side branches arise at steep angles.

**ROLE OF STENTING**

In 2015, stents were used in nearly 100% of PCI procedures. It is not surprising that they are involved in a high percentage of perforations. Some of these perforations are caused by balloon angioplasty or another device used prior to stenting. When this occurs, deployment of a conventional stent is absolutely contraindicated. Stent deployment almost invariably worsens the problem and rarely solves it. The stent serves only to enlarge the perforation, thus converting a potentially manageable problem into a disaster. Covered stents, of course, are the exceptions to this rule and are the most useful tools for managing large perforations. Recent reports of perforation closure using an MGuard stent (2 reports) and Magic Wallstent (1 report) represent exceptions to this rule.

The conundrum of stenting and perforation is that one strives to achieve as large a lumen as possible within the stent, but the larger the stent-artery ratio, the higher is the likelihood of perforation. IVUS guidance and proper preparation of arteries prior to stenting are the best ways to prevent perforation. One should aim for stent-artery ratios of 1:1. If IVUS suggests poorly compliant plaque (eg, diffuse fibrosis with negative remodeling, heavy calcification) or significant eccentricity or both, primary stenting should be avoided. In these cases, the arteries need further preparation prior to stenting. This can be done with cutting balloon, Angioscore, undersized balloons at very high pressures, or cutting or ablating devices. If high pressures for stent deployment are anticipated, a slightly undersized stent should be chosen. This stent can be postdilated with a larger balloon once the initial result has been assessed by IVUS.

**PREVENTION**
Although perforations are relatively uncommon, their sequelae are so devastating that all measures must be taken to prevent them. Most perforations are preventable. Operators must be constantly cognizant of high-risk situations and properly prepare arteries prior to stenting. If an artery cannot be properly prepared, stents should not be used. Oversizing must be avoided. In high-risk situations, devices, balloons, and sometimes stents should be slightly undersized. Routine use of IVUS or OCT is integral to each of these disciplines. Guide wire perforations are best prevented by using hydrophilic wires only when necessary, exchanging these wires for conventional wires whenever possible, and being constantly aware of the potential for guide wire perforation in long, complex cases.

Caveats for prevention of CAP include the following:

1. If inexperienced or low-volume operator:
   a. Avoid treating lesions at high risk for perforation: lesions on bends, eccentric lesions, calcified lesions, bifurcation lesions, branch lesions, distal lesions, lesions requiring devices, acute margin lesions, vein grafts
   b. Avoid devices
2. If experienced and high-volume operator:
   a. Do not do complex cases at same time as diagnostic procedure
   b. Spend extra time before case reviewing films with specific interest in preventing CAP
   c. Use IVUS or OCT routinely before, during, and after treatment
   d. With eccentric lesions, settle for less than optimal result, and do not strive for a circular lumen
   e. When using hydrophilic wires, constantly check for distal migration
   f. Undersize all devices except stent; the goal is to change compliance enough to allow full expansion of coronary stent

Following these guideline, an experienced operator can probably reduce perforation rate to <0.2%, but never to zero.

**MANAGEMENT**
Coronary perforation is an emergency. The window of opportunity for effective treatment can be quite short, frequently less than 1 minute. Treatment delay can mean the difference between life and death. Mortality in type III perforations (large perforations with a jet of contrast) is 20%. This is 10 times the mortality associated with grade I and II perforations. Mortality associated with grade III perforations remains high despite the introduction of covered stents. When pericardial tamponade occurs, mortality increases. Appropriate action in the first minute can prevent the occurrence of tamponade. Every catheterization laboratory should have the following basic materials available to treat perforation.

- Angioplasty balloons
- Pericardiocentesis tray
- Covered stents
- ACT machine

If these materials are not immediately available, the window of opportunity may be lost.

The single most important piece of equipment for the emergency management of perforation is the simple angioplasty balloon. Balloons are the first line of defense, because they are used to temporarily seal the hole while other more definitive measures are prepared. Even in patients who become abruptly hypotensive following perforation, sealing the hole will frequently stabilize blood pressure without concomitant pericardiocentesis or fluid administration. Because the opportunity to stabilize the patient with this approach may last only 30 to 60 seconds, any delay in searching for a balloon outside the catheterization laboratory may result in devastating consequences. Any balloon of any size is satisfactory, and an unprepared balloon is as effective as one that is carefully prepped.

Pericardiocentesis may be necessary to stabilize blood pressure and preserve cardiac output. Materials for pericardiocentesis must be immediately available.

Covered stents are the definitive treatment for CAP. They have revolutionized the treatment of this condition. Covered stents of various sizes and lengths must be immediately available. Stents that are too short may not cover the hole. Stents that are too long may cover important side branches.

Reversal of anticoagulation is a mainstay of treatment. Sometimes this is
the only necessary treatment. Satisfactory reversal of anticoagulation is best
determined by return of ACT to normal.

Prerequisites for the intermediate treatment of CAP include the following:

• A second interventional cardiologist
• Surgical standby
• Echocardiography
• Platelets
• Coils

If the patient becomes hemodynamically unstable or pericardiocentesis
must be performed, a second experienced physician is invaluable. The second
physician also can serve as a sounding board for ideas regarding definitive
care. Sometimes it is necessary to invent solutions to individual perforation
problems. In such cases, the interchange of ideas between 2 experienced
interventional cardiologists may produce a solution that neither could have
devised alone.

Surgical standby has become less and less important during PCI. Some
coronary perforations cannot be solved in the catheterization laboratory.
Sometimes it is better to stabilize the patient with balloon sealing of the
perforation, with or without pericardiocentesis, and then take the patient to
surgery. This is a decision best made by interplay between the interventional
cardiologist and surgeon.

Patients should not be taken to surgery while still actively bleeding into
the pericardium. The transfer time and time to open the chest and gain control
of bleeding exceeds 30 minutes under the best of circumstances. Concomitant
blood loss combined with pericardial tamponade may lead to irreversible
cardiac and end-organ damage.

Surgical mortality is high in these very sick patients—18% in one large
series. Patients frequently have bleeding into the myocardium, which poses a
major surgical problem. All medical efforts to solve the problem should be
exhausted before sending a patient to surgery. Specific exceptions to this
caveat include certain bifurcation lesions, in which covered stenting will
sacrifice 1 or more large side branches, and perforations that involve the
aorta.

The echocardiogram is invaluable in determining the hemodynamic effect
of a perforation and whether or not it has been solved. Small or no pericardial effusion suggests that it will be possible to solve the problem in the catheterization laboratory without pericardiocentesis. Large effusions require pericardiocentesis, continuous pericardial drainage, and a possible trip to the operating room.

In the presence of glycoprotein IIb/IIIa inhibitors or thienopyridines, or both, platelet transfusion may be required to reverse anticoagulation. Because there is an inherent delay in obtaining and infusing platelets, the decision to transfuse platelets must be made early in the treatment course. The urgency of the situation must be properly communicated to the blood bank. Most perforations can be managed without platelet infusion.

Vascular coils may be useful in occluding small branches that have perforated. This is especially true in the case of guide wire perforations. The availability of coils and operator experience with their use can save an otherwise difficult situation. Many interventional cardiologists have no experience with coils. The assistance of an interventional radiologist or neuroradiologist may be required. It is worthwhile to establish a liaison with such individuals in anticipation of needing their help in an emergency.

**TREATMENT ALGORITHM**

**Stay Cool and Never Lose Guide Wire Position**

There are 2 absolute caveats in the management of CAP: stay cool and never lose guide wire position. These 2 caveats are grouped together, because if the operator panics when a perforation is first noticed, he or she may by reflex remove the guide wire. Alternatively, if a small perforation is noted, there is a natural tendency to rationalize it away with such thoughts as “it is only a small branch” or “it will stop spontaneously when the anticoagulation goes away.” In such cases, the guide wire may be removed only to find that the perforation is a much greater problem than originally thought.

A large perforation is a true emergency. However, once bleeding has been controlled (with a balloon), there is usually time to proceed in an orderly manner. If guide wire position is lost, it may be impossible to control bleeding. Recrossing with a guide wire may not be possible. In this setting, the guide wire tends to exit through the perforation.
Recognize Perforation Immediately

It should be the habit of an interventional cardiologist to be vigilant about looking for perforation after device use, balloon dilatation, and stenting. Small perforations recognized early are easy to treat. Even small perforations left untreated can lead to cardiac tamponade and death. When additional balloon dilatation, stenting, or both are performed in the presence of unrecognized small perforations, the perforations invariably enlarge and lead to major bleeding.

First Action: Block the Perforation

As one learns in any elementary first-aid course, it is imperative to control bleeding before undertaking any other treatment. With coronary perforation, inflating a balloon at low pressure across the entrance to the perforation controls bleeding. The essence of this treatment is time. Any balloon—even an unprepped balloon—is suitable. Balloon size is unimportant; the balloon need only be large enough to block the flow of blood. The fastest way to get a balloon in place is to readvance the last balloon used. For this reason, it is a good habit to make a post-PCI injection while the balloon is still in the guiding catheter.

With large perforations, time is so important that a delay of only 30 seconds may create a downward spiral, leading to death. Following major perforation, blood pressure can fall 100 mm Hg in 30 seconds. This is due to a combination of blood loss, pericardial tamponade, and a vagal-mediated reflex (Bezold-Jarisch) from sudden distention of the pericardium. Treatment of this severe hypotension consists of stopping the bleeding and then performing pericardiocentesis. Pericardiocentesis will not be effective if the bleeding is not controlled. In the 30 seconds necessary to open a pericardiocentesis tray, it should be possible to cross the mouth of the perforation and inflate a balloon at low pressure. On occasion, merely controlling the bleeding will allow the pericardium to accommodate the blood; blood pressure will increase spontaneously, and pericardiocentesis can be avoided.

Once bleeding is controlled, pericardiocentesis, if necessary, can be performed in an orderly manner with proper positioning of the patient and sterile preparation of the chest. Prior to pericardiocentesis, blood pressure
should be maintained with intravenous fluids and vasopressors. These 2 measures are usually effective in maintaining a satisfactory blood pressure for 15 to 30 minutes, as long as bleeding is controlled. During this time, first efforts to reverse anticoagulation must be initiated.

**Second Action: Stop and, If Possible, Reverse Anticoagulation**

Although reversal of anticoagulation is fully dependent on the type of anticoagulation in use, the combination of fresh frozen plasma and platelets can be expected to fully reverse virtually any anticoagulant regimen. Procuring and infusing sufficient quantities of these blood products to control bleeding takes more than 1 hour. Therefore, if it appears that blood products will be required, they must be requisitioned at the outset.

**Heparin**

Protamine is a specific antagonist for heparin. It should be available in all catheterization laboratories where PCI is performed. Immediate administration of protamine is always appropriate when perforation occurs in heparinized patients. The usual initial dose of protamine is 10 to 20 mg, depending on how much heparin has been given and on the ACT level. We tend to err on the low side, because protamine itself is anticoagulant, and too much protamine will be counterproductive. Additional protamine is given if the ACT is not normalized with the first dose. Titrating protamine administration in this manner usually results in complete reversal of anticoagulation in 30 minutes.

**Direct Thrombin Inhibition**

Reversal of bivalirudin is less complex. Although fresh frozen plasma is the only way to directly reverse bivalirudin, this is rarely necessary. The short and predictable half-life (25 minutes) of this medication means that merely turning off the infusion will reverse anticoagulation. Normal coagulation should ensue within 2 half-lives (50 minutes). Figure 61-1 shows a large (type III) perforation from the LAD to the right ventricle. This perforation sealed within 30 minutes after discontinuation of bivalirudin anticoagulation. At 25 minutes, the perforation was essentially sealed and the artery was patent. The operator chose to leave a balloon inflated an additional 5 minutes,
during which the mid-LAD occluded within a stent. It is a difficult decision whether to remove the balloon in the presence of a small residual leak and a patent vessel or to proceed with further balloon inflation until the perforation is completely closed. In the former case, there is risk of the perforation reopening, possibly after the patient has left the catheterization laboratory. In the latter case, there is risk of occluding the stented vessel.

**Glycoprotein IIb/IIIa Receptor Inhibitors**

These agents are the most problematic when perforation occurs. Reversal of heparin anticoagulation with protamine will normalize the ACT in patients treated with IIb/IIIa inhibitors, but the antiplatelet effect persists. The only effective way to reverse these agents is with platelet transfusion. Theoretically, platelet transfusion is more effective against abciximab than against eptifibatide or tirofiban, but in practice, all 3 agents should be effectively reversed by platelets. Although there is a simple assay to measure platelet function in the catheterization laboratory, it is not available in most labs. From a practical standpoint, it takes 1 to 2 hours to obtain and transfuse platelets.

Glycoprotein IIb/IIIa receptor inhibitors are most troublesome with small perforations, especially guide wire perforations, which can be solved with low-pressure balloon inflations and reversal of anticoagulation. In the presence of IIb/IIIa inhibition, these small perforations can ooze for hours. Occasionally, they will appear to seal while the patient is in the laboratory and then start to bleed again when the patient is returned to the ward. This can lead to slowly developing pericardial tamponade that manifests surreptitiously in the middle of the night.

Despite these reservations, a practical approach to perforation in the presence of glycoprotein IIb/IIIa inhibitors is to reverse concomitant anticoagulation (heparin or bivalirudin), perform prolonged balloon inflation, and observe the results. In most cases, the problem will resolve without further ado. Because of the long lag time in procuring platelets, these should be ordered as soon as the problem is recognized. If the perforation has been solved before platelets become available, so much the better.

**Third Action: Solve the Problem**

The problem is how to stop the bleeding while retaining antegrade flow. In
small perforations and guide wire perforations, the problem is frequently solved by reversal of anticoagulation and concomitant prolonged low-pressure balloon inflation.

**Covered Stents (Stent Grafts)**

When simple measures fail, covered stents are by far the most effective treatment. In the appropriate setting, deployment of a covered stent across the perforation is a simple, quick, and elegant solution. Bleeding stops immediately, even in a fully anticoagulated patient. The problem with stent grafts is that they are much more difficult to use than ordinary stents.

Because of their bulk and stiffness, they require 7-Fr guiding catheters, and they may not negotiate tortuous or diffusely diseased vessels. They cannot be used to treat small vessels or branches. In large perforations, there may not be time to do the various maneuvers required to deploy these stents.

Side branches represent a major problem for covered stents. If the stent covers the ostium of a side branch, the branch will be sacrificed. If the side branch is small, it can be sacrificed. If the side branch is large, surgery should be considered as an alternative to stent grafting.

Before attempting to deploy a stent graft, it is best to reverse anticoagulation and to minimize bleeding to the greatest extent possible. Graftmaster stent grafts require 7-Fr or larger guiding catheters. If it is necessary to switch from a 6-Fr to 7-Fr catheter, this must be done carefully and, if possible, in an unhurried manner. The exchange is made over a 300-cm 0.014-inch guide wire, preferably a stiff wire such as the Ironman or Platinum Plus. Exchange for one of these wires is best accomplished through an over-the-wire balloon catheter or transit-type catheter. Although it may be possible to place the new wire as a “buddy” wire, this is not always easy to do in the presence of perforation. There is a tendency for the wire to migrate through the perforation or into a subintimal space that leads to the perforation. This is especially likely with the stiff wires that must be introduced. An alternative is to leave a partially occlusive balloon to block the perforation while passing the new wire alongside. The most important caveat is never to lose distal guide wire position. There is a strong likelihood that it will not be possible to recross for previously stated reasons. If this is the case, a fatal outcome may ensue. If an operator is unsure whether he or she has the skills to change the guiding catheter and sheath without losing guide wire position, it may be best to send the patient to surgery with a
balloon inflated across the perforation.

Alternatively, a 7-Fr guiding catheter can be introduced via the contralateral femoral artery while an inflated balloon remains across the perforation.

With the new guiding catheter and a stiff wire in place, it should be possible to deploy the stent graft without undue difficulty. If significant bleeding has occurred during the guiding catheter exchange, it may be prudent to reintroduce a balloon, tamponade the perforation, and make sure that the patient is hemodynamically stable. If there are signs of cardiac tamponade, it may be possible temporarily to stabilize the hemodynamics with intravenous fluid and pressors. Pericardiocentesis may be necessary at this point. It is better to perform pericardiocentesis during relative calm than to have to do so as an emergency while struggling to deploy a stent graft.

Stent grafts must be deployed at high pressure. These are extremely stiff devices that require a minimum of 14 to 16 atm for proper deployment. To avoid endoleak, the stent graft must be long enough to cover the perforation with 4-mm margins on each side. If a shorter margin is necessary to avoid covering a side branch, the operator needs to weigh the importance of losing the side branch versus the possibility of not sealing the perforation.

Once the stent graft is deployed, bleeding should cease immediately. If bleeding does not stop, the graft is too small or underdeployed, it is too short to cover the perforation with adequate margins, or there is a second perforation. Bleeding should again be controlled with a low-pressure balloon while each of these possibilities is considered by careful review of the angiograms. IVUS may be helpful. Even if bleeding is controlled with the covered stent, IVUS should be used to verify full stent deployment. More often than not it will be discovered that the stent graft is underdeployed. Stent grafts available in the United States are “stent sandwiches”—2 stainless steel stents with a layer of fabric between. As a result, the outer diameter of these devices is 0.5 mm greater than the inner diameter. Thus, the stent may appear fully deployed on angiogram when it is in fact grossly underdeployed. IVUS will reveal this discrepancy and guide appropriate postdilation. When one has solved a perforation with stent grafting, there is a tendency to finish the case without further ado. This is a mistake. An underdeployed stent graft has a significant probability (5.7%) of subacute thrombosis.¹¹

The only coronary stent graft available in the United States is the Graftmaster by Abbott (Abbott Park, IL), and this is only available under a
human device exemption protocol that requires institutional review board approval. This device, which was developed 20 years ago, is cumbersome to use, difficult to deploy, and has a high rate of subacute thrombosis and an in-stent restenosis rate >30%. For economic reasons, there is no incentive for industry to develop a better product.

Two production stents have been used successfully to treat Ellis grade II perforations—Magic Wallstent from Boston Scientific and MGuard stent from InspireMD Boston, MA. The Wallstent is a self-expanding stent with tight wire mesh design reported in a single case report to successfully close a grade II LAD perforation. MGuard is a conventional balloon-expandable stent covered with an ultrathin mesh sleeve with pore size <200 μm, whose primary use is to minimize distal embolization when stenting thrombus-laden arteries. In 2 separate case reports, this stent was used successfully to close grade II perforations. Both stents have logistic advantages over Graftmaster in that they are 6 Fr compatible and are considerably more flexible. MGuard has CE mark since 2007, but is not yet available in the United States. Evidence for effectiveness of these 2 stents in the treatment of CAP is only anecdotal.

Exotic Solutions
In some situations, stent grafting will not be possible; these include diffusely diseased arteries, small vessels, and distal branches (including guide wire perforations). In these instances, it is necessary to create solutions that fit the actual circumstances. The focus should be on controlling bleeding as opposed to preserving antegrade flow. In most of these situations, the amount of myocardium at risk is relatively small. The general approach to this problem is to permanently block antegrade flow. Although collateral blood flow may allow continuing leakage through the perforation, this is generally small and self-limiting. When perforations are caused by stents, blocking antegrade flow may be difficult or impossible.

The most effective way to block antegrade flow is through coil embolization. Although this technique is not particularly difficult, it should not be tried for the first time in an emergency situation. If the coils are not deployed precisely, they can occlude the wrong vessel(s). It is worthwhile to learn the technique from an interventional radiologist or neuroradiologist and to know where to obtain coils if they are needed.

An alternative to coils is the intentional underdeployment of a coronary
stent. This can be expected to induce thrombosis when anticoagulation has been reversed. Although I have successfully used this approach, coils represent a more elegant and more secure approach.

**Thrombin Injection**

Injection of Gelfoam\textsuperscript{16} or thrombin through a microcatheter can be used to close distal perforations, especially those caused by guidewires. Figure 61-2 shows a distal branch perforation that was closed with thrombin injection. It was possible to close the perforation while preserving flow in all other branches. This would have been difficult to do with coils.

**Surgery Should Be the Last Resort**

Most perforations can be solved with the methods described. If these methods fail, then surgery is the only other option. The cardiac surgeon should be notified as soon as a perforation is recognized and should participate in the decision-making process. Although surgery is best deferred until other measures have been exhausted, one should not wait until a patient is in extremis before sending him or her to the operating room. If the previously described approach to treatment is followed, it should be possible to maintain the patient in stable condition. Once the decision is made to go to surgery, preparations must be made to ensure that the patient remains stable during the transfer process and during the time necessary to induce anesthesia and open the chest.

Bleeding must be controlled with an inflated balloon across the perforation. If pericardial tamponade is present, the pericardial cavity must be drained before the patient leaves the catheterization laboratory. Although attention to these matters may create ongoing ischemia, maintenance of hemodynamic stability is of primary importance.

When surgery is required, it is important for the surgeon to limit the operation to what is absolutely necessary. The primary goal is to control bleeding from the perforation. It may or may not be necessary to bypass the artery in which the perforation has occurred. Frequently, the perforation occurs as part of a successful opening of the artery in question, and the artery can be expected to stay open once bleeding is controlled. There is little rationale for doing a “complete” operation involving bypassing of multiple vessels and/or valve replacement. Patients who go to the operating room as a
result of CAP are already high risk and have been through a lot before reaching the operating room. They cannot tolerate a long and complex surgical procedure.

This concept is a difficult one to transmit to a cardiac surgeon, who has been trained to do “complete” procedures. It helps if there is a close working relationship between cardiologist and surgeon. It has been my practice to accompany the patient to the operating room and to remain there at least until the perforation is identified and the bleeding controlled. This is a time when surgeon and cardiologist can intelligently discuss what must be done immediately and what can wait for another day.

**SUMMARY**

Perforation as a result of PCI is uncommon but not rare. Any operator who performs several hundred interventions a year can expect at least 1 perforation. The best way to prevent perforations is to recognize situations of increased risk and take appropriate precautions. When a perforation does occur, it is mandatory to promptly recognize it, avoid manipulations that make it worse (eg, stenting), and start treatment immediately.

The cornerstones of treatment are maintaining guide wire position and control of bleeding with a low-pressure balloon across the perforation. Prompt control of bleeding can prevent life-threatening complications such as pericardial tamponade. Reversal of anticoagulation is mandatory. Deployment of a covered stent across the perforation is the ultimate solution, but this is seldom easy to do and not always possible.

Surgery in this setting carries a high mortality. Most perforations can be solved without surgery. It is important always to be prepared to treat perforations without delay. This requires appropriate knowledge and skill as well as the immediate availability of the necessary equipment.

**REFERENCES**


MULTIPLE CHOICE QUESTIONS

1. Lesions at high risk for perforation include which of the following?
   A. Lesions on bends
   B. Bifurcation lesions
   C. Lesions in branches and distal vessels
   D. Calcified lesions
   E. Eccentric lesions
   F. All of the above
   G. None of the above

2. Guide wire perforation is most likely to occur with which of the following?
   A. Stiff wires
   B. Hydrophilic wires

3. Factors relating to prevention of perforation include which of the following?
   A. Avoidance of high-risk lesions
   B. Careful review of diagnostic angiograms prior to starting case
   C. Undersizing devices
D. Use of intravascular ultrasound and optical coherence tomography before, during, and at end of procedure
E. All of the above
F. None of the above

4. Management of perforation may include which of the following?
   A. Maintenance of guide wire position
   B. Tamponade of leak by inflating balloon across perforation
   C. Covered stent
   D. Pericardiocentesis
   E. All of the above
   F. None of the above

5. In management of a perforation, what is the single most important caveat?
   A. Reverse anticoagulation
   B. Tamponade perforation by inflating balloon across lesion
   C. Use covered stent (stent graft)
   D. Maintain guide wire position
   E. Pericardiocentesis

**ANSWERS**

1. F
2. B
3. E
4. E
5. D
Embolization and No-Reflow During Percutaneous Coronary Intervention

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INTRODUCTION

Embolization and coronary no-reflow are rare but important complications during percutaneous coronary intervention (PCI). Recognition and treatment are important in that they may reduce or prevent myocardial necrosis and serious subsequent complications. Additionally, nonclinical events may occur as a result of this phenomenon, and prevention where possible becomes important. Macroembolization usually is due to macro-particles and/or blood clots that may occur during intervention of patients with acute coronary syndromes. No-reflow may occur due to the embolization of micro-particulate matter as debris from coronary lesions, activation of platelets, and/or release of vasoactive substances that may modulate distal vasculature. No-reflow is defined as the reduction of coronary flow in the absence of a proximal occlusive lesion with resultant myocardial ischemia. In PCI of native coronary vessels in absence of acute coronary syndromes, no-reflow may be due to microvascular spasm and/or platelet microemboli. When PCI is performed in thrombotic lesions, such as in acute coronary syndromes, no-reflow may be due to distal embolization of thrombus. During saphenous vein graft intervention and rotational atherectomy, it is most often related to
embolization of degenerated plaque elements including thrombotic and atherosclerotic debris. Any or all of these mechanisms can occur simultaneously.

A number of strategies have been available as adjuncts to reduce embolization, but many have been shown to be ineffective and are no longer available. Many are mentioned here for an historical perspective.

**EXPERIMENTAL STUDIES**

The problem of embolization of plaque material during percutaneous catheter angioplasty and stenting has been recognized since the early development of balloon angioplasty. Shortly after the introduction of balloon angioplasty in an experimental model of angioplasty, effluent debris was collected and analyzed by histologic and polarized light microscopic examinations for gross debris and cholesterol.¹ This study is often widely cited as showing no evidence for significant embolization during balloon angioplasty. Microscopically visible atherosclerotic debris was present in 12% of procedures, and thin-layer chromatography showed evidence of cholesterol embolization in 25%. These findings of atherosclerotic debris in between 12% and 25% of treated vessels is completely in line with clinical studies that followed in patients over the next 2 decades.

Both particle size and amount of the embolic material are important. Small amounts of 15-μm particles have been shown to cause patchy ischemia, while increased numbers of particles can cause decrease in flow. When particles are larger, in the 100 to 300 μm range, a relatively few particles can reduce flow.

**EMBOLIZATION IN CLINICAL STUDIES**

Clinical studies have found evidence for embolization associated with PCI procedures. In the stent era, embolization has been detected in about 20% of simple native vessel stent implantation procedures based on the occurrence of creatine phosphokinase-MB (CPK-MB) enzyme release only. For example, in the STARS trial, patients with type A lesions who had completely
uncomplicated, successful stenting with a single stent were evaluated. In this group, the incidence of CPK-MB release was 20%.\textsuperscript{2} In the STARS registry, which included patients who had dissections, had suboptimal stent results, or required additional stents, the incidence of CPK-MB release was close to 30%.\textsuperscript{3} Similarly, in the STRATAS rotational atherectomy trial, almost 30% of patients had CPK-MB release.\textsuperscript{4} The majority of these enzyme elevations are not associated with clinical events.

Clinically apparent embolization occurs more frequently in saphenous vein graft (SVG) interventions. In-hospital major events occur in almost 15% of these interventions.\textsuperscript{5,6} In contrast to the enzyme elevations seen with PCI in native vessels, these are clinical events including chest pain, electrocardiographic changes, and/or marker elevation. Thus, suspected embolization occurs in 15% to 20% of PCI cases overall.

One of the more severe manifestations of embolization is the no-reflow phenomenon. This was originally identified in experimental models of myocardial infarction.\textsuperscript{7} It is the failure of restoration of myocardial flow despite removal of the epicardial coronary obstruction. This is an infrequent event during PCI, complicating between 0.5% and 3% of procedures. It is most typically associated with reperfusion after acute coronary syndromes, particularly acute ST-segment elevation myocardial infarctions and in SVG interventions. It also occurs as a result of rotational atherectomy. It can also occur, more rarely, in native vessels.

The clinical sequelae of the no-reflow phenomenon can be both acutely and chronically severe. Patients have, in the most profound situations, hemodynamic collapse or a severe ischemic syndrome, depending on the size of the affected vessel territory. Both prevention and treatment have been challenging during the development of catheter intervention.\textsuperscript{8}

**CLINICAL RELEVANCE**

The short-term and long-term consequences of particulate embolization during PCI have been studied extensively. Acute complications include the no-reflow phenomenon, which is slow or no flow in treated vessels, causing prolonged chest pain, and can produce myocardial cell necrosis.

In the Primary Angioplasty and Myocardial Infarction (PAMI) trial, no-
reflow occurred during primary coronary intervention for ST-segment elevation acute infarction in 1.3% of over 1000 patients. Compared with patients who did not have no-reflow during PCI, those with the no-reflow phenomenon had a significantly higher hospital and 6-month mortality. Hospital mortality was 2% without versus 13% with no-reflow ($P = .04$), and at 6 months, it was 3% without versus 31% with no-reflow ($P = .0001$); this illustrates the striking clinical importance of this phenomenon. In another study, data were prospectively collected from over 4200 consecutive patients undergoing PCI to identify those with no-reflow. No-reflow was identified in 3.2% of patients. Patients with no-reflow were more likely to have acute myocardial infarction, unstable angina, and cardiogenic shock or have undergone SVG intervention. No-reflow in this group was also highly predictive of postprocedural myocardial infarction (17.7% vs 3.5% in patients without no-reflow). No-reflow was similarly a strong predictor of in-hospital mortality. Administration of calcium-blocking drugs or nitroprusside was not associated with improved in-hospital outcomes in these patients, although antegrade flow rates improved in patients treated with nitroprusside in this group. Mortality was 7.4% with versus 2% without no-reflow ($P < .001$; odds ratio [OR], 3.6). Late consequences of these events have been characterized in numerous studies, suggesting a relationship between in-hospital CPK elevations, reflective of embolization, and increased late mortality as long as 3 years after the index interventional procedure.

**PARTICULATE ANALYSIS**

A variety of mechanisms for the clinical effects of embolization during PCI have been elucidated (Table 62-1). Most simply, mechanical disruption of the plaque results in fragmentation of plaque elements. A variety of plaque elements can be identified, including plaque fragments, cholesterol crystals, foam cells, and amorphous debris.

<table>
<thead>
<tr>
<th>Proposed Mechanisms of No-Reflo</th>
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<tr>
<td>Microvascular constriction and vasospasm</td>
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<tr>
<td>Distal embolization of thrombus and/or atherosclerotic debris</td>
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<tr>
<td>Oxygen free radical–mediated endothelial injury</td>
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• Capillary plugging by red blood cells and activated neutrophils
• Neutrophil-mediated endothelial cell dysfunction/vasoconstriction
• Intracellular and interstitial edema
• Intramural hematoma
• Loss of capillary integrity due to completed myocardial infarction


In a study of the aspirated particles from 23 SVG procedures retrieved using an extraction system, a mean particle size of 168 μm was noted. The range was large, from a minimal of 6 to a maximum of 815 μm in the minor access, and 7 to 3427 μm in the major access of these particles. Particles were composed of cholesterol clefts, lipid-rich macrophages, fragments of fibrous cap, necrotic lesion core, and fibrin.

Many of the causes of embolization of microscopic debris into the small vessels of the distal microcirculation are well described. This is evidenced by studies of rotational ablation. Debris of varying sizes of particulate has variable effects on microcirculatory plugging. Rotational atherectomy creates particulate debris with a mean particle size of less than 6 μm. These smaller particles pass through the capillary circulation in the same manner as red blood cells. Larger particulate, which comprises about 20% of the rotational atherectomy debris, can be trapped in the microcirculation and contributes to slow flow and CPK elevations.

Hori et al studied the effective particle size and number in a coronary arterial microsphere embolization perfused canine model. Small numbers of 15-μm particle emboli caused patchy myocardial ischemia and a paradoxical regional increase in blood flow from the effect of reactive increased flow to nonaffected adjacent areas. Increasing numbers of emboli caused impaired flow reserve and decreased resting flow. Larger particles (100-300 μm) caused a dramatic reduction in the number of emboli needed to cause decreased resting flow.

**ROLE OF THROMBUS**
Angiographic thrombus is a powerful predictor of PCI complications. In the clinical setting of acute coronary syndromes, macroembolization of clot is well known. Gross distal embolization can be observed even when no thrombus is identified. Many interventionalists have had the experience of watching a fragment of clot, or thrombus, visibly embolize downstream during injections in the middle of PCI procedures.

**VASCULAR REACTIVITY**

Liberation of vasoactive humoral substances such as serotonin has also been implicated in the genesis of slow flow and no-reflow. Serotonin levels have been measured in the distal coronary artery in patients after angioplasty or stenting. Balloon angioplasty caused an increase in coronary sinus serotonin from basal values of 3 ng/mL to almost 30 ng/mL after balloon angioplasty and from 3.5 ng/mL to 114 ng/mL after stenting. This increase in liberation of serotonin was dramatically blunted by the administration of the serotonin antagonist ketanserin. Coronary cross-sectional area distal to the site of dilatation significantly decreased after angioplasty and stenting from 4.33 to 3.3 mm$^2$ after balloon angioplasty, and from 4.27 down to 2.86 mm$^2$ after stenting, consistent with distal vessel modulation. Pretreatment with ketanserin diminished this decrease in distal coronary luminal area.

One candidate protein that may cause coronary no-reflow is tissue factor. This is abundant in atherosclerotic plaque. In 1 study, coronary blood was drawn from 6 patients undergoing coronary intervention with a distal protection device, and the particulate material that was recovered showed tissue factor activity. To examine the role of tissue factor in no-reflow, blood was drawn via a catheter from coronary vessels in 13 patients during no-reflow and after restoration of flow. Mean tissue factor antigen levels were elevated during no-reflow compared with levels after flow restoration (194 vs 73 pg/mL, $P = .02$). Tissue factor induced no-reflow in a porcine model after selective intracoronary injection of atherosclerotic material or purified tissue factor. These data suggest that tissue factor is released from dissected coronary plaque and is 1 of the factors causing the no-reflow phenomenon.

Indirect evidence for the role of vasoactive mediators is seen in the attenuation of rotational ablation flow effects by the use of a vasoactive "cocktail."
The problem of embolization during PCI became particularly apparent during SVG intervention. Both the volume of SVG atheroma and its friable nature make it prone to embolization during intervention (Fig. 62-1).
FIGURE 62-1 Histologic section from a degenerated saphenous vein graft. The thickened wall of the vessel is easily seen. The volume of plaque material is large, and its friable nature can be seen easily.

As many as half of patients with saphenous vein bypass graft (SVBG) have angiographic evidence of atherosclerosis 5 years after surgery. A large
proportion of grafts are severely diseased by 7 to 10 years after surgery. In most PCI trials, the mean age for SVGs undergoing PCI is between 8 and 9 years after the original bypass surgery. In addition to the problems presented by the nature of the graft atheroma itself, patients are obviously a decade older than when their initial bypass surgery was done and represent a group with high frequency of congestive heart failure, prior myocardial infarction, depressed left ventricular function, and other comorbid conditions.

During PCI for SVGs, distal embolization is common. Patients who suffer distal embolization during these procedures have significantly poorer outcomes than patients who do not. The proportion of patients with major adverse in-hospital events after embolization approaches three-quarters, whereas patients without clinical evidence of embolization during their intervention have major adverse event rates in the hospital of less than 20%.\textsuperscript{21}

**PLAQUE REMOVAL DEVICES**

Early attempts to improve the outcome of intervention in SVGs included the use of plaque removal or debulking using directional coronary atherectomy (DCA). In the CAVEAT-2 study (Coronary Angioplasty Versus Excision Atherectomy Trial), patients were randomized to receive DCA versus plain balloon angioplasty (percutaneous transluminal coronary angioplasty [PTCA]). Although angiographic success rate was improved with DCA (from 79% with PTCA to 89.2% with DCA) and 6-month restenosis rates were similar (45.6% for DCA and 50.5% for PTCA), distal embolization occurred more frequently with DCA than PTCA (13.4% vs 5.1%; \(P = .012\)). The risk of thrombus embolization was much higher when visible thrombus was recognized (39% vs 14%). The 1-year outcomes were worse in patients who developed distal embolization. Figure 62-2 shows a simple thrombus aspiration catheter.
Other devices, such as the transluminal extraction catheter (TEC), were developed for plaque and thrombus removal.\cite{22,23} No-reflow was seen in 19% of patients with thrombus and 5% of patients without thrombus. Late complete vessel occlusion was seen in over one-third of patients with thrombus. The excimer laser has also been evaluated as a method of plaque
removal. In an initial series of 495 patients, embolization occurred in only 3.3% of patients and Q-wave infarction in only 2.4% of patients. However, in some laser studies, thrombus-containing lesions were associated with increased rates of embolization and poor clinical outcomes.

Rheolytic thrombectomy, a technique that uses high-velocity saline jets directed retrograde into the open mouth of a Bernoulli device, draws thrombus into the catheter tip for maceration and evacuation. In the Vegas II trial, rheolytic thrombectomy in native coronary vessels and SVGs containing thrombus was compared to urokinase infusion. Over half the patients treated had vein graft as opposed to native vessel thrombus-containing lesions. Rheolytic thrombectomy resulted in a significant decrease in major events at 30 days. Little subsequent study has been conducted of the efficacy of this form of thrombectomy therapy for the treatment of degenerated SVG lesions that are predominantly atherosclerotic rather than thrombotic.24

Another atherectomy (X-Sizer; EV3, Plymouth, MN) device using a cutting device with suction has been evaluated. No difference in acute events or outcomes at 1 year were noted.25,26

A recent meta-analysis of over 9000 patients in 16 trials found that ablative devices failed to reduce complications associated with embolization. Periprocedural myocardial infarctions occurred in 4.4% of patients tested with devices versus 2.5% without (OR, 1.83; 95% confidence interval [CI], 1.43-2.34).27

PREVENTION OF DISTAL EMBOLIZATION IN SAPHENOUS GRAFTS

Covered Stents

The use of conventional bare metal stents had improved the results of catheter therapy for obstructive SVGs but did not demonstrate any reductions in restenosis rate. In addition, the potential for liberation of particulate degree with embolization seems increased by the use of stenting compared to conventional plain balloon angioplasty. One of the first concepts tested to
diminish the potential for embolization using stenting was evaluation of membrane-covered metal stents compared with bare metal stents (Fig. 62-3). A polytetrafluoroethylene (PTFE) membrane–covered balloon-expandable stent was compared with conventional stents in a randomized trial. The concept that the PTFE membrane might trap graft atheroma behind the stent and prevent its liberation was assessed. Over 200 patients were randomly assigned to receive either a conventional metal stent or a membrane-covered stent. Neither restenosis nor acute procedural events were diminished by the use of a membrane-covered stent.

**FIGURE 62-3** Angiographic frames from a saphenous vein graft percutaneous coronary intervention (PCI) in which a polytetrafluoroethylene (PTFE) covered stent was used. A. There is a proximal graft lesion, noted by the circle. The inset shows the covered stent being deployed in the lesion. High pressure is required to fully expand the combination of graft membrane and stent material. In this case, 18 atmospheres was necessary for adequate stent expansion. B. The silhouette of the fully expanded stent in the proximal vessel.

**Distal Occlusive Devices**

Embolic protection devices were developed to prevent the consequences of embolization during SVG PCI. Embolic protection devices fall into 3 categories: distal occlusion, filter, and proximal occlusion devices.
The first device to undergo extensive clinical testing was the PercuSurge GuardWire (Medtronic, Minneapolis, MN).\textsuperscript{32} This device has a distal occlusion balloon mounted on a 0.14-inch angioplasty wire. The balloon is inflated in the distal SVG, intervention is performed, aspiration of the blood column is performed, and then finally, the balloon is deflated. This necessitates total cessation of flow to the target perfusion bed of the SVG. Some patients do not tolerate the ischemia. The system allows recovery of any liberated plaque material by aspiration before balloon deflation and restoration of forward flow in the treated vessel (Figs. 62-4 to 62-7).

**FIGURE 62-4** Focal saphenous vein graft lesion. A. Prior to intervention, a simple graft lesion is seen in the mid-vessel. B. After stenting, an excellent angiographic appearance is noted. This patient was treated with the PercuSurge distal balloon occlusion embolization protection.
Aspirated debris from the simple graft lesion in Figure 62-4. This highlights that even a relatively focal, saphenous graft lesion may liberate a great deal of embolic material. The filter here shows multiple particulate elements of highly variable sizes and composition.
FIGURE 62-6  A. Thrombotic, complex graft lesion with large thrombus and atherosclerotic burden. The patient was treated with the PercuSurge distal balloon occlusion embolization protection. B. Poststent result. Figure 62-7 shows the debris aspirated from this graft during intervention.
FIGURE 62-7 Debris aspirated from the saphenous vein graft shown in Figure 62-6. In contrast to the aspirate in Figure 62-5 from a simple lesion, the aspirate here shows macroscopic elements of thrombus and plaque, in addition to multiple particles of smaller, variable size.

In the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial, patients were randomized to treatment with distal embolization protection versus PTCA without embolic protection prior to stent placement. There was a 42% relative reduction in major adverse cardiac events with use of distal protection, which was driven principally by reductions in myocardial infarction (8.6% vs 14.7%; $P = .008$) and no-reflow phenomenon (3% vs 9%; $P = .02$). The overall composite end point in this subgroup occurred in 10.7% of protection device patients compared with 19.4% of control patients ($P = .008$). The mean total occlusion time for completion of the procedure was 6.5 minutes.

It was concluded that the use of a distal protection total occlusion device during stenting for stenotic SVG disease was associated with a highly significant reduction in major events compared with stenting using a conventional angioplasty guide wire without embolic protection. This represented the first important inroad into preventing the consequences of distal embolization during PCI. The substate of graft intervention represents an ideal model for the development of these devices, since there are no proximal side branches for embolic material to run off into during PCI.

Filters

A second class of embolization protection device is filter based. These devices use a wire micropore filter material in the distal target vessel (Figs. 62-8 and 62-9). A clear advantage of this category of devices is that perfusion is maintained in the distal circulation during the performance of stenting in the vast majority of patients.
FIGURE 62-8 Embolic filter devices. Upper left shows the Guidant Accunet Filter. The upper portion of the upper left figure shows the open filter, and the lower portion of the figure shows the filter constrained in a delivery sheath. (Image used with permission from Guidant, Inc.) Upper right shows the Cordis ANGIOGUARD RX Guidewire System. The lower left shows the FilterWire EZ, which is open in the upper portion of the panel and in the retrieval sheath in the lower portion of the panel. (Image provided courtesy of Boston Scientific. Copyright © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.) Lower right is the Abbott Emboshield filter in the open and constrained configurations. (Image used with permission from Abbott Vascular Devices, Redwood City, CA.) At the time of writing the Accunet, Angioguard and Abbott devices are investigational.
The first device in the filter category to complete a large randomized trial is the FilterWire (Boston Scientific, Natick, MA). In a randomized study of the FilterWire versus GuardWire, device success was 95% with FilterWire compared to 97% with GuardWire. Measures of epicardial flow and angiographic complications were similar between the 2 groups. The primary end point, which was a composite of death, myocardial infarction, or target vessel revascularization at 30 days, occurred in 9.9% of FilterWire patients and 11.6% of GuardWire patients. This represents a clear noninferiority result comparing the 2 devices. It was concluded that distal protection with the FilterWire might be safely used as an adjunctive PCI of diseased SVGs, and compared with distal protection using the GuardWire occlusion and aspiration system, the FilterWire resulted in similar rates of major adverse
cardiac events at 30 days (Fig. 62-10).

![Comparison of clinical event rates in 3 trials with embolization protection devices. MACE, major adverse cardiovascular event.](image)

**FIGURE 62-10** Comparison of the clinical event rates in 3 trials with embolization protection devices. MACE, major adverse cardiovascular event.

In the SAFER and FIRE trials, patients represented typical SVG intervention patients, who are older and have more comorbidity than patients undergoing native vessel PCI.

A review of the National Cardiovascular Data Registry (NCDR) database and Medicare claims data using propensity matching in patients 65 years and older undergoing SVBG intervention examined patients who had a distal protection device versus those who did not. This review revealed a slightly higher incidence of procedural complications in those with a distal protection device, including no-reflow (3.9% vs 2.8%; \( P < .001 \)), vessel dissection (1.3% vs 1.1%; \( P = .05 \)), perforation (0.7% vs 0.4%; \( P = .001 \)), and periprocedural myocardial infarction (2.8% vs 1.8%; \( P < .001 \)). By 3 years, death, myocardial infarction, and repeat revascularization occurred in 25%, 15%, and 30% of patients, respectively.\(^{33}\)

However, another report from the NCDR indicated that embolic protection device use was independently associated with a lower incidence of no-reflow (OR, 0.68; \( P = .032 \)), but not in-hospital mortality (1.0% vs 0.9%; \( P = \) not significant).\(^{34}\)

Despite the great enhancements provided by embolic protection devices, there are limitations to these approaches as well. The major limitation of the
balloon occlusion distal embolization protection system is total occlusion of
the vessel during stent implantation. Additionally, aspiration of the
particulate in the fluid column proximal to the inflated balloon is not
completely efficient, since events still occur in patients treated with this
modality. The balloon and wire system is less steerable than a conventional
angioplasty device. Some embolization may occur when the device is passed
across the lesion, although the balloon occlusion device has a lower profile
than the filter devices. The filter devices require a delivery sleeve to be
placed across the filter, increasing their profile. Iterations in device design
have made both of these classes of device easier to use with each successive
generation.

The filter devices may completely fill with debris, transforming them
effectively into occlusion devices. Trying to recapture the filter once it is
completely full may be problematic, since particulate embolic material might
be suspended in the blood column proximal to the filter. Thus, when a filter
device completely occludes and flow ceases in the target vessel, aspiration of
the blood column below the filter with an aspiration catheter may be
appropriate.

**Proximal Occlusive Devices**

Proximal occlusion devices represent another category of embolization
protection devices. An occlusive balloon is inflated in the vessel origin to
interrupt flow and create a static blood column distally (Fig. 62-11). During
intervention, any particulate will remain in the blood column in the vessel.
PCI can be performed through the balloon and the debris aspirated. This has
the advantage of causing stasis of blood flow proximal to the origin of side
branches. Thus, particulate released during the intervention will not run off
into the capillary bed, which allows the application of this system in both
SVG lesions and also in native vessels. Both SVG and native vessels (35% of
cases) were treated. The overall major adverse clinical event rate was 5.7%
in this nonrandomized group. Embolic material was obtained in the aspirate
from all of the patients enrolled.
FIGURE 62-11 The Proxis proximal occlusion device. Via the guide catheter, a proximal native coronary soft occlusion balloon is deployed. This creates a static blood column including in both the epicardial vessel and also in the side branches of the distal vessel. Through the occlusion balloon system, conventional stents may be placed. After treatment of the vessel, the blood column can be aspirated through the occlusion catheter. This device is investigational and not intended for clinical use at this point. (Image used with permission from Velocimed, Inc., Minneapolis, MN.)
PREVENTION OF DISTAL EMBOLIZATION IN NATIVE VESSELS: ACUTE MYOCARDIAL INFARCTION

Signs of microvascular hypoperfusion occur commonly after successful PCI for acute myocardial infarction. The large thrombus burden associated with these procedures causes embolization to be a common occurrence. Deterioration of flow after initially successful balloon angioplasty, worsened by stent implantation, has been commonly observed. Stent expansion with mechanical abrasion of the lesion by the stent struts, or the so-called “cheese grater effect,” is probably partially responsible. An evaluation of ST-segment elevation myocardial infarction (STEMI) patients using intravascular ultrasound (IVUS) and optical coherence tomography (OCT) noted that OCT-derived lipid and IVUS-derived plaque burden were the best discriminators for myocardial no reflow.\textsuperscript{35}

An early trial that evaluated the use of the FilterWire during primary PCI for acute myocardial infarction\textsuperscript{36} demonstrated improved flow as measured by frame counts, blush score, creatine kinase release, and time to resolution of electrocardiogram (ECG) changes. However, subsequently, a large randomized trial failed to show any differences between balloon occlusion embolization protection and conventional PCI and stenting.

Among patients with STEMI, the use of a distal protection balloon occlusion system was not associated with improvement in the primary end points of ST resolution or infarct size. Despite the capture of visible debris in almost three-quarters of patients, no improvements in myocardial profusion were observed compared to conventional therapy with balloon angioplasty and bare metal stenting.

ASPIRATION THROMBECTOMY

Aspiration thrombectomy (AT) catheters have been employed over the last 10 years. The catheter is a dual lumen catheter with a rapid-exchange port enabling passage over a guide wire that has been passed into the vessel and across the clot. The other lumen is larger and extends the length of the
catheter. A syringe is attached to the proximal end, and suction is applied manually while the catheter is passed back and forth through the clotted area to aspirate the clot (see Fig. 62-2).

Clot aspiration using AT is very successful; however, patient outcomes initially demonstrated improved outcomes, but subsequent randomized trials revealed no difference from balloon angioplasty and stenting. TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study), an early trial assessing AT, demonstrated that, at 1 year, there were reductions in all-cause mortality (4.7% vs 7.6%; \( P = .04 \)) and cardiovascular mortality (3.6% vs 6.7%; \( P = .02 \)).\(^{37}\) This was consistent with other smaller trials.\(^{38}\) Based on these data, AT received wide acceptance.

However, subsequent trials did not support these results. The INFUSE-AMI (Infuse–Acute Myocardial Infarction) trial failed to replicate the findings of the TAPAS trial in a small group of patients, with no differences observed in infarct size with AT at 30 days.\(^{39}\) TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) was a large, multicenter, registry-based randomized clinical trial. This trial found no differences in clinical outcomes assessed at 1 year between AT versus conventional PCI, including all-cause mortality (5.3% vs 5.6%; \( P = .57 \)) or stent thrombosis (0.7% vs 0.9%; \( P = .51 \)).\(^{40}\)

Another randomized trial, TOTAL (Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI), was a large and more definitive trial. No clinical outcome differences were observed at 6 months between patients who received or did not receive AT. These results included the primary outcome of major adverse cardiovascular events (6.9% vs 7.0%; \( P = .86 \)), cardiovascular death (3.1% vs 3.5%; \( P = .34 \)), or stent thrombosis (1.5% vs 1.7%; \( P = .42 \)); stroke rates were higher in patients receiving AT (0.7% vs 0.3%; \( P = .02 \)).\(^{41}\) As a result, AT has not been recommended as routine adjunctive therapy in STEMI.

The potential use of AT in patients presenting with STEMI late with “old” thrombus (>12 hours), in obvious thrombotic occlusions of SVBG, or in situations where there has been obvious distal thrombotic emboli has not been studied to date.
NO-REFLOW: SUPPORTIVE MEASURES

Treatment of no-reflow includes basic supportive measures for the patient, including fluid resuscitation, attention to oxygenation and airway management, and blood pressure maintenance with pressors or inotropes (Table 62-2). Maintenance of blood pressure is especially important, since distal perfusion pressure is necessary for recovery from no-reflow and also for the delivery of pharmacologic therapy to the distal vascular bed. When no-reflow occurs in the right coronary artery or inferior distribution, atropine therapy may be necessary to treat the reflex hypotension and bradycardia that may occur. Intra-aortic balloon pump therapy for blood pressure support is another mainstay of therapy in refractory cases. 42,43

Table 62-2 Initial Evaluation and Treatment of No-Reflow

- Exclude dissection, thrombus, spasm at lesion site (intravascular ultrasound, distal contrast injections, and/or translesion pressure gradient may be useful)
- Achieve adequate activated clotting time (250-300 s with unfractionated heparin if a glycoprotein IIb/IIIa inhibitor has been given, >300 s if one has not been given, and 325-375 s with direct thrombin inhibitors)
- Ensure sufficient oxygenation and airway management
- Treat vagal reactions (intravenous atropine and fluids)
- Maintain adequate perfusion pressure with intravenous fluids, vasopressors, inotropes, and intra-aortic balloon pump, if necessary
- Administer intracoronary nitroglycerin (100-200 μg up to 4 doses) to exclude epicardial spasm
- Consider administering a glycoprotein IIb/IIIa receptor inhibitor
- Administer pharmacologic agents through an infusion catheter or the central lumen of the balloon catheter to assure drug delivery to the distal bed

The basis of most therapy for no-reflow is intracoronary pharmacotherapy.\textsuperscript{44} This will often rapidly restore improved flow and reestablish a more stable condition. A wide array of pharmacologic agents has been used for this therapy. None have shown clear superiority in a trial setting. Most of the practice involved with pharmacotherapy for no-reflow is based on operator experience and anecdote.

No-reflow is likely to be multifactorial in most cases.\textsuperscript{45} It is often difficult to distinguish whether large thrombotic occlusion of the distal vessel, dissection, guide catheter damping, or no-reflow is the etiology of diminished distal runoff. In many cases, it is necessary to treat all of these possible etiologies. Balloon inflations in and distal to the lesion to evaluate the potential for dissection and distal large thrombus formation are frequently necessary. Occasionally, additionally stenting in the inlet or outlet of stented lesions is important to eliminate edge dissections as an etiology of diminished blood flow. Mechanical aspiration may be of value if clot or obvious mechanical obstruction is noted. Intracoronary therapy delivery through the guide catheter, over-the-wire balloon catheter, specialized infusion catheters, or aspiration catheter can be employed.

**PHARMACOLOGIC THERAPY**

Drug treatment has been used as pretreatment to reduce the likelihood of no-reflow and as treatment when it occurs. The success of pharmacologic therapy in reversing no-reflow is probably 2-fold. It may reverse the small vessel vasoconstriction due to release of vasoactive substances from the lesions and, by doing so, allow increased debris passage through the myocardial bed.

Pretreatment with intracoronary verapamil, adenosine, or nitroprusside is a common strategy prior to PCI of SVGs, but there is little evidence to support this practice. Sdringola et al\textsuperscript{46} reported that prophylaxis with multiple doses of adenosine was ineffective in preventing no-reflow. More recently, liraglutide, a glucagon-like peptide-1, has been demonstrated to reduce no-reflow in STEMI patients from 15% to 5%.\textsuperscript{47}

Pharmacologic agents are administered into the affected vascular bed
through a distal catheter. When drugs are given through a guiding catheter, they will preferentially flow to areas that have preserved runoff. For example, with distal circumflex, slow flow injections into a left system guide catheter will result in the injected agent going to the contralateral vessel and never reaching the target vascular bed. Thus, an infusion catheter or an over-the-wire balloon catheter must be delivered distal to the target lesion into the distal vasculature, and injections must be given through this catheter.

Intracoronary nitroglycerin has been the traditional first-line agent for this therapy. The experience with no-reflow responding to nitroglycerin has been poor, and it is not realistic to recommend this as a first-line therapy. A number of other agents have shown more promise (Table 62-3).

Table 62-3 Intracoronary Drug Therapy for No-Reflow

I. First-Line Management
   • Adenosine (10-20 μg bolus)
   • Verapamil (100-200 μg boluses or 100 μg/min up to 1000 μg total dose with temporary pacer on standby)
   • Nitroprusside (50-200 bolus, up to 1000 μg total dose)

II. Evidence Less Strong
   • Rapid, moderately forceful injection of saline or blood (to “unplug” microvasculature)
   • Diltiazem (0.5-2.5 mg over 1 min up to 5 mg)
   • Papaverine (10-20 μg)
   • Nicardipine (200 μg)
   • Nicorandil (2 μg)
   • Epinephrine (50-200 μg)

III. Never shown to be effective
   • Intracoronary nitroglycerin
   • Coronary artery bypass graft
   • Stent placement at site of original stenosis, if widely patent
   • Thrombolytics (eg, urokinase, tissue plasminogen activator)
Agents that have shown positive results in at least small reported series include adenosine, verapamil, nicardipine, and nitroprusside. The anecdotal experience for these agents has been generally positive. The published evidence for the clinical utility of any of these drugs is remarkably small.

Intracoronary calcium blockers are best described. It has been shown that intracoronary verapamil in doses between 50 and 900 μg improved Thrombolysis in Myocardial Infarction (TIMI) flow grade in almost 90% of cases.

Abbo reported a success rate of two-thirds with intracoronary verapamil, especially in cases related to rotational ablation. Kaplan compared intragraft verapamil with nitroglycerin and found improvement in all patients who received verapamil, whereas those who received nitroglycerin had no improvements. Other publications have shown similar results with calcium blocker therapy. The total number of reported cases remains relatively small.

Adenosine has similarly been evaluated in a small number of patients with positive results. In one series of vein graft intervention, adenosine was successful in the majority of cases. Multiple doses and higher doses of adenosine have been found to be more effective than low doses. In an animal model, bolus plus 2-hour constant infusion was superior to bolus injection alone.

One small experience demonstrating the efficacy of nitroprusside exists. Our own experience with this agent has been extremely positive, even in cases refractory to intracoronary calcium blocker administration.

Forceful injection of saline or blood has been described as a method for hydraulically dislodging platelet aggregates or microthrombi from the distal vascular bed. Multiple high-velocity drug doses may be effective as well.

Intravenous and intracoronary platelet glycoprotein IIB/IIIA inhibitors have been described as successful in some cases, but the results seem to be variable. A review of the effects of glycoprotein IIB/IIIA agents in over 4000 patients in the EPIC and EPILOG trials failed to show any benefit from the use of these agents in SVG intervention. Placebo-treated patients had a
16.3% incidence of complications versus 18.6% with abciximab.

A variety of other agents have been described, including a number of other calcium channel blocking drugs. Intracoronary epinephrine has been described as effective in this setting as well and has the appeal that it will not cause blood pressure to decline when it is already a problem. Skelding identified 29 patients in whom intracoronary epinephrine was administered for refractory no-reflow. Administration of a mean dose of 139 ± 189 μg resulted in establishment of TIMI grade 3 flow in 69% of patients. Mean TIMI flow increased from 1 to 2.7 (P = .0001). Heart rate increased on average from 72 to 86 bpm, but no cases of rhythm disturbance were noted. Nicardipine has been studied in animal models and has been effective in our experience. Nicorandil has been used with some success intravenously, as has papaverine.

Intracoronary thrombolytic agents are ineffective, even when thrombotic embolization is grossly visible. Mechanical disruption of these thromboemboli is probably more effective than thrombolytic drugs.

SUMMARY

No-reflow has been a feared complication of PCI since the inception of balloon angioplasty. No-reflow occurs in 0.5% to 3% of cases and is particularly common in intervention for acute myocardial infarction, SVG disease, rotational atherectomy, and less frequently native coronary artery interventions. Recent advances have made the prevention of no-reflow a reality. Embolic protection devices for use in SVG intervention have become routine. Pharmacotherapy for no-reflow has similarly improved. Previously, nitroglycerine was the mainstay of intracoronary therapy after no-reflow occurred, despite its ineffectuality. More recently, therapy with calcium-blocking agents, nitroprusside, adenosine, and possibly epinephrine has proven effective in improving epicardial coronary flow in the no-reflow phenomenon. It remains to be demonstrated whether the acute improvements in epicardial flow correlate with improved late outcomes from no-reflow. It is clear that preventive measures, including embolization protection devices, should be used in high-risk settings for the no-reflow phenomenon. SVG intervention has been proven to be safer with embolization protection, and these devices should be used in conjunction with virtually all SVG
interventions. The application of embolization protection devices to other settings, such as acute myocardial infarction, requires further study.

The use of AT in STEMI was very promising; however, randomized clinical trials demonstrating no advantage and perhaps increased incidence of cerebrovascular accident have dampened enthusiasm for this technique.

REFERENCES


Emergency Surgery Following Percutaneous Coronary Intervention

Michael A. Kutcher

HISTORICAL PERSPECTIVES

As a result of significant technologic improvements over the past 30 years, percutaneous coronary intervention (PCI) has become an increasingly safe and effective procedure. Along with this maturation, the indications for emergency cardiac surgery for failed PCI have been reduced. Nevertheless, some type of surgical backup strategy continues to be a standard of practice for the optimal performance of PCI. To understand this evolution, it is appropriate to start this chapter with an historical perspective.

On September 16, 1977, Andreas Gruentzig performed the first percutaneous transluminal coronary angioplasty (PTCA) in Zurich, Switzerland. Elaborate precautions were taken in the event that emergency coronary bypass surgery was necessary to rescue an unstable patient following a failed PTCA attempt. These provisions included a roller pump coronary perfusion device, an open ready operating room, and the physical presence of a cardiac surgeon and an anesthesiologist in the catheterization laboratory room. Fortunately, the procedure was successful, and the rest is history. Ironically, the birth of angioplasty would not have been possible without the support and interaction of cardiovascular surgeons with cardiologists. Gruentzig freely credited Ake Senning and Marko Turina, his cardiovascular surgeons in Zurich, with allowing him to develop the PTCA.
technique.

Of Gruentzig’s first 50 patients, 7 (14%) needed emergency bypass operations, but surgery was accomplished with no major mortality or morbidity. In June 1979, a PTCA workshop was convened in Bethesda, Maryland, sponsored by the National Institutes of Health National Heart, Lung, and Blood Institute (NIH-NHLBI), at which the initial clinical experience in the technique was discussed. Out of this pivotal meeting, the founding fathers of PTCA took the unprecedented step to commit a fledging procedure and themselves to a comprehensive multicenter registry that would fairly assess safety and efficacy. As a result, the NIH-NHLBI PTCA Registry was formed, setting the standards for the rigorous analysis of PCI that continues to this day in various registries, institutional databases, and multicenter randomized trials. It is with this tradition of open granularity that the evolution of PCI and the role of emergency surgery can be best assessed.

DEFINITIONS

Different degrees and complexity of coronary artery bypass graft (CABG) surgery may be necessary following a failed PCI. The most appropriate definitions of urgency are provided by the National Cardiovascular Data Registry (NCDR) CathPCI Registry version 4.4 data elements.

- **Elective:** The patient’s cardiac function has been stable in the days prior to the operation. Cardiac surgery could be deferred without risk of compromised cardiac outcome.
- **Urgent:** Procedure required during same hospitalization in order to minimize chance of further clinical deterioration. Examples include, but are not limited to, worsening sudden chest pain, congestive heart failure, acute myocardial infarction, anatomy, intra-aortic balloon pump (IABP), unstable angina with intravenous nitroglycerin, or rest angina.
- **Emergency:** Patients requiring emergency operation will have ongoing refractory (difficulty, complicated, and unmanageable) unrelenting cardiac compromise, with or without hemodynamic instability, and be not responsive to any form of therapy except cardiac surgery. An emergency operation is one in which there should be no delay in providing operative intervention. The patient’s clinical status includes any of the following:
a. Ischemic dysfunction (any of the following):
   1. Ongoing ischemia including rest angina despite maximal medical therapy (medical or IABP)
   2. Acute evolving myocardial infarction with 24 hours before surgery
   3. Pulmonary edema requiring intubation

b. Mechanical dysfunction (either of the following):
   1. Shock with circulatory support
   2. Shock without circulatory support

• **Salvage:** The patient is undergoing cardiopulmonary resuscitation (CPR) in route to the operating room or prior to anesthesia induction.

This chapter will focus on the above-listed definitions of “emergency” and “salvage” surgery for failed PCI. Complications and emergency surgery for failed structural heart interventions, including transcatheter aortic valve replacement (TAVR), will be covered by the chapters on these various procedures in this textbook.

The coronary indications for emergency CABG surgery for failed PCI include left main dissection, abrupt occlusion, extensive coronary dissection, perforation, cardiac tamponade, retained equipment fragments, and inability to stabilize the affected vessel.

Urgent systemic problems to be corrected may include hypoxia, hypotension, acute pulmonary edema, ongoing cardiopulmonary resuscitation, cardiogenic shock, and uncontrolled bleeding.

Noncoronary indications may also necessitate emergency cardiac and vascular surgery. These include aortic dissection and severe peripheral vascular access complications.

**LOGISTICS**

Clarification of the actual logistics and role of the surgeon and the operating room facilities is necessary to avoid confusing terms. Appropriate terminology to differentiate the degree of surgical commitment reflects 2 levels of support:

• *Surgical standby* indicates a strict arrangement with an open operating
room and a surgical team immediately available.

- **Surgical backup** indicates that the cardiac surgery suites are available and emergency surgery cases may be added on to the schedule on a first-case basis.

Logistical arrangements for surgical standby or backup during PCI consist of:

- **On-site**: Surgical facilities are physically present in the medical center facility where PCI is performed.
- **Off-site**: Surgical facilities are present in an institution physically separated by a significant distance from the facility where PCI is performed. Timely plans and transportation arrangements are mandatory in the event that a patient requires emergency cardiac surgery for failed PCI.

### INCIDENCE, MORTALITY, AND MORBIDITY OF EMERGENCY CARDIAC SURGERY FOR FAILED PCI

From the 14% emergency surgery rate in Gruentzig’s first PTCA cohort 40 years ago, there have been major evolutionary reductions in the incidence of emergency surgery. The NIH-NHLBI PTCA Registry reported an emergency surgery rate of 5.8% in the years 1979 to 1981 followed by a lower rate of 3.4% in 1985 to 1986, primarily due to technical improvements and better operator experience. With the emergence of intracoronary stents, the incidence dropped even further in the early 2000s to reported rates of 0.14% by the Cleveland Clinic and 0.3% by the Mayo Clinic. Regardless of the low incidence of emergency surgery in these 2 studies, the mortality rate with emergency surgery continued to be high, ranging from 10% to 15%. A recent contemporary review from the NCDR reported emergency surgery rates of 0.18% in nonprimary PCI and 0.93% in primary PCI ST-segment elevation myocardial infarction (STEMI) patients.

In summary, experience from the various PCI registries and literature
indicates that although the incidence of emergency surgery over the years has decreased to acceptably low levels, when it does occur, the consequences of mortality and morbidity continue to remain high.

**FACTORS THAT HAVE REDUCED THE INCIDENCE OF EMERGENCY CARDIAC SURGERY FOR FAILED PCI**

The best approach to reducing the mortality and morbidity of emergency cardiac surgery for failed PCI would be to avoid the need for emergency surgery altogether. Significant technologic improvements have occurred over the past 30 years to make PCI safer and more effective.

There has been a reduction in the French (Fr) size of guiding catheters from 8-, 9-, and 10-Fr to 7-, 6-, and even 5-Fr catheters. The guiding catheters have become much softer, decreasing the likelihood of dissection and complications at the coronary takeoff. Steerable wires have been reduced in diameter size from 0.18-inch to the current standard 0.14-inch diameter. Various soft steering wire tips are available that reduce the chance of perforation or dissection of the coronary intima. Balloon and stent delivery shaft profiles have been significantly lowered over the years from 1.4-Fr to less than 0.5-Fr diameter in a deflated state. The growth of radial artery access for PCI has resulted in the reduction of complications and bleeding.

Along with advances in catheters, there has been a significant improvement in radiologic imaging techniques. Initially biplane fluoroscopy and angiography were thought to be the most effective ways of translating a 1-dimensional plane or imaging to at least 2 dimensions and extrapolating this to 3 dimensions. However, digital fluoroscopic and cine technology is now the standard of practice. This technology has markedly improved the capabilities for more precisely visualizing the coronary artery tree and various coronary angioplasty devices.

Adjunctive pharmacotherapies such as direct thrombin inhibitors, platelet glycoprotein IIb/IIIa receptor agents, and P2Y\textsubscript{12} agents have reduced the thrombotic complications of coronary intervention and the need for emergency surgery.
In the 1990s, the enthusiasm to lower the restenosis rate by using atheroablative devices such as directional coronary atherectomy, rotational atherectomy, transluminal extraction atherectomy, and excimer laser coronary angioplasty was tempered by a higher perforation rate and incidence of emergency surgery. Once experience with the devices became more extensive, the emergency surgery rate was somewhat reduced. However, a meta-analysis of multiple device trials confirmed the clinical impression that when atheroablative devices are compared with standard PTCA, there is no reduction in the restenosis rate and an increase in major adverse cardiac events (5.1% vs 3.3%). As a result, the widespread use of atherectomy devices has fallen out of favor and should be reserved only for very select cases.

The introduction of intracoronary stenting in the mid-1990s and eventual refinements in stent technology and pharmacology in the late 1990s resulted in a reduction in the incidence of emergency surgery by providing a more reliable solution to elastic recoil and coronary dissection. An analysis of the Society for Cardiovascular Angiography and Interventions Registry trends in 16,811 consecutive PCI procedures during this later era documented a 0.3% incidence of emergency surgery when stents were used compared with a 0.7% incidence ($P = .002$) with balloon angioplasty.

The development of polytetrafluoroethylene (PTFE)-covered stents has provided a better option to seal coronary artery perforations. A European series demonstrated that when perforation occurred as a complication of PCI, use of a PTFE stent reduced the incidence of emergency surgery from 88% to 18%. In addition, even if patients went on to surgery, the PTFE stent served as a valuable supportive device and resulted in a reduction of mortality and morbidity.

The wealth of experience and data in various PCI registries has now permitted risk-adjustment scores, which indicate that hemodynamic instability, disease severity, demographics, and comorbid conditions may predict adverse outcomes. The strongest predictors of emergency surgery are cardiogenic shock, acute myocardial infarction (MI), emergency PCI, multivessel disease, and type C lesions.

**STRATEGIES TO REDUCE**
MORTALITY AND MORBIDITY WHEN EMERGENCY CARDIAC SURGERY FOR FAILED PCI OCCURS

When all attempts at a percutaneous solution have failed and emergency surgery is necessary, supporting the patient in the catheterization laboratory prior to transfer to the operating suite is crucial to reduce the already evolving higher chance of mortality and morbidity.

Coronary perfusion catheters that allow balloon inflation while still permitting coronary flow via perforated portals in the catheter shaft were an early PCI era mainstay prior to the development of intracoronary stents. Autoperfusion catheters are no longer made, but standard balloon dilatation catheters may be used to maintain at least partial coronary flow by alternating inflation and deflation sequences. This temporary strategy may stabilize dissected coronary flow or to stanch a perforation prior to emergency surgery in circumstances where a stent cannot be deployed. As mentioned earlier, PTFE-coated stents also may have a role in stabilizing a coronary perforation prior to going to the operating room.

In the case of coronary perforation, attention should be paid to hematologic and hemodynamic instability. There should be a hematologic strategy to stop heparin, consider reversal with protamine, discontinue glycoprotein IIb/IIIa receptor blockers, plan for platelet transfusion, or all of the preceding. This must be done in coordination with the cardiac surgeons as heparin will be needed for CABG surgery. When cardiac tamponade is present, percutaneous pericardiocentesis is helpful in reducing this hemodynamic impediment prior to surgery.

The IABP has been a mainstay to support patients with cardiovascular hemodynamic compromise who require emergency surgery. However, newer percutaneous mechanical circulatory support devices such as the nonpulsatile axial flow Archimedes screw pump (Impella; Abiomed, Danvers, MA) and extracorporeal bypass with membrane oxygenator (ECMO) may be used for catastrophic hemodynamic collapse if there is a delay to transfer to the operating room.

The cardiac surgeon, anesthesiologist, and operating room should be
alerted at the first sign that a patient may need emergency surgery. It is better to err on the side of mobilizing a room and the cardiac surgery team even though the event may eventually be controlled and surgery averted. Appropriate anesthesia backup and control of the airway are paramount in providing support of the compromised patient. Advances in surgical technique over the past 20 years have been instrumental in reducing complications following emergency surgery. Having a more stable patient as a result of the preceding support initiatives may also allow arterial conduits, such as the left internal mammary graft vessel, to be used in the emergency setting.

Lastly, with the development of hybrid catheters and operating room laboratories, extremely high-risk PCI patients may be pre-emptively managed in these suites with close surgical standby if PCI fails and emergency surgery is necessary.\textsuperscript{25}

Figure 63-1 is a flow diagram of strategy options that should be considered or initiated in the catheterization laboratory to support the patient who requires emergency surgery for failed PCI.

**FIGURE 63-1** Failed percutaneous coronary intervention (PCI) emergency surgery strategy. ECMO, extracorporeal membrane oxygenator; IABC, intra-aortic balloon counterpulsation; OR, operating room.
GUIDELINES FOR PCI

The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) 2011 guideline\textsuperscript{13} has recommended that a mechanism of quality assurance review be established and ongoing at each institution performing PCI. Operator statistics and institutional data should be reviewed on at least a quarterly basis. Monitoring outcomes by this mechanism assures a mechanism to review cases of mortality, morbidity, or emergency surgery.

The current 2011 guidelines\textsuperscript{13} continue to recommend that PCI be performed by higher volume operators performing 75 or more cases per year (class I) and that these operators have advanced technical skills and knowledge. Subspecialty certification in interventional cardiology is a class IIa recommendation. PCI should be performed at institutions with fully equipped interventional laboratories and experienced support staff with the anticipation of performing more than 400 cases per year with an on-site cardiovascular surgical program (class I). Options for emergency cardiac surgery should be available for instances of failed PCI and instability. The guidelines recommended against low-volume operators (<75 cases per year) performing PCI who work in low-volume institutions (200-400 cases per year) with or without on-site surgical coverage (class III). An institution with less than 200 procedures per year should reconsider whether to continue to offer PCI service, unless it can be clearly documented that it is in an underserved region due to geography.\textsuperscript{13}

In addressing off-site PCI centers, the 2011 guidelines gave a class IIa recommendation for primary PCI for acute STEMI and a class IIb recommendation for elective PCI if there was an appropriate backup plan and proper case selection.\textsuperscript{13} This was a major change from the previous 2005 guidelines, which gave off-site centers a class IIb indication for primary PCI and a class III indication for elective PCI.\textsuperscript{26} The current 2011 guidelines continues to advise against primary or elective PCI at off-site centers without a proven plan for rapid transport to a surgical center or without appropriate hemodynamic support strategies during transfer (class III).

PCI EXPERIENCE AT CENTERS WITH
OFF-SITE SURGICAL BACKUP

Primary PCI for STEMI

A key meta-analysis of 23 randomized trials in acute MI documented that primary PCI for STEMI is superior to thrombolytic therapy, with significant reductions in death (7% vs 9%), nonfatal reinfarction (3% vs 7%), stroke (1% vs 2%), and combined end point (8% vs 14%). These results were particularly possible if a door-to-balloon time of less than 90 minutes could be achieved. Another meta-analysis of 6 major MI trials assessing a strategy of transfer for primary PCI versus immediate thrombolysis reaffirmed a significant reduction in morbidity and a trend in reduction of all-cause mortality in the transfer PCI group. These analyses have reaffirmed the favorable risk-benefit ratio of primary PCI as the treatment of choice over thrombolytic therapy for early STEMI.

The Primary Angioplasty in Myocardial Infarction Trial-2 (PAMI-2) investigators reported that in 982 patients undergoing primary PCI for acute MI, there was a 0.4% incidence of emergency surgery for failed angioplasty. The Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) documented a 0% emergency surgery rate in 225 primary PCI patients with STEMI who presented to off-site centers. An article by Singh and colleagues from the Mayo Clinic reviewed overall single-center and multicenter experience with primary PCI at off-site centers and concluded that the risk-benefit ratio for mortality, morbidity, and emergency surgery was favorable. These were the historic benchmark studies that established the appropriateness for off-site centers to perform primary PCI for acute STEMI without surgical backup on site.

Elective or Nonprimary PCI

Select Registry Data

As a result of the positive experience of primary PCI for acute MI at off-site centers and with extensive safety and effectiveness data from Europe regarding elective PCI without on-site surgical backup, in the early 2000s,
there was increasing debate in the United States as to whether low-risk, nonemergency, and elective PCI could be extended to off-site centers. This was particularly controversial due to the class III designation given to elective PCI in off-site centers by the 2005 PCI guidelines.\textsuperscript{26}

Over the past 10 years, there have been a number of single-center or combined registry data studies that have assessed the risk-benefit ratio of elective or nonprimary PCI in off-site centers. Among these, there were 2 major registry studies that vigorously assessed the appropriateness of nonprimary PCI in off-site centers.

The pivotal study from the NCDR reported on a large multicenter US database.\textsuperscript{32} Clinical characteristics and in-hospital outcomes were assessed in consecutive PCI cases from January 1, 2004 to March 30, 2006. Of this cohort, 8736 patients who had PCI performed in 60 centers that did not have cardiac surgery on site (off-site) were compared with 299,425 patients at 405 centers that did have cardiac surgery on site (on-site). Off-site facilities performed a median of 134 overall annual PCI procedures, and 72% performed <200 per year, compared with 612 procedures and 6% at <200 per year for on-site facilities ($P < .001$). PCI for STEMI or non-STEMI occurred more frequently at off-site centers than on-site centers (41% vs 29%; $P < .001$). Off-site PCI facilities, relative to on-site facilities, had similar observed rates of success (94% vs 93%), total complications (6.5% vs 6.3%), emergency cardiac surgery (0.3% vs 0.4%), and mortality with emergency surgery (13.6% vs 12.8%). The risk-adjusted odds ratio (OR) for in-hospital mortality of off-site versus on-site centers revealed no difference in overall mortality (OR, 0.90; 95% confidence interval [CI], 0.72-1.14; $P = .388$) or mortality in patients who underwent primary PCI (OR, 0.97; 95% CI, 0.75-1.25; $P = .807$) or nonprimary PCI (OR, 0.86; 95% CI, 0.63-1.16; $P = .319$).

The recently reported retrospective United Kingdom Registry evaluated early and long-term mortality outcomes (median follow-up of 3.4 years) for PCI centers with and without surgical support between the years 2006 and 2012.\textsuperscript{33} A total of 384,013 patients were assessed, of whom 31% (119,096) were treated at off-site surgical centers. Unadjusted mortality rates were lower in patients treated at off-site centers versus on-site centers (2.0% vs 2.2%; $P < .001$). Multivariate adjustment revealed there were no differences in the primary end point of survival between the naive and imputed populations at 30 days (naive population hazard ratio [HR], 0.87; 95% CI, 0.71-1.06; $P = .16$; imputed population HR, 0.99; 95% CI, 0.89-1.09; $P = \ldots$)
This lack of difference carried over to the secondary end points of survival at 1 year (naive population HR, 0.92; 95% CI, 0.79-1.07; \( P = .26 \); imputed population HR, 0.99; 95% CI, 0.92-1.06; \( P = .78 \)) and at 5 years (naive population HR, 0.92; 95% CI, 0.84-1.01; \( P = .10 \); imputed population HR, 0.97; 95% CI, 0.92-1.03; \( P = .29 \)). Of note, there were no differences in mortality in sensitivity analyses performed using a propensity-matched population. The results were consistent regardless of primary or nonprimary PCI indications.

**Key Randomized Clinical Trials**

Regardless of registry and single-center studies, confirmation of the safety and effectiveness of elective PCI at off-site centers can only be definitively confirmed by well-defined randomized studies.

The C-PORT-E trial led by Aversano and colleagues\(^3\) was a large multicenter trial that randomly assigned elective PCI patients to undergo the procedure at either a hospital with or a hospital without on-site cardiac surgery. A total of 18,867 patients were randomly assigned in a 3:1 ratio to undergo PCI at a hospital without on-site cardiac surgery (14,149 patients off-site) or a hospital with on-site cardiac surgery (4718 patients on-site). The primary end point of 6-week mortality rate was 0.9% at off-site hospitals versus 1.0% at on-site hospitals (difference, –0.04 percentage points; 95% CI, –0.31 to 0.23; \( P = .004 \) for noninferiority). The 9-month rates of major adverse cardiac events (the composite of death, Q-wave MI, or target vessel revascularization), which was the coprimary end point, were 12.1% and 11.2% at off-site versus on-site centers, respectively (difference, 0.92 percentage points; 95% CI, 0.04-1.80; \( P = .05 \) for noninferiority). The rate of target vessel revascularization was higher in off-site hospitals (6.5% vs 5.4%; \( P = .01 \)). This was the first major large randomized trial to document that PCI performed at off-site hospitals was noninferior to PCI performed on-site at hospitals for mortality at 6 weeks and major adverse cardiac events at 9 months.

Approximately a year later, the MASS-COMM trial led by Jacobs and colleagues\(^4\) reported on nonemergency PCI patients who were randomized in a 3:1 ratio to have their procedures at an off-site (10 centers) or an on-site (7 centers) facility. A total of 3691 patients were randomized, 2774 to off-site centers and 917 to on-site centers. The primary safety end point of 30-day
major adverse cardiac event rate (composite of death, MI, repeat revascularization, or stroke) was 9.5% in off-site hospitals compared to 9.4% in on-site hospitals (relative risk, 1.00; 95% one-sided upper confidence limit, 1.22; \( P < .001 \) for noninferiority). The coprimary effectiveness end point of major adverse cardiac events at 12 months was 17.3% and 17.8% in off-site and on-site hospitals, respectively (relative risk, 0.98; 95% one-sided upper confidence limit, 1.13; \( P < .001 \) for noninferiority). The rates of death, MI, repeat revascularization, and stroke did not differ significantly between the groups at either time point. The primary end points were analyzed according to the intent-to-treat principle and were tested with the use of multiplicative noninferiority margins of 1.5 (for safety) and 1.3 (for effectiveness). The MASS-COMM study reaffirmed that, in Massachusetts, nonemergency PCI procedures performed at off-site hospitals were noninferior to those performed at on-site hospitals with respect to 30-day and 1-year rates of clinical events.

**Meta-Analyses**

The mortality and morbidity of primary PCI and nonprimary elective PCI at off-site PCI centers versus on-site centers was further affirmed by a number of meta-analysis studies that included robust single-center, multicenter, registry, and randomized studies. The 2 most important of these meta-analyses will be discussed below.

Singh and colleagues\(^{36}\) selected 40 high-quality studies and applied pooled-effect estimates calculated with random-effects models. Analysis of 124,074 patients who underwent primary PCI for STEMI and 914,288 patients who had nonprimary PCI (elective and urgent) demonstrated that procedures at off-site centers were not associated with a higher incidence of in-hospital mortality or emergency bypass surgery.

A more recent meta-analysis by Lee and colleagues\(^{37}\) analyzed 23 high-quality studies and used a mixed-effects model to compare complication rates of 1,101,123 patients after PCI at off-site and on-site centers. They concluded that clinical outcomes and complication rates of PCI in patients treated at off-site centers did not differ from those in patients who had procedures at on-site centers for both primary PCI for STEMI and for nonprimary PCI. They did report temporal trends of improved clinical outcomes for nonprimary PCI in off-site centers since 2007.
SCAI/ACCF/AHA EXPERT CONSENSUS DOCUMENT FOR OFF-SITE PCI

The 2014 update on PCI without on-site surgery backup in the United States was an expert consensus panel convened to update the original 2007 SCAI document on the topic. Of note, many things have changed since 2007, when there were only 28 states with off-site PCI centers performing both primary and elective PCI, 12 states performing only primary PCI, and 10 states where off-site PCI centers were not allowed. In contradistinction, in 2013, there was only 1 state that did not permit off-site PCI, 4 states that permitted only primary PCI, and 45 states that had both primary and elective PCI at off-site centers.

This consensus document is a comprehensive and exhaustive analysis that provides guidelines for the proper performance of PCI centers that do not have surgery on site. A streamlined outline of facility requirements (Table 63-1), personnel requirements (Table 63-2), STEMI treatment recommendations (Table 63-3), and surgical backup and elective case selection (Table 63-4) for off-site PCI centers is provided in this chapter. The reader is advised to refer to the consensus document for more extensive details.

Table 63-1 Facility Requirements for Off-Site PCI Program

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<tr>
<th>Requirement</th>
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<tr>
<td>•  Appropriate supportive equipment</td>
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<td>•  Formal written operational protocols</td>
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<tr>
<td>•  Full hospital administration support</td>
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<tr>
<td>•  Credentialing and governance program</td>
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<tr>
<td>•  Written agreements for immediate transfer and receipt to off-surgical</td>
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<tr>
<td>backup site: begin transport within 30 minutes; receipt at off-site surgery</td>
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<td>center by 60 minutes; on pump within 120 minutes once emergency surgery</td>
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<td>declared</td>
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<tr>
<td>•  Well-equipped and well-maintained catheterization laboratory</td>
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<tr>
<td>•  Appropriate inventory of interventional equipment</td>
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<td>•  Meticulous clinical and angiographic selection criteria for PCI</td>
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<td>•  Participation in national registry such as NCDR</td>
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• Program to track adherence to ACC/AHA-based class I therapy
• Full-service labs for both primary and elective PCI
• Geographic isolation exists if emergency transport time is >30 minutes
• National benchmarking of outcomes
• Quality improvement review of all patients transferred for emergency CABG

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft; NCDR, National Cardiovascular Data Registry; PCI, percutaneous coronary intervention.


Table 63-2 Personnel Requirements for Off-Site PCI Programs

• Experienced catheterization laboratory nursing and support staff
• Appropriate supportive equipment
• CCU staff experienced in monitoring, temporary pacemaker, and IABP
• Personnel capable of intubation and ventilator management
• Operators ABIM certified in interventional cardiology
• Operators perform over 2-year period
• Primary PCI for operators with ≥50 elective and ≥11 primary PCIs per year
• Institution experience: ≥200 elective and ≥36 primary PCIs per year
• Internal review and quality improvement process for underperformers
• Unwise for newly trained interventional cardiologist to start a new off-site program

Abbreviations: ABIM, American Board of Internal Medicine; CCU, cardiac care unit; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

Table 63-3 **STEMI Treatment Recommendations for Off-Site PCI Program**

- Community STEMI process at least as strong as mission lifeline
- Primary PCI as standard of practice for STEMI
- Catheterization facility service “24/7”
- Institution experience: ≥36 primary PCIs per year
- Institutional experience: ≥200 total PCIs per year
- Recognized STEMI receiving center and a liaison/coordinator for communication
- Participation in regional endeavors such as ACTION Registry-GWTG
- Monthly quality improvement multidisciplinary meetings to review metrics of STEMI activation, door-to-balloon time, and other important process metrics

Abbreviations: ACTION, Acute Coronary Treatment and Interventions Outcomes Network; GWTG, Get With the Guidelines; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 63-4 **Recommendations for Off-Site Surgical Backup and Elective Case Selection**

**Interactions with Cardiac Surgeons**
- Heart team approach and communication for PCI case selection
- Initial informed consent for PCI includes terminology indicating the risk of no surgery on-site and the process of emergency transfer if necessary
- Transferring physician will obtain consent if emergency surgery needed

**High-Risk Patients**
- Decompensated congestive heart failure
- Cerebrovascular accident <8 weeks
- Advanced malignancy
• Know clotting disorder
• LVEF ≤30%
• Chronic kidney disease
• Ongoing ventricular arrhythmias
• Unprotected significant left main stenosis
• Multivessel disease with high SYNTAX score
• Single-target lesion that jeopardizes extensive myocardium
• PCI to last remaining conduit to the heart

High-Risk Lesions
• Unprotected left main
• Diffuse disease ≥20 mm
• Extremely angulated ≥90-degree segment or excessive tortuosity
• More than moderate calcification
• Inability to protect major side branches
• Degenerative old vein grafts with friable lesions
• Substantial vessel thrombus
• Any features that could interfere with stent deployment
• Anticipated need for rotational atherectomy, cutting balloon or laser

Strategy for Surgical Backup Based on Risk
• High-risk patient + high-risk lesion = no elective PCI at off-site center
• High-risk patient + non–high-risk lesion = elective PCI but tight surgery backup
• Non–high-risk patient + high-risk lesion = no additional precautions, but be alert
• Non–high-risk patient + non–high-risk lesion = best scenario

Abbreviations: LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With Taxus Drug-Eluting Stent and Cardiac Surgery.
The question of whether the development of PCI centers without surgical backup on site is an appropriate national strategy continues to be an issue, albeit less contentious due to recent publications regarding safety and efficacy of well-designed off-site PCI centers. It would seem logical for off-site programs to demonstrate effectiveness on a “24/7” basis in primary PCI for acute MI before expanding to elective PCI. An argument that elective PCI at off-site centers is necessary to assure high institutional and staff skill levels in a less acute setting than acute MI and to provide more convenient service for their patient and referral base appears to be valid. However, it would seem unacceptable for an off-site PCI center to limit itself to only a “9 to 5” or “boutique” elective PCI program and to not eventually commit resources for “24/7” coverage for primary PCI in acute MI where there is a documented greater mortality and morbidity benefit.

Many centers that wish to perform PCI without an on-site surgical program tend to be smaller institutions with smaller volume cases. Dehmer and colleagues recently reported in an analysis of a contemporary NCDR data sample that on-site cardiac surgery was not available in 83% of facilities performing fewer than 200 PCIs annually, with these facilities representing 32.6% of the facilities reporting, but performing only 12.4% of the PCIs. However, regardless of whether a program has on-site or off-site surgical facilities, even an experienced angioplasty operator is no better than the quality of the catheterization laboratory facilities, the experience of the catheterization laboratory staff, and the skill level of the cardiac surgery team.

In parallel with the development of more effective coronary interventional techniques, the incidence of emergency surgery for failed PCI has dropped precipitously over the past 30 years. But the incidence will never be zero. Some form of surgical backup strategy will always be necessary. Unfortunately, in the few times when emergency surgery is necessary, the
mortality and morbidity are still quite high. The interventional cardiologist must ensure that all reasonable, appropriate options are in place to achieve the most effective and safe care for PCI patients.

The analysis of data is empowering. Interventional cardiologists must continue to actively participate in personal and institutional quality assurance programs. Institutions should contribute data to registries such as the NCDR CathPCI Registry. In that spirit, the vision of Andreas Gruentzig, who was courageous in collecting and analyzing the data of a fledgling procedure, may be best served. This tradition of rigorous self-assessment will continue to result in improved techniques, reassessment of strategies, and reduced mortality and morbidity. It is hoped that these efforts will result in both an incidence of emergency surgery that is “close to zero” and in significantly reduced consequences to the few patients who do require this support mechanism.

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**MULTIPLE CHOICE QUESTIONS**

1. In patients who undergo elective percutaneous coronary intervention (PCI) at hospitals without cardiac surgery on site compared to hospitals that have surgery on site, the incidence of major adverse cardiac events (MACE) is:
   A. Increased
   B. Decreased
   C. Similar
   D. Unknown
   E. Not important

2. In the current contemporary era, what is the best estimate for incidence of death in patients who undergo emergency cardiac surgery for failed PCI?
   A. 1%-3%
   B. 4%-6%
   C. 7%-9%
   D. 10%-15%
   E. 20%-25%

3. All of the following strategies would be appropriate to stabilize a patient with significant acute coronary artery perforation prior to going to emergency cardiac surgery for failed PCI, EXCEPT:
A. Maintain steering wire access if at all possible  
B. Use inflated dilatation balloon to stanch perforation  
C. Implant a bare metal stent to stabilize the vessel  
D. Implant a polytetrafluoroethylene (PTFE)-covered stent  
E. Perform a pericardiocentesis if severe tamponade is present

4. In hospitals that do not have cardiac surgery on site, the strategy for off-site surgical backup based on risk evaluation in elective or nonurgent PCI cases indicates that which of following patients should NOT be treated but should be transferred for PCI at a hospital that has surgery on site?  
   A. Non–high-risk patient + non–high-risk lesion  
   B. Non–high-risk patient + high-risk lesion  
   C. High-risk patient + non–high-risk lesion  
   D. High-risk patient + high-risk lesion  
   E. Indeterminate-risk patient + indeterminate-risk lesion

5. What is the current national contemporary best estimate of the incidence of emergency surgery for failed PCI?  
   A. 0%  
   B. 0.2%-0.4%  
   C. 1%-3%  
   D. 4%-6%  
   E. 12%-14%

ANSWERS

1. C

The issue of safety and efficacy for elective or nonprimary PCI done at centers that do not have surgery on site was a contentious issue in the early 2000s. The equivalence for elective PCI at off-site versus on-site centers has been consistently answered by large registries such the National Cardiovascular Data Registry (NCDR) and the United Kingdom Registry and by meta-analysis. But more importantly, the well-done recent C-PORT-E and MASS-COMM randomized trials have thoroughly resolved that there are no differences in MACE for patients who undergo elective or nonprimary PCI in
centers with or without surgery on site. A key point to make, however, is that all these published studies involved high-quality off-site PCI centers that adhered to accepted high standards of practice.

2. D

Although the incidence of emergency surgery for failed PCI has consistently dropped over the past 30 years, the mortality rate when emergency surgery does occur has not changed significantly and remains high. The rate 10% to 15% rate appears to be an appropriate estimate. This range was based on reported rates in various key published reports, including those by the Cleveland Clinic, Mayo Clinic, and NCDR.

3. C

Acute severe coronary artery perforation is a calamity that requires thoughtful but quick action. It is essential to try to maintain steering wire position as this allows various maneuvers such as inflation of a balloon to stanch the flow or to implant a PTFE-covered (JoMed) stent. Even if the PTFE-covered stent resolves the perforation, it may still be a short-term temporizing strategy as the patient can go on to more stable emergency surgery. Pericardiocentesis may be life-saving if hemodynamically significant tamponade is present. Of all the stabilizing choices, implantation of a noncovered stent, such as a bare metal or drug-eluting stent, is a poor choice because it potentially could make the perforation worse.

4. D

The recent Society for Cardiovascular Angiography and Interventions (SCAI)/American College of Cardiology (ACC)/American Heart Association (AHA) Expert Consensus Document for off-site PCI centers included definitions of what constitutes a high-risk patient and a high-risk lesion.

- High-risk patients: Decompensated congestive heart failure; cerebrovascular accident <8 weeks; advanced malignancy; know clotting disorder; left ventricular ejection fraction ≤30 %; chronic kidney disease; ongoing ventricular arrhythmias; unprotected significant left main stenosis; multivessel disease with high SYNTAX score; single target
lesion that jeopardizes extensive myocardium; and PCI to last remaining conduit to the heart.

- High-risk lesions: Unprotected left main; diffuse disease ≥20 mm; extremely angulated ≥90-degree segment or excessive tortuosity; more than moderate calcification; inability to protect major side branches; degenerative old vein grafts with friable lesions; substantial vessel thrombus; any features that could interfere with stent deployment; and anticipated need for rotational atherectomy, cutting balloon, or laser.

The case of a non–high-risk patient + non–high-risk lesion is the best scenario. In the case of high-risk patient + high-risk lesion, the consensus document strongly recommends that elective PCI should NOT be done at the off-site center. The other scenarios of patient and lesion risk have variable degrees of appropriateness for elective PCI at the off-site center.

5. B

Andreas Gruentzig’s first cohort of percutaneous transluminal coronary angioplasty patients had an emergency surgery rate for failed balloon angioplasty of 14%. Subsequent reiterations of the National Heart, Lung, and Blood Institute registry reported progressively lower rates due to improved technology and the development of intracoronary stents. The best current estimate of 0.2% to 0.4% comes a combination from the Cleveland Clinic (0.14%), Mayo Clinic (0.3%), and NCDR (0.37%).
INTRODUCTION

Sudden cardiac death (SCD) is the leading cause of cardiovascular death and remains an important public health issue. The definition of SCD includes death from natural causes within an hour of a change in cardiovascular status and can occur in patients with or without preexisting cardiovascular disease. Incidence estimates for SCD in the United States vary from 250,000 to 450,000 cases a year, with most estimates in the range of 300,000 to 350,000 per year.\(^1\) Although the worldwide incidence of SCD is difficult to estimate, several studies have shown the rate of SCD is approximately 50 to 100 per 100,000 people.\(^2\) In the United States, SCD accounts for about half of cardiovascular deaths and 15% to 20% of all deaths.\(^2\) In this chapter, we will briefly review the most common etiologies of SCD as well as outline treatment strategies for dealing with patients who present with SCD because these commonly fall under the realm of the interventional cardiologist. A thorough knowledge of emergency resuscitation measures is critical for the interventional cardiologist who is often called to potentially treat patients with SCD, whether this occurs out of or within the hospital (even within the cardiac catheterization laboratory).

Pathophysiology
Diseases of the coronary arteries account for the majority of SCD (Table 64-1). In the Western world, approximately 80% of SCD is caused by coronary artery abnormalities. Coronary artery disease can precipitate SCD by several mechanisms. Acute coronary plaque instability leading to cardiac ischemia or infarction can lead to electrical instability and ventricular fibrillation (VF). Previously infarcted myocardium can precipitate ventricular arrhythmias around areas of scar. Adverse remodeling after a myocardial infarction (MI) can create another substrate for ventricular arrhythmias. Furthermore, stable coronary disease can precipitate SCD. In an autopsy study of 90 cases of SCD attributed to coronary artery disease (CAD), 17 of the 90 cases (19%) had no evidence of prior MI or active coronary plaque. While the majority of patients with SCD from CAD will have VF as their initial cardiac rhythm, VF will degrade to asystole in a short period of time. Therefore, even though the initial rhythm documented by emergency medical systems can be asystole, coronary abnormalities may still be the primary etiology of the arrest.

Table 64-1 Causes of Sudden Cardiac Death
Nonatherosclerotic coronary abnormalities compose a smaller proportion of the etiology of SCD (see Table 64-1). Congenital abnormalities of the coronary arteries are an important cause of SCD. Anomalous coronary arteries are a common cause of SCD in the young, particularly the left
coronary artery arising from the right aortic cusp. SCD is often precipitated by exercise in this patient population. Other rare causes of coronary ischemia or infarction leading to SCD include coronary vasospasm, coronary artery dissection, and coronary artery embolism. Myocardial bridges, while a common (and often benign) finding in up to 70% in autopsy studies, have in some cases been reported to cause SCD, particularly in those with hypertrophic cardiomyopathy.

Nonischemic dilated cardiomyopathies are responsible for 10% to 15% of SCD in the United States. Several reports have shown that 30% to 50% of all deaths in chronic heart failure are secondary to SCD. Ventricular tachycardia (VT) can occur in chronic heart failure during times of stable hemodynamics (scar-mediated ventricular arrhythmias) or during progressive hemodynamic deterioration that may render the myocardium more susceptible to ventricular arrhythmias. Other fatal arrhythmias, including bradyarrhythmias and pulseless electrical activity (PEA), may occur secondary to worsening pump function and decreased cardiac output. Hypertrophic cardiomyopathy is another common cause of SCD, especially in the younger population. Before the advent of modern treatments for patients with valvular diseases, many died from SCD; however, recently the risk has decreased substantially. Virtually all infiltrative and inflammatory myocardial diseases have been shown to cause SCD.

In approximately 5% of SCD cases, there are no identifiable cardiac abnormalities on autopsy; however, in a younger population, this percentage may be higher. Among these, inherited channelopathies and other primary electrophysiologic abnormalities have been implicated in SCD. These include long and short QT syndromes, Wolf-Parkinson-White syndrome, Brugada syndrome, catecholaminergic polymorphic VT, and idiopathic VF. Many of these syndromes are familial, and appropriate family member screening is essential in preventing SCD.

**Risk Factors for SCD**

In the general population without known cardiovascular disease, the risk factors for SCD parallel those of CAD including age, cigarette smoking, hypertension, hyperlipidemia, diabetes, obesity, sedentary lifestyle, and family history of premature CAD. A family history of SCD infers a 1.5-fold
increase in SCD. However, in patients with diagnosed CAD, these risk factors typically no longer hold prognostic significance for SCD. Instead, the left ventricular (LV) ejection fraction seems to be the most powerful predictor of first-episode SCD and is currently used to risk stratify patients for primary prevention implantable cardiac defibrillator (ICD) therapy. Vigorous exercise has been identified as a risk for SCD; however, the overall risk is very low. Patients with prior MI, frequent premature ventricular contractions, and in particular nonsustained VT have a higher risk of SCD.

INITIAL RESUSCITATION MEASURES

The initial role of healthcare providers and the general population is to recognize and diagnose cardiac arrest, followed by the initiation of basic life support (BLS). The initial evaluation needs to be very brief, and the BLS guidelines from the American Heart Association (AHA) recommend that the initial evaluation of an unconscious man should only include checking for breathing. A pulse check is no longer recommended for the general population. After recognition of cardiac arrest, emergency medical systems need to be activated immediately, followed by initiation of cardiopulmonary resuscitation (CPR). High-quality minimally interrupted CPR appears to improve time to return of spontaneous circulation (ROSC) and neurologic recovery in both out-of-hospital and in-hospital cardiac arrest. Pulse checks and rhythm evaluations should only occur during preset intervals (every 2 minutes) and should only delay CPR for a maximum of 10 seconds.

The concept of cardiocerebral resuscitation, where rescue breathing does not interrupt CPR, is based on the finding that high-quality CPR with minimal interruptions improves outcomes in cardiac arrest patients. A meta-analysis of 3 randomized trials comparing compression-only CPR with standard CPR found a statistically significant 22% improvement in survival (Fig. 64-1; risk ratio 1.22; 95% confidence interval [CI], 1.01-1.47). However, a secondary analysis of nonrandomized cohort studies found no benefit for compression-only CPR. It must be noted that this method of CPR is not recommended for children or suspected noncardiac causes of cardiac arrest. While the 2010 AHA guidelines state that compression-only CPR can be used when initial responders are reluctant to perform mouth-to-mouth ventilations, the recommended approach is still to perform 30
compressions followed by 2 rescue breaths. Because the oxygen level in the pulmonary vasculature is likely adequate during the first minutes of cardiac resuscitation, initial rescue breaths are no longer recommended. After the placement of an advanced airway, asynchronous breaths should be performed at a rate of 8 to 10 breaths per minute with no interruption in CPR. Excessive ventilation can be detrimental as animal models have shown that overventilation can lead to reduced success of defibrillation and decreased survival.

**FIGURE 64-1** Meta-analysis of 3 randomized trials comparing survival to hospital discharge between compression-only cardiopulmonary resuscitation (CPR) and routine basic life support. (Reprinted from Hupfl M, Selig HF, Nagele P. Chest-compression-only versus standard cardiopulmonary resuscitation: a meta-analysis. *Lancet*. 2010;376:1552-1557. Copyright © 2010, with permission from Elsevier.)

Automated chest compression devices have been developed as an alternative to manual chest compressions during cardiac arrest (Fig. 64-2). These devices can include circumferential compression around the chest wall or a piston placed at the sternum to perform compressions in the anteroposterior plane. Several of these devices contain both radiolucent as well as radiopaque components, allowing them to be used within the cardiac catheterization laboratory while performing fluoroscopic procedures. Typically, the views required are angulated views (either cranial or caudal with additional left anterior oblique or right anterior oblique angulation). A meta-analysis of randomized trials found that devices using piston-delivered CPR had the same rate of ROSC compared to conventional CPR, whereas devices using load-distributing band CPR did have a better rate of ROSC. A subsequent large randomized trial found no improvement in survival using a piston-based mechanical CPR device over traditional CPR.
Another alternative method of CPR, called active compression-decompression CPR (ACD-CPR) uses a suction device to convert the passive recoil of a compressed chest wall into active expansion, improving venous return (see Fig. 64-2). A Cochrane review of randomized data including approximately 5000 patients found no benefit with ACD-CPR when compared to standard CPR. As such, the guidelines state there is insufficient evidence to support the use of ACD-CPR.

Interposed abdominal compression CPR (IAC-CPR) involves the use of a second rescuer performing mid-abdominal compression during the upstroke of chest compression. A meta-analysis found that in 34 of 38 studies, including animal and mechanical model studies, there was an improvement in ROSC with IAC-CPR compared to regular CPR. There were 4 prospective studies included, and 3 of them found significant improvements in ROSC with the use of IAC-CPR, with 1 of these studies showing improved survival. These 3 studies included in-hospital arrest, while the fourth study that did not find a difference was in out-of-hospital arrests. Given these initial data, the guidelines state that IAC-CPR can be considered by trained practitioners during an in-hospital arrest.

Inspiratory impedance threshold devices (ITDs) allow positive-pressure ventilation but prevent airflow during chest relaxation, thus increasing negative intrathoracic pressures during chest decompression while performing CPR. This increase in negative intrathoracic pressures improves preload and myocardial perfusion. A meta-analysis of randomized trials examining the role of ITD found that the addition of ITD to standard CPR or
device-assisted CPR resulted in improved rates of ROSC and early survival; however, longer term survival was not improved.\textsuperscript{24} Therefore, current guidelines state there is insufficient evidence to support or refute the use of ITD.\textsuperscript{22}

**Defibrillation**

Survival of patients with cardiac arrest relies on high-quality CPR as well as early defibrillation. An initial chest thump, also called a precordial thump, may be attempted to quickly restore electrical stability. The technique involves 1 or 2 blows at the junction of the middle and lower third of the sternum from 8 to 10 inches away. It should not be used for tachycardias without a loss of consciousness. The initial experience of the chest thump was mixed, with some studies showing successful conversion of VT/VF using the technique. However, a subsequent trial found that in 103 patients treated with a precordial thump as the initial strategy, a rhythm change was noted in 17. Only 5 of the cases had ROSC, whereas 10 others had a deterioration in the cardiac rhythm.\textsuperscript{25} Given these conflicting data, the precordial thump is not considered an alternative to conventional treatments such as expedited defibrillation.

Many researchers have adopted the 3-phase model for resuscitation after cardiac arrest.\textsuperscript{26} The initial phase, or electric phase, occurs during the first 4 to 5 minutes after arrest, and immediate defibrillation is essential in the survival of these patients. The second phase, the hemodynamic phase, usually consists of minutes 4 to 10 after cardiac arrest. During this phase, some have theorized that it might be better to improve oxygen delivery with high-quality CPR followed by defibrillation. While this theory is supported in animal models,\textsuperscript{26} randomized trials employing a strategy of 2 to 3 minutes of CPR prior to defibrillation have yielded inconsistent results. One trial of 200 cardiac arrest patients found an improvement in survival in a CPR-first strategy when the response time of the ambulance was greater than 5 minutes,\textsuperscript{27} whereas 2 other studies found no improvement in survival.\textsuperscript{28,29} Notably, current guidelines state there are insufficient data to support the use of 2 to 3 minutes of CPR prior to defibrillation if immediately available.\textsuperscript{30} The third phase, the metabolic phase, occurs after 10 minutes of cardiac arrest. During this phase, early CPR and defibrillation are less effective, and
outcomes are very poor. In these cases, if ROSC is obtained quickly, postresuscitative treatment is essential in improving outcomes.

While defibrillation is essential for ROSC and early defibrillation improves outcomes, interruptions of high-quality CPR must be kept as minimal as possible. Studies have shown that interruptions of CPR for defibrillation can worsen outcomes. Current guidelines recommend CPR be initiated while the defibrillator is being set up and interruptions kept to a minimal. CPR should stop for a rhythm check, followed by defibrillation if necessary, and immediate resumption of CPR prior to another rhythm check. Only a single shock for VT or VF from either an automated external defibrillator (AED) or monophasic or biphasic defibrillator should be used before resuming CPR. Biphasic defibrillators are preferred because of the ability to perform defibrillation with lower energy levels (200 J compared to 360 J with a monophasic defibrillator).

Given the importance of time to defibrillation as a predictor of outcomes, the use of AEDs provides promise for significantly improving outcomes in victims of SCD. The technology of AEDs has improved, and recent models can weigh as little as 2 to 4 kg and cost under $1000. While initial data regarding the use of public access AEDs were uncertain, larger trials have since shown impressive rates of survival when AEDs are used in airports, airplanes, casinos, and police vehicles. A randomized trial studying placement of AEDs in general community sites demonstrated a significant improvement in survival to hospital discharge when a trained first responder used an AED as opposed to CPR alone (23% with AED use, 14% with CPR alone). These results have led to the increased use of AEDs deployed in high-risk areas. Despite this deployment, public access AEDs are only used in a small proportion of out-of-hospital cardiac arrests, although with increasing awareness, their use should grow.

**Advanced Cardiac Life Support**

After initial resuscitative measures are under way, the next step in management is to obtain stable ROSC and stable hemodynamics. Intravenous (IV) or intraosseous (IO) access should be obtained. If the initial rhythm is VT or VF, CPR should continue in 2-minute cycles with rhythm and pulse checks afterward with subsequent defibrillation for recurrent VT/VF.
Although there is minimal randomized evidence to support its use, epinephrine (1 mg IV/IO) is recommended every 3 to 5 minutes. Several recent observational studies have questioned the utility of epinephrine for out-of-hospital cardiac arrest\textsuperscript{34,35}; however, these studies are by definition confounded by indication (ie, patients receiving epinephrine are inherently sicker than those who do not receive it). Higher dose epinephrine is not recommended because trials have failed to show improvements in survival compared with standard-dose epinephrine.\textsuperscript{36,37} Vasopressin (40 mg IV/IO) can be given in place of a dose of epinephrine.\textsuperscript{38} While a randomized trial showed superiority with this strategy over epinephrine alone,\textsuperscript{39} a subsequent meta-analysis of several randomized trials found no benefit.\textsuperscript{40} Another randomized trial that took place after the meta-analysis found that a combination of vasopressin, epinephrine, and steroids (methylprednisolone 40 mg IV once) improved survival compared to epinephrine and placebo (21% survival with favorable neurologic outcome in the combination group vs 8% in the epinephrine plus placebo group).\textsuperscript{41} The conflicting data regarding the use of vasopressors underscore the importance of high-quality CPR and defibrillation to optimize outcomes for cardiac arrest patients.

Antiarrhythmic therapy can be effective in the treatment of refractory VT/VF. Amiodarone (300 mg initial bolus followed by 150 mg bolus as clinically indicated) is the preferred antiarrhythmic.\textsuperscript{38} The ARREST trial showed an improvement in survival to hospital admission with amiodarone use compared with placebo (44% vs 34%), at the cost of an increase in bradycardia and hypotension requiring treatment.\textsuperscript{42} The ALIVE trial found amiodarone to be superior to lidocaine (1-1.5 mg/kg IV followed by 0.5-0.75 mg/kg every 5-10 minutes).\textsuperscript{43} Magnesium sulfate (2 g IV) can be used to treat torsade de pointes\textsuperscript{44}; however, it is not recommended for routine use in VT/VF.

When the initial rhythm is asystole or PEA, no defibrillation is advised, and high quality CPR should be initiated with rhythm and pulse checks every 2 minutes. In this situation, the most critical role of the physician is to reverse any underlying cause of the arrest. Much like in VT/VF, evidence supporting the use of epinephrine and vasopressin during PEA or asystole is lacking; however, guidelines recommend the use of epinephrine (1 mg IV/IO every 3-5 minutes) with vasopressin (40 mg IV/IO) as an alternative to one of the epinephrine doses.\textsuperscript{38} Atropine is no longer recommended for PEA or
asystole, as recent trials have shown no improvement in outcomes and a potential signal of harm.\textsuperscript{45} While transcutaneous pacing can be temporarily effective in patients with bradycardia, it is usually not effective and therefore not recommended in treating patients with asystole who typically require transvenous pacing.\textsuperscript{46}

**Systems of Care**

Despite many advances in the treatment of heart disease, the outcomes after cardiac arrest remain poor. A changing cardiac arrest population with older age and less VF may offset improvements in bystander CPR rates and shorter times to defibrillation.\textsuperscript{47} The etiology of the cardiac arrest is linked to subsequent survival, with very few patients with asystole surviving to hospital admission or discharge and as few as 11% of patients with PEA surviving to discharge.\textsuperscript{48} On the contrary, reports of survival with VF are better than 25%.\textsuperscript{47}

Initial emergency medical care systems involved training firefighters in the treatment of cardiac arrest patients, including the use of defibrillators. Initial reports from Miami, Florida, and Seattle, Washington, during the 1970s reported initial out-of-hospital cardiac arrest survival rates of 14% and 11%, respectively. Adding emergency medical technicians as trained first responders increased these rates of survival to close to 30% in the late 1980s. More recently, overall survival rates have decreased across the United States, likely due to the addition of emergency medical systems in rural areas and increased population density in urban areas (ie, a greater denominator of patients noted to undergo emergency resuscitation measures).\textsuperscript{49} Significant regional variability exists, with 1 study reporting survival to discharge after all cardiac arrests ranging between 3.0% and 16.3% with survival rates of VF arrests between 0% and 39%.\textsuperscript{50} This large variability underlies the importance of community efforts to optimize the treatment of SCD.

The primary efforts to improve outcomes in cardiac arrest include easy access to emergency medical systems (eg, through calling 9-1-1), training community members to perform bystander CPR, AED placement in public areas, dispatcher-assisted CPR, trained first responder defibrillation, and improvements in advanced cardiac life support (ACLS) from healthcare workers.\textsuperscript{51} These changes have improved outcomes in many emergency...
systems like those in Seattle, Washington, where overall survival rates are nearly double those of the nation. The emergency medical system there has made several changes, including equipping fire fighters with AEDs for rapid response to patients with cardiac arrest. In addition, there is a multilevel review process evaluating the response to cardiac arrests.

Partly based on this paradigm and others like it, the AHA has subsequently released a “chain of survival” designed to help improve outcomes in all communities. This chain includes immediate recognition of cardiac arrest and activation of the emergency response system, early CPR with emphasis on chest compressions, rapid defibrillation, effective ACLS, and an integrated post-cardiac arrest care. In addition, a thorough review process to evaluate the response of emergency medical systems is vital to improving outcomes in out-of-hospital cardiac arrests.

IN-HOSPITAL MANAGEMENT

Upon arrival to the hospital, the initial management for victims of SCD concentrates on stabilization of the patient and determining the cause of the arrest. Prompt electrocardiography is recommended in order to diagnose the postreperfusion rhythm and also to determine whether the primary etiology of SCD is related to acute MI. Depending on the arrest time, the initial electrocardiogram (ECG) may represent severe acidosis with attendant hyperkalemia, and thus serial ECGs are often indicated after reversal of these metabolic abnormalities. Adequate ventilation must be maintained to ensure oxygen saturations greater than 94%, with mild permissible hypercapnia to prevent the physiologic cerebral vasoconstriction in response to hypocapnia. Hemodynamics need to be optimized with mean arterial pressures (MAP) of at least 65 mmHg, preferably even 80 to 100 mmHg, in order to maintain cerebral perfusion and reverse any ischemic consequences of the cardiac arrest. An adequate volume status should be maintained with goal central venous pressure of 8 to 10 mmHg. In addition to hemodynamic support, stabilization of the cardiac rhythm is important, and patients with recurrent VT/VF should be treated with antiarrhythmic therapies (eg, amiodarone) as well as consideration for emergent coronary angiography (see below).

Routine laboratory tests can elucidate reversible causes of cardiac arrest,
including electrolyte abnormalities. Prompt echocardiography can be very useful in order to determine the etiology of cardiac arrest, although global left ventricular dysfunction may be a common finding, particularly for patients with longer times to ROSC. Empiric use of transvenous pacemakers for those with atrioventricular or intraventricular conduction abnormalities have not improved outcomes and are only indicated for severe symptomatic heart block. Empiric use of fibrinolytics in cardiac arrest victims does not appear to improve survival. However, use of fibrinolytics when pulmonary embolism is the presumed cause may be beneficial and is recommended.

**Therapeutic Hypothermia**

The most common cause of death in cardiac arrest survivors is neurologic injury, accounting for approximately two-thirds of all in-hospital mortality. The use of therapeutic hypothermia as a means of preserving neurologic function has been studied in several prospective trials. There is minimal evidence to support the use of therapeutic hypothermia in non-VF arrests; however, the use of therapeutic hypothermia in VF arrests is more controversial. Two randomized trials found the use of mild therapeutic hypothermia for survivors of VF cardiac arrest was associated with improved neurologic outcomes compared to standard intensive unit care. One trial randomized 77 patients and found a 23% improvement in outcomes with hypothermia (49% discharged to home or rehab with hypothermia compared with 26% in standard care), and the other trial randomized 136 patients, finding a similar 16% improvement in neurologic outcomes (55% with good recovery or moderate disability in the hypothermia group compared to 39% with standard treatment). However, a follow-up trial tested the hypothesis that the benefit seen with therapeutic hypothermia might be from avoidance of fevers alone, which have been shown to have detrimental effects on neurologic outcomes following cardiac arrest. This larger trial randomized 950 cardiac arrest survivors (with presumed cardiac etiology) to hypothermia with a goal temperature of either 33°C or 36°C. There was no difference in overall mortality (50% in the 33°C group and 48% in the 36°C group; Fig. 64-3), and neurologic outcomes were similar in the 2 groups. Given these findings, recent guidelines now suggest the use of targeted temperature management with target temperature between 32°C and 36°C.
Further, the exact timing and method of cooling is unclear. The 2 randomized trials started cooling at either <2 or <8 hours\textsuperscript{57,58}; however, subsequent registry data revealed that neither time to cooling nor time to goal temperature was associated with better neurologic outcomes.\textsuperscript{61} In addition, prehospital cold saline infusion is of no benefit over initiation of therapeutic hypothermia in the hospital.\textsuperscript{62,63} The duration of hypothermia was 12 or 24 hours in the 2 randomized trials showing benefit; however, most case series have reported 24 hours of cooling.\textsuperscript{53,57,58} Although guidelines have no clear
recommendation regarding the time to initiate cooling, they do state that cooling should continue for 24 hours with gradual rewarming (0.25°C/h).

Cooling can be accomplished with either external cooling devices or internal catheters with feedback mechanisms. Cooling blankets and application of ice bags can also be used; however, it is more difficult to maintain therapeutic hypothermia with these methods. Cold/iced saline given intravenously is a safe way to initiate hypothermia as well.

Therapeutic hypothermia has several complications that require active management by the intensive care team. Shivering will occur in most patients and needs to be treated with heavy sedation. Hypothermia can induce a mild coagulopathy; however, no clear increase in significant bleeding has been reported with therapeutic hypothermia. If significant bleeding does occur, rewarming is likely indicated. Hypothermia additionally impairs leukocyte function; however, significant infections are unlikely if the time of cooling is under 24 hours. Electrolyte abnormalities are common and need to be monitored closely. Cardiac arrhythmias are common, including severe sinus bradycardia; however, this usually does not require treatment.

**Coronary Angiography and Revascularization**

The cardiac catheterization laboratory plays an important role in the management of SCD patients, as the majority of cardiac arrests are etiologically secondary to CAD. SCD survivors with findings consistent with an ST-segment elevation MI on ECG should undergo emergent angiography and revascularization. Many advocate the use of urgent coronary angiography in all survivors of VT/VF arrests given the large proportion of those patients having significant ischemic heart disease. Registry data have shown improved outcomes in those who undergo successful coronary angioplasty compared to those who have not. Others advocate the use of urgent angiography only in patients with ischemic changes on the ECG or a history of antecedent chest pain prior to the arrest. Regardless of the initial treatment decision, cardiac catheterization should be considered for SCD survivors with continued hemodynamic instability, continued elevation in cardiac biomarkers, segmental wall motion abnormalities on echocardiography, or worsening ischemic changes on the ECG. Coronary angiography is reasonable for all survivors of cardiac arrest to rule out CAD as the primary cause of the arrest, unless a clear noncoronary cause for the SCD exists. Even
in the young population, angiography is reasonable to determine if coronary anomalies exist.

In the acute setting, revascularization should be based on appropriate indications (e.g., it should be strongly considered for those with acute coronary syndromes, ongoing ischemia, or severe CAD thought to be the cause of the arrest). If truly stable CAD is found, revascularization should be reserved for those with indications such as ongoing hemodynamic instability or shock. While there is no clear evidence supporting revascularization in SCD survivors, these patients are at the highest risk and may benefit from a more aggressive revascularization strategy, especially when ischemia is the likely precipitant of the cardiac arrest.

A consensus statement by the American College of Cardiology’s Intervention Council has proposed a treatment algorithm for patients with resuscitated cardiac arrest based not only on the initial ECG, but also on patient and presenting factors that would render individual patients more or less suitable for coronary angiography and therapeutic measures within the cardiac catheterization laboratory (including percutaneous coronary intervention and/or institution of hemodynamic support) (Fig. 64-4).65
A notable (nonclinical) input that often plays into the clinical decision making for taking patients to the cardiac catheterization laboratory for angiography and/or revascularization relates to the implications of public reporting of adverse outcomes following coronary revascularization procedures. Patients with cardiac arrest undergoing revascularization are among those with the worst prognosis, and thus there may be reluctance on the part of the treating physician (and hospital) to perform procedures in high-risk patients who may not survive to hospital discharge independent of the procedure performed. To reduce the impact of this on clinical decision making, some states with public outcomes reporting have employed either systematic exclusions for shock patients or those with anoxic brain injury, while others have tried to incorporate high-risk features into multivariable risk adjustment algorithms. Nonetheless, public reporting has been linked to avoidance of procedures in this high-risk population, and this has been linked to adverse outcomes.\(^{66}\)

**Hemodynamic Support**

Maintaining adequate perfusion pressure is vital during the early period after a cardiac arrest to prevent worsening multiorgan dysfunction and especially prevent further cerebral injury. Vasopressors are often required, especially in the setting of therapeutic hypothermia. There is no clear evidence to support which vasopressor to use after cardiac arrest and specifically in the setting of cardiogenic shock. Dopamine, norepinephrine, vasopressin, and epinephrine can all be used to help maintain adequate MAPs. In the specific setting of cardiogenic shock after cardiac arrest, inotropes including dobutamine and milrinone may be necessary. However, both of these agents cause vasodilation, and dobutamine can cause tachycardia. Revascularization should be performed if cardiogenic shock is present and culprit vessels are identified.\(^{67}\)

If initial attempts at hemodynamic stabilization are not successful, further treatment with cardiopulmonary assist devices may be warranted. While the
use of these devices has primarily been in the setting of cardiogenic shock complicating acute MI, a large proportion of these patients are survivors of SCD. An intra-aortic balloon pump (IABP) may provide stabilization of hemodynamics when initial pharmacologic treatment fails; however, routine use of IABP in cardiogenic shock does not appear to be beneficial. If more profound shock is present (or if hemodynamic instability continues despite the use of IABP), ventricular assist devices (VAD) with greater degrees of support can be considered in appropriate patients. These devices are most efficacious if placed early in the shock cycle (eg, prior to percutaneous coronary intervention). The use of a percutaneous transvalvular VAD (Impella; Abiomed), percutaneous left atrial to femoral artery assist device (TandemHeart; Cardiac Assist), percutaneous cardiopulmonary bypass support with use of an extracorporeal membrane oxygenator (ECMO), or surgical left ventricular or biventricular assist devices can all provide greater amounts of support for SCD patients who have refractory shock. Determining in which patients to employ these advanced therapies is often complicated by the uncertain neurologic status of the postarrest patient, as neurologic recovery can often take a few days. At present, there is no clear evidence supporting the use of these advanced therapies as the primary treatment modality for postarrest patients. However, marked improvements in hemodynamics have been shown when comparing the percutaneous VADs to IABP.

ECMO has also been used during cardiac arrest resuscitation, also known as extracorporeal CPR (ECPR). Implementation of ECMO use during cardiac arrests is complex and requires a highly skilled team due to the large cannula sizes and the maintenance of the ECMO circuit after cannulation. Newer self-contained ECMO systems are available and may reduce the need for active management by perfusionists but still require significant multidisciplinary training as well as system-wide decision making regarding the identification of patients who are the best candidates for this therapy. There are limited data supporting the use of ECPR. One prospective study of in-hospital arrests from a presumed cardiac origin and with CPR lasting over 10 minutes, found a 13% increase in survival with good neurologic function compared to unmatched controls (23.7% in the extracorporeal life support group, 10.6% in the CPR-only group; Fig. 64-5). Other registry data have shown promising results, with reported survival to discharge rates of up to 36% in select
populations. Guidelines state there is insufficient evidence to support more generalized use of ECPR; however, in settings where ECPR is readily available, it may be considered when the arrest time is brief and the condition leading to the cardiac arrest is reversible. 


LONG-TERM MANAGEMENT

If the acute treatment of SCD has been successful, long-term management of these patients focuses on determining the cause of the arrest and preventing
further episodes. If not performed in the acute setting, an echocardiogram should be performed, as several causes of cardiac arrest can be identified including cardiomyopathies (ischemic or idiopathic), valvular disease, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (ARVC). Cardiac magnetic resonance imaging (MRI) can also be useful, especially if an infiltrative myocardial disease is suspected. For patients managed without prompt coronary angiography who have recovery of neurologic function, further ischemic testing (angiography is the preferred modality) should be strongly considered. In addition to appropriate revascularization, medical therapies to improve myocardial ischemia and LV dysfunction should be initiated. Many of the treatments that improve general outcomes in patients with LV dysfunction have been shown to reduce the risk of SCD.

**Implantable Cardiac Defibrillator Therapy**

The use of ICD therapy has been extensively studied in the secondary prophylaxis population, and current guidelines recommend ICD therapy over antiarrhythmic therapy for survivors of VT/VF with no reversible cause identified. The AVID trial randomized 1016 patients with documented VF or unstable VT and a reduced LV ejection fraction to antiarrhythmic therapy or ICD implantation. There was a 10% absolute risk reduction in mortality with ICD use (75% 3-year survival in the ICD group vs 65% in the medication group). The CASH trial randomized 349 survivors of VT/VF arrest to ICD or antiarrhythmic therapy and found a nonsignificant 8% reduction in mortality (36.4% mortality with ICD vs 44.9% with amiodarone or metoprolol). The CIDS trial randomized 659 patients with VT/VF with either syncope or cardiac arrest to ICD or amiodarone and found a nonsignificant reduction in overall mortality. A meta-analysis of these trials found a significant 7% reduction in mortality with the use of ICD compared to medical management (Fig. 64-6).
While ICD therapy is indicated in SCD survivors who have no reversible cause, for those with reversible causes, including polymorphic VT or VF secondary to an acute MI, treatment of the underlying condition may be enough to prevent recurrent events. Nonetheless, even after revascularization, for example, residual risk can remain, and as a result, these patients should be seen by an electrophysiologist and further risk stratified. Patients with a persistent reduction in LV ejection fraction after the acute MI should be treated with guideline-directed ICD therapy. In addition, the presence of spontaneous ventricular premature beats or nonsustained VT on Holter monitoring can signal those at increased risk. In selected patients, performance of a provocative electrophysiology (EP) study can help identify those who are at higher risk of recurrent events.

**Antiarrhythmic Drugs**

ICDs remain the standard of care for survivors of SCD; however, antiarrhythmic therapy is often required during long-term management. The primary reason for the addition of an antiarrhythmic is recurrent VT/VF or other arrhythmias causing appropriate (or inappropriate) ICD shocks. A systemic review of randomized studies comparing antiarrhythmic therapy to

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<td>Weaver 1995</td>
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<td>11/31</td>
<td></td>
<td>3.7</td>
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<td>CIDS 2000</td>
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<td></td>
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<td>Total</td>
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<td>315/1060</td>
<td></td>
<td>100.0</td>
<td>0.75[0.64,0.87]</td>
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Test for heterogeneity chi-square=3.97 df=3 p=0.26
Test for overall effect z=-3.75 p=0.0002

placebo in those with ICDs found that antiarrhythmics significantly reduce the number of shocks with no change in overall mortality.\textsuperscript{84} Amiodarone is the preferred agent, and studies have shown its superiority over other agents.\textsuperscript{85} However, long-term toxicity is a concern, and in certain circumstances, other agents should be considered. β-Blockers should also be used, as data suggest a synergistic effect of β-blockers with other antiarrhythmic therapies.

\textbf{Wearable Cardioverter-Defibrillator}

Clinical trials where ICD implantation occurred in patients with reduced LV ejection fraction soon after an MI failed to show improvements in survival, unlike trials that enrolled patients after a 40-day waiting period.\textsuperscript{86,87} Therefore, current guidelines recommend ICD implantation for persistently reduced LV ejection fraction 40 days after MI. During that waiting period, there remains a residual risk of SCD, especially among patients originally admitted with SCD. The use of a wearable cardioverter-defibrillator has been proposed for protection against SCD during the 40-day waiting period. There are no randomized data to compare the effectiveness of the wearable cardioverter-defibrillator compared with no device. However, postmarketing registry data including 8453 patients with recent MI and a reduced LV ejection fraction (\(\leq 35\%\)) found that 1.6% of patients had an appropriate shock (91% of these were from a ventricular arrhythmia).\textsuperscript{88} Given that patients may have improvements in ejection fraction over time and a lesser need for ICD shocks,\textsuperscript{89} a strategy of using a wearable cardioverter-defibrillator after post-MI revascularization in order to potentially avoid permanent ICD placement merits further study. Another use for the wearable cardioverter-defibrillator includes in those patients who require an ICD but are not candidates for an ICD because of infection, vascular access issues, or patient preference. The use of a wearable cardioverter-defibrillator in this population is effective, with similar survival to those treated with ICDs.\textsuperscript{90}

\textbf{CONCLUSION}

Cardiac arrest can occur from many causes, with VT/VF from CAD being the most common etiology. Treatment of these patients requires immediate
resuscitation with early defibrillation and high-quality CPR. Community programs to reduce emergency response times, increase bystander CPR, and increase availability of AEDs will help improve outcomes for the SCD patient. The goals of hospital care are instituting supportive care in order to preserve organ function (especially cerebral function), identifying the cause of the arrest, and optimizing treatment of this underlying cause. For interventional cardiologists, the catheterization laboratory is essential not only in order to diagnose the precipitant of the SCD but also in further stabilizing the patient: providing hemodynamic support when needed and revascularization in those cases where ischemia or infarction has led to the SCD. Beyond the supportive care instituted for these patients while in the hospital, an eye to long-term management of these patients (with appropriate consideration of ICD or wearable cardioverter-defibrillator therapy) is additionally essential in order to effectively transition survivors of cardiac arrest to the posthospital setting.

REFERENCES

8. Eckart RE, Shry EA, Burke AP, et al. Sudden death in young adults: an


84. Ha AH, Ham I, Nair GM, et al. Implantable cardioverter-defibrillator


**MULTIPLE CHOICE QUESTIONS**

1. Which of the following statements is true regarding the use of therapeutic hypothermia in patients surviving sudden cardiac death?
   A. There is clear evidence to support the use of rapid cooling (ie, within the first 2 hours of cardiac arrest).
   B. The largest randomized trial of therapeutic hypothermia found no benefit of cooling to a goal temperature of 36°C compared to 33°C.
   C. Trials have shown a significant increase in bleeding complications in patients undergoing therapeutic hypothermia.
   D. Current recommendations are that therapeutic hypothermia should be continued for 48 hours followed by gradual rewarming.
   E. All of the above are true.
2. Current recommendations for the initial management of cardiac arrest patients include which of the following?
   A. The use of inspiratory impedance threshold devices if available
   B. High-quality uninterrupted cardiopulmonary resuscitation (CPR) if the initial responders are uncomfortable with mouth-to-mouth resuscitation
   C. After placement of an advanced airway, asynchronous respirations should be provided at a rate of 15 to 20 breaths per minute
   D. Interposed abdominal compression CPR (IAC-CPR) should never be used during the initial management of cardiac arrest patients
   E. There are clear data to support the use of automated chest compression devices instead of conventional CPR

3. Which of the following causes of sudden cardiac death is the leading cause in the United States?
   A. Long QT syndrome
   B. Chronic systolic heart failure
   C. Coronary artery disease
   D. Hypertrophic cardiomyopathy
   E. Congenital heart disease

4. Which of the following is no longer currently recommended during advanced cardiac life support?
   A. Epinephrine every 3 to 5 minutes
   B. Placement of a transvenous pacer for those with asystole
   C. Amiodarone (300 mg bolus) to those with refractory ventricular tachycardia or ventricular fibrillation
   D. Atropine (1 mg) to patients with pulseless electrical activity or asystole
   E. B and D
   F. All of the above are recommended

5. Which of the following should be considered by the interventional cardiologist during the management of cardiac arrest survivors?
   A. Early coronary angiography and revascularization in patients with suspected acute coronary syndrome as the primary cause of the cardiac arrest
B. Complete revascularization in patients with continued hemodynamic or electrical instability
C. Use of percutaneous hemodynamic support devices in patients with severe cardiogenic shock even when the neurologic recovery is unclear
D. Consideration of nonemergent coronary angiography in all patients presenting with cardiac arrest
E. All of the above

ANSWERS

1. B
2. B
3. C
4. E
5. E
Part VI MEDICAL MANAGEMENT OF RISK FACTORS

65 Guideline-Directed Medical Therapy for Patients With Stable Ischemic Heart Disease

66 Appropriateness Use Criteria for Revascularization
INTRODUCTION

Guideline-directed medical therapy (GDMT) is an intrinsic part of management of patients with stable ischemic heart disease (SIHD) whether or not revascularization is performed. GDMT for patients with coronary disease is synonymous with secondary prevention and consists of pharmacologic and lifestyle interventions. This chapter synthesizes the evidence base behind guideline-recommended therapies for secondary prevention. Outside of the use of aspirin, we will not discuss strategies of antiplatelet therapy for post-percutaneous coronary intervention (PCI) patients, which are reviewed elsewhere. Additionally, management of anginal symptoms is outside the scope of this chapter, and angina management in patients with SIHD will be discussed only briefly in the context of other targets for secondary prevention and risk factor modification. We will begin by reviewing the GDMT targets for risk factor modification in the 2012 SIHD guidelines. Following this, we will review the other medical therapies that have been shown to prevent death and myocardial infarction (MI) among patients with SIHD.
RISK FACTOR GOALS

Lipid Management

Elevated concentration of low-density lipoprotein (LDL) cholesterol is a major risk factor for the development and progression of atherosclerosis. Therefore, the principal lipid modification strategy recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and the recent American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol is to lower LDL. All patients with coronary disease should be treated with a high-potency statin if tolerated (see below). This does not lessen the importance of nutrition, physical activity, and weight management to reduce the risk of coronary events. Effective dietary strategies to lower LDL cholesterol include replacing dietary saturated fatty acids and trans-fatty acids with unsaturated fatty acids or complex carbohydrates and reducing dietary cholesterol. Specifically, the 2012 SIHD guidelines recommended limiting saturated fat to <7% of total calories; trans-fats to <1% of total; and cholesterol to <200 mg/dL of total. While limiting saturated fat intake to <7% of total calories reduces both LDL cholesterol and high-density lipoprotein (HDL) cholesterol, reducing saturated fat intake lowers LDL more than HDL and has highly beneficial effects on the overall lipid profile and measures of total atherogenic particles, such as non-HDL cholesterol. Currently people in the United States derive between 11% and 15% of total calories from saturated fat. Earlier literature from randomized trials and practice guidelines demonstrated that targeting saturated fat to <7% of total calories lowers LDL by 10% to 15% and reduces risk of ischemic heart disease. In particular, saturated fats with chain lengths of 14 (myristic) and 16 (palmitic) carbons, primarily found in dairy products and red meat, appear most potent in raising serum cholesterol. A meta-analysis by Chowdhury et al reviewed prospective observational studies of dietary fatty acids (32 studies) and fatty acid biomarkers (17 studies) along with randomized controlled trials of fatty acid supplementation (27 studies) and concluded that evidence does not support guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of saturated fatty acids. This meta-analysis required revisions of errors in the original publication and
generated numerous critical letters to the editor. With the revision, the authors showed the inverse association of intake of long-chain \( \omega-3 \) polyunsaturated fatty acids (PUFAs) with cardiovascular disease (CVD) risk is indeed significant. They were criticized for including the Sydney Diet Heart Study, a randomized controlled trial that replaced saturated fats with an experimental diet that included a trans-fat–based margarine. When that study was excluded, the remaining randomized controlled trials found a benefit from replacing saturated fatty acids with PUFAs. A subsequent systematic review and meta-analysis by Farvid et al\(^7\) summarized the evidence regarding the relation of the predominant dietary PUFA, linoleic acid (LA), with coronary heart disease (CHD) risk. They found that compared with the lowest dietary intake of LA, the highest intake of LA was associated with a 15% (95% confidence interval [CI], 0.78-0.92) and 21% (95% CI, 0.71-0.89) reduction in CHD events and mortality, respectively.\(^7\) They found that replacing 5% of energy from saturated fat with dietary LA was associated with a 9% (95% CI, 0.86-0.96) and 13% (95% CI, 0.82-0.94) lower risk of CHD events and mortality, respectively.\(^7\) Chowdhury et al\(^6\) reported similar findings, with a reduction in CVD risk up to 13% (95% CI, 3%-22%) when comparing the highest to lowest tertiles of intake of PUFA. Notably, the effects of PUFA intake on the secondary prevention of CVD was either not evaluated\(^7\) or evaluated with very few studies\(^6\) in these meta-analyses. Increased trans-fat intake raises serum cholesterol, lowers HDL, and increases CHD events.\(^1,2\) The use of liquid vegetable oils, soft margarine, and trans-fatty acid–free margarine is encouraged instead of using butter, stick margarine, and shortening.\(^2\)

Along with therapeutic lifestyle modification, all patients with SIHD should be prescribed a moderate to high dose of statin therapy (Table 65-1) in the absence of contraindications or documented adverse effects. This is a class I recommendation for management of patients with SIHD.\(^1\) Randomized controlled trials of lipid-lowering therapy have repeatedly demonstrated that lowering LDL cholesterol with statin therapy is associated with a reduced risk of adverse cardiovascular events in patients with established ischemic heart disease (IHD) or with multiple risk factors for future IHD events.\(^1\) Prior guidelines and commentary had focused on specific LDL thresholds to guide therapy, with a cutoff of <100 mg/dL in patients with established coronary artery disease and an LDL cholesterol goal of <70
mg/dL as a therapeutic option in patients at very high risk. However, while a paucity of data exist to confirm the use of specific, numeric targets for LDL, the benefits of moderate- to high-dose statin therapy for secondary prevention of IHD is well established. It is in this context that the 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults were published, generating significant controversy. In this guideline, the authors concluded there was insufficient randomized controlled trial evidence to support titrating statin or other medical therapy to achieve a specific LDL or non-HDL target in patients with or without SIHD. Instead of using specific LDL targets as in prior guidelines to guide cholesterol-lowering therapy, this ACC/AHA guideline recommended measuring on-treatment levels of cholesterol only as a tool to gauge adherence with medical therapy. To simplify the identification of patients likely to benefit from statin therapy, the authors identified 4 “statin benefit” groups, the first of which include patients with known SIHD, such as patients after PCI. Per the guidelines, all SIHD patients should receive a high-intensity statin if ≤75 years of age (see Table 65-1) or a moderate-intensity statin if >75 years old. In addition to these major changes, the guideline panel could find no evidence to support the routine use of nonstatin drugs combined with statin therapy to reduce future CHD events. The 2013 ACC/AHA guidelines therefore suggest that the vast majority of SIHD patients undergoing percutaneous revascularization procedures should receive high-intensity statin therapy. If after 4 to 12 weeks of therapy with high-intensity statin there is a less-than-anticipated therapeutic response (anticipated LDL cholesterol reduction of ≥50% or 30%-50% for high- and moderate-intensity statin, respectively), the guidelines recommend assessing adherence to statin and lifestyle modification before additional nonstatin therapies are initiated. If after adherence is documented and the therapeutic response to high- or moderate-intensity statins (see Table 65-1) remains less than anticipated, the addition of nonstatin drug therapy such as bile acid sequestrants can be considered. For patients intolerant of statin therapy, the current ACC/AHA guidelines consider therapy with a bile acid sequestrant, niacin, or both a reasonable therapeutic option (class IIa indication). We refer the interested reader to the ACC/AHA guidelines for detailed recommendations on cholesterol management strategies for patients with familial hypercholesterolemia and
other hypercholesterolemia syndromes.³

### Blood Pressure Management

Hypertension is extremely common among patients with coronary disease and is often less than optimally treated. Lifestyle factors influence blood pressure (BP), and the 2012 SIHD guidelines give a class I indication to counseling all SIHD patients on weight management, increased physical activity, alcohol moderation, sodium reduction, and increased fruit and vegetable consumption. Significant weight loss (average of 10 kg) has been shown to reduce systolic blood pressure (SBP) by 5 to 20 mm Hg.¹⁰ A diet high in fruit, vegetables, and low-fat dairy has also demonstrated improvements in BP,¹¹ as have diets with lower sodium levels.¹² Increased physical activity¹³ and reducing alcohol intake from high to moderate consumption also has beneficial effects on BP.¹⁴

Despite lifestyle modifications, many patients with SIHD require medical therapy for adequate BP control. There is a large body of literature demonstrating that, on average, a reduction in diastolic blood pressure (DBP)
of 5 to 6 mm Hg (10-20 mm Hg SBP) within a population is associated with a 40% reduction in stroke risk and a 20% reduction in risk of IHD.\textsuperscript{15} Despite the abundance of clinical studies, the appropriate BP threshold for initiating medical therapy and specific treatment goals for patients with SIHD remains controversial. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target of $<140/90$ mm Hg in patients with uncomplicated hypertension and of $<130/80$ mm Hg in patients with diabetes or chronic kidney disease (CKD).\textsuperscript{16} Observations from epidemiologic studies have led some to suggest that a target lower than $<130/80$ mm Hg might be appropriate for patients with SIHD or multiple IHD risk factors.\textsuperscript{17} However, excessive reduction in DBP may compromise coronary perfusion in SIHD patients, leading to a “J-shaped” relationship of increased risk of CVD with DBP $<70$ to 80 mm Hg.\textsuperscript{18} Randomized data from the ACCORD trial also demonstrated no benefit from targeting normal BP ($<120$ mm Hg) versus SBP $<140$ mm Hg on fatal and nonfatal CVD events among patients with type 2 diabetes (T2D).\textsuperscript{19} On the other hand, a lower SBP in ACCORD was associated with a lower risk of stroke, albeit with a higher risk of serious adverse events attributed to antihypertensive medications.\textsuperscript{19} It is in this setting that the Eighth Joint National Committee 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8) was released.\textsuperscript{20} While JNC 8 does not specifically address BP control in patients with SIHD, it does recommend treating to BP $<140/90$ mm Hg, a target given a class I recommendation in the 2012 SIHD guidelines.\textsuperscript{1,20}

In patients with uncomplicated hypertension, effective BP lowering is the most important factor in preventing stroke and MI. Clinical trials have failed to demonstrate superiority of any single antihypertensive drug in preventing CVD events.\textsuperscript{1} In many patients with SIHD, the choice of medications to control BP is guided by other compelling clinical indications such as the presence of left ventricular dysfunction, T2D, or CKD (Table 65-2), for which specific medication classes have demonstrated clear evidence of benefit. In recognition of this, the 2012 SIHD guidelines gave a class I recommendation to support the treatment of high BP based on specific patient characteristics and may include angiotensin-converting enzyme inhibitors (ACEi) and/or β-blockers, with the addition of other drugs, such as thiazide diuretics or calcium channel blockers, if needed to achieve a goal BP of
Management of diabetes mellitus continues to pose a quandary with regard to CVD risk. Diabetes is an important risk factor for CVD events and mortality.\textsuperscript{1} Diabetes is also associated with poor outcomes in patients with SIHD, even after adjustment for disease extent and other clinical characteristics.\textsuperscript{21} However, despite multiple randomized trials and observational studies, the efficacy of intensive diabetes therapy in reducing CVD is not well established.\textsuperscript{22} Three seminal trials of intensive glucose control in patients with T2D (ACCORD, VA Diabetes Trial, and ADVANCE) failed to demonstrate an improvement in macrovascular complications or composite outcomes of cardiovascular events and mortality with targeting a hemoglobin A1c (HbA1c) of <7% compared to less stringent control of HbA1c >7%.\textsuperscript{1,23} While intensive glucose control has not demonstrated reductions in macrovascular risk, it has demonstrated notable reductions in morbidity associated with microvascular disease, including retinopathy, nephropathy, and microalbuminuria.\textsuperscript{1,23} Subgroup analyses from the aforementioned trials have also suggested a macrovascular benefit of intensive glycemic control may exist for patients with type 1 diabetes or T2D of short duration and long life expectancy.\textsuperscript{23} Therefore, the 2012 SIHD
guidelines classified an HbA1c target of <7% as reasonable (class IIa) for patients with a shorter duration of diabetes and a longer life expectancy.\textsuperscript{1} Complementing this recommendation, the 2012 SIHD guidelines acknowledge that an HbA1c target of 7% to 9% is reasonable (class IIa recommendation) for older patients, patients with a history of hypoglycemia, and/or patients with microvascular or macrovascular complications.\textsuperscript{1} Regardless of degree of glycemic control, treatment of other modifiable risk factors common in SIHD patients with diabetes, such as hypertension, dyslipidemia, physical inactivity, and smoking, is of paramount importance to reduce cardiovascular risk.\textsuperscript{23,24} If patients and physicians decide to use pharmacologic treatment to improve glycemic control, SIHD guidelines support the use of metformin to reduce diabetic complications, especially for overweight patients.\textsuperscript{1} Available evidence also indicates that rosiglitazone is associated with an excess risk of cardiovascular complications and should not be initiated in patients with SIHD. The US Food and Drug Administration (FDA) has imposed restrictions on the use of this medication, and it has received a class III (harm) indication in the 2012 SIHD guidelines.\textsuperscript{1}

**Physical Inactivity**

The SIHD guidelines recommend 30 to 60 minutes of physical activity 5 to 7 days per week for all patients (class I) and support increasing physical activity, particularly for the most inactive patients.\textsuperscript{1} Virtually all post-PCI patients would benefit from participation in a cardiac rehabilitation program that incorporates supervised exercise into a comprehensive program of secondary CVD prevention.\textsuperscript{1} Despite this benefit, cardiac rehabilitation referral rates remain low, particularly for patients age ≥65 years.\textsuperscript{25} A meta-analysis of 48 randomized controlled trials of exercise interventions of a median of 3 months on duration (95% CI, 0.25-30 months) and with 15 months of follow-up (95% CI, 6-72 months) demonstrated an overall 20% reduction in all-cause mortality; a 26% reduction in total cardiac mortality; and favorable but nonsignificant trends in the occurrence of MI, coronary artery bypass grafting (CABG), and PCI.\textsuperscript{26} The benefits of exercise and cardiac rehabilitation are independent of the actual amount or intensity of exercise and have clear benefits in SIHD patients with and without angina.\textsuperscript{26} The effects of exercise on CVD risk reduction are multifactorial. Exercise
does not lower LDL, but it facilitates weight loss and has other beneficial cardiometabolic effects. Exercise in patients with SIHD is safe, with a rate of major adverse cardiac events (MACE) of approximately 1 in 80,000 patient-hours. Previous SIHD guidelines have recommended that all patients undergo an exercise test before participating in a cardiac rehabilitation program. However, in line with recent recommendations from the World Health Organization, the 2012 SIHD guidelines state that a physical activity history and/or an exercise test is recommended to guide prognosis and exercise prescription.

**Weight Management**

Effective weight management complements many of the secondary prevention targets for patients with SIHD. Regular assessment of patient weight, body mass index (BMI), and/or waist circumference is a class I recommendation in the 2012 SIHD guidelines. Physicians should encourage weight maintenance or reduction through a balance of physical activity and caloric intake to maintain a BMI between 18.5 and 24.9 kg/m$^2$ and a waist circumference <40 inches in men and 35 inches in women. Population studies have repeatedly demonstrated an association between increased BMI and IHD events. Specifically, a large meta-analysis of over 300,000 participants in 21 cohort studies demonstrated that IHD risk increased by 30% and 81% for overweight (BMI 25.0-29.9 kg/m$^2$) and obese (BMI >30 kg/m$^2$) participants, respectively, compared to those of normal weight. This relationship was independent of age, sex, smoking status, and physical activity. After additional adjustment for hypertension and hyperlipidemia, the relationship between BMI and IHD risk was attenuated, but remained statistically significant. These findings suggest that while a portion of the IHD risk of overweight and obesity is conditional on the development of hypertension, hyperlipidemia, and T2D, overweight and obesity also increase risk of IHD through heightened sympathetic tone, hypercoagulability, and inflammation. Interestingly, a similar relationship between BMI and death and CVD events is not consistently observed in cohorts with established IHD. This altered relationship between BMI and IHD risk in patients with established IHD may be due to confounders such as smoking or age or due to the weight loss and lower BMI associated with chronic illness.
clinical trials have examined the effects of weight loss on cardiovascular event rates in patients with SIHD. However, the association of adiposity, overweight, and obesity with other cardiovascular risk factors suggests that weight reduction is indicated in all overweight or obese patients.1

**Smoking Cessation**

The detrimental effects of smoking are clear for patients with IHD. The 2012 SIHD guidelines recommend smoking cessation and avoidance of exposure to tobacco at work and at home (class I).1 The mechanisms of CVD risk from tobacco exposure are well known and include enhanced platelet activity, increased endothelial dysfunction, heightened vasoconstriction, and decreased HDL.1 Although randomized controlled trials have not been performed in patients with SIHD, observational studies strongly suggest that smoking cessation is an important strategy for the secondary prevention of IHD. A meta-analysis of 20 prospective cohort studies in patients with known coronary artery disease (CAD) found a 30% relative risk reduction in mortality for those who quit smoking compared to those with CAD who continued to smoke.29 A similar risk reduction was observed for the occurrence of nonfatal MI.29 The most effective smoking-cessation therapies include both nonpharmacologic and medical interventions. Most of the recommendations to improve quit rates in patients with SIHD are extrapolated from literature in patients without SIHD. Notably, physician advice has a significant effect on smoking quit rates, and the SIHD guidelines recommend physicians inquire about plans for smoking cessation at each visit with patients who continue to smoke. Other useful interventions to improve smoking cessation include self-help programs, behavioral therapy, and possibly exercise interventions.1 Nicotine replacement therapy, sustained-release bupropion, and varenicline all approximately double quit rates. There have been recent concerns of enhanced suicidality and depression in patients prescribed varenicline, which may be an issue for patients with SIHD in whom depression is frequently a comorbid disorder.1 The 2012 SIHD guideline recommends that physicians should use a standardized approach to smoking cessation counseling by using the “6 A’s” framework: Ask, Advise, Assess, Assist, Arrange, and Avoid.1 By applying the 6 A’s framework, physicians can more systematically address principles important to smoking
cessation.

EVIDENCE-BASED PHARMACOLOGIC THERAPIES

Aspirin

Aspirin is the cornerstone of antiplatelet therapy in patients with SIHD. The 2012 SIHD guidelines recommend indefinite aspirin use at 75 to 162 mg in SIHD patients (class I). Aspirin inhibits the cyclooxygenase enzyme and blocks prostaglandin endoperoxide formation, inhibiting platelet aggregation. Major trials and meta-analyses have demonstrated that aspirin use in patients with SIHD leads to a 30% to 50% reduction in vascular events, unstable angina, and revascularization. Importantly, aspirin in a dose of 75 to 162 mg is as effective in secondary prevention as 325 mg and has a lower associated bleeding risk. Aspirin is relatively contraindicated in patients with known allergies to nonsteroidal anti-inflammatory drugs and in patients with the syndrome of rhinitis, asthma, and nasal polyps.

P2Y12 Inhibitors

Clopidogrel, a thienopyridine derivative, is a selective and irreversible inhibitor of the platelet P2Y12 receptor that represents a suitable alternative to aspirin for platelet inhibition for many patients with SIHD. The CAPRIE trial compared clopidogrel 75 mg to aspirin 325 mg in patients with previous stroke, MI, or symptomatic peripheral arterial disease (PAD). There was a small but statistically significant benefit from clopidogrel in the secondary prevention of MI and death in these patients. No additional trials in patients with SIHD comparing aspirin and clopidogrel for the secondary prevention of CVD events have been completed. The 2012 SIHD guidelines recommend the use of clopidogrel for long-term platelet inhibition among patients with SIHD in whom aspirin is contraindicated (class I).

Whether or not patients with SIHD benefit from preventive dual antiplatelet therapy (DAPT) with aspirin and clopidogrel long term is unclear. Evidence from the CURE and CREDO trials indicated that patients with...
recent non–ST-segment elevation myocardial infarction (NSTEMI) or unstable angina benefit from DAPT for 9 to 12 months in terms of reduced risk of death, MI, or stroke, with an increased risk of bleeding, possibly related to aspirin doses >75 mg. In contrast to these positive findings in higher risk patients with recent IHD events, in the CHARISMA trial, DAPT with aspirin and clopidogrel did not reduce the risk of death, MI, or stroke among patients without established IHD but with multiple risk factors. A post hoc analysis of CHARISMA suggests that patients with prior MI, ischemic stroke, or symptomatic PAD might derive greater benefit from DAPT than lower-risk patients, but the role of DAPT in specific high-risk subgroups warrants further study before clear recommendations can be made. With this evidence, the 2012 SIHD guidelines conclude that treatment with aspirin 75 to 162 mg and clopidogrel 75 mg might be reasonable in certain high-risk patients with SIHD. While the newer agents ticagrelor and prasugrel have demonstrated reductions in major adverse cardiac events in the setting of acute coronary syndromes (ACS), their usefulness has yet to be tested in patients with SIHD.

**β-Blockers**

β-Blockers are indicated in the treatment of patients with a history of MI, IHD, and left ventricular dysfunction and in the management of stable angina. β-Blockers decrease heart rate, rate-BP product, and myocardial contractility, decreasing myocardial oxygen demand and cardiac work, and delay the onset of anginal symptoms. β-Blockers reduce death and recurrent MI among patients with a previous MI and are particularly effective in patients with ventricular tachyarrhythmias in the setting of an ST-segment elevation MI. The benefits of β-blockers in the setting of MI are based on studies that predate contemporary management strategies of early reperfusion and modern medical therapy. However, recent observational data suggest β-blocker therapy may be associated with reduced long-term mortality after PCI for acute MI and preserved systolic function. In SIHD, there is solid evidence to show that β-blockers relieve anginal symptoms and improve myocardial ischemia, and they are considered first-line agents for angina relief in the 2012 SIHD guidelines. However, there has not been an appropriately powered randomized controlled trial to determine if β-blockers
improve prognosis in patients with SIHD with normal left ventricular function and no prior MI. A recent analysis from the REACH registry examined the benefit of $\beta$-blockers in over 21,000 SIHD patients and found that $\beta$-blockade did not reduce the rate of CVD death, MI, stroke, hospitalization, or revascularization, even among potentially higher risk patients with prior MI. With the data available at the time, the 2012 SIHD guidelines gave a class I indication to $\beta$-blocker therapy for 3 years for all patients after MI or ACS.1

**Angiotensin-Converting Enzyme Inhibitors**

ACEi have a strong body of evidence to support their use in SIHD patients. The 2012 SIHD guidelines designate a class I recommendation to prescribe ACEi in all patients with SIHD who also have hypertension, diabetes, left ventricular ejection fraction ≤40%, or CKD, unless contraindicated.1 ACEi have pleiotropic effects and have been shown to decrease angiotensin II and increase bradykinin levels. It is thought that beneficial alterations in the balance between angiotensin II and bradykinin could account for reductions in left ventricular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis, along with improved left ventricular remodeling.1 Moreover, ACEi lead to beneficial changes in cardiac hemodynamics and the balance in myocardial oxygen supply and demand. Clinical studies have repeatedly demonstrated reductions in MI, unstable angina, and revascularization in patients after MI with left ventricular dysfunction, regardless of etiology.40 Notably, the benefits of ACEi extend to patients with SIHD without left ventricular dysfunction. The HOPE trial, a randomized controlled trial of ramipril in patients with vascular disease or diabetes and 1 additional CVD risk factor, demonstrated a 22% reduction in risk of death, MI, or stroke among patients receiving ramipril.41 The EUROPA trial further advanced support for the use of ACEi in SIHD without left ventricular dysfunction. In this randomized controlled trial of perindopril in SIHD without left ventricular dysfunction, ACEi demonstrated a 20% increase in the duration of time to an IHD event in patients with SIHD without clinical evidence of heart failure.42 While the benefits of ACEi in these 2 studies is noteworthy, other studies including PEACE, QUIET, and IMAGINE (a post-CABG study) presented conflicting evidence on the benefits of ACEi in SIHD without left
ventricular dysfunction. A 2006 meta-analysis of randomized controlled trials of ACEi in SIHD without left ventricular dysfunction demonstrated a 14% risk reduction in MI, a 23% reduction in stroke, and a 7% reduction in need for revascularization with the use of ACEi. The SIHD guidelines also find it reasonable to use ACEi for vascular protection for patients with SIHD or other vascular diseases (class IIa recommendation).

**Angiotensin Receptor Blockers**

Similar to ACEi, angiotensin receptor blockers (ARBs) also have an important role for vascular protection in patients with SIHD. The 2012 SIHD guidelines give a class I recommendation to support the use of ARBs in SIHD patients with hypertension, diabetes mellitus, left ventricular systolic dysfunction, or CKD who have indications for, but are intolerant of, ACEi therapy. Similarly, the SIHD guidelines find it reasonable to use ARBs in other patients who are ACEi intolerant (class IIa). ACEi and ARB have similar BP-dependent effects on risk of stroke, IHD, and congestive heart failure. Interestingly, however, ACEi appear to have BP-independent vascular benefits that are not observed with usage of ARB.

**Influenza Vaccination**

Influenza vaccination is an important therapy that can meaningfully impact morbidity and mortality in SIHD patients. The SIHD guidelines support annual influenza vaccination with a class I recommendation. Influenza contributes to higher risk for mortality and hospitalization and exacerbates underlying medical conditions. Randomized controlled trial evidence of influenza vaccination in SIHD patients does not exist. However, observational study evidence of influenza vaccination in SIHD demonstrated a nearly 40% mortality reduction with the influenza vaccine during winter months.

**IMPLEMENTATION**

Despite the clear benefit of lifestyle and pharmacologic interventions for
secondary prevention, gaps in the attainment of treatment goals for patients with SIHD continue to exist. The AHA and ACC have developed tools to assist in the attainment of guideline-directed goals. The AHA’s Get With the Guidelines and the ACC’s Guidelines Applied in Practice have made substantial progress in achieving specific benchmarks for the management of SIHD inpatients and outpatients, respectively. As an example, >95% of contemporary patients admitted with ACS are prescribed β-blockers, aspirin, and lipid-lowering therapy upon discharge. Over 90% of these patients also receive smoking cessation counseling. However, other evidence indicates continued room for improved use of guideline-directed medical therapy (GDMT) in the care of patients with SIHD. Using data from 2005 to 2009 in the National Cardiovascular Data Registry, Borden et al demonstrated that fewer than half of SIHD patients were receiving GDMT prior to elective PCI, and only two-thirds received GDMT prior to discharge following PCI. Using data from the REGARDS study, Brown et al recently showed that only 16% of REGARDS participants with a self-reported history of CAD met SIHD goals for aspirin, BP, and LDL cholesterol. Attainment of SIHD targets for physical activity and BMI was also low, at 25% and 22%, respectively. There is still a significant gap in the translation of evidence-based guidelines into practice.

**Improving GDMT in the Inpatient Setting**

Admission for an ACS or elective PCI provides an ideal opportunity to initiate GDMT. In 1 study, routine implementation of all secondary prevention guidelines was associated with reductions in 1-year mortality and recurrent MI. In addition to initiating GDMT, counseling on the importance of adherence with GDMT therapy should occur during an inpatient admission. During a hospital admission, SIHD patients and their family members may be more receptive to messages of behavior change and risk factor modification, such as adherence with prescribed therapy, than they may be as outpatients. Therefore, an inpatient admission can be used to emphasize the importance of behavior change and pharmacologic therapy as complementary to revascularization and as an integral part of IHD management. The ACC/AHA have codified recommendations to improve SIHD care on the individual and systems levels, during both inpatient and outpatient care episodes. These recommendations are summarized briefly
Implementation of these processes is often a multidisciplinary process that should include nurses, social workers, nutritionists, pharmacists, and exercise physiologists who should be assigned specific tasks for the patient’s care.\textsuperscript{50} Table 65-4 describes multiple ways in which the inpatient setting and the electronic medical record (EMR) can be used to improve health behaviors for SIHD patients. Another recommended use of the EMR is to routinely trigger referrals of SIHD patients for cardiac rehabilitation, an intervention that can significantly improve the prognosis for SIHD patients.\textsuperscript{1}

Table 65-3 Evidence-Based Approaches for Improving Health Behaviors and Health Factors in the Outpatient Setting\textsuperscript{46}

- Set specific, obtainable goals with a personalized plan to achieve them (e.g., over the next 3 months, increase fish by 1 serving/week).
- Establish self-monitoring. Develop a plan such as dietary or physical activity diary by web-based or mobile applications.
- Schedule regular follow-up (in-person, telephone, written, and/or electronic) with clear frequency and duration.
- Provide feedback on progress toward goals, including using in-person, telephone, or electronic feedback.
- Increase self-efficacy by increasing patient’s perception that he or she can successfully change his or her behavior.\textsuperscript{a}
- Use motivational interviewing when patients are resistant or ambivalent about change.\textsuperscript{b}
- Arrange long-term support of family, friends, or peers for behavior change in workplace, school, or community-based programs.
- Use a multicomponent approach combining 2 or more of the above strategies into the behavior change efforts.

\textsuperscript{a}Examples of approaches include mastery experiences (reasonable, proximal goals that can be achieved); vicarious experiences (see someone with similar capabilities performing the behavior); physiologic feedback (change in their symptoms is related to worse or improved behaviors); and verbal persuasion (persuasion that you believe in their capability to perform the behavior).

\textsuperscript{b}Motivational interviewing is the use of individual counseling to explore and resolve ambivalence toward behavior change. Major principles include fostering awareness and
resolution of ambivalence in a partnership with the counselor or provider.

**Table 65-4 Evidence-Based Approaches for Improving Health Behaviors in the Inpatient Setting**

- EMR systems for scheduling and tracking visits and follow-up contacts while an inpatient.
- EMR systems to help assess, track, and report on specific health behaviors.
- Paper or electronic toolkits for assessment of key health behaviors, during, before, and after provider visits.
- Electronic systems to provide patient feedback during behavior change and other treatment efforts.
- Provider education on evidence-based behavior change strategies, as well as behavioral targets.
- Efforts to integrate care systems to provide multidisciplinary care by teams of providers.

Abbreviation: EMR, electronic medical record.

**Improving GDMT in the Outpatient Setting**

The outpatient setting is key to the long-term attainment of GDMT and risk factor optimization. **Table 65-3** provides a summary of current evidence-based approaches to improve individual health behaviors in the outpatient setting. In addition to individual- and systems-level recommendations such as the use of EMR and standardized referral processes, the outpatient clinical setting can use specialty clinics to optimize risk factor management. If available, specialty clinics can optimize care of SIHD patients with cardiac rehabilitation programs, lipid clinics, hypertension clinics, and dietary consultation.

For a summary of the AHA/ACC guidelines for the management of patients with SIHD, see **Table 65-5**.

**Table 65-5 AHA/ACC Guideline Summary for the Management of Patients with SIHD**
Risk Factor Modification

Lipid Management

Class I

• Lifestyle
• Diet
• Statin therapy

Class II

• Bile acid sequestrants, niacin, or both for patients intolerant of statins

Blood Pressure Management

Class I

• Lifestyle modification
• Initiate therapy for BP >140/90 mm Hg
• ACEi, (ARB if ACEi intolerant), β-blockers, thiazide diuretics, or calcium channel blockers, target ≤140/90 mm Hg

Diabetes Management

Class IIa

• HbA1c <7% reasonable for diabetes of short duration or long life expectancy
• HbA1c 7%-9% reasonable depending on age and medical history/comorbidities

Class IIb

• Pharmacotherapy for HbA1c targets might be reasonable

Class III

• Rosiglitazone should not be initiated in SIHD

Physical Activity

Class I

• 30-60 minutes of moderate-intensity 5-7 days/week
• Physical activity history and/or exercise test recommended to guide prognosis and prescription
• Cardiac rehabilitation and home-based programs recommended for at-risk patients at first diagnosis

Physical Activity

Class IIa
• Resistance training 2 days/week is reasonable

Weight Management
Class I
• BMI and/or waist circumference, weight counseling, for BMI between 18.5 and 24.9 kg/m²
• Initial weight loss goal between 5% and 10% from baseline

Smoking Cessation Counseling
Class I
• Smoking cessation and avoidance of tobacco at work and home encouraged for all SIHD patients
• Ask, Advise, Assess, Assist, Arrange, Avoid recommended for cessation counseling

Additional Medical Therapy to Prevent MI and Death

Antiplatelet Therapy
Class I
• Aspirin 75-162 mg daily should be continued indefinitely for SIHD in the absence of contraindications
• Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD

Class IIb
• Aspirin 75-162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk SIHD patients

Class III
• Dipyridamole is not recommended as antiplatelet therapy for SIHD patients

β-Blocker Therapy
Class I
• β-Blocker for 3 years in all patients with normal LV function after MI or ACS
• β-Blocker for all patients with LV systolic dysfunction (LVEF ≤40%) with heart failure or prior MI

Class IIb
• β-Blockers may be considered for chronic therapy for all other patients with coronary or vascular disease
**Renin-Angiotensin-Aldosterone Blocker Therapy**

*Class I*
- ACEi prescribed for SIHD patients with hypertension, diabetes mellitus, LVEF ≤40%, or CKD unless contraindicated
- ARBs are recommended for SIHD patients who are intolerant of but have indications for ACEi (above)

*Class IIa*
- ACEi is reasonable for SIHD patients with other vascular diseases
- It is reasonable to use ARBs in other patients who are intolerant of ACEi

**Influenza Vaccination**

*Class I*
- An annual influenza vaccine is recommended for SIHD patients

Abbreviations: ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AHA, American Heart Association; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SIHD, stable ischemic heart disease.

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MULTIPLE CHOICE QUESTIONS

1. What is the most appropriate initial medical therapy to reduce low-density lipoprotein (LDL) cholesterol in among patients with stable ischemic
heart disease (SIHD)?
A. Lowest tolerated dose statin
B. High-intensity statin
C. Ezetimibe
D. Niacin
E. At least 30-60 minutes of moderate-intensity daily aerobic activity

2. Which of the following is true for patients with SIHD and a blood pressure (BP) of 140/90 mm Hg or higher?
A. Specific medications used for treatment of high BP should be based on patient characteristics.
B. All patients should be counseled about the need for lifestyle modification.
C. Antihypertensive drug therapy should be instituted for a BP of 140/90 mm Hg or higher in addition to or after a trial of lifestyle modifications.
D. All of the above

3. What can be expected from intensive glucose control in patients with SIHD?
A. Reduced risk of microvascular disease
B. Reduced risk of myocardial infarction
C. Reduced risk of death
D. Reduced risk of hypoglycemia
E. If achieved with rosiglitazone, risk of cardiovascular complications is reduced

4. Which statement below is true about physical activity for patients with SIHD?
   a. Moderate-intensity physical activity is recommended for 20 minutes 3 times per week.
   b. Participation in cardiac rehabilitation reduces mortality risk by 20%.
   c. Physical activity lowers LDL cholesterol.
   d. The risk of sudden death associated with exercise is 1 in 10,000 patient-hours.

5. What is the class I indication for prescribing an angiotensin-converting
enzyme(ACE) inhibitor for SIHD?
A. Hypertension
B. Diabetes
C. Left ventricular ejection fraction ≤40%
D. Chronic kidney disease
E. All of the above

ANSWERS

1. B

Data from randomized clinical trials have demonstrated that lowering of LDL cholesterol is associated with a reduced risk of cardiovascular events and support intensive LDL cholesterol lowering in patients with SIHD. High-intensity statin therapy includes atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily. Compared to lower doses and lower potency statins, randomized trials have demonstrated a consistent benefit in event reduction with use of high-intensity statins.

2. D

In many patients with SIHD, the choice of medications is guided by compelling indications for specific classes of drugs, and effective BP lowering is the most important factor in preventing stroke or myocardial infarction. Treatment of high BP should begin with lifestyle measures, as weight loss, diet, reduction in sodium intake, and regular physical activity have all been shown to reduce blood pressure. In addition to lifestyle measures, antihypertensive drug therapy will frequently be needed to reach the currently accepted target of BP <140/90 mm Hg.

3. A

Numerous studies have found that intensive glycemic control reduces microvascular complications of diabetes. Recent clinical trials in patients with SIHD, however, have failed to show a reduction in myocardial infarction or mortality. Tighter glucose control is associated with a higher risk of hypoglycemia. Rosiglitazone is associated with an excess risk of
cardiovascular complications and should not be initiated in patients with SIHD.

4. B

The SIHD guidelines recommend 30-60 minutes of physical activity 5-7 days per week for all patients (class I). A meta-analysis of 48 randomized controlled trials of exercise interventions of a median of 3 months in duration (95% CI, 0.25-30 months) and with 15 months of follow-up (95% CI, 6-72 months) demonstrated an overall 20% reduction in all-cause mortality and a 26% reduction in total cardiac mortality. Exercise does not lower LDL cholesterol, but it facilitates weight loss and has other beneficial cardiometabolic effects. Exercise in patients with SIHD is safe, with a rate of major adverse cardiac events (MACE) of approximately 1 in 80,000 patient-hours.

5. E

It is a class I recommendation to prescribe an ACE inhibitor to patients with SIHD who also have hypertension, diabetes, LVEF ≤40%, or chronic kidney disease. Angiotensinreceptor blockers have a class I indication for SIHD patients with hypertension, diabetes, LVEF ≤40%, or chronic kidney disease who are intolerant of ACE inhibitors.
Appropriate Use Criteria for Revascularization

Lloyd W. Klein

The Appropriate Use Criteria for Revascularization (AUC) is a vital instrument supporting high-quality interventional practice that presents, in a pragmatic format, the optimal application of the evidence base and existing guidelines to patient selection for percutaneous coronary intervention (PCI). It is a meaningful response to concerns of overutilization, serves as a quality metric, and establishes the relative roles of coronary artery bypass graft surgery (CABG) and medical therapy in patients with both stable ischemic heart disease (SIHD) and acute coronary syndromes (ACS). The original AUC\(^1\) and a focused update\(^2\) set the standard of practice regarding optimal patient selection for PCI. The AUC has broad implications for the future of cardiovascular health care, especially in regard to case selection, treatment options, and reimbursement. In the future, it will become the foundation for tethering payment decisions and quality assessment to patient-centered therapeutic decision making. Limitations of the first version have been extensively articulated, and a subsequent revision has been published to improve the criteria so they more meticulously take into account how interventional cardiologists evaluate scientific data and apply those conclusions to individual revascularization decisions.

WHY DO APPROPRIATE USE
CRITERIA EXIST?

Today’s generation is the recipient of a myriad of astonishing bioengineering, pharmacologic, and technical innovations over the last 3 decades. These advancements have resulted in the growth and maturity of a new field of treatment for coronary artery disease (CAD). The exponential growth in the number of PCI procedures has resulted in an unprecedented escalation in the cost of health care: approximately 600,000 PCIs are performed in the United States each year\(^3\) at a cost exceeding $12 billion. However, this expense is not accompanied by a measurable outcomes benefit.\(^4\) Moreover, the wide geographic variability of the use of PCI in the United States\(^5,6\) has been interpreted as a demonstration that patients are not being referred for the procedure strictly based on scientific evidence. The divergence in cost versus benefit logically demands a formal evaluation of PCI utilization.

The value of PCI in ACS (ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [NSTEMI], and unstable angina) has been definitively demonstrated: by eliminating the causative coronary obstruction, PCI significantly reduces mortality and recurrent myocardial infarction in this setting. However, in SIHD, there is no proven survival benefit or reduction in subsequent myocardial infarction versus medical therapy. PCI in this circumstance reduces or relieves angina but does not contribute to improvement in hard end points. Furthermore, since patients who undergo PCI are exposed to the risk of periprocedural complications, including death, stroke, bleeding, and myocardial infarction, a judicious approach to case selection is required. Deciding which patients are likely to benefit from PCI is as much a matter of clinical judgment as the application of clinical evidence (clinical trials, registries, meta-analyses, retrospective studies confirmed by additional data).\(^7\) In contemporary practice, the decision of whether PCI, medical therapy, or bypass surgery should be the primary strategy in a given patient can no longer be made based simply on the number of vessels diseased, as it was in the past.\(^8\) Not every patient with a hemodynamically significant stenosis, a positive stress test, or angina experiences improved survival or better angina relief from PCI compared to other treatment modalities. For example, in patients with SIHD, PCI provides only a modest population-average improvement in symptom relief compared with medical therapy.\(^9\) No patient wants to endure the pain
and recuperative process of surgery if there is no incremental benefit; conversely, no patient will accept the cost and hassle of multiple medications and their adverse effects if there is a better alternative. Further, it is reasonable to avoid expensive procedures unless there is some measurable improvement over other options. Because it is not possible to quantitatively scale the expected advantages versus the inherent drawbacks and risks, which ultimately is an individual subjective determination, there is no objective way to compare the different rates of success and adverse events of each treatment method; thus, clinical judgment requires an individual assessment in every case.

It is important that expert practitioners set parameters and then determine the extent to which PCI is performed for appropriate versus inappropriate indications to identify procedural overuse and areas for quality improvement and cost savings. Therefore, a means of evaluating the clinical appropriateness of PCI is necessary; good outcomes and high operator volumes alone are not sufficient to define high quality. These surrogate measures in isolation encouraged the performance of large volumes of low-risk procedures of uncertain appropriateness and the avoidance of high-risk but properly selected cases. Concern regarding overutilization is a crucial issue the profession must address if it is to continue to enjoy the privileges of self-referral and self-regulation. Other potential advantages of specific criteria to guide appropriate case selection are also apparent, including providing guidance for clinicians and patients in making difficult decisions, enabling comparison of a laboratory’s or operator’s outcomes versus a national benchmark, assisting in providing the “right therapy at the right time,” and upholding a patient-centered approach.

In contrast to practice guidelines, which summarize published data to classify levels of utility, or performance measures, which distill the guidelines into specific actions that should be taken programmatically, the AUC integrate the guidelines, clinical trial evidence, and clinical experience to specify what clinical decision is usually optimal. The AUC define the strength of the indications for a procedure, weighing both its benefits and drawbacks. The goal of the AUC is to guide decision making by clarifying expected benefits in specific clinical situations. In 2009, the AUC for coronary revascularization were published, and in 2011, rates of appropriateness in the National Cardiovascular Disease Registry (NCDR)
were reported.\textsuperscript{14} A focused update reflecting updated comparative data between bypass surgery and PCI was published in 2012.\textsuperscript{2} Another update was published after this chapter was submitted. It contains substantial changes that will be reflected in the online version of this book.

**BACKGROUND**

Ethical decision making requires of every physician that procedures should not be performed unless they offer potential benefit to the patient; this principle has been an accepted tenet of medicine since the Hippocratic Oath. How to define benefit and how clinical decisions should be evaluated in this context are constantly changing features of modern medicine. In regard to PCI, the initial notion underlying balloon angioplasty was that the treatment of any single high-grade coronary stenosis that was technically feasible offered benefit over medications. In 2006, the OAT trial demonstrated that not all recent occlusions opened percutaneously had improved outcomes, and this provocative trial was followed the next year by the COURAGE trial,\textsuperscript{9} which suggested that optimal medical therapy in multivessel SIHD may produce similar hard end point outcomes (death, myocardial infarction, and stroke) as complete revascularization with stenting. With the development of drug-eluting coronary stents and improved catheter and guide wire technology, it has become even more ambiguous which patients are best treated with pharmacology, bypass surgery, or a percutaneous procedure. Consequently, the nuances and complexity of determining when a PCI is and is not appropriate is a controversial and active area of investigation.

The first large-scale investigation of an evidence-based classification to define appropriateness studied the relationship between the American College of Cardiology (ACC)/American Heart Association (AHA) recommended indications for PCI and short-term in-hospital outcomes and was performed using data from the NCDR.\textsuperscript{15} After excluding STEMI, the remaining 412,617 PCIs were grouped by indication class: class I, evidence and/or agreement that PCI is useful and effective; class IIa, conflicting evidence and/or divergent opinions, weight is in favor; class IIb, usefulness/efficacy is less well established; and class III, evidence and/or agreement that PCI is not useful or effective and may be harmful. Frequency of indications was as follows: class I, 64%; class IIa, 21%; class IIb, 7%; and class III, 8%. Clinical
success declined across the indication classes (92.8%, 91.7%, 89%, and 85.5% for class I, IIa, IIb, and III, respectively; \( P < .001 \)), whereas adverse events increased. The results of this study demonstrated that most procedures were performed for class I indications and that a significant relationship existed between evidence-based indications recommended by the ACC/AHA Task Force and in-hospital outcomes. The authors concluded that closer adherence to guidelines can reduce variations in care and improve quality and may ultimately result in better outcomes.

In a follow-up study,\(^{16}\) the outcomes in each indication class were evaluated after risk adjustment by the NCDR risk adjustment model. A total of 559,273 PCI procedures were analyzed. Increasing frequencies of risk components were observed across classes I, IIa, IIb, and III. Expected mortalities for each class calculated by the risk adjustment model were close to observed values (expected 0.52%, 0.59%, 1.72%, and 1.96%, respectively; observed 0.49%, 0.63%, 1.88%, and 1.60%, respectively). Thus, the ACC-NCDR risk-adjusted mortality model, when linked to the ACC/AHA PCI guidelines, produced mortality risk estimates by indication class close to actual observed values. The critical implication of this finding was that the model, together with the PCI guidelines, could be used as a powerful analytic tool for quality assurance and assessment of the appropriateness of case selection. Indeed, the recognition that the flipside of the development of an accurate risk prediction model for PCI is its application to quality assurance was the crucial step in the evolution to AUC.

### APPROPRIATE USE CRITERIA FOR REVASCULARIZATION

The essential rationale for the AUC is to provide an evidence-based, clinically applicable assessment of procedural appropriateness without regard to financial considerations or socioeconomic status. The ACC convened a committee to develop AUC derived from the PCI guidelines. The process chosen combined evidence-based medicine, guidelines, and practice experience by engaging a technical panel in a modified Delphi exercise as previously described by RAND.\(^1,17\) The technical panel was composed of 4 interventional cardiologists, 4 cardiovascular surgeons, 8 general
cardiologists and other physicians who treat patients with cardiovascular disease or health outcome researchers, and 1 health plan medical officer (also a physician). One hundred eighty scenarios illustrative of commonly observed clinical situations were developed by a writing committee and scored by the separate technical panel on a scale of 1 to 9. Scores of 7 to 9 indicated that revascularization was considered “appropriate” and likely to improve health outcomes or survival. Scores of 1 to 3 indicated revascularization was considered “inappropriate” and unlikely to improve health outcomes or survival. The mid-range (score of 4-6) indicated a clinical scenario for which the likelihood that coronary revascularization would improve health outcomes or survival was considered “uncertain.” These categories are those mandated by the RAND process. For the majority of the clinical scenarios, the panel only considered the appropriateness of revascularization irrespective of whether this was accomplished by PCI or CABG. In a select subgroup of clinical scenarios in which revascularization was generally considered reasonable, the appropriateness of PCI and CABG individually as the primary mode of revascularization was considered.

Because SYNTAX\textsuperscript{18} had not been published in a peer review format at the time of the meeting of the technical panel (November 2008), the initial document\textsuperscript{1} was written explicitly to concur with the existing guidelines (Figs. 66-1 and 66-2). A revised focused update was later published\textsuperscript{2} that incorporated the SYNTAX results (Fig. 66-3).
FIGURE 66-1 Appropriate Use Criteria in acute coronary syndromes. The fact that the use of coronary revascularization for a particular condition is listed in this figure (appropriate, uncertain, or inappropriate) does not preclude the use of other therapeutic modalities that may be equally effective. See the most current American College of Cardiology/American Heart Association UA/NSTEMI and STEMI guidelines.\textsuperscript{15,16} A, appropriate; CAD, coronary artery disease; HF, heart failure; I, inappropriate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; U, uncertain; and UA/NSTEMI, unstable angina/non–ST-segment elevation myocardial infarction. (Reproduced from Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC Appropriateness Criteria for Coronary Revascularization. \textit{J Am Coll Cardiol.} 2009;53:530-553, Copyright © 2009, with permission from American College of Cardiology Foundation.)
<table>
<thead>
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<th>Symptoms Med. Rx</th>
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**Coronary anatomy**

- CTO of 1 vz.; no other disease
- 1-2 vz. disease; no Prox. LAD
- 1 vz. disease; Prox. LAD
- 2 vz. disease with Prox. LAD
- 3 vz. disease; no Left Main

**Coronary anatomy**

- CTO of 1 vz.; no other disease
- 1-2 vz. disease; no Prox. LAD
- 1 vz. disease; Prox. LAD
- 2 vz. disease with Prox. LAD
- 3 vz. disease; no Left Main
**FIGURE 66-2** Appropriate Use Criteria in patient with stable ischemic heart disease and noninvasive test result. A. Appropriateness ratings by low-risk findings on noninvasive imaging study and asymptomatic (patients without prior bypass surgery). B. Appropriateness ratings by intermediate-risk findings on noninvasive imaging study and CCS class I or II angina (patients without prior bypass surgery). C. Appropriateness ratings by high-risk findings on noninvasive imaging study and CCS class III or IV angina (patients without prior bypass surgery). A, appropriate; CCS, Canadian Cardiovascular Society; CTO, chronic total occlusion; I, inappropriate; Int., intervention; Med., medical; Prox. LAD, proximal left anterior descending artery; Rx, treatment; U, uncertain; vz., vessel. (Reproduced from Patel MR, Dehmer
The decision to perform coronary revascularization is correctly based on a multitude of factors, including the presence of a stenosis-producing ischemia, the severity of symptoms, application of medical therapy, objective evidence of ischemia, the volume of myocardium at jeopardy, the presence of viable myocardium with the potential for reversible dysfunction, and the demonstration of significant coronary stenoses that are treatable with current techniques. Each of these conditions requires substantial testing to demonstrate, and their interrelationships are notably variable.

<table>
<thead>
<tr>
<th>Two-vessel CAD with proximal LAD stenosis</th>
<th>CABG</th>
<th>PCI</th>
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<tr>
<td>Three-vessel CAD with low CAD burden (ie, three focal stenosis, low SYNTAX score)</td>
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<tr>
<td>Three-vessel CAD with intermediate to high CAD burden (ie, multiple diffuse lesions, presence of CTO, or high SYNTAX score)</td>
<td>A</td>
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<tr>
<td>Isolated left main stenosis</td>
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<tr>
<td>Left main stenosis and additional CAD with low CAD burden (ie, one to two vessel additional involvement, low SYNTAX score)</td>
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<tr>
<td>Left main stenosis and additional CAD with intermediate to high CAD burden (ie, three vessel involvement, presence of CTO, or high SYNTAX score)</td>
<td>A</td>
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The failure to find a quantitative method that resolves the uncertainty that attends the subjective interpretation of angiograms impacts the selection of patients for interventional procedures. Coronary angiography is widely recognized to have many imprecisions, especially with a stenosis in the intermediate range, yet it remains the primary diagnostic tool. Adding a physiologic measure of stenosis severity to angiographic assessment enhances the accuracy of diagnosis and optimizes the selection of patients for expensive and risky treatment options. The structure of the AUC is predicated on an assumption that the size of a defect on nuclear scans can be used as the standard for assessing the significance of a stenosis and the amount of myocardium subtended by a critical stenosis.

For purposes of describing the severity of symptoms, the Canadian Classification was used. To define optimization of medical therapy, an assumption was made that at least 2 antianginal drugs constituted a pragmatic clinical definition of “optimal medical therapy,” as described in COURAGE.19

Two different formats were used to summarize the voting results. An algorithmic or decision-tree approach was chosen for the ACS indications, while a matrix method was chosen to summarize the SIHD portion.

**USE OF THE AUC AS A REPORT CARD**

A multicenter, prospective study of all PCI patients within NCDR undergoing PCI between July 1, 2009, and September 30, 2010, at 1091 US hospitals was undertaken.14 The appropriateness of PCI was adjudicated using the AUC. Of 500,154 total PCIs, 355,417 (71.1%) were for ACS (STEMI, 103,245 [20.6%]; NSTEMI, 105,708 [21.1%]; high-risk unstable angina, 146,464 [29.3%]), and 144,737 (28.9%) were for SIHD. In ACS, 350,469 PCIs (98.6%) were classified as appropriate, 1055 (0.3%) as uncertain, and 3893 (1.1%) as inappropriate. For SIHD, 72,911 PCIs (50.4%) were classified as appropriate, 54,988 (38.0%) as uncertain, and 16,838 (11.6%) as inappropriate. The majority of inappropriate PCIs for SIHD were performed in patients with no angina (53.8%), low-risk ischemia on noninvasive stress testing (71.6%), or suboptimal (≤1 medication) antianginal therapy (95.8%). Furthermore, although variation in the proportion of inappropriate PCI across hospitals was minimal for acute procedures, there was substantial hospital
variation for PCI in SIHD (median hospital rate for inappropriate PCI, 10.8%; interquartile range, 6.0%-16.7%). Overall, the rate of inappropriate PCI was 4.1%; hospitals in the lowest quartile had inappropriate PCI rates of ≤1.73% versus ≥4.62% for the highest quartile hospitals.

The New York State Registry corroborated these findings generally in patients with SIHD. In this mandatory state registry, 14% of PCI patients were found to have inappropriate AUC classification, confirming that a small but definite incidence of inappropriate PCI is not a spurious observation. Furthermore, 28% of all PCIs performed in the state lacked sufficient noninvasive test information to be rated. Most concerning was the relatively low percentage (36.1%) of patients undergoing PCI classed as appropriate by AUC.

Bradley et al evaluated the association between patient selection for PCI and postprocedural outcomes. In 203,531 patients undergoing elective PCI, the association between a hospital’s proportion of nonacute PCIs categorized as inappropriate by the 2009 AUC and in-hospital mortality, bleeding complications, and use of optimal guideline-directed medical therapy at discharge (ie, aspirin, thienopyridines, and statins) was evaluated. When categorized as hospital tertiles, the range of inappropriate PCI was 0.0% to 8.1% in the lowest tertile, 8.1% to 15.2% in the middle tertile, and 15.2% to 58.6% in the highest tertile. Compared with lowest-tertile hospitals, mortality was not significantly different at middle-tertile (adjusted odds ratio [OR], 0.93; 95% confidence interval [CI], 0.73-1.19) or highest-tertile hospitals (OR, 1.12; 95% CI, 0.88-1.43; P = .35 for differences between tertiles). Similarly, risk-adjusted bleeding did not vary significantly (middle-tertile OR, 1.13; 95% CI, 1.02-1.16; highest-tertile OR, 1.02; 95% CI, 0.91-1.16; P = .07 for differences between tertiles) nor did use of optimal medical therapy at discharge (85.3% vs 85.7% vs 85.2% for lowest, middle, and highest tertile, respectively; P = .58). Thus, a hospital’s proportion of inappropriate PCIs was not associated with in-hospital mortality, bleeding, or medical therapy at discharge. This finding suggests PCI appropriateness measures aspects of hospital PCI quality that are independent of operator or technical quality. Therefore, PCI appropriateness and postprocedural outcomes are both important metrics of PCI quality. However, PCI appropriateness was not associated with in-hospital survival.

In a follow-up study, the demographics underlying inappropriate PCI as defined by the AUC were evaluated. Of 211,254 nonacute PCIs, 25,749
(12.2%) were classified as inappropriate. After multivariable adjustment, men (adjusted OR, 1.08; 95% CI, 1.05-1.11; \( P < .001 \)) and whites (adjusted OR, 1.09; 95% CI, 1.05-1.14; \( P < .001 \)) were more likely to undergo an inappropriate PCI in comparison with women and nonwhites. Compared with privately insured patients, those who had Medicare (adjusted OR, 0.85; 95% CI, 0.83-0.88), other public insurance (adjusted OR, 0.78; 95% CI, 0.73-0.83), and no insurance (adjusted OR, 0.56; 95% CI, 0.50-0.61) were less likely to undergo an inappropriate PCI (\( P < .001 \)). In addition, compared with urban hospitals, those admitted at rural hospitals were less likely to undergo inappropriate PCI, whereas those at suburban hospitals were more likely. Thus, for nonacute indications, PCIs categorized as inappropriate were more commonly performed in men, whites, and patients with private insurance. The authors concluded that higher rates of PCI in these patient populations might either reflect potential overuse in privileged patients or underuse in disadvantaged populations. Both are problematic: inappropriate procedures expose the patient to unnecessary risk, while underuse in disadvantaged patient groups leads to disparities in care.

**REACTION TO THE USE OF THE AUC FOR QUALITY ASSESSMENT**

Unfortunately, the AUC and its use as a quality metric have become sources of controversy and dispute. Pervasive media attention was unleashed with publication of the NCDR analysis that labeled 4.1% of PCIs in the United States as “inappropriate.” The media, and much of the lay public, were especially drawn to the finding that 11.6% of nonacute, elective PCIs were classified as inappropriate and, additionally, to the wide variation in the rates of inappropriate nonacute PCI across hospitals (0%-50%). These circumstances led to claims that billions of dollars are being spent on completely unnecessary procedures. Superimposed on widely reported fraudulent behavior on the part of a very few but high-profile PCI operators, widespread concern was raised.

The reaction of the interventional community was to assert that there were 3 problems that rendered the study conclusions incorrect: (1) the NCDR members who contributed the data were unaware that auditing for this
The purpose was ongoing, and therefore, the contributed data were not necessarily accurate; (2) the study results merely reflect the flaws of the AUC and do not capture accurately decision making for revascularization; and (3) labeling procedures performed as “inappropriate” is provocative terminology that is actually incorrect; these procedures likely had indications that were not captured by the AUC. To some extent, each of these criticisms has merit. However, the fundamental finding does reflect quite accurately that PCI is being performed in some SIHD patients for indications outside the evidence base. The critical question raised is whether some of the reasoning employed in clinical decision making went unrecognized in the AUC, altering appropriateness determinations in a substantial number of cases. Although perhaps inaccurate when applied to a small minority of specific, individual cases, given the intention to measure quality, falling inside or outside the normal distribution (95% CI, 3%-25%,) should correctly reflect the overall reasoning of appropriateness used.

LIMITATIONS OF THE CURRENT VERSION OF THE AUC

A large number of cases cannot be classified by the AUC, because either a stress test is not available (50% of unclassifiable cases, 8.5% of all PCIs in the NCDR) or the magnitude of ischemic risk is not documented (42% of unclassifiable cases, 7.2% overall). This high percentage of unclassifiable cases threatens the accuracy of the process and represents a loophole in the methodology. The utilization of the terminology “inappropriate” connotes not merely the lack of supportive evidence but rather the presence of negative studies, which was not true in many of the scenarios graded by the technical panel. Moreover, the technical panel conceived “inappropriate” as being related to specific clinical trial evidence of improved mortality and not to the more difficult to objectify measures of improved quality of life and other symptomatic benefits. The “uncertain” classification may also indicate a meaning at odds with its intent: that the appropriateness could not be definitively classified within existing medical knowledge or the current structure of the AUC. The high rate of uncertain indications for elective PCIs
(38%) suggests that more research is needed to clarify the benefits of PCIs for those patients. To clarify these meanings, the AUC nomenclature will be changed going forward: “uncertain” is now described as “may be appropriate” and “inappropriate” as “rarely appropriate.”

The current PCI AUC are matrix based, which sets a few variables as critically important and not modifiable by other factors known to be influential in actual practice, such as age, patient preference, and desire to improve quality of life. The rigid grading system based on just a few criteria that labels a substantial number of procedures as “inappropriate” even when extenuating circumstances may exist, despite the possibility that additional clinical information not captured in the SIHD matrix may be critically important, may lead to incorrect appropriateness assessment.24 Each patient poses a distinct set of variables to consider, and the overlapping indications and conflicting caveats may reasonably result in disparate decision making, depending on one’s emphasis. Some inappropriate or uncertain indications may actually be appropriate, and some appropriate indications may be inappropriate, when taking into account unique clinical and patient factors.

Reliance on the presence and size of stress test imaging modalities, which are not quantitative methods, to evaluate the amount of myocardium at jeopardy, to the exclusion of the coronary angiogram, has raised numerous concerns.8,23,25 Nuclear and echocardiographic stress tests are not quantitative methods and may be inaccurate in particular circumstances; for example, with multivessel disease, with prior infarction, and when target level of physiologic stress is not achieved. Although based on the nuclear substudy of COURAGE,9 the elevation of a retrospective association between outcomes and the size of thallium defects to the level of being the final arbiter of the volume of myocardium at jeopardy and hence, appropriateness, exceeds the authors’ intent and interpretation.26,27 The angiographic demonstration of a 90% proximal stenosis in a dominant right coronary artery is a more accurate assessment of myocardial jeopardy than a “small” inferior defect. In contemporary intervention, the use of fractional flow reserve (FFR) in ambiguous scenarios is now regarded as best practice. The amount of myocardium at jeopardy as assessed angiographically and the use of FFR to assess stenosis severity will very likely be recognized as the gold standards in the next version.24,28 Moreover, with the increasing utilization of coronary computed tomography angiography to detect stenoses noninvasively, it may
be anticipated that stress testing will be less utilized diagnostically in the future.

One of the most controversial aspects of the AUC process is that just 4 of the 17 technical panel members were interventional cardiologists. Marso et al. suggested that the composition of the technical panel likely impacted the AUC ratings significantly. In a follow-up study evaluating concordance with the AUC, most physicians agreed with most of the ratings; however, there was substantial variability. In one particular scenario, that of patients with less than 3-vessel disease with minimal symptoms and on <2 medications, there were significant differences with the AUC voting. This discrepancy exists because mortality is the primary clinical benefit evaluated in clinical trials and was the main outcome considered by the technical panel; future iterations should include consideration of angina relief and quality of life, which are outcomes in which PCI offers substantial advantages.

Most of the acute cases that were labeled as inappropriate by AUC criteria were STEMI patients who were registered as stable and asymptomatic and had PCI performed >12 hours from symptom onset. In SIHD, the majority of inappropriate PCIs occurred in patients who had 1- to 2-vessel coronary disease that did not involve the proximal left anterior descending artery, were on no anti-ischemic therapy, had no or mild angina symptoms, and had low-risk noninvasive studies for ischemia.

A general list of 10 ways to improve a catheterization laboratory’s or operator’s appropriateness score is given in Table 66-1. In particular, it should be recognized that the vast majority of inappropriate scores occur when the patient is taking <2 antianginal medications, has no or low degree of ischemia, and/or has no angina.

Table 66-1 Ten Ways to Improve Appropriateness

| • Study your cases classified as inappropriate or uncertain to determine why each case was scored as it was. |
| • Know the 5 clinical scenarios responsible for 89% of inappropriate elective cases and especially the 3 scenarios describing 82%: none or few symptoms, normal or low-risk stress test, and ≤1 antianginal agent. |
| • Make sure whoever is responsible for coding is filling in the forms correctly, by prospective review, retrospective audit, and ongoing |
education. Take filling out the forms seriously and take ownership of the process.

- Know the Canadian Classification of angina, especially the difference between class II and class III.
- Use medical therapy when appropriate; 2 or more antianginal drugs put the case in a higher category; 96% of inappropriate cases do not use ≥2 drugs.
- State the stress results concisely and clearly in the documentation.
- Know and include data from outside hospitals.
- Use fractional flow reserve in borderline lesions.
- Use the Appropriate Use Criteria for Revascularization in your practice in real time and teach it in educational conferences.
- Recognize the proven value, and the limitations, of percutaneous coronary intervention in clinical practice: Know the evidence base, follow the guidelines, and recognize exceptions without hiding behind them to rationalize when you do not follow them.

With widespread dissemination of this material and the development of tools within most catheterization laboratories to assure adherence, it is unclear whether the AUC still accurately measures appropriateness. The possibility of “gaming” the criteria and the absence of a requirement for strict documentary proof in classification are loopholes of great concern. Another concern is that some PCI in multivessel SIHD is performed after surgeons have declined to operate out of apprehension for high risk, a condition that is not captured in the NCDR.

There is also increasing concern that the AUC as formulated have never been linked to outcomes, as described earlier, even though the original concept was linked to outcome. A recent study from a single institution did not link PCI appropriateness, as determined by the AUC for coronary revascularization, with 30-day or 1-year outcomes. In a cohort of non-ACS patients including 3817 patients in their analysis, 47% (n = 1494) of the cases were considered appropriate, 1.8% (n = 54) were inappropriate, and 51% (n = 1604) were uncertain. Despite similar procedural complications in the 3 groups, a significantly higher rate of in-hospital complications was observed in the inappropriate PCI group (inappropriate, 11%; appropriate, 1.9%; uncertain, 2.4%; $P < .001$). However, this did not translate to a higher rate of
major adverse cardiac events at either 30 days (inappropriate, 7%; appropriate, 3.2%; uncertain, 4.1%; \(P = .32\)) or 1 year (inappropriate, 11.8%; appropriate, 13.1%; uncertain, 15.3%; \(P = .32\)). In multivariable analysis, no associations were observed between procedural appropriateness and either inhospital or 1-year outcomes.

### ADDITIONAL APPROACHES TO APPROPRIATENESS: SCORECARDS AND BENCHMARKING

There have been public reporting and scorecard systems in place in various states for many years. The development of the “Hospital Compare” and, more recently, the “Physician Compare” websites has further expanded public reporting for hospitals and providers. It has never been studied objectively whether these modalities alter referral patterns or incentivize patients away from less expert centers or individuals, and there have been questions raised as to what is their purpose. Although no one can criticize the right of consumers to know more about the person and program to whom they are placing their lives in trust, it is doubtful that the average person comprehends the nature of risk assessment or how to use the figures reported to make rational choices.\(^{31}\) Most lay people, often including hospital administrators, believe that the highest quality operator will have zero mortality, not realizing that adverse outcomes are in fact primarily influenced by high-risk case selection, not competence. The “optimal” goal actually should be in the mid-range of risk-adjusted events.\(^{11}\) Accordingly, there is concern that public reporting impedes the aggressive use of PCI in high-risk but appropriate cases with patients who have no other reasonable options, yet underutilization in these patients is not usually conceived as a significant problem.\(^{32}\)

The NCDR CathPCI Registry, in its quarterly reports to participants, assesses AUC in PCI procedures and benchmarks these to a national reference point.\(^{33}\) The major message from the initial experience is that the indication for every PCI case, particularly those in nonacute clinical scenarios, should be carefully considered and scrutinized. Programs and operators need to be attentive to appropriate documentation of the patient
symptom complex, presentation, ischemic evaluation, anatomy, and whether the patient is on optimal medical therapy.

Duffy\textsuperscript{34} has proposed equating “real value” with appropriateness (Table 66-2). He suggests that appropriateness as currently described is just 1 factor that expresses the value of PCI; the others include clinically defined outcomes, patient-expected outcomes, and relative cost. The fact that a number of factors of great importance in clinical decision making (patient age, comorbidities, patient wishes, cost, ability to take medications, and the risk of the procedure) are not considered in the AUC is cited as a flaw. Defining the “real value” of a procedure would be the preferable route (see Table 66-2).

Table 66-2 Value: New Criteria of Appropriateness

| • How much does the benefit of this procedure (or approach to care) outweigh the risk? |
| • How much will this person’s quality of life improve? |
| • How much will it reduce long- and short-term morbidity (future complications)? |
| • How much will it extend this person’s life expectancy with the quality of life anticipated? |


Nallamothu et al\textsuperscript{35} recently developed a set of performance measures dedicated to PCI focused primarily on elective PCI. They include both accountability measures, which are acceptable for public reporting and for facilitating comparisons across providers, and quality improvement measures, which are intended to drive internal quality improvements. The 4 quality measures include the need for an appropriate indication for elective PCI, based on the AUC. The 7 performance measures involve comprehensive documentation before and after the procedure of variables associated with improved short-term outcome.

**IMPLICATIONS FOR**
Reimbursement for revascularization will likely soon be dependent on its appropriateness, which will be assessed using the AUC or a close modification. Since the AUC and its structure were never intended as a means to determine payment for procedures, there is substantial trepidation within the interventional community over its application for this purpose. Whether or not criteria originally intended for quality assessment and professional improvement can be transferred and accurately used for denial of payment is unexplored. Moreover, as pay-for-performance and other connections between quality and reimbursement are advocated and developed, the flaws in the AUC, which were understandable in a first version, could result in incorrect assessments of operator quality, with significant repercussions for all involved. When the AUC were initially developed, the intention was for application to broad quality assessment; the determination in a particular case was less critical than whether the overall performance of an operator or a laboratory was within 2 standard deviations of the mean. If the AUC did not adequately capture the reasoning for a particular procedure, although annoying, it had no important consequence, but that would no longer be apposite if third-party payers can disallow payment because of an inconsistent stress test result or a low class of angina.

The widespread apprehension is whether, after creating an inflexible matrix of factors that define appropriateness, there is sufficient room in their interpretation to game these criteria and diminish their discrimination (eg, size of stress test defect or number of antianginal medications). The fear all along has been whether physicians, who understand very well the vagueness of such indicators, will continue to be objective in reporting them, recognizing that reimbursement depends on the answers. But further, if the appropriateness decision is made by a person whose job is to find ways to save expenses for a third-party payer, could this vagueness be gamed by insurers and used as an excuse to deny payment even when PCI was appropriate, a fear complicated when administrative rather than medical databases are used to obtain these data.

In 2013, the New York State Medicaid Fee for Service and Medicaid Managed Care disallowed payment for elective cases categorized as rarely appropriate. New York State is also planning a retrospective analysis to
provide the foundation for requesting repayment for cases deemed “inappropriate” performed prior to that date based on the state’s interpretation of the AUC. Payments would be recouped before any medical review is conducted. Analysis would be based on the state’s administrative database and its own algorithm. These initiatives may be just the first step in which the AUC is used by regulatory agencies to link payment to appropriateness.

The Centers for Medicare & Medicaid Services (CMS) has announced a new Recovery Audit Contractor demonstration program to assess whether Medicare payments are going toward procedures that are medically appropriate and necessary.37 This program was implemented in 11 states for a 3-year period starting January 2012. The program is an attempt to revise the current “pay and chase” model of tracking down improper Medicare payments after the fact. The theory is that the most effective way to limit the amount of taxpayer dollars lost to improper payment is to review the medical record and other supporting documentation for the claim before the billing is paid. To date, CMS has given no details as to what “medically appropriate and necessary” criteria they use, whether it is based on the current published guidelines, including the AUC, or a formula of their own choosing.

FUTURE DIRECTIONS

Evaluating the procedural appropriateness of PCI is a complex undertaking requiring comprehensive patient assessment and documentation. The expected benefit associated with all 3 of the available therapeutic approaches varies widely from patient to patient, and a fundamental part of the physician’s job is to determine—based on clinical experience and a grasp of the current medical literature—which treatment is most appropriate for the patient at hand. Moreover, the benefits are usually not homogeneous throughout every population. Even if studies show that a procedure is beneficial for an overall study population, the benefit may be large for some subgroups and negligible (or even harmful) for others. How to incorporate these factors into a quality metric is problematic.

Table 66-3 summarizes the myriad considerations that should go routinely into decision making for revascularization. Although it is probably impossible to construct a decision tree or algorithm that covers every conceivable situation, future iterations of the AUC must do a better job...
simulating the decision making process in order that the physician’s judgment and the patient’s desires and best interests are placed in the forefront. In this regard, the concepts of “value” and “cost-effectiveness” may add significantly to the resolution of the controversy. The most important appropriate use approach is complete and accurate communication of potential risks and benefits of a particular procedure. Clinical judgment and comprehensive patient communication should always be the guide. There will be times when what is best for the individual patient is at variance with AUC and other guidance documents, and future versions of the AUC should incorporate this understanding in its structure.

Table 66-3 Factors Influencing Revascularization Appropriateness

1. Documentation of the presence and anatomic severity of coronary stenosis (angiography, intravascular ultrasound)
2. Correlation with physiologic metrics of stenosis severity (stress testing, fractional flow reserve)
3. Presence, recent changes, and severity of anginal symptoms
4. Triggers of angina
5. Utilization of antianginal medications
6. Prior coronary artery bypass graft or percutaneous coronary intervention?
7. Patient age and activity/stress levels (eg, frailty)
8. Exercise duration
9. Comorbid conditions/life expectancy
10. Complete versus incomplete revascularization
11. Risk of the procedure
12. Does the patient want/is patient able to try medications first? (ie, expected patient compliance)
13. What are the patient’s short- and long-term goals of therapy? (eg, elderly)
14. Which outcomes/benefits can be anticipated? (eg, survival, improved quality of life, diminished angina, less congestive heart failure, presence of viable myocardium, or substantial myocardium at jeopardy)
CONCLUSIONS

The importance of the AUC to the future of public health policy and the role of PCI in treating CAD cannot be overstated. There is increasing recognition by most members of the interventional community that the long-time reliance on operator volume and complication rates as the sole criteria for PCI quality promoted unprecedented growth and expansion, but also resulted in unanticipated negative consequences, including high cost with little population-level outcome benefit, especially in SIHD. Additionally, overutilization by a few ethically challenged individuals superimposed on the unavoidable ambiguity of appropriate case selection and formal indications resulting from continually improving technology, greater technical experience, and limitations in trial design has, understandably, raised serious questions by those who pay for the procedures. The ongoing delay in establishing and standing by criteria for appropriateness creates a vacuum that outside organizations now threaten to fill, by developing their own criteria to regulate the field. Moreover, given the lack of confidence in the current AUC, CMS and other agencies have attempted to define appropriateness, but thus far, these have been mainly superficial and primarily economically inspired. Future versions of the AUC will hopefully successfully address these complex and critical issues.

The vast majority of PCIs are performed in patients who meet criteria that suggest potential benefit based on the existing evidence base. However, the data also show that there are opportunities to improve patient selection for PCI, as well as to design future studies that evaluate outcome benefits of PCI other than mortality and provide objective evidence that properly impacts clinical decision making. Reversing our failure thus far to develop and faithfully implement a system that accurately evaluates interventional decision making and that is truly focused on improving outcomes for our patients is the single most pressing challenge we face. How our profession responds will characterize our field for years to come.

Note: After submission of this chapter a new update to the AUC was issued and the revised chapter will reflect these changes in the online version of this book. Among the changes are new nomenclature for classification: appropriate, may be appropriate and rarely appropriate. Also a new panel was assembled to vote on classification resulting in fewer scenarios falling into
the rarely appropriate category.\textsuperscript{38}

REFERENCES


502.


**MULTIPLE CHOICE QUESTIONS**

1. A 64-year-old man presents to the emergency department with a history of chest pain that began 2 days ago and has now been worsening for the past 3 hours. Electrocardiogram (ECG) shows ST elevations in leads II,
III, and aVF and ST depressions and T inversions in V₁ to V₃. The patient is taken to the cath lab immediately and found to have a 100% occlusion of the right coronary artery, a 70% stenosis of the first obtuse marginal (OM1) branch, and an 80% stenosis of the proximal left anterior descending artery (LAD). The occluded right artery is stented successfully. The operator then proceeds to stent the LAD and OM1 branches. How would the appropriateness of the interventions on the nonculprit lesion be classified?
A. Appropriate
B. May be appropriate
C. Rarely appropriate
D. Indeterminate

2. A 72-year-old man with hypertension and hypercholesterolemia presents with stable angina for 3 months. He is able to walk 3 blocks before getting tired. ECG shows Q waves inferiorly. Medications include aspirin, a β-blocker, and a statin. A stress test shows a fixed inferior defect. Cardiac catheterization shows a 100% occlusion of a very large OM branch filling by collaterals from a diagonal and no other significant disease. The ejection fraction is 45% with an akinetic inferior wall. PCI and stenting of the OM is successful. At 1-month follow-up, the chest pain syndrome has resolved. How would the appropriateness of this procedure be classified?
A. Appropriate
B. May be appropriate
C. Rarely appropriate
D. Indeterminate

3. A 58-year-old attorney presents with severe chest pain that occurs only when he is in court. He is able to play racquetball at his club and golf on the weekends without limitation. He smokes 1 pack per day, has hypertension, and has never had a lipid panel checked. He takes a baby aspirin but refuses to take β-blockers due to erectile dysfunction or nitrates due to headache. Stress nuclear test shows ischemia, with an intermediate risk defect of the anteroapex. Coronary angiography shows a proximal 80% stenosis before the first septal branch and minimal nonobstructive disease in other segments.
Part 1: If a stent was placed, how would the appropriateness of this procedure be classified?
   A. Appropriate
   B. May be appropriate
   C. Rarely appropriate
   D. Indeterminate

Part 2: If fractional flow reserve was performed and was calculated to be 0.78, then how would the appropriateness of stenting be classified?
   A. Appropriate
   B. May be appropriate
   C. Rarely appropriate
   D. Indeterminate

4. An 85-year-old nondiabetic man presents with mild edema consistent with congestive heart failure. He has no chest pain or exertional symptoms. An echocardiogram shows an ejection fraction of 40% with global hypokinesis and moderate mitral insufficiency. The ECG shows left bundle branch pattern. After diuresis and vasodilator therapy are initiated, he improves significantly. Coronary angiography shows significant obstructive disease of all 3 arteries amenable to either stenting or bypass surgery. Which of the following statements is NOT true?
   A. He is not an optimal candidate for coronary artery bypass graft (CABG) due to his age and decreased cardiac function; therefore, multivessel PCI is preferred.
   B. If his SYNTAX score is not low, CABG is a preferable option.
   C. There is insufficient information given to decide on which revascularization strategy, or optimal medical therapy, is best.
   D. There is no rationale to performing a stress test, since it will be highly abnormal, confirming the findings of the angiogram.

5. A 55-year-old man presents with a history of experiencing a single episode of chest pain while on a 30-mile bike ride with friends and family this past weekend and has had no symptoms since then. He has no risk factors and is in excellent health. An ECG shows nonspecific ST changes. He is taken immediately to the cath lab and found to have a 90% mid-LAD coronary stenosis, which is stented. How would the appropriateness
of this procedure be classified?
A. Appropriate
B. May be appropriate
C. Rarely appropriate
D. Indeterminate

ANSWERS

1. C
Nonculprit lesion percutaneous coronary intervention (PCI) at the time of ST-segment elevation myocardial infarction (STEMI) in the absence of hemodynamic compromise is classified as rarely appropriate by the Appropriate Use Criteria, which were developed before Preventive Angioplasty in Acute Myocardial Infarction (PRAMI).

2. C
This patient has no stress test, is not on at least 2 antianginal medications, and is asymptomatic. Performing PCI of a chronic total occlusion in this setting cannot be rationalized.

3. Part 1: B; Part 2: A
It is not possible to know if PCI is warranted based only on the angiogram, according to the Appropriate Use Criteria, since maximal medical therapy has a high likelihood of treating symptoms in this setting. Since this is a proximal LAD stenosis, it would be considered as “may be appropriate.” However, when the fractional flow reserve is performed and shows the lesion to be significant, then stenting is appropriate.

4. C
Age alone does not exclude a patient from candidacy for CABG if frailty, either mental or physical, does not exist. A low SYNTAX score signifies that either PCI or CABG may be reasonable. One can not intuit the findings of a stress test from the coronary anatomy alone since the stress results also integrate medical therapy, exercise tolerance, and conditioning. Either PCI or
CABG may be reasonable in this patient, and medical therapy may also be a judicious strategy if this patient is not an optimal candidate for dual antiplatelet therapy or a surgical procedure.

5. D

It is not possible to know if the stenosis is or is not significant based only on the angiogram, according to the Appropriate Use Criteria. A stress test is required, or it cannot be classified. Even a 90% angiographic finding is insufficient, according to the Appropriate Use Criteria.
Part VII  Preclinical and Clinical Trials

- 67 Preclinical Laboratory Functions
- 68 Cell Therapy for Cardiovascular Diseases
- 69 The Core Laboratory: Quantitative Coronary Angiography
- 70 Reading Clinical Trials
- 71 Publishing Interventional Cardiology Research
Although innovators brainstorm ideas for novel therapies often while working in the clinical setting, these ideas see the earliest translation into reality in the preclinical laboratory. The goal of the preclinical lab is to provide hands-on testing in the animal model to guide focused revisions of a new device or treatment. This is the realm in which devices and treatments move beyond basic prototype, into early versions of an eventual finished product for clinical use in patients. These early versions get tested, revamped, and retested, with the goal of evaluating feasibility, safety, and efficacy. The preclinical lab is also a common ground where interventional cardiologists, engineers, veterinarians, scientists, and industry can meet to collaborate.

The goal of this chapter is to review some of the important requirements of a preclinical laboratory and suggest insights into what makes a preclinical lab successful in the current landscape of translational cardiovascular research.

**HISTORICAL FOUNDATIONS OF THE INTERVENTIONAL PRECLINICAL LABORATORY**
Although animal studies have historical roots over millennia, the field of interventional cardiology and the vital role of the preclinical interventional cardiology lab can be directly traced back to Andreas Gruentzig, the first interventional cardiologist. Gruentzig developed percutaneous coronary balloon angioplasty, building on the work of Mason Sones, Charles Dotter, and Melvin Judkins. In 1958 during an aortogram, Mason Sones inadvertently cannulated and performed an angiogram of the right coronary artery, ultimately demonstrating the diagnostic potential of coronary angiography.

Subsequently, Charles Dotter in 1963 inadvertently recanalized an occluded right iliac artery when he was obtaining access to the abdominal aorta for an aortogram in a patient with renal artery stenosis, demonstrating the potential for transluminal angioplasty. In 1964, Judkins (Dotter’s trainee) and Dotter conducted the first intentional and successful transluminal angioplasty of a short superficial femoral artery stenosis for a patient with a gangrenous toe and nonhealing ulcer who refused surgical intervention. After learning the Dotter technique, Gruentzig added balloons to the Dotter catheters (ultimately iterating until he developed a polyvinylchloride-based double lumen catheter). Between 1972 and 1975, he performed peripheral balloon angioplasty in animals and then transitioned to humans. By 1976, Gruentzig had revised his device to a size appropriate for coronary intervention and continued to demonstrate feasibility, safety, and efficacy of his prototype in the preclinical lab. Specifically, Gruentzig performed a partial ligation of the circumflex artery via thoracotomy in a canine model. He then performed angiography to demonstrate the stenosis as well as to measure the transstenotic pressure gradient. He positioned his balloon at the stenosis and intervened on it by inflating the balloon until he broke the ligature, ultimately resolving the stenosis and the transstenotic pressure gradient. These results were presented at the American College of Cardiology meeting in 1976 in Miami, Florida (Fig. 67-1). By 1977, Gruentzig successfully performed the first human use of coronary angioplasty in a 38-year-old patient with focal, proximal left anterior descending artery stenosis in the setting of unstable angina and positive stress testing. This constituted the invention of the field of interventional cardiology as we know it today, demonstrating the vital role of the preclinical lab.
Since that time, the preclinical interventional cardiology lab has become a mainstay in the vertical integration of the device-based innovation process. The flow from idea to engineering to bench top testing to reengineering to animal lab testing to reengineering and finishing with further animal lab testing was demonstrated by Gruentzig; it has since flourished worldwide.

With foundations in the preclinical lab, many significant device-based contributions to the field of cardiovascular medicine have been developed, ranging from vascular, to hemodynamic, to structural, to electrophysiologic. Given the continuously evolving field of invasive cardiology and the ethos of innovation in the field, preclinical labs have had to evolve in lock step with technologic advancement. For example, some preclinical labs have been focused mainly on coronary disease models, and their accompanying diagnostics and interventions. However, with the rise in structural interventions such as transcatheter aortic valve replacement, mitral interventions, and ventricular assist devices, the expertise of the lab must
evolve to meet the demands of both the new disease models and the new diagnostics/therapeutics to be assessed.

ENVIRONMENT FOR THE INTERVENTIONAL PRECLINICAL LABORATORY

There are currently a number of preclinical interventional cardiology labs across the world. Most either currently operate within or had roots in the academic medical setting. Given the interdisciplinary demands of the type of work done in the interventional cardiology preclinical lab, the academic environment is naturally conducive to it. Innovators can brainstorm with colleagues from different specialties and capitalize on diverse expertise by collaborating across different departments, such as engineering and chemistry. Additionally, university-based administrative groups can assist with management of regulatory issues and contracts.

However, the infrastructure and often bureaucratic nature of the academic setting has not traditionally been designed to function optimally under conditions in which entrepreneurial hands are involved. Specifically, most academic settings have not evolved to provide services to those who comprise the majority of “customers” to the interventional cardiology preclinical lab—often small and large industry partners.

The goal of research sponsored by industry is to generate data in their research and development path, often focused on feasibility, safety, or efficacy. For example, an innovator backed by a small corporate sponsor may have a novel mitral annular repair device that they bring to the preclinical lab for proof-of-concept testing in animals; then after device improvements, they return for further efficacy and safety testing in animals. The generated safety and efficacy data are used for submission in the United States to the Food and Drug Administration as part of an Investigational New Device filing.

With these types of research goals, there are 3 main hurdles that often arise for the typical party wanting to perform translational research in the academic preclinical lab: (1) costs (institution-wide overhead/indirect costs), (2) contractual obligations (intellectual property and publication rights), and (3) regulatory obligations (extended timing for regulatory approval of animal
studies). For example, to investigate the feasibility of a new percutaneous ventricular assist device in a swine systolic heart failure model, an inventor may be burdened with a 50% overhead/indirect cost to the university, may have to sign over all intellectual property and publication rights from the research, and may sink months of time attempting to obtain Institutional Animal Care and Use Committee approval to start the experiment. Although the lab may be incentivized to be involved with cutting edge work, the infrastructure in this example is burdensome. Although some academic centers understand the importance and benefits of such research and are devising new means to accommodate research needed by corporate entities, many are either unable or unwilling to make the necessary adjustments.

Given the practical demands of device development in the United States, the academic interventional preclinical lab requires 3 interconnected types of outputs to thrive and be sustainable: academic, teaching, and industry. While these outputs ideally function together seamlessly, a tailored infrastructure is required to ensure that each aspect is prioritized. If a laboratory’s aim is only academic output, then it is dependent on only traditional and shrinking funding sources for survival. If only industry output is focused on, then the ethos of the lab may be lost. Additionally, as adapted from Suzuki et al, the role of the animal lab should be not only in device development but also in training clinicians in optimal techniques involving new procedures. This diversified approach allows for financial sustainability and academic creativity; however, achieving this trifecta is not an easy task. Academic preclinical labs must face the growing competition of preclinical labs based at independent research institutions, which often have streamlined systems in place to accommodate the accelerating demands of the modern preclinical lab customer. Such environments can be designed to prioritize the needs of the biomedical device, pharmaceutical, and biotechnology industries, while maintaining high academic standards.

**FACILITIES AND EQUIPMENT**

With advances in interventional cardiology spanning vascular to structural disease as well as expansion into hybrid procedures with surgical colleagues, there now exists both a new minimum requirement for preclinical labs as well as opportunity for specialization depending on the research goals of the
institution. Overall, the appearance of the preclinical interventional laboratory resembles that of a clinical cardiac catheterization laboratory. In terms of the various levels of diagnostic capabilities required, this can be preliminarily categorized into vascular versus structural work.

At a minimum for vascular work, a large-animal cardiac catheterization suite is needed, because the core of translational research in our field is the testing of interventional vascular devices and associated drug or biotechnology therapies in clinically relevant, large-animal preparations. Fluoroscopy remains the primary method of imaging for angiography and experimental intervention. For intraluminal assessment, quantitative coronary angiography (QCA) is a basic tool for accurate vessel measurement in the sizing of stent implants and angioplasty balloon catheters. Comprehensive hemodynamic assessment must be possible in order to perform diagnostic evaluation of catheterization procedures but also for basic safety requirements. This includes measurement of left- and right-sided cardiac pressures and cardiac output. Other ancillary equipment items such as activated clotting time (ACT) machines, infusion pumps, and similar apparatus may seem like minor details, but are necessary for a fully functional lab. Figure 67-2 shows a typical preclinical catheterization laboratory.
For structural work, although not previously a mainstay in all preclinical labs, echocardiography is now an essential adjunct both for the analytical assessment of cardiac function and dimensions and as guidance for catheter-based procedures such as endoventricular intramyocardial injection. There are important roles for the various echocardiographic modalities: intracardiac echocardiography (ICE) offers a unique viewpoint from within the cardiac chambers that can assist in real-time navigation during intervention; transthoracic echocardiography (TTE) offers guidance and monitoring of cardiac structure and function before, during, and after an intervention; and transesophageal echocardiography (TEE) offers similar guidance but with enhanced views and resolution. Although less used these days, ventriculography and its associated hardware and software needs are still a requirement. The addition of hardware and software for pressure-volume loop analysis is an additional tool that can help quantify physiologic impacts of interventions throughout the cardiac cycle. Additional newer technologies that provide insight into the performance of intravascular devices and the nature of the vessel wall include intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near-infrared (NIR) spectroscopy. Although not a requirement, the data obtained using these methods can help to differentiate the value of new technologies in the maturing market of intravascular interventions. Finally, magnetic resonance imaging (MRI) and computed tomography (CT) imaging can be of incredible utility if there is a dedicated program to optimize the output from these diagnostics. For example, MRI with contrast agents such as gadolinium or manganese can be used to assess structure, function, pathology, and benefits of interventions, such as stem cell implantations. With advances in hybrid structural procedures, a hybrid suite with dual surgical and interventional capabilities will likely become a necessity in the near future. Figure 67-3 shows a typical preclinical surgical suite, and Figure 67-4 shows a typical preclinical MRI suite.
FIGURE 67-3 Preclinical surgical suite.
Additionally, there are a number of other resources that may be needed based on the device being tested. In the academic setting, these can often be found via interdisciplinary collaboration; a prearranged setup is ideal. To analyze tissue/devices postmortem in the preclinical lab, the ability to prepare, process, analyze, and capture the histologic analysis digitally is necessary. Histologic evaluations of blood vessels, myocardium, and other tissues implanted with devices or other experimental treatments frequently
provide critical data in preclinical research studies (Fig. 67-5).

**FIGURE 67-5** Histology of stented arteries. A. Portion of plastic-slide histotechnology laboratory: (1) water bath; (2) Leica heavy-duty microtome; (3) slide review station; (4) Exakt precision grinder. B. Light microscopy of hematoxylin and eosin–stained methacrylate section of pig coronary artery fixed 1 month after implant of polymer-coated metal stent; remnant of polymer coating (arrows) is seen in stent-strut void (S).
Finally, there are a number of specific intervention-based diagnostic and therapeutic competencies that are required based on the trajectory of the specific preclinical lab. These may include capabilities to evaluate device or vessel thrombogenicity and vasomotor reactivity, assess biochemical components, perform cell and tissue culture, determine gene expression patterns, and potentially fulfill other research needs. One particularly timely example is with regard to the development of stem cells for post–ST-segment elevation myocardial infarction implantation in the left ventricle. Additional core competencies to achieve this will be required on the basic science side. In addition, specific equipment, such as guiding catheters to navigate the ventricle, will also be required. Each of these facilities and equipment requirements are unique to the particular analytic approach; the extent to which they are required depends on the degree of sophistication applied to the study design.

It is important to realize that especially since the preclinical lab interfaces with earlier stage research than the technology used in the clinical lab, it must constantly and aggressively adapt to meet the advancing needs of the innovative research investigator.

**PERSONNEL**

One of the most important aspects of a successful preclinical lab is the staff who run it. The ideal staff are hard-working problem-solvers who are smart, experienced, dedicated, and enthusiastic. The culture of the lab is set by the senior staff who run it, so the selection of these people cannot be underestimated. The current competitive environment of device development demands that a “customer service” approach is taken; otherwise, innovators need not hesitate to select competitor preclinical labs. The reputation of a lab is also paramount. Many researchers will select a lab to work with based on reports of prior experiences from colleagues, so each encounter, whether small or large, must be approached with the utmost professionalism, responsiveness, and attention to detail.
THE MISSION: CONDUCTING TRANSLATIONAL RESEARCH

The preclinical lab plays an essential role in the translation of idea to usable device for humans. In the current environment of device development, this role is becoming progressively challenging to fulfill. Financial burdens, compliance with federal regulations, finding appropriate personnel, and adapting to the rapidly changing demands of the field are just some of the daily challenges that a preclinical lab faces. However, the mission of the preclinical lab remains of utmost importance: to provide the means to perform translational research, such that ideas can be transformed into new effective treatments to improve the care of patients suffering from cardiovascular disease.

REFERENCES

INTRODUCTION

Ischemic heart disease and heart failure continue to be the predominant causes of morbidity and mortality worldwide. Acute myocardial infarction is the most common cause of heart failure and triggers a series of cellular and molecular changes leading to apoptosis, necrosis, hypertrophy of cardiomyocytes, impaired neovascularization, interstitial fibrosis, inflammation, reduced contractility, and pathologic remodeling.\(^1\) Despite advances in medical and device therapy, hospitalization rates and mortality for heart failure continue to remain high, with 1 in 5 patients dying within 12 months of diagnosis.\(^2\) Medical therapy has centered on the treatment of underlying risk factors and on the initiation of antiplatelet, lipid-lowering, $\beta$-adrenergic receptor, and angiotensin antagonist therapy. Interventions designed to facilitate cardiovascular regeneration were not initially pursued because it was assumed that the adult heart is a terminally differentiated postmitotic organ where the number of cardiomyocytes are established at birth, with no potential for regeneration after damage.\(^3\)

Over the last 2 decades, irrefutable evidence has emerged that challenges these concepts due to the discovery of a population of bone marrow–derived
and resident progenitor/stem cells that promote cardiomyocyte and vascular renewal and proliferation. It is now clear that human cardiomyocytes renew throughout a person’s lifespan at a rate that decreases from 1% annual turnover at age 25 to 0.45% at age 75 years.\(^4\) Regeneration of infarcted myocardium requires massive cell replenishment, possibly in the order of a billion cardiomyocytes together with functional integration with supporting cell types.\(^5\) The adult heart, however, has a relatively low number of cardiac progenitor cells with a low proliferation rate that cannot compensate for the large losses of cardiomyocytes seen after an acute myocardial infarction. Cell-based therapies offer a novel strategy to repair and regenerate injured and nonviable cardiac and vascular tissue.

In the past decade, there has been an influx of clinical trials investigating the safety and efficacy of both autologous and allogeneic stem/progenitor cells for cardiovascular repair and regeneration. To date, phase I and phase II cell therapy trials have been conducted in patients with refractory angina pectoris, acute myocardial infarction, ischemic and nonischemic heart failure, and peripheral vascular disease. While a variety of cell types and delivery techniques have been used, the majority of clinical trials have used a catheter-based approach to target delivery of cells to areas of ischemia or dysfunction. Herein we will review potential mechanisms of action of stem cells, mechanisms of cellular delivery, and cell types currently being studied for cardiovascular regeneration, and review ongoing clinical trials. Characteristics of stem cells being investigated in cardiovascular cell therapy are summarized in Table 68-1.

Table 68-1 Characteristics of Stem Cells Used in Cardiovascular Cell Therapy
MECHANISMS OF ACTION

Mechanisms by which cell therapy leads to cardiovascular repair and regeneration remain a subject of controversy (Fig. 68-1). Although differentiation or transdifferentiation into new cardiac or vascular cells was initially believed to be the primary mechanism, recent studies suggest that stimulation of endogenous precursor cells, secretion of growth factors and cytokines (paracrine effect) that promote vasculogenesis and prevents apoptosis, or rarely, fusion of donor cells with host cells may be potential mechanisms. Together, these cellular changes result in enhanced perfusion, reduced infarct size, improved left ventricular remodeling, and ultimately improved cardiac function and patient mortality.
FIGURE 68-1 Potential mechanisms underlying the cardioprotective actions of stem cells: differentiation into cells of cardiac lineages; activation of antiapoptotic signaling; promotion of angiogenesis and reendothelialization; paracrine effects on resident progenitors and myocytes leading to cellular proliferation; and favorable paracrine effects on the extracellular matrix. (Reproduced from Sanganalmath SK, Abdel-Latif A, Bolli R, Xuan YT, Dawn B. Hematopoietic cytokines for cardiac repair: mobilization of bone marrow cells and beyond. Basic Res Cardiol. 2011;106:709-33, with permission from Springer.)

CELL DELIVERY

The main objective of cell therapy is to deliver the ideal concentration of cells needed for cardiac regeneration with the lowest risk to the patient. The clinical setting and underlying cardiac pathology influence local signaling and affect transplanted cell survival and retention. Currently, stem cells can be delivered for cardiac diseases into the coronary arteries or veins, systemically by intravenous injection, or by direct intramyocardial injection using open surgical or transendocardial approaches (Table 68-2).
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td></td>
</tr>
</tbody>
</table>
| 1. Intravenous infusion                       | Cells are delivered intravenously. Relies on physiologic homing signals for cells to home to injured tissues.  
*Disadvantages:* Lower level of cell delivery to target areas. |
| 2. Intracoronary artery administration        | Cells delivered directly to myocardial regions via standard angioplasty balloon catheter into coronary artery lumen with either (1) balloon deflated or nonocclusive or (2) stop-flow method using intermittent balloon arterial occlusion. In the stop-flow method, the balloon is placed at the site of the former infarct-vessel occlusion. With the balloon inflated at low pressures for 2 to 4 minutes, 2 to 3 mL of cell suspension is infused. Balloon inflation prevents backflow of cells while facilitating infusion of cells into the infarcted zone.  
*Advantages:* Direct infusion into areas of interest and homogenous cell engraftment.  
*Disadvantages:* Cannot deliver cells into occluded arteries. Large cells may cause embolization of coronary microvasculature. Modest cell retention rates compared to intramyocardial injection. |
| 3. Catheter-based intramyocardial administration | Cells are delivered via a percutaneous catheter either transendocardially or by transcoronary venous injection.  
*Advantages:* Less invasive than surgical injection. Procedure can be repeated over time.  
*Disadvantages:* Increased risk of perforation. |
| 3a. Transendocardial injection                | Injection needle catheter is advanced retrograde across the aortic valve and positioned against the endocardial surface. Often combined with catheter mapping systems to localize delivery to viable, ischemic, or scarred myocardium. |
| 3b. Retrograde transcoronary venous Injection  | Injection needle catheter is advanced into the coronary sinus through the right atrium. Cells are injected directly into the myocardium.  
*Advantages:* Utilizes the venous system. Offers alternative delivery mechanism for patients with occluded coronary arteries. |
| 4. Direct surgical intramyocardial injection   | Cells are injected into infarct border zones or ischemic or infarcted myocardium under direct visualization during open revascularization procedures.  
*Advantages:* Allows targeting of localized myocardium without disturbing surrounding tissue and vasculature.  
*Disadvantages:* Invasive procedure with increased risk to patient. |
| 5. Engineered monolayer tissue transplantation | Cells are mounted on physical scaffolds to enhance cell adherence and survival. Multiple materials are under investigation. Can be implanted epicardially or by myocardial injection.  
*Advantages:* Novel solution to poor cell engraftment and survival.  
*Disadvantages:* Regulatory and rejection hurdles. |
| **Peripheral Vascular Disease**               |                                                                                                                                              |
| Intramuscular                                 | Cells are directly injected into affected muscles of the lower extremity. Goal is to create a collection of cells with paracrine activity in the ischemic area. The fate of injected cells is unknown, and cell retention rates vary between 0.44% and 10% after 4 days. Cells are either injected in a symmetric grid with a fixed number of injections in the ischemic muscle or along the occluded native arteries. The latter approach benefits from preformed collaterals, which have the highest density parallel to the axial arteries.  
*Advantages:* Direct delivery of large numbers of cells to target areas. |
| Intra-arterial                                | Cells are directly injected into occluded arteries of the lower extremity. Target limb arteries were selectively cannulated through a transfemoral approach with an over-the-wire catheter balloon that is advanced as distally as possible and positioned proximal to the occlusive vascular lesions, typically at the distal femoral or popliteal artery. At this point, the balloon is inflated to block antegrade blood flow, and the cells are slowly infused over 3 minutes. After infusion, the balloon is deflated, and antegrade blood flow is restored.  
*Advantages:* Direct infusion into areas of interest and homogenous cell engraftment.  
*Disadvantages:* Difficult to deliver cells to areas subtended by occluded arteries. |
Intravenous infusion of stem cells is associated with the lowest rates of cell retention. Even in the setting of acute myocardial infarction where local release of cytokines enhances homing of stem cells, the majority of intravenously infused cells become trapped in the pulmonary, hepatic, and splenic microvasculature, and few reach areas of infarcted myocardium. Moreover, the size of stem cells affects delivery to target areas, with a greater percentage of larger mesenchymal stem cells (20 μm) being trapped in the pulmonary vasculature than smaller bone marrow mononuclear cells (7 μm).

Intracoronary infusion circumvents the pulmonary and hepatic first-pass effect by delivering cells directly into target areas of myocardium and is the most common strategy used in acute myocardial infarction trials. After over-the-wire positioning of a balloon catheter in the stented area of the infarct-related artery, coronary blood flow is stopped for approximately 2 to 4 minutes by inflation of the balloon at low pressures while the cell product is infused into the coronary artery (stop-flow technique). Mechanistically, cessation of flow maximizes contact between stem cells and the microcirculation of the infarct-related artery and optimizes cellular “homing time”; however, studies have demonstrated conflicting results. Advantages include direct infusion into the infarct and peri-infarct territory, but intracoronary infusion of larger mesenchymal stem cells has been associated with embolization of the microvasculature. Finally, uptake of stem cells into the ischemic myocardium is considerably lower than that achieved by intramyocardial delivery but is better than intravenous administration.

Percutaneous retrograde delivery via the coronary sinus is an alternative method for delivery of cellular products. Although only a few studies have used it for the delivery of stem cells, this technique has been used for many years to deliver cardioplegic solutions during cardiovascular surgery and for protection against myocardial ischemia in patients undergoing high-risk percutaneous coronary intervention. The technique involves placement of a catheter into the coronary sinus via cannulation of either the internal jugular or femoral vein. A single or double balloon is inflated, followed by infusion of the cell product for 5 to 30 minutes at a pressure approximately 20 mL higher than sinus pressure. In comparison to other methods of cell delivery, retrograde coronary sinus delivery appears to be safe, allow for more homogenous delivery across the myocardium, and have similar retention rates to intramyocardial delivery. This technique also allows for delivery of
stem cells to ischemic areas of myocardium in patients with occlusive coronary artery disease and severe subtotal aortic stenosis.\(^{14}\)

Transendocardial injection is performed percutaneously with retrograde advancement of the injection-needle catheter across the aortic valve and positioned against the endocardial surface. Cells are injected directly into the desired endocardial surface by advancing a small-caliber injection needle into the myocardium.\(^7\) Injection sites may be localized to the desired segment of the myocardium by mapping catheter systems. The NOGA injection catheter (Myostar; Cordis Corporation, Miami Lakes, FL) enables 3-dimensional electromechanical mapping of the left ventricle and provides real-time voltage and linear shortening data for delivery of transendocardial injections. In humans, normal regional myocardial function is indicated by high electrical activity and high local linear shortening. The presence of an abnormal or low unipolar potential (≤6 mV) and impaired mechanical activity (low linear shortening ≤4%) is interpreted as abnormal electromechanical activity and characterizes infarcted areas. When mechanical activity is impaired but electrical activity is normal or near normal, the area of interest can represent ischemic, stunned, or hibernating myocardium (Fig. 68-2).\(^{15}\)

Direct intramyocardial cell delivery can also be performed under direct visualization during coronary bypass surgery or using a percutaneous laparoscopic approach (mini-thoracotomy).\(^{16}\) Although these techniques are more invasive and associated with adverse effects, including perforation and pericardial effusion, cell retention is greatest with intramyocardial injection, and higher numbers of cells can be injected without risk of downstream embolization.\(^{17}\) While routinely used in clinical trials in patients with chronic heart failure (Table 68-3), its safety has not been studied in the setting of acute myocardial infarction, where injured myocardium is more vulnerable to rupture.\(^7\)
FIGURE 68-2 Unipolar voltage and local linear shortening maps with the corresponding 2-dimensional quantitative polar maps. Red color indicates the normally low unipolar voltage at the base of the heart (mitral valve area) with concomitant loss of electrical activity at the basal septal and anterior regions and akinesis in the entire septal wall and partial akinesis in the anterior wall. Blue color indicates a normal voltage signal (normal myocardium), whereas green and yellow colors indicate decreased viability and wall motion at the infarct border zone, respectively. The obvious discrepancy between viable myocardium and severe wall motion disturbance in the anteroseptal areas suggests the presence of hibernating myocardium. Brown points represent the locations of the NOGA-guided intramyocardial injections at the border zone of infarction, in diaphragmatic septal areas. LLS, local linear shortening; RAO, right anterior oblique.\textsuperscript{15} (Reprinted by
permission from Macmillan Publishers Ltd: Gyongyosi M, Dib N. Diagnostic and
prognostic value of 3D NOGA mapping in ischemic heart disease. *Nat Rev Cardiol.*
2011;8:393-404.)

**Table 68-3** *Summary of Clinical Trials of Stem Cell or Progenitor Cell Delivery to the Heart*
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Follow-Up (Months)</th>
<th>No. of Cells Injected</th>
<th>Method of Delivery</th>
<th>Significant Clinical End Points</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skeletal Myoblasts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARVEL158</td>
<td>23</td>
<td>6</td>
<td>4.0 \times 10^6 or 8.0 \times 10^6</td>
<td>TCIM</td>
<td>None</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>SEISMIC13</td>
<td>40</td>
<td>6</td>
<td>1.5-8.0 \times 10^6</td>
<td>TCIM</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>CAUSMIC159</td>
<td>23</td>
<td>12</td>
<td>0.3-6.0 \times 10^6</td>
<td>TCIM</td>
<td>Improved NYHA (P &lt; .05) Improved MLHFQ score (P = .004)</td>
<td></td>
</tr>
<tr>
<td>MAGIC160</td>
<td>97</td>
<td>6</td>
<td>4.0 \times 10^6 or 8.0 \times 10^6</td>
<td>TEIM</td>
<td>None</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td><strong>Bone Marrow Mononuclear Cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REGENT146</td>
<td>200</td>
<td>6</td>
<td>1.8 \times 10^6</td>
<td>Intracoronary</td>
<td>EF + 5% (P = .0079)</td>
<td></td>
</tr>
<tr>
<td>BONAMI161</td>
<td>101</td>
<td>3</td>
<td>9.8 \pm 0.9 \times 10^7</td>
<td>Intracoronary</td>
<td>Improved myocardial viability (P = .06)</td>
<td></td>
</tr>
<tr>
<td>HEBE199</td>
<td>200</td>
<td>4</td>
<td>3.0 \pm 1.6 \times 10^8</td>
<td>Intracoronary</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>REPAIR-AMI45</td>
<td>204</td>
<td>4</td>
<td>2.4 \pm 1.7 \times 10^8</td>
<td>Intracoronary</td>
<td>EF + 5.5% (P = .001); Recurrent MI, revascularization</td>
<td></td>
</tr>
<tr>
<td>ASTAMI18,52</td>
<td>100</td>
<td>6, 36</td>
<td>\sim 6.8 \times 10^2</td>
<td>Intracoronary</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>FINCELL46</td>
<td>80</td>
<td>6</td>
<td>4.0 \pm 2.0 \times 10^4</td>
<td>Intracoronary</td>
<td>EF + 4.0% (P = .03)</td>
<td>None</td>
</tr>
<tr>
<td>TIME18</td>
<td>120</td>
<td>6</td>
<td>1.5 \times 10^6</td>
<td>Intracoronary</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Late TIME46</td>
<td>87</td>
<td>6</td>
<td>1.5 \times 10^6</td>
<td>Intracoronary</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>SCAMI142,163</td>
<td>42</td>
<td>6, 36</td>
<td>3.2 \times 10^6</td>
<td>Intracoronary</td>
<td>EF + 5.6% (P = .03)</td>
<td>None</td>
</tr>
<tr>
<td>BOOST14</td>
<td>60</td>
<td>18</td>
<td>2.5 \pm 1.9 \times 10^9</td>
<td>Intracoronary</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>TOPCARE-AMI141,154</td>
<td>20</td>
<td>4, 12, 60</td>
<td>2.1 \pm 7.5 \times 10^8</td>
<td>Intracoronary</td>
<td>EF + 8.0% (P &lt; .001)</td>
<td>None</td>
</tr>
<tr>
<td>SWISS-AMI165</td>
<td>200</td>
<td>4</td>
<td>1.5 \pm 1.2 \times 10^8</td>
<td>Intracoronary</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Chronic Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CELLWAVE148</td>
<td>103</td>
<td>4</td>
<td>Shock wave + 2.4 \pm 1.7 \times 10^3</td>
<td>Intracoronary</td>
<td>EF + 2.2% (P = .02), Improved regional wall thickening, \downarrow MACE (HR, 0.58; P = .02)</td>
<td></td>
</tr>
<tr>
<td>TAC-HFT192</td>
<td>65</td>
<td>12</td>
<td>Not reported</td>
<td>TCIM</td>
<td>Improved MLHFQ score (P = .005)</td>
<td></td>
</tr>
<tr>
<td>FOCUS-CCTRN190</td>
<td>92</td>
<td>6</td>
<td>9.9 \pm 0.6 \times 10^7</td>
<td>TCIM</td>
<td>EF + 2.7% (P = .03)</td>
<td>None</td>
</tr>
<tr>
<td>FOCUS-HF196</td>
<td>30</td>
<td>6</td>
<td>3.0 \times 10^7</td>
<td>TCIM</td>
<td>Improved MLHFQ (P = .009)</td>
<td></td>
</tr>
<tr>
<td><strong>Refractory Angina</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beeres et al167</td>
<td>25</td>
<td>12</td>
<td>8.4 \pm 2.9 \times 10^7</td>
<td>TCIM</td>
<td>\downarrow CCS (P &lt; .01), \downarrow QALY (P &lt; .01)</td>
<td></td>
</tr>
<tr>
<td><strong>CD34+/CD133+ Bone Marrow Mononuclear Cells</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Bartunek et al167</td>
<td>35</td>
<td>4</td>
<td>1.3 \pm 0.2 \times 10^7</td>
<td>Intracoronary</td>
<td>EF + 7.1%, defect size –5.5%</td>
<td>None</td>
</tr>
<tr>
<td>Quyyumi et al168</td>
<td>31</td>
<td>6</td>
<td>5/10/15 \times 10^6</td>
<td>Intracoronary</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Dose</td>
<td>Dose Details</td>
<td>Intervention</td>
<td>Primary Effect</td>
<td>Secondary Effect</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td><strong>Chronic Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vrtovec et al.⁶⁹</td>
<td>110</td>
<td>60</td>
<td>1.1 ± 0.3 x 10⁵ Intracoronal</td>
<td>EF + 5.7% (P &lt; .02), 6-min walk +133 m (P &lt; .001), decreased mortality (P &lt; .01)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>DANCEL-ChF⁷⁰</td>
<td>32</td>
<td>12,84</td>
<td>1) 6.5 ± 3.8 x 10⁴ 2) 8.9 ± 3.6 x 10⁴ Intracoronal</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Refractory Angina</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losordo et al.⁵²</td>
<td>167</td>
<td>12</td>
<td>1 x 10⁹ cells/kg or 5 x 10⁹ cells/kg TCIM</td>
<td>J Angina (P &lt; .04)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Wang et al.⁷⁹</td>
<td>112</td>
<td>3,6,12</td>
<td>5.6 ± 2.3 x 10⁷ Intracoronal</td>
<td>J Angina (P &lt; .01), J myocardial perfusion (P &lt; .001)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Mesenchymal Stem Cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gao et al.¹¹</td>
<td>43</td>
<td>12,24</td>
<td>3.1 ± 0.5 x 10⁶ Intracoronal</td>
<td>None</td>
<td>Arterial occlusion during infusion</td>
<td></td>
</tr>
<tr>
<td>Hare et al.⁸⁰</td>
<td>53</td>
<td>6</td>
<td>6, 16, 50 x 10⁶ cell/kg Intravenous</td>
<td>EF + 5.2% (P &lt; .03), J ventricular tachycardia episodes (P &lt; .003)</td>
<td>None</td>
<td></td>
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<td><strong>Refractory Angina</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Haack-Sorensen et al.⁹⁰</td>
<td>31</td>
<td>12</td>
<td>2.2 x 10⁷ TCIM</td>
<td>J MET (P &lt; .001), J CCS (P &lt; .001), J SAQ and QoL (P &lt; .001)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC-HFT⁹²</td>
<td>65</td>
<td>12</td>
<td>Not reported TCIM</td>
<td>Improved MLHFQ score (P &lt; .02), improved 6-min walk (P &lt; .03), reduced infarct size (P &lt; .004)</td>
<td>None</td>
<td></td>
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<tr>
<td>C-CURE⁹¹</td>
<td>48</td>
<td>6,24</td>
<td>6/12 x 10⁶ TCIM</td>
<td>EF + 6.5% (P &lt; .01), LVESV, J 6-min walk test</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>POSEIDON⁹⁰</td>
<td>30</td>
<td>13</td>
<td>2/10/20 x 10⁷ TCIM</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Ixmyelocel-T Cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ixmyelocel-T⁹³</td>
<td>61</td>
<td>12</td>
<td>≤1.5 x 10⁹ TCIM</td>
<td>J MACE (P &lt; .05), J 6-min walk distance, improved MLHFQ score</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ixmyelocel-T⁹⁵</td>
<td>114</td>
<td>12</td>
<td>Not reported TCIM</td>
<td>J All-cause deaths, CV and ADCHF admissions (P &lt; .034)</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Less frequently used methods of delivery include direct surgical intramyocardial injection and engineered monolayer tissue transplantation. Both methods are invasive and require direct visualization of the myocardium. They are summarized in Table 68-2.

### STEM AND PROGENITOR CELLS USED IN CARDIOVASCULAR DISEASES

#### Embryonic Stem Cells
Human embryonic stem cells are pluripotent cells derived from blastocysts that can differentiate into a multitude of adult cells including cardiomyocytes, endothelial, and smooth muscle cells. After aggregation to form embryoid bodies, embryonic stem cells form spontaneously contracting cardiomyocytes within 1 to 4 days. When injected into infarcted rodent myocardium, embryonic stem cell–derived cardiomyocytes regenerated the infarcted myocardium, leading to reduced ventricular dilation and preserved regional and global contractile function. However, their therapeutic use is complicated by immunologic rejection, propensity for teratoma formation, and ethical considerations. The risk of teratoma formation may be mitigated by grafting ex vivo predifferentiated embryonic stem cell–derived cardiomyocytes.

**Induced Pluripotent Stem Cells**

Induced pluripotent stem cells (iPSCs) mitigate the legal and ethical concerns related to embryonic stem cells. iPSCs are somatic cells that have been reprogrammed to express an embryonic phenotype. Seminal experiments by Takahashi and Yamanaka used oct4, sox2, nanog, lin28, klf4, and c-myc transgenes to reprogram adult murine somatic cells into iPSCs with subsequent differentiation into functional cardiomyocytes. Treatment of human iPSCs with activin A and bmp4 can direct differentiation into human cardiac fibroblasts, and injection of these transgenes into murine models of myocardial infarction results in improved cardiac function and adverse ventricular remodeling. iPSCs can also be generated using microRNAs. Mouse fibroblasts converted to the cardiomyocyte phenotype by transfection with microRNAs 1, 133, 208, 499, and JAK inhibitor I expressed cardiomyocyte-specific genes and proteins and exhibited sarcomeric organization, spontaneous calcium oscillations, and mechanical contractions characteristic of cardiomyocytes. Despite these promising results, use of iPSCs in humans has been limited due to concerns over their oncogenicity. Potent oncogenes (c-myc) used for reprogramming, involvement of the p53 pathway, and the epigenetic memory of iPSCs increase their risk for somatic tumor development.

**Skeletal Myoblasts**
Skeletal myoblasts are skeletal muscle precursors that possess a contractile phenotype and are relatively resistant to ischemia and oxidative stress.\textsuperscript{29} Although skeletal myoblasts can differentiate into functionally competent myofibers after engraftment, they suffer a high attrition rate, and only 7.4% of transplanted cells survive at 72 hours.\textsuperscript{30} Surviving myofibers fail to develop intercalated discs and remain electromechanically isolated from host myocardium, which may promote the generation of ventricular arrhythmias.\textsuperscript{31} In human studies, autologous skeletal myoblasts harvested from the quadriceps muscle and cultured in vitro were transplanted using the NOGA-guided catheter into areas of scarred myocardium (unipolar voltage \(<7.0 \text{ mV}\)). Although initial studies claimed benefits, there was an associated increase in arrhythmias (see Table 68-3).\textsuperscript{29,32} The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial randomized 97 patients undergoing coronary artery bypass surgery with reduced left ventricular ejection fraction (LVEF; \(<35\%\)) to receive either autologous myoblast injections (4.0 \(\times\) \(10^8\) or 8.0 \(\times\) \(10^8\) cells) or placebo. At 6 months, myoblast transfer did not improve regional or global LVEF compared to controls. While cell therapy was associated with a higher number of arrhythmic events, it did not result in significant differences in major adverse cardiac events.\textsuperscript{16} However, administration of periprocedural amiodarone may be successful in reducing the number of arrhythmic events.\textsuperscript{33}

Bone Marrow–Derived Stem and Progenitor Cells

Ischemic tissue damage stimulates recruitment and homing of endogenous bone marrow–derived progenitor and stem cells via the release of numerous cytokines including granulocyte colony-stimulating factor (G-CSF), stem cell factor, vascular endothelial growth factor, stromal cell–derived factor-1 (SDF-1), and erythropoietin.\textsuperscript{34} Locally derived SDF-1 augments vasculogenesis and subsequently contributes to ischemic neovascularization in vivo by augmenting endothelial progenitor cell recruitment to ischemic tissues.\textsuperscript{35} In addition, the SDF-1/CXCR4 axis regulates progenitor cell proliferation and survival as well as several intracellular signaling pathways.\textsuperscript{36}

Bone marrow–derived stem and progenitor cells are attractive candidates for cell therapy because of their accessibility and renewability. The human
bone marrow houses several progenitor cell populations including hematopoietic stem cells, endothelial progenitor cells, mesenchymal stem cells, and others. The largely paracrine mechanisms underlying the regenerative potential of bone marrow–derived stem/progenitor cells include (1) release of antiapoptotic cytokines that improve survival of cardiomyocytes in the infarct border zone,37 (2) secretion of angiogenic factors that promote angiogenesis and vasculogenesis,38 (3) stimulation of resident cardiac and vascular stem cells,39 and (4) induction of mitosis.40 To date, unselected bone marrow mononuclear cells, selected CD34+ progenitor cells, selected CD34+/CD133+ progenitor cells, and mesenchymal stem cells have been employed in human clinical trials in a variety of clinical settings.

**Bone Marrow Mononuclear Cells**

**Acute Myocardial Infarction**

Several trials have been conducted in patients with acute ST-segment elevation myocardial infarction (MI) using intracoronary infusions of bone marrow mononuclear cells (see Table 68-3). The Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial was an early randomized controlled trial to demonstrate functional improvement.41 Cells were harvested by bone marrow aspiration and delivered into the infarct-related artery using the stop-flow technique at 4.9 ± 1.5 days after ST-segment elevation MI in 29 subjects, and circulating mononuclear cells were given to 30 controls. After 4 months, LVEF significantly increased (50% ± 10% to 58% ± 10%, \( P < .001 \)), and end-systolic volumes significantly decreased (54 ± 19 mL to 44 ± 20 mL, \( P < .001 \)) without differences between the 2 cell groups.42 In the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration Trial (BOOST), 60 patients were randomized to receive either autologous bone marrow mononuclear cells (mean 2.5 × 10⁹) or placebo, delivered 4.8 ± 1.3 days after ST-segment elevation MI and percutaneous coronary intervention (PCI).43 At 6 months, LVEF was significantly improved in the cell therapy versus control group (6.7% vs 0.7%, respectively; \( P = .0026 \)). However, early improvements in LVEF did not persist at 18 months and did not translate into decreased major adverse cardiovascular events at 5 years.44
of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial is the largest trial to date using bone marrow mononuclear cells in acute MI. 45 Two hundred four patients were randomized to receive intracoronary infusion of either bone marrow mononuclear cells (2.4 ± 1.7 × 10⁸ cells) or placebo after 4.4 ± 1.4 days after ST-segment elevation MI and PCI. At 4 months, the improvement in LVEF was significantly greater in the cell therapy group compared to controls (5.5% ± 7.3% vs 3.0% ± 6.5%, \( P = .01 \)). 45 At 12 months, the occurrence of major adverse cardiovascular events was significantly lower in the cell therapy group compared to controls (23 vs 40 events, respectively, \( P = .01 \)). 45 Finally, the Finnish Stem Cell (FINCELL) study randomized 80 subjects to receive intracoronary infusion of autologous bone marrow mononuclear cells (4.0 ± 2.0 × 10⁸ cells) or placebo 2 to 6 days after ST-segment elevation MI and PCI. 46 At 6 months of follow-up, the bone marrow mononuclear cells treatment group had significant improvement in LVEF compared to the placebo group (4.0% ± 11.2% vs –1.4% ± 10.2%, \( P = .03 \)). There were no differences in major adverse cardiovascular events or arrhythmias between the 2 groups. 46

In contrast, several trials have failed to demonstrate benefit from intracoronary administration of bone marrow mononuclear cells. The randomized, double-blind, placebo-controlled Timing in Myocardial Infarction Evaluation trials (TIME and Late TIME) found that intracoronary infusion of bone marrow mononuclear cells either 3 to 7 days (TIME) after MI or 14 to 21 days (Late TIME) after MI had no effect on recovery of global or regional left ventricular function compared to placebo. 47, 48 The Intracoronary Infusion of Mononuclear Cells From Bone Marrow or Peripheral Blood Compared With Standard Therapy in Patients After Acute Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention (HEBE) trial randomized 200 patients with acute MI to receive either intracoronary infusion of bone marrow mononuclear cells, circulating mononuclear cells, or standard therapy without placebo infusion 3 to 8 days after acute MI. 49 At 4 months, there were no significant differences in LVEF, infarct size, or major adverse cardiac events. 50 Similarly, the Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction (ASTAMI) trial reported no significant change in LVEF or major adverse cardiovascular event rates at 6 or 36 months. 51, 52
Several meta-analyses of trials evaluating efficacy of intracoronary autologous bone marrow mononuclear cell therapy in ST-segment elevation MI have been conducted.\textsuperscript{53–56} In a recent meta-analysis of 22 trials enrolling 2037 patients, of whom 1218 received bone marrow mononuclear cell therapy, treatment was found to be safe and was associated with modest improvements in LVEF (±2.1%), reduction in infarct scar size (−2.7%), and preservation of left ventricular end-systolic volume (−4 mL) without increase in short-term adverse event rate.\textsuperscript{56} Subgroup analyses revealed that improvements in LVEF were more likely among patients (1) with lower baseline LVEF, (2) who received more than $1 \times 10^6$ cells, and (3) who received treatment 5 to 30 days after infarction.\textsuperscript{54} In another meta-analysis of 50 studies enrolling 2625 patients with ischemic heart disease (either acute or chronic), treatment with bone marrow mononuclear cells was associated with a modest improvement in LVEF (±3.95%), smaller infarct size (−4.03%), and reduced LV end-systolic volume (−5.23 mL).\textsuperscript{57} Similarly, subgroup analysis revealed that improvements in LVEF were greater among patients with (1) lower baseline LVEF and (2) patients who received more than $4 \times 10^7$ cells.\textsuperscript{57} Both analyses highlight the importance of timing, dose, and MI size as determinants of response to stem cell therapy in patients with acute MI. Importantly, compared to patients who received standard therapy, patients treated with bone marrow mononuclear cells experienced significant decreases in all-cause mortality (odds ratio [OR], 0.39), cardiac mortality (OR, 0.41), recurrent MI (OR, 0.25), and in-stent thrombosis (OR, 0.34). There were no statistical differences in ventricular arrhythmias between groups.\textsuperscript{57}

**Chronic Heart Failure**

The Effect of Shock Wave-Facilitated Intracoronary Cell Therapy on LVEF in Patients With Chronic Heart Failure (CELLWAVE) trial randomized 103 patients with chronic postinfarction heart failure in 2 steps.\textsuperscript{58} Patients were first randomized (2:2:1; single-blind) to receive echocardiographically guided low-dose (0.014 mJ/mm$^2$), high-dose (0.051 mJ/mm$^2$), or placebo shock wave targeted to the left ventricular anterior wall 24 hours prior to cell administration. Preconditioning of chronic ischemic tissue with shock wave therapy has been shown to improve recruitment of circulating endothelial
progenitor cells via enhanced expression of chemoattractant factors (ie, SDF-1, vascular endothelial growth factor [VEGF]) in animal models.\textsuperscript{59} Patients receiving shock wave pretreatment were then randomized in a second step (1:1; double-blind) to receive intracoronary infusion of either bone marrow mononuclear cells or placebo, whereas patients receiving placebo shock wave received intracoronary infusion of bone marrow mononuclear cells.\textsuperscript{58} At 4 months, compared to patients receiving shock wave therapy alone, patients receiving shock wave therapy and bone marrow mononuclear cells had significantly improved LVEF (1.0\% vs 3.2\%, respectively, \( P = .02 \)), regional wall thickening (0.5\% vs 3.6\%, respectively, \( P = .01 \)), and decreased incidence of major adverse cardiac events (hazard ratio, 0.58; \( P = .02 \)).\textsuperscript{58} The Transendocardial Delivery of Autologous Bone Marrow Mononuclear Cells on Functional Capacity, Left Ventricular Function, and Perfusion in Chronic Heart Failure (FOCUS-CCTRN) trial randomized 92 patients with ischemic cardiomyopathy with LVEF ≤45\% to receive transendocardial injection of 9.9 ± 0.6 × 10\(^7\) bone marrow mononuclear cells or placebo in a 2-to-1 ratio. At 6 months, patients who received bone marrow mononuclear cells demonstrated significant improvements in LVEF compared to control (1.4\% vs −1.3\%, \( P = .03 \)).\textsuperscript{60} However, no change in end-systolic volume, maximal oxygen consumption, or reversibility of ischemia on single-photon emission computed tomography was observed. In exploratory analysis, higher CD34\(^+\) or CD133\(^+\) cell counts were associated with greater absolute unit increase in LVEF. Every 3\% higher level of CD34\(^+\) cells was associated with an average of 3.0\% greater absolute unit increase in LVEF in multivariable regression modeling. Similarly, every 3\% higher level of CD133\(^+\) cells was associated with an average of 5.9\% greater absolute unit increase in LVEF.\textsuperscript{60} These findings support the concept that both cell type and number of cells infused may be important factors in determining the benefit derived from cell therapy.

**Selected Bone Marrow–Derived Stem Cells**

**CD34\(^+\) Bone Marrow Mononuclear Cells**

Whether selected populations of bone marrow mononuclear cells enriched for progenitor cells are likely to be more effective than unselected mononuclear
cells has been explored in several early-phase trials. CD34+ cells are enriched for progenitor cells and localize more avidly to peri-infarct regions than unselected cells. CD34+ bone marrow mononuclear cells are relatively uncommon (1%-2%) and are capable of transdifferentiating into hematopoietic, endothelial, and smooth muscle cells, and rarely to cardiomyocytes in vivo. Coexpression of CD34 with CD133 identifies cells enriched for early precursor cells. In addition, coexpression of VEGF receptor-2 on CD34+ cells may constitute a phenotypically and functionally distinct population of cells enriched for endothelial progenitors.

**Acute Myocardial Infarction**

The Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) trial randomized 200 patients with acute MI and reduced LVEF (<40%) to receive intracoronary infusion of 1.8 × 10^8 unselected bone marrow mononuclear cells, 1.9 × 10^6 selected CD34+/CXCR4+ cells, or placebo 7 days following ST-segment elevation MI. At 6 months, treatment with either CD34+ or mononuclear cells did not improve LVEF or volumes compared to controls. However, in patients with baseline postinfarction LVEF <37% (median), infusion of unselected cells had a median LVEF improvement of 6.0% (P = .007), and selected CD34+/CXCR4+ cells had a median LVEF improvement of 7.0% (P = .01), indicating that cell therapy may provide the most benefit in patients with the most severely impaired LVEF after MI. In addition, there was a trend toward a greater proportion of patients receiving CD34+/CXCR4+ cells to improve LVEF compared to those receiving unselected cells, suggesting that selected CD34+ cells may be more therapeutic than unselected mononuclear cells. Finally, Bartunek et al randomized 35 patients with acute MI treated with PCI to receive intracoronary administration of CD133+/CD34+ bone marrow cells (1.3 ± 2.2 × 10^7 cells) 11.6 ± 1.4 days after infarction or standard medical care. At 4 months, patients receiving cell therapy experienced improvements in LVEF (from 45.0% ± 2.6% to 52.1% ± 3.5%, P < .05) and perfusion defect size (from 28.0% ± 4.1% to 22.5% ± 4.1%, P < .05) compared to controls. However, patients receiving intracoronary cell therapy had significantly higher rates of in-stent restenosis.
Chronic Heart Failure

Vrtovc et al\textsuperscript{68} randomized 110 patients with dilated cardiomyopathy to receive intracoronary administration of CD34\textsuperscript{+} cells (1.1 ± 0.3 × 10\textsuperscript{6} cells) or placebo. CD34\textsuperscript{+} cells were mobilized with G-CSF and collected via apheresis. Patients underwent myocardial scintigraphy, and cells were injected in the artery supplying segments with the greatest perfusion defect. At 1 and 5 years, CD34\textsuperscript{+} cell therapy was associated with increased LVEF, increased 6-minute walk distance, and decreased N-terminal B-type natriuretic peptide.\textsuperscript{68,69} LVEF improvement was more significant in patients with higher myocardial homing of injected cells as determined by cell labeling.\textsuperscript{69} During the 5-year follow-up, mortality was lower in the cell therapy group compared to controls (14\% vs 35\%, \( P = .01 \)).\textsuperscript{69} The Danish Stem Cell Study–Congestive Heart Failure (DANCELL-CHF) trial studied the benefit of repeated bone marrow mononuclear cell infusions in patients with chronic ischemic heart failure.\textsuperscript{70} Thirty-two patients with LVEF <45\% received 2 treatments of intracoronary CD34\textsuperscript{+} bone marrow stem cells 4 months apart. Patients received a mean of 6.5 ± 3.8 \times 10^{8} bone marrow cells on the first infusion and 8.9 ± 3.6 \times 10^{8} cells on the second infusion. At 12 months, there was no change in LVEF.\textsuperscript{70} At 7 years, post hoc analysis revealed increased CD34\textsuperscript{+} cell count was significantly associated with survival (hazard ratio, 0.9; \( P = .04 \)), indicating that repeated injections of high numbers of CD34\textsuperscript{+} cells may improve long-term survival in patients with chronic ischemic heart failure.\textsuperscript{71}

Chronic Ischemia

In a phase II randomized controlled trial, 167 patients with refractory angina were randomized to receive 1 of 2 doses (1 × 10\textsuperscript{5} or 5 × 10\textsuperscript{5} cells/kg) of mobilized autologous CD34\textsuperscript{+} cells or an equal volume of placebo.\textsuperscript{72} Treatment was distributed into 10 sites of ischemic but viable myocardium as determined by the NOGA mapping system, as described previously. At 6 months, patients in the low-dose cell therapy group had significantly decreased angina frequency and improved exercise tolerance as compared to patients receiving placebo. Interestingly, there was a lack of dose response, and patients receiving high-dose cell therapy did not experience the same improvements in angina frequency and exercise tolerance seen in the low-
dose cell therapy group. Clinical trials evaluating the use of CD34+ bone marrow mononuclear cells in the treatment of cardiovascular diseases are ongoing and are summarized in Table 68-4.

Table 68-4 Ongoing Phase II/III Clinical Trials Involving Stem Cells
<table>
<thead>
<tr>
<th>Clinical Trial Identifier and Phase</th>
<th>Stem Cell Type</th>
<th>Cardiac Condition</th>
<th>No. of Patients</th>
<th>Method of Delivery</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02059512 Phase III</td>
<td>BMMNC</td>
<td>Ischemic heart failure</td>
<td>100</td>
<td>Intracoronary</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>NCT01569178 Phase III</td>
<td>BMMNC</td>
<td>Ischemic heart failure</td>
<td>3000</td>
<td>Intracoronary</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>NCT01693042 Phase III</td>
<td>BMMNC</td>
<td>Ischemic heart failure</td>
<td>676</td>
<td>Intracoronary (single vs repeat injections)</td>
<td>Mortality</td>
</tr>
<tr>
<td>NCT01969890 Phase III</td>
<td>G-CSF BMMNC mobilization</td>
<td>Ischemic heart failure</td>
<td>1530</td>
<td>Intravenous</td>
<td>Death, MI, hospitalization</td>
</tr>
<tr>
<td>NCT00936819 Phase II</td>
<td>EPC</td>
<td>Ischemic heart failure</td>
<td>100</td>
<td>Intracoronary</td>
<td>LVEF</td>
</tr>
<tr>
<td>NCT01568910</td>
<td>CD34+</td>
<td>Refractory angina</td>
<td>291</td>
<td>TCIM</td>
<td>Exercise time, angina frequency</td>
</tr>
<tr>
<td>NCT00950274 Phase II/III</td>
<td>CD133+</td>
<td>Ischemic heart failure, CABG</td>
<td>142</td>
<td>TEIM</td>
<td>LVEF</td>
</tr>
<tr>
<td>NCT01753440 Phase II/III</td>
<td>MSC</td>
<td>Ischemic heart failure, CABG</td>
<td>30</td>
<td>TEIM</td>
<td>LVEF, myocardial segmental perfusion</td>
</tr>
<tr>
<td>NCT01394432 Phase III</td>
<td>MSC</td>
<td>Ischemic heart failure</td>
<td>50</td>
<td>TCIM</td>
<td>LVEF</td>
</tr>
<tr>
<td>NCT01655209 Phase III</td>
<td>MSC</td>
<td>Ischemic heart failure</td>
<td>135</td>
<td>Intracoronary</td>
<td>LVEF</td>
</tr>
<tr>
<td>NCT01759212 Phase III</td>
<td>MSC (allogeneic)</td>
<td>Ischemic heart failure, LVAD</td>
<td>5</td>
<td>TEIM</td>
<td>Myocardial perfusion</td>
</tr>
<tr>
<td>NCT01770613 Phase II</td>
<td>MSC (allogeneic)</td>
<td>Ischemic heart failure</td>
<td>50</td>
<td>Intravenous</td>
<td>MACE</td>
</tr>
<tr>
<td>NCT01458405 Phase II</td>
<td>MSC (allogeneic)</td>
<td>Ischemic heart failure</td>
<td>274</td>
<td>Intracoronary</td>
<td>Infarct size</td>
</tr>
<tr>
<td>NCT02032004 Phase III</td>
<td>MSC (allogeneic)</td>
<td>Heart failure (all etiologies)</td>
<td>1730</td>
<td>TCIM</td>
<td>Time to first heart failure-related major adverse event</td>
</tr>
<tr>
<td>NCT02123706 Phase IIa</td>
<td>MSC (allogeneic)</td>
<td>Nonischemic heart failure</td>
<td>20</td>
<td>Intravenous</td>
<td>SAE</td>
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<tr>
<td>NCT02052427 Phase II</td>
<td>ADRC</td>
<td>Ischemic heart failure</td>
<td>45</td>
<td>TCIM</td>
<td>Change in MLHFO</td>
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<tr>
<td>NCT01758406 Phase II</td>
<td>CSC</td>
<td>Ischemic heart failure</td>
<td>50</td>
<td>Intracoronary</td>
<td>Death, arrhythmia, hospitalizations</td>
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<tr>
<td>NCT02099500 Phase II</td>
<td>ADRC</td>
<td>Peripheral vascular disease</td>
<td>200</td>
<td>Intramuscular</td>
<td>ABI, adverse events</td>
</tr>
<tr>
<td>NCT01483898 Phase III</td>
<td>Multicellular iKmyelocel-T</td>
<td>Peripheral vascular disease</td>
<td>41</td>
<td>Intramuscular</td>
<td>Amputation-free survival</td>
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</table>

Abbreviations: ABI, ankle-brachial index; ADRC, adipose-derived regenerative cell; BMMNC, bone marrow mononuclear cell; CABG, coronary artery bypass graft; CSC, cardiac stem cell; EPC, endothelial progenitor cell; G-CSF, granulocyte colony-stimulating factor; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; MLHFO, Minnesota Living With Heart Failure Questionnaire; MSC, mesenchymal stem cell; TCIM, transcatheter intramyocardial; TEIM, transendocardial intramyocardial.

**Mesenchymal Stem Cells**
Mesenchymal stem cells are rare, nonhematopoietic, multipotent cells of mesodermal origin that constitute 0.01% to 0.001% of bone marrow nucleated cells. The most abundant source of mesenchymal stem cells is the bone marrow, but they can be derived from the umbilical cord, amniotic fluid, placenta, testis, and adipose tissue. The International Society for Cell Therapy defines mesenchymal stem cells as cells that (1) adhere to plastic in standard culture conditions; (2) express CD73, CD90, and CD105 in the absence of CD34, CD45, HLA-DR, CD14, CD11b, CD79a, or CD19 surface molecules; and (3) have capacity for differentiation to osteoblasts, adipocytes, and chondroblasts in vitro. Mesenchymal stem cells maintain endogenous stem cell niches; contribute to the creation and maintenance of cardiovascular, connective, and skeletal tissues; and are attractive candidates for cell therapy because of their ease of proliferation in culture, potential for both myocardial and vascular repair, and immune-privileged status.

Mesenchymal stem cells influence neighboring cells by direct cell-to-cell interaction and by paracrine release of an array of soluble growth factors and cytokines that include SDF-1, chemokine receptor (CXCR)-4, hepatocyte growth factors, insulin-like growth factor-1, basic fibroblast growth factor, hypoxia-inducible factor-1α, VEGF, angiopoietin-1, tumor necrosis factor-α, interleukin-1, interleukin-6, and plasminogen activator. Intracoronary administration of human mesenchymal stem cell–conditioned medium in a murine model of acute MI increased capillary density, reduced myocardial infarct size, and improved systolic and diastolic function.

Unlike other bone marrow–derived cells, mesenchymal stem cells possess immune properties that make them potential candidates for safe allogeneic therapy in immunocompetent patients. Their relatively immune-privileged phenotype prevents activation of host immune cells because they lack surface expression of major histocompatibility complex class II antigens and costimulatory molecules for T-cell induction. Furthermore, mesenchymal stem cells downregulate lymphocyte proliferation and suppress the maturation and function of immune cells via the secretion of soluble factors. Under optimal conditions, the progeny of colony-forming unit–fibroblasts can be expanded for upward of 50 population doublings.

Experimental studies of mesenchymal stem cell transplantation in acute MI and ischemic cardiomyopathy have reported biologic and functional benefits that include attenuation of myocardial scar and infarct size,
improvement in regional and global ventricular function, and increased vascular density and myocardial perfusion.\textsuperscript{80–82} In murine models of acute MI, intramyocardial injection of human-mesenchymal stem cells or cells expressing Akt resulted in a dose-dependent increase in vascular density and neovascularization, with accompanying improvements in LVEF.\textsuperscript{83,84} Potential hazards of mesenchymal stem cells include risks of off-target tissue growth such as ossification and/or calcification, cardiac nerve sprouting, and arrhythmogenicity.\textsuperscript{85,86} Additionally, intracoronary injection of the relatively large mesenchymal stem cells has been associated with cell aggregation and embolization.\textsuperscript{11,87}

Clinical trials using autologous and allogeneic mesenchymal stem cells have been conducted in patients with acute MI, chronic heart failure, and stable angina (see Table 68-3).

**Acute Myocardial Infarction**

Hare et al\textsuperscript{88} conducted a randomized, double-blind, placebo-controlled trial using intravenous allogeneic human mesenchymal stem cells (Prochymal; Osiris Therapeutics, Baltimore, MD) in 53 patients with acute MI. Human mesenchymal stem cells were isolated from bone marrow aspirates obtained from a single unrelated donor who was not human leukocyte antigen matched to recipients. Patients were randomized to receive either a single intravenous infusion of Prochymal (at 3 dose-escalation cohorts of 5, 16, and $50 \times 10^5$ cells/kg body weight) or placebo suspension delivered at a rate of 2 mL/min.\textsuperscript{88} At 6 months, there was reduced ventricular tachycardia and improved expiratory volumes in the Prochymal-treated patients compared to controls. While the study was not powered to detect differences in LVEF, cardiac magnetic resonance imaging performed in a subgroup of patients (20 Prochymal patients and 14 placebo patients) demonstrated a progressive increase in LVEF relative to baseline in Prochymal- but not in placebo-treated patients ($+5.2\% \pm 1.9\%, P = .003$).\textsuperscript{88} Importantly, there were no differences in major adverse event rates between groups, indicating that intravenous infusion of allogeneic mesenchymal stem cells is safe in patients with acute MI. A larger phase II clinical trial is currently recruiting (see Table 68-4).
Chronic Ischemia

In the Direct Intramyocardial Mesenchymal Stromal Cell Injection in Patients With Severe Refractory Angina Trial, 31 patients with stable coronary artery disease, moderate to severe angina, LVEF >40%, and no further revascularization options received autologous mesenchymal stem cells (mean 2.2 × 10^7 cells). Bone marrow mesenchymal stem cells were culture expanded for 6 to 8 weeks, stimulated with VEGF for 1 week, and injected into ischemic but viable areas of myocardium as determined by the NOGA mapping system. Autologous mesenchymal cells were safe and resulted in improved exercise duration, quality of life, and angina frequency at 12 months.

Chronic Heart Failure

The Comparison of Allogeneic Versus Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy (POSEIDON) trial studied 30 patients with ischemic heart failure and LVEF <50% who were randomized to receive transendocardial injection of 20 × 10^6, 100 × 10^6, or 200 × 10^6 autologous or allogeneic mesenchymal stem cells. At 1 year, relative to baseline, autologous but not allogeneic cell therapy was associated with an improvement in the 6-minute walk test and the Minnesota Living with Heart Failure Questionnaire score. While both allogeneic and autologous cells reduced end-diastolic volumes, this did not translate into significantly improvements in LVEF. No significant donor-specific immune reactions were observed with allogeneic mesenchymal stem cells, and several trials evaluating their use are under way (see Table 68-4).

The Cardiopoietic Stem Cell Therapy in Heart Failure (C-CURE) trial randomized 48 patients with chronic ischemic heart failure (LVEF <40%) to receive either lineage-specified cardiopoietic cells derived from autologous mesenchymal stem cells or standard of care. In the cell therapy arm, bone marrow was harvested and isolated mesenchymal stem cells were exposed to a cardiogenic cocktail. Derived cardiopoietic stem cells were delivered by endomyocardial injections guided by electromechanical (NOGA) mapping. At 24 months, patients receiving cell therapy demonstrated a 7.0%
improvement in LVEF compared to controls, in whom LVEF remained unchanged ($P < .0001$). In addition, cell therapy was associated with a reduction in left ventricular end-systolic volume ($-24.8 \pm 3.0 \text{ mL vs } -8.8 \pm 3.9 \text{ mL}, P < .0001$) and improved 6-minute walk distance ($+62 \pm 18 \text{ m vs } -15 \pm 20 \text{ m, } P < .01$) compared with controls.\textsuperscript{91}

The Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy (TAC-HFT) trial randomized 65 patients with ischemic cardiomyopathy and LVEF <50% to receive endomyocardial injections of mesenchymal stem cells, bone marrow mononuclear cells, or placebo.\textsuperscript{92} At 1 year, there were no differences in serious adverse events between groups. Compared to placebo, treatment with mesenchymal stem cells resulted in improved symptoms, increased 6-minute walk distance, and reduced left ventricular infarct size. In comparison, treatment with bone marrow mononuclear cells resulted in improved symptoms only.\textsuperscript{92}

Finally, the Safety and Efficacy of Ixmyelocel-T trial was a randomized phase IIA clinical trial using Ixmyelocel-T (Vericel, Ann Arbor, MI) in the treatment of dilated ischemic and nonischemic cardiomyopathy.\textsuperscript{93} Ixmyelocel-T is an expanded multicellular therapy cultured from autologous bone marrow mononuclear cells and is composed of myeloid and lymphoid cells that express CD45 and CD90, which are hallmarks of mesenchymal stromal cells.\textsuperscript{94} Compared to bone marrow, Ixmyelocel-T contains approximately 50- and 200-fold the number of M\textsubscript{2}-like macrophages and mesenchymal stromal cells, respectively.\textsuperscript{93} A total of 61 patients were randomized to receive Ixmyelocel-T (up to $1.5 \times 10^6$ cells) administered via intramyocardial injection directed by the NOGA injection catheter or by direct visualization via mini-thoracotomy.\textsuperscript{93} At 1 year, patients with ischemic cardiomyopathy treated with Ixmyelocel-T experienced significantly fewer major adverse cardiac events compared to controls (14% vs 56%, respectively, $P < .05$). In addition, cell therapy was associated with improved New York Heart Association (NYHA) class, 6-minute walk distance, and Minnesota Living with Heart Failure Questionnaire scores. However, there was no benefit of cell therapy in nonischemic cardiomyopathy (see Table 68-3).\textsuperscript{93}

This was followed by the Ixmyelocel-T for Patients With Heart Failure Trial, a prospective, randomized, double-blind, placebo-controlled, phase IIB
trial that recruited 126 patients with NYHA class III or IV symptomatic heart failure due to ischemic cardiomyopathy with an implanted defibrillator, LVEF ≤35%, who were ineligible for revascularization. Ixmyelocel-T (n = 60) or placebo (n = 66) was injected via a NOGA catheter into the viable myocardium. The primary efficacy end point of all-cause death or rehospitalization for heart failure was observed in 49% of patients in the placebo group and 38% of patients in the Ixmyelocel-T group, a 37% reduction in cardiac events (risk ratio, 0.63; \( P = .034 \)). In addition, 75% of placebo participants had serious adverse events compared to 53% in the Ixmyelocel-T group (\( P = .02 \)). To date, this has been the largest cell therapy trial in patients with ischemic heart failure that has demonstrated significant reduction in clinical cardiac events in patients receiving cell therapy.

**Adipose-Derived Progenitor Cells**

Adipose tissue has emerged as a promising source of stem cells for cell-based therapies. The stromal vascular fraction represents 10% of adipose tissue and contains a mixed, multipotent population of cells including preadipocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, resident monocytes/macrophages, lymphocytes, and adipose-derived progenitor cells. Adipose-derived progenitor cells can be easily obtained by liposuction and prepared as fresh cells for immediate autologous transplantation without need for culture and expansion. They share many cell surface markers with bone marrow–derived mesenchymal stem cells or stromal cells and skeletal muscle–derived cells and can differentiate into multiple cell lineages including cardiomyocytes and endothelial and smooth muscle cells. Furthermore, stem cell yields from adipose tissue are significantly greater than from bone marrow; the average frequency of adipose-derived stem cells in processed lipoaspirate is 2% of nucleated cells, and their yield is approximately 5000 fibroblast colony-forming units per gram of adipose tissue, compared with approximately 100 to 1000 colony-forming units per milliliter of bone marrow. Current methods used for isolating stem cells rely on collagenase digestion followed by centrifugal separation to isolate the stromal vascular fraction from adipocytes. Isolated adipose-derived stem cells are then expanded in monolayer culture on standard tissue culture plastics with a basal medium containing 10% fetal
bovine serum.\textsuperscript{102} The beneficial effect of adipose-derived progenitor cells is predominantly due to paracrine effects of their soluble factors rather than their differentiation into mature lineages.\textsuperscript{96}

The Adipose-Derived Regenerative Cells in Patients With Ischemic Cardiomyopathy (PRECISE) trial randomized 36 patients with chronic ischemic cardiomyopathy (LVEF ≤45%) in a 3:1 ratio to receive adipose-derived progenitor cells or placebo.\textsuperscript{103} Progenitor cells were isolated from adipose tissue harvested by liposuction, and $4.2 \times 10^7$ cells or placebo was injected into areas of viable myocardium using the NOGA injection catheter. At 6 months, patients treated with cell therapy demonstrated increased left ventricular mass (from $128.1 \pm 26.0$ to $149.5 \pm 32.4$, $P < .001$) and wall motion score index on magnetic resonance imaging (from $2.1 \pm 0.6$ to $1.7 \pm 0.9$, $P = .04$) compared to patients receiving placebo, who remained unchanged from baseline. However, this did not translate into significant differences in LVEF or major adverse cardiovascular events.\textsuperscript{103}

**Resident Cardiac Progenitor Cells**

Resident cardiac progenitor cells that promote cardiomyocyte renewal and proliferation include side population cells, Sca-1$^+$, Islet-1$^+$, and c-kit$^+$ cardiac progenitor cells, cardiospheres, and epicardium-derived progenitor cells. While relatively rare, these cells are likely committed to a cardiomyocyte fate, giving them a distinct advantage over other progenitor cells for heart failure therapy (Fig. 68-3).
Side Population Cardiac Progenitor Cells

Side population cells are characterized by their ability to efflux Hoechst dye in an ABC transporter-dependent manner and are found in skeletal muscle, bone marrow, and cardiac tissue. Within the heart, side population cells range from 0.03% to 3.5% of total mononuclear cardiac cells. When cultured with adult or neonatal cardiomyocytes, they differentiate into functional cardiomyocytes and express muscle-specific transcription factors and cardiac specific proteins, including α-sarcromeric actinin and troponin-I. When infused intravenously into infarcted rats, side population cells have been shown to engraft into injured myocardium and differentiate into cardiomyocytes and endothelial and smooth muscle cells. In humans, side population cells are located in the atria but demonstrate the ability to mobilize to areas of ischemic myocardium. No clinical trials have so far been performed with these cells.

Sca-1+ Cardiac Progenitor Cells

Stem cell antigen-1 (Sca-1) is a member of the ly-6 family, initially reported as a cell surface marker for hematopoietic stem cells. Sca-1+ cells are found in the bone marrow, myocardium, skeletal muscle, and blood vessels. In vitro, Sca-1+ cells differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells. Transplantation of Sca-1+ cells derived from human fetal hearts into mice with acute MI resulted in improved LVEF and ventricular remodeling at 3 months. Sca-1+ cells generated human cardiomyocytes and blood vessels without fusion of human and murine nuclei. To date, there have been no clinical trials with Sca-1+ cells.

Islet-1+ Cardiac Progenitor Cells
Islet-1\(^+\) is a LIM-homeodomain transcription factor that plays a crucial role during cardiac embryogenesis and gives rise to the right ventricle, outflow tract, and atria.\(^{111}\) While abundant in neonatal hearts, Islet-1\(^+\) cells rapidly decline with age.\(^{112}\) In murine models, intramyocardial gene transfer of Islet-1\(^+\) to the border zone of infarcted hearts resulted in improved left ventricular function, enhanced vascularization, and reduced myocardial fibrosis.\(^{113}\) Transplanted Islet-1\(^+\) cells differentiated into endothelial and smooth muscle cells 25 days after injection. No clinical trials using Ilset-1\(^+\) cells have been conducted.

**C-kit\(^+\) Cardiac Progenitor Cells**

C-kit is a tyrosine kinase receptor for stem cell factor. In the heart, c-kit\(^+\) cells are heterogeneous but rare (1 per 10,000 myocytes), and only a minority (7%-10%) express early cardiac transcription factors such as GATA4, Mef2, and Nkx2.5. C-kit\(^+\) cells from human myocardial samples differentiate predominantly into cardiomyocytes and to a lesser extent into endothelial and smooth muscle cells. When injected into the infarcted myocardium of immune-deficient rodents, human c-kit\(^+\) cells form new cardiomyocytes, arterioles, and capillaries.\(^{114}\) Endothelial progenitor cells derived from c-kit\(^+\) cells express Flk-1, can differentiate into cardiomyocytes, and can be found on the walls of coronary arteries.\(^{115}\)

The Administration of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy (SCIPIO) trial was a first-in-human, phase I, randomized, open-label trial of autologous c-kit\(^+\) cells in patients with ischemic cardiomyopathy and LVEF ≤40% in need of coronary artery bypass grafting.\(^{116}\) A total of 33 patients were randomized to receive either intracoronary infusion of 1 million c-kit\(^+\) cells (n = 20) or standard-of-care therapy (n = 13). C-kit\(^+\) cells were harvested from the right atrial appendage during coronary artery bypass grafting, processed, and reinfused intracoronarily into patients 4 months after surgery. Compared to controls, patients receiving c-kit\(^+\) cells demonstrated improved LVEF (from 27.5% ± 1.6% to 41.2% ± 4.5%, \(P = .013\)), reduced infarct size (–9.8 ± 3.5 g, \(P = .039\)), and increased left ventricular mass (+31.5 ± 11.0 g, \(P = .035\)) at 1 year.\(^{116}\) There were no adverse events associated with stem cell harvest.
during coronary artery bypass grafting.

**Cardiosphere and Cardiosphere-Derived Cells**

Cardiospheres are outgrowth cells derived from cultured cardiac explants that grow as self-adherent clusters in vitro. Cardiosphere cells from mice and humans are clonogenic, express stem and endothelial progenitor cell antigens/markers, and appear to have properties of adult cardiac stem cells. They are capable of long-term self-renewal and can differentiate in vitro and after ectopic or orthotopic transplantation to cardiomyocytes, endothelial cells, and smooth muscle cells. Cardiospheres are heterogeneous and contain cardiac progenitor cells in the center surrounded by mesenchymal cells, endothelial cells, and cardiomyocytes in the periphery. To obtain enough cardiosphere cells for therapeutic use, cells can be cultured and expanded as a monolayer of cardiosphere-derived cells over many passages. Human cardiosphere-derived cells are capable of differentiating into all 3 cardiovascular cell types, in vivo and in vitro. They can be easily isolated from a small amount of endocardium and expanded without losing differentiation potential.

The Intracoronary Cardiosphere-Derived Cells for Heart Regeneration After Myocardial Infarction (CADUCEUS) trial was a prospective, randomized, phase I study to evaluate the safety and efficacy of cardiosphere-derived cells in patients with reduced LVEF (≤45%) secondary to ischemic cardiomyopathy. Autologous cardiosphere-derived cells were harvested and expanded from endomyocardial biopsies. Twenty-five patients were randomized to receive infusion of either 12.5 to 25 × 10⁶ cardiosphere-derived cells or placebo into the infarct-related artery 45 to 90 days after MI. Compared to controls, patients treated with cardiosphere-derived cells showed reduction in scar mass (–11.9 ± 6.8 g vs –1.7 ± 7.8 g, respectively, \( P = .008 \)), increased viable heart mass (22.6 ± 9.4 g vs 1.8 ± 8.7 g, respectively, \( P < .001 \)), and improved regional contractility (35.9% ± 31.8% vs 28.4% ± 22.4%, respectively, \( P = .008 \)) at 1 year. These promising initial results have led to the initiation of a larger phase III study using allogeneic cells in patients with recent anterior MI (see Table 68-4).

**Epicardium-Derived Progenitor Cells**
Epicardium-derived progenitor cells are identified by the transcription factors Wilms tumor 1 and/or T-box 18 and can differentiate into cardiomyocytes or endothelial or smooth muscle cells. Wilms tumor 1+ epicardial cells arise from progenitors that express Nkx2.5 and Islet-1, suggesting that they share a developmental origin with these multipotent progenitors. In murine models, MI induces quiescent epicardial cells to become pluripotent epicardium-derived progenitor cells that express stem cell markers c-kit+ and CD34+. During cardiac development, thymosin β4, an actin monomer-binding protein, is expressed in the myocardium, providing a paracrine stimulus to epicardium-derived progenitor cells to promote their inward migration and differentiation into coronary smooth muscle cells. Treatment of cultured adult murine heart explants with thymosin β4 stimulates capillary-like tube formation of adult coronary endothelial cells and increases embryonic endothelial cell migration and proliferation in vitro. Together these studies demonstrate that epicardium-derived progenitor cells provide an attractive population of cells to be used in cardiac regeneration and/or repair. However, these findings must first be validated in humans.

Mobilization of Stem Cells

Granulocyte Colony-Stimulating Factor

G-CSF is a 25-kDa cytokine that regulates both growth and differentiation of hematopoietic progenitor cells and has been routinely used for the treatment of neutropenia and for bone marrow transplantation as it mobilizes bone marrow cells. Various mechanisms have been proposed for the beneficial effects of G-CSF in the infarcted heart, including acceleration of the healing process, protection of salvaged cardiomyocytes from apoptosis, reduction of myocardial fibrosis, and regeneration of the myocardium. The G-CSF receptor is expressed on cardiomyocytes, and it activates the Janus family tyrosine kinase 2 (Jak2) and downstream signaling molecule signal transducer and activator of transcription 3 (STAT3) to prevent cardiomyocyte apoptosis. Importantly, G-CSF mobilizes bone marrow cells, especially CD34+ mononuclear cells, that home to the infarcted myocardium.
**Acute Myocardial Infarction**

There have been several clinical trials studying the utility of G-CSF in acute MI (see Table 68-3). The first was the Effect of Intracoronary Infusion of Peripheral Blood Stem Cells Mobilized With G-CSF on LVEF and Restenosis After Coronary Stenting in Myocardial Infarction (MAGIC) trial.\(^{132}\) Twenty-seven patients with MI who underwent coronary stenting were randomized into 3 groups: G-CSF alone (10 μg/kg × 4 days), G-CSF–mobilized peripheral blood cells (1.0 \(\times 10^9\) cells), or placebo. At 6 months, patients receiving intracoronary infusion of G-CSF–mobilized cells had significant improvements in LVEF. These improvements were not seen in patients who received G-CSF alone.\(^{132}\) Despite these promising results, the study was terminated early due to the high rate of in-stent restenosis observed in patients who received G-CSF (70%) compared to controls. The Front-Integrated Revascularization and Stem Cell Liberation Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor (FIRSTLINE-AMI) Trial randomized 30 patients with acute ST-segment elevation MI undergoing PCI to receive subcutaneous G-CSF at 10 μg/kg for 6 days.\(^{133}\) G-CSF mobilized CD34\(^+\) cells with a 20-fold increase from baseline to day 6, and LVEF improved from 48% to 54% at 4 months and to 56% at 12 months.\(^{133}\)

However, these promising initial results were not repeated in subsequent clinical trials. The Stem cell Mobilization Induced by Subcutaneous Granulocyte Colony-Stimulating Factor to Improve Cardiac Regeneration After Acute ST-Elevation Myocardial Infarction (STEMMI) Trial and the Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells (REVIVAL-2) trial randomized 78 patients and 114 patients with ST-segment elevation MI, respectively, with a similar treatment protocol, but found no effect at 6 months.\(^{134,135}\) Meta-analyses of 10 trials including 445 patients using stem cell mobilization with G-CSF in patients with ST-segment elevation MI found no significant improvement in infarct size or LVEF, although those with lower LVEFs may derive a benefit.\(^{136}\) Importantly, no increase in cardiovascular events or incidence of in-stent restenosis was observed with G-CSF treatment.\(^{132,136}\)

**Chronic Heart Failure**

The G-CSF Stimulation and Coronary Reinfusion of Mobilized Circulating
Mononuclear Proangiogenic Cells in Patients With Chronic Ischemic Heart Disease (TOPCARE-G-CSF) trial randomized 32 patients with previous MI (>3 months) and left ventricular dysfunction to receive either 5 or 10 μg/kg of G-CSF followed by targeted intracoronary infusion of mobilized and cultured circulating mononuclear cells into the infarct-related artery. Although safe, at 5 years, there were no appreciable differences in NYHA class, global left ventricular function, and cardiopulmonary exercise capacity between treatment groups.

FUTURE OF CARDIAC CELL THERAPY

Several large phase II and phase III clinical trials evaluating the use of various stem cells in patients with both acute MI and chronic ischemic heart failure are under way (see Table 68-4). The largest is the Effect of Intracoronary Reinfusion of Bone Marrow–Derived Mononuclear Cells on All-Cause Mortality in Acute Myocardial Infarction (BAMI) trial (ClinicalTrials.gov identifier: NCT01569178). BAMI is a 3000-patient, multinational, multicenter, randomized, controlled, phase III study evaluating the effect on all-cause mortality of a single intracoronary infusion of autologous bone marrow–derived mononuclear cells in patients with ischemic cardiomyopathy (LVEF <45%) after successful reperfusion for acute MI. The Double-Blind, Randomized, Sham-Procedure-Controlled, Parallel-Group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (CEP-41750) in Patients With Chronic Heart Failure due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology Trial will randomize 1730 patients with chronic heart failure to receive transendocardial injection of allogeneic mesenchymal precursor cells or placebo (ClinicalTrials.gov identifier: NCT02032004).

Early clinical experience with largely autologous cell therapy in humans with advanced cardiovascular disease has been somewhat disappointing when compared to the dramatic results observed in experimental animals. These discrepancies are partly because experimental studies are conducted in models without chronic disease and exhaustion of endogenous progenitor cell capacity, which are important considerations in humans with advanced disease. The number and functionality of autologous bone marrow–derived cells are sensitive to pathologic states such as aging, inflammation, and
cardiovascular risk factors. Thus, angiogenic capacity and numbers of transplanted cells are lowest in those with the most advanced cardiovascular diseases.\textsuperscript{139,140} Moreover, recipient characteristics may be equally important in determining efficacy. Little attention has been paid in early clinical trials to the dose of cells administered; cell doses have varied by more than a 1000-fold. There is increasing evidence that higher doses of intracoronary-delivered mononuclear cells after acute MI are accompanied by greater therapeutic effect. Delivery methods and their feasibility have important impact on cell retention and safety. In certain cases, timing of cell therapy, particularly after acute MI, is crucial because very early administration may lead to poor survival of injected cells due to the hostile environment with inflammatory cell infiltration, and delayed administration is likely to encounter irreversible fibrosis and scar. Because of the aforementioned limitations of autologous stem cells and the expense and time it takes for ex vivo expansion, the potential of allogeneic “off-the-shelf” cell therapy using cells from young healthy donors poses an attractive alternative and is currently being investigated in several trials (see Table 68-4).

**CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE**

Peripheral arterial disease (PAD) is a common and underdiagnosed pathologic condition afflicting over 8 million Americans and over 200 million patients worldwide.\textsuperscript{141} Symptoms of PAD include claudication and walking limitation, progressing to critical limb ischemia with rest pain; nonhealing ulcers; and amputations.\textsuperscript{142} The most common cause of PAD is atherosclerosis, but rarely, it is secondary to thromboangiitis obliterans.\textsuperscript{143} Despite surgical or endovascular revascularization, up to 30% of patients have unrevascularizable disease that allows use of cell-based regenerative therapies as alternative treatment modalities.\textsuperscript{144}

Multiple cell types have been investigated in preclinical and clinical trials for the treatment of PAD (Table 68-5). These include unselected bone marrow and peripheral blood mononuclear cells, selected mononuclear cells, adipose-derived cells, and mesenchymal stem cells. These trials have been conducted in subjects with claudication and those with critical limb ischemia.
In addition, cytokine-induced mobilization of bone marrow mononuclear cells has been performed for apheresis of mobilized bone marrow mononuclear cells. The goal of cell therapy in PAD is to promote neovascularization and enhance collateral formation to improve blood flow to ischemic tissue, thereby alleviating symptoms and enhancing limb preservation.

Table 68-5 Summary of Peripheral Arterial Disease Cell Therapy Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. of Controls</th>
<th>Type of Cell</th>
<th>Follow-Up</th>
<th>Outcomes</th>
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<tr>
<td>Tateishi-Yuyama et al145</td>
<td>22</td>
<td>24</td>
<td>BMMNC or BMMNC and PBMC</td>
<td>4, 24 weeks</td>
<td>Improved ABI, TcPO2, limb salvage</td>
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<td>Huang et al146</td>
<td>14</td>
<td>14</td>
<td>G-CSF–mobilized PBMC</td>
<td>3 months</td>
<td>Improved ABI, TcPO2, limb salvage</td>
</tr>
<tr>
<td>Ozturk et al147</td>
<td>20</td>
<td>20</td>
<td>G-CSF–mobilized PBMC</td>
<td>12 weeks</td>
<td>Improved ABI, TcPO2, 6-min walk distance</td>
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<td>Prochazka et al172</td>
<td>42</td>
<td>54</td>
<td>BMMNC</td>
<td>12 months</td>
<td>Improved ABI, limb salvage, no effect on TcPO2</td>
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<tr>
<td>Walter et al173</td>
<td>19</td>
<td>21</td>
<td>BMMNC</td>
<td>3, 6 months</td>
<td>Improved TcPO2, limb salvage, no effect on ABI</td>
</tr>
<tr>
<td>Iafirati et al174</td>
<td>34</td>
<td>12</td>
<td>BMMNC</td>
<td>1, 4, 8, 12 weeks</td>
<td>Improved ABI, TcPO2, limb salvage</td>
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<tr>
<td>Idel et al175</td>
<td>51</td>
<td>46</td>
<td>BMMNC</td>
<td>3-4 years</td>
<td>Improved ABI, TcPO2, limb salvage</td>
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<td>RESTORE-CLI149</td>
<td>58</td>
<td>28</td>
<td>Expanded, multiscellular therapy</td>
<td>12 months</td>
<td>Improved limb salvage</td>
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<td>ACT34-CLI150</td>
<td>16</td>
<td>12</td>
<td>Enriched CD34+ BMMNC</td>
<td>6, 12 months</td>
<td>Improved limb salvage, no effect on ABI</td>
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<td>Marino et al152</td>
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<td>NA</td>
<td>ADRC</td>
<td>3 months</td>
<td>Decreased ulcer size and depth</td>
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<tr>
<td>Poole et al156</td>
<td>80</td>
<td>79</td>
<td>G-CSF</td>
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</tbody>
</table>

Abbreviations: ABI, ankle-brachial index; ADRC, adipose-derived regenerative cells; BMMNC, bone marrow–derived mononuclear cells; G-CSF, granulocyte colony-stimulating factor; NA, not applicable; PBMC, peripheral blood–derived mononuclear cells; TcPO2, transcutaneous oxygen pressure.

**Clinical Trials in PAD With Bone Marrow Mononuclear Cells**

The Therapeutic Angiogenesis Using Cell Transplantation (TACT) trial was the first randomized controlled trial to evaluate the use of bone marrow mononuclear cells in the treatment of PAD.145 In the first arm, 25 patients with unilateral leg ischemia (ankle-brachial index <0.6) received intramuscular injections of bone marrow mononuclear cells (mean 1.6 billion cells) into the gastrocnemius muscle of the ischemic limb and saline into the
less ischemic limb. In the second arm, 22 patients with bilateral leg ischemia received intramuscular injections of bone marrow mononuclear cells in one leg and peripheral blood mononuclear cells in the other. At 4 weeks, ankle-brachial index and transcutaneous oxygen pressure were significantly improved in limbs injected with bone marrow mononuclear cells with concomitant relief in rest pain and pain-free walking time.

Huang et al randomized 28 diabetic patients with critical limb ischemia to receive intramuscular injections of G-CSF mobilized mononuclear cells or placebo. Mononuclear cells were isolated from peripheral blood samples collected after 5 days of daily subcutaneous G-CSF injections. At 3 months, patients receiving cell therapy had significantly improved ankle-brachial index, improved limb ulcer healing, and decreased rates of limb amputation compared to controls. Using a similar protocol, Ozturk et al randomized 40 diabetic patients with critical limb ischemia to receive G-CSF mobilized peripheral blood mononuclear cells or placebo. At 12 weeks, patients receiving cell therapy had significantly improved ankle-brachial indexes, transcutaneous oxygen measurement, and 6-minute walking distance. In both studies, treatment with G-CSF and mononuclear cells was safe and well tolerated.

**Selected Bone Marrow Mononuclear Cells**

Ixmyelocel-T (also known as tissue repair cells) is a closed-culture system expanded patient-specific mixture of bone marrow mononuclear cells enriched for CD90+ cells (expressed on mesenchymal stem cells) and CD45+/CD14+/autofluorescence+ cells (expressed on activated macrophages). The expansion of these 2 cell lines is thought to provide both the endothelial progenitor cells and the cytokine-induced supportive environment needed for angiogenesis and tissue repair. The Use of Tissue Repair Cells in Patients With Peripheral Arterial Disease to Treat Critical Limb Ischemia (RESTORE-CLI) trial is a phase II trial that randomized 86 patients with critical limb ischemia with no options for revascularization to receive intramuscular injections of Ixmyelocel-T or placebo. Patients underwent a mini-bone marrow harvest, and cells were administered by >20 intramuscular injections. At 12 months, treatment with Ixmyelocel-T cells significantly prolonged the time to treatment failure defined as major
amputation, all-cause mortality, doubling of total wound surface area from baseline, or de novo gangrene.\textsuperscript{149} The encouraging results of the RESTORE-CLI trial have led to the initiation of a larger phase III clinical trial.

The Autologous CD34\textsuperscript{+} Cell Therapy for Critical Limb Ischemia (ACT34-CLI) trial is a phase II study evaluating the benefit of autologous G-CSF mobilized CD34\textsuperscript{+} mononuclear cells in patients with critical limb ischemia.\textsuperscript{150} Twenty-eight patients were randomized to receive $10^5$ or $10^6$ CD34\textsuperscript{+} cells/kg or placebo administered by intramuscular injection into 8 sites within the ischemic lower extremity. At 12 months, a dose-dependent trend toward reduced amputation rate was observed with CD34\textsuperscript{+} cell therapy.\textsuperscript{150}

\textbf{Clinical Trials in PAD With Adipose-Derived Regenerative Cells}

The mechanism of ulcer healing by adipose-derived stem cells is based on direct differentiation toward lineage-committed cells or on the production of angiogenic growth factors.\textsuperscript{151} In 10 patients with chronic nonhealing ulcers, 270 g of fat was suctioned from the abdomen, and adipose-derived progenitors were isolated using the Celution system and injected around the ulcer edges.\textsuperscript{152} At 3 months, there was reduction in both diameter and depth of the ulcer, decreased pain, and complete healing of the ulcer in 60% of cases.\textsuperscript{152} This has prompted the initiation of a larger randomized control trial (see Table 68-4).

\textbf{Clinical Trials in PAD With Mesenchymal Stem Cells}

In 41 type 2 diabetic patients with bilateral critical limb ischemia and foot ulcers, bone marrow mesenchymal stem cells, bone marrow–derived mononuclear cells, or normal saline was injected intramuscularly. The ulcer healing rate of the mesenchymal stem cell group was significantly higher than that of mononuclear cell group at 6 weeks and reached 100% 4 weeks earlier than the mononuclear cell group. After 24 weeks, the improvements in limb perfusion induced by the mesenchymal stem cell transplantation were more significant than those by mononuclear cells in terms of pain-free walking time, ankle-brachial index, transcutaneous oxygen pressure, and
magnetic resonance angiography analysis.\textsuperscript{153}

**Clinical Trials in PAD With Bone Marrow Mobilization**

Both experimental and current clinical data indicate that granulocyte-macrophage colony-stimulating factor (GM-CSF) has the capacity to mobilize a variety of progenitor cells including endothelial progenitors that promote neoendothelialization of denuded arteries and improve ischemia in experimental models.\textsuperscript{154,155} A phase I (G-PAD-1) study in subjects with PAD and intermittent claudication demonstrated feasibility and potential efficacy of thrice-weekly subcutaneous injections of GM-CSF at doses ranging from 3 to 10 μg/kg for 2 weeks in improving endothelial dysfunction and symptoms of claudication compared to placebo. In a follow-up phase IIA (G-PAD-II) study, 4 weeks of thrice-weekly treatment with GM-CSF (500 μg/d) improved treadmill walking time and quality of life in subjects with PAD and intermittent claudication. There was a significant but modest improvement of approximately 1 minute in treadmill exercise time after 3 months of therapy.\textsuperscript{156}

A recent meta-analysis by Fadini et al\textsuperscript{143} of 37 cell therapy trials in 701 patients with PAD found that autologous cell therapy was effective at improving ankle-brachial index (from a mean of 0.46 to 0.63), improving pain-free walking distance (from 76 to 402 seconds), and increasing rates of ulcer healing (OR, 3.54). Intramuscular administration of bone marrow mononuclear cells appeared to be more effective than either intra-arterial administration or use of mobilized peripheral blood cells. Overall, procedures for harvesting and administration of progenitor cells were well tolerated.\textsuperscript{134} Wang et al\textsuperscript{157} recently published a meta-analysis of 31 studies involving 1214 patients with PAD. Treatment with autologous bone marrow–derived cells results in significantly improved ankle-brachial indexes at 12, 24, and 48 weeks ($P < .05$) and improved TcO\textsubscript{2} values at 4 and 8 weeks ($P < .001$). Cell therapy was also associated with decreased pain in the short term (<8 weeks; $P < .05$) as well as increased amputation-free survival at 1 and 3 years ($P < .00001$ and $P = .0003$, respectively).\textsuperscript{157} Treatment with autologous bone marrow stem cells was safe and well tolerated and may provide benefit in patients with PAD who are not eligible for revascularization.\textsuperscript{157}

To date, there have been very few randomized clinical trials evaluating
cell therapy in the treatment of PAD (see Table 68-5). Most studies have recruited relatively small numbers with varying degrees of PAD severity ranging from intermittent claudication to critical limb ischemia, and the cell products have largely been autologous bone marrow–derived cells. Reported end points in critical limb ischemia studies have included ankle-brachial index, transcutaneous oxygen saturation, angiography, amputation-free survival, and pain scales. In claudication trials, pain-free walking time/distance, total walking times on treadmill, and walking questionnaires have been also used. Larger clinical trials are under way (see Table 68-4).

CONCLUSION

Although at this time no data support either cell-based or specific stem cell therapies as standard clinical practice for cardiovascular repair, there is a wealth of early clinical data demonstrating the safety, feasibility, and early efficacy of cell-based therapy. The mechanisms by which stem/progenitor cells improve cardiovascular function continue to be investigated with evidence supporting paracrine effects that lead to increased angiogenesis, decreased apoptosis, and induction of endogenous stem cells. Several questions being addressed include (1) the optimal cell type for each disease state, (2) the use of autologous versus allogeneic cells, (3) the optimal cell number, (4) the ideal route of delivery, (5) the timing and frequency of cell therapy in each clinical scenario, and (6) the regulatory and commercial challenges for advancement of this field. Stem cell therapy has the potential to help millions of patients with advanced cardiovascular disease, but its role and clinical practice remains to be defined.

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**MULTIPLE CHOICE QUESTIONS**

1. Which of the following is not a proven mechanism for cell therapy–mediated cardiovascular repair and regeneration?
A. Differentiation or transdifferentiation into new cardiac or vascular cells
B. Secretion of growth factors and cytokines that promote vasculogenesis and prevent apoptosis
C. Stimulation of endogenous cardiac precursor cells
D. Entire organogenesis from injected stem cells

2. Which of the following cellular delivery mechanisms results in the highest retention of delivered cells to the myocardium?
   A. Intracoronary arterial administration to areas of interest with intermittent balloon catheter inflation (stop-flow)
   B. Intravenous injection into a peripheral vein
   C. Direct intramyocardial injection using open surgical or catheter-based approaches
   D. Engineered monolayer tissue transplantation

3. The injection of which stem cell type has been associated with increased risk of ventricular arrhythmias?
   A. Skeletal myoblasts
   B. Bone marrow–derived stem and progenitor cells
   C. Mesenchymal stem cells
   D. Resident cardiac progenitor cells

4. Which of the following are factors that affect the success of stem cell transplantation in the treatment of cardiovascular disease?
   A. Type of stem or progenitor cells transplanted
   B. Ease and feasibility of cell harvesting and culture
   C. Timing of cell therapy
   D. Number of cells administered and retained in target areas
   E. All of the above

5. Which of the following characteristics make mesenchymal stem cells ideal for allogeneic (ie, off the shelf) transplantation?
   A. Paracrine release of soluble growth factors and cytokines
   B. Lack of expression of major histocompatibility complex class II antigens
   C. Downregulation of lymphocyte proliferation and suppression of
immune cell maturation
D. Ability and potential for ex vivo culture and expansion of >50 population doublings
E. All of the above

ANSWERS

1. D
Mechanisms by which cell therapy leads to cardiovascular repair and regeneration remain a subject of controversy. Although differentiation or transdifferentiation into new cardiac or vascular cells was initially believed to be the primary mechanism, recent studies suggest that stimulation of endogenous precursor cells, secretion of growth factors and cytokines (paracrine effect) that promote vasculogenesis and prevent apoptosis, or rarely, fusion of donor cells with host cells may be potential mechanisms. Together, these cellular changes result in enhanced perfusion, reduced infarct size, improved left ventricular remodeling, and ultimately improved cardiac function and patient mortality. Entire organs are not formed from administered stem cells. Most of the regenerated tissue is formed from endogenous cells.

2. C
Intravenous infusion of stem cells is associated with the lowest rates of myocardial cell retention as the majority of intravenous infused cells become trapped in the pulmonary, hepatic, and splenic microvasculature. Intracoronary infusion circumvents the pulmonary and hepatic first-pass effect by delivering cells directly into target areas of myocardium. When delivered using a stop-flow method with intermittent balloon arterial occlusion, there is increased homing to the supplied areas. However, infusion of larger mesenchymal stem cells has been associated with embolization of the microvasculature. Although more invasive and associated with a greater risk of myocardial perforation, transendocardial injection leads to the greatest rates of cell delivery and retention, especially when used in conjunction with electromagnetic mapping catheter systems. Although promising, the use of engineered monolayer tissue transplantation has not been studied in human
Skeletal myoblasts are skeletal muscle precursors that possess a contractile phenotype and are relatively resistant to ischemia and oxidative stress. Although skeletal myoblasts can differentiate into functionally competent myofibers after engraftment, they suffer a high attrition rate. Surviving myofibers fail to develop intercalated discs and remain electromechanically isolated from the host myocardium, which may promote the generation of ventricular arrhythmias. While cell therapy was associated with a higher number of arrhythmic events, it did not result in significant differences in major adverse cardiac events, and the administration of periprocedural amiodarone may be successful in reducing the number of arrhythmic events.

Initial clinical trials involving stem cells were heterogeneous, and the number of cells delivered and retained differed by more than a 1000-fold. There is increasing evidence that higher doses of intracoronary-delivered mononuclear cells after acute myocardial infarction are accompanied by greater therapeutic effect. Delivery methods and their feasibility have important impact on cell retention and safety. In certain cases, timing of cell therapy, particularly after acute myocardial infarction, is crucial as very early administration may lead to poor survival of injected cells due to the hostile environment with inflammatory cell infiltration and delayed administration is likely to encounter irreversible fibrosis and scar. Due to limitations in autologous stem cells and the expense and time it takes for ex vivo expansion, the potential of allogeneic “off-the-shelf” cell therapy using cells from young healthy donors poses an attractive alternative.

Mesenchymal stem cells are rare nonhematopoietic, multipotent cells of mesodermal origin that constitute 0.01% to 0.001% of bone marrow nucleated cells. They influence neighboring cells by direct cell-to-cell interaction and by paracrine release of an array of soluble growth factors and cytokines. Unlike other bone marrow–derived cells, mesenchymal stem cells possess immune properties that make them potential candidates for safe
allogeneic therapy in immune-competent patients. Their relatively immune-
privileged phenotype prevents activation of host immune cells because they
lack surface expression of major histocompatibility complex class II antigens
and costimulatory molecules for T-cell induction. Furthermore, mesenchymal
stem cells downregulate lymphocyte proliferation and suppress the
maturation and function of immune cells via the secretion of soluble factors.
Under optimal conditions, the progeny of colony forming unit fibroblasts can
be expanded for upward of 50 population doublings. Their immune-
privileged phenotype and capacity for ex vivo expansion make them ideal
candidates for allogeneic transplantation.
The Core Laboratory: Quantitative Coronary Angiography

Vivian G. Ng
Alexandra J. Lansky
Johan H. Reiber

BASIC PRINCIPLES OF CORONARY ANGIOGRAPHY AND IMAGING

Coronary angiography remains the gold standard for imaging coronary anatomy and defining the extent and precise location of coronary artery disease. Optimal coronary angiography is dependent on a thorough knowledge of coronary anatomy and a systematic imaging sequence protocol that enables visualization of all coronary segments, particularly areas of vessel overlap, bifurcations, or tortuous anatomy. A basic map of the coronary anatomy is delineated in Figure 69-1, and the optimal views for imaging each coronary segment are summarized in Table 69-1 (Figs. 69-2 through 69-5). Although standard views are generally consistent from one patient to the next, the precise angulations tend to vary based on the variations in anatomic orientations. A number of coronary segment numbering systems have been established; the most commonly used is the Coronary Artery Surgery Study (CASS) numbering system derived from the Bypass Angioplasty Revascularization Investigation (BARI) study,\(^1\) which assigns a unique number to each coronary vessel segment and its branch.
vessels and has gained wide acceptance in interventional clinical trials (Table 69-2).

**FIGURE 69-1** Schematic diagram of the coronary anatomy. AM, acute marginal artery; CB, conus branch; D, diagonal branch; LAD, left anterior descending artery; LCA, left coronary artery; LCx, left circumflex; OM, obtuse marginal artery; PD, posterior descending artery; PL, posterior lateral artery; RCA, right coronary artery; RV, right ventricular artery; S, septal branch; SN, sinus nodal artery.

<table>
<thead>
<tr>
<th>Table 69-1 Views for Optimal Visualization of the Coronary Anatomy</th>
</tr>
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<tbody>
<tr>
<td><strong>AP</strong></td>
</tr>
<tr>
<td>Left main</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>LCx</td>
</tr>
<tr>
<td>RCA</td>
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<td></td>
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Abbreviations: AP, anteroposterior; LAO, left anterior oblique; LAD, left anterior descending (artery); LCx, left circumflex; LM, left main; OM, obtuse marginal; PDA, peripheral distal artery; PLSA, posterolateral spinal artery; RAO, right anterior oblique; RCA, right coronary artery.
FIGURE 69-2 Anteroposterior view of the left coronary artery. Ideal view to visualize the left main coronary segment.
FIGURE 69-3 Left anterior oblique (LAO) view of the left and right coronary arteries. Ideal view to visualize the mid and distal left anterior descending and right coronary arteries.
FIGURE 69-4 Right anterior oblique (RAO) view of the left coronary and right coronary arteries. Ideal view to visualize the left circumflex and mid-right coronary arteries.
FIGURE 69-5 Left lateral (LLat) view of the left and right coronary arteries. Ideal view to visualize the mid and distal segments of the left anterior descending and right coronary arteries.

Table 69-2 Coronary Artery Surgery Study (CASS) Numbering System
<table>
<thead>
<tr>
<th>Segment</th>
<th>CASS Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA, proximal</td>
<td>1</td>
</tr>
<tr>
<td>RCA, mid</td>
<td>2</td>
</tr>
<tr>
<td>RCA, distal</td>
<td>3</td>
</tr>
<tr>
<td>PDA</td>
<td>4</td>
</tr>
<tr>
<td>PLSA</td>
<td>5</td>
</tr>
<tr>
<td>RPL1</td>
<td>6</td>
</tr>
<tr>
<td>RPL2</td>
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</tr>
<tr>
<td>RPL3</td>
<td>8</td>
</tr>
<tr>
<td>RPL4</td>
<td>9</td>
</tr>
<tr>
<td>RV</td>
<td>10</td>
</tr>
<tr>
<td>Left main</td>
<td>11</td>
</tr>
<tr>
<td>LAD, proximal</td>
<td>12</td>
</tr>
<tr>
<td>LAD, mid</td>
<td>13</td>
</tr>
<tr>
<td>LAD, distal</td>
<td>14</td>
</tr>
<tr>
<td>Diagonal 1</td>
<td>15</td>
</tr>
<tr>
<td>Diagonal 2</td>
<td>16</td>
</tr>
<tr>
<td>Septal</td>
<td>17</td>
</tr>
<tr>
<td>Left circumflex, proximal</td>
<td>18</td>
</tr>
<tr>
<td>Left circumflex, distal</td>
<td>19</td>
</tr>
<tr>
<td>Obtuse marginal 1</td>
<td>20</td>
</tr>
<tr>
<td>Obtuse marginal 2</td>
<td>21</td>
</tr>
<tr>
<td>Obtuse marginal 3</td>
<td>22</td>
</tr>
<tr>
<td>LPL1</td>
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</tr>
<tr>
<td>LPL2</td>
<td>24</td>
</tr>
<tr>
<td>LPL3</td>
<td>25</td>
</tr>
<tr>
<td>Left PDA</td>
<td>27</td>
</tr>
<tr>
<td>Ramus (optional)</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: LAD, left anterior descending (artery); PDA, peripheral distal artery; PLSA, posterolateral spinal artery; RCA, right coronary artery; RV, right ventricle. A prefix of “1” is added to the CASS segment to designate saphenous vein grafts and numbered according to the location of the distal anastomotic insertion site of the conduit; a prefix of “2” is affixed to designate an arterial grafts.
The progression and regression of coronary atherosclerotic lesions is a dynamic process.\textsuperscript{2,3} Compensatory mechanisms, known as \textit{coronary artery remodeling}, is a complicating factor in the angiographic evaluation of the severity and extent of coronary atherosclerosis. \textit{Coronary artery remodeling} is characterized by a compensatory enlargement of the atherosclerotic coronary artery that occurs in the early stages of plaque formation\textsuperscript{4,5} and results in the preservation of the luminal cross-sectional area (and angiographic appearance) of the artery, thus minimizing the hemodynamic effects of the atherosclerotic plaque. As the maximal stretching capacities of the vessel are reached, the expansion of the vessel stops, and further plaque deposition begins to impinge on the lumen. It is only once the lumen of the vessel becomes compromised that it becomes visible on x-ray arteriography, which visualizes only the 2-dimensional contrast-filled lumen.

\textbf{Qualitative Angiography}

Typically, atherosclerosis is characterized angiographically as a series of focal narrowings on a background of diffuse atherosclerosis within the entire coronary artery system. Because x-ray arteriography depicts only the coronary lumen, it tends to underestimate the presence of diffuse atherosclerosis and is essentially unable to detect the early stages of coronary atherosclerosis. Cross-sectional imaging of the coronary arteries is better assessed in these early stages by intravascular ultrasound (IVUS), which can provide real-time high-resolution cross-sections of the arterial wall and demonstrate the presence or absence of plaque deposition and compensatory arterial enlargement.

\textbf{Qualitative Assessment of Lesion Morphology}

Several angiographic morphologic characteristics have been identified that have short- and long-term prognostic implications on outcome after coronary intervention with balloon angioplasty and stent implantation.\textsuperscript{6} Recent studies evaluating the prognostic implication of morphologic characteristics on patients undergoing intracoronary stenting demonstrate that these remain predictors of angiographic success, but not clinical outcome. Specific lesion morphologic criteria that contribute to the complexity of a lesion include:
1. Lesion location (proximal, mid, distal, ostial, or anastomotic). Ostial lesions begin within 3 mm of the origin of a major epicardial artery. Anastomotic lesions begin within 3 mm of the insertion of a saphenous vein graft (SVG) or arterial conduits into the native vessel.

2. Lesion length, which is classified as discrete (<10 mm in length), tubular (10-20 mm in length), or diffuse (≥20 mm in length).

3. Eccentricity of the lesion.

4. Angulation of the lesion (Fig. 69-6), classified as mild (<45°), moderate (45°-89°), or severe (≥90°).
FIGURE 69-6 Left anterior oblique (LAO) view of the right coronary artery. Demonstrates a moderately angulated stenosis on a 90° bend.

5. Presence of thrombus (Fig. 69-7).
FIGURE 69-7 Left anterior oblique view of the right coronary artery. This view demonstrates a classic large globular thrombus at the lesion site.

6. Vessel tortuosity (Fig. 69-8), classified by the number of bends present before reaching the target lesion: none/mild (<2 bends), moderate (2 bends >75° or 1 bend >90°), or severe (2 bends >90°).
FIGURE 69-8 Left anterior oblique view of the right coronary artery. This view demonstrates a moderately to severely tortuous vessel with 2 bends more than 90° prior to reaching the stenosis.

7. Calcification.
8. Ulceration, defined by the presence of a crater or lumen flap in the area of
9. Aneurysm, defined by a lumen expansion of at least 50% in the region of maximum stenosis (Fig. 69-9).

![FIGURE 69-9](image)

**FIGURE 69-9** Left and right anterior oblique views of the right coronary artery (RCA). This view demonstrates a large coronary aneurysm in the proximal segment of the RCA.

10. The presence of a bifurcation of the parent vessel with a branch vessel.

These criteria have been used to define the complexity of a lesion and are the basis of the modified American Heart Association (AHA)/American College of Cardiology (ACC) complexity score. Although this scoring system was initially created and validated for predicting outcomes after balloon angioplasty, its utility persists in the modern era of percutaneous coronary interventions. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, patients with moderate- or high-risk non-ST-segment elevation myocardial infarctions were randomized to heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin with glycoprotein IIb/IIIa inhibitor, or bivalirudin alone. After angiography, the patients were triaged to medical therapy, percutaneous intervention, or coronary artery bypass grafts. Among patients treated with percutaneous coronary interventions and who had formal angiographic analysis, patients with type C lesions had higher 30-day rates of mortality (1.2% vs 0.6%; \( P = .049 \)) compared to those without type C lesions. By multivariable analysis, type C lesions were independently
associated with myocardial infarction (odds ratio, 1.37; 95% confidence interval [CI], 1.04-1.80; \( P = .02 \)) at 30 days. Thus, angiographic lesion complexity continues to provide important prognostic information.

1. Type A lesions are characterized by focal (<10 mm length) concentric lesions with smooth contours, little or no calcification, less than totally occlusive, nonangulated (<45° bend), not ostial, without major side branch involvement, and without thrombus.

2. Type B lesions are categorized as type B1 or B2 lesions depending on whether a single or more than 1 B characteristic is present. These include tubular lesions (10-20 mm length), with moderate to severe calcification, eccentric plaque, moderate proximal tortuosity, irregular contour, angulation 45° or more and less than 90°, ostial location, involving a bifurcation, or containing thrombus.

3. Type C lesions have 1 or more of the following complex characteristics: diffuse (≥2 cm length), degenerated SVG, total occlusion, excessive proximal tortuosity, or extreme angulation (≥90°).

**Assessment of Collaterals**

Many factors contribute to the growth of collaterals, including hypoxemia and the release of angiogenic factors. Collateral identification and quantification are important in the context of clinical trials assessing growth factors and revascularization techniques. Collaterals are defined by their site of origin as ipsilateral (collateral between the left anterior descending [LAD] artery and left circumflex [LCx] artery or vice versa), as bridging (collateral originates from the same coronary artery) (Fig. 69-10), or as contralateral (collateral from the left to right coronary artery or vice versa) (Fig. 69-11). The Rentrop Collateral Classification grades the collateral according to the extent of filling of the major epicardial vessel the collateral is supplying.\(^8\) Other less well-validated parameters that have been used for assessing collaterals include the collateral size; the collateral frame count, measured by the number of frames from opacification of the guiding catheter to the filling of the collaterals; and collateral density, measured as the number of collaterals (>1 mm) per square centimeter in a region of interest.\(^9\)
FIGURE 69-10 Right anterior oblique view of the right coronary artery (RCA). Demonstrates a total occlusion in the mid-RCA, with bridging right to right collaterals filling the distal vessel.
Assessment of Flow

The traditional method for assessing and grading epicardial flow was defined by the Thrombolysis in Myocardial Infarction (TIMI) Study Group and was graded according to the following criteria:

1. Grade 0 refers to no anterograde flow beyond the point of arterial occlusion.
2. Grade 1 is defined by the appearance of contrast beyond the point of arterial obstruction but fails to opacify the entire distal coronary bed.
3. Grade 2 is defined by contrast opacification of the entire coronary bed.
distal to the stenosis but at a rate of entry and/or clearance that is slower than in the other epicardial vessels unaffected by the stenosis. Complete filling of the artery and its major and minor branches occurs after more than 3 full cardiac cycles, or alternatively, delayed contrast washout in the target lesion territory may occur, compared with comparable areas of myocardium not perfused by the target lesion.

4. Grade 3 is defined as complete or normal perfusion, with anterograde flow of contrast and complete filling of the artery with its major and minor branches within 3 full cardiac cycles.

Other measures of epicardial perfusion include continuous variables. The TIMI frame count is defined by the number of frames necessary for the contrast column to completely fill the coronary artery at a constant acquisition frame rate. The corrected TIMI frame count is a similar measure that corrects for variability in coronary lengths by using specific anatomic landmarks and specifically corrects for the longer length of the LAD coronary artery.  

The prognostic importance of establishing TIMI-3 flow in patients with acute myocardial infarction has been demonstrated to be the predominant determinant of survival after thrombolytic and primary intervention reperfusion strategies.  

Patients reperfused with primary angioplasty within 2 hours of symptom onset have lower mortality and greater myocardial salvage after primary percutaneous transluminal coronary angioplasty (PTCA) than patients with delayed reperfusion. The importance of early reperfusion is also emphasized in patients spontaneously achieving TIMI-3 flow prior to primary PTCA, as demonstrated in 10% to 20% of patients at the time of initial angiography. Factors influencing early spontaneous reperfusion may include endogenous fibrinolysis and/or pretreatment with aspirin, adenosine diphosphate (ADP) antagonists, and heparin. In an analysis of the 2507 patients from the 4 major Primary Angioplasty in Myocardial Infarction (PAMI) trials, TIMI-3 flow was present at initial angiography (spontaneous reperfusion) in 16% of patients. No baseline demographic characteristics clearly predicted spontaneous reperfusion; however, early reperfusion with initial TIMI-3 flow prior to PTCA was a powerful and independent predictor of in-hospital and late survival in patients undergoing a mechanical reperfusion strategy. The independent impact of initial TIMI-3 flow on survival persisted even when
corrected for postprocedural TIMI-3 flow.\textsuperscript{23} This observation suggests that early pre-PTCA reperfusion has benefits independent of promoting the ultimate restoration of TIMI-3 flow. Furthermore, in the contemporary era of drug-eluting stents, dual antiplatelet therapy, and glycoprotein IIb/IIIa infusions, spontaneous recanalization of the culprit artery continues to be associated with improved outcomes. In the HORIZONS-AMI trial, ST-segment elevation myocardial infarction (STEMI) patients were randomized to either bivalirudin or heparin plus glycoprotein IIb/IIIa inhibitors. Patients with spontaneous TIMI-2 or -3 flow on baseline angiography had lower 1-year mortality rates compared to patients with TIMI-0 or -1 (2.5\% vs 3.9\%, \( P = .04 \)). In addition, spontaneous reperfusion was an independent predictor of improved 1-year survival.\textsuperscript{24}

In contrast, in non–ST-segment elevation myocardial infarctions (NSTEMI), TIMI flow may be less predictive of outcomes. In the ACUITY trial, patients with TIMI-0/1, TIMI-2, or TIMI-3 flow had similar mortality rates at 1 year. Although patients with TIMI-0/1 flow were less likely to achieve TIMI-3 flow postprocedurally, TIMI-0/1 flow was not an independent predictor of 1-year mortality (\( P = .61 \)). Thus, reduced epicardial flow in moderate- and high-risk patients undergoing percutaneous coronary intervention (PCI) is not predictive of outcomes.\textsuperscript{25} It is unclear whether this is related to the pathophysiologic differences between the STEMI and NSTEMI patients. Nevertheless, these results suggest that emergent intervention to restore TIMI-3 flow early is less critical in NSTEMI patients compared to STEMI patients.

Although the main focus of coronary revascularization has been to restore normal epicardial blood flow, it is now widely accepted that normal epicardial blood flow does not necessarily equate to normal microvascular perfusion. Among patients with normal TIMI flow after revascularization, only 19\% to 28\% of patients achieve normal microvascular flow.\textsuperscript{26-29} Reduced perfusion at the tissue level after revascularization may be related to myocardial edema, microvascular spasm, or loss of microvascular integrity as well as distal thromboemoboli.\textsuperscript{30-32} Myocardial blush grade (MBG) is an angiographic surrogate of myocardial perfusion.\textsuperscript{33} The myocardial blush scoring system is based on the extent of ground-glass appearance within the myocardial territory subtended by the coronary artery of interest (Fig. 69-12). MBG is graded as follows:
FIGURE 69-12 Right anterior oblique view of the left coronary artery after primary intervention for acute myocardial infarction of the left anterior descending artery (LAD). A. Region of interest demonstrates minimal myocardial blush in the myocardial territory of the LAD (blush score = 0/1). B. Region of interest demonstrates normal myocardial blush (ground-glass appearance) in the myocardial territory of the LAD (blush score = 3).

1. MBG 0 suggests no ground-glass appearance.
2. MBG 1 is minimal ground-glass appearance.
3. MBG 2 is incomplete opacification of myocardium.
4. MBG 3 is normal myocardial opacification.

Although survival is lowest among patients without TIMI-3 flow after revascularization, MBG has also been shown to be independently predictive of mortality in acute myocardial infarctions after thrombolytic therapy and
after mechanical reperfusion.\textsuperscript{26,27,34} Furthermore, MBG provides risk stratification even among patients with TIMI-3 flow. Thus, despite achieving normal TIMI-3 flow after reperfusion therapy, patients with abnormal microvascular perfusion (MBG 0/1) have a persistently elevated mortality rate compared with patients with TIMI-3 flow and normal MBG.\textsuperscript{28,29,35}

In addition to the importance of MBG in risk stratifying STEMI patients, studies suggest that MBG is predictive of outcomes in NSTEMI patients. In the ACUITY trial, 3115 patients with non–ST-segment elevation acute coronary syndromes (NSTEMI) underwent PCI and had MBG analyzed by a core laboratory. MBG 0/1 was associated with higher rates of composite ischemia (death, myocardial infarction, or ischemia-driven revascularization) at 30-day follow-up and was an independent predictor of 30-day ischemia-driven revascularization. Furthermore, even if TIMI-3 flow was achieved in the culprit vessel, MBG-0/1 was still associated with worse 30-day outcomes. However, at 1 year, patients with or without normal myocardial perfusion had similar outcomes. Thus, MBG provides prognostic information for short-term outcomes in patients with NSTEMI.\textsuperscript{35} Additionally, abnormal myocardial perfusion in areas supplied by nonculprit vessels has also been associated with worse outcomes even when TIMI-3 flow is restored to the culprit vessel.\textsuperscript{36–40} When nonculprit MBG was evaluated in the ACUITY trial, patients with nonculprit MBG 0/1 had higher mortality rates even when there was TIMI-3 flow in the culprit vessel. In fact, in a multivariable analysis, MBG 0/1 in a nonculprit vessel was the strongest predictor of 1-year mortality in patients with culprit vessel TIMI-3 flow. Although abnormal myocardial perfusion in the culprit vessel is often attributed to the distal embolization of thrombus, this mechanism cannot explain impaired perfusion in nonintervened vessels. Instead, impaired perfusion in nonintervened vessels may be related to diffuse inflammation that is triggered by activation of inflammatory pathways locally at the site of plaque disruption.\textsuperscript{36} Therefore, impaired myocardial blush in culprit and nonculprit vessels provides important risk stratification information in NSTEMI patients.

**SYNTAX SCORE**

The SYNTAX score was developed in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial as a means to characterize the
location, severity, and complexity of coronary artery lesions.\textsuperscript{41} The coronary tree is divided into 16 segments, and the segments are weighted by a multiplication factor based on the amount of blood flow normally provided to the left ventricle by each segment. In addition to weighing the amount of myocardium in jeopardy because of a lesion, the SYNTAX score also takes into consideration the severity and complexity of the lesion based on morphologic features such as bifurcation disease, trifurcation disease, ostial lesions, length, tortuosity, heavy calcification, thrombus, and diffuse disease. A score is provided for each lesion, and a summated score is provided for an overall SYNTAX score. Higher SYNTAX scores reflect more disease and possibly more complex disease. An interactive online program consisting of 12 preliminary questions with follow-up subquestions aids in calculating the SYNTAX score (\url{www.syntaxscore.com}). Within the SYNTAX trial, patients with low or intermediate scores had similar outcomes when treated with PCI or coronary artery bypass grafting. However, patients with high SYNTAX scores had worse outcomes when treated with PCI instead of coronary artery bypass grafting. Thus, in addition to providing a method of quantifying the complexity and severity of coronary artery disease, the SYNTAX score could potentially help guide revascularization therapy. However, the complexity of performing this scoring tool may limit its routine use in clinical practice. Although the SYNTAX score has an acceptable interobserver reproducibility and intraobserver reproducibility when performed by core lab technicians,\textsuperscript{42,43} there is poor reproducibility among untrained cardiologists.\textsuperscript{43} The reproducibility among cardiologists improves after additional training with core lab staff.\textsuperscript{43}

**PRINCIPLES OF VENTRICULOGRAPHY AND ANALYSIS CONSIDERATIONS**

Left ventriculography is most accurately performed using 30° right anterior oblique (RAO) and 60° straight left anterior oblique (LAO) (to minimize overlap of the apex and the diaphragm) projections. To evaluate function and wall motion abnormalities quantitatively, the end-diastolic and end-systolic
frames with the minimum and maximum volumes are selected from a well-opacified normal (nonpremature ventricular contraction) sinus beat. Endocardial contours can be traced using commercially available software. Wall motion is most commonly measured by the centerline method along 100 chords constructed perpendicular to a centerline midway between the end-systolic and end-diastolic contours and normalized by the end-diastolic perimeter to standardize chord lengths. This results in a dimensionless shortening fraction, a linear equivalent of the volume ejection fraction. Abnormality in chord motion is reported in units of standard deviation from the mean of normal biplane left ventriculograms, with negative values indicating hypokinesis and positive values indicating hyperkinesis. The centerline method has been extensively validated.

To minimize measurement variability and increase sensitivity and specificity using this method, wall motion in each territory is computed from the average motion of the chords confined to the most abnormally contracting 50% of the territory. The region of the left ventricle in the RAO and LAO projections considered the territory of each coronary artery has been defined from patients with isolated stenoses and infarcts of the LAD, the right coronary artery (RCA), and the LCx (Table 69-3). LCx disease results in widely variable hypokinesis over the entire contour of the left ventricle that spans both anterior and inferior distributions. This is a consequence of the variable anatomy of the LCx, with left dominant systems exhibiting inferior distribution hypokinesis, and right or balanced systems exhibiting anterior hypokinesis. Extended search chord regions have been identified based on patients with known LCx infarcts to increase the sensitivity of detecting LCx regional hypokinesis. In the 30° RAO view, chords 48 to 80 are specific to the LCx (chords 0-21 and 81-100 are excluded because of variability associated with overlap from RCA and LAD territories, making these regions nonspecific to the LCx). The RAO view is less specific than the LAO view for assessing LCx disease. In the 60° LAO view, LCx infarcts result in longer regions of hypokinesis compared to the RAO view, with extended LCx-specific chords spanning from chords 10 through 100 being more sensitive than the previously defined limited chord region of 19 to 67. The LAO view is more specific and sensitive in evaluating the LCx in a right dominant coronary system.

Table 69-3 Left Ventriculography Centerline Method: Defining Arterial Territories
Based on Chords Numbers

<table>
<thead>
<tr>
<th>Coronary Artery</th>
<th>30° RAO Biplane</th>
<th>30° RAO Single</th>
<th>30° LAO Plane</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>12-68</td>
<td>10-67</td>
<td>50-100</td>
</tr>
<tr>
<td>RCA</td>
<td>52-84</td>
<td>51-80</td>
<td>38-74</td>
</tr>
<tr>
<td>LCx right dominant</td>
<td>12-68</td>
<td>(LAD like)</td>
<td>10-100(^4)</td>
</tr>
<tr>
<td>LCx left dominant</td>
<td>52-84</td>
<td>(RCA 48-80 like)</td>
<td>10-100(^5)</td>
</tr>
</tbody>
</table>

\(^4\) LAO best for evaluation LCx of R dominant system behaves more like LAD.
\(^5\) Extended search chords for LCx territory (original limited to chords 19-67).

Abbreviations: LAD, left anterior descending (artery); LAO, left anterior oblique; LCx, left circumflex; RAO, right anterior oblique; RCA, right coronary artery.

**PRINCIPLES OF QUANTITATIVE CORONARY ANGIOGRAPHY**

The field of quantitative coronary angiography (QCA) has evolved tremendously since the mid-1980s concurrently with advances in image acquisition.\(^47\) First-generation QCA systems, developed in the 1980s, were based on 35-mm cine-film analysis. However, cine-film–based x-ray systems were rapidly replaced by complete digital systems. The wide acceptance of the cineless cardiac catheterization laboratory has been spurred by several advantages, including a reduction in radiation exposure necessary for equivalent image processing, reduction in storage space with online image archiving and retrieval, and universal networking.\(^48\)

Second-generation QCA systems (1990-1994) had further improvements in the quality of the edge detection, more frequently applied to digital images (which is not a mere application of the algorithm for cine-based analysis to digital analyses), and included corrections for the overestimation of small vessel sizes (< ~1.2 mm).\(^49\) Digital systems are characterized by well-defined and constant nonlinear functions (the white compression), absence of grain noise, and ability to apply edge enhancement, all of which improve image quality.

Third-generation (1995-1998) QCA systems provided solutions for the quantitative analysis of complex lesion morphology using, for example, the Gradient Field Transform (GFT)\(^50\) and improved diameter function calculations.\(^51\) Fourth-generation QCA systems, available since 1999, are characterized by simplified portability to digital DICOM (Digital Imaging
and Communication in Medicine) viewers, network connectivity, improved reporting and database facilities, and options for specialized QCA functions, such as drug-eluting stent analyses. Although most modern QCA packages are based on the linear programming approach (ie, minimal cost algorithm) for contour detection, there are still differences in the qualities of these packages that must be documented by extensive validation reports.

**Basic Principles of Quantitative Coronary Arteriography**

For a QCA package to be applicable in a routine clinical or research environment, a number of requirements must be met, which include the following: (1) minimal user interaction in the selection and processing of the coronary segment to be analyzed; (2) minimal editing of the automatically determined results; (3) short analysis time (10 seconds or less); and (4) highly accurate and precise results, with small systematic and random errors. These criteria should be demonstrated by extensive validation studies using phantom and routinely acquired clinical studies.

**Basic Principles of Automated Contour Detection**

The general principles and characteristics of a modern QCA software package that satisfies these requirements are best illustrated by the QCA-CMS (Clinical Measurement Solutions, MEDIS) algorithms. The QCA operator selects (Fig. 69-13A) the coronary segment to be analyzed by defining the start and end points of the arterial segment. An arterial pathline through the arterial segment is computed automatically (Fig. 69-13B). The contour-detection procedure is carried out in 2 iterations relative to a model. In the first iteration, the detected pathline is the model. To detect the contours, scanlines are defined perpendicular to the model (Fig. 69-13B). For each point or pixel along such a scanline, the corresponding *edge-strength value* (local change in brightness level) is computed as the weighted sum of the corresponding values of the first- and second-derivative functions applied to the brightness values along these scanlines (Fig. 69-14). The resulting edge-strength values are input to the minimal cost analysis (MCA) contour-detection algorithm, which searches for an optimal contour path along the entire segment (Fig. 69-13C). The individual left and right vessel contours detected in the first iteration now serve as models in the second iteration, in
which the MCA contour-detection procedure is repeated relative to the new models.

**FIGURE 69-13** Basic principles of the minimum cost analysis (MCA) contour-detection algorithm. A. Initial segment. B. Scanlines defined. C. Straightened for analysis; contours calculated. D. Contours returned to initial image; diameter measurements performed.
FIGURE 69-14 Schematic presentation of the brightness profile of an arterial vessel assessed along a scanline perpendicular to the local pathline direction and the computed first derivative, second derivative, and the combinations of these first and second derivative functions; the maximal values of the last functions determine the edge positions.

To correct for the limited resolution of the entire x-ray system, the MCA algorithm is modified in the second iteration based on an analysis of the quality of the imaging chain in terms of its resolution, which is of particular importance for the accurate measurement of small diameters, as in coronary obstructions. If such a correction were not applied, significant overestimation of vessel sizes smaller than approximately 1.2 mm would occur. If the QCA operator does not agree with 1 or more parts of the detected contours, they
can be edited in various ways. However, each manual editing is followed by a local MCA iteration, so that the newly detected contours are truly based on the local brightness information. In other words, the operator indicates roughly where the contour should be detected, and the MCA algorithm searches for the final contour based on the available image information (Fig. 69-13D).

**Calibration Procedure**

Image calibration is performed on a nontapered portion of the contrast-filled catheter using an MCA edge-detection procedure similar to that applied to the arterial segment. In this case, however, additional information is used in the edge-detection process because this part of the catheter is characterized by parallel boundaries. Catheter calibration is frequently the weakest link in the analysis chain because of the variable image quality of the displayed catheters and the potential problem of out-of-plane magnification, which can occur when the catheter and the coronary segment are positioned at different distances from the image intensifier. Biplane calibration can overcome this limitation\(^{56-58}\) but is rarely applied in routine QCA.

**Coronary Segment Analysis**

A diameter function is determined from the contours of the arterial segment (Fig. 69-15). Calculation of the width of a vessel segment along its trajectory is not a trivial task, especially not in a situation of complex anatomy.\(^{51}\) The most widely used parameter to describe the severity of a coronary obstruction is the percentage of diameter narrowing. Calculation of this parameter requires computation of a reference diameter, which can be derived in 1 of 2 ways: (1) a “user-defined” reference diameter is identified by the user at a so-called normal portion of the vessel, or (2) the interpolated reference diameter value is calculated, requiring no user interaction and accounting for vessel taper. The interpolated reference diameter function is calculated by an iterative regression technique that excludes the influence of obstructions or ectatic segments. In cases of extensive ectatic segments, the user can “flag” the portion of the vessel segment (Fig. 69-16B), and the corresponding diameter values are excluded in the subsequent calculation of the reference diameter function. However, correction cannot be made in the presence of
diffuse atherosclerosis along the vessel segment, because angiography is a 2-dimensional lumenogram. The difference in area between the detected lumen contours and the interpolated reference contours is a measure for the atherosclerotic plaque (see Fig. 69-15).

**FIGURE 69-15** The results of the minimal cost analysis, including the reconstructed original vessel contours, plaque area (shaded), and the diameter function, are presented for QCA-CMS V4.0. All the derived absolute and relative quantitative coronary angiography (QCA) parameters are presented in the QCA DICOM box (left).
FIGURE 69-16 Example of a vessel with an ectatic area. A. Straightforward application of the reference diameter function would lead to arbitrary, erroneous results; in this case, in significant tapering of the reference diameter function (arrow). B. By “flagging” the proximal ectatic area, a nontapering reference diameter function (arrow) results with appropriately reconstructed vessel reference contours.

The interpolated reference diameter value corresponding to an obstruction is taken as the value of the reference diameter function at the site of the obstruction, thereby neither overestimating nor underestimating the reference. From the reference diameter value and the obstruction diameter, the percent diameter narrowing is calculated. This automated approach has been found to
be very reproducible. From the calculated diameter function, many
parameters can be determined including obstruction symmetry, inflow and
outflow angles, and the area of the atherosclerotic plaque.

Modern contour detection approaches are based on the MCA algorithm,
which has been demonstrated to be fast and robust for images that may vary
significantly in image quality. This approach has been shown to work very
well as long as the vessel and lesion outlines are relatively smooth. However,
complex vessel morphology may occur before (ulcerated lesions) and after
coronary intervention (dissections).

Densitometry

Because the x-ray arteriogram is a 2-dimensional projection image of a 3-
dimensional structure, measured vessel sizes may be of limited value in
vessels with very irregular cross-sections. Many efforts have been devoted to
deriving information from densitometric measures based on the brightness
within the coronary arteries. If a valid relation between density and arterial
dimensions could be established, other parameters such as the arterial cross-
sectional area could be derived from a single angiographic view.

Unfortunately, densitometry has not provided reliable results, particularly
from cine film,\textsuperscript{59} and as a result, the interest in it has largely diminished. It
may be of interest to revisit the densitometric approaches for the digital
systems in which the entire transfer function of the x-ray system is better
controlled and more stable than with the use of cine film.

QCA of Bifurcations

Bifurcation lesions are coronary artery lesions that are located near or involve
the ostium of a side branch.\textsuperscript{60} A single description based on the section of the
coronary artery and percent stenosis do not adequately characterize the
involvement of the side branch. The Medina Classification classifies
bifurcation lesions by dividing the bifurcation into 3 segments: (1) main
branch proximal, (2) main branch distal (MBD), and (3) side branch (SB). A
binary value (0, 1) is assigned to each branch in the above described order
representing whether a lesion with a >50\% stenosis is present (assigned 1) or
not (assigned 0).

Conventional QCA methodologies cannot be directly applied to
bifurcation lesions because of several obstacles, including image acquisition, defining vessel segments, and accurately identifying reference vessel diameter. For example, while standard QCA requires 2 orthogonal views that are at least 30° apart, there is often only 1 view in which bifurcation lesions are well visualized without foreshortening of either vessel and without vessel overlap. Furthermore, accurately determining the reference vessel diameter of the parent vessel and of the branches is a fundamental challenge to QCA analysis of bifurcation lesions. The diameters of coronary vessels decrease as the proximal main vessel bifurcates, a phenomenon well described in the coronary vasculature and defined by Murray’s law ($D_1^3 = D_2^3 + D_3^3 + \ldots$). Thus, the diameter of the main vessel “steps down” after the branch point. This is problematic because traditional QCA algorithms assume minimal vessel tapering. This results in the reference vessel diameter of the proximal segment of the main branch being underestimated while the reference vessel diameter of the distal main branch is overestimated.

Two dedicated QCA programs are available to improve QCA analysis of bifurcation lesions by decreasing the amount of editing by the user, systematic and random error, and processing time: the Medis Medical Imaging Systems bifurcation application (QAngio XA V 7.3, Leiden, the Netherlands) and CAAS 5 Pie Medical Bifurcation Imaging software (Maastricht, the Netherlands). In both systems, the user defines the proximal start point and the 2 distal branches. Pathlines are created semi-automatically and may be adjusted manually. The arterial contour is generated for all 3-vessel segments following a minimum cost algorithm.

The programs differ in how they define the bifurcation and its measurements. Medis Medical uses 2 bifurcation models depending on the angulation of the side branch. A T-shaped bifurcation model is used when there is a wide angle between the distal main branch and the side branch, whereas a Y-shaped bifurcation model is used when there is a narrow angle between the distal main branch and the side branch. Three separate reference vessel diameters are calculated for the 3 segments (proximal main branch, distal main branch, and side branch) using the conventional Medis straight analysis. The reference vessel diameter for the carinal region is determined from a reconstruction of the 3 segments. In contrast, the carinal region in the CAAS 5 Pie Medical Bifurcation Imaging software is defined as a best fit circle drawn with its center located where all the centerlines meet (point of
bifurcation) and with its edges touching the carina and both vessel walls. The centerlines are lines drawn through the center of each segment. A polygon of confluence is then drawn by drawing lines connecting the luminal walls bounding the circle. This defines the carinal region. Areas outside of the polygon of confluence are analyzed like single vessels.

These systems have been validated in a phantom validation study looking at 6 bifurcation models created in Plexiglas. As expected, the conventional QCA programs underestimated the reference vessel diameter in the main branch while overestimating the reference vessel diameter in the side branch. However, both the CAAS 5 Pie and the Medis Medical software showed high and comparable accuracy and precision in determining the reference vessel diameter and mean luminal diameter and should be used for any bifurcation analysis.65

Functional Assessment of Coronary Artery Lesions

The goal of coronary artery interventions has moved away from revascularization of coronary artery obstructions solely based on visual characteristics to revascularization of coronary artery disease that has objective evidence of ischemia. Fractional flow reserve (FFR)-guided PCI is a major advance in the diagnosis of ischemia in the catheterization laboratory. When patients with stable angina are selectively treated with PCI based on FFR, there is a reduction in major adverse cardiac events rates (death, myocardial infarction, repeat revascularization) compared to angiography-guided PCI alone66 or compared to optimal medical therapy.67 FFR is now a class IA recommendation in the European Society of Cardiology and a class IIa (Level of Evidence A) recommendation in the US joint guidelines.68,69 However, this procedure is not risk-free and requires systemic anticoagulation and the placement of an intracoronary wire. Recently, a method of determining FFR via QCA (FFRQCA) has been developed.70

The current FFRQCA application is simple and can be obtained using standard diagnostic angiographic techniques. Two angiographic projections of each coronary artery with minimal overlap and foreshortening are obtained at least 25° apart. At least 1 projection should be obtained during intracoronary or intravenous adenosine-induced hyperemia in addition to using intracoronary nitroglycerin. A 3-dimensional reconstruction is built based on these images and the hyperemic volumetric flow rates derived from
TIMI frame count and adjusted to parent and daughter vessel flow distribution. The patient’s hematocrit and mean arterial pressure are also inputted into the FFRQCA software. FFRQCA is then derived from computational fluid dynamics applied to the reconstruction of the patient’s entire coronary tree including side branches. By including side branch evaluations, the software can better approximate the amount of myocardium at risk. This method eliminates the risk associated with guide wire and intracoronary wire placement. The processing time for a complete longitudinal FFR computation of each coronary vessel and its side branches is expected to be less than 2 minutes in a fully integrated and automated program. In addition to individual lesion evaluations, FFRQCA would allow for a complete evaluation of the coronary tree.

FFRQCA has been demonstrated to have good diagnostic accuracy (88%), negative predictive value (91%), and positive predictive value (82%) compared with invasive FFR, with an area under the receiver operating characteristic curve of 0.93 in a patient population with intermediate lesions.\(^7^0\) The ease of performing this analysis with minimal impact on routine image acquisition could lead to rapid incorporation of this technology. This diagnostic tool will likely prove valuable in risk stratifying patients with ischemic heart disease by aiding in the identification of lesions causing significant ischemia and by reducing revascularization of insignificant lesions.

**FUTURE DIRECTIONS**

Further development and refinements of networking capability from the catheterization laboratory to the cardiologist’s office and referring hospitals will have major implications on the rapidity and cost of transfer of vital patient information in the form of electronic medical records (EMR), for improved patient care, clinical research, and patient and physician education. Integration of other quantitative modalities, such as QCA and quantitative intravascular ultrasound,\(^5^6\) and in the future, novel diagnostic modalities such as infrared imaging will facilitate and guide the optimal interventional therapy for patients with established obstructive coronary disease and vulnerable plaque. Other angiographic measurement options including 3-dimensional reconstruction\(^5^6,7^1\) and other derived data such as wall shear
stress based on computational fluid dynamics, stress, and strain on the vessels in relation to the sites of the development of local atherosclerosis will further complement derived patient-specific data parameters to optimize therapeutic decision making and outcomes.

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On September 16, 1977, Andreas Gruentzig performed the first coronary angioplasty on a 38-year-old businessman with unstable angina and a discrete proximal left anterior descending (LAD) artery lesion. The procedure was a success, and on subsequent angiograms at 10 years and 23 years, the patient continued to have a patent artery.\textsuperscript{1,2} Gruentzig reported his first series of favorable results and immediately called for a prospective randomized trial comparing it to bypass surgery.\textsuperscript{3,4} The field of interventional cardiology was born, and percutaneous transluminal coronary angioplasty (PTCA) quickly spread, with multiple operators in many countries gaining experience.

Today, percutaneous coronary intervention (PCI) is the dominant form of coronary revascularization. The practice of interventional cardiology has changed dramatically to include numerous diagnostic, pharmacologic, and technologic advances. The challenge for the practicing interventionalist is deciding when to adopt new therapies or technologies, in which patients and clinical situations to apply them, and at what cost. Fortunately, in keeping with Gruentzig’s initial emphasis, the field now requires rigorous scientific
studies to evaluate these new therapies and technologies. As a consequence, the interventional cardiologist is faced with a large body of medical literature of varying quality.

Therefore, a framework for reading and evaluating the medical literature is necessary to make the best decisions for patient care. This practice, termed evidence-based medicine, is defined by Sackett et al\(^5\) as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” Much of the general framework used in this chapter and in most of the current practice of evidence-based medicine has been adapted from the in-depth guide on evaluating and teaching the medical literature provided by Sackett et al.\(^6\) The goal of this chapter is to provide some tools and specific examples that help the reader become facile at reading and evaluating the medical literature, specifically clinical trials with a focus on interventional cardiology.

Sackett and colleagues\(^5,6\) have identified 3 steps as integral to the practice of evidence-based medicine. They are as follows: (1) asking a clinical question and finding an answer, (2) reading the answer article, and (3) applying the results to individual patient care. The first step, asking a clinical question and finding an answer, is not addressed directly in this chapter. With the increase in electronic resources, including PubMed, MEDLINE, and additional online references, most clinicians have access to the medical literature. The majority of the discussion focuses on reading the clinical trial article. Finally, there is a section on applying the results to the care of the individual patient. Many of the principles used in this chapter for evaluating the medical literature can be found in detail in the *JAMA User’s Guide to the Medical Literature* series.\(^7-10\)

**CASE SCENARIO**

You are in the cardiac catheterization lab with a cardiology fellow seeing a 62-year-old businessman with hypertension. The patient recently presented with increasing angina, for which he was admitted to the hospital and ruled out for a myocardial infarction. He was treated with 300 mg of clopidogrel on the night of admission and is now referred for cardiac catheterization. After discussing the diagnostic and potential interventional procedure with the patient, the fellow asks you if it would appropriate to treat the patient with
bivalirudin and provisional glycoprotein IIb/IIIa inhibitor (GPI), because she recalls reading a trial on its benefits. You tell the fellow that is a good question, and she should bring the REPLACE-2 trial to the next catheterization lab meeting for discussion. During your discussion with the fellow, you learn that another patient, a 70-year-old gentleman with an ST-segment elevation myocardial infarction is being brought to the catheterization lab. You ask the fellow to also bring the EUROMAX trial to the next cath lab meeting.

DOES THIS ARTICLE ADDRESS THE QUESTION?

To determine if an article answers a clinical question, a clearly defined clinical question is required. The clinical question is made up of 4 parts: the population or clinical problem, the intervention, the control, and the outcome of interest. The population or clinical problem should be defined as clearly as possible. For instance, in the case presented earlier, this could be a patient with unstable angina and obstructive coronary artery disease. The intervention should be easy to define in many of the clinical situations in interventional cardiology. These can range from pharmacologic to device therapies. Again, in the case of the 62-year-old gentleman above, the intervention is percutaneous intervention with bivalirudin and provisional GPI use. The comparison group may either be a placebo or the current standard of care. This also may be a pharmacologic therapy, interventional device, or usual standard care practices. In this case, the comparison group is heparin and GPI use. Finally, the outcome of interest can be many things. Often, the reader can determine if the outcome measure used in the clinical trial is of interest and clinically important. Death, myocardial infarction (MI), need for urgent target vessel revascularization, or bleeding might all be considered important outcomes for this clinical situation.

In this example, the clinical question could be phrased as, “In patients with coronary artery disease, does percutaneous intervention with bivalirudin and provisional GPI use compared to heparin and GPI use decrease death, MI, urgent target vessel revascularization, or bleeding?” Using these simple
criteria, many clinicians will be able to glance quickly through article titles to determine if the question is addressed. Once this first step in reading a clinical trial is accomplished, the reader can move to step 2, determining if the results are valid.

ARE THE RESULTS VALID?

Determining if the results reported in a clinical trial are valid is the most important and time-consuming step in reading an article. The goal of determining the validity of a study design is to ensure the results reported are accurate. If the experiment or the clinical trial was set up in an unbiased manner, then the results are believable. However, if there is a major flaw in the experimental design, then the reader may interpret the results cautiously and potentially disregard the results. Unfortunately, for many clinical questions about therapeutics, there is no perfect clinical trial design. Therefore, many trials have some aspects that are well designed and conducted and others that are not. The practice of applying the rigorous criteria for validity and determining each trial’s strengths and weaknesses helps lend weight to findings and ultimately helps makes clinical decisions. This ability to weigh different study results helps the reader practice the “judicious use of the best available evidence.”

In addition, understanding clinical trial design helps put future clinical trial results into the context of prior findings with an understanding of previous limitations in the medical literature. The criteria for evaluating the validity of a study depend on the type of study question: therapy, prevention, diagnosis, etiology, or harm. In this section, we review the validity methodology for therapy questions, as these are the most common questions addressed in the medical literature. However, the criteria for the other types of studies are also easily available for review in the JAMA series on using the medical literature.10,13,14

Step 1

Assess Randomization

The first step in determining the validity of a clinical trial evaluating a
therapy is to determine if the study was randomized and follow-up was complete. Randomization is a crucial step in evaluating a therapy and should be considered one of the cornerstones of good trial design. Randomization assures the equal distribution of both measured and unmeasured characteristics that may have an effect on the measured outcome. Not all methods of randomization are the same. Patients can be randomized to a therapy by simple, block, and stratified randomization methods.

Simple randomization is random allocation of either the experimental therapy or the control therapy to the patients. This is usually accomplished with computer-generated random numbers. However, in trials with smaller numbers of patients, there can sometimes be imbalances in the number of patients in each arm of the trial depending on where in the random number sequence enrollment is completed. For this reason, block randomization is used. Block randomization creates blocks (eg, of 4 or 6) in which there are equal numbers of patients receiving the experimental or control therapy. In this fashion, even if enrollment stops in the middle of a block, the imbalance between the numbers of patients in each group is limited.

Stratified randomization is used to achieve balance between important characteristics that may affect the outcome without losing the benefits of randomization. For example, the number of diabetic patients receiving an interventional therapy such as a type of stent may play an important role on the rate of restenosis, the outcome of interest. In this case, a separate randomization sequence would be developed for diabetic and nondiabetic patients. In this manner, the trial would continue to be randomized and have equal numbers of diabetic patients in each group.

The value of randomization cannot be emphasized enough, particularly in interventional cardiology trials. Numerous unmeasured variables that may affect the pharmacologic and device therapies used in addition to the experimental therapy are best controlled with randomization. Without randomization, observational cohorts must attempt to control for these factors by first identifying all of the variables and then applying statistical methods. For this reason, studies evaluating therapies without randomization must be seen as describing associations and not reflecting true effect. Several examples exist in which the findings from observational data were not confirmed in randomized controlled trials, the most notable of which is the effect of estrogen replacement therapy on cardiovascular outcomes.
Assess Loss to Follow-Up

After randomization is determined, the reader must focus on accounting for the patients in the trial. In accordance with the CONSORT guidelines for reporting randomized controlled trials, many trials now provide a diagram showing the flow of all patients in a clinical trial. This helps the reader quickly determine the dropout rate and follow-up of the study. If 500 patients are randomized to a particular interventional device and only 400 are seen in follow-up, then a potential for an unmeasured effect of the therapy exists. While no loss to follow-up would be ideal in preserving the benefits of randomization, this is seldom the case. Sackett et al\textsuperscript{6} have proposed a 5-and-20 rule of thumb, whereby <5\% loss to follow-up leads to little bias and >20\% loss to follow-up poses a serious threat to validity of the results. In trials where a considerable number of patients (~20\%) are lost to follow-up, significant caution must be used in interpreting the results. Even if the patients are not able to undergo all follow-up exams and procedures, the investigators must be able to report the outcome of these patients. If these data are not available, one way to assess whether the loss to follow-up can affect a trial’s results is to assume the worst-case scenario for the missing patients and to see how that would affect the results presented.

Step 2

Look for Blinding

The second step in evaluating the validity of clinical trial design in testing a therapy is in determining blinding. The goal of blinding is to ensure that once randomized, patients get care that is similar outside of the studied or control therapy. Blinding has numerous potential benefits depending on the trial design and individuals or groups that have been blinded. Blinding may reduce biased psychological responses to interventions and increase rates of complying with trial regimen among patients; reduce differential withdrawal, dose adjustment, or interventions by trial investigators; and most importantly, reduce information bias while analysis of the data is performed.\textsuperscript{15}

Blinding should be applied to as many potential parties as possible. In the case of pharmacologic therapies, the medical staff providing care, the patients, and the outcomes assessors can and should all be blinded. This
becomes more difficult in trials evaluating devices in interventional cardiology. It may not be feasible to blind the operator to the type of stent or the use of an atherectomy device. However, the patients, the other medical staff, the clinicians who see the patients in follow-up, the interventionalists who perform repeat angiograms, and the outcomes assessors can all be blinded to the therapy.

In the example cases, the investigators in the REPLACE-2 trial went to great lengths to retain blinding. Prior to randomization, the interventionalist specified a preference for abciximab or eptifibatide as the GPI of choice for the intervention. Each patient then received 3 infusions. In 1 treatment arm, patients received bivalirudin, heparin placebo, and GPI placebo, and in the other treatment arm, patients received bivalirudin placebo, active heparin, and active GPI. A blinded activated clotting time (ACT) was then performed, and active drug was given if the ACT was less than 225 seconds. Finally, if the interventionalist determined that provisional GPI was required, the active bivalirudin arm received active GPI, while the heparin and GPI arm received placebo GPI. In this fashion, blinding of the patients and medical staff was retained, which helped ensure patients in both arms of the trial received similar care during the procedure and afterward. On the other hand, the EUROMAX trial was an open-label trial—both the investigators and the patients were aware of which treatment was being administered. To minimize reporting bias that may be associated with open-label design of trials, the EUROMAX trial had an independent clinical events committee to adjudicate events blindly using standardized end point definitions.

**Compare Baseline Characteristics**

The next step is to determine if the patients were similar at the start of the trial. Most clinical trials present the baseline characteristics of the patients in the first table. If randomization was successful, the patients should be similar with regard to most characteristics. However, if the sample size for a randomized trial is very large, even modest differences may yield statistical significance. In such instances, the reader must be able to differentiate statistical significance from clinical relevance. As mentioned earlier, some important characteristics that affect the outcome may have been stratified, thus ensuring equal numbers of patients in each group. In smaller trials, there are often small differences in the groups. However, we would caution against
making any significant conclusions from these differences and would continue to lend weight to the process of randomization. At best, differences in the groups and direction of potential effect on the results should be noted prior to reading the results.

**Check for Intent-to-Treat Analysis**

The last part of the second step should be to determine how the patients were evaluated at the end of the trial. Specifically, was the analysis of the patients done based on the groups they were randomized to at the start of the trial, regardless of any crossover or dropout? This is defined as the *intent-to-treat principle* and is crucial in interventional clinical trials. This must be differentiated from an analysis of patients who received successful treatment. For example, if a group of patients were randomized to stent implantation or angioplasty, but the analysis for the outcome of urgent target vessel revascularization was carried out only in the group of patients who successfully underwent stent implantation, then the results would be biased toward the stent group. The stent may be difficult to deliver, and patients who were unable to undergo stent implantation may have higher rates of the desired outcome. Therefore, in both pharmacologic and device trials in interventional cardiology, the intent-to-treat principle is critical because it provides a conservative view of the benefit of a therapy, one that may be closer to actual practice.

In the Intra-aortic Balloon Counterpulsation and Infarct Size in Patients With Acute Anterior Myocardial Infarction Without Shock (CRISP AMI) trial, patients with anterior ST-segment elevation myocardial infarction without shock were randomized to receive either routine intra-aortic balloon counterpulsation (IABC) plus PCI or PCI alone. One hundred sixty-one patients were randomized to the IABC plus PCI group, while 176 were randomized to PCI alone. Of the 176 randomized to receive PCI alone, 15 patients crossed over and also received IABC therapy (5 prior to PCI and 10 after PCI). However, these patients were analyzed as part of the PCI-only group to preserve intent-to-treat analysis.

**Step 3**
Assess the Analysis Plan for Intended Comparison

The third step in determining the validity of a clinical trial is assessing the analysis plan. The analysis plan starts with the intended comparison. When the clinical trial is set up and reported, the investigators should specify the intended comparison groups clearly. In addition, when more than 1 therapy is being tested, the comparison groups must be prespecified and appropriate.

For example, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial compared angioplasty with stenting, with or without abciximab, in patients with acute MI. Patients were randomized in a 2-by-2 factorial design, meaning that patients were randomized to angioplasty or stenting and then each group was randomized again to abciximab use or not. The results are that some patients received angioplasty alone, angioplasty with abciximab, stenting alone, and stenting with abciximab. This design conserves resources and addresses 2 questions: What is the value of angioplasty or stenting, and what is the value of abciximab or not?

However, to answer these questions appropriately, the correct groups must be compared. To determine the utility of percutaneous transluminal coronary angioplasty (PTCA) versus stenting in acute MI, the comparison in the trial should be all patients who received PTCA (50% of the patients) versus stenting (50% of the patients). Likewise, when answering the question of the utility of abciximab, the comparison groups must be all patients who received abciximab, irrespective of PTCA or stent status (50% of the patients), versus all patients who did not receive abciximab (50% of the patients). When this latter comparison was carried out, the value of abciximab was found to be significant.

Note the statistical power, or ability to detect the difference between therapies for the primary analysis, that the investigators have chosen for the study. The statistical power depends on many factors, including the criterion for statistical significance that is used, magnitude of the effect that is to be observed, and the sample size of the study. The study should state and meet the minimum sample size required to adequately power the study to detect a specified difference in therapies on the primary outcome. If the minimum sample size is not met for a study, it may fail to detect a difference in treatments for the primary outcome even if one exists. For example, in the EUROMAX trial, it was determined that a sample size of 2200 patients...
would provide a power of 80% for the primary outcome, which was a composite of death from any cause or major bleeding not related to coronary artery bypass grafting (CABG) at 30 days, at a 2-sided $\alpha$ level of 0.05. The primary outcome of the EUROMAX study was originally the composite of death from any cause, reinfarction, or non-CABG major bleeding but was changed during the course of the trial to reduce the necessary sample size to obtain a power of 80%. This is in fact unusual because rarely does a trial reduce the events in the composite as that will reduce the total number of events and would not positively affect power. Reviewers should recognize and review this when seen in the description of a study.

Aside from not performing the correct comparisons, another pitfall is making multiple comparisons at the conclusion of a clinical trial. As mentioned above, the power is calculated for the primary analysis. Multiple comparisons that are performed after the completion of the trial may not have the power to detect a difference, or they may find a difference by chance. A classic example of multiple comparisons yielding a chance finding is the published report from the ISIS-2 investigators that patients with the astrologic sign Libra did not gain a benefit from the use of aspirin at the time of acute MI. This finding clearly does not have a physiologic basis, but it demonstrates the ability of multiple comparisons (12 astrologic signs) to uncover a false finding. Therefore, findings from subgroup analysis should be considered similar to observational analysis. They are hypothesis generating but do not indicate a true effect and should be viewed with caution in trials that demonstrate a consistent benefit of a therapy.

**Check Whether the Trial Assessess Superiority or Noninferiority**

After determining the comparison groups, determine whether the analysis plan is set up to assess superiority or noninferiority. A contemporary trial design in interventional cardiology to account for the rapidly changing pharmacologic and device therapies is the *noninferiority analysis plan*. To understand noninferiority, we must first review the classic superiority trial design. Traditionally, when therapy A was compared against placebo or usual care, the trial was set up to test whether the therapy improved outcome. To do this, the investigators generally postulate that therapy A will lead to a prespecified percentage improvement in the outcome; for example, 30%
improvement in the rate of restenosis. Then the power calculation is used to
determine the number of patients required to demonstrate that percentage
improvement. If the findings are statistically significant, then the therapy has
led to at least the prespecified degree of improvement, if not more. If the
results are not statistically significant, then the therapy has been found to not
improve outcomes by the prespecified amount (eg, 30% improvement in
restenosis in the previous example). The EUROMAX trial was designed to
test whether bivalirudin, initiated during transport for PCI in patients with
ST-segment elevation MIs, was superior to heparin with optional use of GPIs
in contemporary practice. The EUROMAX trial concluded that prehospital
initiation of bivalirudin was indeed superior to heparin with optional use of
GPIs and reduced the primary composite outcome of death or non-CABG
major bleeding at 30 days ($P = .001$), a finding that was driven by the
bleeding reduction. This design mixed both efficacy and safety findings and
should be evaluated as such. Although this design allows the evaluation of
potential superiority of 1 therapy, this trial design does not answer whether
the intervention arm of bivalirudin is superior for reduction in classic major
adverse cardiac events, a finding of interest with the extended infusion.

In contrast to the classic superiority clinical trial design, the noninferiority
trial design attempts to test if a new experimental therapy is not inferior to a
control therapy by retaining a prespecified percentage of the effect of the
control therapy. In the case of the REPLACE-2 trial comparing bivalirudin to
heparin and GPI, noninferiority was defined as the ability of bivalirudin to
retain 50% of the benefit of GPI therapy. Hence, based on the previous
studies, the upper confidence interval for 50% of the benefit of GPI plus
heparin versus heparin therapy was set at an odds ratio of 0.92 (Fig. 70-1). If
the effect of bivalirudin crosses this upper boundary, then the conclusion
would be that bivalirudin does not meet the prespecified noninferiority
criteria, and bivalirudin may indeed be inferior to GPI therapy. Therefore, in
a noninferiority trial, the experimental arm can be slightly worse, identical, or
slightly better in outcome compared with the control, and noninferiority can
be claimed depending on whether the outcome falls within prespecified
boundaries. The findings of the REPLACE-2 trial did find bivalirudin to not
be inferior to GPI plus heparin therapy.
It should be noted, however, that there are examples of trials that have demonstrated the superiority of a therapy, even when the initial trial design is noninferiority. A notable example in interventional cardiology includes the randomized trial of tirofiban versus abciximab in patients undergoing percutaneous revascularization. A 2-tailed analysis of the 95% confidence interval found tirofiban to have a hazard ratio of 1.01 to 1.57 compared to abciximab, demonstrating the superiority of abciximab. It should also be noted that there is no current consensus on the exact boundaries that are prespecified for noninferiority trials. The novel oral anticoagulant studies demonstrate prespecified noninferiority boundaries for warfarin comparator trials.

An important point of clarification is that equivalence does not carry the same meaning as noninferiority with regard to clinical trial design. To establish the equivalence between 2 therapies, both noninferiority and nonsuperiority must be established. This means that the effect of a new therapy and its confidence intervals on both sides must be similar to the control therapy. In fact, the effect of the new therapy could be less than or greater than the control therapy. To demonstrate this, significantly more patients are required to prove true equivalence. It is for this reason that many clinical trials comparing 2 therapies are designed as noninferiority trials, especially when 1 therapy is the standard of care.

Noninferiority trials will continue to occur in interventional cardiology as newer therapies and devices are discovered. As each new therapy is found with some specific advantage, such as cost, ease of use, or safety, trials are
required to demonstrate that the therapy is at least as effective as the prior standard of care. This was the driving force for the design for the TARGET trial, which was designed specifically to demonstrate that tirofiban was noninferior to abciximab because of its considerable cost benefit.

**Design Issues Specific to Interventional Cardiology**

Many of the validity criteria described for evaluating the methodology of therapy clinical trials thus far should be applied to all interventional cardiology trials. However, there are trial issues specific to the field of interventional cardiology that require discussion.

In addition to the noninferiority design already discussed, interventional trials require specific consideration when dealing with devices. To understand the total effect of a new device, the safety and therapeutic effect must be understood. Also, the learning curve required to be able to successfully use the experimental device must also be investigated.

Currently, a new device goes through significant study in the steps prior to the phase III pivotal efficacy and safety trial. Along the way, the device is tested in preclinical studies followed by phase I first-in-human trials, and then phase II optimal use or “dose-ranging” studies. The safety of the device can be evaluated by combining all the data. In addition, a sense of the clinical learning curve is also demonstrated.

Finally, the large phase III therapeutic efficacy trials address many of these same issues. However, as stated earlier, these trials can often not be blinded. Therefore, particular attention must be paid to postapproval surveillance. Often, rare adverse events can be detected only by this method. Unfortunately, complication rates for postapproval device therapy may be vastly underreported, making evaluation of new devices difficult. Both the US Food and Drug Administration (FDA) and industry are working hard to standardize the process for both this special type of therapy trial and postapproval monitoring.

**Step 4**

**Determine a Validity Score**

The fourth and final step in evaluating the validity of a clinical trial design is
to determine a validity score. No clinical trial design is absolutely ideal, and no clinical trial design is absolutely without merit. However, there may be some clinical trials that have fatal flaws in their design that may preclude reviewing the results. In fact, the entire exercise of determining the validity of a clinical trial design and methodology is to assess the strength with which the reader may feel the results mirror actual truth.

As a result, we have found it helpful to stop after reviewing the validity of a clinical trial design and answer 2 simple questions. The first is, “Should the results be viewed?” If the trial is set up with a fatal flaw—the therapies were not randomized or blinded, for example—then the reader should consider not reviewing the results at all. The second question is, “On a scale of 1 to 10, with 10 being the ideal clinical trial design for the specific question, how well was the trial set up?” We have found that putting a numeric value on the validity of the trial design helps in the future when weighing the results and applying them to patient care. If the readers are satisfied with the validity score they assigned to the trial, they should proceed to the interpretation of the results.

WHAT ARE THE RESULTS?

Once the reader determines that the trial was set up with suitable methodology, the results should be interpreted. In general, the results of the treatment effect are presented with regard to a prespecified primary outcome measure.

For example, the SIRIUS trial evaluated the sirolimus-eluting stent versus a standard, bare metal BX Velocity stent in 1058 patients with a newly diagnosed coronary lesion in a native coronary artery. The primary outcome was failure of the target vessel, defined as a composite of death from cardiac causes, MI, and repeated percutaneous or surgical revascularization of the target vessel. Target vessel failure occurred in 21.0% of the patients in the standard stent group and 8.6% of patients in the sirolimus-eluting stent group ($P < .001$). The investigators report that this difference was driven largely by a decrease in the need for target vessel revascularization (16.6% in the standard stent group vs 4.1% in the sirolimus-eluting stent group; $P < .001$).

When looking at the results, it is important to assess whether risk
reduction between therapies is presented as an absolute risk reduction or a relative risk reduction. For example, the above results from the SIRIUS trial are significant and may be better understood in terms of absolute risk reduction as discussed below.

**Absolute Risk Reduction**

The absolute risk reduction (ARR) is a simple calculation that can be performed for any outcome, and it can provide a sense of the overall magnitude of effect. The ARR is defined as the difference in the rates of outcomes for the tested therapy versus the control therapy. In the example of the SIRIUS trial described earlier, the ARR associated with a sirolimus-eluting stent compared to a standard stent for the outcome of target vessel failure is 21.0% – 8.6% = 12.4%. This means 12.4% fewer patients treated with sirolimus-eluting stents will have target vessel failure compared to standard stent therapy.

The ARR can be used to calculate the number needed to treat (NNT). The NNT is calculated as 1/ARR, or, in the earlier example, 1/0.124 = 8. The NNT can be used to express the results of a trial and its magnitude in terms of patients required to demonstrate the desired outcome. In our example, this would be stated as 8 patients must be treated with sirolimus-eluting stent to prevent 1 episode of target vessel failure at 9 months, the duration of follow-up in the clinical trial.

Once multiple trial results are converted to NNTs for each outcome, then it becomes easier to determine the weight of findings from each clinical trial finding. Similar to the SIRIUS trial, the results of the landmark ISIS-2 trial evaluating aspirin, streptokinase, both, or neither in patients with acute MI can also be summarized using NNT.21 The number of patients with acute MI who must be treated with 162 mg of aspirin or streptokinase compared to placebo to prevent 1 vascular death at 5 weeks is 36. In addition, 19 patients must be treated with the combination of aspirin and streptokinase to prevent 1 death within 30 days. These numbers underscore both the strength of the clinical trial findings and the synergy of the therapies when used in combination.

**Relative Risk Reduction**
In contrast to AAR, the relative risk reduction takes into account the actual rate of an outcome. Specifically, the relative risk reduction is calculated by dividing the difference between the therapies by the control event rate (Table 70-1). For example, the CAPRIE trial evaluated 75 mg of clopidogrel a day versus 325 mg of aspirin to reduce the risk of a composite outcome composed of ischemic stroke, MI, or vascular death. In total, 19,185 patients were randomized, and the event rate was 5.32% in the clopidogrel-treated patients versus 5.83% in the aspirin-treated patients. This difference was found to be statistically significant ($P = .043$).

Table 70-1 Calculating Absolute and Relative Risk Reductions

<table>
<thead>
<tr>
<th>Example Rates</th>
<th>Outcome (ie, Restenosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy A (for patients undergoing cardiac catheterization)</td>
<td>3%</td>
</tr>
<tr>
<td>Control therapy (standard therapy for patients undergoing catheterization)</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Formula</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>Control event rate – experimental event rate</td>
<td>5% – 3% = 2%</td>
</tr>
<tr>
<td>RRR</td>
<td>Control event rate – experimental event rate/control event rate</td>
<td>5 – 3/5 x 100 = 40%</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>1/ARR</td>
<td>1/0.02 = 50</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, absolute risk reduction; RRR, relative risk reduction.

In the CAPRIE trial, the investigators correctly report an 8.7% relative risk reduction in favor of the clopidogrel-treated patients. However, the absolute risk reduction (5.83% – 5.32%) is 0.51%. This translates to an NNT of 196. This means the clinician would have to treat 196 patients with clopidogrel instead of aspirin for at least 1 year to prevent 1 ischemic stroke,
MI, or death. Hence, this example demonstrates how the NNT and ARR may provide a better view of the overall strength of trial results compared to relative risk reduction calculations. The use of these terms may help the clinician determine whether the clinical trial findings are clinically important.

**What Are the Adverse Effects?**

The last part of evaluating the results of a clinical trial includes determining any adverse events. Most trials report the rate of adverse events with indication of whether the results are significant. For instance, in the GUSTO trial, tissue plasminogen activator (tPA) resulted in a 0.23% increase in hemorrhagic stroke compared to streptokinase. This percentage can be termed a 0.23% absolute risk increase in hemorrhagic stroke in patients treated with tPA, correlating to a number needed to harm (NNH) of 434. Restated, 434 patients with acute MI must be treated with tPA versus streptokinase to lead to 1 additional hemorrhagic stroke. In this manner, adverse effects of therapies can be put into context with the therapeutic benefits so that clinicians can weigh all the risks and benefits prior to determining clinical significance.

**Statistical Significance Versus Clinical Significance**

Statistical significance is a mathematical evaluation. Clinical trials set out to answer a question by determining the magnitude of effect that would be meaningful to practicing clinicians. They then determine the number of patients needed to adequately address the question with a specific degree of certainty, also known as the power of the trial. Finally, the results are said to meet statistical significance if the findings have less than 5% chance of representing a chance finding. It should be noted that the $P$ value of .05 is an arbitrary standard, and certainly, the level of significance for secondary analyses may require more rigorous statistical standards.\(^{25}\)

In contrast, clinical significance may vary tremendously. The trial assumptions, including the magnitude of the effect, the cost of the therapy, and the outcome tested, may all affect the individual clinician’s determination of clinical significance. The CAPRIE trial, mentioned earlier, did not lead to a change from aspirin to clopidogrel for patients with atherosclerotic disease. However, the CURE trial, which evaluated clopidogrel plus aspirin versus
aspirin alone and found a 2.1% ARR in a composite of death from cardiovascular causes, nonfatal MI, and stroke in patients with acute coronary syndromes, did lead to a change in practice.\textsuperscript{26}

Finally, clinical significance may vary depending on the location of practice, patient population, or provider outlook. The GUSTO trial demonstrated an ARR of 1% in death at 30 days for tPA with intravenous heparin, compared to streptokinase and intravenous heparin in patients with acute MI.\textsuperscript{27} This changed clinical practice in the United States but was not immediately adopted in other parts of the world.

**CONCLUSIONS**

We reviewed a method for reading clinical trials involving therapies with an emphasis on interventional cardiology. The process of determining if the trial answers your clinical question, evaluating the trials for valid methodologic design, and reviewing the results should help provide a framework for a lifelong review of the medical literature. The process of reading the medical literature ends with applying the results to the patient care.

In applying the results to patient care, special emphasis should be placed on whether relevant outcomes, both beneficial and adverse, were considered. Restenosis rates in trials with drug-eluting stents seem like reasonable outcomes. However, practicing clinicians may not routinely perform cardiac catheterizations on asymptomatic patients at 6 months, and this may indeed inflate the rate of the outcome of interest. Also, clinicians must weigh the risks and benefits of each individual therapy with patient characteristics and preferences. This is the art of medicine, and improving one’s ability to appraise the literature critically should only help with this process.

We hope that we have provided some helpful tips and warnings about pitfalls that should help with the critical appraisal of the literature. With the ever-changing face of interventional cardiology; our review of clinical trial design, including noninferiority trial design; valid trial methodology, including randomization and blinding; and assessment of trial results using ARR and NNT should provide the tools to continue to stay abreast of an ever-changing scientific field.
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In my 10 years as editor-in-chief of *JACC: Cardiovascular Interventions*, we have selected about 1500 original research articles for publication. In recent years, the acceptance rate has been around 9%, so the editors have had to be very selective. Papers with high enough priority to be published in the journal have certain characteristics that I will describe in this chapter. There are, however, several other fine journals concentrating on publishing articles specific to interventional cardiology, and some of them have different interests. Also, general cardiology journals and the most selective medical journals also publish interventional cardiovascular papers. So the thought when preparing a research paper should not be, “Will it get published?” but, instead, “Which journal is best suited for my submission?” The answer to that question usually lies in the project itself. A well-planned research project will almost always result in a publishable paper. Knowledge of the type of papers published in each journal will aid in deciding where to send the paper.

When I assumed the role of editor-in-chief of *JACC: Cardiovascular Interventions* and associate editor of *JACC*, Tony DeMaria, the editor-in-chief of *JACC*, had stimulated the associate editors to reflect on how to get a paper published in a highly rated journal.\textsuperscript{1,2} I have modified those ideas over the years and will give you my advice as to what interventional cardiology journals are looking for. The first principle is the project itself. Without a well-planned research project, a publishable paper cannot be written. So what
are the fundamental characteristics of an excellent research paper?

CHARACTERISTICS OF A RESEARCH PAPER

The 3 characteristics that editors are looking for in a research paper are novelty, accuracy, and importance. This thought process of “Is it new, true, and relevant?” goes through the mind of reviewers as well. Perhaps even before these characteristics are considered, the question “Is it interesting?” is entertained. Since the job of editors and reviewers is primarily to select papers that qualify for their journal, one should not underestimate the impact of the first impression. Is it interesting or not?

Novelty

If the question being addressed has not been studied before, then it is ranked highly as novel. There are, of course, levels of novelty, and all authors attempt to justify why the project was undertaken. If the investigation has been done, then it should address what needs to be done in addition. Is it a much larger series or a comparison that confirms prior inadequately powered communications? Does it address a unique application or a unique population that has not been adequately studied? Numerous papers submitted to the journal are sometimes directed toward subsets of large pivotal trials. If these were not reported in the main paper, and especially if prespecified and addressing interesting questions, they are considered to have some novelty.

Accuracy

Is the question addressed in a way that the answers will be true? This does not mean that the findings of the investigation will reflect ultimate truth. No scientific study can claim that, but the findings must be accurate as they relate to the study. The study group characteristics and the protocol are critical components. It is not my interest here to provide a thesis on methodology for designing and performing research or on statistical methods that are valid for various investigations. However, power calculations must be considered.
Here, the input of experts in statistical methods should be encouraged. The methods must be capable of withstanding scrutiny, and they should be validated and reproducible as shown by prior work. They should be as precise as possible, and this will vary based on the data sources that are available for the work. Prospectively collected data are usually superior, but precision in the collection of those data, as well as in collecting retrospective data, is important in judging the validity of a study. Confounding variables can seldom be completely eliminated but must be considered and minimized. Randomization is assumed to remove confounding but does not always do so, and for nonrandomized comparisons, unrecognized confounders are important to consider. When results of nonrandomized comparisons seem too good to be true, the cause is commonly the presence of systematic confounders that cannot be accounted for. We may find that “The sicker patients did worse,” but we may not have identified why they were at greater risk.

**Importance**

The relevance of studies carries a lot of weight when considering publication. Importance of a study is usually viewed in a hierarchical ranking. At the top are things that have implications for patient management. When that reaches the level of potentially changing practice, the highest level of importance has been reached. Areas of relevant importance include when studies establish diagnoses, quantify severity or risk, or define mechanisms by which outcomes are determined. Even when the study is not adequate to establish any of these but generates a novel hypothesis, the paper may be of interest. However, it is true that the statement “This paper is only hypothesis generating” is frequently part of the review of a rejected paper. If the study fails to provide more than a hypothesis for further study, that should be indicated rather than insinuating that the paper answers important questions. In that case, the importance of the hypothesis and the strength of evidence pointing to why it should be studied will be helpful. Finally, even if a study is well done, but the result is not important at all, one should wonder why it was initiated. At an editorial board meeting, when an associate editor discussing a paper says, “So what,” it is a very damaging comment. The methods may have been correct, but the finding is not important.
CONSIDERATIONS WHEN INITIATING A STUDY

I said that a well-planned project usually results in a publishable paper, and I would reemphasize that 90% of a successful paper lies with the planning and execution of the project. Before initiating a study, several questions must be considered. First, identify the question. Then, make sure it has not already been answered. Having a patient base available is not in itself a reason to initiate a project. The question should precede the resources to address it. Then a hypothesis must be generated. Consider the type of study that might address the issue. Some questions cannot be answered without a randomized comparison, while others can. Evaluate whether the resources are available to conduct the study. Is the patient base adequate at 1 institution, or are collaborations necessary? Can a database be accessed, and what is the quality of those data? Consider personnel and financial resources for the study. The final question that should be asked is: “Will the product that is produced be worth the effort that will be necessary?” This is not to say that the answers are predictable; if so, the research is not needed. However, are the question and whatever answers may be obtained interesting?

Type of Study

There is an opinion among many that randomized controlled trials always receive preferential treatment and that there is a bias toward publishing these studies. In the clinical realm, certainly randomized trials are necessary for some questions, but other questions are better answered in other ways. Studies submitted for publication are registries, meta-analyses of prior trials and outcomes research in broad populations, as well as randomized controlled trials. Preclinical studies range from bench testing of new devices or evaluation of existing devices to translational studies using animal models and human feasibility studies. Some questions are addressed with surrogate end points. Pharmacodynamic evaluation of drugs and vascular responses to interventions are examples. When studies of surrogate end points are done, one should be clear on how these surrogates may be related to clinical events, including prior correlation to clinical outcomes.
Strengths and Weaknesses of Randomized Trials

The main strength of randomized controlled trials is the elimination of significant baseline variables, whether recognized or not. It is assumed that if an adequate sample size is enrolled, then the randomization process will evenly distribute factors that are not measured. Some questions cannot be answered without randomization. Since bias on the part of the patient or healthcare team member can influence outcomes, blinding of treatment assignment is also a necessary part of some trials. However, randomized controlled trials can have downsides as well. Common errors are poor design and methods, inadequate power, and highly refined selection criteria that prevent the findings from being applied to patients of interest. On the other hand, some trials can be so broad in their selection that the subjects who do benefit from a therapy are lost in the “forest.” When these mega-trials are carried out, thoughtful consideration of subgroups should be prespecified and, if possible, adequately powered. For many questions, randomization is not possible. Some questions cannot be answered without randomized controlled trials, but some randomized controlled trials cannot answer certain questions.

Strengths and Weaknesses of Nonrandomized Trials

Broader and more inclusive populations can be studied in nonrandomized trials. It is almost always necessary to have a comparator group for nonrandomized trials. Results of registries may look impressive, but the question “Compared to what?” is a killer for publication. Always include a comparator group, and remember that the quality of such a study will depend on how comparable is the comparator. Well-done registries, especially prospective ones, can add validity to smaller randomized trials. The major weakness of nonrandomized comparisons is the unrecognized confounders. Data from many registries come from databases, the quality of which is essential for a believable outcome. Administrative databases are designed primarily for billing and reimbursement reasons, and the clinical data from those codes are often weak and incomplete. Nonetheless, increasing emphasize on “big data” can identify trends that can stimulate more valid investigation of subsets of interest for subsequent randomized trials and well-controlled prospective registries.
Meta-Analyses and Review Papers

Before beginning a study using meta-analytic methods or writing a review, make sure there has not been a reasonably well-done or more recently published one. Also consider the question the meta-analysis is attempting to answer. If the individual components, be they randomized trials or registries, are all in the same direction, a meta-analysis adds little. Meta-analyses are most helpful when there is conflicting information and when larger numbers enable the examination of subsets. The validity of the information gained will depend on the quality of the studies that are included and the homogeneity of the population and methods of the component trials. The best meta-analyses are those utilizing trials with common data entry. In addition, studies are valuable that pool all the baseline and outcome data from individual trials and analyze that data in a new data set. Of course, variation between trials in inclusion criteria, methods, and definitions also limits this approach. Recently, network meta-analysis has gained some acceptance as a way not only to compare treatments among trials comparing similar therapies, but also to draw conclusions from multiple comparisons when some therapies have never been tested directly against each other.

Review papers are frequently invited by journals, but some come de novo for consideration. If such a project is considered, make sure the review is needed because it has not been done recently and because there is new information. Avoid writing a piece that looks more like a book chapter than a review article. Include personal perspectives and make recommendations. Avoid simply providing a synopsis of articles on the subject. Show how the review integrates prior work.

PREPARATION OF A PAPER

The title is the first element seen and should accurately and interestingly capture what the paper is addressing without excessive length. Search engines sometimes look at the first words of a title, so put the key words first. The introduction should clearly state the background for the question (briefly), the question that is being addressed, and the population that is being studied. The methods should be described in specific detail. The validity of the methods should be supported with references. The patient acquisition should be
detailed, as should the control group if the study is nonrandomized. The results should be the easiest part. The primary end point result should be given first before presenting secondary analyses. Details of the results are usually displayed in tabular format but are best appreciated visually in graphs. In crafting the discussion, present the important results in the first paragraph, and do not merely repeat the results section but emphasize synthesis. Give a scholarly and complete review of the pertinent literature but avoid excessive length.

A FEW OTHER TIPS

Consider the length of the author list and realize that including as authors those who do not contribute to the paper is inappropriate. Ensure that the abstract reflects the full paper. Remember that editors and reviewers see the abstract first, so it should be compelling. Remember the figures. Sometimes these are an afterthought, but reviewers and readers are visual animals, and well-designed figures of results and illustrations of case examples are very powerful. All the journals have word limits; do not try to fill space by reaching this limit, and do not exceed the limit. The old adage “If I had more time, I would have written a better paper” is one to which attention should be paid. When the authors are not expert in English grammar, it is often advantageous to enlist a native English speaker to help edit a paper. Although at *JACC: Cardiovascular Interventions* we do not reject papers because of incorrect grammar, a well-written paper is much easier for reviewers to comprehend. If the paper is worth accepting, the grammar can be fixed, but a paper that does not require extensive editing is appreciated by the editors and reviewers. Of course before completing a paper, pay close attention to the instructions to authors on the website of the journal.

In an attempt to appeal to the ever-shortening attention span of readers, we have instituted an alliterative set of questions to provide the clinical perspective. Each paper ends with what’s known, what’s new, and what’s next. By doing this, we hope the reader will get a quick glimpse of which articles are of most interest to them. But in reflecting on it, these three questions should also be considered before starting any project that results in a publishable research paper.
REFERENCES


MULTIPLE CHOICE QUESTIONS

1. Which of the following papers likely receive the highest priority?
   A. A retrospective registry of 50,000 patients collected over 15 years.
   B. A randomized trial of 24 patients examining clinical outcomes.
   C. A pooled analysis of four moderate-sized trials using patient specific data.

2. Randomized trials are best suited to:
   A. Provide accurate results.
   B. Eliminate confounders.
   C. Change practice

3. The most important studies are those that:
   A. Quantify risk.
   B. Establish a diagnosis.
   C. Influence practice.

4. Confounding variables in large databases can be eliminated by propensity matching.
   A. Yes
   B. No

ANSWERS

1. C
2. B
3. C
4. B
Part VIII  Reimbursement and Hospital Finance

Cost-Effectiveness in Interventional Cardiology

Quality Assurance and Quality Improvement in Interventional Cardiology
INTRODUCTION

The management of cardiovascular diseases, especially coronary artery disease, has been revolutionized after Dr. Mason Sones performed the first coronary angiography in 1960 and Dr. Andreas Gruentzig pioneered percutaneous coronary intervention in 1977. Since 1977, percutaneous techniques for coronary angioplasty have significantly evolved. Interventional cardiology has emerged as a subspecialty of cardiology with tremendous potential of impacting patient outcomes in a broad spectrum of cardiovascular diseases including, but not limited to, acute coronary syndromes, stable coronary artery disease, heart failure syndromes, and valvular heart diseases. From the development of ever-improving coronary interventional equipments and techniques to facilitate treatment of the most complex coronary disease to the introduction of catheter-based therapy for nonoperable aortic stenosis, interventional cardiology has seen a major transformation in therapeutic possibilities over the last decade, and the continuously expanding horizon of interventional cardiology well demonstrates its potential beyond just coronary intervention as first witnessed in 1977. Nonetheless, selecting a specific therapy and offering it to the right
patient become challenging in our society of limited resources. Careful evaluation of available evidence becomes vital in determining the appropriateness of a specific intervention, considering both clinical efficacy and cost-effectiveness. Cost-effectiveness of the most significant therapeutic developments in interventional cardiology over the last 2 decades is reviewed in this chapter. A basic approach in cost-effectiveness analysis is briefly reviewed here.

**BASIC APPROACHES AND METHODS OF COST-EFFECTIVENESS ANALYSIS**

**Incremental Cost-Effectiveness Ratio (ICER)**

ICER is a widely utilized and accepted standard to evaluate cost-effectiveness of a particular intervention, and the majority of the studies that are discussed in this chapter have used an ICER as the fundamental metric. The ICER is defined as the incremental cost of providing a specific intervention or therapy divided by the incremental gain in the health benefit.

Thus, any new intervention will be compared to a previous type of care, often the current standard of care. Often the ICER is compared to a standard willingness-to-pay threshold, eg, $50,000 per life-year gained. Values of the ICER below the threshold, also known as the ceiling ratio, would be considered a socially acceptable healthcare expenditure to gain 1 year of life. Thus, in principal, any service that falls below the threshold would be considered cost effective. However, there is no socially acceptable threshold, there are uncertainties in the measurement of cost and efficacy, and society will often spend more than the threshold for patients in acute settings (rule of rescue). This has limited the use of cost-effectiveness analysis for determining policy. However, cost-effectiveness can expose the assumptions underlying our decisions, which can add setting policy.

**Utility Assessment**

Utility is a measure of overall health and functioning, generally scaled from 0 to 1. Thus, for a patient with coronary artery disease suffering from angina, a
utility of 0 would be death and 1 would be perfect health and functioning without chest pain. Utility integrates multiple measures of health status (eg, functional status, symptoms) into a single number (utility or quality of one’s life). However, utility is difficult to measure. It may be estimated from cumbersome trade-off methods such as standard gamble or time trade-off, but survey methods such as the health utility index or EQ-5D tend to be more universally used although less exact.

**Quality-Adjusted Life-Years (QALY)**

Survival time alone, in general, is not considered a satisfactory measure of an outcome in a patient with a utility of <1. Utility may be combined with survival to give QALY, an overall measure that incorporates survival and health status. Utility assessment provides the strongest base to estimate quality-adjusted survival. Incremental gain in QALYs is often used as the measure of overall health benefit, describing not just survival but also quality of that survival, and is often used as a more salient denominator in willingness-to-pay thresholds. Estimation of QALY can be explained with an example of severe angina. Let us consider that living 5 years of life with severe angina is equivalent to 4 years spent in good health. Here the quality adjustment would be 0.8 (4 years in good health/5 years with severe angina); 1 year with severe angina would be 0.8 QALY. Using this equation, 10 years of life with severe angina would be equivalent to 8 QALYs free from angina.

**Life Expectancy**

Time plays an important role in cost-effectiveness analysis. The time horizon of the analysis (determined by the analyst) is the time frame over which the effect of an intervention on cost and health is evaluated. Ideally, time horizon should cover the entire period over which the intervention may have an effect. Such time periods often span across a patient’s lifetime where the intervention affects mortality. Therefore, the selection between lifetime horizon and time horizon based on study follow-up significantly affects the analysis. Life expectancy over a fixed time horizon is similar to the area under the survival curve. For a specific group of patients, for example, surgery may reduce mortality from 3% to 1%, with additional perioperative mortality of 3%. On the other hand, medical therapy for the same group of
patients may reduce mortality from 3% to only 2% with no upfront added mortality. Here estimation of life expectancy, with either medical or surgical therapy, as a function of time horizon (lifetime vs specific cutoff used in the study) would reveal that medical therapy is superior in short-term (in trial) follow-up, but surgical therapy provides a long-term survival benefit.  

**Costing**

Selection of the “perspective” is crucial in cost-effectiveness analysis because societal, payer, and patient perspectives affect specific costs and effects included in the analysis. Societal perspective is the most commonly utilized perspective in cost-effective analysis (CEA). Societal CEAs are often more comprehensive than those performed based on patient or payer perspectives. From a societal perspective, cost is not the same as price; cost is the value of the next best use of the resource. In determining costing, the societal perspective incorporates all resource costs associated with the use of an intervention including physician time, other healthcare resources, and the use of nonhealthcare resources such as caregiver time. Costing methodology also often involves indirect costs, future costs, and the valuation of costs. Indirect costs distinguishes “direct healthcare costs” from “direct nonhealthcare costs” (such as child care costs for a parent undergoing treatment, costs of transportation, and cost of the time a family member spends caring for a disabled relative).

**Modeling With Markov Analysis Versus CEA Alongside Clinical Trials**

QALYs, cost, and the ICER are considered vital measures for CEA. The duration of many clinical trials is usually not long enough for an accurate estimation of the long-term course of a clinical disease. This limits the accurate estimation of the changes in life-years and QALYs with a specific therapy and thus incremental gain in life-years or QALYs. CEA based on in-trial data, in terms of cost per life-year or QALY gained, has limited utility for economic decision making due to short-term follow-up in clinical trials. Therefore, long-term projections of short-term results are often required to estimate cost per life-year or QALY gained. This can be done by developing
a model based on short-term event rates for projecting an average life expectancy and lifetime cost of therapies to derive lifetime ICER or lifetime cost per QALY gained. This can be done by utilizing a Markov decision analytic model. The Markov model is particularly utilized when the disease process involves risk that is continuous over time, when the timing of the event is important, and when the important events (such as myocardial infarction [MI]) occur repeatedly over time. A Markov model is defined by a set of mutually exclusive and exhaustive health states. At any point in time, a person can reside in only 1 health state and for fixed increments of time (known as Markov cycle length). People are assumed to transition from one health state to another depending on a set of transition probabilities. Values are assigned to individual health states, which represent the cost and utility of spending 1 Markov cycle length in that health state. Such values, when combined with time spent in individual health states, help derive estimates of average cost and effect to calculate long-term (beyond trial period) cost-effectiveness of different treatments. A comprehensive review of Markov modeling is beyond the scope of this chapter. However, it can be simplified by CEA of the PLATO (Platelet Inhibition and Patient Outcomes) trial.

The PLATO trial compared ticagrelor and clopidogrel for prevention of cardiovascular events in 18,624 patients presenting with acute coronary syndrome over 12 months. The composite of death from vascular cause, MI, or stroke occurred significantly less frequently in patients receiving ticagrelor compared to clopidogrel (9.8% vs 11.7%, \( P < .0001 \)). Ticagrelor was also associated with significant reduction in MI alone (5.8% vs 6.9%, \( P = .005 \)) and death from any cause (4.5% vs 5.9%, \( P < .001 \)). Rate of major bleeding was comparable between the ticagrelor and clopidogrel groups (11.6% vs 11.2%, \( P = .43 \)). CEA was performed using PLATO data in the Swedish health setting. CEA based on in-trial data, performed over a 12-month period, demonstrated that the total cost was €96 higher in the ticagrelor group than the clopidogrel group. QALYs, estimated based on EQ-5D, were 0.0006 higher in ticagrelor-treated patients compared to clopidogrel-treated patients. For the in-trial period of 12 months, ICER was €160,000/QALY gained with ticagrelor (much higher than the willingness-to-pay threshold of €20,000/QALY gained). Lifetime estimates of CEA, QALY, and cost were created using a Markov model based on the 1-year decision tree from PLATO. The initial start state in the long-term Markov
extrapolation model was either “post MI,” “post stroke,” “no event,” or “dead” (based on the prespecified end point in PLATO). For patients with “no event” in the 12-month period, the annual risk of mortality was estimated based on the age-specific mortality rates from Swedish life tables, and the annual risk of nonfatal MI and nonfatal stroke was estimated based on the observed hazard function of clopidogrel-treated patients. Survival after nonfatal events was modeled by estimating the hazard ratio considering the increased hazard for death after MI or stroke relative to the standard risk of death from life tables. Annual costs associated with the “no event” state and costs after “nonfatal events” were estimated in the Markov model. Cumulative long-term cost was estimated based on the cost in each state of the Markov model. Long-term QALYs were estimated based on age adjustment and by applying decrements with each nonfatal MI and stroke. Lifetime CEA for acute coronary syndrome patients based on Markov model demonstrated an ICER of €2372/life-year gained and €2753/QALY gained, both well within the willingness-to-pay threshold. Therefore, this lifetime CEA demonstrates the limitation of the cost analysis based on in-trial data due to the trial’s short-term follow-up.

**Cost-Effectiveness Plane**

The cost-effectiveness plane is a 2-dimensional display of incremental effectiveness versus incremental cost. Thus, points on the plane represent a graphical display of the ICER. As described in Figure 72-1, it is divided into 4 quadrants. Quadrant B is the most cost effective since it introduces more effective newer treatment strategies at less cost than control treatment option. Conversely in quadrant D, the new therapy is less effective and costs more; it does not make sense from societal perspective to adopt treatment with an ICER in quadrant D. Quadrants A and C both introduce subjectivity in the interpretation of ICER, as the new therapy offers increased effectiveness at increased cost (or decreased effectiveness at lower cost).
FIGURE 72-1 Cost-effectiveness plane. Quadrant B demonstrates that the new treatment is dominant and should be accepted. In quadrant D, new treatment is dominated by control and should not be adopted. In quadrants A and C, adoption of new treatment is reasonable. Incremental cost-effectiveness ratio (ICER) for new therapy should be interpreted against socially acceptable threshold. Occasionally, ICER of new therapy may appear attractive for certain subgroup of population. CER, cost-effectiveness ratio.

**Statistical Approaches in CEA**

**Bootstrap Analysis and the Cost-Effectiveness Plane**

There is uncertainty in the estimation of both effectiveness and cost. CEA must take this into account. Where patient level data from clinical trials are available, the error in calculation of the ICER due to the play of chance (stochastic error) can be evaluated. Thus, using available patient-level data from clinical trials, the 95% confidence intervals (CIs) of both cost and effectiveness can be estimated. The most often used methodology is bootstrap analysis where an empiric estimate of a sampling distribution is made by drawing a large number of samples with replacements from the original data. The bootstrap approach has been considered the most appropriate general method for comparing treatment costs, since it does not make any distributional assumptions in comparing differences in costs and QALYs (or other outcome measures) between the 2 treatment groups. Each estimate of cost and effectiveness derived from the dual bootstrap may then be used to
form an estimation of the ICER.

**Graphical Display of the Distribution of the ICER**

The points from the conjoint bootstrap analysis may then be displayed in the cost-effectiveness plane, offering a graphical representation of the distribution of the ICER.\(^\text{18,19}\) Alternatively, uncertainty due to the play of chance may also be displayed as a cost-effectiveness acceptability curve, where for any willingness-to-pay threshold the probability of the new therapy being cost effective is plotted.\(^\text{3}\) The x-axis is the willingness-to-pay threshold, and the y-axis is the probability of being cost effective. The points on the curve represent the fraction of the ICERs below any threshold. The cost-effectiveness acceptability curve and the display of the distribution of the ICERs in the cost-effectiveness plane are complementary representations of the same data. The ICER distribution on the cost-effectiveness acceptability curve for ticagrelor in acute coronary syndrome (ACS) from the PLATO trial is demonstrated in *Figure 72-2*. The probability of ICER for ticagrelor compared to clopidogrel being \(<20,000/QALY\) gained approached 100% for a wide range of ACS presentations, making ticagrelor a dominant strategy compared with clopidogrel.\(^\text{15}\)
FIGURE 72-2 Cost-effectiveness acceptability curves for ticagrelor in acute coronary syndrome (ACS; based on PLATO trial data). Cost-effectiveness acceptability curve for ticagrelor compared to clopidogrel in PLATO trial demonstrated ticagrelor to be a dominant antiplatelet agent with a high probability for incremental cost-effectiveness ratio (ICER) well under the willingness to pay threshold in a wide spectrum of patients with ACS. NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; QALY, quality-adjusted life-years. (Reproduced from Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Eur Heart J. 2013;34(3):220-228, by permission from Oxford University Press.)

Sensitivity Analysis

Bootstrap analysis, however, will only assess uncertainty due to the play of chance. There may also be bias, where variables used to determine the ICER have additional uncertainty. This may be assessed by sensitivity analysis in addition to the bootstrap analysis. When patient-level data are not available, such as in Markov model simulations, then sensitivity analysis is the only method available to consider the distribution of the ICER. Parameters used in estimating both effectiveness and cost may be varied within limits, often
established from the literature. The validity of assumptions from which parameters for CEA are derived is very important. Sensitivity analysis is performed using different assumptions (reasonable variations in the parameters used in CEA) to derive cost-effectiveness estimates. If these estimates are not significantly different, it underscores the validity of CEA.  

This concept can be further understood with an example of the CEA in the PLATO trial. In the analysis discussed earlier, cost of ticagrelor was considered to be €2.21 per patient per day (as reimbursed in Sweden). The lifetime CEA, based on Markov model, demonstrated ICER of €2372/life-year gained and €2753/QALY gained. If the cost of ticagrelor is considered €3.00 per patient per day, ICER per QALY gained was €4874 (still well below the willingness-to-pay threshold). If the cost and QALY estimates are considered equal for clopidogrel- and ticagrelor-treated groups, cost per QALY was €5204. Here the cost-effectiveness results are only driven by the differences in the clinical events, as demonstrated in the PLATO trial. Similar results were observed with variations in the parameters used for the long-term Markov model and different subgroups such as patients with ST-segment elevation MI (STEMI), non–ST-segment elevation MI (NSTEMI), unstable angina (UA), and diabetes. Thus, the sensitivity analysis demonstrates validity of various assumptions used in the CEA by consistently demonstrating ticagrelor to be a dominant strategy compared to clopidogrel for patients presenting with ACS.

**Interpretation and Projections From Randomized Clinical Trials**

Short-term trial data are often extrapolated to lifetime estimates to arrive at cost per life-year gained or cost per QALY gained. These lifetime estimates for new treatment are often compared against other conventionally accepted treatment strategies. Such lifetime estimates have important implications on policy setting. Interpretation and generalization from clinical trials with few years of follow-up to lifetime outcomes should be done with caution. Survival, utility, cost structure, practice patterns, and resource utilization can have a wide range of variations, with uncertainty becoming greater the more that short-term data are extrapolated.
Primary Percutaneous Coronary Intervention Versus Thrombolysis in Acute Myocardial Infarction

Primary percutaneous coronary intervention (PCI) is widely accepted as the preferred treatment modality for patients presenting with acute MI, with intravenous thrombolysis reserved for patients who cannot be transferred to a PCI-capable hospital within 60 minutes from presentation. Compared to thrombolytics, primary angioplasty has demonstrated less in-hospital mortality, lower in-hospital and 6-month rates of reinfarction, and less death. Further, primary angioplasty is associated with lower rates of fatal bleeding complications, including intracranial hemorrhage. The cost of either approach depends on initial hospitalization, initial cost of revascularization, subsequent readmission, subsequent investigations and interventions, adjuvant use of antiplatelet and anticoagulant agents, outpatient care, and work loss.

Five-year comparative effectiveness of angioplasty versus thrombolytic therapy was evaluated in a cohort of 395 patients enrolled between 1990 and 1993. All-cause mortality was significantly lower in the angioplasty group compared to the streptokinase group during the first 30 days (1% vs 7%, \( P = .01 \)) and during 5-year follow up (13% vs 24%, \( P = .01 \)). The streptokinase group required significantly higher revascularization procedures during the 5-year follow-up period. This study demonstrated that per patient, total medical charges at the end of the follow-up period were lower in the primary angioplasty group compared to the streptokinase group ($16,090 vs $16,813, \( P = .05 \)). Total charges per patient for those who were alive at the end of follow-up trended toward being lower in the angioplasty group ($18,664 vs $21,772, \( P = .08 \)). This medical cost consisted of days spent in the hospital, diagnostic and therapeutic procedures, and medications used during the follow-up period calculated as per-hospital charges in 1992.

In a substudy of the CAPTIM trial (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction), the cost efficacy of primary PCI was compared against alteplase, a more potent thrombolytic
agent than streptokinase.\textsuperscript{23} In the overall study (randomized multicenter trial of 840 patients), investigators compared primary PCI to prehospital thrombolysis for patients presenting with STEMI. All prehospital thrombolysis patients were transferred to a PCI center for further management and rescue angioplasty. The trial showed that primary angioplasty was not better (for death, nonfatal MI, and stroke) than prehospital thrombolysis with rescue PCI at 30 days, but the primary PCI group had a significantly lower composite of death, nonfatal MI, stroke, revascularization, and major bleeding (34\% vs 61\%, \(P = .0001\)). In the cost-efficacy substudy, 299 patients were enrolled at 3 participating sites between 1997 and 2000. Cost data were prospectively collected during initial hospitalization and during 1-year follow-up. The primary PCI group had significantly lower cost of hospitalization by $883 compared to the thrombolysis group.\textsuperscript{23} Longer length of hospitalization and cost of thrombolytic agents offset the initial higher cost of angioplasty. This difference in cost persisted at 1 year ($1224 lower in the angioplasty group than the prethrombolysis group, \(P < .04\)).\textsuperscript{23}

Cost and health outcomes comparing primary PCI and thrombolysis in patients presenting with STEMI have been more comprehensively evaluated in the SWEDES trial.\textsuperscript{24} The trial compared strategies of primary PCI with enoxaparin and abciximab versus thrombolysis with enoxaparin. Antiplatelet regimens were similar. In-hospital and 1-year clinical outcomes (death, nonfatal MI, stroke) were similar between the 2 groups.\textsuperscript{24} Quality-adjusted weight was obtained using EQ-5D questionnaire to calculate quality-adjusted survival. At 1 year, cost of intervention per patient in the PCI group was higher than the thrombolysis group ($4602 vs $3807, \(P = .047\)). The cost of antiplatelet agents was also higher in the PCI group ($1309 vs $1202, \(P = .001\)). The cost of hospitalization was higher in the thrombolysis group ($9278 vs $7244, \(P = .02\)). Combined cost of care per patient at 1 year was not significantly different between the 2 groups ($25,315 in PCI group vs $27,819 in thrombolysis group). Quality-adjusted survival remained marginally higher in the PCI group compared to the thrombolysis group (0.759 vs 0.728). In cost utility analysis, there was a trend toward $2504 less annual cost per patient and a 0.031 gain in quality-adjusted survival in the PCI group compared to the thrombolysis group. This trend, although statistical nonsignificant, appeared to be driven by less repeat hospitalizations in the PCI group. As depicted in Figure 72-3, PCI remained a cost-effective
strategy in 88% and 89% of bootstrap replications when using threshold values of $50,000 and $100,000/QALY gained, respectively.

**FIGURE 72-3** Primary percutaneous coronary intervention (PCI) is more cost effective than thrombolysis in patients presenting with ST-segment elevation myocardial infarction (STEMI) at 1 year follow-up (SWEDES trial). Graphical distribution of the incremental cost and quality-adjusted survival with primary PCI in STEMI patients compared to thrombolysis, based on 5000 bootstrap replications. Primary PCI is a favorable strategy since majority of the bootstrap replications are in right lower quadrant of cost-effectiveness plane and below the socially accepted threshold of $50,000/QALY gained. QALY, quality-adjusted life-year; USD, US dollars. (Reproduced from Aasa M, Henriksson M, Dellborg M, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction-Results of the Swedish Early Decision reperfusion Study (SWEDES) trial. *Am Heart J*. 2010;160:322-328, Copyright © 2010, with permission from Elsevier.)

In summary, primary PCI, as a first-line therapy in the management of patients with STEMI, is cost effective up to 5 years, primarily due to reduced rates of repeat hospitalization in the follow-up period.22–24

*Early Invasive Versus Conservative Management of Patients Presenting With UA/NSTEMI*
Clinical outcomes with an early invasive strategy are superior compared to the conservative management for patients presenting with UA or NSTEMI. Both strategies affect cost of care at several levels including hospitalization, emergency room visits, diagnostics and interventions, cardiac medications, rehabilitation and nursing home stay, and outpatient physician follow-up.

The TACTICS-TIMI-18 trial (Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive Versus Conservative Strategy–Thrombolysis in Myocardial Infarction-18) demonstrated that the composite of death, MI, or rehospitalization for ACS at 6 months was significantly lower in the early invasive group (within 48 hours) compared to the conservative group (16% vs 21%, \(P = .03\)). The treatment strategy in TACTICS-TIMI-18 was contemporary and inclusive of both coronary stenting and use of glycoprotein IIb/IIIa inhibition, favoring generalizability of clinical and economic findings to current clinical practice. Average initial cost of hospitalization appeared higher with an early invasive therapy compared to the conservative approach ($15,714 vs $14,047). As expected, initial rates of hospitalization and revascularization procedures (PCI and coronary artery bypass grafting [CABG]) were higher with an early invasive approach despite the significantly shorter length of stay especially in the high-risk populations (older, diabetic, and ischemic electrocardiogram [ECG] changes). This early increase in cost, however, was offset by lower 6-month follow-up costs for the early invasive arm, primarily due to reduced rates of rehospitalization. Total 6-month cost, therefore, remained comparable between the 2 treatment strategies. The ICER for death or MI prevented was $25,478 with an early invasive approach. Considering the time horizon of 6 months and CEA based on in-trial data, QALY and health utility status remained unchanged between the 2 groups.

However, applying life expectancy data from both these methods to the entire TACTICS-TIMI-18 study population demonstrated a significant advantage to the early invasive approach. The Framingham Heart Study and PURSUIT/Duke trial projections were used to estimate lifetime cost-effectiveness. Specifically, this analysis revealed that ICER with an early invasive approach for NSTEMI/UA patients is within society’s willingness-to-pay threshold (ICER of $16,272/life-year gained using Framingham Heart Study and ICER of $22,538/life-year gained based on the PURSUIT trial).

Economic benefits of the early invasive approach as observed in
TACTICS-TIMI-18 remained unchanged when subsequent developments in medical therapy and revascularization approaches were considered (eg, drug-eluting stents [DES]). The RITA-3 trial (Randomized Intervention Trial of Unstable Angina-3) demonstrated that high-risk patients (older, diabetic, positive biomarkers, and ST-segment changes on ECG) had the highest economic benefit of the early invasive approach at 5-year follow-up. The TACTICS-TIMI-18 trial provided insight into this observation, but RITA-3 (larger sample and longer follow-up) conceptualized it more definitively. Further, clinical efficacy of the early invasive approach was demonstrated in a United Kingdom–based population at 5-year follow-up compared to the conservative therapy in a randomized multicenter comparison of 1810 patients presenting with NSTEMI (composite of death and nonfatal MI: 16.6% vs 20%, \( P = .04 \)). The ICER with either strategy among low-, intermediate-, and high-risk patients was compared to societal threshold of £20,000 to £30,000 per QALY gained. A Markov model was constructed to evaluate lifetime cost-effectiveness beyond the 5-year trial follow-up. This multivariate model created low-, intermediate-, and high-risk groups based on 5-year prediction of death or MI. The ICER was approximately £55,000, £22,000 and £12,000 per QALY gained for the low-, intermediate-, and high-risk groups, respectively.

It appears that the early invasive approach compared to conservative management for patients presenting with UA/NSTEMI is cost effective, especially for the high-risk patient population,  

**Optimal Medical Therapy (OMT) Versus Initial Revascularization in Stable Coronary Artery Disease (CAD)**

The COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) provides the most comprehensive long-term outcomes data of stable CAD patients managed with OMT compared to PCI plus OMT in 2287 patients with 4.6-year follow-up. There was no difference in the primary end point of death or MI between groups; however, the PCI group had more angina relief and improved quality of life. Index resource utilization was significantly higher in the PCI group compared to the OMT group ($12,162 vs $752), but subsequent resource utilization was comparable
($22,681 vs $23,996, respectively). The higher in-trial cost was driven by higher initial cost of PCI. CEA of COURAGE trial demonstrated that addition of PCI as an initial management strategy for symptomatic chronic stable angina patients results in an ICER between $168,000 and $300,000 per life-year or QALY gained. Life expectancy beyond the trial period was estimated by Framingham survival data. In-trial and lifetime cost estimates for the PCI group remained significantly higher than the medical therapy group ($11,410 and $9451, respectively). The ICER/QALY gained for PCI was $206,229 for the trial period and $168,019 for lifetime. Therefore, medical therapy appeared to be dominant (better outcome at lower cost) (Fig. 72-4A). The cost-effectiveness acceptability curve demonstrated that at the $50,000 ICER/QALY gained threshold, PCI was rarely cost effective for the in-trial period, and there was only a 25% probability for lifetime. At the $100,000 threshold, the probability of ICER/QALY gained with PCI was <25% for the in-trial period and 41% for lifetime (Fig. 72-4B). This raised a question of which patients with chronic angina may derive cost-effective benefit from PCI as an initial management approach. In another cost-effectiveness substudy of the COURAGE trial, the ICER for PCI was evaluated in 3 quartiles of patients with chronic angina. These quartiles were defined by identifying health status among 3 domains of Seattle Angina Questionnaire (physical limitation, angina frequency, and quality of life). The ICER for PCI ranged from $80,000 to $330,000 for patients with intermediate to severe angina (lowest and middle quartile), whereas it ranged from $520,000 to $3 million in mild (upper quartile) angina. Therefore, at any level of angina severity, PCI as an initial strategy did not appear to be cost effective at socially acceptable cost thresholds.
Joint distribution of cost & effectiveness differences

ICER point estimate:
$188,019/QALY gained

(cost difference: $9451,
QALY difference: 0.036)

$50,000/QALY gained threshold

$100,000/QALY gained threshold

A

Mean effectiveness difference (PCI-medical therapy)

Cost-effectiveness acceptability curve

Probability of ICER below threshold

Incremental CE ratio threshold ($)

B
FIGURE 72-4 Joint distribution of cost and effectiveness differences in cost-effectiveness plane (COURAGE trial). A. Percutaneous coronary intervention (PCI) was dominated by medical therapy at an ICER threshold of $50,000/QALY and $100,000/QALY gained. B. CE acceptability curve shows that PCI was cost effective <25% of the time for the ICER threshold of $50,000/QALY and 41% of the time for the ICER threshold of $100,000/QALY on lifetime horizon, making medical therapy a dominant initial strategy for stable coronary artery disease. CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years. (Reproduced from Weintraub WS, Boden WE, Zhang Z, et al. Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. Circ Cardiovasc Qual Outcomes. 2008;1(1):12-20.)

The BARI-2D trial (Bypass Angioplasty Revascularization Investigation-2 Diabetes) randomly compared revascularization plus OMT (1176 patients; 378 with CABG and 798 with PCI) versus OMT alone (1192 patients) in a total of 2368 patients with type 2 diabetes mellitus and CAD over a 5-year follow-up and demonstrated comparable all-cause mortality as well as combined death/MI/cerebrovascular accident between the 2 groups. Four-year cost analysis showed that prompt revascularization (either catheter based or surgery based) was not favorable compared to OMT for in-trial or lifetime cost estimates. In the PCI stratum, medical therapy yielded slightly higher QALY compared to PCI (3.25 vs 3.22) at significantly lower cost ($67,800 vs $73,400, P = .02) for the in-trial period, making it the dominant strategy (quadrant B in the cost-effectiveness plan). Prompt revascularization with CABG was more costly and less effective at 4 years compared to medical therapy. However, lifetime estimates showed that CABG compared to medical therapy increased survival from 12.9 to 13.42 years at only marginally higher cost ($235,500 vs $210,900), yielding an ICER of $47,000/life-year gained. Therefore, prompt revascularization with PCI did not appear to be cost effective compared to medical therapy. However, revascularization with CABG may be cost effective for lifetime estimates.

Methods of Revascularization for Left Main or Multivessel Coronary Artery Disease

Although CABG is still considered the revascularization method of choice for multivessel or left main coronary disease, PCI has become an increasingly utilized revascularization method for certain multivessel and left main CADs,
largely due to the advent and evolution of DES. Long-term follow-up data from randomized clinical trials comparing CABG and PCI for multivessel coronary disease have suggested that both groups are comparable in death and nonfatal MI. However, the PCI group has significantly increased rates of repeat revascularization procedures during 8 to 12 years of reported follow-up.\textsuperscript{31,32}

Initial cost comparison data between CABG and PCI comes from EAST (Emory Angioplasty Versus Surgery Trial). Total costs of CABG and PCI were comparable during the 8-year follow-up period ($46,548 vs $44,491).\textsuperscript{31} However, initial observations in EAST demonstrated higher revascularization costs with PCI, which were confirmed in subsequent economic and quality-of-life data analyses in the BARI trial (Bypass Angioplasty Revascularization Investigation). CEA of the BARI trial over a 12-year follow-up period suggested that the initial higher medical cost of bypass surgery was offset by lower subsequent revascularization procedures and hospitalizations during follow-up compared to PCI ($123,000 for CABG vs $120,750 for PCI, $P = \cdot .55).\textsuperscript{32} Initial cost of CABG was 54\% higher than PCI, but the ICER for CABG at 12 years compared to PCI was $14,300/life-year gained for the in- trial period and $13,300/life-year gained for lifetime.\textsuperscript{32} Using the Duke Activity Status Index and RAND Mental Health Inventory V, the QALYs were 6.45 years for PCI and 6.58 years for CABG, yielding an ICER of $11,300/QALY gained for CABG.\textsuperscript{32} Despite the use of balloon angioplasty as the percutaneous revascularization method in EAST and BARI, increased rates of revascularization and the associated cost persisted with the use of BMS. For instance, the ARTS trial (Arterial Revascularization Therapy Study) demonstrated comparable death and MI at 3 years between CABG and PCI, but significantly increased rates of repeat revascularization in the PCI arm. The ICER for CABG per event-free patient (death, MI, or cerebrovascular accident [CVA]) was €10,492 at 3 years (well below the ICER threshold of €20,000-30,000/QALY or life-year gained).\textsuperscript{33}

Early studies that demonstrated higher rates of repeat revascularization in patients with multivessel CAD, especially with diabetes, attributed these findings largely to the use of balloon angioplasty or BMS for revascularization in the PCI group, which are known to perform less well than DES.\textsuperscript{32,33} The FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel
Disease) compared the outcomes of multivessel coronary disease with either PCI using DES or CABG in patients with diabetes. At 5 years of follow-up, the primary composite of death, nonfatal MI, and CVA was significantly higher in the PCI group compared to CABG (26.6 vs 18.7, \( P = .005 \)), again demonstrating that CABG as a revascularization strategy outperformed PCI in this population, despite the use of the most contemporary and best-performing percutaneous material.\(^{34}\) Index hospitalization cost was higher in the CABG group compared to DES-PCI by $8622. Five-year cumulative cost was also slightly higher in the CABG group by $3641.\(^{34}\) However, CABG was associated with a gain in life expectancy of 0.794 years and an overall quality-adjusted life expectancy of 0.663 QALY.\(^{34}\) Therefore, economic analysis demonstrated robust cost-effectiveness for CABG over DES-PCI, with lifetime estimated ICER of $8132/QALY gained (99.2\% of bootstrap replications < $50,000/QALY gained) and $6791/life-year gained, and persisted across a wide range of subgroups (based on SYNTAX score, age, hemoglobin A1C, and number of vessels involved).\(^{34}\)

The consideration for angiographic complexity in 3-vessel or left main CAD and their variable impact on clinical and economic outcomes when DES-PCI is compared with CABG was evaluated in the SYNTAX trial (Synergy Between PCI With TAXUS and Cardiac Surgery). One-year results from the SYNTAX showed a significantly higher composite of major adverse cardiac and cerebrovascular events (MACCE) in the PCI group compared to CABG, primarily driven by increased rates of repeat revascularization.\(^{35}\) However, when the clinical outcomes were compared based on the complexity of coronary anatomy, only a high SYNTAX score (≥33) was associated with higher events in the PCI group.\(^{35}\) The ICER for CABG compared to PCI based on interaction between SYNTAX score and QALY demonstrated PCI to be a dominant strategy in 3-vessel CAD with low (<23) and intermediate (23-32) SYNTAX scores as well as for isolated left main disease at 1 year.\(^{35}\) However, the ICER for 3-vessel disease with high SYNTAX score was favorable for CABG at $43,486/QALY.\(^{35}\) Again, the 5-year clinical outcomes of SYNTAX demonstrated that the composite of MACCE was significantly lower in the CABG group compared to DES-PCI (26.9\% vs 37.3\%, \( P < .0001 \)).\(^{36}\) Rates of MI and repeat revascularization were significantly higher in PCI with comparable death and stroke. MACCEs for CABG were comparable with DES-PCI for low SYNTAX score and for left
main coronary disease.\textsuperscript{36} For intermediate and high SYNTAX score, DES-PCI had significantly higher MACCEs at 5 years.\textsuperscript{36} Five-year economic data from SYNTAX are currently ongoing. Initial economic data for 5-year follow-up presented at the Transcatheter Cardiovascular Therapeutics Conference in 2013 demonstrated that the cost of initial hospitalization remained higher with CABG (by $10,036) compared to DES-PCI.\textsuperscript{37} In-trial cost remained $5619 higher in the CABG group at 5 years with 0.1 QALY gained. Lifetime estimates suggested 0.412 QALY gained for CABG, yielding an ICER of $16,537/QALY gained.\textsuperscript{37} Cost-effectiveness of CABG versus PCI based on SYNTAX score showed CABG as a dominant strategy for high SYNTAX score (>32) with an ICER of $8219/QALY gained.\textsuperscript{37} For low SYNTAX score (<23), PCI remained a dominant strategy, including for left main disease.\textsuperscript{37} For intermediate SYNTAX score (23-32), the ICER for CABG was $36,790/QALY gained, making CABG a reasonably cost-effective strategy.\textsuperscript{37}

In summary, cost-effectiveness of CABG versus PCI for multivessel and left main CAD depends largely on the presence of diabetes and SYNTAX score. For patients with diabetes and high SYNTAX score (>32), CABG appears to be cost effective compared to PCI. For low SYNTAX score (<23), PCI appears to be dominant. For intermediate SYNTAX score (23-32), CABG appears to be cost effective in the long term.\textsuperscript{31–37}

\textit{Ischemia-Driven Revascularization}

The FAME trial (Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention) demonstrated that ischemia-driven revascularization by fractional flow reserve (FFR) compared to angiography-guided revascularization resulted in an improved composite of death, nonfatal MI, and repeat revascularization at 1 year.\textsuperscript{38} FFR is defined as the ratio of maximum blood flow in the distal coronary artery in the presence of a significant stenosis to maximum blood flow in a normal vessel.\textsuperscript{39} It is calculated by simultaneous pressure measurement in the aorta and distal coronary artery beyond the stenosis of interest after achieving maximum hyperemia with pharmacologic vasodilatation. An FFR value of <0.75, and more recently ≤0.80, has been demonstrated to reliably identify significant coronary stenosis.\textsuperscript{39} The FAME trial randomly compared angiography-
guided PCI to FFR (≤0.8)-guided PCI in a total of 1005 patients for the primary composite end point of death, nonfatal MI, and repeat revascularization at 1 year. The 1-year event rate was significantly lower in the FFR-guided PCI group compared to the angiography-guided PCI group (13.2% vs 18.3%, \( P = .02 \)). Freedom from angina was comparable between the 2 groups at 1 year. The FAME-2 trial subsequently compared outcomes (primary composite end point of death, MI, and urgent revascularization) of initial PCI for ischemic coronary stenosis (FFR <0.8) with medical therapy in a total of 1220 patients. The primary end point was significantly lower in the PCI group (4.3% vs 12.7%, \( P < .001 \)), primarily driven by lower rates of urgent revascularization at 7-month follow-up.\(^40\) The trial results were consistent with the COURAGE trial, meaning PCI was more effective in relieving angina and improving quality of life. However, the COURAGE trial demonstrated that initial PCI was not a cost-effective strategy in the management of stable CAD.\(^20\) It becomes important to investigate whether initial PCI becomes more cost effective in the management of ischemia-only (FFR <0.8) stable coronary stenosis. Cost-effectiveness data from the FAME-2 trial demonstrated that cumulative cost at 1 year was higher in the PCI group compared to the medical therapy group ($12,646 vs $9763, \( P < .001 \)),\(^40\) but that PCI was associated with a significant increase in patient utility from baseline as estimated by EQ-5D (0.054 vs 0.0001). Assuming that utility of PCI linearly declines over 3 years with unchanged cost difference between the 2 strategies, ICER for PCI remained at $36,000/QALY gained.\(^40\) The ICER for PCI increases more than the $50,000 threshold if utility of PCI declines at 2 years or utility of medical therapy increases at 3 years. Further, the ICER for PCI as estimated based on angina severity at baseline revealed that PCI may remain cost effective for Canadian Cardiovascular Society (CCS) class 2 to 4 angina ($27,000/QALY) but not for CCS class 0 to 1 angina ($102,000/QALY).\(^40\)

In summary, limited cost-effectiveness data suggest that PCI compared to medical therapy may be a cost-effective strategy for the initial management of stable CAD with demonstrated ischemia (FFR ≤0.8), especially for angina severity of CCS class 2 and greater.\(^40\) Additional clinical trial data in patients with more severe levels of ischemia are needed to resolve this issue.
COST-EFFECTIVENESS OF CORONARY STENTS

Balloon Angioplasty Versus Coronary Stenting in Acute Myocardial Infarction

Although balloon angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) compared to coronary stenting is somewhat antiquated and minimally used for the management of acute MI, the Stent-PAMI trial and its CEA have provided a cost-efficacy comparison between the 2 strategies for patients presenting with acute MI. The Stent-PAMI trial, a multicenter randomized comparison of PTCA with stenting or PTCA alone, included 900 patients and demonstrated that the combined end point of death, reinfarction, stroke, and ischemia-driven target vessel revascularization was significantly lower in the stent group over 6 months of follow-up.\(^{41}\) This difference was primarily driven by an increased rate of ischemia-driven target vessel interventions in the PTCA group due to a significantly increased rate of vessel restenosis at 6 months.\(^ {41}\) Cost utility analysis comparing QALYs between the 2 groups was performed at 1 month, 6 months, and 1 year.\(^ {42}\) Mean hospital cost was $1900 higher in the stent group, and 1-year follow-up cost was $1000 lower in the stent group. The aggregate 1-year medical care costs were $976 higher in the stent group compared to the PTCA group (\(P = .02\)). After several cost assumptions in 2001, the overall 1-year cost of stenting was only $343 more than the PTCA group (\(P = .21\)).\(^ {42}\) Base-case cost utility analysis for the in-trial period with utilities assessed by EQ-5D showed an ICER for the stent group at $65,066/QALY gained at 1 year.\(^ {42}\) However, the ICER improved to $22,067/QALY gained with cost assumptions in 2001 compared to in-trial costs. These cost improvements were largely attributed to the technical improvements in coronary stents, stent delivery systems, and price competition, making ICER more favorable for stent use in acute MI.\(^ {42}\) Therefore, primary PCI with coronary stenting has been established as a more effective economic strategy compared to balloon angioplasty for over a decade now.

First-Generation Drug-Eluting Stents Versus Bare Metal
**Stents**

Bare metal stents (BMS) have provided a significant advantage over balloon angioplasty for the treatment of coronary disease. However, BMS usage was plagued with a tendency toward scar tissue formation within the stent during its healing process that resulted in significant restenosis. The first-generation Cypher sirolimus-eluting stent (SES) and the soon-to-follow Taxus paclitaxel-eluting stent (PES) were the first DES approved by the US Food and Drug Administration (FDA). Their development revolutionized percutaneous intervention, as the elution of antiproliferative drugs significantly reduced rates of in-stent restenosis. The SIRIUS (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions) and TAXUS IV trials demonstrated that the SES and PES, respectively, when compared to BMS, significantly reduced the rates of repeat revascularization in patients undergoing coronary stenting by way of this process.\(^{43,44}\) CEA of SIRIUS and TAXUS trials also demonstrated robust cost reduction with DES for de novo native severe coronary disease.\(^{43,44}\) For these reasons, DES is widely accepted over BMS whenever feasible and has become the standard of care.

**Second- Versus First-Generation Drug-Eluting Stents**

The zotarolimus-eluting stent (ZES) and everolimus-eluting stent (EES) constitute second-generation DES. Several studies have evaluated safety, efficacy, and cost-effectiveness between second-generation and first-generation DES. Three-year clinical outcomes of Endeavor ZES compared to Cypher SES, as studied in the ENDEAVOR III trial, demonstrated that ZES use significantly decreased rates of MI and composite of death or MI compared to SES.\(^{45}\) The ICER was $57,002/QALY gained, with 41% of bootstrap replicates showing an ICER <$50,000/QALY.\(^{45}\) The ENDEAVOR IV trial compared 2-year clinical efficacy, safety, and economic outcomes between Endeavor ZES and Taxus PES stents for single de novo CAD in 1548 patients and demonstrated that target lesion failure (TLF; composite of cardiac death, MI, and target vessel revascularization) and target lesion revascularization (TLR) were comparable between Endeavor and Taxus DES.\(^{46}\) CEA demonstrated that ZES and PES were comparable with respect to quality-adjusted survival (1.58 vs 1.57 years, \(P = .83\)) and cumulative cost
at 2 years ($19,621 vs $20,029, \( P = .44 \)).\(^4\) The SPIRIT IV trial with 3687 patients provided the largest randomized comparison between Taxus PES and Xience V EES.\(^4\) SPIRIT IV provided a real-world comparison between alternate DES platforms since it included multivessel and multilesion intervention without protocol-driven angiographic follow-up. TLF at 2 years was significantly reduced in the EES arm compared to PES (6.9% vs 9.9%, \( P = .003 \)).\(^4\) MI, ischemic-driven TLR, and stent thrombosis were also significantly reduced with Xience V EES with a nonsignificant difference in all-cause and cardiac mortality.\(^4\) Resource utilization data analysis suggested comparable index procedural cost for EES and PES. Total target vessel revascularization–related costs were $661 lower per patient at 2 years in the EES group compared to the PES group (\( P = .013 \)).\(^4\) However, the cost of non–target vessel revascularization was higher in the EES group by $441 per patient, making total cardiovascular-related cost at 2-year follow-up comparable between the EES and PES groups ($22,061 vs $22,355 per patient). The EES group had $272 lower cost at 2 years per patient with 0.0064 QALY gained compared to PES.\(^4\) CEA (Fig. 72-5) demonstrated that EES was economically attractive, with 64% bootstrap replicates falling in the right lower quadrant of the cost-effectiveness plane (dominant) indicating ICER <$50,000/QALY.\(^4\)

![Figure 72-5](image.png)

**FIGURE 72-5** Joint distribution of cost and effectiveness differences in cost-effectiveness plane (SPIRIT IV trial). A. Joint distribution of the cost and efficacy (for target vessel revascularization) differences at 2 years for the everolimus-eluting stent (EES) versus paclitaxel-eluting stent (PES) demonstrated EES to be a dominant strategy with $273 lower cost and 0.0064 higher quality-adjusted life-years with an ICER below $50,000/QALY (solid circle), with 64.8% of bootstrap replicates falling in the lower right-hand quadrant. B. Cost-effectiveness acceptability curve indicated the
probability (85.7%) that the EES is economically attractive compared to the PES.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.


**Economics of Drug-Eluting Stents Beyond Randomized Trials**

DES have emerged as a cost-effective strategy (especially second-generation DES) compared to BMS, primarily by decreasing the cost of repeat revascularization and MI after the index procedure. However, it is important to evaluate this cost saving strategy in real-world situations where cost-effectiveness is affected for a variety of reasons, such as off-label use and absence of protocol-driven resource utilization.

With safety concerns due to DES-related stent thrombosis, in January 2007, the FDA issued an advisory to restrict the use of DES for unapproved or untested indications. In response to this, the use of DES fell substantially, likely due to limited use of DES for a more select group of patients (eg, diabetes, long segment stenosis, small vessel) compared to their previous unrestricted use. The strategy of unrestricted versus selective use of DES was evaluated at the population level in the EVENT registry (Evaluation of Drug-Eluting Stents and Ischemic Events). Clinical outcomes and cardiovascular cost in 10,144 patients were evaluated between 2 time periods (2004-2006: unrestricted use era; and in 2007: selective use era). Ninety-two percent of patients undergoing PCI during the unrestricted era received at least 1 DES, while only 68% of patients in the selective use era received DES. One-year rates of death and MI were comparable between the 2 eras; however, TLR was slightly increased during the selective use era (4.1 vs 5.1, \( P = .03 \)). Total cardiovascular care cost per patient was lower during the selective use era ($401 per patient with 95% CI, $131-$671, \( P = .004 \)), with an increased initial hospitalization cost in the unrestricted DES use (due to more number of DES placed) not offset by lower rates of TLR. Risk-adjusted ICER for unrestricted versus selective use of DES was $16,000 per TLR avoided, $27,000 per any repeat revascularization, and $433,000 per QALY gained. The probability of an ICER <$10,000 per TLR avoided was
Selective use of DES, therefore, appears more cost effective.

COST-EFFECTIVENESS OF ADJUVANT MEDICAL THERAPY WITH PCI

Antiplatelet Agents

Glycoprotein IIb/IIIa Inhibitors

Initial studies have demonstrated that the use of glycoprotein IIb/IIIa inhibitors (GPIs) has reduced 30-day composite of death, MI and repeat revascularization after angioplasty (36% relative risk reduction at 2 days) in patients presenting with ACS compared with patients who did not receive a GPI. Early benefits of GPIs appeared more pronounced in high-risk patients and persisted with coronary stenting. CEA of the RESTORE trial (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) demonstrated that the early clinical benefit after high-risk angioplasty with tirofiban could be achieved at an insignificant incremental cost for the initial hospitalization and at 30 days compared to the placebo. However, patient risk was noted to play heavily into the cost breakdown. Among patients undergoing PCI at low (<5%) probability of events (in-hospital death, MI, or emergent additional revascularization), the ICER for GPI use was unfavorable (>50,000/event averted). At intermediate probability of events (5%-7%), the ICER was marginally cost effective (<50,000/event averted at $750 cost of therapy and >$50,000/event averted at $1000 cost of therapy). At high probability of events (>7%), GPI use was highly cost effective, with the ICER ranging from approximately $25,000 to $36,000 per event averted.

Clopidogrel

The addition of clopidogrel to aspirin alone for medically treated NSTEMI patients provided robust clinical benefit for secondary prevention (20% relative risk reduction in composite of cardiovascular mortality, nonfatal MI,
and stroke), as demonstrated in the CURE trial. The total cost of care was $442 higher in the clopidogrel arm compared to placebo for the trial period (cost difference primarily driven by cost of clopidogrel). The ICER for clopidogrel was $6318/life-year gained with 94% bootstrap-derived ICER estimates <$50,000/life-year gained for the in-trial period. Lifetime estimates, projected based on the Framingham study, showed that the ICER for clopidogrel was $9820/life-year gained. Superior clinical efficacy and cost-effectiveness of clopidogrel plus aspirin compared to aspirin alone was also demonstrated in NSTEMI patients undergoing PCI up to 1 year (PCI-CURE). Total cost per patient in the entire follow-up period (inclusive of initial and subsequent hospitalization along with cost of clopidogrel) was $423 higher in the clopidogrel group in which PCI was performed during either the initial or subsequent hospitalization, whereas it was $90 higher for the clopidogrel group undergoing early PCI during only the initial hospitalization. The ICER for clopidogrel was $4775/life-year gained among all patients and was $935/life-year gained among the early PCI group. The COMMIT trial (randomized comparison of a total 45,852 STEMI patients receiving clopidogrel plus aspirin vs aspirin plus placebo) demonstrated that adding clopidogrel to aspirin for STEMI patients for an average of 2 weeks provided a 9% relative risk reduction in death, reinfarction, or stroke at 4 weeks. For STEMI patients, using CURE data to model events between 28 days and 1 year and assuming treatment with clopidogrel for 1 year, lifetime CEA demonstrated that the ICER for clopidogrel was $10,691/life-year gained. The strategy of using clopidogrel plus aspirin compared to aspirin alone for up to 1 year appears to be dominant for patients presenting with ACS.

**Prasugrel**

The conventional antiplatelet regimen of aspirin plus clopidogrel has been substantially improved with the advent of newer thienopyridine (prasugrel) and nonthienopyridine (ticagrelor) agents. Safety and efficacy of prasugrel (60-mg loading dose followed by 10 mg daily maintenance) versus clopidogrel (300-mg loading dose followed by 75 mg daily maintenance) for intermediate- to high-risk NSTEMI patients undergoing planned PCI was evaluated over 6 to 15 months in a total of 13,608 patients in the multicenter,
randomized TRITON-TIMI-38 trial.\textsuperscript{55} The original trial and the economic substudy both demonstrated a reduction in the composite of cardiovascular death, MI, or stroke.\textsuperscript{55} TIMI major bleeding episodes not related to CABG were higher in the prasugrel arm. Initial hospitalization costs (inclusive of periprocedural bleeding and MI) were similar between the 2 groups.\textsuperscript{55} Excluding the cost of study drug, total (initial and follow-up) hospitalization costs were $517 lower in the prasugrel group, with the majority of the cost offsets being due to reduced rates of repeat hospitalization involving PCI.\textsuperscript{55} However, the mean cost of study drug was $308 higher for the prasugrel group compared to the clopidogrel group. Therefore, the cumulative medical care cost (study drug, initial and subsequent hospitalization) was $221 less per patient with prasugrel. Treatment with prasugrel compared to clopidogrel (for 14.6 months) increased life expectancy by 0.102 years and QALYs by 0.095, making it a dominant strategy (ICER < $50,000/life-year gained in 99.8\% bootstrap replicates).\textsuperscript{55} The ICER for prasugrel remained favorable ($9727/life-year gained) when the generic cost of clopidogrel was considered at $1 per day. The ICER for prasugrel remained at $20,714/life-year gained in 84\% of bootstrap estimates when the most conservative cost model was created, including cost of life expectancy lost due to increased bleeding, generic cost of clopidogrel, and cost of care due to life-years gained with prasugrel.\textsuperscript{55}

### Ticagrelor

The addition of ticagrelor to aspirin significantly reduced the composite of vascular death, MI, or stroke without increasing the bleeding complications compared to clopidogrel in the PLATO trial for ACS patients with and without ST-segment elevation.\textsuperscript{15} As described earlier, long-term cost-effectiveness of this strategy has been evaluated from a healthcare perspective in Euros (€) using short-term base-case analysis from trial data and long-term analysis beyond the trial period using a Markov extrapolation model (data extrapolated primarily from the PLATO outcomes).\textsuperscript{15} The ICER for ticagrelor was €2752/QALY gained (incremental cost of ticagrelor to be €362 with QALY gained of 0.13).\textsuperscript{15} The ICER for ticagrelor remained favorable in a variety of ACS and patient subgroups, as displayed in the cost-effectiveness acceptability curve in Figure 72-2.
In summary, use of clopidogrel along with aspirin demonstrates robust cost-effectiveness for the secondary prevention of patients presenting with ACS. Use of ticagrelor as a second antiplatelet agent is cost saving across a broad spectrum of ACS patients. For patients presenting with ACS and undergoing PCI, use of prasugrel appears to be cost effective compared to clopidogrel.

**Anticoagulants**

**Bivalirudin**

Advances in anticoagulation strategies during PCI have warranted a reevaluation of their cost-effectiveness in the modern era. The ACUITY trial (Acute Catheterization and Urgent Intervention Triage Strategy) established that a GPI plus heparin-based antithrombotic strategy increased rates of bleeding with comparable ischemic events (death, MI, and ischemia-driven revascularization) when compared to bivalirudin alone for patients with intermediate- to high-risk ACS at 30 days managed with an early invasive approach. Similarly, patients undergoing primary PCI for STEMI in the HORIZONS-AMI trial had a significantly lower rate of net adverse clinical events with bivalirudin compared to GPI plus unfractionated heparin at 30 days (9.2% vs 12.1%; response rate [RR], 0.76; 95% CI, 0.63-0.92; \( P = .005 \)). This was due to a lower rate of major bleeding (4.9% vs 8.3%; RR, 0.60; 95% CI, 0.46-0.77; \( P <.001 \)) with similar MACE (composite of death, MI, stroke, and target vessel revascularization: 5.4% and 5.5%; \( P = .95 \)).

Economic analysis of the ACUITY trial showed that the cost of anticoagulation in US hospitals differed significantly based on the regimen chosen. During the initial hospital stay, bivalirudin monotherapy resulted in a $600 net cost savings per patient compared to heparin plus GPI and $200 net cost savings per patient compared to heparin plus provisional GPI therapy. The initial cost savings with bivalirudin monotherapy persisted at 30 days compared to any GPI-based regimen. Attributed cost calculations suggested that both major and minor bleeding episodes were independent drivers of increased in-hospital cost in the heparin plus GPI group. Cost-effectiveness of bivalirudin over heparin plus GPI was also demonstrated for STEMI patients undergoing primary PCI. A UK health service–based economic
analysis of HORIZONS-AMI was performed with a lifelong time horizon combining a decision analytic model and a Markov model to derive lifetime estimates. A bivalirudin-alone strategy was dominant (in 99% of replicates in a probabilistic sensitivity analysis with the ICER <€20,000/QALY gained) over heparin plus GPI with per-patient lifetime savings of €267 and an incremental gain of QALY of 0.09 years. The above data support the notion that bivalirudin is cost effective, as a treatment for both STEMI and ACS. However, current practice often utilizes GPIs only as bailout and not as protocol-based therapy. In light of this, the recent HEAT trial (How Effective Are Antithrombotic Therapies in Primary PCI) compared the strategy of bivalirudin monotherapy with bailout GPI versus unfractionated heparin monotherapy plus bailout GPI in patients undergoing primary PCI for STEMI. In this single-center, randomized trial involving over 1800 patients, the primary end point (composite of all-cause mortality, stroke, reinfarction, or unplanned revascularization) occurred more frequently in the bivalirudin group versus the heparin group (8.7% vs 5.7%, \( P = .01 \)) at 28 days. Use of bailout GPI and major bleeding episodes were comparable between the 2 groups. The HEAT trial, therefore, questions the cost-effectiveness demonstrated in the HORIZONS-AMI trial with bivalirudin. Although demonstrated in a single-center experience, it appears that heparin is superior compared to bivalirudin when used with bailout-only GPI, likely due to the significant cost savings associated with heparin use. This initial observation warrants further investigation in determining the optimal medical and cost-effective anticoagulation strategy during primary PCI for STEMI.

**Enoxaparin**

When compared to heparin, enoxaparin has the ability to achieve more consistent anticoagulation without the need for effect monitoring. In light of this, the ExTRACT-TIMI 25 trial compared enoxaparin with heparin when used as the anticoagulant for STEMI management. Enoxaparin was found to be superior to unfractionated heparin in patients presenting with STEMI undergoing thrombolysis with a 2.1% absolute reduction in death or MI and significantly reduced rates of nonfatal major bleeding, nonfatal disabling stroke, and nonfatal intracranial hemorrhage at 30 days. Total cost (hospitalization and follow-up) at 30 days was $102 higher with enoxaparin compared to unfractionated heparin. Further, estimated lifetime cost beyond
the trial period was $1105 higher in the enoxaparin group. The ICER of enoxaparin compared to unfractionated heparin was $880/life-year gained at 30 days (99.9% bootstrap replicates < $50,000/life-year gained), $5700/life-year gained for lifetime beyond the trial period (99.9% estimates < $50,000/life-year gained), and $4700/QALY gained, making the use of enoxaparin a cost-effective strategy.  

COST-EFFECTIVENESS OF TRANSCATHETER AORTIC VALVE REPLACEMENT FOR AORTIC STENOSIS

Transcatheter aortic valve replacement (TAVR) is a landmark development in interventional cardiology and underscores the potential of transcatheter therapies for advanced and life-threatening cardiovascular diseases such as severe aortic stenosis. During TAVR, diseased native aortic valve is displaced and is functionally replaced with a bioprosthetic valve delivered on a catheter either retrograde through the femoral artery (known as transfemoral TAVR [TF-TAVR]) or antegrade through the left ventricular apex (known as transapical TAVR [TA-TAVR]). Long-term management options are limited for patients with severe aortic stenosis who have prohibitive operative mortality (inoperable) or high operative risk. Such patients utilize a significant amount of medical resources. Analysis of clinical and economic outcomes of medically managed patients with severe aortic stenosis from a Medicare database demonstrated 88% mortality over 5 years with 1.8 years of mean survival. During a 5-year follow-up period, the average patient experienced 4 to 5 hospitalizations, mainly heart failure related, with total 5-year healthcare cost of $63,844 per patient and annual follow-up cost of $29,278 per year alive. This cost was composed of initial and subsequent hospitalizations, requirement of skilled nursing, and physician reimbursements. A substantial number of severe aortic stenosis patients are medically managed and do not undergo surgical aortic valve replacement because of inoperable status or high surgical risk. The estimated cost of providing care to medically managed patients with severe aortic stenosis...
among the entire Medicare population approaches $1.3 billion/year. TAVR has emerged as an attractive strategy for such patients. Cost-effectiveness of TAVR has been performed for the Edwards SAPIEN valve system (Edwards Lifesciences, Irvine, CA).

**TAVR for Patients With Prohibitive Risk for Surgical Aortic Valve Replacement (Inoperable)**

Efficacy and safety of TAVR were compared to standard therapy for patients who were considered inoperable due to prohibitively higher operative mortality in the PARTNER trial (cohort B), which was a multicenter randomized trial including a total of 358 patients between 2007 and 2009. Compared to standard therapy, TAVR resulted in a 20% reduction in mortality, improved functional status, and reduced hospitalization rates at 1 year. The mean cost of the TAVR procedure was $42,806, and the mean cost of the initial TAVR hospitalization was $78,542. Mean cost of follow-up hospital care was significantly lower in the TAVR group compared to the standard therapy, primarily driven by reduced rates of cardiovascular hospitalization ($18,074 vs $44,099, \( P < .001 \)). Total cost of care at 12 months (initial procedure and follow-up) was $52,455 higher in the TAVR group compared to medical therapy, driven by cost of the initial procedure and longer length of rehabilitation and skilled nursing. Health utilities were statistically higher for the TAVR group compared to the control group at 12 months, estimated by EQ-5D (0.72 vs 0.62, \( P < .05 \)). The lifetime ICER for TAVR was $50,212 compared to standard therapy with a gain in life expectancy of 1.6 years (Fig. 72-6). QALY gain with TAVR was not as robust as life-years gained, resulting in a slightly higher ICER/QALY gained of $61,889 with the majority of bootstrap iterations falling between ICER/QALY thresholds of $40,000 to $60,000 (Fig. 72-7). The ICER/QALY gained or ICER/life-year gained for TAVR, compared to medical therapy, was slightly higher than the conventionally considered willingness-to-pay threshold of $50,000. However, it is either comparable or favorable to the ICER of most advanced cardiovascular procedures such as use of defibrillators in the primary prevention of sudden cardiac death, initial PCI for stable angina, atrial fibrillation ablation, hemodialysis, and destination left ventricular assist devices. Similar CEAs from the UK
National Health Services perspective demonstrate that TAVR for inoperable patients is cost effective compared to medical therapy over a 10-year time horizon with an ICER/QALY gained of £16,100 (societal cost-effectiveness threshold considered below £20,000/QALY gained).\textsuperscript{64}

**FIGURE 72-6** Cost-effectiveness plane for transcatheter aortic valve replacement (TAVR) in inoperable patients compared to standard therapy in the PARTNER trial (cohort B). The cost-effectiveness plane with the joint distribution of projected lifetime mean incremental costs and life expectancy of TAVR versus medical therapy indicated the difference between 2 groups for life-years gained (1.6 years) on the x-axis and the cost ($79,837) on the y-axis (dark dot) with surrounding lifetime incremental cost-effectiveness ratio point estimates derived from 5000 bootstrap replications of the study sample (white dots). LE, life expectancy; LYG, life-years gained. (Reproduced from Reynolds MR, Magnuson E, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation. 2012;125(9):1102-1109.)
FIGURE 72-7 Cost-effectiveness acceptability curve for transcatheter aortic valve replacement (TAVR) in inoperable patients with severe aortic stenosis compared to standard therapy in PARTNER trial (cohort B). Cost-effectiveness acceptability curve of TAVR versus medical therapy. The plot of the probability of cost-effectiveness, calculated as the proportion of bootstrap iterations falling below a given cost-effectiveness threshold, against a wide range of incremental cost-effectiveness ratio (ICER) thresholds demonstrated that nearly all iterations of the study sample resulted in ICER ratios between $40,000 and $60,000 per life-year gained. (Reproduced from Reynolds MR, Magnuson E, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation. 2012;125(9):1102-1109.)

The recently published US trial comparing the self-expanding Medtronic CoreValve (Medtronic, Minneapolis, MN) to standard therapy for inoperable patients with severe aortic stenosis has demonstrated a 1-year survival benefit of CoreValve over medical therapy and has planned a prespecified economic analysis that would give further insight into cost-effectiveness of TAVR in this patient population.65

**TAVR for Patients With High Risk for Surgical Aortic Valve Replacement**
TAVR in patients considered high, but not prohibitive, risk for perioperative mortality was compared with surgical aortic valve replacement (SAVR) in cohort A of the PARTNER trial. Initial trial outcomes at 1 year and subsequently reported outcomes at 2 years demonstrated comparable rates of mortality and stroke. Quality of life with TAVR was not significantly different than SAVR at 1 year. Economic analysis has been separately performed for TF-TAVR (assumed to be performed in the catheterization laboratory) and TA-TAVR (assumed to be performed in the operating room) compared to SAVR due to fundamental differences in both techniques. The acquisition cost of the Edwards SAPIEN valve was $30,000 versus $5277 for a standard bioprosthetic aortic valve. For TF-TAVR patients, initial procedural cost was significantly higher for TAVR compared to SAVR ($36,652 vs $14,475), but overall initial hospitalization costs appeared comparable to SAVR due to reduced intensive care unit stay and reduced length of hospitalization ($72,219 vs $76,067). For TA-TAVR, both procedural and overall initial hospitalization costs were significantly higher than for SAVR. Resource utilization between initial hospital discharge and 12-month follow-up appeared comparable between TAVR (TF-TAVR and TA-TAVR) and SAVR with fewer rehabilitation and skilled nursing requirements in the TAVR group. For the overall 12-month study period, the TF-TAVR cohort had marginally lower ($1250) cost of care compared to SAVR, and the TA-TAVR cohort had a $9906 higher cost of care compared to SAVR. The pooled analysis demonstrated a slightly higher 12-month cost for TAVR as a whole compared with SAVR ($100,504 vs $98,434), with an ICER for TAVR of $76,877/QALY gained. However, there were significant variations in the bootstrap replications of ICER, primarily due to significant cost differences in the TAVR group depending on access site. Specifically, TF-TAVR was an economically attractive strategy with ICER <$50,000/QALY gained for the trial period in 71% bootstrap replications compared to SAVR (Fig. 72-8A). TA-TAVR remained dominated by SAVR in 86% of bootstrap replicates, making it economically an unattractive strategy at 12 months compared to SAVR for high-risk severe aortic stenosis patients who do not have favorable femoral vessel anatomy for TF-TAVR (Fig. 72-8B).
FIGURE 72-8 Cost-effectiveness plane for high-risk severe aortic stenosis undergoing transcatheter aortic valve replacement (TAVR) compared to surgical aortic valve replacement (AVR) in the PARTNER trial (cohort A). The ICER/QALY gained for (A) transfemoral (TF) and (B) transapical (TA) TAVR as a function of joint distribution of cost (TAVR – AVR) and gain of QALY (TAVR – AVR) at 12-months.
The solid circles represent base-case estimates, and the surrounding open circles represent ICER estimates for 1000 bootstrap replications of the study sample. The dashed lines represent a willingness-to-pay threshold of $50,000/QALY gained. TAVR appeared to be a dominant strategy for the TF cohort but was dominated by AVR for the TA cohort. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year. (Reproduced from Reynolds MR, Magnuson E a, Lei Y, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). J Am Coll Cardiol. 2012;60(25):2683-92, Copyright © 2012, with permission from Elsevier.)

**TAVR for Patients With Intermediate Risk for SAVR**

Limited data exist regarding safety and efficacy of TAVR for patients with intermediate operative risk, and several multicenter, randomized clinical trials are currently under way to evaluate TAVR compared with SAVR for this patient group. The SURTAVI trial is evaluating the self-expanding Medtronic CoreValve versus SAVR for patients with severe symptomatic aortic stenosis with intermediate surgical risk (Society of Thoracic Surgeons [STS] score–predicted perioperative mortality of 4%-10%; ClinicalTrials.gov identifier: NCT01586910). At the time of publication of this chapter, the PARTNER II trial is ongoing and evaluating the second-generation SAPIEN XT and third-generation SAPIEN 3 heart valve systems for a wide range of symptomatic severe aortic stenosis patients including inoperable, intermediate-risk (STS-predicted surgical mortality of 4%-8%), and high-risk (STS-predicted surgical mortality of >8%) patients (ClinicalTrials.gov identifier: NCT01314313). Trial results from a single-center, prospective study evaluating patients with intermediate-risk severe aortic stenosis do exist. This study from the Netherlands used propensity matching in 84 patients undergoing placement of TF-TAVR with the third-generation CoreValve (€17,590 per valve) versus SAVR with the bioprosthetic Carpentier-Edwards PERIMOUNT magna valves (Edwards Lifesciences; €2700).\(^{67}\) In-hospital and 1-year mortality were comparable between TAVR and SAVR.\(^{67}\) As expected, initial hospitalization cost was higher with TAVR compared to SAVR (€40,802 vs €33,354).\(^{67}\) The lack of a significant cost difference between groups during follow-up did not offset the initial higher cost with TAVR (1-year total cost: €46,217 vs €35,511, \(P < .009\)). However, the small number of patients, nonrandomized trial design, and cost analysis
without ICER limit generalizability of results.

In summary, for patients with severe aortic stenosis, TAVR appears to be cost effective for inoperable patients compared to medical therapy.\textsuperscript{63,64} For high-risk patients, TAVR performed via transfemoral access, as opposed to transapical access, is an economically attractive strategy compared to SAVR.\textsuperscript{66} Insufficient evidence exists for cost-effectiveness comparisons between TAVR and SAVR for intermediate-risk patients.

**COST-EFFECTIVENESS OF RADIAL VERSUS FEMORAL APPROACH FOR PERCUTANEOUS CORONARY INTERVENTION**

Although recognized early on as an alternate access site, radial artery access has gained momentum in recent years and is being embraced among interventionalists in the United States and worldwide. Several favorable aspects of transradial intervention include increased patient comfort, reduced bleeding complications, and lower mortality compared to the femoral approach among STEMI patients.\textsuperscript{68,69} Along with clinical benefit, transradial intervention is also cost saving, as demonstrated by cost comparisons between transradial (TRI) and transfemoral (TFI) intervention at 5 high-volume centers (total 7121 PCIs; 17% radial and the rest femoral) in the United States using a retrospective dataset obtained from the National Cardiovascular Data Registry–CathPCI database.\textsuperscript{69} Patients undergoing radial intervention were younger, less likely to undergo primary PCI for STEMI, and had fewer risk factors. Bivalirudin was less frequently used in TRI.\textsuperscript{69} Cost data were obtained from each hospital’s accounting unit, tallied from the day of PCI through discharge. TRI had lower rates of bleeding and reduced unadjusted in-hospital mortality compared to TFI.\textsuperscript{69} Adjusted cost of TRI was $830 lower compared to TFI.\textsuperscript{69} This cost reduction was mainly driven by reduced postprocedural cost with TRI, partly as a result of reduced bleeding but primarily as a result of length of hospital stay. Cost savings of TRI compared to TFI were incremental as the risk of bleeding increased
($642 for low risk, $706 for intermediate risk, and $1621 for high risk). The major cost-saving strategy with TRI in this study due to reduced length of stay was consistent with a previous cost analysis from the EASY trial. The EASY trial (single-center, randomized trial of 1005 patients) demonstrated clinical noninferiority out to 30 days of bolus-only GPI and same-day discharge compared to standard GPI infusion for 12 hours and an overnight stay after an uncomplicated TRI. Since patients were randomized after PCI, cost of hospitalization excluding PCI, subsequent urgent revascularization, and hospitalization or emergency room visits for any reason up to 30 days were included in the economic analysis. Thirty-day cost analysis demonstrated a higher cost in the inpatient group compared to the outpatient group, driven by the initial extra night spent in the hospital without significant difference in resource utilization between discharge and 30 days (mean cost difference of $1141 per patient). There are several limitations in extrapolating these findings to the US health care system. First, safety of same-day discharge after uncomplicated PCI should be established in a large, multicenter randomized trial. Second, there is a potential disincentive from a hospital perspective due to the US reimbursement system where reimbursement for inpatient PCI is significantly higher than outpatient PCI. Overall, however, TRI is considered a cost-effective strategy.

COST-EFFECTIVENESS OF VASCULAR CLOSURE DEVICES AFTER PERCUTANEOUS CORONARY INTERVENTION

Closure devices are routinely used for femoral access site hemostasis. Cost-effectiveness data for vascular closure devices are limited and are primarily represented by Angio-seal (St. Jude Medical, Saint Paul, MN). The equivalent safety and efficacy of the Angio-seal collagen-based closure device compared to manual compression have been established in multiple randomized trials. Cost efficacy of Angio-seal was demonstrated in a single-center economic analysis involving 3943 patients undergoing PCI. Pooled analysis of the randomized trial data was used to predict vascular
complication rates among those undergoing hemostasis via Angio-seal versus manual compression, and direct cost related to the vascular complications was obtained from hospital-level billing data.\textsuperscript{71} Cost attributed to a vascular complication was derived with a case-control analysis between patients with and without vascular complication in each group. A base-case decision analytic model demonstrated net cost savings of $44 per case for patients treated with the Angio-seal closure device compared to manual compression, making it a cost-effective strategy.\textsuperscript{71}

REFERENCES


Pinto DS, Stone GW, Shi C, et al. Economic evaluation of bivalirudin with or without glycoprotein IIb/IIa inhibition versus heparin with


**MULTIPLE CHOICE QUESTIONS**

1. What is the most common method used for cost-effectiveness analysis?
   - A. Sensitivity analysis
   - B. Incremental cost-effectiveness ratio
   - C. Bootstrap analysis
   - D. Markov analysis
   - E. Health utility assessment

2. What quadrant of cost-effectiveness plane is considered most cost effective?
   - A. Upper right
   - B. Upper left
   - C. Lower right
   - D. Lower left

3. What is the concept used in Markov decision-analytic model?
   - A. Projection of cost per life-year or quality-adjusted life-year (QALY) gained based on short-term results
   - B. Projection of 10-year cost per QALY gained based on 2-year results
C. Projection of health utility changes after short-term intervention
D. Projection of long-term survival based on short-term results

4. Which antiplatelet agent, when used in combination with aspirin, has been demonstrated to be cost effective across a wide spectrum of patients with acute coronary syndrome (ACS) for secondary prevention?
   A. Clopidogrel
   B. Prasugrel
   C. Ticagrelor
   D. Ticlopidine
   E. Cilostazol

5. Which access route is shown to be the least cost effective in patients undergoing transcatheter aortic valve replacement (TAVR)?
   A. Transfemoral
   B. Transapical
   C. Transcaval
   D. Transaortic

ANSWERS

1. B
Incremental cost-effectiveness ratio (ICER) is the most widely used and accepted method to evaluate cost-effectiveness of a particular intervention. Authors have found that ICER has been used in the majority of studies as a fundamental metric evaluating cost-effectiveness of a new therapy. The ICER is defined as the incremental cost of providing a specific intervention or therapy divided by the incremental gain in the health benefit. ICER is usually compared to a standard willingness-to-pay threshold, eg, $50,000/life-year gained.

2. C
The cost-effectiveness plane (CEP) is a 2-dimensional display of incremental effectiveness versus incremental cost where the x-axis represents incremental cost of a new therapy compared to the conventional therapy and the y-axis
represents incremental effectiveness of the new therapy compared to the standard treatment. Thus, points on the plane represent a graphical display of the ICER. The CEP is divided into 4 quadrants. The lower right quadrant is the most cost effective since it introduces more effective newer treatment strategies at a lower cost than the standard treatment option. Such newer therapies are known as “dominant” therapies over standard treatment.

3. A

The duration of many clinical trials is usually not long enough for an accurate estimation of the long-term course of a clinical disease. This limits the accurate estimation of the changes in life-years and QALYs with a newer therapy and thus incremental gain in life-years or QALYs over standard therapy. Therefore, the cost-effectiveness analysis based on the data collected during the clinical trial follow-up period has a limited utility for economic decision making. Long-term projections based on short-term results are required to estimate cost per life-year or QALY gained. Markov analysis allows modeling for average life expectancy and lifetime cost of therapies to derive lifetime ICER or lifetime cost per QALY gained based on short-term event rates and cost data collected during the in-trial period.

4. C

As a second antiplatelet agent along with aspirin, ticagrelor has been demonstrated to be cost effective compared to clopidogrel in reducing the composite of vascular death, myocardial infarction, or stroke without increasing the bleeding complications for ACS patients with and without ST-segment elevation (PLATO trial). Prasugrel has been shown to be cost effective compared to clopidogrel only for patients presenting with ACS and undergoing percutaneous coronary intervention (TRITON-TIMI-38 trial).

5. B

The cost-effectiveness analysis of the PARTNER cohort A trial, comparing TAVR versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and high surgical risk, demonstrated significant variations in the distribution of ICER depending on the access route for TAVR. The 12-month overall cost of care was lower with transfemoral TAVR (TF-TAVR) compared to SAVR, whereas it was significantly higher
with transapical TAVR (TA-TAVR) compared to SAVR. This cost difference was primarily driven by higher cost of initial hospitalization with TA-TAVR.
Interventional cardiology consists of several related procedures that are performed in the coronary, peripheral, and cerebral vascular systems, as well as the central aorta, the cardiac valves, and the structural units (parenchyma) of the heart itself. Almost all of the procedures are performed under radiographic fluoroscopic guidance in a cardiac catheterization laboratory (cath lab), or sometimes a “hybrid” laboratory that can also function as a surgical operating room. Often the fluoroscopic imaging is complemented with intravascular ultrasound, transthoracic or intracardiac echocardiography, and rotational computed tomographic angiography (CTA). Thus, the modern cath lab is a complex, highly technologically sophisticated facility where both patients with chronic, stable conditions as well as patients with life-threatening illnesses are evaluated and treated. Therefore, it is essential to have an active quality assurance and improvement (QA/QI) program in place. This program will need to consider all aspects of the risks encountered by patients undergoing procedures in the cath lab, as well as by staff working there. This will of course include radiation risk and methodologies for reducing it. However, radiation risk is an extensive subject on its own and will not be covered in this chapter.
GENERAL COMPLICATIONS FROM INVASIVE CARDIOVASCULAR PROCEDURES

With the tremendous growth and increased experience of invasive cardiovascular training programs, paralleling the general overall growth in cardiac catheterization as a common diagnostic procedure, there has been a decline in the risks of undergoing an invasive procedure. Complication rates with general diagnostic catheterization and angiography are quite low. Major adverse cardiovascular events (MACE) such as death, stroke, myocardial infarction (MI), and emergency surgery typically occur in <0.1% of diagnostic procedures.\(^1\) However, for cardiovascular procedures where therapeutic intervention is attempted, the story is very different (Tables 73-1 and 73-2). Complication rates may be much higher and may be widely different between institutions.

Table 73-1 In-Hospital and Short-Term Complications Following Elective Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Year of Publication</th>
<th>Death (%)</th>
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<th>CABG (%)</th>
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<td>EVENT (registry)</td>
<td>2009</td>
<td>0.1</td>
<td>6.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: [—,—], not reported; ACC, American College of Cardiology; CABG, coronary artery bypass grafting; DR, data registry; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; Neuro, neurologic (stroke/transient ischemic attack/other); NHLBI, National Heart, Lung, and Blood Institute; RCT, randomized controlled trial.


Table 73-2 In-Hospital and Short-Term Complications Following Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction in the Stent Era
In addition to the MACE events listed in Tables 73-1 and 73-2, there are several other serious events that are of clinical importance and typically are incorporated into the QA/QI program. The foremost of these are acute kidney injury (AKI), bleeding, and blood transfusions. The reasons for this are illustrative of many of the larger quality issues in general.

**Acute Kidney Injury (AKI)**

A large-scale analysis of almost 1 million percutaneous coronary intervention (PCI) patients from >1200 hospitals revealed that AKI occurred in approximately 7.1% of the patients, and 0.3% (3000 patients) had a new requirement for dialysis. A number of factors were found to be independently associated with developing AKI, and these could help serve as clinical predictors of the event (Fig. 73-1). The occurrence of AKI was quite serious, inasmuch as rates of death, bleeding, and MI were all significantly increased when AKI occurred (Fig. 73-2).
**FIGURE 73-1** Independent predictors of acute kidney injury (AKI) or dialysis. A. Independent predictors of any AKI (including dialysis). B. Independent predictors of dialysis only. (Reproduced from Tsai TT, Patel UD, Chang TI, et al. Contemporary

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR  (95% CI)</th>
<th>Predictor</th>
<th>OR  (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast 75 units</td>
<td>1.14 (1.13, 1.15)</td>
<td>NSTEMI/UA vs Non-ACS</td>
<td>1.51 (1.48, 1.54)</td>
</tr>
<tr>
<td>Age 10 years</td>
<td>1.15 (1.14, 1.16)</td>
<td>DM</td>
<td>1.61 (1.59, 1.64)</td>
</tr>
<tr>
<td>Mild GFR vs Normal</td>
<td>1.21 (1.19, 1.24)</td>
<td>Prior CVD</td>
<td>1.27 (1.24, 1.30)</td>
</tr>
<tr>
<td>Prior HF</td>
<td>1.32 (1.29, 1.35)</td>
<td>NSTEMI/UA vs Non-ACS</td>
<td>1.51 (1.48, 1.54)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.92 (1.87, 1.98)</td>
<td>DM</td>
<td>1.61 (1.59, 1.64)</td>
</tr>
<tr>
<td>2 Weeks HF</td>
<td>2.04 (1.99, 2.08)</td>
<td>Prior card arrest</td>
<td>1.72 (1.65, 1.81)</td>
</tr>
<tr>
<td>IABP before procedure</td>
<td>2.13 (1.92, 2.35)</td>
<td>Mod GFR vs Normal</td>
<td>1.75 (1.71, 1.80)</td>
</tr>
<tr>
<td>STEMI vs Non-ACS</td>
<td>2.60 (2.53, 2.67)</td>
<td>Prior card shock</td>
<td>2.92 (2.80, 3.04)</td>
</tr>
<tr>
<td>Severe GFR vs Normal</td>
<td>3.59 (3.47, 3.71)</td>
<td>Severe GFR vs Normal</td>
<td>3.59 (3.47, 3.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

<<< Less likely AKI  More likely AKI>>>  <<< Less likely dialysis  More likely dialysis>>>


**Bleeding and Transfusion**

Invasive cardiovascular procedures can be accompanied by unwanted and unexpected bleeding. While it might be thought that blood transfusion is simple and effective for treating blood loss when necessary, many studies have shown that both bleeding and blood transfusions are serious clinical events in themselves and are harbingers of worsened outcomes. In a large analysis of >1 million PCI procedures at >1100 hospitals, major bleeding within 72 hours of the procedure was found in 5.8% of patients (60,000 cases), which is a very substantial number.\(^3\) Periprocedural bleeding has been found to be related to increased mortality by almost double over the subsequent year at least (Table 73-3 and Fig. 73-3).\(^4,5\) Furthermore, analyses of blood transfusion events in PCI patients, even when adjusted for coexistent anemia and blood loss, have found transfusion to be related to long-term mortality (Fig. 73-4).\(^6\)

**Table 73-3** Rates of Adverse Events in Patients With and Without Post-PCI Bleeding
<table>
<thead>
<tr>
<th>Outcome</th>
<th>In-Hospital Bleeding (n = 14,107)</th>
<th>No In-Hospital Bleeding (n = 447,204)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission for bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>0.9 (0.7-1.0)</td>
<td>0.3 (0.3-0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 months</td>
<td>3.9 (3.5-4.3)</td>
<td>1.9 (1.9-2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30 months</td>
<td>5.9 (5.2-6.6)</td>
<td>3.4 (3.3-3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>6.7 (6.2-7.2)</td>
<td>5.7 (5.6-5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 months</td>
<td>30.6 (29.5-31.7)</td>
<td>24.1 (23.9-24.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30 months</td>
<td>51.4 (49.4-53.3)</td>
<td>43.5 (43.2-43.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>2.3 (2.1-2.6)</td>
<td>1.0 (1.0-1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 months</td>
<td>13.7 (13.1-14.3)</td>
<td>6.9 (6.8-6.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30 months</td>
<td>24.1 (23.2-25.0)</td>
<td>14.2 (14.1-14.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

**FIGURE 73-3** Association between bleeding and/or transfusion in percutaneous coronary intervention (PCI) and 1-year mortality. TIMI, Thrombolysis in Myocardial

To help identify ahead of time and possibly prevent bleeding in PCI, several bleeding risk models have been developed, one of which is shown in Table 73-4. This model is based on a risk scoring system and uses 10 clinical variables available at the bedside. Points are given for each level of the variables, and the summed points can be used to classify patients into low-, medium-, and high-risk groups for bleeding. The model has been found to be useful in identifying PCI patients at higher risk for bleeding events (Fig. 73-4).
Table 73-4 **NCDR CathPCI Bleeding Risk Score**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Age, years</td>
<td>&lt;60</td>
</tr>
<tr>
<td></td>
<td>60-70</td>
</tr>
<tr>
<td></td>
<td>71-79</td>
</tr>
<tr>
<td></td>
<td>≥80</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>20-30</td>
</tr>
<tr>
<td></td>
<td>31-39</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Shock</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Cardiac arrest within 24 hours</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Hb</td>
<td>Hb &lt;13</td>
</tr>
<tr>
<td></td>
<td>13 ≤ Hb &lt; 15</td>
</tr>
<tr>
<td></td>
<td>Hb ≥15</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PCI status</td>
<td>Elective</td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
</tr>
<tr>
<td></td>
<td>Emergency/salvage</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; Hb, hemoglobin level; NCDR, National Cardiovascular Data Registry; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

FIGURE 73-5 Risk of post–percutaneous coronary intervention bleeding based on the National Cardiovascular Data Registry CathPCI bleeding risk score. Scores of <25 are low risk, scores of 25 to 65 are medium risk, and scores >65 are high risk. (Reproduced from Rao SV, McCoy LA, Spertus JA, et al. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention. JACC Cardiovasc Interv. 2013;6:897-904.)

Risk models such as these for AKI and bleeding, as well as others for risk-adjusted mortality, often are the primary focuses of a QA/QI program. This may especially be true in the early stages of a new QA/QI program that has just been initiated.

VARIATIONS AND QUALITY

The quality imperative throughout medicine and cardiology, but particularly in procedure-based interventional cardiology, specifies that regular, comprehensive, and detailed analyses of (1) patient selection, (2) processes of care, and (3) outcomes will lead to reductions in adverse events and thereby to improvements in safety and quality of care. It is for these reasons that QA/QI programs in interventional cardiology have come into existence. One of the major focus areas for these programs is the variations in practices.
between operators and between institutions, and the possible relationships between such variations and adverse events. Variations therefore have become a major subject area for review. Examining variations is one way to begin to understand processes that may be at work and how they might relate to outcomes, both good and bad. Several examples can be given for illustration.

**Detection of Coronary Artery Disease (CAD)**

An analysis of >560,000 patients with no history of prior MI or revascularization, undergoing elective diagnostic catheterization at 691 hospitals found there was wide variation between hospitals in detecting obstructive CAD, even when allowances were made for the amount of obstructive disease that might be considered significant (Fig. 73-6). Variations in clinical practice patterns that determine suitability of patients for diagnostic angiography presumably underlie these variations.

![Hospital variability in detection of coronary artery disease. Curves represent the distribution based on various definitions of coronary artery disease by degrees of stenosis severity.](image)

**FIGURE 73-6** Hospital variability in detection of coronary artery disease. Curves represent the distribution based on various definitions of coronary artery disease by degrees of stenosis severity. (Reproduced from Douglas PS, Pate MR, Bailey SR, et al. Hospital variability in the rate of finding obstructive coronary artery disease at elective, diagnostic coronary angiography. *J Am Coll Cardiol.* 2011;58:801-809.)

**Treatment of CAD**

In a survey of >5000 patients with angiographically proven significant coronary disease at 130 hospitals in Europe, the proportions of patients
treated with medications, PCI, or bypass surgery varied widely across the hospitals (Fig. 73-7). Patient and physician preference, clinical characteristics of the patients, and local customs may all have influenced the decision making. But this illustrates that even once CAD is detected its management may differ markedly from one region to another. The Dartmouth Atlas of Cardiovascular Health Care had indicated the same was true in the United States.


Patients with atrial fibrillation (AF) often receive oral anticoagulation, and while this decreases risk for stroke, it increases bleeding risks. In AF patients who develop ST-segment elevation MI (STEMI) and undergo primary PCI, the choice of a drug-eluting stent (DES) or bare metal stent may have serious implications, since DES may necessitate prolonged poststent therapy with dual antiplatelet agents. In an analysis of >14,000 AF patients undergoing primary PCI for STEMI at several hundred hospitals, the variation across hospitals in the proportion of patients treated with DES varied from none to

**Procedural Success**

In an analysis of >19,000 carotid artery stent (CAS) procedures at 188 hospitals, the risk-adjusted rates of stroke or death varied 4-fold across the hospitals, ranging from 1.2% up to 4.7% (Fig. 73-9).11 A study of >22,000 PCI attempts on chronic total occlusions (CTO) at >1000 sites by 60 operators over a 4-year period found that procedural success rates varied across the operators (Fig. 73-10).12 Success rates were higher with greater operator experience. A review of almost 15,000 Medicare fee-for-service beneficiaries ≥65 years of age who underwent transcutaneous aortic valve replacement (TAVR) at 417 hospitals in a 3-year interval examined short- and long-term outcomes.13 There were 2-fold or greater differences in 30-day and 1-year risk-standardized mortality rates after TAVR across the hospitals, ranging from 3.8% to 10.2% (at 30 days) and 11.8% to 25.6% (at 1 year).

Mortality and 1-Year Costs

Value in interventional cardiology focuses on measuring quality of outcomes achieved relative to costs for a cycle of care. This is difficult to study in a uniform manner unless there are data from a single integrated organization. The US Veterans Health Administration (VA) comes very close to this. In a study of >19,000 patients undergoing PCI at 60 VA hospitals, risk-adjusted and risk-standardized mortality was examined, as well as the 1-year costs of care for the patients. The standardized mortality was noted to vary across the hospitals, but only within a narrow band. However, the 1-year standardized costs varied much more broadly (Fig. 73-11). Actual costs varied almost 5-fold, ranging from approximately $20,000 up to $100,000.

Summary

These few examples mentioned here serve to illustrate the phenomenon of variability that occurs virtually everywhere. The sources of all these variations are not known, and certainly variations in themselves do not necessarily imply poor quality or poor practices. In fact, sometimes an analysis of variations helps identify “good practices” that can lead to better outcomes. But either way, variations in practices and outcomes are often the starting point for examination of the deeper issues at work.

DOMAINS OF QUALITY ASSURANCE/QUALITY IMPROVEMENT PROGRAMS

There are 3 basic topic areas or domains into which QA/QI programs may be divided (Table 73-5). The general elements are: (1) structure and organization; (2) processes of care; and (3) outcomes. Each of these domains has several subsidiary topics within it. The American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions (SCAI) have published an expert consensus document on cardiac catheterization laboratory standards.¹ This expert consensus document specifies that a robust QA/QI program containing these and other elements is an essential feature for all cath labs (Table 73-6).

Table 73-5 Outline of Basic Elements in a Cath Lab Quality Assurance/Quality Improvement (QA/QI) Program

<table>
<thead>
<tr>
<th>Structure-Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cath Lab QA/QI committee that meets regularly</td>
</tr>
<tr>
<td>• Written credentialing process with periodic review and updating of credentialing rules</td>
</tr>
<tr>
<td>• Initial operator credentialing for specific procedures, with periodic recredentialing</td>
</tr>
<tr>
<td>• Continuing education requirements, with records maintained by QA/QI</td>
</tr>
</tbody>
</table>
committee
  • Periodic reports on weekly, monthly, or quarterly schedule

Process of Care
  • Angiographic quality review
  • Completion of reports review
  • Standardized order sets
  • Preprocedure checklists
  • Guidelines and appropriateness review
  • Handling of emergencies
  • Staffing and personnel
  • Ancillary services

Outcomes
  • Mortality: actual and risk-adjusted
  • Adverse events: acute kidney injury, bleeding, transfusion, stroke, cardiac arrest, need for emergency surgery, others
  • Radiation exposure: patients and staff
  • Radiographic contrast dose
  • Infection

Table 73-6 American College of Cardiology/Society for Cardiovascular Angiography and Interventions Expert Consensus Document Basic Components of a (QA/QI) Program for Cath Labs

  • Committee with chairman and staff coordinator
  • Database and data collection
  • Data analysis, interpretation, and feedback
  • QA/QI implementation
  • Goals outlined to eliminate outliers, reduce variation, and enhance performance
  • Tools available to accomplish data collection and analysis
  • Feedback mechanisms in place
Educational provisions for staff and operators
• Incorporation of practice standardization/guidelines
• Professional interaction and expectation
• Incentives for high-quality metrics
• Adequate financial support for QI personnel
• Administrative oversight and action plans
• Thresholds for intervention
• Appropriate use assessment


**Structure and Organization**

Structure and organization usually encompass the managerial aspects of a QA/QI program within the institution. The exact arrangements will vary from one hospital to another. The QA/QI program may be independent of the general hospital-wide quality improvement program, or it may be a component of it. There should be a committee with a chair that meets regularly. The program should be a peer-review process and meant to be constructive and not punitive. Credentialing and recredentialing for specific procedures should be within the purview of this committee.

**Processes of Care**

The majority of the work of the QA/QI program will be process reviews. All of the patient care processes must be considered for review from time to time and whenever appropriate. It is generally known that deficiencies can arise and quality can be compromised whenever clinical workflow surrounding a process of care occurs capriciously (ie, haphazardly) and is not managed carefully. Correcting significant errors, improving quality of care for patients, and improving clinical outcomes often can all be achieved by carefully analyzing processes of care and their associated workflow patterns. At times, a single adverse event, such as an unexpected death, a cardiac arrest, or a major bleeding event, will trigger an immediate review of the causes and
consequences, along with an examination of the responses by staff members. Often it is just these single events that initiate the study of workflow patterns with an idea toward improving them. These are learning opportunities that the QA/QI program must utilize and build upon in constructive and creative ways. The QA/QI program must not be seen only as a punitive exercise, or else support and participation will not be forthcoming.

**Outcomes**

The only way to study outcomes is by collecting and analyzing data. Therefore, it is necessary for the cath lab to have a vigorous data collection system in place. The national registries (National Cardiovascular Data Registry [NCDR]) operated by the ACC were started as quality improvement activities, with the goal of standardizing data collection and providing comparative analyses of outcomes to participating institutions. These were seen as complementing or supplementing the work that institutions were already engaged in. Approximately 90% or more of all cath labs in US hospitals now participate in the CathPCI module of the NCDR. These participating cath labs receive regular reports detailing their specific outcomes metrics for a number of outcomes, along with comparisons to similar hospitals and to national averages (Fig. 73-12). Hospitals of course can and do analyze their own data in conjunction with these reports, examining other measures that may be of interest to them individually (local demographics, length of stay, costs, etc). The essential, critical element underlying all such activity is accurate data.
### Executive Summary

**CathPCI Registry®**

National Outcomes Report(999997) compared to Rolling Four Quarters (R4Q) for US Hospitals ending 2014Q3

**Section II: Quality Metrics**

- To support self-assessment and quality improvement at the provider, hospital, and/or healthcare system level.

<table>
<thead>
<tr>
<th>Statins prescribed at discharge</th>
<th>Distribution of Hospital Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
<td>US Hospitals 50th Qtr</td>
</tr>
<tr>
<td>95.0%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Proportion of patients (without a documented contraindication) prescribed a statin at discharge. [Detail Line:2002]</td>
<td></td>
</tr>
</tbody>
</table>

**PCI Outcome Metrics**

<table>
<thead>
<tr>
<th>Emergency CABG post-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>0.0%</td>
</tr>
<tr>
<td>Proportion of PCI patients with post procedure Emergency CABG. [Detail Line:1986]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of PCI procedures with a post procedure MI (among hospitals routinely collecting post-PCI biomarkers)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>1.51%</td>
</tr>
<tr>
<td>Your hospital’s proportion of biomarker positive, post procedure myocardial infarction. Inclusions: Submissions with &gt;= 90% of pts with biomarkers coded; LOS&gt;=1; Elective patients [Detail Line:1803]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of PCI procedures with post procedure MI (among hospitals who do not routinely collect post-PCI biomarkers)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>0.00%</td>
</tr>
<tr>
<td>Your hospital’s proportion of biomarker positive, post procedure myocardial infarction. Inclusions: Submissions with &lt; 90% of pts with biomarkers coded; LOS&gt;=1; Elective patients [Detail Line:1804]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of PCI procedures with post procedure stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>0.00%</td>
</tr>
<tr>
<td>Your hospital’s proportion of patients with stroke post procedure. [Detail Line:1811]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Composite: Proportion of PCI patients with death, emergency CABG, stroke or repeat target vessel revascularization.</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>2.55%</td>
</tr>
<tr>
<td>Your hospital’s proportion of patients with death, emergency CABG, stroke or repeat target vessel revascularization post procedure up to hospital discharge. Excludes patients with stroke and/or elective, urgent or salvage CABG during same admission. [Detail Line:1801]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCI in-hospital risk adjusted mortality (patients with STEMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>6.50%</td>
</tr>
<tr>
<td>Your hospital’s PCI in-hospital risk adjusted mortality rate for patients with STEMI adjusted using the NCDR® risk adjustment model. [Detail Line:2045]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCI in-hospital risk adjusted mortality (STEMI patients excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>My Hospital</td>
</tr>
<tr>
<td>0.87%</td>
</tr>
<tr>
<td>Your hospital’s PCI in-hospital risk adjusted mortality rate for patients with other diagnoses (not STEMI) using the NCDR® risk adjustment model. [Detail Line:2054]</td>
</tr>
</tbody>
</table>

**FIGURE 73-12** Sample page from the American College of Cardiology National Cardiovascular Data Registry CathPCI Registry institutional report. (Available at www.cvquality.acc.org/~media/QII/NCDR/Sample%20Reports/CathPCI_Registry_2014Q3_Sample_Report.ashx. Accessed February 1, 2016. Used with permission from the American College of Cardiology Foundation.)
ACCREDITATION

One way to approach QA/QI in the cath lab is through professional society accreditation. There is an organization for this, the Accreditation for Cardiovascular Excellence (ACE). ACE operates a rigorous cath lab evaluation and accreditation program that provides on-site reviews and written assessments of the cath lab along with suggestions for improvement. Not all cath labs that apply will receive accreditation upon first review. Once accreditation is received, it is time limited, so that reaccreditation can be obtained and is encouraged. The entire program is viewed as an iterative method to review operational details and outcomes and remedy any deficiencies that may be noted. The ACE program has 12 basic topic areas that are initially reviewed as part of the overall schematic plan, as shown in Table 73-7 (available at: www.cvexcel.org). In 2017 the ACC began offering cath lab and other accreditation services, based on the national NCDR registries. (available at: www.accreditation.acc.org).

Table 73-7 Elements of Review in the Accreditation for Cardiovascular Excellence Standards for Cardiac Cath Lab Accreditation

- Facility
- Equipment
- Leadership structure
- Physician extenders and cardiology fellows
- Nursing personnel
- Technologists and other personnel
- Reporting of results
- Procedure indications and informed consent
- Procedure preparation and conduct
- Patient outcomes at discharge or short term (30 days)
- Quality assurance
- Radiation safety

RESULTS

Establishing a QA/QI program can be a frustrating and time-consuming activity. While it is often relatively easy to tabulate adverse outcomes and identify quality gaps, formulating effective strategies to deal with these problems can be challenging. Furthermore, when there are several adverse outcomes or quality gaps that have been identified, prioritizing them in some logical and meaningful order can be difficult. Every institution will be different and take a different approach. Changes will not occur quickly nor will results be observed immediately. Patience and persistence are required. An example of a successful quality improvement initiative, a multicenter one, comes from the Northern New England Cardiovascular Study Group. This consortium of 10 hospitals chose to tackle the problem of contrast-induced AKI, which, as described earlier, is an unwelcome adverse event in cardiovascular procedures. The hospitals were divided into an intervention group, a control group, and a benchmark group. The intervention hospitals agreed to form multidisciplinary teams, participate in monthly conference calls, participate in a process of identifying best practices, implement changes in patient care, and report on their individual strategies, achievements, and problems. The structures and features of these multidisciplinary teams that were formed at the intervention hospitals almost exactly match the design features described earlier for an effective QA/QI program. The results of the effort are exceptionally encouraging (Fig. 73-13). The multicenter initiative was able to significantly reduce the rates of AKI by 21% at intervention hospitals, while no changes in AKI were observed at benchmark or control hospitals. It is important to keep in mind that it required more than a year to effectively demonstrate improvements.

CONCLUSIONS

Increasing attention is being focused on QA/QI throughout interventional cardiology. We are called upon both as individual operators as well as hospital systems to demonstrate that adverse events are being minimized, while outcomes are being improved. As new technologies emerge and new procedures are developed, we must show that these can permit safer and more successful approaches to existing clinical problems and/or permit more difficult problems to be treated that might have gone untreated before. In addition, we are called upon to demonstrate that not only are individual procedures safe and effective in their immediate outcomes, but also they have value to patients over longer periods of time when compared to alternative treatments that can be employed. Only by establishing robust QA/QI
programs will these efforts be able to succeed.

REFERENCES


**MULTIPLE CHOICE QUESTIONS**

1. What are the 3 basic topic domains in a quality assurance/quality improvement (QA/QI) program?
   A. Variability; mortality; adverse events
   B. Meetings; publications; adverse events
   C. Structure; processes; outcomes
   D. Peer review; work flow; outcomes

2. True or false? The major adverse event rates associated with general diagnostic cardiac catheterization procedures have declined over the past 2 decades.

3. Risk-adjustment models have been developed for all of the following adverse events with percutaneous coronary intervention (PCI) EXCEPT:
   A. Bleeding
   B. Acute kidney injury (AKI)
   C. Mortality
   D. Stroke
4. A catheterization laboratory QA/QI program should have all of the following features EXCEPT:
   A. Committee with chair
   B. Regular meetings
   C. Written process for credentialing
   D. Regular periodic reports
   E. Punitive disciplinary actions

5. True or false? Variations in physician practices, hospital processes of care, and clinical outcomes are part of the nature of medicine, are expected and natural, and should not be subject to examination in a catheterization laboratory QA/QI program.

ANSWERS

1. C

A robust and comprehensive QA/QI program can generally be described as having 3 features or aspects: *structure*, which refers generally to the managerial organization of the QA/QI program; *processes*, which refers to the arrangement of medical care activities; and *outcomes*, which refers to the types of events that are examined. Within this broad tripartite layout, there are many subsidiary topics.

2. True

One of the more gratifying findings that has been noted over 30 years of documentation of general diagnostic catheterization laboratory procedures is that adverse events like death, myocardial infarction, stroke, and emergency surgery have declined. In modern studies, these adverse events occur in fewer than 1% of cases and, generally, in 0.1%. The same has not been true overall for interventional procedures, although for some interventional procedures and some adverse outcomes, event rates have declined. The risk-treatment paradox for interventional procedures likely plays a role in this; as experience with a procedure grows, such that adverse event rates in “simple” cases decline, that procedure is then performed in more higher risk cases. This can lead to a non-zero “plateau” in overall adverse event rates with intervention.
3. D

The National Cardiovascular Data Registries (NCDR) of the American College of Cardiology (ACC) have developed and validated a number of risk-adjustment models for certain procedures. This permits a more fair and balanced comparison of different institutions, which may have populations that vary in their procedural risks. For PCI, risk-adjustment models exist for death, bleeding, AKI, new need for dialysis, and 30-day readmission. As yet, there are no validated models for stroke with PCI.

4. E

The focus of a catheterization laboratory QA/QI program must be on identifying, documenting, analyzing, and understanding features that impact quality of care and outcomes. This generally means examining patient selection, processes of care, and adverse events. These activities must involve all levels of personnel working in the catheterization laboratory and its affiliated units: physicians, nurses, technicians, assistants, and clerical staff. The environment must be engaging, thoughtful, inquisitive, and, above all, fair. It is exceedingly rare for deliberate, single-individual actions to cause an adverse event. Much more commonly, there are chains of actions that lead to adverse events. It is these action chains that need to be identified and altered or corrected. Then the corrective action must be followed and observed to document that it worked. This requires the active engagement and willing participation of everyone involved. Hostile, punitive, and blame-finding activities discourage participation and poison the system, ultimately undermining it.

5. False

Variations are a fact in every aspect of medicine and life itself. Observing variations can be a rewarding and fruitful way of examining system behavior. Attempting to link variations to adverse events and outcomes can be tedious and unproductive. Much of the time, no association can be found where one was thought to exist. However, patient and persistent observation, documentation, and analysis are required. Occasionally, 1 or more observed variations will be able to be linked to an adverse event or outcome, and the insights gained will lead to improvements in patient care. This makes the examination of variations a necessary and vital part of a catheterization
laboratory QA/QI program.
Part IX  Principles of Innovation

74  Innovation and Interventional Cardiology: Looking Back, Thinking Ahead
75  Principles of Innovation: Transforming Clinical Needs into Viable Inventions
76  Web-Based Learning
77  Medical Simulation in Interventional Cardiology
The field of interventional cardiology has been driven by technical innovation. In a remarkable progression of needs identification, invention, testing, and refinement, innovators have developed nonsurgical techniques to see into the heart, diagnose a wide array of conditions, and deliver potent therapies. The pathways to innovation were not always simple or straightforward. Many of these inventors persevered despite being told by peers that what they were trying to do was infeasible and foolhardy. Some of most momentous contributions came from innovators who recognized the significance of a serendipitous event, applied newly available technologies to a longstanding clinical need, maximized the value of a previous discovery by casting it in a different light, or refined nascent tools and techniques to make them safer and more effective. Collectively, the efforts of these creative, determined individuals laid the foundations of a dynamic field that integrates diagnostics with the minimally invasive treatment of ischemic heart disease and other cardiac conditions.

BACKGROUND OF INNOVATION
The Pioneers

One of the earliest pioneers of cardiac catheterization, Werner Forssmann, was a German surgical resident who saw the need for a safer, more direct way to deliver drugs to the heart for cardiac resuscitation. He was interested in accessing the right heart via the venous system, but was not permitted to conduct a study because of the prevailing certainty that any foreign penetration of the heart would be instantaneously fatal. However, Forssmann was familiar with previous catheter experiments on animals, as well as accounts of accidental incursions in which the patients had survived.\(^1\) In 1929, he threaded a urethral catheter into his own right atrium via his left antecubital vein and documented the catheter position by x-ray. Although the significance of his achievement was recognized by some, its merit was overshadowed by the consensus that his work was unacceptably dangerous. While Forssmann initially persisted in his research, the condemnation of his peers and loss of several academic positions caused him to abandon cardiology.\(^2\)\(^3\)

Years later, building on Forssmann’s work, André Cournand and Dickinson Richards went on to routinely catheterize both the right heart and the pulmonary artery, establishing the safety of the procedure in association with their groundbreaking research into cardiopulmonary physiology. By analyzing blood taken from the heart via a catheter, Cournand and Richards were able to detect hemodynamic abnormalities characteristic of congenital heart disease and pulmonary heart disease, measure the actions of cardiac drugs, perform studies of traumatic shock, and explore the physiology of heart failure.\(^4\) For this research, they were awarded the Nobel Prize in 1956, which they shared with Forssmann.\(^3\) Notably, while Forssmann was reportedly trying to develop a therapeutic technique, the essential advancements in the understanding of right heart physiology and pulmonary blood flow that followed came from innovators who focused on catheterization as a diagnostic tool.

Serendipity, and the genius to recognize its potential, has also played an important role in the history of interventional cardiology. F. Mason Sones, Jr., a pediatric cardiologist, was interested in improving the ability to visualize the coronary arteries. He conducted numerous animal experiments in which he placed an aortic catheter close to the coronary ostia for the delivery of contrast dye, but experienced little success.\(^1\) In 1958, while
performing an aortogram on a patient for an unrelated purpose, the catheter slipped out of position and contrast dye was injected directly into one of the patient’s coronary arteries. Although this caused asystole, Sones was able to resuscitate the patient and recognized in the process that the near-fatal slip had allowed him to clearly visualize the small coronary vessels for the first time. Sones went on to pioneer a technique that used specially shaped catheters to safely produce selective, high-quality images. Although the new imaging technique was initially met with skepticism, the ability to accurately diagnose blockages in the coronary arteries opened the door for the development of tools and techniques for revascularization.\textsuperscript{1,5}

Up to that point, advances in catheterization had made dramatic contributions to the understanding of human circulation and the ability to diagnose arterial stenoses. However, it took another unexpected event to make the transition to therapeutic intervention. In 1963, Charles Dotter, a vascular radiologist in Portland, Oregon, unintentionally recanalized a patient’s iliac artery by passing a catheter through an occlusion in the attempt to perform an abdominal aortogram.\textsuperscript{1} In retrospect, this was the first time a condition that was normally treated with major surgery was approached with a minimally invasive, catheter-based technique.\textsuperscript{6} Dotter’s intervention marked the beginning of endovascular therapeutic techniques. He and his then-fellow, Melvin P. Judkins, went on to develop a technique for percutaneous transluminal dilation of peripheral arteries using a series of sequentially larger, rigid catheters (the “Dotter procedure”).\textsuperscript{7,8}

Around the same time, Thomas Fogarty, a surgical resident working with Dotter, identified the need for a safer, less traumatic way to remove vascular thrombus than through open surgery. He designed a novel, balloon-tipped catheter that could be inserted through a small incision in the vessel wall and passed through the thrombus. The balloon was then inflated with saline and pulled back so that the balloon dragged the thrombus out with it. Fogarty’s simple, elegant embolectomy technique went on to replace open surgical thrombectomy as the method of choice.\textsuperscript{9} (See text box on Tom Fogarty.) Subsequently, Fogarty and Dotter worked together on a catheter to treat arterial stenoses that used a balloon to increase the lumen diameter. However, their progress was ultimately limited by the fact that the available latex balloon material was too compliant to exert sufficient force on the lesions.\textsuperscript{1}
The Modern Era

In Europe, where Dotter’s catheter-based angioplasty technique was received with more interest than in the United States, a young German physician, Andreas Gruentzig, learned the method from a mentor. After relocating from Germany to Zurich, Switzerland, in 1970, Gruentzig used the technique to perform peripheral and renal artery recanalizations. Recognizing that Dotter’s approach could only enlarge the lumen to the size of the catheter, he sought to improve the balloon concept by working with a polymer chemist to develop a balloon made of a tougher material that could exert more force on the plaque. Gruentzig launched the modern field of interventional cardiology when he performed the first coronary balloon angioplasty in 1977.¹

Tom Fogarty, MD

While an operating room scrub technician in the late 1950s, a young Tom Fogarty removed the finger from a surgical glove and, using fly-fishing techniques, tied it to the end of a urethral catheter. With this crude bit of engineering, Fogarty invented the first balloon catheter for the vascular system. The resulting device, the Fogarty embolectomy catheter (Fig. 74-1), eventually became the standard of care for surgical embolectomy. Since then, Dr. Fogarty has received more than 70 patents for a range of surgical and interventional products, including balloons used for laparoscopic hernia repair, a device for minimally invasive breast cancer diagnosis and therapy, and a self-expanding stent graft for percutaneous abdominal aortic aneurysm repair. In his distinguished career, Dr. Fogarty has founded or co-founded more than 30 medical technology companies and serves as a scientific advisor to numerous others.
Many of the early practitioners of angioplasty were inspired by Gruentzig to be inventive and entrepreneurial. In the years that followed the initial
procedure, the innovations conceptualized by these clinicians propelled the field forward. Milestone technologies include John Simpson’s over-the-wire method for the delivery of angioplasty catheters, and his atherectomy device for plaque removal (see text box on John Simpson). Ulrich Sigwart and Julio Palmaz (see text box on Julio Palmaz) addressed problems of arterial recoil and restenosis through the development of coronary stents. Patient outcomes were further improved through numerous refinements to the stent design, as well as successive generations of drug-eluting stents and adjunct protective devices.

Gruentzig’s contribution to the culture of innovation in interventional cardiology was nearly as defining as his balloon catheter. A dynamic, free-spirited physician, Gruentzig was known for his charismatic and enthusiastic style as a clinician and teacher. He pioneered the live-demonstration course, which has become the signature educational and cultural event in the field, and serves as a showcase for new technologies. Gruentzig also provided a role model for much of what was to occur at the interface of innovation, entrepreneurship, and practice in interventional cardiology. He was a principal figure in the company that produced his balloon catheter, and for a while, even personally decided which physicians could purchase the devices.

Similarly, the innovators of the interventional tools that followed also helped found and grow start-up companies that competed to develop the best new technologies. As the industry expanded rapidly, the unusually close interaction between physicians and companies was reinforced by clinical and financial success. Young interventionalists learned from their mentors how to interface with companies and became the next generation of innovators. Other physicians became involved in device testing via preclinical and clinical trials. These individuals and the culture they created propelled interventional cardiology to a unique position at the epicenter of technical innovation and entrepreneurship in the early part of the 21st century. As 1 measure of the rate of technology innovation, cardiovascular devices account for more than half of all devices receiving premarket approval (original and supplements) from the US Food and Drug Administration (FDA)\textsuperscript{10} (Fig. 74-4).
John Simpson, MD, PhD

John Simpson began his career as a physician innovator by inventing the over-the-wire angioplasty catheter, a device that formed the basis for Advanced Cardiovascular Systems (ACS, now Guidant). Later, Dr. Simpson invented the Simpson AtheroCath, the first catheter for directional atherectomy (Fig. 74-2). Since then, Dr. Simpson has helped found numerous other companies in interventional cardiology, including Perclose, LuMend Inc., Fox Hollow Technologies, and Avinger, Inc.

FIGURE 74-2 The Fox Hollow Technologies atherectomy device.

Notable inventions:
• Over-the-wire angioplasty catheter
• Suture-based interventional closure device
• Simpson AtheroCath (directional atherectomy)
• Avinger catheter systems (image-guided atherectomy)

Selected roles as founder/director:
• Advanced Cardiovascular Systems (ACS)
• Devices for Vascular Intervention (DVI)
• Perclose
• LuMend
• Fox Hollow Technologies
• De Novo Ventures
• Avinger, Inc.

**Julio Palmaz, MD**

After attending a lecture by Andreas Gruentzig on the advantages and limitations of balloon angioplasty in 1978, Julio Palmaz invented the idea of the balloon-expandable stent *(Fig. 74-3)*. Although his path was not easy, Dr. Palmaz eventually convinced Johnson & Johnson to acquire his technology, which formed the basis for the Johnson & Johnson Interventional Systems division. A key inventor of the endovascular stent graft for treatment of abdominal aortic aneurysms, Dr. Palmaz has also worked to improve the materials used for stenting and has been an active proponent of implantable nanodevices for in vivo diagnostics.
FIGURE 74-3 An early Palmaz-Schatz stent before and after balloon deployment.

Notable inventions:
• Balloon-expandable vascular stent
• Endovascular abdominal aortic aneurysm stent graft

Selected roles as founder/director:
• Advanced BioProsthetic Surfaces
• Palmaz Scientific
• Palmaz Vineyards

The climate for technology innovation in the United States and abroad, however, is undergoing a historic change. Today’s value-oriented healthcare environment in major developed markets means that new technologies must also represent cost-effective solutions. To maximize their chances for reimbursement and adoption, innovators must demonstrate value by comparing a new therapy to the current standard of care in terms of clinical effectiveness, relevant outcomes such as survival and quality of life, and cost reduction.

In addition, heightened regulatory scrutiny in both the United States and Europe has substantially increased the amount of money and time required to
bring a new device to market. The protracted timeline has added significantly to the risk profile for investors, reducing traditional venture investment in device technology. Against this backdrop, US innovators are pursuing new pathways such as nontraditional funding sources or moving clinical trials and/or entire companies overseas. Perhaps most importantly, the types of innovations most likely to get funding in this environment will be therapies with the potential to make a major difference in the quality of care, patient satisfaction, or cost reduction, rather than those technologies that offer only an incremental improvement over the existing standard of care.

Coupled with these new forces of value-based innovation and tightened regulatory oversight, the culture of entrepreneurship for physicians has changed dramatically, particularly in the United States. Compared to the early days of angioplasty, there is much stronger attention to potential financial conflicts of interest for physicians who invent and/or test new technologies. In the current climate, transparency of financial involvement with companies is mandated by federal (“sunshine”) laws, and in general, physicians with financial interests in a company or product are strongly discouraged or prohibited from participating in human trials of the technology. Even as these and other market realities have added additional layers of complexity to the innovation process, new opportunities are emerging. Advanced developing markets such as China and India offer vast patient populations that are increasingly suffering chronic conditions such as heart disease, diabetes, and hypertension. In these countries, the rapidly growing middle class is demanding improved healthcare services, medical technologies, and related interventions, factors that in turn are stimulating improvements in healthcare infrastructure and expanded insurance coverage. However, innovators must approach these markets strategically, since they tend to be highly price sensitive, with unique challenges based on cultural differences and local conditions that must be carefully considered.

In this chapter, we explore the landscape of innovation in our field by examining the common characteristics of successful innovators, describing some of the essential tools required for developing and assessing new cardiovascular technologies, and looking ahead to some of the most significant challenges facing the next generation of innovators.

COMMON QUALITIES OF
SUCCESSFUL INNOVATORS

Careful examination of the lives and careers of several well-known physician entrepreneurs reveals a number of shared characteristics and traits that contributed to their success. Interestingly, many of these qualities contradict commonly held ideas about the interests and innate skills one would expect to find in an innovator. In this section, we outline some of the key factors that lead to important innovations and, in the process, highlight some potential misconceptions and myths about the development of new technologies.

Focus on the Patient

**Myth:** Medical technology innovators are innate tinkerers; success requires a mechanical mind.

**Fact:** Successful medical innovators identify important clinical problems and seek to solve them; success requires focus on the patient.

The familiar image of a great inventor is someone with extraordinary technical curiosity and expertise—the type of person who spent his or her childhood taking apart household appliances or building machines in the garage. Indeed, many technology inventors are inveterate tinkerers. In order to apply their analytic minds to the solution of everyday problems, these individuals often choose engineering or another technical profession. However, the inventor of medical devices and products does not necessarily fit this mold. The defining characteristic of the medical innovator is not mechanical aptitude, but the ability to recognize critical shortcomings in current medical practice.

John Simpson exemplifies this kind of innovator; one who identified problems and devised solutions without a “how it works” background. He spent much of his youth on a farm and never developed an interest in electronics, taking things apart, or any of the other childhood activities often associated with inventors. During his education, Simpson pursued a PhD in immunology along with his medical training, but stayed away from engineering and technological fields. As a physician-innovator, Simpson developed the original over-the-wire angioplasty system, directional atherectomy, and numerous other innovations. For each of these technologies
and the companies he ultimately built around them, Simpson was deeply involved on the clinical side, but he left the engineering and manufacturing to other, more capable hands. “I know my limits,” Simpson emphasized. “I didn’t even try to interfere with the engineers.” Instead, he stayed focused on the ultimate goal. “You fix the patient and you win,” he summarized succinctly.\textsuperscript{11}

Along the same lines, another common misconception about physician-innovators is that in order to be successful, they must also be shrewd businessmen. Julio Palmaz cites his own experience as a counterexample, noting that he was unable to convince his university that his invention of the stent was worth patenting and that he struggled unsuccessfully to attract financial backing until he partnered with Richard Schatz.\textsuperscript{12} Tom Fogarty, who has started more than 30 companies, describes himself an “idea generator” and “enabler” but not someone who can run a company. His goal has always been to turn fledgling medical device companies over to experienced managers as soon as possible.\textsuperscript{13}

In short, the key aspect of medical technology innovations is that they solve an important problem in clinical practice. Innovators have to “…keep the patient in front of the vision,” emphasized Simpson.\textsuperscript{11} Unquestionably, the innovation process involves many other complex elements, all of which must be addressed to bring an idea from concept to commercialization. However, it is the identification of an acute clinical need that forms the foundation of a successful business opportunity. The fundamental intellectual discipline is needs finding.

\textbf{Relationships}

\textbf{Myth:} Successful physician-innovators are lone geniuses who single-handedly bring a concept to life.

\textbf{Fact:} Successful physician-innovators recognize their own limitations and surround themselves with a team of talented individuals to bring their ideas to fruition.

As with any other professional undertaking, relationships are essential to the success of the physician-innovator. For the young innovator, the most important early relationship is with a mentor. Successful device entrepreneurs can all point to mentors whose influence, support, and enthusiasm were
instrumental to their success. Andreas Gruentzig was training in peripheral vascular disease at the Ratchow Clinic in Darmstadt, Germany, when he first heard Dr. Eberhart Zeitler speak about Charles Dotter’s early work with peripheral recanalization. Gruentzig was intrigued by the concept, but his chief at the time abhorred the idea of forcing a catheter into a narrowed artery, and vowed that such treatments would not be performed in his hospital.\(^8\) As a result, Gruentzig moved on to University Hospital in Zurich, where he was able to find several mentors who were more open-minded and supportive. Among these were the chief of medicine, Dr. Walter Siegenthaler, and the head of cardiology, Dr. Wilhelm Rutishauser. Dr. Rutishauser assisted Gruentzig in his critical move from the department of radiology into cardiology, which was a political and practical necessity for him to initiate his research program in angioplasty.\(^{14}\)

While some universities now offer formal programs that teach the process of innovation, there is no substitute for hands-on mentoring. Tom Fogarty, who credits an early surgeon mentor with helping him get into the cadaver lab to test his balloon catheter, tutoring him on appropriate bench models, and ultimately being the first surgeon willing to use his device, noted that, “Being in the environment promotes [innovation]; it’s more of a mentoring issue than it is reading a book on how to innovate.” Carrying that tradition forward, he explained that when working with students, he makes sure that they have experienced the surgical environment and have personally observed any clinical problem they are trying to address. “Before they start doing anything, I get them to understand how the problem is currently handled, not only in the operating room but also so that they have some insight into what is involved in the postoperative care, how long it takes, and what some of the follow-up issues are.”\(^{13}\)

As a need is identified and a project begins to take shape, different relationships—partnering with experts in other areas—become a critical component of success. Even the most iconic medical innovators are quick to acknowledge scores of colleagues who brought key abilities to their fledgling companies. Success comes from identifying and acknowledging areas of personal limitation and enlisting the aid of those who can be most helpful. As Simpson explained, “It’s always a team effort. The whole concept that there’s some special visionary out there who does all this stuff by his or herself is flawed as far as I’m concerned. It’s about putting together a group of individuals that each make a real, genuine contribution and can work together
to develop something that is really special.”¹¹ For a medical technology venture, success requires people with expertise in medicine, engineering, manufacturing, regulatory affairs, reimbursement, fundraising, finance, management, marketing, and sales, among other areas.

The story of Gruentzig’s development of the first coronary balloon exemplifies the need to partner for key expertise. During the early development of angioplasty balloons, Gruentzig experimented with a number of materials, all of which proved to be too compliant to be effective in dilating arterial stenoses. The breakthrough came when he approached a professor emeritus of chemistry, Dr. Andreas Hopf, who introduced Gruentzig to polyvinylchloride. Using this material, Gruentzig was able to make the thin-walled noncompliant balloons necessary for angioplasty. As innovator-entrepreneurs progress in their careers, they typically develop significant networks of individuals with diverse areas of expertise. These networks can be enormously helpful to the aspiring inventor in the process of building a comprehensive team. Fogarty summarized this concept as follows: “Value creation in developing new devices comes from multiple sources. If you think just because you had the idea you brought all the value, you’re not going to get there because somebody has to implement that idea and one individual can’t do it.”¹³

**Independent Thinking**

**Myth:** Successful physician-innovators pursue a concept only after building consensus approval from colleagues in their field.

**Fact:** Successful physician-innovators often need to push through major skepticism and discouragement from their colleagues and the medical establishment.

The typical physician is not especially adept at identifying which promising medical technologies will ultimately be successful. This phenomenon is not unique to medicine—many design and consulting firms exist on the principle that innovation is best done using the unique perspective of an outsider. Experience teaches people to view their profession only as it exists today without questioning its foundations in any meaningful way. A classic example is telegraph operators, who notoriously failed to appreciate the changes in behavior that would result from voice
Physicians are particularly susceptible to this professional conservatism because the format of medical school tends to discourage the inquisitiveness required of an innovator. Fogarty observed, “You do no harm by doing what you’ve always done before, and … in the field of medicine, I think the way we’re taught certainly deters innovation.” Much of medical training is devoted to learning the current standard of care in terms of symptoms and treatment guidelines. Because of the volume of information to be learned, little time remains to question the status quo.

The medical culture also affects the would-be innovator in the early stages of testing and promoting an idea. Most successful innovators have numerous stories of the initial disbelief and discouragement that they encountered from their peers. Fogarty invented his thrombectomy balloon during a time when it was widely believed that any manipulation of the intima would cause additional thrombosis. The balloon, designed to rub across the intima in order to remove clot, was therefore considered to be unsafe. More specifically, as Fogarty recalls, the surgeons who saw his first prototype told him that his idea was “crazy, inappropriate and dangerous.” However, Fogarty noted that at the time, he was only in his first year of medical school. He explained, “I didn’t know enough about medicine to know if it would work or not—and that’s probably one of the best attributes of not knowing something. You’re not deterred because you don’t know, and I think that’s often how a lot of new approaches are tried.”

Ultimately, even after collecting clinical data to support his claims, Fogarty was unable to publish his work; 3 journals rejected his manuscript for publication because his results defied conventional wisdom. Eventually, the volume of data that Fogarty and others generated in support of the thrombectomy balloon forced a change in thinking, and the technique became accepted.

The lesson, clearly, is that the physician-innovator must be willing to buck professional conservatism in order to be successful. Innovation occurs when an individual champions a new technique, despite initial unpopularity, until sufficient data exist to convince the medical community of its merit. For this reason, the typical inventor needs to be an independent thinker with both the skills to identify promising new technologies and the conviction to pursue them.
Perseverance

**Myth:** The best innovators succeed because they do not allow failures to occur.

**Fact:** Successful innovators accept that major setbacks occur and are driven to persevere because of a strong belief in the clinical need and their solution to it.

Disparagement from the medical community is only 1 of the hardships that the typical medical technology venture may face. Setbacks can occur at any step along the way, from fundraising through design development, clinical trials, and commercialization. The successful entrepreneur accepts this uncertainty and presses forward, motivated by conviction in the clinical need and the benefits his or her solution will offer. Fogarty, in fact, calls failure “a preamble to success.” He related, “When something doesn’t work, the information obtained about what not to do often that leads you down the path of what you should do. If there’s a need, there’s a need, and just because what you try to do to address it doesn’t work the first time, doesn’t mean the need goes away.”

Julio Palmaz’s experience with the coronary stent offers a telling example of persevering despite encountering significant obstacles on multiple fronts. At the time of his invention, implantation of metallic structures into arteries was so novel that most physicians could not believe that it might be successful. They understood the potential structural benefits of a stent, but were certain that any foreign structure placed within the artery would thrombose. In fact, when early human trials showed a high rate of thrombosis, many physicians believed that their fears had been affirmed. Undeterred, Palmaz revised the implantation technique to include anticoagulation, and other investigators (notably Antonio Colombo) modified the implantation technique so that thrombosis became a manageable issue.

Due in part to these clinical issues, Palmaz also encountered difficulties obtaining funding. “There were so many other techniques that were being evaluated at the time that stents had to wait their turn,” he recalled. Alternatives to angioplasty from atherectomy to brachytherapy had the attention of funding agencies, leaving Palmaz unable to obtain grant support or private funding.

In the course of pursuing an innovation, setbacks naturally occur. One
approach for managing this is, simply, persistence. When Palmaz and his associates approached established vascular device companies with his initial stent results, the response was uniformly negative. None of these companies were willing to shoulder the significant risk that remained in getting the stent to market. After months of trying, the stent team finally found a backer in Johnson & Johnson, which was just trying to enter the catheterization market at the time. The support of this company was sufficient to bring the product to market, and all of the rejections leading up to that point became an instructive footnote.

While persistence is essential, it is also important to point out that every major development program experiences 1 or more significant changes in direction, some of which can be drastic. Entrepreneurs should avoid becoming so enamored of their invention in its original form that they are unwilling to evolve or modify their concept in response to new information.

**PREPARING FOR A FUTURE IN INNOVATION**

With these qualities of successful physician-innovators in mind, what should a physician entering the specialty of interventional cardiology do to prepare to become a part of the culture of innovation? To answer this question, we interviewed a number of interventional cardiologists who have made names for themselves as successful innovators. While some of their insights and recommendations were unique to their own experience, a number of suggestions that emerged were consistent from one physician to the next. Often, these insights reinforced the importance of the character traits mentioned previously. In this section, we explore their insights and provide concrete advice for those wishing to join this innovative culture. (See Table 74-1.)

Table 74-1 *Anticipating the Future*
New Technology: The Next 10 Years

The older age and desire of people to remain active and healthy will be an important force for technologies that improve quality of life. These may range from smart surgical or interventional techniques to artificial audio and visual replacement, e.g., cochlear and retina implants. The challenge is to make good technology for a price affordable to a large part of the world’s population. In that respect, I have become much more optimistic than five years ago. If we can make a mobile telephone for five euros, smart medical devices should also be affordable.

—Nico Rijp

The imaging revolution changing everything. Our ability to non-invasively image, to detect disease before or soon after it becomes clinically manifest, to visualize actual disease processes (not just structure), and to be able to respond, appropriately, therapeutically, based on what imaging reveals is radically transforming the practice of medicine and will continue to do so the next ten years, especially with advances in molecular imaging and target therapeutics.

—Gregg W. Stone

Global Markets

In countries like India, physicians are very cost sensitive, patient centric and socially sensitive. The price of imported technology is a major concern and there is limited capital for high risk ideas with a developing regulatory environment. Because of this frugal mindset, the innovations championed here are essentially low cost and without frills. However, if their quality is ensured, these innovations will change the way procedures are done, not only in India but will be relevant to the rest of the world.

—Balbham Bhargava, Professor of Cardiology, All India Institute of Medical Sciences; director, Stanford India Bioscience

Atherosclerosis

We are entering into an era of what has been termed vascular reparative or restorative therapy. This means that we will no longer implant permanent devices, but rather will implant temporary solutions that do their job and then disappear. One example of this is the use of bioresorbable coronary artery scaffolds, which serve the purpose of a metal stent-plaque stent for one to two years, and then will fully resorb, restoring the coronary artery as close as possible to its native, pristine state, with normal dimensions and vasomotor responses. Such a therapy may also facilitate prophylactic treatment of vulnerable plaque, thereby preventing heart attack and sudden death. This is a dream which may be realized within ten years.

—Jeffrey W. Moses

Congestive Heart Failure

Witness the advent of bi-ventricular pacemakers and defibrillators in that population as evidence of what fairly simple device development in that area can do to affect a huge cohort of patients. Futuristic therapies—cell therapy and other pro-remodeling therapies of one kind or another—have incredible potential markets, therefore are incredible potential areas for device development.

—Campbell Rogers, Chief Medical Officer, HeartWare

Valvular Disease

I see little reason to doubt that within ten to fifteen years, most valves will be treated percutaneously, either through ways to dacilitate them, or ways to repair them, or ways to replace them. All of these technologies are existent today that make sense and have shown reasonable feasibility, I think that will only get better.

—Stephen O’Rourke

There are several significant challenges around the percutaneous treatment of valvular disease. From the patient’s perspective, the biggest challenge is availability, because most of the minimally invasive treatments are approved only for high risk patients who cannot tolerate a surgical procedure. From a provider’s perspective, the biggest challenge is that the approved devices are always one or two generations behind, and although they work well, they are often bulky, difficult to use, and at times associated with significant morbidity. The latest generation devices, which feature significant enhancements in profile and other characteristics that improve the precision of implantation, remain in very long term clinical trials in the US And from an economic perspective, because the regulatory pathway makes it so difficult to get to commercialization, instead of three or four approved values competing for market share, every three to four years, there is one new value. So there is no free market pressure on cost.

—Maurice Buchbinder

Peripheral Vascular Disease

Outside the US, there seems to be a strong sentiment towards the concept of "have nothing behind." The idea that implantation of a permanent metallic prosthesis should be avoided if at all possible. Peripheral artery disease is a chronic and relentless disease process and vascular specialists should avoid therapies that could complicate future interventions if they fail.

—John R. Laird, Professor of Medicine and Medical Director, UC Davis Vascular Center

We face enormous challenges when it comes to achieving ideal results ... in terms of optimizing angiographic and clinical outcomes, as well as improving patients’ quality of life and longevity. As compared to the coronary arteries, the peripheral arteries have more extensive, lengthy blockages and we haven’t only digested but we have developed different strategies and treatments based on what works best. Moreover, because there are multiple specialties treating this disease, figuring out more specifically what constitutes a good outcome will require more collaboration and cooperation amongst all the stakeholders—in both our patients. I personally think that outcomes need to be measured not just by patency of an artery or the distance a patient can walk, but also the patients’ perceptions, by their functional status, and by economics—and what did we achieve, how much did it cost to get them, and was it of value to the patient? This is the concept of value-driven health care. Again, we need good clean data to assess this properly.

—Kenneth Rosenfeld

The real game changer in the next ten years will be much of the guess work in cardiovascular diagnostics and treatments. New technologies may be based on the use of nanoparticles and artificial intelligence. One example of this is the development of disease state. These modeling technologies have the potential to reduce the number of unnecessary procedures while focusing resources on those patients with the greatest needs.

—Fred St. Goar, Interventional Cardiologist, El Camino Hospital and Fogarty Institute for Innovation

The field of percutaneous intravascular replacement will have a huge impact on how we treat patients with mitral regurgitation and advanced cardiac disease. Mitral regurgitation is four to five times more prevalent than aortic valve disease, affects patients across many decades of life, and often involves significant co-morbidities. To date, medical therapy has been the treatment of choice because surgery is often contraindicated given the significant morbidity and poor ventricular function associated with this condition. Moreover, these catheter-based intravascular therapies, which are already on the near horizon, will drive advancements in the ancillary devices needed to make the procedures successful such as enhancements in imaging modalities like 3D or 4D transesophageal echocardiography to guide the procedures, and innovative new approaches for non-invasive vascular access and closure.

—Maurice Buchbinder

The process and maturity of medical device innovation has rapidly traversed borders in the past half a dozen years. From joint ventures in China to cost basis implementations in India, device development has taken on a global role and partnerships in those market-expanding countries are essential for success. Geographic markets can provide isolated values and then be leveraged to other regions of the world.

—Peter Fitzgerald, Professor of Medicine and Director, Center for Research in Cardiovascular Interventions, Stanford Medical Center
Training for Innovation

As discussed in the previous section, the most important characteristic of the successful physician innovator is a primary focus on the needs of the patient. Our interviewees echoed this sentiment, reinforcing the need for would-be physician-innovators to be actively involved in patient care. As Jay Yadav, founder and chief executive officer (CEO) of CardioMEMS, Inc., explained, “If you just try to stay in an ivory tower and are not hands-on, chances are you’re not going to find the right problems and acceptable solutions. There are a lot of solutions that sound great on paper, but are not really implementable in a clinical setting.”

In order to be innovative, an individual must often synthesize knowledge over more than 1 discipline in order to solve a clinical problem in a new way. Early innovations in interventional cardiology were technologically straightforward, so physicians with little additional training were able to make those leaps single-handedly. As the field continues to mature, the physicians we interviewed envision that the technical and scientific knowledge required for successful innovations will steadily increase.

Several interviewees felt particularly strongly that basic science will play a significant role in future innovations and should be emphasized in training. Nicolas Chronos, chief medical officer at Endotronix, Inc., and CEO at Cardiology Care Clinics, encouraged future inventors to understand the biology as much as they can, and then seek out people who have the expertise needed in other areas, for example, in inflammation. “I don’t think that people like ourselves are ever going to become experts in inflammation, but at least [we can understand] the implications for other biological processes,” he said. Similarly, Nico Pijls, Professor of Cardiology at Catharina Hospital in Eindhoven, the Netherlands, suggested that training in physiology and at all of the basic sciences should be in-depth. “There should be a sound interest and desire to know what is the basis of things, what is the task of every part of the body, why is a particular process in physiology going on,” he stated. “Through sound physiologic thinking … the need for new inventions will be uncovered.”

Although a solid foundation in basic science was perceived as critical to the future of innovation in the field, the interviewees were less eager to recommend lengthy engineering training for physicians. There was a perception that while physicians should gain some familiarity with these
technologies, overall their time is better spent outside an engineering classroom. Stephen Oesterle, senior vice president of medicine and technology at Medtronic, Inc., observed that many of the technologies that are finding application in medical devices come from the information technology (IT), communications, data analytics, MEMS (micro-electromechanical systems), and low-power microelectronic industries. He suggested that, while it would be challenging for practicing physicians to take engineering courses in each of these disciplines, there are several comprehensive trade journals that frequently report on the early stages of companies pursuing these technologies. “I have also found willing mentors in several of the leading technical universities who can serve as ‘translators’ as I seek deeper understanding,” Oesterle added. Yadav agreed, emphasizing the need to focus on solving clinical problems, rather than learning engineering. “It’s not so much if you’re an engineer or not … really the key thing is to look with a questioning mind. Don’t assume that the way something is being done right now is the optimal way of doing it. Chances are it’s not. It can be improved on.”

In addition to scientific skills, several of the successful entrepreneurs recommended business training for the aspiring physician-innovator. None recommended a formal business degree, instead believing that the necessary skills could be learned through a short course or on the job. “I think most interventional cardiologists can learn business if they have an interest and an aptitude for it. I think that’s much more learnable, in some ways, than some of the engineering and physics involved in innovation,” said Tim Fischell, CEO at Ablative Solutions, Inc. Oesterle agreed that going to business school was not necessary for most physician entrepreneurs, but felt that some basic financial competence was necessary. “A rudimentary knowledge of how to read an operating statement and evaluate a balance sheet is essential,” he said. “The cost of raising capital through venture sourcing, convertible loans and other debt vehicles should be understood. The more one can understand about the dynamics of venture funding, the better.” Oesterle noted that many business schools offer short modules that cover the basics of finance, and suggested that books on the topic can also suffice, “unless one plans to be the chief executive through the later stages of a start up.”

Thus, innovative physicians should focus on being physicians first, emphasizing good patient care and thorough knowledge of the underlying
science. While basic financial competence is important, the interviewees felt that deeper expertise in key areas could be acquired most effectively by reaching out to specialists as needed.

The Changing Landscape

The experts also commented on changes that they perceive are occurring in the field of medical-technology entrepreneurship. Broadly, there is a perception that true innovation is becoming more difficult because of changes in the nature of technologies themselves, the restrictive regulatory environment, the reduced availability of traditional funding, and challenges around reimbursement. Reflecting back on the development of his balloon embolectomy catheter, Fogarty estimated that it cost between $12,000 and $15,000 to get the device into commercial use, and noted that, at the time, the regulatory path consisted of peer scrutiny and informed consent from the patient. “There are just a lot more things that you have to deal with now, versus what you could do then,” he said.

According to Gregg W. Stone, Professor of Medicine at Columbia University and Director of Cardiovascular Research and Education at Center for Interventional Vascular Therapy at Columbia University Medical Center, one outcome of the difficult regulatory environment in the United States is that, while many medical device ideas still originate in the United States, a significant portion of product development has moved overseas. Initial destinations include “think tank” geographies such as Israel, with the likelihood that more innovation and development will move east as countries such as China and India continue to gain economic strength. He added, “A worrisome trend is that some start-up and mature companies are actually no longer developing products for the US market because of the time and expense to get devices approved here.”

With regard to possible future changes in the regulatory environment, the predictions were varied. Stone suggested that, in many respects, the US FDA may get somewhat easier to navigate. “Although while speculative, I believe that in the future, legislation will be passed that will provide FDA with more post-market regulatory power, which will allow them to ease up a little bit on the premarket side.” He added, “That said, though, I don’t see the FDA softening up any time soon on their relatively rigorous requirements to demonstrate safety and efficacy, usually through randomized trials for novel
technologies and therapies.”

Other interviewees warned against being too optimistic about changes in regulatory policy. “Even when the FDA commissioners come up and say, ‘We have to be kinder and gentler and we have to be more compliant,’ the FDA is the FDA, and it remains for the foreseeable future a gating mechanism,” said Maurice Buchbinder, an interventional cardiologist at Alvarado Hospital Medical Center in San Diego, California.

With regard to the reduced amount of venture funding available for medical devices, some experts see this winnowing out less valuable pursuits, rather than putting the brakes on all innovation. “It’s just going to put a priority on the types of innovations that are going to be game changers,” said Stone. “We’re not going to be able to spend hundreds of millions of dollars for incremental changes in devices and patient outcomes. There will always be room for major advances that will extend life and provide patients with a substantially better quality of life, but the onus will be on us to demonstrate that.”

In today’s cost-conscious environment, reimbursement has surpassed regulatory approval as a top concern for many device innovators. Increasingly, government entities and private insurers are basing their reimbursement decisions on whether a technology represents a good value. Accordingly, the experts agreed that successful innovators increasingly need to take cost-effectiveness into consideration early in the innovation process in order to be able to make quantitative statements about the economic value of their approach. This typically involves researching available clinical evidence, comparing the costs of the new therapy to the current standard of care, and especially for technologies with longer term effects, developing value models to project the long-term quality of life and cost benefits of treatment. Oesterle summarized the challenge as follows:

“It used to be that a medical device was approved on the basis of safety and some demonstrated efficacy. Today a much larger burden of evidence is required; particularly with regard to reimbursement. Developed markets need to reduce the amount of money spent on healthcare and are demanding technologies with manifest cost benefit. New devices must be either less costly or have demonstrated improved outcomes that can be readily translated to cost savings. Improved technology is not necessarily valued in the absence of clear value story.”
In addition to these policy changes, the interviewees each had a number of comments to make about the future of clinical practice in areas ranging from atherosclerosis to structural heart disease. The experts agreed in very broad terms about the current challenges facing cardiology, but each had a unique view of what the future holds for clinical care (see Table 74-1). Innovation by its very nature is unexpected, so it should come as no surprise that even respected authorities in the field would disagree on the devices that will be adopted into clinical practice in the future!

SUMMARY

In this chapter, we have described a number of traits held in common among the most successful physician-innovators and provided advice directly solicited from a number of contemporary inventors and entrepreneurs. The key messages are simple:

• Focus on the patient and the clinical need.
• Build a good team (around your limitations).
• Be persistent in the face of disbelief and discouragement.
• Focus on cost-effectiveness and economic value early on.

John Simpson summarized the most important components of innovation as follows, “If you’ve got people that bring commitment and willingness to persevere in adversity, then you can make special things happen, if you stay focused on doing something really clinically relevant.” As interventional cardiologists, we are in a privileged position of being in an environment of major clinical needs every day. The skills required to identify these needs and create significant new technological solutions are in fact very similar to those we have already developed in our training and practice.

ACKNOWLEDGEMENT

The authors wish to thank Stacey Paris McCutcheon for her skilled editorial work and her role in interviewing and compiling the comments of the innovators quoted in this chapter.
REFERENCES


Nowhere is the opportunity to innovate as inviting as in the field of medicine, and no specialty has been as productive in the development of new technologies as cardiology. Because heart disease remains the most common cause of death in developed economies such as the United States (and is a growing threat in middle and low-income countries around the world), new developments in cardiology can affect an especially large population and have a tremendous impact. Advances in our understanding of human physiology, genetics, and molecular biology continue to define the fundamental mechanisms responsible for disease. Through these insights, we gain new perspectives and tools with which to create novel solutions. Regardless of the specific clinical problem to be solved, a common innovation process can be applied. It is this basic approach for creating new medical technologies that we hope to convey within this chapter.

Even though there are many revisions in the latest version of this book, we kept this chapter essentially intact from the first edition. This is because the skills required to innovate are enduring. They are typically not taught in medical school, yet they have been critical to the advancement of interventional cardiology. It has been difficult for people in medicine to learn formal principles of innovation, as they are usually taught only in engineering programs. However, this trend has begun to change, and numerous medical
training programs have begun offering curricula targeted at this very issue. As history has demonstrated many times, clinicians and scientists make very good innovators. Although it is important for engineers to be skilled in the fundamental principles of innovation, clinicians and scientists have an essential role to play during the early stages of the innovation process (need finding and concept creation) and, as a result, they should learn these skills so they can participate fully in the important interdisciplinary work of creating new medical technologies.

Developing a new medical technology is a rewarding but often arduous process. The greatest success comes to those who understand the many necessary steps in the innovation process and can plan and execute a strategy to address each one efficiently and effectively.

**INNOVATION: THE BASIC STEPS**

*Innovation* is defined as the process of creating something new. As developers of a medical technology, we seek to address a real clinical need with the goal of not only creating something new, but also creating something better and/or more cost effective. The basic process of focused innovation is very simple and is summarized in Figure 75-1.
Although the innovation process is one that may be used by someone new to a field (top orange arrow), you may enter this process at any stage (orange arrows). In general, it is best to run this process rigorously from beginning to end without skipping steps to avoid the biases that come with arriving at a solution too soon. Regardless of where you enter, awareness of all steps and sensitivity to the need for iteration (blue arrows) can further improve on a good initial idea. As such, each step is briefly described below.

**Step 1: Objective Definition**

Starting with a clearly defined objective is critically important to keep you on the path to focused innovation. Being focused can prevent wasting time and
energy on creative but tangential ideas that do not meet the intended objective. A well-defined objective limits one’s focus to a reasonably sized clinical area where the application of time, research, and creative energy is likely to yield a real outcome. An objective contains the general need area being addressed plus any goals or constraints such as a time horizon or resources that will be required (eg, to enable a significant incremental advancement in mitral valve repair within a 5-year timeframe). It is a good idea to write down this goal and refer back to it occasionally as a project takes shape so that the objective becomes a mission statement for the project. In some cases, it may become clear during the development of the project that the overall goal must change.

Although focus, at any one time, on a single objective is ideal, it is also important to engage people with different backgrounds in your investigation. Medicine itself is a broad field in which an in-depth understanding of different disciplines (eg, anatomy, physiology, pathophysiology) is required to understand a problem and arrive at meaningful solutions. However, a mastery of other fields (eg, physics, electronics, engineering, mechanics) and how they may be applied to solve medical problems can yield some of the most novel inventions with greater impact. For these reasons, the ideal team is a multidisciplinary one that is diverse but remains focused on the defined objective.

Another advantage of defining an objective at the start of the innovation sequence is a practical one—in general, innovators work best within a defined area of expertise. Although there are examples of wildly creative individuals\(^1\),\(^2\) whose inventions span many disciplines and technologies, it is difficult with this type of approach to develop the depth necessary to reliably generate significant advances in medicine. More commonly, this broad style of inventorship results in patents that lie in wait for science to catch up to what has been proposed (“submarine patents”). This approach can be financially rewarding in some situations, but generally does not provide an effective pathway to technology innovation.

**Step 2: Need Finding and Identification**

Most successful medical technology inventors would say that identifying an important clinical need is the single most essential step in the innovation process. Clinical needs can be identified in many different ways. Often they
are recognized by a clinician involved in patient care when a frustrated physician wishes for a better solution to a clinical problem (eg, “if only we could have repaired this mitral valve with a less invasive approach, sparing the patient major surgery”). Needs can also be recognized by those who are not within the field of medicine, or by those who are actively seeking unmet clinical needs (eg, an entrepreneur). Such an intentional innovator must do exhaustive research and observation to evaluate a clinical problem and all existing solutions to it, carefully understanding the strengths and limitations of each. Here again, it is often helpful to involve people of different backgrounds who may not have the biases of an expert deeply entrenched in the conventions of a particular specialty. An outsider to the field is likely to question even the most basic of assumptions and may uncover a true need that is not apparent, even to the specialist (latent needs). Finding clinical needs is a fundamental skill that improves with experience. Some of the most notable innovators in cardiology have demonstrated their abilities as serial need finders (Dotter, Simpson, Fogarty; see Chapter 74).

The characteristics of a “good” need depend on personal and professional objectives. If one were to have the opportunity to choose from an array of needs, the magnitude of the potential patient outcome benefit and the size of the available market/population would certainly top the list of considerations. Although one could list many other factors, such as accessibility of the market, reimbursement, or regulatory environment, having a burning passion for the need is probably the single most important factor for success.

Once a need area has been identified, it is critically important to precisely define the need by producing a need statement. A need statement can be deceptively simple: It is a one-line description of the clinical problem, stated as clearly as possible. Each need statement must explicitly identify the problem that requires solving, the patient population that it most directly affects, and desired outcome that population wants from a new solution. Although at first it seems like an unnecessarily formal exercise to write down a need statement, it is an absolutely essential step to really understanding the need and communicating it effectively to others. Following are some examples of need statements from interventional cardiology:

- A less invasive approach to reduce mitral regurgitation in patients with congestive heart failure that enables patients who are poor surgical candidates to be eligible for the therapy.
• A better technique for directing a guide wire safely and efficiently across a chronic total occlusion that allows a single operator to access 90% of CTOs within 30 minutes.
• A minimally invasive method for restoring myocardial contractile function after myocardial infarction to prevent clinical heart failure.

It is important to differentiate carefully between needs and solutions, and focus on understanding the clinical need first. This includes paying close attention to the way in which the need and its attributes are described, as embedding a solution within the need statement can substantially narrow or bias subsequent steps in the innovation process. For example, the statement “The need for a more torqueable Teflon catheter to perform balloon angioplasty...” is heavily biased. Solutions to this need would clearly be restricted to catheter-based solutions and those using Teflon materials. More importantly, these solutions would exclude superior concepts that employ something besides a catheter. It is also a useful technique to write multiple versions of the need statement that both focus more narrowly on the central problem and/or the size of the population, as well as zoom back from them (called need scoping). The result should be a set of need statements that clearly outlines variations of the clinical problem and population, and suggest several pathways for creative improvement. An example of a narrowly focused need statement might be: “A way to prevent smooth muscle cell migration in response to stenting...”; whereas a more broadly scoped need statement may read more like: “A better way to prevent restenosis after stenting....” Finding the appropriate level of specificity of a need may take some time, and brainstorming at every level can be a very useful exercise. The most productive level of focus usually becomes clear only later, once solutions have been proposed and fertile ground for invention has been exposed.

**Step 3: Need Validation and Screening**

Once you have identified one or more unmet clinical needs, the need validation process begins. In this step, you must verify that the needs you found are indeed experienced by others. It is also important to characterize the features required of an ideal solution that would motivate key stakeholders to potentially change their behavior and adopt it. We call these
characteristics *need criteria*. There are two types of need criteria—must-haves and nice-to-haves. Both types stem from your in-depth need research and should be objectively defined based on what matters most to the affected stakeholders. This includes parameters defined by the patient (eg, risk-benefit, comfort, efficacy, fit), physician (eg, ease of use, complications), hospital (eg, cost tolerance), payer (eg, cost versus future cost savings), as well as other stakeholders. With this constellation of information, the process of needs screening may now begin. The goal of this process is to identify objectively the most optimal need to be addressed, given the criteria developed during need finding and validation. One method is to define categories such as magnitude of patient impact, efficacy (or lack thereof) of existing solutions, etc., create a ranking system, and then allow the needs under consideration to “compete” against one another. A spreadsheet or database can simplify your assessment and enable you to make rapid updates as new information becomes available. Ultimately, your goal is to choose a single need to take forward that represents the best all-around opportunity for innovation.

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**Step 4: Concept Creation**

With need validation and screening completed, it is time to create potential solutions. This stage of the process is widely misunderstood. The popular model for the concept creation process is some mystical “aha” by the lone, brilliant inventor. In fact, brainstorming is best done with a team. Selecting the right people to brainstorm with is one of the key determinants of success. Generally, such people should be highly creative, cooperative, and experienced in the technical and/or clinical area of interest. The team members should understand that they may be helping create some new intellectual property that may ultimately be of financial value, but that the brainstorming stage is only a small part of the process of invention, which includes the substantial work of need finding, verification, and specification that occurs before it.

There are several rules for successful brainstorming.\(^4\) Perhaps most important is that the participants should create a positive session that encourages open thinking and wild ideas. Critical comments and judgment should be held back until later in the process. Participants should build on the ideas of others; the collective strength of the team carries it much further than
any individual can alone. Another important tip is to have the group focus on generating as many ideas as possible, regardless of how unrealistic they may seem; the goal at this stage is quantity over quality. A typical 60- or 90-minute brainstorming session should generate as many as a hundred or more different ideas, which may be grouped in clusters of concepts. Some groups like to use concept mapping techniques to record the branching pattern of new idea creation visually. It is certainly helpful to have a large whiteboard or other writing surface and encourage participants to draw their concepts. It may even be useful to have some materials on hand cardboard, clay, foam board to create very quick and rough conceptual prototypes.

It may often be necessary to have several brainstorming sessions on a given need. It may also be useful to have different people involved in these sessions. Remember throughout the process of inventing that it is critical to document the evolution of new ideas and their anticipated applications. Any significant writing on a whiteboard should be copied or photographed; any rough models should be saved. This helps organize and build mature ideas and enables the inventors to substantiate their rights to intellectual property.

**Step 5: Concept Evaluation and Screening**

Successful brainstorming produces a large array of potential solutions to a need. The next step is to distinguish the ideas worth pursuing from those that are not. Although the brainstorming process is unconstrained and strives for quantity of ideas, concept evaluation and screening introduces reality into the equation. The goal is to have the winning solution emerge from the list and to understand the features of that solution that need improvement in order to become successful.

The most important mechanism for the first screening should already be at hand, and it is the need criteria (see Step 3). A simple rating of how well each of the concepts will potentially address the need criteria results in an initial ranking. If an idea does not seem to have the potential to satisfy the must-have need criteria, it should be immediately set aside (or reimagined to better address the criteria). Nice-to-have criteria can be used to further move concepts up or down the list of promising solutions based on how well you think each concept will perform against them. Often, this initial screening activity permits the inventor to reevaluate the merits of each solution, suggesting modifications or improvements. From the highest-ranking ideas,
one can further screen out the best solution by imposing additional metrics. Some examples of these might include an assessment of the technical feasibility of the idea, the likelihood of adoption, potential ease-of-use, or the expected timeline of clinical trials and regulatory approval. Developing a reproducible scoring system helps keep this process objective. Some research may be necessary to support the scoring process, and often iteration of the process and idea is required.

**Step 6: Concept Development and Implementation**

Once you have selected your target concept, you can now begin the exciting journey toward making it a reality. Some important questions to pose at this stage are as follows: Is this an idea that is so significant that it could be the foundation of a company, or is it simply an incremental improvement that is better licensed to an existing manufacturer? Are the clinical and technical foundations established enough to justify bringing in investors, or is this still a research project that requires further development in an academic setting? To answer these questions, it is helpful to look at comparable companies or projects at similar stages. If you are working in a university setting, much of the work at this stage may be performed by the technology licensing office, but if you truly want to establish this invention as a reality, it is often necessary for the inventor to take a pivotal driving role. To move your idea from this point, it is now necessary to dig into your med-tech inventor’s toolkit (described next) and pull all the pieces into place.

Whatever approach the technology takes, the inventor has the opportunity to play a central role in the early development and implementation of the technology. The next section describes the essential tools to make this a productive experience.

**THE MED-TECH INVENTOR’S TOOLKIT**

*The Team*

Regardless of the fact that many famous and successful inventors like to
work alone, the benefits of working with multidisciplinary teams have been extolled in many texts. Even those who choose to invent alone realize that a team is almost always necessary to take their invention to the next level. The most important thing you can do as an innovator is understand your personal strengths and weaknesses. Assemble your team based on how the additional members complement your abilities. It is also important that your team fit the task at hand. Initially, you may not need much help, but as the project moves forward, you must bring in other people to accomplish the next set of goals. Once you lay out a plan for your business (Fig. 75-2), the evolving set of requirements logically translates into a sequence of skills necessary to move the project forward, and you then can build your team on that basis.

**FIGURE 75-2** Milestones and expertise sequence.

### Intellectual Property

#### The Basics

At the core of any great company or new product is its intellectual property. *Intellectual property (IP)* is defined as any creation of the human mind or intellect that has some value in the marketplace and that ultimately can be reduced to a tangible form. IP can be an idea, invention, expression, unique name, business method, industrial process, or even a chemical formula. IP can take on many forms. One, called the *utility patent*, is most commonly used in the medical industry. A utility patent describes a novel invention that can be used to perform a task. Typically it details a device (eg, surgical instrument) or method (eg, procedure or manufacturing process).

A patent gives its assignee the right to exclude others from practicing an
invention. In receiving that right, the assignee must permit disclosure of the invention openly to the public (hence the name *patent*, which means “to open”). In the United States and internationally, a patent term is 20 years from the *filing date* (date the patent application was filed with the US Patent and Trademark Office [USPTO]).

**The Laboratory Notebook**

A properly maintained notebook is an important tool in your toolkit. The more detailed and well maintained your notebook is, the more valuable it is in supporting your claim of invention should any IP dispute occur. Following are a few key points to remember:

- Get a bound notebook with numbered pages. Although it is allowable to paste in material on existing, bound pages, never tear out or try to add pages.
- Date and sign each page. Never ever backdate! Even if an idea occurred on a previous day, always date your notebook with the actual date matching the signature. It may be important to add an explanation for the delay in writing an entry into your notebook, but do not falsify. Dishonesty here is fraud.
- Have a non-inventor witness and date each page. Do this every few weeks; it doesn’t need to be each day. Ideally, this person would be skilled enough in the art to understand the invention.
- Sign over the edge of material that you paste or tape into the notebook, so that your signature or initials span both the bound page and the pasted-in material.
- Cross out blank spaces to ensure that no retroactive entries could be made.
- Never whiteout anything! Use a single line to strike through any errors and initial the correction.

**Inventorship and Ownership**

Legally, the definition of *inventor* is a very specific one. To be an inventor, one must have contributed (partially or totally) to the invention and participated in its reduction to practice. If you invent something on your own, then you are considered the sole inventor, as long as this work was not
performed as a “work for hire” or bound by some other contractual obligation. If someone adds to any part of a claim, then they are a joint inventor, regardless of whether their contribution was large or small. Unless bound by other contractual arrangements, rights to the patent are shared equally by all inventors. This means that each inventor can use the invention, but neither can exclude the other inventor(s). It is very important to include each inventor when filing a new patent. If inventors are not properly acknowledged, a patent may be declared invalid, rendering it of no value to any party involved.

As of 2013, the United States operates under a first-to-file patent system, which means that patent rights are granted to the first person(s) to file a patent application for protection of an invention, regardless of the date of actual invention. With this approach, the evidentiary date of first invention is less important than when the US operated under a first-to-invent patent system. However, it is still important to document and date your ideas in your laboratory notebook as soon as you have them. In the US, which is often a substantial portion of the market for medical technologies, if you compete with someone else who filed a patent at the same time, the courts will consider your notebooks to determine who had the idea first. It is the inventor who shows documented proof of earliest invention who receives patent rights. Laboratory notebooks can also play useful roles in other legal proceedings. But, as a general rule, it is essential to file your ideas with the patent office (not just document them) as soon as possible to protect your rights.

Many physicians are asked to speak publicly about their research. Public disclosure is defined as disclosure done outside the terms of a confidentiality agreement (see next section). Be aware that public disclosure has important patent consequences. If you disclose your invention prior to filing a patent application, you may be at risk of losing your rights over the invention.

Confidentiality

Inventors often must define the difficult balance between secrecy and disclosure while trying to advance their ideas. It is necessary to disclose your ideas to others to build your team and teach others in your field, but such disclosures put your ideas at risk. Confidentiality agreements can be used to discourage others from sharing or using your ideas, but often these
agreements are very difficult to enforce. In general, it is always a good practice to limit your disclosure to non-confidential matters until you have placed the receiving party under a confidentiality agreement.

How to Get Started?

Start an IP assessment by going online and searching for evidence of your idea in the literature or patent archives. The US Patent and Trademark Office (USPTO) patent database⁶ and Google Patents⁷ are two excellent sources for finding patent information. Innovators can conduct literature searches using PubMed⁸ and Google Scholar,⁹ among other sources. After searching the literature and relevant patent databases, if the idea still appears to be novel, the next step is to file either a provisional or a full utility patent application. All patents ultimately require a utility patent application for consideration, but provisional patents offer a low-cost way to protect your idea for a limited period of time. A utility patent application includes the following:

- An abstract: a brief description of the invention.
- The specification: text in which the background of the idea, the idea itself, and its various uses are described in detail. This includes drawings that are included in the application.
- The claims: a numbered list of the exact characteristics of the invention that the applicant believes are novel and for which the applicant is seeking legal rights.

Because the legal phrasing in the application is so important, it is recommended that you work with a patent lawyer to assemble the application. The cost of creating and filing a utility patent application in the United States is usually $5,000 to $15,000, most of which is the cost of legal counsel. After filing, the USPTO responds to the claims in the application, making arguments for or against rights to each of the claims individually. This process is called patent prosecution and can often be a substantial process that can last for months or years. Finally, if the patent is granted (usually in a revised form), it is called an issued patent, and you or the organization that owns the patent are designated as the assignee.

A provisional patent application (PPA) is a type of fast-track submission for inventors who want to get the earliest possible file date without having to
commit the investment necessary for a full utility patent application. The PPA can be a somewhat more informal application than the utility patent submission. As such, some inventors choose to prepare and file their own PPAs without hiring legal counsel until they file a utility patent application on the invention. Other inventors opt for professional legal counsel in creating the PPA to ensure the most robust protection early in the patenting process. The cost of filing a PPA is $100-400, and the application does not undergo any formal review or approval process by the USPTO. It merely serves to hold the filing date. As long as the inventors submit a utility patent application within one year of filing the PPA, they are granted the earlier PPA filing date for both.

One concept concerning patent rights is often misunderstood: the difference between patentability and the ability to practice. An invention is patentable if it has at least 1 claimed element that is novel. Although a patent grants permission to exclude others from practicing an invention as described in the claims, it does not necessarily provide its inventor the freedom to practice (i.e., manufacture or sell the technology or perform the procedure) the invention without infringement. To infringe a patent means that one has literally followed every step claimed by an existing patent. So, for example, if your invention incorporates another invention (in its entirety), but builds on it with a novel addition, it may be necessary for you to license rights to the other patent before practicing your invention.

For more information on the mechanics of filing patents and the legal aspects of creating new companies and technologies, there are several excellent references specifically for new inventors.\textsuperscript{10,11}

\textbf{Market Assessment}

It is best to make an early assessment of the market to determine the potential size of the opportunity in order to ensure that it warrants investing significant time and resources. The essential steps are to characterize and quantify the potential customers and understand how the demand for the new technology may evolve over time. A well-developed market analysis is an essential part of a business plan.

To properly assess the value of an idea, it is necessary to define its application in some detail. If the concept is a “disposable” or “implantable,” its use is defined by the number of procedures or patients in which it is used.
Alternatively, if it is a reusable product, the market depends on the number of hospitals or operating rooms that use it. A good starting point is to estimate from the literature the number of treatable patients within a typical year. This number multiplied by the estimated price per use serves as the total potential market per year. Demographic changes, preventive measures, access to the appropriate healthcare providers, and other factors that affect the size of the future patient population should be considered when rendering these types of estimates. Physician adoption rates vary widely between specialties, and the best estimates of these rates can be determined by examining comparable technologies. If, however, no such comparable technologies are available, a model can be derived by considering several factors: the severity of the clinical need, risk tolerance of the patient and physician population, appropriate patient inclusions/exclusions, other available competitive treatment options, and the risk-benefit profile of your technology.

When conducting market research, physician feedback can be very valuable. However, one must recognize that customers (physicians) often do not recognize their own needs, particularly considering breakthrough technologies. More often than not, they adapt to available technologies and are relatively comfortable with what is at hand. Also, one must consider physician culture; some specialties embrace new ideas (interventional cardiology is a prime example), whereas others reproach them. Although customer input is very helpful in this assessment, it is important to weigh and filter these factors carefully to differentiate between negative feedback that is fundamental and that which simply reveals resistance to change.

Clinical, Regulatory, and Reimbursement Considerations

Healthcare technologies are highly regulated, and thus, it is very important to understand the various paths to approval and reimbursement before spending significant resources to develop an idea. Although the fundamental aspects are not likely to change soon, specific regulations and reimbursement parameters can change dramatically over time and can be heavily linked to current sociopolitical issues. It is therefore essential that one consult with experienced professionals in the field before casting one’s plan into action.

In the United States, the Food and Drug Administration (FDA) oversees all commercial medical devices, biotechnology, and pharmaceutical products. In other countries, there are similar regulatory bodies, although their roles
vary widely. Although the focus of US regulators is often to prove efficacy and safety equal to or beyond that of existing technologies, the CE mark process (the approval pathway for the European Union) is more focused on safety and quality. Figure 75-3 is a chart showing a few typical paths a new medical device, biologic, or drug might take through the US FDA or European Competent Authority process. These are just a few examples; the actual process must be customized as appropriate for every individual technology.

![Figure 75-3](image)

**FIGURE 75-3** Sample processes toward approval of medical products in the United States. BLA, Biologic License Application; IDE, Investigational Device Exemption; IND, Investigational New Drug; NDA, New Drug Application; PMA, Pre-Market Approval.

The litigious nature of the US market demands a higher level of scrutiny on behalf of the FDA in comparison to the situation in Europe. Thus, quite often devices and drugs can be tested on humans and commercialized much sooner outside the US than within. There are important philosophic and ethical issues that this disparity creates. Overseas patients have access to the latest and potentially greatest medical advances much earlier; however, Americans benefit from the knowledge resulting from repeated human experience and follow-up before these new approaches are released to the US population. Until there is normalization in the way different cultures approach risk, these regulatory differences are likely to remain.

Product labeling is a significant element of the regulatory process and is
fundamentally important when formulating a clinical development strategy. The claim(s) a manufacturer makes regarding the performance of a technology is the key factor that determines how regulatory bodies determine the product must be tested. Whatever is claimed must be proven; therefore, if this proof is derivable only through extensive and expensive clinical testing, then that is dictated by the nature of the claims. Many books and websites detail these regulations and policies.\textsuperscript{12,13}

Having a reimbursement strategy for a new technology is equally as important as the regulatory issues in designing an approach to clinical trials. A clinical trial must be designed and powered to demonstrate that the new technology is worth reimbursing. If the reimbursement process has not been carefully considered early on, the costs required to commercialize the product can be grossly underestimated, and expensive clinical trials may need to be repeated.

Regulatory and reimbursement pathways that appear to be particularly difficult discourage investors or potential corporate partners. Those who understand how to navigate the process successfully can wield a significant competitive advantage. For those who do not have this experience readily at hand, there are many high-quality consulting firms that specialize in these fields, as well as recruiters available to help you add this expertise to your team.

**Ethical Considerations**

It is critically important to be aware of the potential conflicts of interest involved in bringing a new, for-profit technology forward into a healthcare setting. At every stage in the development process, you should evaluate choices against your own values. For example, when one identifies a clinical need to address, it is appropriate to ask several questions, such as:

- Should I work on this problem?
- Am I trying to increase the quality or duration of life?
- What impact would that have on the patient, caregiver, family, society, and the healthcare system?

For example, reducing mortality after major stroke seems like a noble goal, but one should consider the impact on the size and debility of the affected
patient group. Environmental issues also come into play: What are the implications of disposable versus reusable products? In manufacturing, consider the ramifications of manufacturing risk on employees (safety), the product being sold (integrity), and so on. In forming a business strategy, to what extent should consideration be given to access by people of different geographic and socioeconomic groups? Clearly, these and related questions can be difficult to answer, but it is essential to raise these issues early and reflect on the core values behind the technology that is being created.

A common ethical dilemma facing clinician inventors is the balance between financial gain from the application of a new technology and the responsibilities of ethical patient care. Many academic, hospital, and corporate organizations are wrestling with this delicate balance. Without the clinical leadership provided by physician inventors, many of our most significant technologies would not be available today. At the same time, there are clearly examples of perceived financial conflict of interest and, arguably, situations in which patients have been put at risk inappropriately. With proper oversight by independent ethical review boards and rigorous scientific peer review, it is possible to proceed wisely on a case-by-case basis. Establishing a credo is a good way to acknowledge these issues and generate the open discussion necessary to establish balance. Corporations such as Johnson & Johnson and Medtronic have integrated their credo deeply into their culture and the way they do business.\textsuperscript{14,15} Although this credo can function effectively for corporations, such a document can also provide value for organizations operating in university or not-for-profit settings.

**Communication Tools**

There are three main communication tools that are important in the successful communication of a new technology: prototypes, business plans, and presentations. Prototypes serve a multitude of early-stage functions. However, crude they may be, prototypes communicate an invention to others, help determine its feasibility, and identify challenges that may arise as it is developed further (eg, scaling it up or down, fitting it to different anatomies, manufacturing it). A tangible model is far more useful than a description or drawing of an invention. Those reviewing a technology (eg, investors, physicians) will be able to provide much better feedback with a real, three-dimensional prototype. Placing a prototype into the hands of an end-user can
also be very informative. By observing how they handle the device and what features give them the greatest satisfaction or difficulty, it is possible to learn important lessons unachievable through other means.

Business plans are another powerful communication tool. Developing and writing a plan enhances the likelihood of success of any technology development program. Although the business plan is useful to potential investors, the process of creating a plan is even more important to the innovator because it forces one to think strategically about the project that is about to be launched. A plan must tell a story. It should explain the primary motivation, the unmet clinical need, market opportunity, and the proposed business solution. Once the solution is established and clearly described, the plan should outline the development path and basics of how the company or group will bring the technology to market. Important issues should be identified and addressed, but the explanations and text should be succinct. A clear, well-organized, and concise plan communicates as much about the innovator as it does the project, and can be an important step to successful financing. An outline of a typical med-tech business plan is presented in Table 75-1.

Table 75-1 Business Plan Outline

<table>
<thead>
<tr>
<th>Executive Summary</th>
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<tbody>
<tr>
<td>Background and Clinical Need Being Addressed</td>
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<tr>
<td>The Market</td>
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<tr>
<td>The Proposed Idea and Business Model</td>
</tr>
<tr>
<td>Research and Development</td>
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<tr>
<td>Regulatory, Reimbursement, and Clinical Pathway/Strategy</td>
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<td>Intellectual Property</td>
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<tr>
<td>Competition</td>
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<tr>
<td>Proposed Use of Funds</td>
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<tr>
<td>Financials</td>
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<tr>
<td>The Team</td>
</tr>
</tbody>
</table>

The plan must communicate clearly why someone should be interested in
the technology and describe succinctly a compelling strategy for sustainable competitive advantage and profitability. Most audiences prefer a shorter plan (10-15 pages) than a longer one. For more detailed suggestions on how to write a winning plan, there are many sources available.16,17

The third main communication tool is the presentation, or the “pitch.” As an innovator, you must always be prepared to present your idea. Chance provides encounters with people whose feedback or support may be important. For these occasions, it is important to have a prepared, up-to-date, “30-second elevator pitch”—a rehearsed summary of the idea that communicates all its salient aspects succinctly. There should be different pitches for different anticipated audiences. Eventually, when it is time to present the concept more formally (eg, to potential investors), a polished presentation is required. Typically, these presentations are given to a wide audience including nonclinicians/nonscientists. It is important to determine in advance exactly who will be in your audience, their backgrounds, interests, and concerns, and tailor the presentation specifically to each unique audience. Detail the clinical need and the strategy for developing a sustainable competitive advantage toward profitability, and explain clearly what is being asked from the audience, as well as any returns they might gain from participating. Fundamentally, if your business plan tells a compelling story, it will be of great interest to investors.

**Financial Considerations**

Once the basic business plan is formulated, the innovator must develop a financing plan to get it off the ground. By examining the most significant value-building milestones at each stage, it is possible to determine approximately how much funding is necessary initially and how many infusions of capital may be required over the life of the business. It is rare that one is able to obtain enough capital to finance an entire venture in a single round of financing. Usually, new ventures are funded in stages, providing an opportunity to reassess the progress and value of the venture at each stage, essentially lowering the risks for investors. The chart in Figure 75-4 illustrates a few typical examples of how value roughly tracks with milestones and cash requirements.
Assessing Cash Requirements

The skill required to estimate accurately the cash required to launch a new venture can be gained only by experience. Overestimating these costs can discourage potential investors; on the other hand, underestimating costs may cause the business to fail simply because of lack of funds.

Med-tech venture start-up costs can vary significantly, depending on the size and scope of the project. For example, a simple class I surgical instrument provider may be able to start up with less than $1 million, whereas a typical medical device or biotech company often requires tens to hundreds of millions of dollars to reach profitability. Over the life of a new company, the expenses and sources of risk shift from development costs to more standard execution costs such as sales, marketing, and manufacturing. It is often the earlier, more risky expenses that are the hardest to assess, and thus, usually after all the expected expenses are tabulated, most entrepreneurs expand the amount of funding that they seek to offset the impact of the unknown.

Funding Sources and Financing Strategy
Finding resources can be the most challenging and daunting task for the innovator. Following is a list of the most common funding sources as well as their pros and cons.

**Government or Other Grants**

Government funding through small business innovation research grants (SBIRs), the advanced technology program (ATV), the National Institutes of Health (NIH), or other such grants is an excellent way to fund highly research-oriented projects. Although some grant processes can be highly political and burdened with bureaucracy, innovators rarely sacrifice any ownership or loss of control in the process.18

**Angel Investors and Self-Funding**

At the earliest stage, it is very common to draw funding from friends and family, self-funding, or “angel” investors. These resources are best applied to the initial patent and feasibility work and can often help an entrepreneur frame the opportunity better for more professional investors. If access to such resources or contacts is not immediately available, there are some well-known angel investor groups that can be approached.19 Although some of these groups have been moving into larger and later-stage financing, financing your company exclusively with angel money through several rounds can make later-stage financing more difficult when cash requirements exceed those of your angel network. Angels typically demand less of the company early on and tend to be more flexible than other investors; however, companies without professional investors risk a significant value reset later if early valuations were set outside of prevailing market conditions.

**Venture Capital**

Venture capital is the source that is usually tapped for cash-intensive opportunities that require substantial cash and time investment before returning profits. A complete list of venture groups and their interest areas can be obtained from the National Venture Capital Association (NVCA) or one of the many available handbooks on venture capital.20 Access to venture capital is rarely obtained through a “cold call” or an uninvited business plan.
The vast majority of venture groups rely on their extensive network of contacts to establish the credibility of incoming ideas and entrepreneurs. These contacts cut across academic, industry, and investment domains, and your reputation and demonstrated ability to advance such ventures can have enormous impact. It is therefore very important for the innovator to develop these relationships or find ways of accessing this network of people. Once those links are established, it is much easier to gain access to the venture capital community. Venture capitalists (VCs) add discipline and focus to a business as well as financial resources, but in return they often require substantial percentages of the company as well as other conditions that further limit their risk and increase their control. Unlike angels, who may be happy to invest in a long-standing business that throws off dividends, VCs make their returns through “exits” or liquidity events (such as acquisitions or initial public offerings [IPOs]). It is very important that the goals of the innovator align with the goals of the investors, particularly with VC investors, because most of them play an active and pivotal role in the decision making for the company.

**Banks**

Although banks are good places to get equity loans on your house, they are traditionally not good places to obtain financing for new businesses that are far from profitability. Banks have a much lower risk tolerance and do not usually place very much value on intangibles such as IP or technology.

**Vendors**

Vendors, customers, or other business partners can be very creative and strategic sources of capital. In general, these relationships are best structured once you have something to offer in return (eg, purchased services or other rights), but it is still possible to arrange preferred pricing or other cash-relief arrangements. These relationships vary widely and offer an alternative to traditional financing approaches by minimizing cash requirements.

**Corporate Partnerships**

Corporate or strategic investors can be an excellent source of capital and
other resources for a new or developing business. In general, strategic investors tend to be less price sensitive and more interested in the strategic value to their own businesses. It is usually better to bring such investors into the picture later, because the involvement of such players in a business can have a direct impact on the liquidity options later. Although each deal is different, traditionally, these partnerships can involve the corporation gaining access to equity, intellectual property, distribution, or development rights in exchange for cash or other resources. Many of the larger corporations (eg, Johnson & Johnson, Pfizer, Medtronic) have groups dedicated to partnerships that can be approached.

Public Equity

Under current market conditions, public equity accessed via an initial public offering (IPO) in the stock market or acquisition of a corporation is an option generally reserved either for biotech companies that have passed into phase III testing or medical device companies with revenue growth and profits. This threshold can change dramatically with market conditions. Several investment banks (eg, Piper Jaffray, JP Morgan, UBS Securities) have developed specialized practices focused on the med-tech space and are essential for any company contemplating this pathway. Online resources such as the Electronic Data Gathering, Analysis, and Retrieval System (EDGAR) can be used to study recent IPO activity and easily allows users to compare the fundamentals of these businesses.21

Incubators

Since the mid-1990s, multiple incubators have been formed to help early innovators bring their new concepts forward. These entities, such as ExploraMed, the Foundry, In-Cube, the Innovation Factory, and SyneCor, focus on identifying new ideas themselves or working with clinicians/scientists with ideas who do not wish to commercialize them alone. In general, incubators combine these ideas with funding, appropriate staff, and expertise in return for a significant portion of the equity of resulting companies.
KEY RESOURCES

There are many other sources to turn to for more specific information and advice. Undoubtedly, the most useful resource is one or more mentors who have succeeded in developing new technologies in a given area. There are plenty of resources even if a mentor is not available, especially with the availability of the Internet. Following are a few suggestions:

• Stanford Biodesign has published a comprehensive textbook\(^2\) that outlines the process of medical technology innovation in detail and provides references for each step in the process. An accompanying video library can be found online (www.ebiodesign.org).

• Offices of Technology Licensing: For those affiliated with an academic or government medical center, the technology licensing office can provide support in filing patents. They often finance the patent application process and explain how to license technology in order to start up a new business.

• The National Center for Biologic Information (NCBI) (www.ncbi.nlm.nih.gov): The NCBI has an extensive publicly available database that permits users to search articles, books, and other media covering almost all areas that relate to the field of medicine.

• The Food and Drug Administration (FDA) (www.fda.gov): The FDA’s website can help with regulatory and clinical trial strategy. It provides guidelines (required performance, safety, efficacy, and preclinical and clinical data) for different types of devices. The website also provides a more detailed description of the regulatory process and up-to-date information on the approval status of existing and emerging devices.

• The US Patent and Trademark Office (USPTO) (www.uspto.gov): The USPTO’s website allows users to search issued and filed patents online for free.

FINAL THOUGHTS

In this chapter, we have provided a basic primer on how to take a new technology idea to the next level. There are several excellent references cited here that are useful for those who wish to develop a deeper understanding of the issues. Just as in clinical medicine, however, the best source of expertise
is experience. Clinicians and biomedical scientists have the enormous advantage of being on the front lines of need finding, where technology opportunities present themselves. The technology innovation process does not require mystical insight—just the willingness to work hard and pay attention to some of the fundamentals we have outlined here. The biggest mistake is not taking the first step.

REFERENCES


Web-Based Learning

Lawrence W. Gimple

INTRODUCTION

Remarkable advances are regularly made in the science, clinical practice, and procedural applications of interventional cardiology, challenging the interventional cardiologist to systematically integrate new knowledge into a demanding, complex, and fast-paced environment. The rapid expansion of the evidence base for cardiovascular medicine has occurred contemporaneously with transformative changes in information technology. The Internet originated as a Department of Defense project in 1969, and the World Wide Web entered the national consciousness in 1991 with the introduction of the first graphical web browser, called Mosaic. Over the next few decades, the World Wide Web has become a ubiquitous presence in daily life that has affected all aspects of communication and social interaction. Not surprisingly, the Internet has also become a major means of distributing a broad range of educational materials. The Internet was so pervasive that in 2013, there were more than 2 trillion Google searches representing nearly 6 billion searches per day, presumably by individuals seeking information. With the rapid growth of mobile devices, people can basically access information and learn anywhere and at any time. Online learning has affected educational domains from preschool to professional education, and each area has its unique attributes and challenges. In this chapter, however, only the most important aspects of web-based learning as it pertains to the interventional cardiologist will be presented.
WEB-BASED LEARNING AND ADULT LEARNING THEORY

Adult learning strategies (called andragogy) originated in ancient times; for example, both Plato’s Academy and Aristotle’s Lyceum were focused on adult education. Although much academic work at American universities has focused on children from kindergarten through high school (known as pedagogy, or the science of teaching children), adult learning theory expanded and acquired a stronger theoretical basis with the work of Malcolm Knowles and others in the 1970s. Adult learning theory continues to evolve, and newer theories known as “transformative learning theory” are being actively explored in the academic literature. Transformative learning relates to changing one’s perspective on one’s self and one’s place in the larger social context.

Adult learning theory, according to Knowles, is based on a number of assumptions:

1. As a person matures, his or her self-concept moves from that of a dependent personality toward one of a self-directing human being.
2. Adults accumulate a growing reservoir of experience, which is a rich resource for learning.
3. The readiness of an adult to learn is closely related to the developmental tasks of his or her social role.
4. There is a change in time perspective as people mature—from future of knowledge to immediacy of application; thus, an adult is more problem-centered than subject-centered in learning.
5. Adults are mostly driven by internal motivation, rather than external motivation.
6. Adults need to know the reason for learning something.

An important assumption of adult learning relates to accumulated life experiences as a rich resource for learning. Indeed, medical residency, general cardiology fellowship, and interventional cardiology training are steeped in the ongoing experiential development of the core competencies of the Accreditation Council for Graduate Medical Education, which include medical knowledge, patient care, practice-based learning and improvement,
systems-based practice, professionalism, and interpersonal skills and communication. In each of these domains, adult learning theory can lend insight into the kinds of behaviors that are best associated with acquisition and integration of new knowledge into established practice patterns. The reduction in work hours over the past decade has additionally fragmented the time that residents and fellows spend in the hospital engaged in patient care and education. Self-directed learning, initially known as “self-teaching,” has become a critical component of physician education. “Virtual learning environments” including web-based learning may be well suited to many aspects of self-directed learning but success may vary significantly among individuals and across cultures.²

Much of the learning associated with interventional practice occurs when the interventional cardiologist confronts a new problem or a constellation of problems that are unfamiliar. Adult learners typically learn based on specific needs, and learning is reinforced when there is an immediate application of learning. Thus new patient problems often present “teachable moments” that offer unique opportunities to both learn and integrate complex new information. Adults often want to choose what they learn and how to learn it; web-based learning environments offer a broad spectrum of content, and learners can seek the kinds of learning experiences that are best suited to them as individuals. Adult learners like to know why they need to learn certain types of information; learning new information as it pertains to a specific patient or problem can fulfill this inherent need.

The arrival of enhanced social media capabilities of Web 2.0 has offered increasing opportunities for professional interactions to occur that help to establish “communities of practice” that result when interventional cardiologists interact regularly around common clinical problems or concerns. These activities had traditionally occurred during local case presentation conferences or during a cardiac catheterization laboratory conference. For cardiologists who are more separated geographically from colleagues yet still wish to interact regularly and share patient experiences or challenges, web-based learning methods may allow for the development of “virtual communities of practice” in which participants may use the powerful communication tools of the web to create shared meaning and experience, to observe more experienced operators perform common procedures, and to develop a sense of community with a group of colleagues who share their clinical interests.
In 2010, the US Department of Education\textsuperscript{3} performed a meta-analysis of more than 1000 scientific studies of online and web-based learning focusing on those reports that (1) contrasted web-based and face-to-face learning, (2) measured learner outcomes, (3) employed rigorous scientific methods, and (4) provided adequate data to calculate the magnitude of the learning effect. With respect to the evidence based on adults, the key findings of this meta-analysis included the following:

- Students in online conditions performed modestly better, on average, than those learning the same material through traditional face-to-face instruction.
- Instruction combining online and face-to-face elements had a larger advantage relative to purely face-to-face instruction than did purely online instruction.
- Effect sizes were larger for studies in which the online instruction was collaborative or instructor-directed than in those studies where online learners worked independently.
- The effectiveness of online learning approaches appears quite broad across different content and learner types.
- Effect sizes were larger for studies in which the online and face-to-face conditions varied in terms of curriculum materials and aspects of instructional approach in addition to the medium of instruction.
- Elements such as video or online quizzes do not appear to influence the amount that students learn in online classes.
- Online learning can be enhanced by giving learners control of their interactions with media and prompting learner reflection.

A large number of important unanswered questions remain with respect to web-based learning, especially related to the specific techniques in web-based instruction that make online learning most effective. Over the past few decades, numerous academic and professional organizations have developed that support the educational science underlying theories of online learning, including Merlot (Multimedia Resource for Learning and Online Teaching; \url{www.merlot.org}), Sloan-C (Sloan Consortium; \url{www.sloanconsortium.org}), and the National Science Digital Library (\url{www.nsdl.org}). Additionally, the number of academic journals publishing original research in web-based learning continues to grow.
Mobile technologies and smartphones have transformed the cultural landscape and the opportunities for information delivery. A recent survey in *Time* magazine reported that 9 of 10 Americans carry a mobile device and access it regularly. While mobile phones were nearly nonexistent a generation ago, *Time*’s poll reported that currently 25% of people check their phones every 30 minutes and 20% do so every 10 minutes. Thirty-three percent of Americans feel anxious if they are separated from their phones for even short periods of time. Seventy-five percent of Americans age 25 to 29 years sleep with their phones, and twice as many people would pick their phones over their lunch if forced to choose.4

A full discussion of “mobile learning” or “just-in-time learning” is beyond the scope of this chapter, but it is important to consider the potentially transformative implications of information delivery to learners in real time and at the point of care. Just-in-time education can potentially provide patient-specific answers to clinical questions at the moment the provider needs to know. The opportunities for clinically relevant learning at highly “teachable moments” are obvious. Text-based applications running on the web, such as UpToDate, ClinicalKey, mobile manuals, Epocrates, and many others, offer mobile access to specific clinical information on mobile devices. Increasing levels of integration with electronic medical health records for specific patient allows the possibility for both alerts and instruction relevant to specific patient care situations to be offered in real time. Such integration of electronic medical health records with just-in-time education is still in its infancy. As a particular example, the rapidly expanding fields of cardiovascular genetics and genomics are producing new knowledge at a rapid rate, and this information will not be widely familiar to many practicing physicians. Similarly, physicians will often be uncertain as to when such information is even relevant for a particular patient or disease state. Thus cardiovascular genetic data might be examples of “chunks of knowledge” that could provide “just-in-time” education to practicing cardiologists caring for patients with certain cardiomyopathies.

**Limitations**

Web-based learning is still in an early phase in subspecialty medical education, and many challenges face the organizations and groups that develop learning materials for interventional cardiologists. The rapid
expansion of learning platforms, mobile devices, and technology standards has offered both opportunities and challenges. One of the greatest challenges relates to the rapid evolution of knowledge and clinical information. Case studies, guidelines, and clinical trial results can rapidly become obsolete as new science is developed. When clinical information is embedded in enduring materials, its relevancy is quickly dated and it requires significant financial resources and effort to keep clinical information up to date, especially when it is in noneditable formats such as video or web-based packages. Clearly, the current significant use of web-based learning sites would seem to confirm that physicians desire to use online resources in education, but objective demonstration of improved physician performance or patient outcomes from these learning interactions is still lacking, especially for online educational methods that teach cognitive or procedural skills.

The quality and reliability of much educational content remains uncertain. Whereas medical journals have formal peer-review processes that have been developed over many years, online content can appear on the web from any number of sources. Much of the web-based learning in interventional cardiology comes from major cardiology societies such as the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American Heart Association, or the European Society of Cardiology. Much of this content undergoes a form of peer-review. Other content may come from other Accreditation Council for Continuing Medical Education–approved sites such as universities or hospital-based research foundations. However, medical educational content can also be user-generated or even crowd-sourced from comment fields, blogs, or wikis, methods where the quality and source of information may be unclear.

**Selected Glossary of E-Learning Terms**

**Apps** are small computer programs, or “applications,” that typically run on mobile devices such as smartphones or tablets (such as iPad or Google Nexus) but also on a computer or laptop. For medical uses, an app might contain mathematical formulas that allow one to calculate creatinine clearance, CHA\textsubscript{2}DS\textsubscript{2}-VASc score for atrial fibrillation stroke risk, or a Thrombolysis in Myocardial Infarction (TIMI) risk score. Other examples of apps are email, games, or mobile web browsers.
**Blended learning** refers to using web-based teaching methods together with more traditional classroom-based methods. This is sometimes referred to as hybrid learning, or “flipping the classroom,” since the latter allows lectures to be given asynchronously via the web while classroom time is reserved for higher level, integrative learning.

**Blog**, derived from the word “weblog,” is an e-learning or social media tool that allows the ongoing discussion of a particular topic or theme, often in response to a prompt. Blogs allow social interaction and engagement with a wider audience of blog readers or members. Topics are often maintained and archived in reverse chronological order for ongoing review.

**Content** is a broad term that describes the actual material to be received or learned. In the electronic world, content varies widely in complexity ranging from very small elements (eg, a phrase, image, or sound) to complex larger structures such as learning exercises, lessons, entire curricula, or even games. In some contexts, a simple piece of content might be considered a “knowledge chuck” or “learning object” that could be used as a modular building block for e-learning.

**Learning Content Management Systems (LCMS)** are required to administer all of the complex relationships that exist among pieces of content such as organization, storage, assigning meta-tags, previous uses, productions steps, relationships with other content, technical specifications, editorial review status, copyright considerations, or other management functions. Optimally content management systems would interact seamlessly with the content, with authoring tools, with production processes, with learner management systems, and with content delivery systems.

**E-learning** is a broad and evolving term that involves the use of electronic media and/or the Internet to promote education. E-learning may encompass multiple types of technology-facilitated education including multimedia, computer-based training, online education, or distance learning.

**Experience API (formerly known as “Tin Can”)** is an API (application programming interface) that has been called the “next-generation SCORM (Sharable Content Object Reference Model).” Experience API will allow data from a diverse set of educational activities to be collected and
recorded by a learning management system in a fashion that facilitates the creation of online curricula that mix online learning with traditional (real-world) educational activities.

**Learning management system (LMS)** is the software that focuses on the management of the learner, or “end-user.” An LMS typically manages the administrative aspects of educational websites including the tracking of users and membership, documentation of interactions, reporting, and other common administrative functions such as username, passwords, and e-commerce. Some systems manage certificates, transcripts of work completed, or a broader learning portfolio.

**Learning objective** is a clear, structured, and measurable statement of the behavior or performance that the learner needs to accomplish to be sure that the desired learning has actually occurred. A well-structured learning objective has 3 parts: a measureable verb, the important condition under which the performance is to occur, and the definition of acceptable performance.

**List serv** is an automated method for managing and distributing content by email to a specified recipient list. A list serv may support or replace other e-learning functions by pushing content to users who prefer to receive information by email. The resulting communications resemble a newsgroup or forum. List servs have been used by academic catheterization lab directors to facilitate educational correspondence.

**Massive open online courses**, or MOOCs, allow a single instructor to offer a course to a nearly unlimited number of learners simultaneously. Perhaps the best-known platform is Coursera, which is an online provider that partners with many of the best-known universities around the world to offer full courses for anyone with an Internet connection and at no cost. MOOCs typically offer many of the advantages of online learning including providing master instructors to teach the courses and peer assessments to review learner-generated content. Blended learning is a common aspect of MOOC courses. One MOOC instructor, Harvard’s Michael Sandel, became so famous after teaching a course called “Justice” that he achieved celebrity status in Korea, and his philosophy course has had more than 20 million views in China (with subtitles).\(^7\)

**Needs assessment** is a structured procedure that occurs prior to creating e-
learning material for identifying and prioritizing the educational needs of the community. This is accomplished by analyzing the gap between present educational state and the desired state or outcome.

**Podcasts** are electronic files, often audio and video, that are distributed over the Internet. These are typically viewed or heard on computers or mobile devices such as smartphones or personal players such as iPods.

**SCORM**, or Sharable Content Object Reference Model, allows educational content to be shared widely by differing learning management systems by specifying the standards and coding for web-based e-learning. Thus SCORM-compliant educational modules created with one product can be shared on educational sites using a different learning management system. SCORM was created as part of the Advanced Distributed Learning (ADL) Initiative from the Department of Defense.

**Social media** is often experienced as a phenomenon in mass markets but is increasingly used in professional environments including web-based interactions for physicians. Many of these sites allow the user to create a personal profile that is shared widely. Examples include Facebook, Twitter, LinkedIn, Doximity, Skype, Youtube, and many more.

**Synchronous and asynchronous e-learning**: Synchronous learning requires that both the teacher and learner be present at the same time. Common examples would include a classroom lecture or a traditional seminar in a classroom. In an e-learning environment, the interactions would require the educator and the learner to be online at the same time to allow direct interaction as in a video-conference or virtual classroom.

Asynchronous learning allows the educator and the learner to be separated by both space and time. Technologies such as email, blogs, discussion boards, social networking, and wikis support asynchronous e-learning and allow greater flexibility in the time domain. Learners may work at their own pace, review material repeatedly, and feel less time pressure when reviewing educational material or producing responses.

**Web 2.0** is a broad term given to the second generation of web methods that allowed for sharing of content among participants and for greater creation of content by users. Most Web 2.0 applications use dynamic generation of pages, typically from content held in a database, rather than
relying on static, hard-coded web pages. Wikis, video sharing, and enhanced social networking are enabled by these enhanced technologies.

**Webcast** is a transmission of audio and video over the Internet much like a television broadcast. This technology delivers prepared educational content to a learner over the Internet with limited interactivity.

**Webinar** uses more advanced Internet technologies than a webcast, allowing for audience participation and interaction with the learning activity. It may be a presentation, workshop, lecture, or seminar that is managed over the web. In a webinar, the audience can interact with the teachers and with each other in real time, and the overall educational encounter can be archived for later, asynchronous viewing.

**Wiki** is a website or related environment where the end-users themselves can create and edit content individually or by collaborating with others. Typically a wiki requires no additional software and allows for distributed or crowd-sourcing creation of content. Wikipedia is the best-known example.

## COMMON E-LEARNING FORMATS IN INTERVENTIONAL CARDIOLOGY

**Board Review Preparation and Questions**

A significant body of literature supports the use of questions with annotated responses to enhance long-term learning, rather than just “assessing knowledge.” While the actual board examination is required for credentialing, there an increasing body of evidence that assessment questions can have a significant educational effect when they are designed specifically to produce learning.\(^8-14\) Well-designed questions should not only address important medical content and knowledge, but must also be well structured to support learning. Well-constructed, relevant questions can provide learners with practice retrieving information from memory, give learners feedback about their material, focus learners’ attention on the most important learning material, and repeat core concepts for reinforcement. It has been demonstrated that these beneficial effects are apparent whether the questions...
are presented before or after the associated learning material. It has been
demonstrated that when students are tested on material and successfully recall
or recognize it, they will remember it better in the future than if they had not
been tested, a phenomenon known as the testing effect.\textsuperscript{13} Testing has been
demonstrated to provide benefits during web-based self-instruction for
professional students,\textsuperscript{10} has been shown to improve long-term retention,\textsuperscript{11}
and has been shown to improve outcomes on semester exams.\textsuperscript{12}

The American College of Cardiology’s CathSAP 4 (Cath Self-Assessment
Program) is an extensive online (or print) course in cardiac catheterization
and interventional cardiology. The course utilizes hundreds of peer-reviewed,
American Board of Internal Medicine (ABIM)–style self-assessment
questions to coordinate study and is designed to be used to prepare for initial
board certification or recertification. It contains learning chapters focused on
a broad array of clinical and scientific topics related to the cardiac
catheterization laboratory and includes self-assessments, board preparation
examinations, and interventional cardiology Maintenance of Certification
modules.\textsuperscript{15}

TCTMD Prime also includes digital slides and webcast versions of slide
presentations presented at Cardiovascular Research Foundation’s annual
Fellows Courses and the Transcatheter Cardiovascular Therapeutics (TCT)
Self-Assessment/Board Review Course.

\textbf{Live Case Demonstrations}

Patient demonstrations have been used in classic medical grand rounds and
for bedside teaching for generations. In 1846, Dr. William T. G. Morton
made history when he performed the first public surgery using anesthesia
(inhaled ether) in the Ether Dome of the Massachusetts General Hospital. In
the Internet age, “live case demonstrations” have become a common method
of web-based education with live demonstrations occurring regularly at
national meetings and broadcast from labs around the world to large
audiences at national meetings or scientific sessions. Such live case
demonstrations include cases related to coronary revascularization, structural
and valvular heart disease, and other invasive and interventional procedures
commonly performed by interventional cardiologists. Potential educational
advantages of this case format include the ability of the learner to directly
observe actual case examples of specific methods and to hear experts
Comment both broadly on medical topics and on the finer details of a specific case procedure. In many meetings, these live cases draw large physician audiences. Two-way communication between the local lab and the meeting room allows moderated discussion including multimedia presentation and playback of case images and information in real time. Case demonstrations are archived and available as web-based learning opportunities at sites such as Cardiosource (http://www.cardiosource.org/en/Lifelong-Learning-and-MOC/Education/Mt-Sinai/CCC-Live.aspx) or TCTMD Prime (http://www.tctmd.com/).

Despite the common use of this educational format, however, questions have been raised regarding the educational value, potential patient risk, ethics, use of investigational devices or off-label use of approved devices, and conflict of interest related to the marketing and use of medical equipment. In response to these concerns, the relevant medical societies representing the practice of cardiology (Society for Cardiovascular Angiography and Interventions/American College of Cardiology Foundation/Heart Rhythm Society/European Society of Cardiology/Sociedad Latinoamericana de Cardiología Intervencionista/Asian Pacific Society of Interventional Cardiology) issued a “Statement on the Use of Live Case Demonstrations at Cardiology Meetings.” This statement included discussion of the educational concerns, live versus prerecorded sessions, the use of a moderator, concerns regarding patient risk related to the overall format, patient rights and informed consent, goals for cases and patient selection, and a code of conduct for live case demonstrations with emphasis on patient safety and privacy, informed consent, conflict of interest, regulatory considerations, and educational imperatives. The writing committee concluded that data examining the educational value and patient risks associated with live case presentations are “sparse.” The writing committee was unable to determine if the educational benefits of live case demonstrations outweigh the potential negative consequences. Other professional societies, including surgical subspecialties, have also struggled with these issues.

**Case-Based Learning**

Case-based learning has long been a centerpiece of medical education, reflecting the fact that each patient and situation are unique. The case study
method was initially introduced at the Harvard Business School more than a century ago and utilized specific real-world business examples to teach business methods. Case-based learning has been the basis of many academic weekly “Cardiac Cath Conferences,” which formed the basis of learning for many cardiologists and cardiac fellows.

Case-based presentation formats in cardiovascular medicine are highly suited to web-based learning. The presentation of case information including digital video such as angiography, echocardiography, computed tomography, or cardiac magnetic resonance imaging is well suited to broadband delivery over the Internet. Case-based learning resembles the learning process that most physicians experienced during medical training. Clinical issues are discussed in the context of specific patient examples, allowing for a more sophisticated consideration of diagnostic and therapeutic options. Research has shown that active learning techniques, such as case studies, are superior to the lecture method. The relative effectiveness of the various methods for online case-based learning is not yet evidence based, although the introduction of higher-order questions and answer responses, in general, has been shown to promote longer-term learning retention. In recent years, the introduction of social media, blogging, and learner feedback has added an additional dimension to the learning experience.

*Journal Club*

Journal club has been a mainstay of the academic medical experience for generations. In a typical journal club, a recent or classic article from the medical literature is presented and discussed among a group of peers. The journal club can provide a structured format to review the background or a scientific question, the methods actually employed in research including statistical concepts, and the results. The implications of the medical literature can then be discussed and placed in a scientific, clinical, and historical context. The relationship of a scientific article to existing clinical guidelines can be reviewed and discussed.

Web-based learning is well suited to a journal club, especially in the context of the presentation of slides, digital video, and user feedback and discussion. The use of social media can promote interactivity.
Live Discussion, Interviews, Lectures, and News

As the modern information age has led to an explosion of new knowledge and technologies, the news-reporting industry has become increasingly fragmented and web-based. Many mainstream newspapers have experienced declines in print readership as online sources of information have expanded. Similarly, interest in specific medical topics in cardiovascular medicine have led to an expanded use of web-based sites that report both medical news and interventional cardiology–specific information including late-breaking information from major international meetings. Educational and informational content, including news from scientific sessions such as the Society for Cardiovascular Angiography and Interventions, American Heart Association, the American College of Cardiology, and the European Society of Cardiology, is now routinely presented and consumed online.

Educational content from these venues, and others, are routinely presented as webcasts on major channels such as Cardiosource, WebMD/Medscape/theHeart.org, or SCAI.org. Information is often presented as interviews with principal investigators or as moderated panel discussions among experts. Some of this content provides continuing medical education (CME) credit.

Traditional Journals

Most journals related to cardiovascular medicine and/or interventional cardiology are available online, and many are formatted for mobile devices such as smartphones or tablets.

TOP E-LEARNING ENVIRONMENTS FOR INTERVENTIONAL CARDIOLOGY

Creating and maintaining accurate, current, and evidence-based educational materials for e-learning for interventional cardiology require a highly committed and collaborative group of educators and clinicians working over extended periods of time. No small group of individual operators or clinicians has the breadth of experience and knowledge to run and sustain an e-learning
environment while maintaining clinical excellence over prolonged periods of time. Outstanding websites must also have adequate technology collaborations and innovation to remain compatible with evolving technical requirements. Thus the most sophisticated e-learning sites are typically coordinated by medical societies, well-funded foundations, or universities. Currently, no single site provides a truly optimized environment, which would include updated course materials, curricular organization, integration with learning objectives and competency-based models, opportunities for reflective learning, and coordination with a lifelong learning portfolio. Nevertheless, superb interventional cardiology e-learning websites provide abundant educational opportunities in important clinical areas. Many of these sites rely on their members or partners to create educational content that is frequently “repurposed” or archived from society meetings or courses for e-learning.

**Cardiosource (www.cardiosource.com)**

Cardiosource is a rich environment that integrates many of the educational resources and journals of the American College of Cardiology. It integrates learning material from its self-assessment programs (SAPs) that are updated on a regular basis, from clinical guidelines, from the Journal of the American College of Cardiology (JACC), from its educational conferences and board review courses, from unique “apps” that are customized for mobile devices, and from customized learning materials prepared for the site. The materials are searchable across multiple categories of interest and the type of credit desired. The clinical topics are broad and include acute coronary syndromes, arrhythmias and electrophysiology, congenital heart disease, heart failure and cardiomyopathies, invasive cardiovascular angiography and intervention, noninvasive imaging, pericardial diseases, prevention, pulmonary hypertension and venous thromboembolic diseases, stable ischemic heart disease, standard electrocardiography, stress testing, valvular heart disease, and vascular medicine.

Content presentation types include JACC journals (with CME credit), expert analysis, patient cases, meetings on demand, live course recommendations, courses and conferences, meeting on demand programs, self-assessment programs, and self-assessment quizzes. Live-archived interventional cases are available for both coronary and peripheral
interventions. There are materials for guideline education, journal clubs, practice management, and clinical trial reviews. Course material is typically offered with a “pretest” to assess readiness and baseline knowledge and a “posttest” to assess comprehension. Progress through the material is coordinated in a learning portfolio.

Mobile resources (for cell phones and/or tablets) include an Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator (for compatibility with recent lipid guidelines), ACCEL, ACC Connect, AnticoagEvaluator, CardioSmart Explorer for iPad 2, CardioSource Mobile App, CardioSource WorldNews for iPad, Heart Songs (to learn heart sound interpretations), and JACC iPad Edition for electronic journal delivery and reading. Additional point-of-care tools are anticipated with respect to newer guidelines such as valvular heart disease.

**Web-Based Learning With Respect to the American Board of Internal Medicine Board Certification and Maintenance of Certification (MOC)**

Ongoing educational programs in interventional cardiology relate not only to managing a rapidly changing knowledge base, guidelines, and clinical trial results, but also have direct implications for certification and credentialing. The American Board of Internal Medicine (ABIM) has recognized that processes designed to expand and measure knowledge and performance every 10 years are no longer sufficient. The ABIM has thus implemented additional requirements that apply to all ABIM board-certified physicians, regardless of when they were initially certified.\(^\text{24}\) Beginning in 2014, in addition to reporting board certification on its website, the ABIM has begun reporting whether or not each ABIM board-certified physician is “Meeting MOC Requirements” (ie, continuously engaging in MOC activities). Many interventional cardiologists are ABIM board-certified in 3 specialties: Internal Medicine, Cardiovascular Disease, and Interventional Cardiology. The Interventional Cardiology board certification was initially offered in 1990, and thus, there are no “grandfathered” physicians in interventional cardiology with respect to interventional board certification. Additionally, a valid ABIM certification in cardiovascular disease is required to maintain certification in interventional cardiology (although it is noted that one does
not need to maintain certification in Internal Medicine to maintain certification in Cardiovascular Disease). Thus, the new ABIM rules have direct implications for interventional cardiologists of all generations with respect to board certification and/or MOC requirements.

Cardiosource (www.cardiosource.com)

Cardiosource offers a significant web-based learning environment structured with a learning portfolio to support the life-long learning process associated with the new MOC requirements. The site includes self-assessments, educational activities, MOC tracking, and recommendations for both online and in-person activities that carry credit toward certification. This includes a “MOC Status Report” for American College of Cardiology Foundation (ACCF) educational activities in support of ABIM certification and/or MOC requirements. The “self-assessment” environment is particularly rich with quizzes including echocardiography; cardiac arrhythmias; heart failure; peripheral, vascular, aortic, and carotid disease; imaging; pericardial disease; congenital heart disease; valvular heart disease; pulmonary artery hypertension; and invasive and interventional practice. Cardiosource is managed by the ACCF.

The Society for Cardiovascular Angiography and Interventions (www.scai.org)

The Society for Cardiovascular Angiography and Interventions (SCAI) offers a broad array of e-learning courses and programs that are organized into the SCAI eLearning Library. SCAI has a membership of over 4000 adult and congenital interventional cardiologists, organized into 20 committees that focus on areas such as establishing standards and guidelines for cardiac catheterization and angiography, training, credentialing, and safety and quality assurance for cardiovascular procedures.

The majority of the educational programs are included with membership, although some programs require payment for CME credit. The eLearning library includes an online curriculum covering multiple topics including a transradial interventional program (TRIP), a fellows in training curriculum (Interventional Cardiologists Institute), high-risk percutaneous coronary intervention (PCI), mastering fractional flow reserve (FFR)–intravascular
ultrasound (IVUS), peripheral vascular disease, a SCAI-QIT (quality improvement toolkit) webinar series, and a SCAI Scientific Sessions meeting on demand.

Each of these courses contains a detailed curriculum and starts with a pretest to assess knowledge and concludes with a posttest to assess learning.

TRIP includes lectures in starting a program and developing as a radialist, primary PCI, radial access, hemostasis and postprocedural management, catheter selection, guide catheter selection and manipulation, right heart catheterization from the arm, and radial approaches to peripheral procedures.

The Interventional Cardiologists Institute includes a wide array of courses including basic concepts for the interventional cardiologist; cath lab basics; valvular, structural, and congenital heart disease; intracoronary imaging and physiology; patient- and lesion-specific approaches; acute myocardial infarction; anticoagulation; coronary stenting; advanced PCI techniques and devices; high-risk groups and complications; cardiac imaging; peripheral vascular disease; and carotid artery disease.

The High-Risk PCI Online Curriculum includes the rationale and evidence for cardiac assist in high-risk PCI, hemodynamic principles of acute percutaneous circulatory support, identifying high-risk patients, available support devices, hemodynamics of percutaneous left ventricular support devices during high-risk coronary interventions, management issues (including noninvasive assessment) while on support, high-risk PCI case presentations, and support for ST-segment elevation myocardial infarction, cardiac arrest, and right ventricular failure.

The extensive FFR-IVUS Curriculum includes fundamentals of coronary pressure and flow derivation of FFR, technique, pitfalls and artifacts of FFR, fundamentals of IVUS imaging, technique, artifacts and image interpretation, clinical applications, appropriate use criteria, and guidelines.

The Peripheral Vascular Disease Curriculum includes acute limb ischemia, critical limb ischemia, claudication, aortoiliac occlusive disease, femoropopliteal disease, brachiocephalic arterial disease, venous thromboembolic disease, abdominal aortic aneurysms, mesenteric disease, renal artery stenosis, catheter-based interventions for failing hemodialysis accesses, infrapopliteal peripheral arterial disease, and intracranial arterial stenotic disease.

The e-learning section also includes an extensive “slide library” of
archived PowerPoint presentations. Future online offerings from SCAI will include sections entitled “Image of the Week,” “Cath Conference,” “Journal Scan,” and “Annotated Bibliographies.”

**The American Heart Association (www.heart.org)**

The American Heart Association (AHA) is extensively involved in e-learning across a range of cardiovascular conditions that are common in the practice of interventional cardiology including training in ST-segment elevation myocardial infarction, basic life support for healthcare providers, pediatric advanced life support, workplace training with respect to basic life support, cardiopulmonary resuscitation (CPR), automatic external defibrillation (AED), and advanced cardiovascular life support including training for experienced providers. Because the AHA and the International Liaison Committee on Resuscitation (ILCOR) coordinate much of the scientific work that underlies these important aspects of cardiovascular care, these organizations are uniquely positioned to organize guidelines and statements while providing much of the instructor network infrastructure that supports such training. The AHA provided the first CPR guidelines in 1966 and updates them every 5 years. AHA courses have trained millions of people and created a national network prepared for basic life support emergencies.

Interventional cardiologists are involved at multiple levels in the care of cardiac arrest survivors in the acute phase including evaluation in the emergency department, cardiac catheterization laboratory, or coronary care unit, making determinations regarding immediate therapies to be offered such as immediate coronary angiography and reperfusion therapy and/or therapeutic hypothermia. The timing, sequencing, and management of such interventions is not straightforward. As leaders of the hospital-based cardiology teams caring for such patients, interventional cardiologists play a central role in both developing systems of care and participating in direct patient care.

The AHA has extensively integrated e-learning systems into the widespread instruction of emergency cardiovascular care for healthcare providers and for the general public. Many of these courses offer blended learning experiences where didactic teaching is done using web-based teaching while a “hands-on” experience is provided in a more traditional, face-to-face setting. Depending on course specifics, e-learning courses are
delivered into 1, 2, or 3 parts. Courses that only involve cognitive learning can be completed online in 1 part. For courses that contain psychomotor skills such as CPR, students must complete an in-person “skills session” in addition to online learning. A skills session is composed of skills practice and skills testing. This e-learning system effectively blends cognitive learning with skills training.

**European Society of Cardiology (http://www.escardio.org)**

The ESC eLearning platform of the European Society of Cardiology contains a rich environment of e-learning tools focused on interventional cardiology through the European Association of Percutaneous Cardiovascular Interventions (EAPCI). EAPCI is open to health specialists including cardiologists, angiologists, radiologists, surgeons, cardiovascular technicians, physicians working in the industry, and researchers. More than 5600 colleagues from 125 different countries globally hold membership in EAPCI. The e-learning material is organized into sections entitled Knowledge, Skills, and Professional Development. The Knowledge module consists of 48 courses assigned among topics including basic science, pharmacology, imaging, procedural techniques, indications and patient selection, and management of complications. The site is rich in multiple-choice questions. The Skills module includes a case logbook with a focus on primary PCI, PCI in unstable angina, PCI in stable patients, and complicated cases. There is additionally a focus on procedural skills, safety, complications, and the laboratory accreditation process. A Professional Development module organizes a professional profile and 360-degree appraisals.

**TCTMD (www.tctmd.com)**

TCTMD contains an extensive catalog of online e-learning resources related specifically to interventional cardiology. The web environment includes recent news from cardiology conferences globally and focuses on information about the latest devices and drugs used in the daily practice of cardiovascular medicine.

TCTMD is produced and administered by the Cardiovascular Research Foundation (CRF; www.crf.org). Subscription to the basic features of TCTMD is free after registration. Paid annual subscription access to more
advanced content at TCT is also available. “Prime TCTMD” is designed for e-learning and self-assessment and includes presentations from the TCT Board Review Course with self-assessment in PowerPoint slides and in web case format. At additional cost, “Gold TCTMD” includes a library of case videos from TCT meetings and other meeting materials. “Platinum TCTMD” additionally adds live broadcasts from the main arena of the TCT conference and other TCT venues as well as archived versions of live broadcasts for 1 year.

TCTMD reports that the majority of funding for its e-learning environment is derived from unrestricted sponsorships and grants from medical device and pharmaceutical companies.

**WebMD, Medscape, and theHeart.org**

Medscape is a part of the WebMD Health Professional Network that includes theHeart.org and provides health information across a wide array of topics. For cardiovascular e-learning, the integrated Medscape Cardiology/theHeart.org environment provides both news and an e-learning environment. The combined website contains features such as “Test Your Knowledge,” HeartWire news, news from major conferences, and most popular news. Additionally, there are editorial series, columnists, business of medicine, trials slides of the month, and journal articles.

Medscape and HeartWire ([theHeart.org](http://theHeart.org)) also maintain a regular and ongoing collection of audio podcasts that can be obtained by (free) subscription or individual download to computers or mobile devices such as cell phones or personal players (such as iPods). These are available from sights such as Apple iTunes. A broad range of current and late-breaking information is regularly presented including renal denervation, transcatheter aortic valve replacement, prevention, and other areas.

**Apps**

Numerous useful apps are available for computers, tablets, and mobile devices from sources such as Apple iTunes. Apps related to interventional cardiology include CARDIO3 Atlas of Interventional Cardiology and the ASCVD Risk Estimator, but a nearly endless collection of useful cardiology and medical apps is available covering a wide range of topics from
electrocardiogram interpretation to clinical trials information to American College of Cardiology courses. These apps can provide structured educational content or “just-in-time knowledge chunks” that can assist the interventional cardiologist at the bedside. Apps are available in small-screen formats and in larger formats for tablets such as iPad, and additional apps regularly appear on the market.

**Massive Open Online Courses (MOOC)**

To date (2017) MOOCs related specifically to interventional cardiology have not been developed.

**E-Books**

E-books bridge the divide between print-based publishing paradigms of previous generations and the evolving web-based e-learning opportunities presented by modern digital technologies. Amazon reported that their e-book sales surpassed printed book sales in April 2011 and that e-book sales made up 23% of the total book market in 2012. Currently popular e-book platforms include the Kindle, Nook, iPad, and smartphones. E-books can also be read on a computer. Distinct advantages of e-books include rapid (nearly immediate) delivery on demand, presentation of multimedia material such as digital video (angiograms and echocardiography), decreased production and distribution costs, implementation of “widgets” than can allow additional interaction with content, increased ease of translation to other languages, ability to modify font size for ease of reading, ability to read in the dark on many platforms, and text-to-speech software. Numerous e-books are available related to interventional cardiology (and even more related to cardiology generally), and these increasingly leverage the multimedia capabilities of the platform. Board review books, handbooks, traditional textbooks, books regarding coronary stenting, and many others are available through Amazon’s Kindle Store, through Apple iBooks Store, or from other vendors.

Digital publishing software for creating e-books with enhanced multimedia capabilities is rapidly evolving and becoming available to the consumer market. Programs such as Adobe Digital Publishing Suite for eBooks and Apple’s iBooks Author allow creation of multimedia e-books for
various platforms, and the latter allows the author to create e-book galleries, video, interactive diagrams, 3-dimensional objects, and standard text-based content for delivery by, and only by, iTunes to iBooks.

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Medical Simulation in Interventional Cardiology

Andrew Klein
John C. Messenger

Medical simulation comprises the artificial representation of a real-world medical environment with sufficient realism to facilitate learning through immersion, reflection, feedback, and practice without the risks inherent to a similar real-life experience. As a result, simulation’s re-creation of a real-world process/system permits operators to practice/rehearse various scenarios that may range from routine practice to rare events including complications. One central purpose of simulation is for “safe learning,” ie, learning without a real-world consequence if errors occur. As such, simulation has a long history of use in professions that require the execution of precise physical and neurocognitive tasks in high-risk environments. For example, simulation has been used to train pilots and other professions where mistakes can have disastrous consequences. We know from the aviation industry as well as other nonmedical fields that simulators are effective teaching tools, improve learner success, enable repetitive practice of tasks in a range of conditions, and enhance task safety. Despite the ability of simulators to recreate numerous high-risk and complex environments, the uptake of simulation for the training and assessment of interventional cardiologists has lagged. This chapter will review the use of medical simulation in the realm of interventional cardiology as it stands today in hopes that it will continue to grow and be integrated more effectively into training and practice.
Interventional cardiology is a relatively new field, having only been in existence for just over 3 decades. Many current operators have been practicing since its inception and have vast experience, essentially precluding a need for simulation prior to the turn of this century. Previously, coronary interventions were only being performed in high-volume centers by high-volume operators. However, since Andreas Gruentzig’s first foray into the heart in September 1977, there have been many changes in the landscape of interventional cardiology. No longer are we as a profession performing only coronary interventions. Where previously invasive surgery represented the only option for patients, thanks to countless technologic advancements and the pioneering nature of numerous physicians/scientists/industry partners, patients with structural heart disease, peripheral arterial disease, and coronary disease now have minimally invasive options. However, with the expansion of interventional cardiology beyond the coronary vessels has come the challenge/inability of most interventionalists to practice all 3 subsets of interventional cardiology, ie, coronary, structural, and peripheral. This fact, coupled with demands for “centers of excellence,” along with an ever competitive market further underscore the need for an environment where the interventional cardiologist can assimilate new skills, rehearse rare emergency procedures, and perhaps provide evidence of their own. Simulation can provide such an environment.

In fact, interventional cardiology is a field well suited for simulation.\(^8\) Simulation can be used to both educate and improve performance by enabling repetitive practice of tasks in a range of difficult clinical conditions.\(^9\)\(^-\)\(^11\) Education in an era where work hour restrictions are a reality has also proven challenging. This, in addition to the well-publicized decrease in coronary percutaneous coronary intervention (PCI) volume over the past decade, drug-eluting stents, and appropriate use criteria, has led to a newer generation of interventionalists who will never attain the clinical experience/volume of their predecessors. Compounding this are the constant advances in techniques and devices and the ever present pressure to reduce costs while enhancing quality all within an environment where patient safety is paramount.\(^12\) The emergence of hospital departments, national bodies, high-profile conferences, and scholarly journals focused solely on patient safety seeks to serve the growing societal pressure for transparency in medical practice, in concert with public expectations for reductions in medical error.\(^13\) Thus, there is a resounding need for a “safe” environment where physicians may practice
their current skill set and/or attain new skills without subjecting patients to real harm. The days of “see one, do one, teach one” are gone and perhaps will be replaced with “see one, do several in a simulated environment and then more with a proctor, and then only after a certain volume be permitted to teach one.” Fortunately, technology has also advanced in the realm of medical simulation, and today there are multiple high-fidelity medical simulators available that can provide operators with a wide range of clinical scenarios in all 3 realms of interventional cardiology. Simulation provides a medium by which providers can learn and practice despite explosions in technology and limitations in procedural volume and work hours. Simulation thus provides an answer of how to train, test, and practice in the 21st century where only the highest quality health care will be accepted.

Another application of simulation has been its use to test individuals in a “safe environment.” The Federal Aviation Administration and several other nonmedical professions require simulation as part of routine training and/or maintenance of competency and annual skills training. Recently, governing bodies such as the American Board of Internal Medicine (ABIM), the National Board of Medical Examiners (NBME), and the Accreditation Council for Graduate Medical Education (ACGME) have been investigating the use of simulation to assure procedural competency and patient safety. Indeed, the ABIM has incorporated the use of simulation into their Maintenance of Certification program, and the ACGME has mandated that simulation be a current component of all interventional cardiology fellowship training programs. These applications of simulation have come despite a lack of large-scale studies showing improved patient outcomes with simulation in the field of interventional cardiology.

EVIDENCE FOR SIMULATION

Although the comprehensive review of the evidence of all simulation studies is beyond the scope of this chapter and has been performed elsewhere, it is important to review the origins of simulation in procedural fields. The evidence that a simulation-based curriculum is useful and valid in procedural fields originates from the surgical realm, specifically from laparoscopic surgery. In the 1980s, with the advent of minimally invasive laparoscopic surgery followed by a large number of patient complications from this new
technique, several credentialing societies developed guidelines on the proper 
acquisition of laparoscopic skills prior to performing this surgery on real 
patients.\textsuperscript{17} Although initially performed in animals, with the advent of newer 
technologies, simulated laparoscopic training eventually became possible. 
Scott et al,\textsuperscript{18} in 2000, clearly demonstrated that a 4-week simulation course 
on “box simulators” enhanced the performance of laparoscopic 
cholecystectomy in the operating room.\textsuperscript{18} To date, there have been 2 large 
randomized clinical trials\textsuperscript{19,20} that confirm the ability of a virtual reality 
simulator to enhance operative speed and economy of movement and 
decrease technical error. This was further confirmed in a Cochrane review\textsuperscript{21} 
that involved 23 trials with over 600 participants. The benefits of virtual 
reality training extend beyond practicing on a model as the trainee can 
practice in an educationally oriented and safe environment, at progressively 
more challenging levels, which leads to a proficiency-based approach to 
skills acquisition.\textsuperscript{13} It is a logical extension that if simulation training can be 
used to enhance the proficiency of surgeons performing a laparoscopic 
cholecystectomy, such training should be valid in enhancing the skills of an 
interventional cardiologist.

In this era with heightened emphasis on cost containment, quality, and 
outcomes, simulation has shown some promise. Although not in 
interventional cardiology per se, simulation-based training of residents in the 
proper aseptic insertion of central venous catheters was shown not only to 
reduce the incidence of catheter-related bloodstream infections, but also to 
have a net savings of $700,000 from reduction in rates of infections.\textsuperscript{22} To 
date, there are no studies that have shown simulation training in 
interventional cardiology to be able to reduce healthcare costs. However, one 
can imagine a simulation-based training module for interventional cardiology 
that would incorporate various aspects of cost-savings measures such as 
proper guide selection or stent selection, thus precluding the current trial-and-
error technique often employed by inexperienced operators.

\textbf{INTERVENTIONAL CARDIOLOGY 
SIMULATION}
Diagnostic Cardiac Catheterization

Diagnostic cardiac catheterization is now over half a century old and has evolved to include both femoral as well as radial approaches. The sheer volume of cardiac catheterizations has made the use of simulation for diagnostic catheterization from the femoral approach limited as fellows in training usually obtain their required procedural numbers to become certified in this procedure. In fact, there is a clear dearth of studies involving this area. Simulation, however, can provide a safe arena in which operators may encounter rare complications of diagnostic catheterization. All of the major simulation vendors have simulations including diagnostic cardiac catheterization, and most provide simulated complications that permit the learner to see these potential complications and how they would treat them in a benign simulated world as well as provide feedback if their treatment was not correct.

The use of simulation for transfemoral diagnostic catheterization has likely been muted due to the large group of operators well versed in its technique. For transradial catheterization, due to the well-documented “learning curve” that comes with this technique, the limited number of highly experienced operators, and the push for increased use due to its enhanced safety, there has been a remarkable interest in the use of simulation. In fact, transradial catheterization is an ideal procedure for simulation, ie, it involves a large group of operators who already have a basic skill set/knowledge base (left heart catheterization) but who must now learn how to approach it differently. Simulation provides a venue wherein operators can safely learn to apply their skill set in this new approach. Additionally, there is the opportunity here to use simulation to assess procedural competence, although to date, this has not been studied or validated.

Most of the major simulator companies provide transradial coronary simulations (Table 77-1) and provide users with the opportunity to encounter several unique scenarios including anatomic variants such as radial and/or brachial loops, aberrant origins of the radial artery, and variations in aortic arch anatomy. Commonly encountered issues such as spasm can also be simulated. These simulations also allow operators to learn the behavior of different catheters than those used for transfemoral cases. There are numerous transradial courses currently available that incorporate simulation as part of its curricula, including the Society for Cardiovascular Angiography
and Interventions (SCAI)–sponsored Transradial Intervention Program (TRIP), which features expert proctors working with radial trainees on simulators.

Table 77-1 Listing of Procedures Available per Simulator Company
<table>
<thead>
<tr>
<th>Procedure</th>
<th>CAE</th>
<th>MSC</th>
<th>Mentice</th>
<th>Symbionix</th>
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</thead>
<tbody>
<tr>
<td><strong>Coronary</strong></td>
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<tr>
<td>PCI</td>
<td>X</td>
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<tr>
<td>Coronary</td>
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<td>SVG</td>
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<td>FFR</td>
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<td>IABP</td>
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<tr>
<td>Rotational Atherectomy</td>
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<td>RHC</td>
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<td>Radial</td>
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<tr>
<td><strong>Structural</strong></td>
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<tr>
<td>Transeptral</td>
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<td>PFO/ASD</td>
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<tr>
<td>PABV</td>
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<td>PMBV</td>
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<td>Alcohol Septal Ablation</td>
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<td>Evolve</td>
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<td>LAA Closure</td>
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<tr>
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<tr>
<td>Coiling</td>
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<td>Neuro-coiling</td>
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<td>Thrombectomy</td>
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<td>Atherectomy</td>
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<td>TEVAR</td>
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<td>EVAR</td>
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<tr>
<td><strong>Adjunct Imaging</strong></td>
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<td>IVUS</td>
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<td>OCT</td>
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<tr>
<td>ICE</td>
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<tr>
<td>TEE</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</tbody>
</table>

An X delineates that the procedure listed is available through the simulator company. Each company is in development of additional simulators; please visit their websites for an updated list. CAE (www.caethealthcare.com); Medical Simulation Company (MSC) (www.medsimulation.com); Mentice (www.mentice.com); and Symbionix (www.symbionix.com).

Abbreviations: ASD, atrial septal defect; Evolve, percutaneous repair of the mitral valve for mitral regurgitation; EVAR, endovascular aneurysm repair; FFR, fractional flow reserve; IABP, intra-aortic balloon pump; ICE, intracardiac echocardiography; IVUS, intravascular ultrasound; LHC, left heart catheterization; OCT, optical coherence tomography; PABV, percutaneous aortic balloon valvuloplasty; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; PMBV, percutaneous mitral balloon valvuloplasty; RHC, right heart catheterization; SFA, superficial femoral artery; SVG, saphenous vein graft; TAVI, transcatheter aortic valve implantation; TEVAR, thoracic endovascular aneurysm repair.

Percutaneous Coronary Intervention (PCI)

Simulation of PCI has also evolved. Currently, numerous simulations of complex clinical scenarios including acute myocardial infarction, shock, multivessel disease, chronic total occlusion, bifurcation lesions, left main intervention, and elective PCI are available. These simulations require operators to manage the whole case including periprocedural pharmacology, assessment and treatment of hemodynamic and electrical instability, and selection of equipment and interventional strategy. For performance assessment purposes, numerous metrics can be measured including catheter selection, advancement, and coronary cannulation, wire manipulation, appropriate device selection, lesion coverage, stent expansion, residual disease, and “fluoroscopic” time. In addition to standard PCI equipment, some companies have partnered with various simulation companies and offer device-specific simulations, including rotational atherectomy and distal protection devices for saphenous vein graft intervention (eg, Boston Scientific Corp. with Medical Simulation Corp.).

Structural Heart Intervention

There has been an explosion in the array of catheter-based procedures for the treatment of structural heart disease over the last decade. These procedures include closure of atrial septal defects (ASD)/patent foramen ovale (PFO), left atrial appendage (LAA) occlusion, and transcatheter mitral and aortic valve therapies. These interventions are often complex and require operators to be well versed in the hemodynamic perturbations of each process and how to determine the degree and severity of each process. Operators must have a solid understanding of all the relationships of the heart in 3 dimensions and have an understanding of the adjunctive imaging techniques such as transesophageal echocardiography (TEE) and intracardiac echocardiography (ICE) used for guidance. With limited formalized training programs available and the high demand for the development of structural heart disease programs, this arena is well suited for the use of simulation. In response to this demand, most of the companies offer these simulations (see Table 77-1). Recently, technologic advances have also permitted the incorporation of adjunctive imaging involving TEE and ICE in simulated transseptal catheterizations, further enhancing the realism of the simulations.
Although the data are scarce in this area, there is 1 small randomized trial evaluating conventional versus simulator-based training in transseptal puncture technique that showed that simulator training resulted in shorter training time and greater procedural ability and efficiency. Even with the lack of data, many device companies are using simulation to train potential customers. In fact, the US Food and Drug Administration (FDA) has actually required simulation training be part of product training for multiple approved technologies including distal embolic protection devices (FilterWire, Boston Scientific Corp.), carotid stenting, and transcatheater aortic valve replacement (TAVR) (Sapien, Edwards Lifesciences). St Jude Medical, the largest manufacturer of ASD closure devices, actually requires simulator training for certification in the use of their Amplatzer occluder devices. Finally, there are LAA occluder simulations that likely will require simulator training upon their approval.

**Endovascular Intervention**

Importantly, simulation has been extensively studied and used in the endovascular realm. This has been driven by surgical colleagues. Traditionally trained in open techniques, in the late 1990s, there began a movement to incorporate endovascular training into surgical training programs. Surgeons previously had learned how to adopt new technology via simulation with laparoscopic surgery and thus have provided the majority of the data in simulation.

The endovascular procedure that has received the most intense interest, scrutiny, and study is carotid artery stenting (CAS). In fact, CAS is ideal for simulation. CAS has a unique learning curve and disastrous outcomes if poorly performed that have been widely published. With this in mind, an FDA panel in 2004 voted to accept a proposal that virtual reality (VR) simulation would be an important component of a training package for carotid stenting. This was followed by endorsement of VR simulation for CAS by all of the major societies.

With the support of the FDA and the major societies, simulation of CAS subsequently became the most studied of any transcatheter procedure. VR simulation for CAS has been shown to shorten learning curves, assess the impact of CAS training, as well as differentiate between levels of
endovascular experience. Simulation has been used to level the “playing field,” at least a simulated playing field, between experienced and inexperienced operators, in 1 study where training on simulators permitted learners to match experts in a direct comparison study. Hence, driven by mandate and support, the use of simulation has been shown to be effective in CAS from which most of the data and support for simulation are extracted. Indeed, if simulation training can assist in making CAS safer, then it should assist in making all procedures safer.

In the lower risk arena of non-CAS interventions, all of the companies have renal, iliac, and superficial femoral artery/popliteal endovascular interventions simulated (Table 77-1). Simulators have been used in the training of vascular surgery residents to assess the impact of didactic and cognitive training, underscoring the need to incorporate both psychomotor and cognitive skill development. In one study involving renal versus iliac intervention, simulation training clearly demonstrated that the skill set for 0.035-inch versus 0.014-inch wire manipulation is separate and distinct and that a stepwise and hierarchical training curriculum should be developed for acquisition of endovascular skill using VR simulation to supplement training on patients.

There is a well-publicized “VR to OR (operating room)” randomized trial involving simulation training for catheter-based therapy for lower extremity occlusive disease. This small study involved 20 general surgery residents who were randomly assigned to either simulation-based training or none for catheter-based therapy of lower extremity arterial disease. All subjects then performed 2 “real procedures” in an angiography suite on patients and underwent global performance assessment by an attending surgeon blinded to their training status. Residents trained on a simulator scored higher than controls on the first and second operating room angiogram and intervention. This study is the only one to date to critically assess whether simulation training can actually have an impact on performance of a real vascular procedure. Whether this impact is long lasting or cost effective remains unknown.

PATIENT-SPECIFIC VIRTUAL REALITY SIMULATION
Patient-specific VR simulation (PSVR) represents the most recent and exciting technologic advancement in medical simulation. Specifically, image processing has been accelerated to permit standard computed tomography or magnetic resonance imaging Digital Imaging and Communications in Medicine (DICOM) data to be imported into some simulators. This provides operators the chance to “rehearse” a procedure in a simulated environment using the patient’s actual vascular anatomy before performing the procedure on that patient. The operator would have the ability to test various techniques/strategies without subjecting the patient to any harm. Patient-specific rehearsal is a major advancement in the use of simulation because this concept of simulated rehearsal allows practice of a specific event (ie, an intervention), as opposed to merely acting as a generic training tool to practice a specific skill. This permits procedural planning (cognitive rehearsal) and “hands-on” rehearsal (psychomotor rehearsal) but will need to be evaluated further.

Although now commercially available, a glimpse of PSVR simulation was provided in 2007. Using PSVR simulation of a real patient’s arch anatomy and carotids, an operator rehearsed CAS in a demonstration of the power of this technology that was called “mission rehearsal.” The operator was able to perform CAS using patient-specific anatomic data on the “patient” using a simulator before entering the catheterization suite and performing the real procedure. The operator was able to “work through” the challenges one might face during CAS such as arch negotiation and catheter selection and decipher the best of several possible approaches and address potential complications before performing the real procedure on the real patient. Because it is well known that tortuous anatomy, complex lesion morphology, and difficult device access lead to increased procedural time, fluoroscopy exposure, contrast use, and complications during CAS, the PSVR permitted all of this to be “practiced” in advance. Additionally, by moving the C-arm using the imported patient-specific DICOM data, one can select the optimal working view wherein vessel overlap/foreshortening is minimized, precluding contrast and radiation, as well as select stent diameter and length before the real case. In one study of PSVR CAS simulation, simulation significantly influenced the real case in terms of optimal fluoroscopy C-arm position, choice of selective catheter, choice of sheath or guiding catheter, and balloon dilatation strategy. Operators who have access to such PSVR
simulators can rehearse the procedure prior to going into the angiography suite.

**APPRAOCH TO THE INTEGRATION OF SIMULATION**

While numerous high-fidelity VR simulators (Fig. 77-1) are now available, the true challenge of simulation is how to integrate simulation into a coherent, structured, proficiency-based training program. Each transcatheter procedure requires the operator to have a concrete foundation of knowledge including an understanding of the anatomy of the area as well as all the intricacies of the pathophysiology present prior to performing the procedure.\(^{36,44}\) The learning of advanced technical skills has little or no meaning unless an operator also knows how and when to use these skills.\(^{45,46}\) Cognitive skills, including a complete knowledge of anatomy, error detection, forward planning, and decision making, must be taught concomitantly with didactic methodologies before a novice operator commences psychomotor skills training.\(^{36,47}\) These cognitive skills must be included in any training program.\(^8\)
The SCAI-sponsored Transradial Intervention Program (TRIP) represents an example of how to integrate simulation into a cohesive training program. The TRIP curriculum is comprised of (1) a cognitive module and (2) a technique module. The cognitive module is provided in a didactic fashion by experienced radial operators. In this section, trainees obtain the knowledge base of in whom to perform this technique and how. Specifically, patient selection/preparation is followed by details of radial artery access.
Periprocedural pharmacotherapy and forearm and aortic arch anatomy (normal and variations) are reviewed in depth. Proper catheter selection and various techniques to obtain hemostasis are reviewed. Trainees are provided knowledge of how to prevent and manage common complications of this technique. Following this cognitive section, the technical aspects of the procedure are demonstrated in a simulated catheterization laboratory environment. Operators learn about equipment choices and catheter manipulation in a “1-on-1” fashion with faculty, develop catheter skills, and learn tactile feedback in a simulator environment. Providing such a structure to the simulation-based learning experience increases its educational impact. The critical aspect is the use of high-fidelity simulators to develop and hone psychomotor skills in a safe environment wherein each operator starts with the knowledge base upon which these skills can be added. TRIP is unique in its composite approach and likely should serve as a model for future educational efforts involving simulation.

**POSITION STATEMENTS**

Recently, the SCAI released a document surveying the current state of medical simulation in interventional cardiology. This document examines in depth the details of each commercially available simulator within North America and the currently available simulation platforms. Embedded within this document are data from a recent ABIM/ACC/SCAI survey that was sent to all ACGME-accredited interventional cardiology programs within the United States (n = 132) in an effort to ascertain the current use of simulation in these programs since the mandate from ACGME to incorporate simulation-based training in some fashion within all training programs. This survey underscores the numerous barriers to the uptake of simulation in interventional cardiology. Few programs agreed that the simulators mimicked actual catheterization well or that the simulator experience was similar to real life or could enhance skill in the real catheterization laboratory. Although unquestionably tainted by a selection bias of surveying only academic and more experienced operators (program directors), these statements underscore the inherent challenges that simulation proponents encounter. The SCAI document also outlines a number of recommendations from the society for simulation moving forward including:


1. We anticipate the eventual requirement that fellows in invasive specialties will be expected to demonstrate competency in the procedures they are being trained to perform in practice. To prepare for this, we recommend that SCAI as a society, in conjunction with the ACC and ABIM develop a set of standardized cases that embodies the essential psychomotor and knowledge base skill sets required to be an interventional cardiologist.

2. These standardized cases should be developed and integrated with a standardized didactic curriculum that meets current evidenced based learning standards as dictated by the Accreditation Council for Graduate Medical Education (ACGME) and Core Cardiovascular Training Symposium (COCATs). This curriculum and the simulations should be available on all simulation platforms to maximize fellow training and testing at all SCAI events including the Fall Fellows Course.

3. We advocate for the initiation of large scale studies to evaluate the impact of simulation in a number of key areas including: (a) feasibility and efficacy of a simulation-based training curricula as a training modality for both fellows and more experienced operators learning new procedures and (b) reliability and validation of simulation as a tool for the maintenance of competency.

4. Finally, we recommend that formal simulation training programs be included in the annual scientific sessions and integrated into the program for fellows and practicing physicians.

FUTURE CHALLENGES AND DIRECTIONS FOR SIMULATION

Interventional cardiology has been slow to adopt simulation as part of its training programs despite the obvious benefits of its use as well as data from other fields. Part of this has been the relative dearth of data showing improved performance and a translation into real-world practice. For procedures common within cardiology, such as left and right heart catheterization, a potential explanation lies in the relatively high volume of these procedures that are performed each year. This has propelled continuation of the apprentice model wherein fellows learn by “practicing on real patients.” In turn, there is a natural reluctance to formally incorporate
simulation into training programs and hence its study for the purposes of cardiology education. Critics of simulation cite the large inherent “costs” of simulation. These costs include both monetary (eg, the cost of the simulators, upkeep) and the cost of time away from real patients. In fact, the cost of a single VR simulator can be much as $100,000, which precludes most training programs from ever having their own VR simulator. Additionally, hospitals with trainees already incur greater costs because of having trainees who are not as efficient at procedures as attending physicians. Indeed, approximately $50,000 is spent per surgical resident over a training period of 4 years secondary to increases in operative time and the inherent decreased efficiency that occurs when operating with a trainee. How can we expect these programs to also cover the cost of simulation-based training, even if it increases efficiency? Will there be an adequate return on the investment? Who is to cover these costs? These are all unanswered questions. As noted elsewhere, with numerous subspecialties now using simulation for training, perhaps institutions might see the cost-effectiveness of having a VR simulator and/or simulation center that could be used across specialties. Another cost-effective option to secure simulation-based training is to send trainees to regional simulation centers or to enhance societal efforts at exposing trainees to simulation at annual meetings.

Despite this, the major professional societies have taken substantial increased interest in incorporating simulators into training and certification. By virtue of the rapidity of exposure and programmed variations in anatomy, clinical complexity, or ensuing complications, there is little doubt that simulator training can enhance the operator learning curve and potentially improve actual patient safely. The challenge however is providing the data to definitively show this benefit and then prove it to be cost effective. Even with a lack of several large studies, the ACGME now mandates that simulation must be incorporated into each cardiology and interventional cardiology fellowship training program.

CONCLUSION

The integration of simulation-based training into interventional cardiology is long overdue, but appears to be making forward progress. Numerous randomized clinical trials, systematic reviews, and meta-analyses have
confirmed the benefits of simulation to enhance clinical practice across a multitude of specialties. The traditional approach of “see one, do one, teach one” is rapidly being replaced with the more progressive concept of “learn the operation before the operating room.” Interventional cardiologists, a pioneering group by nature, have ventured beyond the coronaries to complex arenas such as percutaneous valvular replacement, endovascular revascularization, and carotid stenting. Our profession is evolving rapidly and with this comes new devices, techniques, and challenges. Simulation provides the ability to rapidly teach techniques, hone requisite skills, and evaluate the impact of training, all within a world that is without harm to the patient. We must continue to evolve and determine how best to incorporate simulation into our training programs, our maintenance of certification programs, and our profession as a whole.

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