ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic)


Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation

WRITING COMMITTEE MEMBERS
Alan T. Hirsch, MD, FACC, FAHA, Chair; Ziv J. Haskal, MD, FAHA, FSIR, Co-Chair; Norman R. Hertzler, MD, FACS, Co-Chair; Curtis W. Bakal, MD, MPH, FAHA, FSIR; Mark A. Creager, MD, FACC, FAHA; Jonathan L. Halperin, MD, FACC, FAHA†; Loren F. Hiratzka, MD, FACC, FAHA, FACS; William R.C. Murphy, MD, FACC, FACS; Jeffrey W. Olin, DO, FACC; Jules B. Puschett, MD, FAHA; Kenneth A. Rosenfield, MD, FACC; David Sachs, MD, FACR, FSIR‡; James C. Stanley, MD, FACSS§; Lloyd M. Taylor, Jr, MD, FACSS§; Christopher J. White, MD, FACC, FAHA, FESC, FSCAI¶; John White, MD, FACS§; Rodney A. White, MD, FACS$.

TASK FORCE MEMBERS
Elliott M. Antman, MD, FACC, FAHA, Chair; Sidney C. Smith, Jr, MD, FACC, FAHA, Vice-Chair; Cynthia D. Adams, MSN, APRN-BC, FAHA; Jeffrey L. Anderson, MD, FACC, FAHA; David P. Faxon, MD, FACC, FAHA**; Valentin Fuster, MD, PhD, FACC, FAHA, FESC**; Raymond J. Gibbons, MD, FACC, FAHA, ACS**; Sharon A. Hunt, MD, FACC, FAHA; Alice K. Jacobs, MD, FACC, FAHA; Rick Nishimura, MD, FACC, FAHA; Joseph P. Ornato, MD, FACC, FAHA; Richard L. Page, MD, FACC, FAHA; Barbara Riegel, DNSc, RN, FAHA

TABLE OF CONTENTS

1. INTRODUCTION ................................ e465
1.1. Preamble .................................... e465
1.2. Definitions .................................. e466
1.3. Vascular History and Physical Examination... e470

2. LOWER EXTREMIT Y PAD ................. e471
2.1. Epidemiology ................................. e471
2.1.1. Risk Factors .......................... e471
2.1.2. Prevalence .............................. e472
2.2. Prognosis and Natural History ........... e475
2.2.1. Coprevalence of Coronary Artery Disease and Carotid Disease .............. e475
2.2.2. Risk of Cardiovascular Events ...... e476
2.2.3. Prognosis of the Limb ................ e476
2.3. Other Causes of Lower Extremity PAD .... e476
2.4. Clinical Presentation ....................... e477
2.4.1. Asymptomatic .......................... e477
2.4.2. Claudication ............................ e480
2.4.3. Critical Limb Ischemia ............... e483
2.4.4. Acute Limb Ischemia ................. e487
2.4.5. Prior Limb Arterial Revascularization.. e489
2.5. Diagnostic Methods ...................... e490
2.5.1. Ankle- and Toe-Brachial Indices, Segmental Pressure Examination ...... e491
2.5.2. Pulse Volume Recording ................ e497
2.5.3. Continuous-Wave Doppler Ultrasound . e498
2.5.4. Treadmill Exercise Testing With and Without ABI Assessments and 6-Minute Walk Test .. e498
2.5.5. Duplex Ultrasound ...................... e500
2.5.6. Computed Tomographic Angiography... e501
2.5.7. Magnetic Resonance Angiography .... e502
2.5.8. Contrast Angiography .................. e503
2.6. Treatment ............................... e505
2.6.1. Cardiovascular Risk Reduction ........ e505
2.6.1.1. Lipid-Lowering Drugs ............ e505
2.6.1.2. Antihypertensive Drugs .......... e506
2.6.1.3. Diabetes Therapies ............... e506
### 3. RENAL ARTERIAL DISEASE

#### 3.1. Prevalence and Natural History

- **3.1.1. Clinical End Points of Renal Artery Disease**
  - e534

#### 3.2. Clinical Clues to the Diagnosis of RAS

- **3.2.1. Pathophysiology and Disease Categories**
  - e541

#### 3.3. Pathophysiology and Disease Categories

- **3.3.1. Atherosclerosis**
  - e542

- **3.3.2. Fibromuscular Dysplasia**
  - e542

- **3.3.3. Other Causes of Renal Artery Disease**
  - e543

#### 3.4. Diagnostic Methods

- **3.4.1. Renal Scintigraphy**
  - e544

- **3.4.2. Duplex Ultrasound**
  - e544

- **3.4.3. Computed Tomographic Angiography**
  - e545

- **3.4.4. Magnetic Resonance Angiography**
  - e545

- **3.4.5. Catheter Angiography**
  - e545

- **3.4.6. Renin**
  - e546

- **3.4.6.1. Selective Renal Vein Renin Studies**
  - e546

- **3.4.6.2. Plasma Renin Activity: Captopril Test**
  - e546

#### 3.5. Treatment of Renovascular Disease: Renal Artery Stenosis

- **3.5.1. Medical Treatment**
  - e547

- **3.5.2. Indications for Revascularization**
  - e548

- **3.5.2.1. Asymptomatic Stenosis**
  - e548

- **3.5.2.2. Hypertension**
  - e550

- **3.5.2.3. Preservation of Renal Function**
  - e551

- **3.5.2.4. Impact of RAS on Congestive Heart Failure and Unstable Angina**
  - e553

- **3.5.3. Catheter-Based Interventions**
  - e554

- **3.5.4. Surgery for RAS**
  - e555

- **3.5.4.1. Fibromuscular Dysplasia**
  - e556

- **3.5.4.2. Arteriosclerotic Renal Artery Occlusive Disease**
  - e556

- **3.5.4.3. Results of Operative Therapy**
  - e557

---

*AAVS/SVS when Guideline initiated, now merged into SVS.
†Society for Vascular Medicine and Biology official representative.
‡Society of Interventional Radiology official representative.
¶Society for Cardiovascular Angiography and Interventions official representative.
**Former Task Force member during this writing effort.
††Immediate Past Chair.

This document was approved by the American College of Cardiology Foundation Board of Trustees in October 2005 and by the American Heart Association Science Advisory and Coordinating Committee in October 2005.


This article has been copublished in the March 21, 2006, issue of the Journal of the American College of Cardiology (J Am Coll Cardiol. 2006;47:e1–e192).

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org) and the American Heart Association (www.americanheart.org); †† Single copies of this document are available by calling 1-800-253-4636 or writing the American College of Cardiology Foundation, Resource Center, at 1111 Old Georgetown Road, Bethesda, MD 20814-1699. Ask for reprint number 71-0349. To obtain a copy of the Executive Summary published in the March 21, 2006, issue of the Journal of the American College of Cardiology and the March 21, 2006, issue of Circulation, ask for reprint number 71-0348. To purchase bulk reprints (specify version and reprint number): Up to 999 copies, call 1-800-611-6083 US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1789, fax 214-691-6342, or e-mail pubauth@heart.org.


Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American College of Cardiology Foundation. Please direct requests to copyright_permissions@acc.org.

© 2006 by the American College of Cardiology Foundation and the American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.106.174526
5. ANEURYSMS OF THE ABDOMINAL AORTA, ITS BRANCH VESSELS, AND THE LOWER EXTREMITIES

5.1. Definition .................................. e564
5.2. Abdominal Aortic and Iliac Aneurysms ............ e564
  5.2.1. Prevalence .......................... e564
    5.2.1.1. Generalized Arteriomegaly .... e564
  5.2.2. Etiology .......................... e564
    5.2.2.1. Hereditary Risk Factors .... e564
    5.2.2.2. Atherosclerotic Risk Factors . e565
    5.2.2.3. Collagenase, Elastase, Metalloproteases .... e569
    5.2.2.4. Congenital Aneurysms .......... e569
    5.2.2.5. Inflammatory Aneurysms .... e570
    5.2.2.6. Infectious Aneurysms ....... e570
  5.2.3. Natural History ........................ e571
    5.2.3.1. Aortic Aneurysm Rupture .... e571
    5.2.3.2. Common Iliac Aneurysms .... e576
    5.2.3.3. Local Compression or Erosion. e576
  5.2.4. Diagnosis ................................ e576
    5.2.4.1. Symptomatic Aortic or Iliac Aneurysms .......... e576
    5.2.4.2. Asymptomatic Aortic or Iliac Aneurysms .......... e576
    5.2.4.3. Physical Examination .... e577
    5.2.4.4. Incidental Radiological Findings .. e577
    5.2.4.5. Diagnostic Imaging ........ e578
    5.2.4.6. Screening High-Risk Populations . e580
  5.2.5. Observational Management ................ e581
    5.2.5.1. Blood Pressure Control and Betablockade .... e581
    5.2.5.2. Follow-Up Surveillance .... e582
  5.2.6. Open Aortic Aneurysm Repair ........ e582
    5.2.6.1. Infrarenal AAAs ............ e583
    5.2.6.2. Juxtarenal, Pararenal, and Suprarenal Aortic Aneurysms .......... e585
  5.2.7. Endovascular Aortic Aneurysm Repair .... e588
    5.2.7.1. Introduction ........... e588
    5.2.7.2. Preoperative Cardiac Evaluation .. e591
    5.2.7.3. Early Mortality and Complication Rates ........ e591
    5.2.7.4. Late Survival and Complication Rates ........ e594
  5.2.8. Prevention of Aortic Aneurysm Rupture .. e597
    5.2.8.1. Management Overview .... e597
  5.3. Visceral Artery Aneurysms .................. e600
    5.3.1. Splenic Artery Aneurysms ........ e600
    5.3.2. Superior Mesenteric Artery Aneurysms .... e600
    5.3.3. Management Options ............. e603
  5.4. Lower Extremity Aneurysms .................. e603
    5.4.1. Etiology .......................... e603
    5.4.2. Natural History .......................... e604
    5.4.2.1. Popliteal Aneurysms ........ e604
    5.4.2.2. Femoral Artery Aneurysms .... e606
    5.4.3. Management .......................... e606
    5.4.3.1. Popliteal Aneurysms ........ e607
    5.4.3.2. Femoral Aneurysms .......... e608
    5.4.3.3. Catheter-Related Femoral Artery Pseudoaneurysms .......... e611

Appendix 1. Relationships With Industry: Writing Committee .................................. e615
Appendix 2. Relationships With Industry: Peer Reviewers .................................. e617
Appendix 3. Abbreviations.......................... e619
References ........................................ e620

1. INTRODUCTION

1.1. Preamble

It is important that the medical professions play a significant role in critically evaluating the use of diagnostic procedures and therapies in the detection, management, and prevention of disease states. Rigorous and expert analysis of the available data documenting absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, whose charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures. Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop written recommendations for clinical practice. Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write or update guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing groups are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as well as frequency of follow-up and cost-effectiveness. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will be the primary basis for recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of
interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at each meeting, and updated and reviewed by the writing committee yearly and as changes occur. Please see Appendix 1 for author relationships with industry and Appendix 2 for peer reviewer relationships with industry.

The practice guidelines produced are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient’s best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all of the circumstances presented by that patient.

These guidelines were approved for publication by the governing bodies of the American College of Cardiology (ACC) and the AHA and have been officially endorsed by the following collaborating organizations: Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society for Vascular Surgery; and Society of Interventional Radiology; as well as by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Intersociety Consensus; and Vascular Disease Foundation. The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be considered current unless they are updated, revised, or sunset and withdrawn from distribution. The executive summary and recommendations are published in the March 21, 2006 issue of the Journal of the American College of Cardiology and the March 21, 2006 issue of Circulation. The full text is published on the ACC and AHA World Wide Web sites. Copies of the full text and the executive summary are available from both organizations.

Elliott M. Antman, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

Raymond J. Gibbons, MD, FACC
Immediate Past-Chair, ACC/AHA Task Force on Practice Guidelines

1.2. Definitions

Peripheral arterial disease (PAD) encompasses a range of noncoronary arterial syndromes that are caused by the altered structure and function of the arteries that supply the brain, visceral organs, and the limbs. Numerous pathophysiological processes can contribute to the creation of stenoses or aneurysms of the noncoronary arterial circulation, but atherosclerosis remains the most common disease process affecting the aorta and its branch arteries. These guidelines primarily address the diagnosis and management of atherosclerotic, aneurysmal, and thromboembolic PAD.

Whereas the term “peripheral arterial disease” encompasses a large series of disorders affecting arterial beds exclusive of the coronary arteries, this writing committee chose to limit the scope of the work of this document to disorders of the abdominal aorta, renal and mesenteric arteries, and lower extremity arteries. The guideline is thus presented as an introduction, followed by 4 sections that address these anatomic arterial regions. Clinical management guidelines for other arterial beds (e.g., the thoracic aorta, carotid and vertebral arteries, and upper extremity arteries) have been excluded from the current guideline to focus on the infradiaphragmatic arterial system and in recognition of the robust evidence base that exists for the aortic, visceral, and lower extremity arteries. The guideline is also organized to follow an anticipated “chronology” of clinical care of patients with PAD. As such, the full-text guideline is written with the presumption that many readers will search the guideline for specific advice on management of PAD patients at different phases of their illness. Thus, in selected instances, recommendations and some portions of the text are repeated.

The clinical manifestations of PAD are a major cause of acute and chronic illness; are associated with decrements in functional capacity and quality of life; cause limb amputation; and increase risk of death. The systemic nature of the atherosclerotic process also contributes to development of concomitant disease of the arteries to the heart and brain. Consequently, patients with PAD often face an associated increased risk of cardiovascular ischemic events, such as myocardial infarction (MI), ischemic stroke, and death. Overall, the manifestations of PAD are thus associated with a large personal, social, and economic burden in the United States, Europe, South America, and Asia, and PAD is increasingly recognized as a health burden worldwide.

Inasmuch as the burden of PAD is widespread, these guidelines are intended to assist all clinicians who might provide care for such patients. In particular, these guidelines are designed to aid primary care clinicians, vascular and cardiovascular specialists, trainees in the primary care and vascular specialties, nurses, physical therapists, and rehabilitative personnel who seek clinical tools that can improve the proper evaluation and management of patients with PAD and associated thromboembolic disease. This document provides recommendations and supporting evidence for the short- and long-term management of patients with PAD in both inpatient and outpatient settings. Recommended diagnostic and therapeutic strategies are supported by the best available evidence and expert opinion. The application of these strategies, combined with carefully reasoned clinical judgment, promotes the use of preventive strategies, improves the rates of diagnosis of each syndrome, and decreases the rates of amputation, ischemic renal failure, mesenteric ischemia,
aneurysmal rupture, MI, stroke, and death. The ultimate goal of the guideline is to improve the quality of life for people with PAD.

The Committee to Develop Guidelines for Peripheral Arterial Disease conducted comprehensive searching of the scientific and medical literature relevant to PAD. Literature searches were conducted in PubMed/MEDLINE and a clinical trials database. Searches were limited to publications in English and human subjects. The committee reviewed all compiled reports from computerized searches and conducted additional searching by hand. Committee members also recommended applicable articles outside the scope of formal searches.

In addition to broad-based searching on PAD, specific targeted searches were performed on the following subtopics: amputation, aneurysm, ankle-brachial index, antihypertensive drugs, antiplatelet and antithrombotic drugs, arteriography, beta blocker, “blue-toe” syndrome, calcification, catheter-based intervention, chronic limb ischemia, claudication, compression, computed tomography, coprevalence of cardiovascular/carotid disease, diabetes, diagnosis, endovascular treatment, etiology, exercise/rehabilitation, femoral pseudoaneurysms, follow-up, homocysteine lowering, imaging, location and prevalence, lower extremity pulse exam, magnetic resonance angiography, management of ischemia, measurement, medical/pharmacological management, mesenteric, natural history, pathology, pregnancy risk, preoperative assessment/evaluation, prevalence, renal function, smoking cessation, statins, stent, surgical intervention, thrombolysis, ultrasound, vascular surgery. The list of subtopics is not exhaustive.

As a result of these searches, more than 1300 references were used as the major evidence base in the final Guideline, with many times this number of references reviewed by the Committee. Using evidence-based methodologies developed by the ACC/AHA Task Force on Practice Guidelines, the committee wrote guideline text and recommendations. Literature citations were generally restricted to published manuscripts appearing in journals listed in Index Medicus. Because of the scope and importance of certain ongoing clinical trials and other emerging information, published abstracts were cited when they were the only published information available.

It is hoped that readers will be best served as they utilize this guideline by their examination of the methods of evidence review that guide all writing committees (http://www.acc.org/clinical/manual/manual_introltr.htm). A classification of recommendation and a level of evidence have been assigned to each recommendation. Classifications of recommendations and levels of evidence are expressed in the ACC/AHA format as follows.

Classification of Recommendations

Class I: Conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

• Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

• Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

• Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

Table I delineates the classification of recommendations and level of evidence.

This guideline was developed by a writing committee whose members had expertise in vascular medicine and cardiovascular medicine, vascular surgery, vascular and interventional radiology, and hypertension and renal disease, with committee membership derived from the ACC, the AHA, the Society for Vascular Surgery, the Society of Interventional Radiology, the Society for Vascular Medicine and Biology, the Society for Cardiovascular Angiography and Interventions, the ACC Board of Governors, and the ACC/AHA Task Force on Practice Guidelines.

This writing committee recognizes the prodigious effort and international contribution of the “Management of Peripheral Arterial Disease” document developed by the TransAtlantic Inter-Society Consensus (TASC) Working Group (http://www.tasc-pad.org/) (1). The TASC is an internationally derived, collaboratively created consensus that provides an evidence-based, detailed review of the diagnosis and treatment of intermittent claudication, acute limb ischemia, and critical limb ischemia (CLI). The efforts of TASC have defined the standard of excellence in the treatment of peripheral arterial disease. At this writing, the TASC Working Group is in the process of updating its 2000 document. Readers are encouraged to consult, in addition to this guideline, the revised TASC document when it becomes available.

The ACC/AHA Writing Committee was charged with building on the work of TASC to create a guideline for a broader audience to include primary care clinicians as well as vascular specialists. This guideline also encompasses a larger, yet still limited, scope. In addition to lower extremity PAD, this guideline includes a focus on aortic and branch
Table 1. Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>Classification of Treatment Effect</th>
<th>Class I</th>
<th>Class IIa</th>
<th>Class IIb</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
<td>Procedure/Treatment SHOULD NOT be performed/administered</td>
<td></td>
</tr>
</tbody>
</table>

**Level A**

- **Multiple (3-5) population risk strata evaluated**
  - General consistency of direction and magnitude of effect
  - Recommendation that procedure or treatment is useful/effective
  - Sufficient evidence from multiple randomized trials or meta-analyses

**Level B**

- **Limited (2-3) population risk strata evaluated**
  - Recommendation that procedure or treatment is useful/effective
  - Limited evidence from single randomized trial or non-randomized studies

**Level C**

- **Very limited (1-2) population risk strata evaluated**
  - Recommendation that procedure or treatment is useful/effective
  - Expert opinion, case studies, or standard-of-care

---

**“Size of Treatment Effect”**

- **Class I**
  - Benefit >> Risk
  - Procedure/Treatment SHOULD be performed/administered

- **Class IIa**
  - Benefit >> Risk
  - Additional studies with focused objectives needed
  - It is reasonable to perform procedure/administer treatment

- **Class IIb**
  - Benefit >> Risk
  - Additional studies with broad objectives needed; Additional registry data would be helpful
  - Procedure/Treatment MAY BE CONSIDERED

- **Class III**
  - Risk >> Benefit
  - Procedure/Treatment SHOULD NOT be performed/administered
  - Since it is not helpful and may be harmful

---

**Suggested phrases for writing recommendations**

- **should** is recommended
- **is indicated** is useful/effective/beneficial
- **may/might be considered** may/might be reasonable
- **is not recommended** is not indicated
- **should not** is not useful/effective/beneficial

---

*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.*

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers’ comprehension of the guidelines and will allow queries at the individual recommendation level.
Aneurysmal disease, renal arterial, and visceral arterial disease. Thus, the purposes of this guideline are to (1) aid in the recognition, diagnosis, and treatment of PAD of the aorta and lower extremities, addressing its prevalence, impact on quality of life, cardiovascular ischemic risk, and risk of CLI; (2) aid in the recognition, diagnosis, and treatment of renal and visceral arterial diseases; and (3) improve the detection and treatment of abdominal and branch artery aneurysms.

The term “peripheral arterial disease” includes a diverse group of disorders that lead to progressive stenosis or occlusion, or aneurysmal dilation, of the aorta and its noncoronary branch arteries, including the carotid, upper extremity, visceral, and lower extremity arterial branches. PAD is the preferred clinical term that should be used to denote stenotic, occlusive, and aneurysmal diseases of the aorta and its branch arteries, exclusive of the coronary arteries.

Historically, the term “peripheral vascular disease” has been used to most inclusively describe the noncardiac diseases that affect the circulation as a whole. Thus, this term encompasses a myriad of pathophysiological syndromes that affect the arterial, venous, and lymphatic circulations; accordingly, it includes all vascular diseases that alter end-organ perfusion. Arterial diseases include those disorders that cause either fixed obstruction or normal vascular reactivity of the arteries that supply a given tissue; the obstruction impairs blood delivery and can produce ischemia. Venous diseases include those disorders that impair normal venous function, usually involve both altered venous structure and function, and may include thromboembolism. These disorders include venous valvular incompetence and venous hypertension, deep venous thrombosis, pulmonary embolism, the postthrombotic syndrome, and varicose veins. Lymphatic diseases are a consequence of congenital or acquired processes that may cause progressive destruction or abnormal function of the microvascular lymphatic networks; these disorders are usually clinically manifested as lymphedema. Thus, the term “peripheral vascular disease” is broadly inclusive of all vascular disorders.

The term “peripheral arterial occlusive disease” is used in a manner analogous to that of PAD, although it specifically excludes the functional (vasoreactive) or aneurysmal disorders that affect the noncoronary arteries. “Lower extremity arterial disease” includes disorders that affect the leg arteries and does not include diseases of the aorta, carotid, upper extremity, or visceral arteries.

“Arteriosclerosis obliterans” includes those arterial diseases that are defined by the process of atheroma formation and calcium deposition in the arterial wall. “Atherothrombosis” similarly defines the mutual roles of atherosclerosis and thrombosis in the formation of arterial stenoses that lead to plaque rupture and thrombotic occlusion. “Atherosclerotic vascular disease” includes those arterial syndromes that have an atherosclerotic origin, exclusive of aneurysmal, thromboembolic, arteritic, and vasoreactive causes.

For the purposes of this guideline, we utilize the term “peripheral arterial disease” to broadly encompass the vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiological processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremity.

Peripheral arterial disease is often a consequence of systemic disease processes that affect multiple arterial circulations, although clinically recognized disease in more than 1 organ system is not always present. These systemic pathophysiological processes are diverse and include atherosclerosis, degenerative diseases, dysplastic disorders, vascular inflammation (arteritis), and both in situ thrombosis and thromboembolism. Clinicians who provide care for individuals with PAD should recognize this diversity of pathophysiological causes of this syndrome because this recognition is required to create an inclusive differential diagnosis and comprehensive long-term treatment plan. The most common cause of PAD worldwide is atherosclerosis, and thus the epidemiology and clinical consequences of PAD are closely associated with classic atherosclerosis risk factors (e.g., smoking, diabetes, hypertension, hyperlipidemia, family history, and the postmenopausal state) and more recently defined risk factors (e.g., hyperhomocysteinemia and a variety of others) (2-5).

Peripheral arterial disease may also be caused by degenerative disorders that lead to a loss of the structural integrity and subsequent dilation of the arterial wall. The pathophysiology of some specific progressive arterial degenerative diseases is relatively well understood (such as the collagen abnormalities that underlie Marfan and Ehlers-Danlos syndromes) (6-10), whereas the vascular defect responsible for most degenerative diseases remains elusive (e.g., Erdheim’s cystic medial necrosis, arteriomegaly, neurofibromatosis, and most of the so-called atherosclerotic aneurysms). Arterial wall degeneration can lead to aneurysm formation or dissection that may result in arterial rupture or occlusion.

The most common dysplastic disease is fibromuscular dysplasia (FMD), which may affect many noncoronary arterial beds, especially the renal arteries, carotid arteries, and iliac arteries (11,12). The vasculitic diseases may also affect any arterial bed, and the spectrum of clinical syndromes associated with vasculitis is broad (13-20). Large vessels (the aorta and its first- and second-order branches) may be involved by giant cell arteritis (Takayasu’s disease), Behçet’s syndrome, relapsing polychondritis, and vasculitis associated with arthropathies. Medium-sized vessels (conduct muscular arteries and branches) are classically the target of polyarteritis nodosa or temporal arteritis (a form of giant cell arteritis), although Wegener’s or lymphoid granulomatosis, Churg-Strauss syndrome, and Kawasaki disease also affect vessels of this size. Radiation-associated arteritis can affect vessels of any size. Small-vessel disease (arterioles and microvessels) occurs most frequently in association with systemic disorders such as rheumatoid arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue or autoimmune diseases. Thromboangiitis obliterans (Buerger’s disease) is an arterial oblitative and thrombotic process that is most frequently (but not invariably) observed in young
individuals who smoke tobacco; it behaves like a vasculitis and can affect arteries of all sizes (smaller distal limb arteries more frequently than larger proximal arteries), as well as superficial veins (21-23).

The primary prothrombotic diseases may be caused by (a) specific abnormalities in the clotting system (e.g., protein C, protein S, or antithrombin III deficiencies; factor V Leiden or prothrombin mutations; hyperhomocysteinemia; or other abnormalities); (b) the presence of a lupus anticoagulant or anticardiolipin antibody; and (c) the prothrombotic state associated with many malignancies and inflammatory bowel disease (24). Thromboembolic arterial occlusive disease affects both large (macroembolic) and small (microembolic) vessels (25-29). Macroemboli usually originate from a cardiac source (such as thrombus in the left atrial appendage, atrial fibrillation, ventricular thrombus secondary to MI or heart failure), whereas microemboli may have either a cardiac source (typically a diseased native valve or a thrombogenic prosthetic valve) or an arterial source (most often a ruptured cholesterol-containing plaque that produces distal atheroembolization).

The term “vasospastic diseases” refers to the pathological vasoconstriction that may affect any muscular vessel in the body (30-33). Migraine headache, cerebral vasospasm associated with intracranial bleeding, Prinzmetal’s angina, Raynaud’s phenomenon, and ergot toxicity are all well-recognized vasospastic syndromes. In the extremities, vasospasm may occur as a primary event (primary Raynaud’s phenomenon) or secondary to an underlying disease process such as scleroderma or systemic lupus erythematosus (secondary Raynaud’s phenomenon).

### 1.3. Vascular History and Physical Examination

**RECOMMENDATIONS**

**Class I**

1. **Individuals at risk for lower extremity PAD (see Section 2.1.1, Table 2)** should undergo a vascular review of symptoms to assess walking impairment, claudication, ischemic rest pain, and/or the presence of nonhealing wounds. *(Level of Evidence: C)*

2. **Individuals at risk for lower extremity PAD (see Table 2)** should undergo comprehensive pulse examination and inspection of the feet. *(Level of Evidence: C)*

3. **Individuals over 50 years of age should be asked if they have a family history of a first-order relative with an abdominal aortic aneurysm. (Level of Evidence: C)*

Vascular diseases are common, and prompt treatment can diminish disability and death. Preservation of individual health (improved functional status and survival) and achievement of public health goals (e.g., diminished rates of amputation and fewer cardiovascular ischemic events and death) can be fostered by establishment of an accurate vascular diagnosis. As for all illnesses, excellence in care begins with the collection of an accurate history of the present illness, review of systems, and physical examination.

**Vascular Review of Systems**

In an ideal clinical world, each patient would offer their clinician a detailed accounting of symptoms that impair normal body functions or cause pain or disability, which would provide clues to an underlying disease state. However, patients do not always report symptoms that may be vital to their health, and they do not always associate specific symptoms with underlying arterial disease (e.g., the walking impairment of claudication, the presence of a poorly healing wound, or abdominal pain in the presence of an abdominal aneurysm). In this context, clinicians can specifically request these data by asking patients to offer a review of symptoms (ROS). The ROS is used to unmask symptoms in the following domains: head, eye, ear, nose, throat, and the lymphatic, dermatologic, pulmonary, cardiac, gastrointestinal, genitourinary, musculoskeletal, neurological, or rheumatologic systems. Traditionally, there has been no routine vascular ROS, and this may contribute to the documented underdiagnosis of vascular diseases. This guideline, drafted with the mandate to improve care for patients with PAD, offers suggestions for creation of a vascular ROS.

Key components of the vascular ROS (not usually included in the ROS of the extremities) and family history include the following:

- Any exertional limitation of the lower extremity muscles or any history of walking impairment. The characteristics of this limitation may be described as fatigue, aching, numbness, or pain. The primary site(s) of discomfort in the buttock, thigh, calf, or foot should be recorded, along with the relation of such discomfort to rest or exertion.

- Any poorly healing or nonhealing wounds of the legs or feet.

- Any pain at rest localized to the lower leg or foot and its association with the upright or recumbent positions.

- Postprandial abdominal pain that reproducibly is provoked by eating and is associated with weight loss.
• Family history of a first-degree relative with an abdominal aortic aneurysm (AAA).

The Vascular Physical Examination

Ideally, critical components of the bedside clinical evaluation are common among all clinicians and congruent between primary care and specialty practices. Such a common core physical examination and methods to record its findings are fundamental if clinical data are to be transferred (a) from one caregiver to the next within a practice or (b) from primary caregiver to consultant. Such an approach has been central to the establishment of the best clinical practices for heart disease (in which all practitioners utilize a common examination of neck veins, palpation of the point of maximal impulse, intensity of heart sounds, and intensity and location of murmurs); pulmonary disease (in which all practitioners utilize a common examination of diaphragmatic excursion, inspiratory effort, and clarity of breath sounds); and neurological disease (in which all practitioners utilize a common examination of cranial nerve function and global sensory and motor function). The pulse examination, although critical to good care, has well-defined limitations. Recognition of the limited sensitivity, specificity, and predictive value of the pulse examination has led to recognition that this examination must be supplemented by objective vascular testing (see Section 2.5) (34).

Key components of the vascular physical examination include the following:

• Measurement of blood pressure in both arms and notation of any interarm asymmetry.
• Palpation of the carotid pulses and notation of the carotid upstroke and amplitude and presence of bruits.
• Auscultation of the abdomen and flank for bruits.
• Palpation of the abdomen and notation of the presence of the aortic pulsation and its maximal diameter.
• Palpation of pulses at the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial sites. Performance of Allen’s test when knowledge of hand perfusion is needed.
• Auscultation of both femoral arteries for the presence of bruits.
• Pulse intensity should be assessed and should be recorded numerically as follows: 0, absent; 1, diminished; 2, normal; 3, bounding.
• The shoes and socks should be removed, the feet inspected, the color, temperature, and integrity of the skin and intertriginous areas evaluated, and the presence of ulcerations recorded.
• Additional findings suggestive of severe PAD, including distal hair loss, trophic skin changes, and hypertrophic nails, should be sought and recorded.

2. LOWER EXTREMITY PAD

2.1. Epidemiology

2.1.1. Risk Factors

The major cause of lower extremity PAD is atherosclerosis. Risk factors for atherosclerosis such as cigarette smoking, diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia increase the likelihood of developing lower extremity PAD, as they do for other manifestations of atherosclerosis (Figure 1).

Figure 1. Risk of developing lower extremity PAD. The range for each risk factor is estimated from epidemiological studies (see text). The relative risks take into consideration current smokers versus former smokers and nonsmokers, presence versus absence of diabetes and hypertension, and highest versus lowest quartile of homocysteine and C-reactive protein. The estimate for hypercholesterolemia is based on a 10% risk for each 10 mg per dL rise in total cholesterol. Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
Cigarette smoking is an exceptionally powerful etiologic risk factor for lower extremity PAD (35). It is 2 to 3 times more likely to cause lower extremity PAD than coronary artery disease (36). Large epidemiological studies have found that smoking increases the risk of lower extremity PAD by 2- to 6-fold and the risk of intermittent claudication by 3- to 10-fold (3,37-40). More than 80% of patients with lower extremity PAD are current or former smokers (38,40). The risk of lower extremity PAD increases in a powerful dose-dependent manner with the number of cigarettes smoked per day and the number of years smoked (36,41-43).

Diabetes mellitus increases the risk of lower extremity PAD by 2- to 4-fold (35,40,44-46) and is present in 12% to 20% of persons with lower extremity PAD (40,45). In the Framingham Heart Study, diabetes increased the risk of intermittent claudication by 3.5- and 8.6-fold in men and women, respectively (37). The risk of developing lower extremity PAD is proportional to the severity and duration of diabetes (46,47). The risk of developing CLI is also greater in diabetics than nondiabetics (48,49). Diabetic patients with lower extremity PAD are 7- to 15-fold more likely to undergo a major amputation than nondiabetics with lower extremity PAD (49-51).

Lipid abnormalities that are associated with lower extremity PAD include elevated total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia (3,43,45,52). The risk of developing lower extremity PAD increases by approximately 5% to 10% for each 10 mg per dL rise in total cholesterol (44,53,54). In epidemiological studies, total cholesterol levels are generally higher in patients with intermittent claudication than in those without lower extremity PAD (38,52,55). Similarly, levels of LDL are higher and HDL levels are lower in patients with lower extremity PAD than in age-matched controls (40,54,56-58). Elevated levels of triglycerides have been reported to be associated with lower extremity PAD in some studies but not in others (59-63). The relationship between hypertriglyceridemia and lower extremity PAD usually remains intact, albeit with some interstudy variability, when adjusted for the presence of other risk factors (3,35,52).

Hypertension is associated with lower extremity PAD, although the association is generally weaker than that with cerebrovascular and coronary artery disease (35,54,63,64). Hypertension increased the risk of developing lower extremity PAD in some studies but not in others (3,38,54,65). In the Framingham Heart Study, hypertension increased the risk of intermittent claudication 2.5- to 4-fold in men and women, respectively, and the risk was proportional to the severity of high blood pressure (37).

Elevated levels of homocysteine are associated with a 2- to 3-fold increased risk for developing atherosclerotic arterial disease (66,67). The European Concerted Action Project has estimated that fasting homocysteine concentrations greater than the 80th percentile (i.e., greater than 12.1 micromoles per liter) are associated with a 2-fold increased risk of atherosclerotic vascular disease, including PAD, coronary artery disease, and stroke, independent of traditional risk factors (68). A meta-analysis of studies relating homocysteine to atherosclerotic vascular disease found an odds ratio (OR) for coronary artery disease and stroke of approximately 1.5 for each 5 micromoles per liter increment in homocysteine level and a comparable association with lower extremity PAD (66). In one study, a 5 micromole per liter rise in total homocysteine increased the risk of lower extremity PAD by 44% (69). Approximately 30% to 40% of patients with lower extremity PAD have high levels of homocysteine (5). Elevated homocysteine levels are prevalent in both younger and elderly patients with lower extremity PAD (70,71). Approximately 25% of patients with intermittent claudication have plasma homocysteine levels exceeding the 95th percentile (72). Hyperhomocysteinemia also appears to increase the risk of progression of lower extremity PAD (5,73). The etiologic role of homocysteine remains unknown, because no positive homocysteine-lowering lower extremity PAD interventional trials have been reported.

Elevated levels of C-reactive protein, a serological marker of systemic inflammation, are associated with lower extremity PAD. Among previously healthy people participating in the Physicians’ Health Study, there was a 2.1-fold increased risk of developing lower extremity PAD in those men whose C-reactive protein concentrations were in the highest quartile (4). This study also noted that C-reactive protein levels were higher in individuals who subsequently developed lower extremity PAD and highest in those who ultimately required vascular surgery (4). Moreover, in this study population, levels of soluble intercellular adhesion molecule-1, a leukocyte adhesion molecule that is upregulated by inflammatory cytokines, were independently associated with the future development of lower extremity PAD (74).

### 2.1.2. Prevalence

Lower extremity PAD is a common syndrome that affects a large proportion of most adult populations worldwide (35,54). The prevalence of lower extremity PAD has been defined by a series of epidemiological investigations that have used either claudication as a symptomatic marker of lower extremity PAD or an abnormal ankle-to-brachial systolic blood pressure to define the population affected. In general, the prevalence of lower extremity PAD is dependent on the age of the cohort studied, the underlying atherosclerosis risk factor profile of the cohort, and the presence of other concomitant manifestations of atherosclerosis (e.g., clinical coronary or cerebrovascular disease or past organ transplantation) (35,54).

PAD can be present in subclinical forms that can be detected by use of sensitive vascular imaging techniques. Such techniques may reveal early manifestations of arterial disease before it is detected by either limb pressure measurements or clinical symptoms. When so defined, as, for example, by measurement of the intimal-medial thickness in the carotid or femoral artery, early forms of PAD are easily detected in populations at risk. The Atherosclerosis Risk In
Communities (ARIC) study surveyed 4 race and gender strata to demonstrate that mean carotid far-wall intimal-medial thickness was consistently greater in participants with prevalent clinical cardiovascular disease than in disease-free subjects. Similarly, the prevalence of cardiovascular disease was consistently greater in ARIC participants with progressively thicker intimal-medial thickness (75). These data document the substantially greater arterial wall thickness observed in middle-aged adults with prevalent cardiovascular disease.

As a symptomatic expression of lower extremity PAD, claudication defines a subset of the total population with the disease. The Framingham Heart Study initially described the high prevalence of lower extremity PAD by assessing the prevalence of claudication in a large cohort study of 2336 men and 2873 women between the ages of 28 and 62 years who were initially assessed at standardized examinations every 2 years since 1948 (76). The Rose claudication questionnaire was used to define the prevalence of intermittent claudication as a marker of lower extremity PAD. This study demonstrated that the annual incidence of lower extremity PAD increased with age and in response to the prevalence of atherosclerosis risk factors (76). The age-specific annual incidence of intermittent claudication for ages 30 to 44 years was 6 per 10,000 men and 3 per 10,000 women, and this incidence increased to 61 per 10,000 men and 54 per 10,000 women within the ages of 65 to 74 years. In this initial Framingham cohort, the investigators noted that intermittent claudication was twice as prevalent among men as among women (76). A risk profile of age, sex, serum cholesterol, hypertension, cigarette smoking, diabetes, and coronary artery disease was associated with an increased risk of developing claudication. Male sex, increasing age, and smoking conferred a 1.5-fold increased risk for developing intermittent claudication. Diabetes and stage 2 or greater hypertension were associated with more than a 2-fold increase in intermittent claudication, whereas clinical evidence of coronary artery disease almost tripled the risk (40).

Criqui and colleagues have evaluated the prevalence of PAD among a population of 613 men and women in southern California utilizing a battery of 4 noninvasive tests (the Rose questionnaire, pulse examination, ABI, and pulse-wave velocity) to assess the prevalence of lower extremity PAD (77) (Figure 2). Use of the Rose questionnaire severely underestimated the prevalence of lower extremity PAD, which demonstrates the insensitivity of this tool to assess true population rates for lower extremity PAD. Use of the history and physical examination alone also was associated with a low sensitivity for detecting lower extremity PAD (78). Lower extremity PAD detection increased 2 to 7 times over the detection rate of the Rose questionnaire when the ABI (ankle-brachial index) and pulse-wave velocity techniques were applied. On the other hand, an abnormal limb-pulse examination overestimated the prevalence by 2-fold. When the objective noninvasive ABI and pulse-wave velocity techniques were used, the prevalence of lower extremity PAD in this population was 2.5% among individuals 60 years and younger, 8.3% among those aged 60 to 69 years, and 18.8% among those 70 years and older (78).

The San Luis Valley Diabetes Study evaluated the prevalence of lower extremity PAD among diabetics in a Hispanic and a white population (79). The abnormal ankle/arm ratios used in this study were an ABI of 0.94 at rest, 0.73 after exercise, and 0.78 after reactive hyperemia. The prevalence of lower extremity PAD was 13.7% with this diagnostic criteria. Notably, a history of intermittent claudication or an absent}

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Prevalence of peripheral arterial disease (PAD) by age. Reprinted with permission from Criqui MH, Fronek A, Barrett-Conner E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;71:510-5 (77).
pulse examination were uncommon findings within this population (79).

The Edinburgh Artery Study in 1988 randomly selected 1592 individuals aged 55 to 74 years with intermittent claudication determined by the World Health Organization questionnaire, the ABI, and the hyperemia test. These participants were followed up prospectively for 5 years for subsequent cardiovascular events and death (80). The prevalence of intermittent claudication was 4.5%, and the incidence was 15.5 per 1000 person-years (80). In individuals who were symptomatic initially, 28.8% continued to have pain after 5 years, 8.2% underwent revascularization or amputation, and 1.4% developed ischemic ulcers. The prevalence of intermittent claudication in a series of epidemiological surveys is displayed in Figures 3 and 4.

Lower extremity PAD is also common in other populations with a high prevalence of atherosclerosis risk factors, including individuals in geriatric practices, long-term care facilities (81,82), and the transplant population (83,84). In these cohorts, lower extremity PAD alters quality of life and is associated with adverse clinical outcomes.

The relevance of these epidemiological data to current medical practice has been most recently assessed in both a regional lower extremity PAD detection program (85) and a

Figure 3. Prevalence of intermittent claudication in various studies. Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

Figure 4. Mean prevalence of intermittent claudication in large population studies. Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
national survey of lower extremity PAD in primary care practices, the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study (86). The PARTNERS study was a large cross-sectional survey designed to determine the prevalence of lower extremity PAD in American primary care practices. This study used the ABI technique in a targeted cohort of 6979 patients evaluated in 350 large-volume primary care practices in 25 American cities. Patients 70 years and older or aged 50 to 69 years with a history of cigarette smoking or diabetes were evaluated prospectively during the course of routine office practice. The diagnosis of lower extremity PAD was established by either a prior chart diagnosis or by demonstration of an ABI of 0.90 or less during the study screening. By this technique, lower extremity PAD was detected in a high fraction (29%) of the study population. Within this population, 13% of these patients had lower extremity PAD only, and 16% had both lower extremity PAD and another form of atherosclerotic cardiovascular disease (a clinical manifestation of coronary artery disease, cerebrovascular disease, or aortic aneurysmal disease). Although lower extremity PAD was prevalent in this targeted population, the diagnosis was new in 55% of those patients with PAD only and in 35% of patients who had both lower extremity PAD and cardiovascular disease. The prevalence of tobacco use (23% current, 37% former), hypertension (69%), hyperlipidemia (47%), and diabetes (38%) was elevated in the lower extremity PAD-only cohort. Comparable epidemiological surveys have now corroborated these patterns of lower extremity PAD in essentially every population studied (87-91). Thus, current epidemiological and community survey data demonstrate a high prevalence of lower extremity PAD in individuals in the United States, Europe, and Asia that increases with advancing age and with exposure to atherosclerosis risk factors.

2.2. Prognosis and Natural History

2.2.1. Coprevalence of Coronary Artery Disease and Carotid Disease

The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant coronary artery disease and cerebrovascular disease (35,92). These cardiovascular ischemic events are more frequent than ischemic limb events in any lower extremity PAD cohort (Figure 5) (93). There is approximately a 2- to 4-fold excess of coronary artery disease and

Figure 5. The natural history of atherosclerotic lower extremity peripheral arterial disease (PAD). Individuals with atherosclerotic lower extremity PAD may be: (a) asymptomatic (without identified ischemic leg symptoms, albeit with a functional impairment); (b) present with leg symptoms (classic claudication or atypical leg symptoms); or (c) present with critical limb ischemia. All individuals with PAD face a risk of progressive limb ischemic symptoms, as well as a high short-term cardiovascular ischemic event rate and increased mortality. These event rates are most clearly defined for individuals with claudication or critical limb ischemia (CLI), and less well defined for individuals with asymptomatic PAD. CV indicates cardiovascular; MI, myocardial infarction. Adapted with permission from Weitz JI, Byrne J, Clagett GP, et al. Circulation. 1996;94:3026-49 (93).
2.2.2. Risk of Cardiovascular Events

As a consequence of coexisting coronary and cerebrovascular disease, there is an increased risk of MI, stroke, and cardiovascular death in patients with lower extremity PAD. There is a 20% to 60% increased risk for MI and a 2- to 6-fold increased risk of death due to coronary heart disease events (38,103-107). The risk of stroke is increased by approximately 40%. In the ARIC study, men with lower extremity PAD were 4 to 5 times more likely to have a stroke or transient ischemic attack than those without lower extremity PAD, although in women, the association was not significant (108). In the Edinburgh Artery Study, lower extremity PAD severity correlated with the frequency and extent of significant carotid artery stenosis (100). The severity of lower extremity PAD correlates with the severity and extent of significant carotid artery stenosis (102). Conversely, approximately one third of men and one fourth of women with known coronary or cerebrovascular disease also have lower extremity PAD (35). Thus, physicians caring for patients with lower extremity PAD should be aware of the frequent coexistence of coronary and cerebrovascular disease. Specific recommendations for screening for coronary and cerebrovascular disease in the patient with lower extremity PAD are beyond the scope of this document.

2.2.3. Prognosis of the Limb

The prognosis of the limb is determined by the extent of arterial disease, the acuity of limb ischemia, and the feasibility and rapidity of restoring arterial circulation to the foot. For the patient with chronic arterial occlusive disease and continued progression of symptoms to CLI (e.g., development of new wounds, rest pain, or gangrene), the prognosis is very poor unless revascularization can be established. For patients with acute occlusive events (i.e., sudden embolic occlusion of an extremity with little underlying arterial disease), the long-term prognosis of the limb is related to the rapidity and completeness of revascularization before the onset of irreversible ischemic tissue or nerve damage (see Section 2.6.3.2).

Few studies of the natural history of PAD have been performed to objectively quantify disease progression. Claudication symptoms usually remain stable and do not worsen or improve at rapid rates (93). The temporal progression of symptoms across arterial beds in patients with known atherosclerotic disease has also been studied on a limited basis. A large series of patients with claudication have been followed up with respect to their subsequent clinical outcome in the study by Muluk et al., which has demonstrated that many patients may present with claudication in the absence of any coronary ischemic symptoms and that a history of angina and MI is not a useful predictor of death (118). Moreover, in that study, a history of claudication, by itself, was not an adequate predictor of major amputation risk after 10 years of follow-up. Additional studies in the same group of patients demonstrated that 2 clinical factors, reduced ABI and diabetes mellitus, were associated with the development of ischemic rest pain and ischemic ulceration. These studies suggested that other local pathophysiological factors (e.g., inflammatory factors and local plaque rupture) may be better linked to the adverse clinical course of lower extremity events experienced by some individuals with claudication. Delineation of these factors will require future longitudinal cohort studies.

2.3. Other Causes of Lower Extremity PAD

It is commonly assumed by both practitioners and patients alike that atherosclerosis is the sole cause of both stenotic and aneurysmal lower extremity PAD, because of the predominance of this particular etiology in the coronary circulation. However, as noted in the introduction to this guideline, PAD is caused by a diversity of etiologies beyond atherosclerosis. Thus, clinicians should be wary of assuming such an origin in the absence of consideration of a broad differential diagnosis. Aneurysms may be associated with atherosclerosis or they may be due to underlying hereditary (familial) or acquired (e.g., due to smoking or trauma) etiologies. Renal arterial disease may be due to atherosclerosis, FMD, or arteritides. Lower extremity PAD may be atherosclerotic, thromboembolic, inflammatory, or traumatic. It can be due to aneurysmal disease, trauma, adventitial cysts, entrapment
syndromes, or congenital abnormalities. Accurate diagnosis and identification of the specific cause are necessary if individual patients are to receive ideal pharmacological, endovascular, surgical, or rehabilitative interventions. This guideline has therefore been structured with an attempt to ensure that the diverse spectrum of causes are considered for each clinical manifestation of lower extremity PAD. Readers should note that such a differential diagnosis varies by anatomic site, patient demographic cohort, and clinical presentation.

2.4. Clinical Presentation

2.4.1. Asymptomatic

RECOMMENDATIONS

Class I

1. A history of walking impairment, claudication, ischemic rest pain, and/or nonhealing wounds is recommended as a required component of a standard ROS for adults 50 years and older who have atherosclerosis risk factors and for adults 70 years and older. (Level of Evidence: C)

2. Individuals with asymptomatic lower extremity PAD should be identified by examination and/or measurement of the ABI so that therapeutic interventions known to diminish their increased risk of MI, stroke, and death may be offered. (Level of Evidence: B)

3. Smoking cessation, lipid lowering, and diabetes and hypertension treatment according to current national treatment guidelines are recommended for individuals with asymptomatic lower extremity PAD. (Level of Evidence: C)

4. Antiplatelet therapy is indicated for individuals with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular ischemic events. (Level of Evidence: C)

Class IIa

1. An exercise ABI measurement can be useful to diagnose lower extremity PAD in individuals who are at risk for lower extremity PAD (Table 2) who have a normal ABI (0.91 to 1.30), are without classic claudication symptoms, and have no other clinical evidence of atherosclerosis. (Level of Evidence: C)

2. A toe-brachial index or pulse volume recording measurement can be useful to diagnose lower extremity PAD in individuals who are at risk for lower extremity PAD who have an ABI greater than 1.30 and no other clinical evidence of atherosclerosis. (Level of Evidence: C)

Class IIb

Angiotensin-converting enzyme (ACE) inhibition may be considered for individuals with asymptomatic lower extremity PAD for cardiovascular risk reduction. (Level of Evidence: C)

The majority of individuals with lower extremity PAD do not experience recognizable limb ischemic symptoms, and by this definition, they are “asymptomatic.” However, the classification of a patient as asymptomatic has traditionally implied that the individual has neither (a) limb ischemic symptoms nor (b) other “symptomatic” consequences of systemic atherosclerosis. For the purposes of this guideline, asymptomatic lower extremity PAD implies the absence of classic leg claudication symptoms. As noted below, this definition is under revision because data demonstrate that lower extremity PAD, even without classic claudication, is often associated with leg dysfunction, diminished functional status, and increased cardiovascular ischemic risk. In other words, individuals with classic asymptomatic lower extremity PAD have measurable limb dysfunction and adverse cardiovascular outcomes. Individuals with asymptomatic lower extremity PAD may also have other causes of leg pain (e.g., lumbar disk disease, spinal stenosis, sciatica, or radiculopathy), muscle strain, neuropathy, or compartment syndrome.

Prevalence of Asymptomatic Lower Extremity PAD by Traditional Epidemiological Classification

Intermittent claudication is the most common symptom in patients with lower extremity PAD. Patient interviews, however, can be both an insensitive and poorly reproducible tool to define lower extremity PAD symptoms. In epidemiological surveys, population-based classification of lower extremity PAD symptom status is performed by use of standardized questionnaires. These have traditionally included the World Health Organization Rose questionnaire (119), the Edinburgh Modification of the Rose questionnaire (120,121), and others. Data from such surveys in both the United States and Europe have demonstrated that asymptomatic lower extremity PAD is 2 to 5 times more prevalent than symptomatic lower extremity PAD.

Criqui et al. evaluated the prevalence of lower extremity PAD and leg ischemic symptoms in an older population of 613 men and women in southern California, with an average age of 66 years, using a battery of 4 noninvasive tests (segmental blood pressure, Doppler-derived flow velocity, postocclusive reactive hyperemia, and pulse-reappearance halftime) (77). In this survey, 11.7% of the population had large-vessel lower extremity PAD on noninvasive testing, in which “large-vessel” lower extremity PAD was equivalent to the common ABI definition of lower extremity PAD. The prevalence of intermittent claudication in this population was 2.2% in men and 1.7% in women. Abnormal femoral or posterior tibial pulses were present in 20.3% of men and 22.1% of women. Thus, the fraction of individuals with intermittent claudication dramatically underestimated the true prevalence of lower extremity PAD. Moreover, use of the peripheral pulse examination alone dramatically overestimated the true prevalence of lower extremity PAD. Overall, symptomatic lower extremity PAD was present in approximately one fifth of the population with objective evidence of lower extremity PAD. This study demonstrated that a high fraction of indi-
individuals with lower extremity PAD does not have claudication, as classically defined.

The San Luis Valley Diabetes Study evaluated the prevalence of lower extremity PAD among diabetics in a Hispanic and a non-Hispanic white population (79). In that study, the diagnosis of lower extremity PAD was established by an ABI of 0.94 at rest, 0.73 after exercise, and 0.78 after reactive hyperemia. The prevalence of lower extremity PAD was 13.7% with these diagnostic criteria. In this population, a history of intermittent claudication was an uncommon finding.

The predominance of asymptomatic patients in lower extremity PAD populations was also demonstrated in the Rotterdam Study (40). The age- and sex-specific prevalence of lower extremity PAD and intermittent claudication was measured in a population-based study of 7715 elderly subjects (40% men, 60% women) aged 55 years and older with the ABI and the World Health Organization/Rose questionnaire, respectively. Lower extremity PAD was considered present when the ABI was less than 0.90 in either leg. The prevalence of lower extremity PAD was 19.1% (95% confidence interval [CI] 18.1% to 20.0%): 16.9% in men and 20.5% in women. Symptoms of intermittent claudication were reported by 1.6% (95% CI 1.3% to 1.9%) of the study population (2.2% in men, 1.2% in women). Of those with lower extremity PAD, 6.3% reported symptoms of intermittent claudication (8.7% in men, 4.9% in women). Conversely, the presence of claudication symptoms was also an imperfect marker (i.e., had poor specificity) for lower extremity PAD, because an ABI less than 0.90 was found in only 69% of those with claudication symptoms. This study confirmed that the vast majority of lower extremity PAD patients have no classic claudication symptoms.

The Edinburgh Artery Study evaluated a cohort of 1592 individuals aged 55 to 74 years for the presence of intermittent claudication and lower extremity PAD as determined by the World Health Organization questionnaire, the ABI, and assessments of reactive hyperemia. The prevalence of intermittent claudication was 4.5%, and the incidence was 15.5 per 1000 person-years (120,121). In individuals who were symptomatic initially, 28.8% continued to have pain after 5 years, 8.2% underwent revascularization or amputation, and 1.4% developed ischemic ulcers (121). Of those individuals who were asymptomatic, 8.0% had advanced PAD with significant blood flow impairment (120).

**Asymptomatic Lower Extremity PAD, Limb Symptoms, and Limb Function**

These data on the prevalence of asymptomatic lower extremity PAD traditionally relied on survey instruments that classified all patients into 2 major categories (asymptomatic and claudication). Yet, many individuals with lower extremity PAD have leg symptoms that are atypical (e.g., the discomfort does not entirely resolve promptly with rest) owing to comorbid conditions. In recognition of this clinical reality, more recent lower extremity PAD symptom investigations have used more sensitive and specific questionnaires that characterize symptoms within each limb and permit recording of atypical leg pain. One such instrument is the Walking Impairment Questionnaire (122). The San Diego claudication questionnaire is a standardized questionnaire based on the Rose claudication questionnaire that is usually administered by certified health interviewers. This questionnaire allows for lateralization of leg symptoms (right, left, or both) and categorizes leg symptoms as either classic claudication (meeting all Rose criteria below), atypical leg pain that is exertional (but does not meet all Rose criteria), or no leg pain. The use of this tool in a community survey of nearly 7000 elderly, high-risk individuals in primary care practices in the United States in the PARTNERS survey (86) demonstrated a lower extremity PAD prevalence of 29%; in addition, leg symptoms were evaluated with the San Diego questionnaire. Of those individuals in whom the only manifestation of atherosclerosis was lower extremity PAD (there was no concomitant clinical evidence of other cardiovascular disease), individuals were segregated into 2 cohorts based on whether their personal physicians had established the lower extremity PAD diagnosis before the performance of the ABI measure during office-based lower extremity PAD screening. Of those individuals with previously diagnosed lower extremity PAD, 26% were asymptomatic, 62% had atypical leg pain, and only 13% had typical claudication. Of those individuals with newly diagnosed lower extremity PAD, 48% were asymptomatic, 46% had atypical leg pain, and only 6% had typical claudication. In summary, the ratio of leg symptoms in a population screened for lower extremity PAD depends on the population surveyed, the symptom assessment instrument used, and the inclusion of individuals with previously established lower extremity PAD versus previously undiagnosed individuals. For most individuals with lower extremity PAD in office practices, efforts to detect early lower extremity PAD are likely to identify individuals at high cardiovascular ischemic risk, who do not have classic claudication, and in whom atypical leg symptoms are common.

With these more sensitive questionnaires and other tools that assess leg function, it is now clear that individuals with asymptomatic lower extremity PAD have a worse quality of life and limb function than an age-matched cohort. McDermott et al. evaluated the ABI and measures of upper and lower extremity functioning in 933 women in the Women’s Health and Aging Study (123). Within this cohort, 328 subjects (35%) had lower extremity PAD as defined by an ABI less than 0.90. Asymptomatic lower extremity PAD was common, with 63% of these individuals reporting no exertional leg pain. However, even among these individuals with asymptomatic lower extremity PAD, worsening of lower extremity function was documented by a series of objective measurements. Thus, individuals with a low ABI but no claudication were characterized by a slower walking velocity, poorer standing balance score, slower time to arise from a seated position, and fewer blocks walked per week, even after adjustments were made for age, sex, race, cigarette smoking, and other comorbidities. Additional data have been...
In these guidelines, all patients with lower extremity PAD, regardless of symptom status, are placed in a high-risk category. Based on data, current U.S. national hypertension and lipid treatment guidelines may not be adequate for those at high risk. On the basis of available interventional data, it is imperative that individuals with newly detected lower extremity PAD be provided with accurate information regarding cardiovascular and limb ischemic risk and be provided with access to individualized treatments to diminish such risk.

**Asymptomatic Lower Extremity PAD and Cardiovascular Outcomes**

Individuals with asymptomatic lower extremity PAD do not enjoy a benign prognosis, because most have systemic atherosclerotic disease. Individuals with asymptomatic lower extremity PAD are characterized by a risk factor profile comparable to that of those with symptomatic lower extremity PAD (64,126). For example, the Limburg PAOD Study evaluated a cross section of 3650 subjects aged 40 to 78 years. In that survey, patients with asymptomatic lower extremity PAD had a risk-factor and comorbidity profile comparable to that of symptomatic patients (64). Overall, the high prevalence of diabetes, a history of past or current smoking, hypertension, and/or hypercholesterolemia placed such individuals at a markedly increased risk of atherosclerotic ischemic events, including MI and stroke (64,127), and higher degrees of internal carotid artery stenosis (128,129). On the basis of these data, current U.S. national hypertension and lipid treatment guidelines include all patients with lower extremity PAD, regardless of symptom status, as a high-risk category. In these guidelines, all patients with lower extremity PAD should achieve risk reduction and specific treatment targets comparable to individuals with established coronary artery disease (129a,294).

**Clinical Implications: Asymptomatic Lower Extremity PAD in Office-Based and Community-Based Detection Programs**

In addition to individuals who have overt clinical lower extremity PAD who present with claudication or more severe limb ischemic symptoms, a larger cohort of individuals are at risk for lower extremity PAD on the basis of their age and risk factors. Individuals who are at risk include those 70 years and older, those 50 years and older who have a history of any atherosclerosis risk factor (smoking, diabetes, hypertension, or elevated cholesterol levels), and individuals with diabetes who are 49 years old or younger who have such atherosclerosis risk factors. Establishment of the lower extremity PAD diagnosis in these at-risk individuals has the potential to alter the intensity of treatment goals.

The ABI allows for lower extremity PAD detection at all stages of the disease process; however, the ABI does not always provide reliable data to detect lower extremity PAD, as is more extensively reviewed in Section 2.5. For individuals with noncompressible ankle arteries and ABI values greater than 1.30, the toe-brachial index, pulse volume recordings, and Doppler waveform measurements can provide diagnostic information to document the presence of lower extremity PAD. For individuals at risk of lower extremity PAD with borderline or normal ABI values (0.91 to 1.30), an exercise ABI test can also unmask the lower extremity PAD diagnosis. Although these tests have been demonstrated to be useful tools to accomplish lower extremity PAD detection, the impact of early PAD detection on either limb or cardiovascular ischemic event outcomes or on survival has not yet been evaluated in prospective trials. It may not be possible to ethically design or complete these trials, because the benefits of systemic atherosclerosis risk reduction interventions (whether biobehavioral or pharmacological) have been established in other atherosclerotic syndromes. In the absence of lower extremity PAD-specific interventional data, it is imperative that individuals with newly detected lower extremity PAD be provided with accurate information regarding cardiovascular and limb ischemic risk and be provided with access to individualized treatments to diminish such risk.

The initial responsibility for the detection of lower extremity PAD should be with the primary care provider, because such providers are best positioned to determine an at-risk population and to initiate educational, lifestyle, and cardiovascular risk reduction therapies. Public screening programs may also play a role in lower extremity PAD disease detection, especially if programs are directly linked to effective educational and treatment interventions. Programs of lower extremity PAD detection, whether applied in office practice or in community-based detection programs, should ideally utilize the epidemiological database to apply the detection
Office-Based Clinical History

The detection of lower extremity PAD requires the deliberate collection of a vascular (lower extremity PAD) history and review of systems (see Section 1.3, Vascular History and Physical Examination). However, primary care clinicians should not assume that patients with lower extremity PAD and claudication will spontaneously offer a classic exertional history of leg pain, just as patients with angina only rarely offer a classic history of central chest pressure, accompanied by a positive Levine sign (“a clenched fist placed over the sternum to describe the location and squeezing quality of the pain”). As well, clinicians should be aware that descriptions of “claudication” may be atypical, including not only predominant exertional muscle symptoms but also symptoms from concomitant diseases that can mask classic claudication. “Typical” lower extremity ischemic symptoms may have such an indolent onset that patients attribute their exercise intolerance to the deconditioning of aging and may not bring this history as a chief complaint to their primary provider. The exercise limitation may be noted first by a spouse or other close family member rather than by the patient. In this context, patients with lower extremity PAD may be incorrectly assumed to be asymptomatic. Thus, a history of walking impairment or of other leg ischemic symptoms should usually be included in a standard ROS of patients at risk for lower extremity PAD.

Use of Other Diagnostic Tools in Asymptomatic Lower Extremity PAD Patients

As noted above, individuals without clinically evident lower extremity PAD symptoms or associated cardiovascular ischemic symptoms have not been shown to benefit from more aggressive and costly efforts to localize lower extremity PAD anatomy (e.g., by use of duplex ultrasound or other tools of the noninvasive vascular laboratory or by MRA or other imaging techniques). In addition, there is currently no evidence that patients with asymptomatic lower extremity PAD benefit from the performance of other cardiovascular risk-assessment tools (beyond establishment of the lower extremity PAD diagnosis itself; e.g., by use of pharmacological stress testing, coronary calcium scores, carotid intimal-medial thickness studies, or coronary angiography). In the absence of data suggesting that additional testing can further stratify lower extremity PAD patients into a higher-risk group or that these data offer treatment options beyond standard risk reduction interventions, such studies are not recommended.

2.4.2. Claudication

RECOMMENDATIONS

Class I

1. Patients with symptoms of intermittent claudication should undergo a vascular physical examination, including measurement of the ABI. (Level of Evidence: B)

2. In patients with symptoms of intermittent claudication, the ABI should be measured after exercise if the resting index is normal. (Level of Evidence: B)

3. Patients with intermittent claudication should have significant functional impairment with a reasonable likelihood of symptomatic improvement and absence of other disease that would comparably limit exercise even if the claudication was improved (e.g., angina, heart failure, chronic respiratory disease, or orthopedic limitations) before undergoing an evaluation for revascularization. (Level of Evidence: C)

4. Individuals with intermittent claudication who are offered the option of endovascular or surgical therapies should: (a) be provided information regarding supervised claudication exercise therapy and pharmacotherapy; (b) receive comprehensive risk factor modification and antiplatelet therapy; (c) have a significant disability, either being unable to perform normal work or having serious impairment of other activities important to the patient; and (d) have lower extremity PAD lesion anatomy such that the revascularization procedure would have low risk and a high probability of initial and long-term success. (Level of Evidence: C)

Class III

Arterial imaging is not indicated for patients with a normal postexercise ABI. This does not apply if other atherosclerotic causes (e.g., entrapment syndromes or isolated internal iliac artery occlusive disease) are suspected. (Level of Evidence: C)

Claudication is defined as fatigue, discomfort, or pain that occurs in specific limb muscle groups during effort due to exercise-induced ischemia. Individuals with claudication have sufficient blood flow so that limb ischemic symptoms are absent at rest. With increased local muscular demand for metabolic support during exercise, blood flow in individuals with lower extremity PAD and claudication is inadequate to meet this demand, and limb muscular fatigue and/or pain results. Lower extremity ischemia is usually due to atherosclerotic lower extremity PAD and occasionally other causes, including emboli, radiation arteritis, Buerger’s disease (thromboangiitis obliterans), other arteritides, coarctation, popliteal entrapment, cystic adventitial disease, FMD, and trauma. Vascular claudication due to lower extremity PAD is produced by exercise and is relieved with rest and is therefore traditionally referred to as “intermittent claudication,” or simply “claudication.” The pathophysiology of claudication...
is considerably more complex than can be accounted for by the supply–demand mismatch that results from stenotic disease itself (132). However, diagnosis and treatment can be guided by an understanding of the lower extremity PAD arterial anatomy.

The anatomic site of the arterial stenosis is often associated with specific leg symptoms. Occlusive disease in the iliac arteries may produce hip, buttock, and thigh pain, as well as calf pain. Occlusive disease in the femoral and popliteal arteries is usually associated with calf pain. Occlusive disease in the tibial arteries may produce calf pain or, more rarely, foot pain and numbness. The pathophysiology of claudication is complex; it is not merely a response to limitations in blood flow but also includes a wide range of skeletal muscle (e.g., metabolic), neurological, and inflammatory effects (132). Critical limb ischemia may cause rest pain, ulcerations, or gangrene, as discussed in Section 2.4.3. The severity of the ischemia can be classified according to either the Fontaine or Rutherford categories (Table 3). These categories are most commonly used in research settings but may also have value in improving the clarity of communication of lower extremity PAD severity within office practices and in referral from primary practitioner to vascular specialist (1).

Vascular claudication must be distinguished from other illnesses that cause exertional leg pain, which have been called “pseudoclaudication.” These other causes include severe venous obstructive disease, chronic compartment syndrome, lumbar disease and spinal stenosis, osteoarthritis, and inflammatory muscle diseases. Distinguishing features of these various causes of leg pain are summarized in Table 4 (1). The clinical history should also include risk factors for atherosclerotic disease, such as smoking, diabetes, hypertension, hyperlipidemia, and a family history of atherosclerotic disease. In addition to the historical factors that distinguish intermittent claudication from other causes of leg pain, the physical examination should document the presence of diminished pulses in the femoral, popliteal, posterior tibial, and dorsalis pedis arteries. Signs of systemic atherosclerosis (86), as a clue to a vascular cause of claudication, include femoral bruits, which may be present owing to turbulence from focal stenoses. Bruits may also be present in the carotid arteries and renal arteries as a sign of systemic atherosclerosis. Claudication is usually also associated with reduced ankle blood pressures in the affected leg, which causes a diminished ABI. Some patients may have normal ankle pressures at rest with abnormal low ankle systolic pressures (and thus low ABI values) detectable only after exercise (see Section 2.5.4). Individuals with long-standing diabetes, patients with chronic renal failure, and the very elderly have densely calcified vessels that are poorly compressible and may have spuriously high ankle pressures and ABI values.

The ABI should be measured in all patients with claudication. For individuals who present with classic claudication and in whom the ABI is borderline or normal (0.91 to 1.30) or supranormal (greater than 1.30), alternative diagnostic strategies should be used, including the toe-brachial index, segmental pressure examination, or duplex ultrasound, to confirm the lower extremity PAD diagnosis (see Section 2.5). This strategy is necessary to distinguish claudication from pseudoclaudication, provides an estimate of the overall severity of occlusive disease in the extremity, and serves as a baseline to assess temporal changes due to disease progression or intervention. The ABI correlates only weakly with treadmill-based walking ability for any individual patient. For example, some patients with a low ABI report minimal walking impairment, whereas some with a higher ABI report marked walking impairment (133). This is due at least in part to the wide range of comorbidities that can coexist with intermittent claudication in patients who have PAD (124). Systemic atherosclerotic disease, medical comorbidities, and back, hip, and knee symptoms may have a greater impact on an individual’s quality of life than claudication, such that lower extremity revascularization may not significantly improve quality of life (134). Because the natural history of claudication is relatively benign (from the limb perspective), with few patients progressing to CLI or amputation (118,135), decisions regarding revascularization of individuals with claudication should be based on improving quality of life. Patients with a low ABI, a significant walking impairment, and no or mild comorbidities would be expected to benefit the most from any claudication intervention, including exercise, pharmacotherapy, or revascularization (133).

Table 3. Classification of Peripheral Arterial Disease: Fontaine’s Stages and Rutherford’s Categories

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fontaine</th>
<th>Rutherford Category</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>IIA</td>
<td>Mild claudication</td>
<td>1</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>IIB</td>
<td>Moderate-severe claudication</td>
<td>2</td>
<td>Moderate claudication</td>
</tr>
<tr>
<td>III</td>
<td>Ischemic rest pain</td>
<td>3</td>
<td>Severe claudication</td>
</tr>
<tr>
<td>IV</td>
<td>Ulceration or gangrene</td>
<td>4</td>
<td>Ischemic rest pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>Minor tissue loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>Ulceration or gangrene</td>
</tr>
</tbody>
</table>

Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Location of Pain or Discomfort</th>
<th>Characteristic Discomfort</th>
<th>Onset Relative to Exercise</th>
<th>Effect of Rest</th>
<th>Effect of Body Position</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent claudication</td>
<td>Buttock, thigh, or calf muscles and rarely the foot</td>
<td>Cramping, aching, fatigue, weakness, or frank pain</td>
<td>After same degree of exercise</td>
<td>Quickly relieved</td>
<td>None</td>
<td>Reproducible</td>
</tr>
<tr>
<td>Nerve root compression (e.g., herniated disc)</td>
<td>Radiates down leg, usually posteriorly</td>
<td>Sharp lancinating pain</td>
<td>Soon, if not immediately after onset</td>
<td>Not quickly relieved (also often present at rest)</td>
<td>Relief may be aided by adjusting back position</td>
<td>History of back problems</td>
</tr>
<tr>
<td>Spinal stenosis</td>
<td>Hip, thigh, buttocks (follows dermatome)</td>
<td>Motor weakness more prominent than pain</td>
<td>After walking or standing for same length of time</td>
<td>Relieved by stopping only if position changed</td>
<td>Relief by lumbar spine flexion (sitting or stooping forward)</td>
<td>Frequent history of back problems, provoked by intra-abdominal pressure</td>
</tr>
<tr>
<td>Arthritic, inflammatory processes</td>
<td>Foot, arch</td>
<td>Aching pain</td>
<td>After variable degree of exercise</td>
<td>Not quickly relieved (and may be present at rest)</td>
<td>May be relieved by not bearing weight</td>
<td>Variable, may relate to activity level</td>
</tr>
<tr>
<td>Hip arthritis</td>
<td>Hip, thigh, buttocks</td>
<td>Aching discomfort, usually localized to hip and gluteal region</td>
<td>After variable degree of exercise</td>
<td>Not quickly relieved (and may be present at rest)</td>
<td>More comfortable sitting, weight taken off legs</td>
<td>Variable, may relate to activity level, weather changes</td>
</tr>
<tr>
<td>Symptomatic Baker's cyst</td>
<td>Behind knee, down calf</td>
<td>Swelling, soreness, tenderness</td>
<td>With exercise</td>
<td>Present at rest</td>
<td>None</td>
<td>Not intermittent</td>
</tr>
<tr>
<td>Venous claudication</td>
<td>Entire leg, but usually worse in thigh and groin</td>
<td>Tight, bursting pain</td>
<td>After walking</td>
<td>Subsides slowly</td>
<td>Relief speeded by elevation</td>
<td>History of iliofemoral deep vein thrombosis, signs of venous congestion, edema</td>
</tr>
<tr>
<td>Chronic compartment syndrome</td>
<td>Calf muscles</td>
<td>Tight, bursting pain</td>
<td>After much exercise (e.g., jogging)</td>
<td>Subsides very slowly</td>
<td>Relief speeded by elevation</td>
<td>Typically heavy muscled athletes</td>
</tr>
</tbody>
</table>

Adapted from J Vasc Surg. 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
2.4.3. Critical Limb Ischemia

RECOMMENDATIONS

Class I

1. Patients with CLI should undergo expedited evaluation and treatment of factors that are known to increase the risk of amputation (see text). (Level of Evidence: C)

2. Patients with CLI in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk. (Level of Evidence: B)

3. Patients with a prior history of CLI or who have undergone successful treatment for CLI should be evaluated at least twice annually by a vascular specialist owing to the relatively high incidence of recurrence. (Level of Evidence: C)

4. Patients at risk of CLI (ABI less than 0.4 in a nondiabetic individual, or any diabetic individual with known lower extremity PAD) should undergo regular inspection of the feet to detect objective signs of CLI. (Level of Evidence: B)

5. The feet should be examined directly, with shoes and socks removed, at regular intervals after successful treatment of CLI. (Level of Evidence: C)

6. Patients with CLI and features to suggest atheroembolization should be evaluated for aneurysmal disease (e.g., abdominal aortic, popliteal, or common femoral aneurysms). (Level of Evidence: B)

7. Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection. (Level of Evidence: B)

8. Patients with CLI and skin breakdown should be referred to healthcare providers with specialized expertise in wound care. (Level of Evidence: B)

9. Patients at risk for CLI (those with diabetes, neuropathy, chronic renal failure, or infection) who develop acute limb symptoms represent potential vascular emergencies and should be assessed immediately and treated by a specialist competent in treating vascular disease. (Level of Evidence: C)

10. Patients at risk for or who have been treated for CLI should receive verbal and written instructions regarding self-surveillance for potential recurrence. (Level of Evidence: C)

Critical limb ischemia is defined as limb pain that occurs at rest or impeding limb loss that is caused by severe compromise of blood flow to the affected extremity. The term “critical limb ischemia” should be used for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity and is to be distinguished from acute limb ischemia (1). Unlike individuals with claudication, patients with CLI have resting perfusion that is inadequate to sustain viability in the distal tissue bed. Although it may be challenging at times to ascertain the limb prognosis in patients presenting with lower extremity ischemic rest pain, ulceration, or gangrene, CLI is defined de facto by most vascular clinicians as those patients in whom the untreated natural history would lead to major limb amputation within 6 months. Critical limb ischemia is usually caused by obstructive atherosclerotic arterial disease; however, it can also be caused by atheroembolic or thromboembolic disease, vasculitis, in situ thrombosis related to hypercoagulable states, thromboangiitis obliterans, cystic adventitial disease, popliteal entrapment, or trauma. Factors that can contribute to the development or exacerbation of CLI include syndromes that are known to reduce blood flow to the microvascular bed, such as diabetes, severe low cardiac output states, and, rarely, vasospastic diseases. Other conditions that accelerate or compound CLI include those in which demand for blood and nutrient supply is increased markedly, such as infection, skin breakdown, or traumatic injury.

Atherosclerotic arterial occlusive disease that precipitates CLI is most often diffuse or multisegmental, involving more than 1 arterial anatomic “level.” Frequently, because of the systemic nature of the atherosclerotic process and a predilection for symmetrical disease, the contralateral limb may also be affected by ischemic symptoms and may also demonstrate objective signs of ischemia on examination.

Patients with CLI present with a spectrum of clinical manifestations, depending on the degree of ischemia and the time course of its development. The Rutherford clinical categories (described previously) are used to classify the degree of ischemia and salvageability of the limb; CLI is also a component of the Fontaine clinical classification system (Table 3).

Critical limb ischemia is associated with a very high intermediate-term morbidity and mortality. Patients with lower extremity PAD have a 3 to 5 times overall greater risk of cardiovascular mortality than those without this disease. Those with more advanced lower extremity PAD, as manifested by CLI, have even greater risk of experiencing cardiovascular ischemic events (86,103,106,136,137). Thus, care strategies for individuals with CLI must recognize the cardiovascular ischemic burden. Ideal care strategies for individuals with CLI will therefore include recognition of the possibility of severe coronary artery disease, cerebral vascular disease, or aortic aneurysmal disease and include the impact of these illnesses on patient outcomes with or without specific CLI interventions. In addition, such long-term integrated care plans will offer risk factor modification for secondary prevention of cardiovascular ischemic events, to maximize the possibility of achieving an improved long-term morbidity and mortality (113,136,138,139).

Clinical Presentation

 Patients with CLI usually present with limb pain at rest, with or without trophic skin changes or tissue loss. The discomfort is often worse when the patient is supine (e.g., in bed) and may lessen when the limb is maintained in the dependent position. Typically, narcotic medications are required for analgesia; the pain commonly may disturb sleep and render the patient severely disabled, often unable to walk. The quality of life for patients with severe CLI can be worse than that of patients with terminal cancer (1,140,141). Some individu-
als with diabetes and CLI may present with severe CLI and tissue loss but no pain because of concomitant neuropathy. Critical limb ischemia may develop in a small subset of individuals who are already being closely monitored within a medical practice for lower extremity PAD and claudication. However, severe limb ischemic symptoms may also be the initial presentation of lower extremity PAD, with rest pain, ulceration, or even frank gangrene serving as the first manifestation of lower extremity arterial insufficiency. This acute onset of symptoms may suggest thromboembolic disease, sudden multisegmental in situ thrombosis, thromboangiitis obliterans, or an inflammatory arteritis. The diagnosis of CLI may be obscured by associated neuropathic conditions. Individuals with baseline diabetic neuropathy may have impaired or absent sensation in the distal limb arterial territories most at risk for ischemia. Furthermore, susceptibility to infection and the presence of microvascular disease in individuals with diabetes makes it more likely that ischemia in these patients will progress rapidly. Finally, the ischemic process itself can be primarily responsible for causing neuropathy: once gangrene is present, the patient’s sensory nerves may be damaged, and the patient may no longer feel the pain associated with ulceration. Tissue damage may thereby progress undetected or ignored. Those factors that are known to increase the risk of limb loss in patients with CLI are delineated in Table 5.

**History**

It is important for clinicians who evaluate patients with CLI to distinguish between ischemia that is acute versus chronic, because the diagnostic and therapeutic approaches and prognoses differ significantly. Acute limb ischemia (described in Section 2.4.4) requires urgent evaluation and intervention, whereas CLI usually does not. However, for individuals with CLI, it remains fundamentally important for the clinician to determine the time course of development of the ischemia. If the clinical history and physical examination suggest relatively rapid progression, then early or “semiurgent” revascularization may be required to prevent further deterioration and irreversible tissue loss. In addition to careful assessment of the time course of the ischemic syndrome, a vascular history should be obtained. This should include evaluation for arterial disease in other territories, assessment of global risk factors for atherosclerosis (described in Section 2.1.1), and clarification of any specific precipitating factors or events (e.g., trauma, infection, surgical manipulation, or removal of a toenail) that may have caused initial skin ulceration. The objectives for the diagnostic evaluation of patients with CLI are summarized in Table 6. Specific investigations that are helpful in evaluating patients with CLI are summarized in Table 7.

**Physical Examination**

Evaluation of patients for CLI requires systematic assessment of pulses and tissue perfusion to identify the level of obstructive lesions and potential involvement of other threatened extremities. Signs of chronic ischemia, including dependent rubor, early pallor on elevation of the extremity, and reduced capillary refill, should be confirmed. Peripheral manifestations of atheroemboli, such as livido reticularis, should be sought, as should their potential sources (e.g., AAA). Distinctions should be made between ulcers that are arterial and those that are venous or neurotrophic (Tables 8, 9, and 10). In the absence of neuropathy, arterial ulcers are usually exquisitely painful and tender to palpation. Motor and sensory function should also be assessed in the lower extremities. Patients with open ischemic ulcers involving the extremities often have associated local infection or cellulitis.

### Table 5. Factors That Increase Risk of Limb Loss in Patients With Critical Limb Ischemia

<table>
<thead>
<tr>
<th>Factors that reduce blood flow to the microvascular bed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Severe renal failure</td>
</tr>
<tr>
<td>Severely decreased cardiac output (severe heart failure or shock)</td>
</tr>
<tr>
<td>Vasospastic diseases or concomitant conditions (e.g., Raynaud’s phenomenon, prolonged cold exposure)</td>
</tr>
<tr>
<td>Smoking and tobacco use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors that increase demand for blood flow to the microvascular bed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection (e.g., cellulitis, osteomyelitis)</td>
</tr>
<tr>
<td>Skin breakdown or traumatic injury</td>
</tr>
</tbody>
</table>

### Table 6. Objectives for Diagnostic Evaluation of Patients With Critical Limb Ischemia

The diagnostic evaluation of patients with critical limb ischemia should be directed toward the following objectives:

- Objective confirmation of the diagnosis
- Localization of the responsible lesion(s) and a gauge of relative severity
- Assessment of the hemodynamic requirements for successful revascularization (vis-a-vis proximal vs. combined revascularization of multilevel disease)
- Assessment of individual patient endovascular or operative risk

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
In the diabetic population or in immunocompromised individuals, these infections tend to be polymicrobial and require systemic antibiotic therapy (1). Individuals who have had prior symptoms of CLI remain at future risk of development of recurrent symptoms or signs of CLI. Thus, regular surveillance during subsequent physical examinations should be performed, with thorough inspection of the feet, including the heels, toes, and interdigital spaces, to evaluate the patient for early signs of skin breakdown or ulceration.

Office Testing Strategies

The evaluation of patients presenting with CLI should include a complete blood count, chemistries (including fasting blood glucose and renal function tests), electrocardiogram, and ABI. In the absence of noncompressible vessels, measurement of an absolute systolic blood pressure 50 mm Hg or lower at the ankle and 30 mm Hg at the toe will often imply that amputation may be required in the absence of successful revascularization (1,140). Individuals with CLI who present with clinical features to suggest atheroembolization should be evaluated for more proximal aneurysmal disease (e.g., abdominal aortic, popliteal, or common femoral aneurysms). Atheroembolism is suggested by onset of signs and symptoms of CLI after recent endovascular catheter manipulation, the onset of associated systemic fatigue or muscle discomfort, symmetrical bilateral limb symptoms, livido reticularis, or rising creatinine values.

General Approach to Management of CLI in Office Practice

Treatment of CLI is dependent on increasing blood flow to the affected extremity to relieve pain, heal ischemic ulcerations, and avoid limb loss. Individuals with minimal or no skin breakdown or in whom comorbid conditions prevent consideration of revascularization can occasionally be treated by medical therapies in the absence of revascularization. Individual therapies are much more likely to be successful when CLI is detected promptly and tissue necrosis is minimal. To accomplish this, patients who are at risk for or have been treated for CLI should be informed that symptoms of CLI should be brought to medical attention promptly. Medical care strategies have included the use of antiplatelet agents,

Table 7. Investigations for Evaluating Patients With Critical Limb Ischemia (CLI)

To achieve the objectives listed in Table 6 above, the following investigations should be used in patients with CLI:

- Clinical history and examination, including the coronary and cerebral circulation
- Hematologic and biochemical tests: complete blood count, platelet count, fasting blood glucose, hemoglobin A1c, creatinine, fasting lipid profile, and urinalysis (for glycosuria and proteinuria)
- Resting electrocardiogram
- Ankle or toe pressure measurement or other objective measures for the severity of ischemia
- Imaging of the lower limb arteries in patients considered for endovascular or surgical intervention
- Duplex scan of the carotid arteries should be considered in selected patients at high risk (defined as individuals with cerebrovascular ischemic symptoms or in whom the risk of carotid revascularization is less than the short-term risk of stroke)

A more detailed coronary assessment may be performed in selected patients in whom coronary ischemic symptoms would otherwise merit such an assessment if CLI were not present (such coronary assessments should usually not impede associated CLI care)

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

Table 8. Differential Diagnosis of Common Foot and Leg Ulcers

<table>
<thead>
<tr>
<th>Origin</th>
<th>Cause</th>
<th>Location</th>
<th>Pain</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main arteries</td>
<td>Atherosclerotic lower extremity PAD, Buerguer's disease, acute arterial occlusion</td>
<td>Toes, foot</td>
<td>Severe</td>
<td>Irregular, pink base</td>
</tr>
<tr>
<td>Venous</td>
<td>Venous disease</td>
<td>Malleolar</td>
<td>Mild</td>
<td>Irregular, pink base</td>
</tr>
<tr>
<td>Skin infarct</td>
<td>Systemic disease, embolism, hypertension</td>
<td>Lower third of leg</td>
<td>Severe</td>
<td>Small after infarction, often multiple</td>
</tr>
<tr>
<td>Neurotrophic</td>
<td>Neuropathy</td>
<td>Foot sole</td>
<td>None</td>
<td>Often deep, infected</td>
</tr>
</tbody>
</table>

PAD indicates peripheral arterial disease.

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
Table 9. Foot Physical Examination and Differential Diagnosis of Neuropathic and Neuroischemic Ulcers

<table>
<thead>
<tr>
<th>Neuropathic Ulcer</th>
<th>Neuroischemic Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless</td>
<td>Painful</td>
</tr>
<tr>
<td>Normal pulses</td>
<td>Absent pulses</td>
</tr>
<tr>
<td>Typically punched-out appearance</td>
<td>Irregular margins</td>
</tr>
<tr>
<td>Often located on sole or edge of foot or metatarsal head</td>
<td>Commonly located on toes</td>
</tr>
<tr>
<td>Presence of calluses</td>
<td>Calluses absent or infrequent</td>
</tr>
<tr>
<td>Loss of sensation, reflexes, and vibration sense</td>
<td>Variable sensory findings</td>
</tr>
<tr>
<td>Increase in blood flow (arteriovenous shunting)</td>
<td>Decrease in blood flow</td>
</tr>
<tr>
<td>Dilated veins</td>
<td>Collapsed veins</td>
</tr>
<tr>
<td>Dry, warm foot</td>
<td>Cold foot</td>
</tr>
<tr>
<td>Bone deformities</td>
<td>No bony deformities</td>
</tr>
<tr>
<td>Red appearance</td>
<td>Pale, cyanotic</td>
</tr>
</tbody>
</table>

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

Table 10. Etiologic Classification of Foot and Leg Ulcers

- Venous obstruction and insufficiency
- Arterial etiologies
  - Larger arteries
  - Atherosclerotic lower extremity PAD
  - Thromboemboli, atheroemboli
  - Thrombangiitis obliterans
- Microcirculatory
  - Diabetic microangiopathy
  - Vasculitis
- Collagen vascular diseases
- Neuropathic
- Diabetes mellitus
- Infectious
  - Leprosy
  - Mycotic
- Hematologic
  - Sickle cell anemia
  - Polycythemia
  - Leukemia
  - Thalassemia
  - Thrombocytosis
- Malignancy
  - Squamous cell carcinoma
  - Kaposi’s sarcoma
  - Secondary metastases
- Lymphosarcoma, mycosis fungoides
- Miscellaneous
  - Gout
  - Pyoderma gangrenosum
  - Necrobiosis lipoidica
  - Vitamin B12 deficiency
- Drugs
  - Artifactual or factitious

PAD indicates peripheral arterial disease.
Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
The severity of acute limb ischemia depends on the location and extent of arterial obstruction and the capacity of the collaterals to perfuse the ischemic territory. Severity may be influenced by the status of systemic perfusion (cardiac output and peripheral resistance). Acute limb ischemia is often associated with thrombosis due to atherosclerotic plaque rupture, thrombosis of a lower extremity bypass graft, or lower extremity embolism originating from the heart or a proximal arterial aneurysm. When embolic occlusion affects a vascular bed not previously conditioned by collaterals, the resulting ischemic syndrome is typically severe. Collateral development in relation to the severity and chronicity of pre-existing ischemia due to atheromatous obstructive arterial disease lessens the severity of ischemia when acute thrombotic arterial occlusion develops. Arterial embolism is more likely than arterial thrombosis to cause sudden, severe, limb-threatening ischemia. The hallmark clinical symptoms and physical examination signs of acute limb ischemia include the 5 “Ps” that suggest limb jeopardy: pain, paralysis, paresthesias, pulselessness, and pallor. Some clinicians would also include a sixth “P,” polar, to indicate a cold extremity. In certain clinical settings, however, arterial embolism can occur without symptoms, whereas thrombosis can produce sudden, severe limb ischemia. The clinical diagnosis of arterial embolism is suggested by (a) the sudden onset or sudden worsening of symptoms, (b) a known embolic source (including atrial fibrillation, severe dilated cardiomyopathy, left ventricular aneurysm, atheromatous plaque in the aorta or proximal limb arteries, or mural thrombus lining the wall of an aortic or arterial aneurysm), (c) the absence of antecedent claudication or other manifestations of obstructive arterial disease, or (d) the presence of normal arterial pulses and Doppler systolic blood pressures in the contralateral limb.

Arterial emboli typically lodge at branch points in the arterial circulation where the caliber of the arterial lumen diminishes. Embolism to the aortoiliac bifurcation (“saddle embolus”) may produce bilateral lower-limb ischemia occasionally associated with reversible paraplegia and a high mortality rate (143,144). Embolic occlusions at sites of arterial bifurcation may cause more profound ischemia when collaterals of perfusion are interrupted, as occurs when the profunda femoris artery is compromised by embolism to the more proximal common femoral artery.

Acute limb ischemia may also occur as a result of acute arterial thrombosis superimposed on a stenotic atherosclerotic plaque. A common site of thrombosis is the superficial femoral artery, although occlusion may occur anywhere from the aorta to the digital arteries. Rarely, an extrinsic local factor such as popliteal entrapment, cystic adventitial disease, or repetitive trauma may be the precursor of arterial thrombosis. The location of the obstruction in relation to other axial arteries in the region of the obstructed vessel and the collateral flow they provide also affects the severity of ischemia. The longer the obstructive lesion, the more collateral pathways that are interrupted. Thrombosis tends to propagate proximally in an artery, up to the next large side branch. The low-flow state distal to the obstructing thrombus also encourages distal propagation of thrombus. This is the rationale for treating patients promptly with systemic anticoagulation.
Typically, pulselessness, pallor, paresthesias, paralysis, and coolness characterize acutely ischemic limbs, and assessment of these features is aided by comparison with the contralateral limb. It may be difficult to determine whether pulse deficits are new or old in patients with PAD without a history of previous symptoms, a recorded examination, or the finding of similar pulse deficits in the contralateral leg. Pedal pulses may be normal in cases of microembolism owing to dependency. The pain of acute limb ischemia is less often localized to the forefoot, often extends above the ankle, and is less influenced by dependency. The pain of acute limb ischemia may sometimes be absent or may diminish due to the recruitment of collaterals or because neurosensory loss interferes with perception. Weakness and numbness are commonly associated with persistent severe acute limb ischemia, and it is important to determine whether the limb dysfunction is worsening or improving over time. It is also crucial to determine whether the patient had previous claudication or arterial interventions, whether the patient had arterial or aortic aneurysm, and whether there is an established diagnosis of heart disease with particular reference to atrial fibrillation, patient foramen ovale or atrial septal defect, or ventricular dysfunction. The patient should also be evaluated for concurrent diseases and risk factors for atherosclerosis.

Typically, pulselessness, pallor, paresthesias, paralysis, and coolness characterize acutely ischemic limbs, and assessment of these features is aided by comparison with the contralateral limb. It may be difficult to determine whether pulse deficits are new or old in patients with PAD without a history of previous symptoms, a recorded examination, or the finding of similar pulse deficits in the contralateral leg. Pedal pulses may be normal in cases of microembolism owing to proximal disruption of atheromatous plaque. Skin pallor may be observed early after the onset of ischemia, but over time, cyanosis becomes more common. Coolness, particularly when the opposite extremity is warm, is a typical finding, and an abrupt line of transition in temperature or color is generally 1 limb segment below the level of arterial obstruction. These levels should be correlated with pulse palpation and should be marked or recorded during the initial examination as a baseline for subsequent comparison. Evaluation of “capillary” return, which reflects the emptying and refilling of subpapillary venules, is subject to considerable environmental and interobserver variation, but capillary return is usually slow or absent in acute limb ischemia.

Some, but not all, patients with sensory loss describe numbness or paresthesias, but pre-existing sensory deficits in diabetic patients can lead to confusion. Sensory deficits may be subtle in the early phase of acute limb ischemia; appreciation of light touch, 2-point discrimination, vibratory perception, and proprioception are usually lost before perception of deep pain and pressure. Motor deficits indicate advanced, limb-threatening ischemia, in part because foot movement is produced mainly by more proximal muscles. Dorsiflexion or plantar flexion of the great toe is produced by muscles that originate just below the knee that are innervated by the peroneal nerve that passes through the anterior tibial compartment. Ischemia may be less profound in these proximal locations than distally, so detection of early motor weakness requires testing the intrinsic muscles of the foot in comparison with the contralateral foot. The intrinsic foot muscles cause movement of the toes and help support the arches of the foot. Persistent pain, sensory loss, and toe muscle weakness are among the most important findings that identify the patient with threatened limb loss. Muscle rigor, tenderness, and pain on passive movement are late signs of advanced ischemia predictive of tissue loss.

**Differential Diagnosis**

The differential diagnosis of acute limb ischemia involves exclusion of conditions that mimic arterial occlusion, identification of nonatherosclerotic causes of arterial occlusion, and differentiation of ischemia caused by an arterial thrombosis from embolism. Nonatherosclerotic causes of acute limb ischemia include arterial trauma, vasospasm, arteritis,
hypercoagulable states, compartment syndromes, arterial dissection, and external arterial compression, such as occurs with a popliteal cyst.

Vasospasm may rarely produce the same symptoms as acute limb ischemia. Other conditions that may mimic arterial occlusion are low cardiac output, especially when superimposed on chronic lower extremity occlusive disease; acute deep venous thrombosis, especially when associated with features of phlegmasia cerulea dolens; and acute compressive peripheral neuropathy. The latter conditions should be distinguishable by palpable pulses, unless chronic arterial occlusive disease or an intense vasoconstrictor response coexists. In acute compressive neuropathy, skin temperature may be normal or above normal, which is quite unusual for ischemia that causes similar pain. In cases of venous thrombosis, cyanosis and coolness may be present, and pulses may be difficult to palpate in the presence of edema, but edema does not occur with acute arterial occlusion unless diagnosis is delayed long enough to allow dependent swelling to develop.

Difficulties in palpating arterial pulses may be resolved by detection of unobstructed arterial Doppler signals over distal arteries. This is helpful in cases of vasospasm when distal pulses may be difficult to feel; the velocity signals may sound blunted but remain biphasic. Patients with advanced congestive heart failure may develop acute limb ischemia, particularly when chronic arterial insufficiency is present.

Treatment

Acute limb ischemia is a situation that requires prompt diagnosis and treatment to preserve the limb. (See Section 2.6.3 for discussion and recommendations for treatment.) Early treatment is also necessary to prevent systemic illness and/or death that might result from the metabolic abnormalities associated with tissue necrosis. Although the technical ability to recanalize or revascularize occluded arteries that perfuse ischemic tissues has improved significantly, the pathophysiology of the local and systemic clinical sequelae associated with reperfusion of an ischemic limb is only partially understood. Revascularization of an ischemic extremity may be complicated by reperfusion injury to the damaged tissues and may precipitate systemic responses, including cardiac, renal, and pulmonary dysfunction.

2.4.5. Prior Limb Arterial Revascularization

RECOMMENDATIONS

Class I

Long-term patency of infrainguinal bypass grafts should be evaluated in a surveillance program, which should include an interval vascular history, resting ABIs, physical examination, and a duplex ultrasound at regular intervals if a venous conduit has been used. (Level of Evidence: B)

Class IIa

1. Long-term patency of infrainguinal bypass grafts may be considered for evaluation in a surveillance program, which may include conducting exercise ABIs and other arterial imaging studies at regular intervals (see duplex ultrasound recommendations, Section 2.5.5). (Level of Evidence: B)

2. Long-term patency of endovascular sites may be evaluated in a surveillance program, which may include conducting exercise ABIs and other arterial imaging studies at regular intervals (see duplex ultrasound recommendations, Section 2.5.5). (Level of Evidence: B)

Patients who have previously undergone revascularization procedures require careful long-term care and vascular follow-up to detect both the recurrence of disease at revascularized sites and the development of new arterial disease at remote sites. In spite of increasing short-term success rates for both endovascular and surgical revascularization procedures, the possibility of recurrence remains throughout the lifetime of the patient. Early revascularization interventions for recurrent hemodynamic compromise are preferred, because delay in detection or treatment can lead to higher morbidity and poorer outcome (145-150).

Participation in a follow-up surveillance program is imperative for patients undergoing both percutaneous and surgical revascularization. However, the recommended frequency of surveillance visits depends on the burden of disease in the individual patient, the specific procedure that was performed and its expected outcome, and the clinical syndrome for which the patient originally presented. Aortic and common iliac arterial level procedures have greater durability than infrainguinal procedures and therefore require less frequent surveillance. In contrast, infrainguinal revascularization for CLI, either by surgical or percutaneous methods, is associated with higher restenosis and graft failure rates and therefore requires more intense surveillance. There are inadequate data to permit creation of consensus-based standards to define exact time intervals for surveillance visits after each type of revascularization procedure. In the absence of evidence-based standards, the clinical time frame customarily has been based on the judgment of the vascular specialist, by evaluation of the specific level and type of revascularization procedure and by taking into account specific patient characteristics (Tables 12, 13, and 14).

The detection of a flow-limiting lesion has significant implications that permit improved maintenance of the long-term patency of the instrumented native vessel or graft. The benefits of early intervention for preservation of long-term patency have been well established, particularly for autogenous vein grafts. As a result, past recommendations have been made that follow-up of autogenous vein bypass graft be performed with duplex ultrasonography at intervals of 1, 3, 6, 12, 18, and 24 months postoperatively and then annually thereafter (1). Prompt evaluation with invasive techniques
Surveillance programs should be performed in the immediate postoperative period and at regular intervals for at least 2 years

Table 12. Surveillance Program for Aortoiliac and Infrainguinal Transluminal Angioplasty

Patients undergoing aortoiliac and infrainguinal transluminal angioplasty for lower extremity revascularization should be entered into a surveillance program, which consists of:

- Interval history (new symptoms)
- Vascular examination of the leg with palpation of proximal and outflow vessel pulses
- Postexercise ABI recording

Surveillance programs should be performed in the immediate post-PTA period and at intervals for at least 2 years

ABI indicates ankle-brachial index; PTA, percutaneous transluminal angioplasty.

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

Table 13. Surveillance Program for Infrainguinal Vein Bypass Grafts

Patients undergoing vein bypass graft placement in the lower extremity for the treatment of claudication or limb-threatening ischemia should be entered into a surveillance program. This program should consist of:

- Interval history (new symptoms)
- Vascular examination of the leg with palpation of proximal, graft, and outflow vessel pulses
- Postexercise ABIs
- Periodic measurement of resting and, if possible, postexercise ABIs
- Duplex scanning of the entire length of the graft, with calculation of peak systolic velocities and velocity ratios across all identified lesions

Surveillance programs should be performed in the immediate postoperative period and at regular intervals for at least 2 years

- Femoral-popliteal and femoral-tibial venous conduit bypass at approximately 3, 6, and 12 months and annually

ABI indicates ankle-brachial index.

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

ABI determinations may be useful in some individuals. These modalities are clearly useful for patients in whom there is evidence of recurrent narrowing at the intervention site. Similarly, distal or small-caliber endovascular sites (with or without stenting) at high risk of restenosis may merit more careful noninvasive evaluation. Whereas the role of surveillance duplex imaging of autogenous and prosthetic grafts has been evaluated (see Section 2.6.3.4.3), the utility and role of duplex ultrasound and other noninvasive diagnostic modalities (MRA and computed tomographic angiography [CTA]) for such routine surveillance of endovascular sites have yet to be determined.

There is no uniformly accepted threshold for repeat angiography and intervention in the patient with evidence of recurrent stenosis. Patients who have recurrent symptoms in association with evidence of hemodynamic compromise require restudy and repeat intervention. Likewise, evidence of rapidly progressive restenosis, even in the absence of symptoms, should provide a clue that may identify individuals who might benefit from future invasive management. For grafts as well as native vessels, a stenosis of less than 50% appears to be associated with favorable prognosis and patency. In contrast, a stenosis greater than 70% is a harbinger of poor long-term patency, and thus, reintervention may be warranted (154,155).

2.5. Diagnostic Methods

Patients with vascular disorders can usually be assured that an accurate anatomic diagnosis will be made with modern noninvasive vascular diagnostic techniques (e.g., ankle- and toe-brachial indices, segmental pressure measurements, pulse volume recordings, duplex ultrasound imaging, Doppler waveform analysis, and exercise testing). These tests will usually provide adequate information for creation of a therapeutic plan. When required, these physiological and anatomic data can be supplemented by use of MRA and CTA and selective use of invasive aortic and lower extremity angiographic techniques. This section will review the evidence base that defines the benefits and limitations of each of
these vascular diagnostic techniques, as summarized in Table 15.

The noninvasive vascular laboratory provides a powerful set of tools that can objectively assess the status of lower extremity arterial disease and facilitate the creation of a therapeutic plan. Although there are many diagnostic vascular tests available, the clinical presentation of each patient can usually be linked to specific and efficient testing strategies (Table 16). The combined use of physiological noninvasive data and imaging studies can provide information vital to the choice of interventional approaches. The physiological noninvasive tests (e.g., ankle, toe, and segmental blood pressures and ratios) are relatively inexpensive, can be performed at no risk, and provide prognostic information. These examinations in patients with lower extremity PAD permit the clinician to (a) objectively establish the presence of the lower extremity PAD diagnosis, (b) quantitatively assess the severity of disease, (c) localize lesions to specific limb arterial segments, and (d) determine the temporal progression of disease or its response to therapy.

Quality assurance of noninvasive vascular laboratory techniques is maintained by the Intersocietal Commission for Accreditation of Vascular Laboratories (ICAVL; www.icavl.org), which serves as an intersocietal, interdisciplinary peer review organization that represents each medical specialty and vascular technology professional organization that is involved in noninvasive vascular testing. The primary goals of the ICAVL are to recognize testing facilities performing high-quality studies (as verified by a program of ongoing quality assurance), to issue certificates of recognition of such quality service, and to maintain a registry of accredited laboratories. The “Essentials and Standards for Accreditation of Vascular Laboratories” address the qualifications of medical and technical personnel, instrumentation, testing protocols, diagnostic criteria, quality assurance, patient safety policies, and facilities. Accreditation has also been provided by the American College of Radiology. Accreditation has led to improved quality of testing, increased standardization of testing protocols and diagnostic criteria, improved quality assurance procedures, an increase in the number of certified technologists, and improved ongoing noninvasive vascular diagnostic educational opportunities. Such an ongoing system to assess other noninvasive (e.g., MRA or CTA) and invasive vascular techniques does not yet exist.

2.5.1. Ankle- and Toe-Brachial Indices, Segmental Pressure Examination

RECOMMENDATIONS

Class I

1. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with exertional leg symptoms, with nonhealing wounds, who are 70 years and older or who are 50 years and older with a history of smoking or diabetes. (Level of Evidence: C)

2. The ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower extremity PAD and establish a baseline. (Level of Evidence: B)

3. The toe-brachial index should be used to establish the lower extremity PAD diagnosis in patients in whom lower extremity PAD is clinically suspected but in whom the ABI test is not reliable due to noncompressible vessels (usually patients with long-standing diabetes or advanced age). (Level of Evidence: B)

4. Leg segmental pressure measurements are useful to establish the lower extremity PAD diagnosis when anatomic localization of lower extremity PAD is required to create a therapeutic plan. (Level of Evidence: B)

Ankle-Brachial Index

The ABI is a measurement that provides objective data that serves as the standard for the diagnosis of lower extremity PAD in field epidemiological surveys, in vascular laboratories, and in office practice. The ABI offers prognostic data that are useful to predict limb survival, wound healing, and patient survival. The ABI can be used either as a screening tool for lower extremity PAD or to monitor the efficacy of therapeutic interventions. The ABI is performed by measuring the systolic blood pressure from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries after the patient has been at rest in the supine position for 10 minutes (Figure 6). Optimal recordings are obtained with blood pressure cuffs that are appropriately sized to the patient’s lower calf (immediately above the ankle), and systolic pressures are recorded with a handheld 5- or 10-mHz Doppler instrument. In normal individuals, there should be a minimal (less than 12 mm Hg) interarm systolic pressure gradient during a routine examination. Inasmuch as the incidence of atherosclerotic subclavian and axillary arterial occlusive disease is higher in individuals with atherosclerotic lower extremity PAD, both arm pressures must be recorded. If the arm blood pressures are not equal, then the presence of a subclavian or axillary arterial stenosis is presumed present, and the higher blood pressure is used for subsequent blood pressure ratio calculations. Pulse wave reflection in healthy individuals causes the ankle pressure to be 10 to 15 mm Hg higher than the brachial arterial systolic pressure, and thus the normal ankle-arm brachial index systolic blood pressure ratio is greater than 1.00. Calculated ABI values should be recorded to 2 decimal places.

The ABI has been validated against lower extremity contrast angiography to determine its sensitivity, specificity, and accuracy as a lower extremity PAD diagnostic tool. Lijmer et al. used a receiver operating characteristic (ROC) analysis to demonstrate that with an ABI diagnostic threshold of 0.91, the sensitivity of the ABI was 79% and specificity was 96% to detect stenoses of 50% or more reduction in lumen diam-
### Table 15. Noninvasive and Invasive Vascular Diagnostic Tools: Benefits and Limitations

<table>
<thead>
<tr>
<th>Diagnostic Tool*</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ankle-brachial indices (ABIs)</strong></td>
<td>A quick and cost-effective way to establish or refute the lower extremity PAD diagnosis (see text)</td>
<td>May not be accurate when systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff (non-compressible pedal arteries), as occurs in a small fraction of diabetic or very elderly individuals</td>
</tr>
<tr>
<td><strong>Toe-brachial indices</strong></td>
<td>A quick and cost-effective way to establish or refute the lower extremity PAD diagnosis (see text) Can measure digital perfusion when small-vessel arterial occlusive disease is present Useful in individuals with noncompressible posterior tibial or dorsalis pedis arteries</td>
<td>Requires small cuffs and careful technique to preserve accuracy</td>
</tr>
<tr>
<td><strong>Segmental pressure examination</strong></td>
<td>Useful to establish or refute the PAD diagnosis (see text) Useful to provide anatomic localization of lower extremity PAD when these data are required to create a therapeutic plan Can provide data to predict limb survival, wound healing, and patient survival Useful to monitor the efficacy of therapeutic interventions</td>
<td>May not be accurate when systolic blood pressure cannot be measured by inflation of an air-filled blood pressure cuff owing to noncompressible pedal arteries, as occurs in a small fraction of diabetic or very elderly individuals</td>
</tr>
<tr>
<td><strong>Pulse volume recording</strong></td>
<td>Useful to establish the diagnosis of PAD in vascular laboratories or office practice Helpful in predicting the outcome in CLI and risk of amputation Can be used to monitor limb perfusion after revascularization procedures</td>
<td>Usefulness maintained in patients with noncompressible vessels (ABI value greater than 1.3) Qualitative, not quantitative, measure of perfusion May not be accurate in more distal segments Less accurate than other noninvasive tests in providing arterial anatomic localization of PAD May be abnormal in patients with low cardiac stroke volume</td>
</tr>
<tr>
<td><strong>Continuous-wave Doppler ultrasound</strong></td>
<td>Useful to assess lower extremity PAD anatomy, severity, and progression Can provide localizing information in patients with poorly compressible arteries Can provide quantitative data after successful lower extremity revascularization</td>
<td>“Pulse normalization” downstream from stenoses can diminish test sensitivity Test specificity greater for patent superficial femoral arteries than for aortoiliac occlusive disease Does not provide visualization of arterial anatomy Limited accuracy in tortuous, overlapping, or densely calcified arterial segments, and insensitive for iliac arteries (in context of obesity, bowel gas, and vessel tortuosity)</td>
</tr>
<tr>
<td><strong>Duplex ultrasound</strong></td>
<td>Can establish the lower extremity PAD diagnosis, establish anatomic localization, and define severity of focal lower extremity arterial stenoses Can be useful to select candidates for endovascular or surgical revascularization</td>
<td>Useful tool to provide graft surveillance after femoral-popliteal or femoral tibial or pedal surgical bypass with venous (but not prosthetic) conduit Accuracy is diminished in proximal aortoiliac arterial segments in some individuals (e.g., due to obesity or the presence of bowel gas) Dense arterial calcification can limit diagnostic accuracy Sensitivity is diminished for detection of stenoses downstream from a proximal stenosis Diminished predictive value in surveillance of prosthetic bypass grafts</td>
</tr>
</tbody>
</table>

*Continued on Next Page*
<table>
<thead>
<tr>
<th>Diagnostic Tool*</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toe-tip exercise testing, with pre-exercise and postexercise ABIs</strong></td>
<td>Useful to diagnose lower extremity PAD when resting ABI values are normal Can be performed in the absence of a treadmill, with increased convenience and low cost</td>
<td>Provides qualitative (rather than quantitative) exercise diagnostic results Lower workload may not elicit symptoms in all individuals with claudication</td>
</tr>
<tr>
<td><strong>Treadmill exercise testing, with and without pre-exercise and postexercise ABIs</strong></td>
<td>Helps differentiate claudication from pseudoclaudication in individuals with exertional leg symptoms Useful to diagnose lower extremity PAD when resting ABI values are normal Objectively documents the magnitude of symptom limitation in patients with claudication, especially when used with a standardized treadmill protocol Demonstrates the safety of exercise and provides data to individualize exercise prescriptions in individuals with claudication before initiation of a formal program of therapeutic exercise training</td>
<td>Requires use of a motorized treadmill, with or without continuous electrocardiogram monitoring, as well as staff familiar with exercise testing protocols</td>
</tr>
<tr>
<td><strong>Magnetic resonance angiography (MRA)</strong></td>
<td>Useful to assess PAD anatomy and presence of significant stenoses Useful to select patients who are candidates for endovascular or surgical revascularization</td>
<td>Tends to overestimate the degree of stenosis May be inaccurate in arteries treated with metal stents Cannot be used in patients with contraindications to the magnetic resonance technique (e.g., pacemakers, defibrillators, intracranial metallic stents, clips, coils, and other devices)</td>
</tr>
<tr>
<td><strong>Computed tomographic angiography (CTA)</strong></td>
<td>Useful to assess PAD anatomy and presence of significant stenoses Useful to select patients who are candidates for endovascular or surgical revascularization Helpful to provide associated soft tissue diagnostic information that may be associated with PAD presentation (e.g., aneurysms, popliteal entrapment, and cystic adventitial disease) Patients with contraindications to magnetic resonance angiography (e.g., pacemakers or defibrillators) may be safely imaged Metal clips, stents, and metallic prostheses do not cause significant CTA artifacts Scan times are significantly faster than for MRA</td>
<td>Single-detector computed tomography lacks accuracy for detection of stenosis Spatial resolution lower than digital subtraction angiography Venous opacification can obscure arterial filling Asymmetrical opacification of the legs may obscure arterial phase in some vessels Accuracy and effectiveness not as well determined as MRA Treatment plans based on CTA have not been compared with those of catheter angiography Requires iodinated contrast and ionizing radiation (although radiation exposure is less than with catheter angiography) Because CTA requires administration of iodinated contrast, use is limited in individuals with established renal dysfunction</td>
</tr>
<tr>
<td><strong>Contrast angiography</strong></td>
<td>Definitive method for anatomic evaluation of PAD when revascularization is planned</td>
<td>Invasive evaluation is associated with risk of bleeding, infection, vascular access complications (e.g., dissection or hematoma), atheroembolization, contrast allergy, and contrast nephropathy May provide limited visualization of tibial-pedal vessels in patients with CLI and poor inflow to the leg Below-knee vessels may be difficult to identify by digital subtraction angiography Multiple projections may be necessary to visualize eccentric lesions</td>
</tr>
</tbody>
</table>

*Tools are listed in order from least invasive to most invasive and from least to most costly.

CLI indicates critical limb ischemia; PAD, peripheral arterial disease.
Table 16. Typical Noninvasive Vascular Laboratory Tests for Lower Extremity PAD Patients by Clinical Presentation

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Noninvasive Vascular Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic lower extremity PAD</td>
<td>ABI</td>
</tr>
<tr>
<td>Claudication</td>
<td>ABI, PVR, or</td>
</tr>
<tr>
<td></td>
<td>segmental pressures</td>
</tr>
<tr>
<td></td>
<td>Duplex ultrasound</td>
</tr>
<tr>
<td></td>
<td>Exercise test with ABI</td>
</tr>
<tr>
<td>Possible pseudoclaudication</td>
<td>Exercise test with ABI</td>
</tr>
<tr>
<td>Postoperative vein graft follow-up</td>
<td>Duplex ultrasound</td>
</tr>
<tr>
<td>Femoral pseudoaneurysm; iliac</td>
<td>Duplex ultrasound</td>
</tr>
<tr>
<td>or popliteal aneurysm</td>
<td></td>
</tr>
<tr>
<td>Suspected aortic aneurysm;</td>
<td>Abdominal ultrasound, CTA, or MRA</td>
</tr>
<tr>
<td>serial AAA follow-up</td>
<td></td>
</tr>
<tr>
<td>Candidate for revascularization</td>
<td>Duplex ultrasound, MRA, or CTA</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; ABI, ankle-brachial index; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; PAD, peripheral arterial disease; PVR, pulse volume recording.


eter (156). Similarly, Fowkes, using a comparable ABI threshold of 0.90, showed that the ABI has a sensitivity of 95% and a specificity of 100% compared with angiography (120). Fiegelson et al. (157) measured a sensitivity of 89% and a specificity of 99% compared with angiography, using only posterior tibial measurements with a threshold of 0.8. That study demonstrated that the ABI had a positive predictive value of 90%, a negative predictive value of 99%, and an overall accuracy of 98%. Nassoura et al. assessed the diagnostic discrimination of the ABI compared with angiography after vascular occlusive injury due to trauma (158) and demonstrated that the ABI had a sensitivity of 72%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 96%. Thus, the overall accuracy of the ABI to establish the lower extremity PAD diagnosis has been well-established.

The interobserver variability of the ABI measurement has been evaluated in multiple investigations. Baker and Dix tested 35 men with claudication at 7 different times each and found a standard deviation of 0.07, which led them to conclude that the change in ABI must be greater than 0.15 (2 standard deviations) to be significant (159). Their results were identical to those obtained by Carter (160). Strandness et al. reported the variability of ABI measurements performed on 4 subjects on 3 different days with different observers, which yielded an ABI interday standard deviation of 0.06 (161). Yao assessed the ABI on different days in 179 patients using 4 technicians to determine a measurement variance of 0.08 (162). When 69 patients were assessed on 6 different days using the same technician, the measurement variance was 0.05. These results suggest that most of the variance is due to the measurement method, not to differences between observers. Overall, the ABI is considered to have a reproducibility of approximately 0.10.

Ouriel and Zarins demonstrated that the ABI may provide better discrimination than the absolute ankle pressure alone for distinguishing between normal limb arteries and those with lower extremity PAD (163). These authors also demonstrated that neither the absolute ankle pressure nor the ABI can differentiate normal limbs from asymptomatic limbs with arteriographically determined disease, because neither pressure-based assessment nor the ABI at rest can predict the hemodynamic supply-demand relationship with exercise. This may be a key reason why the ABI does not reliably predict the magnitude of ischemic symptoms.

Abnormal ABI values represent a continuous variable less than 0.90. ABI values are often considered to be mildly to moderately diminished when they are between 0.41 and 0.90 and severely decreased when less than or equal to 0.40. These relative categories have prognostic value. For example, an ABI value greater than 0.50 suggests that progression to critical leg ischemia is unlikely during the subsequent 6.5 years of follow-up (164). In contrast, when the ABI is less than 0.40, patients are more likely to experience ischemic rest pain. Similarly, the low ankle systolic blood pressure in such individuals bodes poorly for the healing of ischemic wounds. The presence of a severely decreased ABI thus identifies individuals who are at particularly high risk of subsequent development of rest pain, ischemic ulceration, or gangrene (162).

McLafferty et al. investigated the value of the ABI to assess the progression of lower extremity PAD after vascular surgery (165). In that investigation, a change in ABI of 0.15 was used as the criterion to define progression of the disease, and baseline and postoperative angiography or duplex scanning was performed approximately 3 years later. In this clinical context, the ABI had a sensitivity of 41%, specificity of 84%, positive predictive value of 59%, and an accuracy of 68% for
strongly suggest lower extremity PAD, the presence of a normal or high ABI should not be presumed to rule out this diagnosis, and an alternative diagnostic test (e.g., toe-brachial pressure, Doppler waveform analysis, pulse volume recording, exercise ABI test, or duplex ultrasound) should be performed.

The ABI may not be accurate in individuals in whom systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff. The incidence of noncompressible arteries is highest in diabetics and elderly patients; in these individuals, it may be impossible to abolish the systolic pressure signal despite cuff inflation to pressures in excess of 200 mm Hg. Despite the artificially high systolic pressure, these individuals may have arterial disease, and cardiovascular event rates have been noted to be increased in one population that was characterized by a high prevalence of diabetes and other risk factors (166). This finding has not been confirmed in other population studies. Patients with either severely stenotic or totally occluded iliofemoral arteries may also have a normal ABI value at rest if sufficient collaterals are present. Thus, for patients in whom symptoms detecting disease progression, thus demonstrating the potential utility of this technique to monitor lower extremity PAD progression after surgical intervention.

The ABI may not be accurate in individuals in whom systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff. The incidence of noncompressible arteries is highest in diabetics and elderly patients; in these individuals, it may be impossible to abolish the systolic pressure signal despite cuff inflation to pressures in excess of 200 mm Hg. Despite the artificially high systolic pressure, these individuals may have arterial disease, and cardiovascular event rates have been noted to be increased in one population that was characterized by a high prevalence of diabetes and other risk factors (166). This finding has not been confirmed in other population studies. Patients with either severely stenotic or totally occluded iliofemoral arteries may also have a normal ABI value at rest if sufficient collaterals are present. Thus, for patients in whom symptoms strongly suggest lower extremity PAD, the presence of a normal or high ABI should not be presumed to rule out this diagnosis, and an alternative diagnostic test (e.g., toe-brachial pressure, Doppler waveform analysis, pulse volume recording, exercise ABI test, or duplex ultrasound) should be performed.

The importance and potentially unique value of the ABI have been expanded by epidemiological studies (44,105,107,109). The diagnosis of lower extremity PAD by an abnormal ABI is predictive of other clinical stigmata of systemic atherosclerotic disease. Newman and coworkers have confirmed the inverse relationship between the ABI and atherosclerosis risk factors, as well as its relationship with the presence of both cardiovascular and cerebrovascular disease (44). For example, the presence of a low ABI was predictive of total and cardiovascular mortality (relative risk of cardiovascular mortality in the low ABI cohort was increased approximately 3- to 4-fold) in a cohort of 1537 elderly men.
and women followed in the Systolic Hypertension in the Elderly Program (SHEP) (105). McKenna et al. documented a 5-year mortality of approximately 30% and 50% in patients with an ABI of 0.70 and 0.40, respectively (109). The relationship between ABI and morbidity and mortality in patients with lower extremity PAD has also been quantitated by Sikkink et al., who demonstrated that the 5-year cumulative survival rate was 63% for subjects with a resting ABI less than 0.50, 71% for subjects with an ABI between 0.50 and 0.69, and 91% for subjects with an ABI between 0.70 and 0.89 (167). Thus, 5-year survival in patients with lower extremity PAD is well predicted by the ABI value itself. Despite the increasing use of more sophisticated vascular diagnostic tests (e.g., intimal medial thickness, vascular compliance, or arterial duplex ultrasonography), the ABI is linked to a robust epidemiological database, which permits prediction of future cardiovascular ischemic events.

The epidemiological database and vascular laboratory experience with ABI testing have led to increasing use of the ABI examination in office practice. It has been proposed that the ABI should be considered a routine test for all patients who are at risk of lower extremity PAD. As described previously, the PARTNERS investigation evaluated use of the ABI applied to a target population of individuals aged 70 years and older or 50 years of age and in whom other atherosclerosis risk factors (especially tobacco use and diabetes) would be expected to increase the prevalence of lower extremity PAD (86). The average time required to perform the ABI in primary care office practices is approximately 15 minutes, and these ABI data are valued by clinicians (168). The utility of the ABI to detect lower extremity PAD has long been endorsed by the American Diabetes Association and the AHA, which had published an original recommendation to perform this test in individuals with insulin-dependent diabetes who were aged 35 years and older and patients with 20 years’ duration of diabetes (169). This application of the ABI to office practice has been updated by an American Diabetes Association consensus statement that suggested that the ABI be performed in all individuals with diabetes who are aged 50 and older, in diabetic individuals younger than age 50 who have other atherosclerosis risk factors, and in individuals with diabetes of more than 10 years’ duration (170). Application of the ABI is now considered appropriate in targeted populations known from the epidemiological database to be at risk (Table 2), including individuals 49 years of age and younger with a history of diabetes and 1 other risk factor; those 50 to 69 years of age with a history of smoking or diabetes; those 70 years of age and older; those with an abnormal lower extremity pulse examination; and individuals with known atherosclerotic coronary, carotid, or renal artery disease. Nevertheless, at the present time, the cost of measurement of the ABI in office practice with handheld equipment without pulse volume recording (PVR) or Doppler waveform tracings is usually not reimbursed by healthcare payers. In contrast, measurement of the ABI in association with standardized vascular laboratory equipment has an associated (and reimbursed) current procedural terminology code (171).

**Segmental Pressure Measurements**

Arterial pressures can also be measured with plethysmographic cuffs placed sequentially along the limb at various levels (172,173). In most vascular laboratories, these blood pressure cuffs are placed at the upper thigh, the lower thigh, the upper calf, and the lower calf above the ankle. Use of a 3-cuff system (with only 1 thigh cuff) is another acceptable method. The systolic blood pressures obtained from the lower extremities can also be indexed relative to the brachial artery pressure, in a manner analogous to the ABI. These measurements provide a noninvasive corollary to intra-arterial pressure measurements.

In contrast to ABI studies, the segmental pressure analysis is able to accurately determine the location of individual arterial stenoses. For example, the presence of a prominent systolic pressure gradient between the brachial artery pressure and the upper thigh systolic pressure signifies the presence of an aortoiliac stenosis. A pressure gradient located between the upper and lower thigh cuffs would signify a lesion of the superficial femoral artery. Gradients between the lower thigh and upper calf cuffs identify a distal superficial femoral or popliteal arterial stenosis, and gradients between the upper and lower calf cuffs identify infrapopliteal disease. In most laboratories, a gradient of greater than 20 mm Hg between adjacent segments is interpreted to represent a physiologically important focal stenosis. Thus, segmental pressure measurements can identify the location and magnitude of many arterial stenoses noninvasively. As with the ABI, segmental pressure measurements may be artifactually elevated or uninterpretable in patients with noncompressible vessels.

**Toe-Brachial Index Measurements**

Many individuals with long-standing diabetes, elderly patients, and individuals who require dialysis for end-stage renal disease may have noncompressible leg arterial segments due to medial calcification. This may preclude accurate assessment of either the ABI or segmental pressure measurements in a subset of these patient cohorts. Such noncompressible arteries are suggested when the ABI is greater than 1.3 or when there is an abnormal augmentation in a measured lower extremity systolic pressure beyond the normal physiological amplification of systolic pressure from the heart to the limb arterial segment (usually greater than 20 mm Hg or 20% higher than the brachial systolic pressure). In such individuals, diagnostic information to establish the lower extremity PAD diagnosis can be obtained by the measurement of toe systolic pressure and calculation of the toe-brachial index, and toe-brachial index values less than 0.7 are usually considered diagnostic for lower extremity PAD (174-179). The toe pressure measurement remains a sensitive diagnostic test in such patients because digital arteries are usually spared the calcinosis that alters compressibility of
more proximal arteries. This test is performed by placement of a small occlusive cuff on the proximal portion of the great or second toe, with the return of toe pulsatility (which represents the systolic perfusion pressure) assessed by use of a plethysmographic detection device.

2.5.2. Pulse Volume Recording

RECOMMENDATION

Class IIa

Pulse volume recordings are reasonable to establish the initial lower extremity PAD diagnosis, assess localization and severity, and follow the status of lower extremity revascularization procedures. (Level of Evidence: B)

Arterial inflow into the lower extremities is pulsatile, and such inflow leads to measurable changes in lower-limb volume with each cardiac cycle. Measurement of these cyclical volume changes can be documented by a plethysmographic technique to provide qualitative or quantitative data regarding the adequacy of limb perfusion in patients with lower extremity PAD. Pulse volume recordings provide a method to evaluate the arterial pressure waveform profile via the use of either a pneumoplethysmograph or a mercury-in-silastic strain gauge. Both of these devices can be applied in a segmental manner from the thigh to the ankle to assess the change in limb volume between diastole and systole. When such data are recorded on chart paper, the magnitude of the pulse volume provides an index of large-vessel patency and correlates with blood flow.

Pneumoplethysmographic devices are in most widespread use both in vascular laboratories and as a component of office-based vascular diagnostic devices, with a large thigh cuff placed proximally and with calf and ankle cuffs used more distally. An arm (brachial) cuff PVR tracing is also recorded to provide an index of normal pulsatility in a presumably well-perfused limb. When such data are recorded on chart paper, the magnitude of the pulse volume and pulse volume (amplitude) provide a global physiological measurement of large-vessel patency and correlates with blood flow. Any sequential diminution in pulsatility (upstroke and amplitude) signifies the presence of a flow-limiting stenosis in the more proximal arterial segment (173,180). Pulsatility is usually a qualitative (or rarely, semiquantitative) measurement, with normal values set by each vascular laboratory.

The accuracy of the PVR has been assessed by comparison to direct measurements of arterial pressure gradients in the aortoiliac segments in 52 limbs of 45 patients with lower extremity PAD (181). Measurement of low PVR amplitude correlated with arterial segmental pressure gradients of 10 mm Hg at rest or with gradients of 20 mm Hg induced by injection of the vasodilator papaverine. The accuracy of combined segmental pressure measurements and PVRs has been assessed with an angiographic “gold standard” in a prospective study of 50 patients with lower extremity PAD (182). Doppler waveform tracings from the femoral, popliteal, and tibial arteries were used to calculate the pulsatility index and inverse damping factor and compared with the arteriographic data by independent observers. Both the combined PVR-segmental pressure and the Doppler waveform techniques offered an overall diagnostic accuracy in the 90% to 95% range. The PVR-segmental pressure technique accurately predicted the severity of iliac and superficial femoral artery obstruction and distinguished iliac from proximal superficial femoral artery disease. However, the PVR-segmental pressure method was less accurate in more distal (e.g., tibial artery) segments.

Pulse volume recording tracings have been evaluated and can serve as a facile method to assess the adequacy of limb perfusion in the early postoperative hours after aortofemoral surgical reconstruction (183). In this context, PVR pulsatility correlated well with electromagnetic measures of arterial blood flow and provided information useful in predicting technical procedural limitations.

The PVR has been evaluated for its ability to predict limb prognosis (propensity for amputation). Kaufman et al. studied the relationship of PVR tracings to limb outcome in 517 patients with lower extremity PAD (184). Pulse volume recording tracings correlated well with ankle systolic blood pressure and provided similar prognostic information. Within 1 year of follow-up, 97.9% of 96 patients with jeopardized limbs and flat tracings underwent limb salvage surgery, 85.7% of patients with jeopardized limbs and nearly flat tracings underwent surgery, and 41.9% of those with minimal symptoms and nearly flat recordings required surgical revascularization (p less than 0.001). The prognostic value of PVR tracings in predicting risk of amputation has also been evaluated in a small patient cohort with diabetes before and after renal transplantation. Makisalo et al. studied 129 consecutive diabetic (n equals 34) and nondiabetic (n equals 95) renal transplantation patients and measured the predictive value of clinical factors (e.g., pretransplant lower extremity PAD and claudication) and noninvasive vascular perfusion measurements (ABI, toe-brachial index, and PVRs) on lower-limb amputations, renal allograft survival, and patient survival during a 5-year period of follow-up (178). A low PVR amplitude (below 5 mm) was observed before transplantation in 82% of the diabetic patients and 36% of the nondiabetic patients. During the 5-year follow-up period, abnormal toe-brachial index and PVR values (and diabetes) at the time of transplantation were the greatest predictors for proximal foot amputations. In summary, the presence of a low pulse volume serves as a measurable hallmark that correlates with other signs of limb jeopardy and an adverse prognosis.

In summary, the PVR technique is useful as an initial diagnostic test for patients with suspected lower extremity PAD and to assess limb perfusion after revascularization procedures, and it can predict risk of CLI and amputation. Pulse volume recordings can provide a tool to evaluate small-vessel disease when applied to the feet. They are also useful in individuals with noncompressible vessels in whom ABIs and segmental pressures are spuriously elevated. Although PVRs...
are useful and cost-effective, especially as a screening tool in office practices or vascular laboratories, other noninvasive techniques can provide more quantitative perfusion data and better arterial anatomic lower extremity PAD localization.

2.5.3. Continuous-Wave Doppler Ultrasound

**RECOMMENDATION**

Class I

Continuous-wave Doppler ultrasound blood flow measurements are useful to provide an accurate assessment of lower extremity PAD location and severity, to follow lower extremity PAD progression, and to provide quantitative follow-up after revascularization procedures. *(Level of Evidence: B)*

Continuous-wave Doppler ultrasound is used to obtain velocity waveforms and to measure systolic blood pressure at sequential segments of the upper or lower extremities and is a traditional component of a noninvasive peripheral arterial evaluation. Use of this technique permits initial estimation of disease location and severity, follow-up of disease progression, and quantitation of the effects of revascularization therapies (185).

One commonly used quantitative indirect measure for detection of proximal occlusive disease is the peak-to-peak pulsatility index, defined as the peak systolic velocity (or frequency shift) minus the minimum or most reversed diastolic velocity (or frequency shift), divided by the mean blood flow velocity (or frequency shift; Figure 7). Normally, the pulsatility index increases from the more proximal to the more distal segments of the lower extremities (186). A decrease in the pulsatility index between adjacent proximal and distal anatomic segments implies the presence of occlusive disease between these 2 locations. The degree of decline in the pulsatility index value is usually proportional to the severity of occlusive disease (187). However, downstream from moderate stenosis, the velocity pulse waveform may revert to a normal waveform within a short distance (approximately 3 to 5 vessel diameters), depending on the severity of stenosis (188,189). This latter phenomenon of “pulse normalization” distal to some arterial stenoses is a diagnostic limitation. Thus, the presence of a high-resistance-type waveform (defined as rapid forward systolic flow, followed by a short period of rapid reversed flow, and then low-velocity forward flow in late diastole) does not provide irrefutable evidence of the absence of more proximal occlusive disease.

![Pulsatility Index](image)

**Figure 7.** Pulsatility index. \( \text{V}_{\text{max}} \) indicates peak systolic velocity; \( \text{V}_{\text{min}} \), minimum diastolic velocity; \( \text{V}_{\text{mean}} \), mean blood flow velocity.

Analysis of the morphology of the Doppler waveform can add useful localizing information to that obtained by segmental blood pressure recording alone. For example, a unilaterally depressed proximal thigh measurement could be due to occlusive disease in either the ipsilateral common or external iliac arteries or the proximal portion of the superficial femoral artery. A low-resistance Doppler waveform or a pulsatility index of less than approximately 4.0 for the common femoral artery would indicate that occlusion most likely involves the common or external iliac artery, whereas a high-resistance Doppler waveform or a pulsatility index greater than 4.0 would suggest that the iliac arteries are relatively free of disease and that occlusion primarily involves the proximal superficial femoral artery, frequently in conjunction with lesions of the deep femoral artery (190). For unknown reasons, some patients with occlusion of the superficial femoral artery, in the absence of aortoiliac disease, demonstrate a low-resistance waveform and a depressed pulsatility index of the common femoral artery. This constellation of findings results in false-positive studies that suggest aortoiliac disease, decreases the positive predictive value of the test, and lessens the specificity of the test for aortoiliac occlusive disease compared with results obtained in patients with patent superficial femoral arteries (190,191). Doppler waveform analysis also can provide useful localizing information in patients with poorly compressible arteries and in patients with a normal resting ABI.

The benefits of Doppler waveform analysis, along with recognition of its limitations, can be maximized if the blood flow waveform analysis is combined with ultrasound grayscale visualization of the arterial wall. Such “duplex” imaging now represents one of the most widely used noninvasive vascular laboratory techniques.

2.5.4. Treadmill Exercise Testing With and Without ABI Assessments and 6-Minute Walk Test

**RECOMMENDATIONS**

Class I

1. Exercise treadmill tests are recommended to provide the most objective evidence of the magnitude of the functional limitation of claudication and to measure the response to therapy. *(Level of Evidence: B)*

2. A standardized exercise protocol (either fixed or graded) with a motorized treadmill should be used to ensure reproducibility of measurements of pain-free walking distance and maximal walking distance. *(Level of Evidence: B)*

3. Exercise treadmill tests with measurement of pre-exercise and postexercise ABI values are recommended to provide diagnostic data useful in differentiating arterial claudication from nonarterial claudication ("pseudoclaudication"). *(Level of Evidence: B)*
4. Exercise treadmill tests should be performed in individuals with claudication who are to undergo exercise training (lower extremity PAD rehabilitation) so as to determine functional capacity, assess nonvascular exercise limitations, and demonstrate the safety of exercise. (Level of Evidence: B)

Class IIb
A 6-minute walk test may be reasonable to provide an objective assessment of the functional limitation of claudication and response to therapy in elderly individuals or others not amenable to treadmill testing. (Level of Evidence: B)

Exercise testing may be extremely useful (a) in establishing the diagnosis of lower extremity PAD when resting measures of the ABI are normal, (b) to objectively document the magnitude of symptom limitation in patients with lower extremity PAD and claudication, (c) to objectively measure the functional improvement obtained in response to claudication interventions, (d) to differentiate claudication from pseudoclaudication in individuals with exertional leg symptoms, and (e) to provide objective data that can demonstrate the safety of exercise and to individualize exercise prescriptions in patients with claudication before initiation of a formal program of exercise training.

Most exercise testing for patients with lower extremity PAD and claudication should use motorized treadmills programmed to provide less intense progressive workloads than are commonly used for healthy individuals or patients with coronary heart disease (e.g., the Gardner-Skinner, Hiatt, or Naughton protocols) (192-194). The treadmill test should record the time of onset of leg symptoms, laterality and specificity muscle group(s) involved, the presence of associated coronary ischemic symptoms, and the total walking time. Continuous electrocardiographic monitoring, although not required to evaluate lower extremity PAD, may provide useful diagnostic data regarding inducible myocardial ischemia in many individuals, even if the patient with claudication cannot achieve 85% of their age-predicted peak heart rate or workload.

During treadmill testing, the patient should be asked to indicate when any exercise-limiting symptoms occur; whether symptoms represent typical claudication, atypical limb discomfort, joint pain, or general fatigue; or if exercise is limited by chest pain or other cardiovascular symptoms. Patients should be asked to walk to their maximally tolerable claudication symptom to most accurately define peak walking time during treadmill exercise, because failure to do so may lead to underestimation of the true peak walking capacity of the patient. Exercise should be stopped when mandated by symptoms or if objective signs of myocardial ischemia are observed (e.g., abnormal blood pressure response at peak exercise, more than 2.0 mm of ST depression, or significant dysrhythmias). For patients who do not develop specific limb or cardiovascular symptoms, exercise may be terminated when patients achieve a high functional end point. After completing the test, the patient is asked to resume the supine position, and both brachial and ankle pressures are recorded at 1-minute intervals until they reach the pre-exercise baseline. In this way, the onset of claudication, maximal walking distance, and absolute and percentage decreases in ankle blood pressure or ABI at the first postexercise minute can be obtained (195).

Measurement of the ankle blood pressure and the ABI at rest and immediately after exercise yields objective data to grade the dynamic functional significance of an arterial stenosis. The postexercise ankle systolic pressure and ABI measurement relies on the principle that walking induces profound peripheral vasodilatation and decreased leg peripheral resistance. In normal individuals, the brachial and ankle blood pressures rise together and maintain their normal relationship with exertion. In contrast, in the presence of arterial occlusive disease, an abnormal hemodynamic response results. In individuals with lower extremity PAD, despite the increased central blood pressure, maximal exercise-induced ischemic vasodilation in the claudicating limb is associated with development of a significant blood pressure gradient across the lower extremity arterial stenosis. Thus, in the individual with vasculogenic claudication, the postexercise ankle blood pressure (and usually the ABI) will fall from its baseline value. For example, in individuals with symptoms of thigh and buttock claudication due to iliac arterial stenoses, the resting ABI may be normal. Measurement of a normal index at baseline with a subsequent diagnostic ABI fall immediately after exercise may reveal the functional significance of a high-grade stenosis that significantly limits ambulation. In contrast, the patient with pseudoclaudication due to spinal stenosis (or other nonarterial functional limitation) will demonstrate a normal postexercise ABI, despite exercise-limiting symptoms suggestive of claudication (162,195). Both the absolute fall in postexercise ankle blood pressure and the percent fall in ABI value have been used as diagnostic criteria after exercise, with variable diagnostic thresholds (162,195,196).

Exercise ABI and ankle blood pressure measurements may therefore be useful in establishing the diagnosis of lower extremity PAD when there is a high index of suspicion of lower extremity PAD, yet measures of the ABI at rest are normal. A simplified form of exercise testing can utilize a pedal plantar flexion test when a treadmill is not available in office practice. In this test, individuals with suspected lower extremity PAD but in whom the ABI is normal at rest are asked to stand flat-footed and perform 50 sequential, symptom-limited ankle plantar flexions and thus raise the heels maximally off the floor. Postexercise ABI values measured with this “tip-toe” test are similar to those recorded after treadmill exercise (197). The role of treadmill exercise tests in individuals who will initiate a program of supervised exercise is discussed more completely in Section 2.6.2.1.

There are limitations to the use of treadmill testing that relate to patient characteristics (e.g., comorbid conditions that prevent treadmill walking) and to access to motorized devices or to personnel trained to operate them. For example,
treadmill walking performance can be associated with significant anxiety in the elderly. Corridor walking, such as that associated with the 6-minute walk, has been evaluated recently and can potentially offer a more representative measure of walking ability during daily life. Current data demonstrate that the 6-minute walk test is reliable in patients with lower extremity PAD and is sensitive to change in walking endurance after exercise interventions. Thus, a 6-minute walk test can serve as an alternative objective method of assessing walking endurance in older men and women (198-200).

2.5.5. Duplex Ultrasound

RECOMMENDATIONS

Class I

1. Duplex ultrasound of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD. (Level of Evidence: A)

2. Duplex ultrasound is recommended for routine surveillance after femoral-popliteal or femoral-tibial-pedal bypass with a venous conduit. Minimum surveillance intervals are approximately 3, 6, and 12 months, and then yearly after graft placement. (Level of Evidence: A)

Class II

1. Duplex ultrasound of the extremities can be useful to select patients as candidates for endovascular intervention. (Level of Evidence: B)

2. Duplex ultrasound can be useful to select patients as candidates for surgical bypass and to select the sites of surgical anastomosis. (Level of Evidence: B)

Class IIb

1. The use of duplex ultrasound is not well established to assess long-term patency of percutaneous transluminal angioplasty. (Level of Evidence: B)

2. Duplex ultrasound may be considered for routine surveillance after femoral-popliteal bypass with a synthetic conduit. (Level of Evidence: B)

Duplex ultrasound of the extremities can be used to diagnose the anatomic location and degree of stenosis of lower extremity PAD. Duplex ultrasound also has broad clinical utility for evaluation of aneurysms, arterial dissection, popliteal artery entrapment syndrome, evaluation of lymphoceles, and assessment of soft tissue masses in individuals with vascular disease. Although duplex ultrasound includes images, either in black and white or color format, the primary clinically relevant information derived from duplex studies has been validated from analysis of the velocity of blood flow (201-209). Quantitative criteria used to diagnose stenoses are based on peak systolic velocity and peak systolic velocity ratios within or beyond the stenosis compared with the adjacent upstream segment, the presence or absence of turbulence, and preservation of pulsatility. In general, peak systolic velocity ratios have been found to be the most accurate diagnostic criterion. A ratio greater than 2 is commonly used to diagnose a stenosis greater than 50% diameter (201,202,205,207), although other ratios have been used (203,204,206,210). Some studies have attempted to further calibrate the duplex technique to distinguish between degrees of stenosis between 50% and 75% versus 75% and 99% (203,204,207,210).

The sensitivity and specificity for the diagnosis of stenoses greater than 50% diameter from the iliac arteries to the popliteal arteries are each approximately 90% to 95%. A meta-analysis compared the accuracy of the duplex Doppler technique performed with or without color imaging guidance. For a specificity of 95%, the sensitivity of color-guided duplex was 93% compared with 83% for noncolor duplex methods (211). Accuracy of the duplex examination depends on the ability of the technique to visualize the vessel adequately. Therefore, accuracy is diminished in examinations of the iliac arteries if bowel gas or tortuosity obscures the iliac vessels. Dense calcification can also obscure flow, particularly if flow is slow. If there are multiple stenoses downstream from a first stenosis, the downstream stenoses are detected with less sensitivity, approximating 60% to 65%, perhaps owing to slow flow and the presence of collateral vessels (203,212).

Duplex ultrasound can be used for preintervention decision making. This technique can predict whether a patient has anatomy suitable for angioplasty with an accuracy of 84% to 94% (210,213). It has been used as a substitute for arteriography for infrainguinal bypass grafting to select the most appropriate tibial vessel for distal anastomosis (214-216), although the final determination may require intraoperative angiography (217). However, some authors have suggested that duplex methods are inferior to angiography for evaluation of tibial arteries for distal bypass (218). An outcomes study has recently been published that demonstrates no difference in patency of infrapopliteal bypass grafts in nonrandomized cohorts of patients evaluated by preoperative duplex versus angiographic methods (214).

Duplex ultrasound has been used for postrevascularization surveillance of graft patency with mixed results. Vein grafts fail because of the development of stenoses either within the body of the graft, at the anastomosis, or upstream or downstream from the graft. These stenoses may threaten the graft even if the patient is asymptomatic and the ABI is unchanged. Duplex ultrasound surveillance studies allow detection of these stenoses before graft thrombosis with greater sensitivity than evaluation by clinical history (limb ischemic symptoms), physical examination, or use of the resting ABI (155,219-224). Case series have indicated that revision of such asymptomatic stenoses improves long-term graft patency. For example, Mattos et al. found that vein grafts that were revised on the basis of positive duplex ultrasound findings have a 90% 1-year patency rate, similar to grafts with initially normal duplex examinations (219). Grafts that were not revised despite the presence of a duplex ultrasound-detected stenosis had a patency rate of only 66%.
at 1 year. However, 2 randomized trials have offered conflicting results. Lundell et al. reported a 3-year primary assisted patency rate of vein grafts monitored with duplex ultrasound of 78% versus 53% for those followed up clinically and with the ABI (225). Ihlberg et al. (226), in contrast, reported no such differences in 1-year primary assisted patency. Despite the discrepant results from these randomized trials, duplex surveillance of vein grafts is widely accepted as valuable and necessary (226). Surveillance intervals are usually 4 to 6 weeks after graft placement, then 3, 6, 9, and 12 months and annually for venous conduit. Intervals for surveillance of synthetic grafts have not been well defined.

Duplex ultrasound surveillance of synthetic grafts is of questionable value. Several studies have found no improvement in patency of grafts when clinician decisions were guided in settings in which synthetic grafts were monitored with duplex studies (225,227,228). Several other studies have successfully detected stenoses or found some improvement in patency (229,230). The lack of consistent value offered by this testing strategy may be due to duplex-associated technical challenges, such as an inability to visualize the stenosis; vascular anatomic care challenges (e.g., the discovery of stenoses that are not amenable to revision); or procedural challenges, such that the subsequent graft revision does not serve to improve long-term graft patency.

Duplex surveillance after angioplasty procedures is also of questionable value. Immediately after angioplasty, several studies suggested that velocities in the treated segment may be abnormally elevated and do not predict decreased subsequent patency rates (231-233). This may be due to percutaneous transluminal angioplasty (PTA)–produced vessel dissections that successfully remodel over time. Two contradictory studies suggest that elevated velocities immediately after PTA do predict early PTA failure (234,235). Duplex ultrasound is useful in evaluations for recurrent chronic stenoses (148,234,236-238). Although it is reasonable to assume that revisions of post-PTA restenoses that are detected by duplex ultrasound studies might improve long-term patency, there are no published studies that have evaluated this, and therefore, this assumption is unsupported.

2.5.6. Computed Tomographic Angiography

RECOMMENDATIONS

Class IIb
1. Computed tomographic angiography of the extremities may be considered to diagnose anatomic location and degree of stenosis of PAD. Computed tomographic angiography requires intravenous injection of iodinated contrast, which opacifies the arteries. The angiographic image is constructed from multiple cross-sectional images and then presented as a maximum-intensity projection, similar to the appearance of standard arteriography. The image can be rotated 3-dimensionally in space to view any oblique projection.

Use and assessment of CTA for the extremities is at an early developmental stage. Early studies have used technology in which 1 cross-sectional image was acquired at a time (single-detector technology). This limited the length of the vessel that could be imaged because of limits from X-ray tube heating, time to acquire multiple images, and total volume of contrast used. New multidetector technology allows acquisition of as few as 4 and as many as 64 simultaneous cross-sectional images. This has permitted CTA to be performed progressively faster, with less contrast material, thinner sections, and greater detail (239-244). The latest generation of computed tomography scanners may acquire up to 64 or more simultaneous images. The clinical variability inherent when computed tomography scanners of a range of technical sophistication are deployed limits the generalizability of statements of accuracy (derived from published reports) in a rapidly changing imaging environment.

Results from single-detector computed tomography studies have shown excellent accuracy for detection of occlusions, with sensitivities and specificities of 94% to 100% (245). Accuracy for detection of stenoses is lower. Rieker et al. reported a sensitivity of only 36% to 58% for detection of stenoses greater than 75% diameter when interpreting the maximum-intensity projection, although sensitivity improved to 73% to 88% when each of the individual cross-sectional images was also analyzed (245). Tins et al. found that CTA and catheter angiography provided concordant results 85% of the time, but CTA was characterized by worse interobserver agreement (78% vs. 87%). Computed tomographic angiography missed short stenoses owing to use of a slice thickness of 4 to 5 mm (246).

Several studies have reported results using multidetector computed tomography techniques (240-244,247,248). These have been relatively small series, inclusive of only 18 to 65 patients, but results have been excellent. Sensitivity for stenosis greater than 50% has ranged from 89% to 100% with specificity ranging from 92% to 100%. One study examined 85 infragenual bypass grafts in 65 patients with CTA compared with duplex ultrasound and/or angiography as the “gold standard.” Sensitivity for stenosis greater than 50% was 97% to 100%, with a specificity of 100% (242). Not all of these studies were performed with investigators blinded to the results of the angiogram used as the gold standard comparison. Computed tomography studies could be performed from the celiac artery to the feet with 100 to 180 mL of contrast. Image acquisition time was 35 to 66 seconds. Radiation dose was one fourth the dose used in catheter angiography. In clinical use, radiation doses are dependent...
on the computed tomography scanner and protocol used and may vary considerably.

The CTA method has potential diagnostic advantages compared with catheter angiography. The 3-dimensional (3D) images can be freely rotated in space, which permits evaluation of eccentric stenoses. The intravenous injection of contrast during CTA will fill all collateral vessels and opacify arteries distal to occlusions that may be occult by catheter angiography (231,233,245,247). Computed tomographic angiography images tissues surrounding the opacified lumen of the artery and has demonstrated that some popliteal stenoses and occlusions are due to aneurysms, popliteal entrapment, and cystic adventitial disease, which are not detected with catheter angiography (249). Computed tomographic angiography also has potential disadvantages compared with catheter angiography. Spatial resolution is lower than with digital subtraction angiography. Venous opacification can obscure arterial filling. Asymmetrical opacification of the legs may cause CTA to miss the arterial phase in some vessels. The huge number of cross-sectional images generated (up to 2000 currently) may overwhelm the workstations used for image processing (247).

CTA has potential advantages over MRA. Patients with pacemakers or defibrillators, who are excluded from imaging within magnetic resonance machines, may be imaged safely with CTA. Metal clips, stents, and prostheses usually do not cause significant CTA artifacts that limit diagnostic utility. Computed tomographic angiography has higher resolution and can provide images of calcification in the vessel wall. Scan times are significantly faster with CTA than with MRA. Claustrophobia is far less of a problem. Computed tomographic angiography also has potential disadvantages compared with MRA. It requires iodinated contrast, which may be nephrotoxic in azotemic patients. It also requires ionizing radiation, although the radiation dose is less than with catheter angiography (247).

Despite these potential advantages, the accuracy and effectiveness of CTA are not yet as well determined as with MRA. Only a few studies have been published to compare the 2 techniques, and these have included small numbers of patients who have undergone lower extremity preprocedural CTA. Interpretations of CTA-derived data have not been blinded consistently. Physician confidence in the treatment decision may be lower with CTA than with catheter angiography. Thus, use of CTA might lead to a much higher rate of recommendation for further imaging studies (250). Similarly, postrevascularization surveillance of individuals via use of CTA has not been studied. Therefore, although the application of lower extremity CTA is considered extremely promising, recommendations for its routine clinical use are yet not as robust as for MRA.

2.5.7. Magnetic Resonance Angiography

RECOMMENDATIONS

Class I

1. Magnetic resonance angiography of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD. (Level of Evidence: A)

2. Magnetic resonance angiography of the extremities should be performed with gadolinium enhancement. (Level of Evidence: B)

3. Magnetic resonance angiography of the extremities is useful in selecting patients with lower extremity PAD as candidates for endovascular intervention. (Level of Evidence: C)

Class IIb

1. Magnetic resonance angiography of the extremities may be considered to select patients with lower extremity PAD as candidates for surgical bypass and to select the sites of surgical anastomosis. (Level of Evidence: B)

2. Magnetic resonance angiography of the extremities may be considered for postrevascularization (endovascular and surgical bypass) surveillance in patients with lower extremity PAD. (Level of Evidence: B)

In a manner similar to duplex ultrasound, MRA of the extremities can be used to diagnose the anatomic location and degree of stenosis of PAD. Magnetic resonance angiography evaluation is based on imaging the arteries, similar to standard arteriography. Assessment of the accuracy of MRA depends on the MRA technique used and the standard against which it is compared. Magnetic resonance angiography techniques continue to evolve and improve. Techniques employed include 2-dimensional time of flight, 3D imaging, and contrast enhancement with gadolinium, subtraction, cardiac gating, and bolus chase. These techniques may be used in combination, because each has its advantages and disadvantages (251). Magnetic resonance angiography has been compared with catheter angiography and intraoperative angiography. For studies that compare the ability of MRA versus catheter angiography to detect pedal vessels in patients with CLI, the standard of accuracy has been intraoperative angiography.

A multicenter comparison of MRA with catheter angiography that used intraoperative angiography as the standard found that both techniques had similar accuracy. Sensitivity and specificity for identification of patent segments were each 81% to 85%. For identification of normal segments (i.e., segments suitable for bypass), the sensitivity of contrast angiography was slightly less than MRA (77% vs. 82%), but its specificity was better (92% vs. 84%) (252). A meta-analysis of MRA compared with catheter angiography demonstrated that the sensitivity and specificity of MRA for detection of stenoses greater than 50% were both in the range of...
90% to 100%, with greatest accuracy when gadolinium-enhanced MRA was used (253). The most current studies report similar results, with agreement between MRA and catheter angiography of 91% to 97% (254). A meta-analysis compared the accuracy of gadolinium-enhanced MRA versus color duplex ultrasound and found that the sensitivity for detecting arterial segments with greater than 50% diameter stenosis was better for MRA than for duplex ultrasound (98% vs. 88%), with similar specificities (96% vs. 95%) (255).

Some studies claim that MRA is superior to catheter angiography in detection of outflow vessels suitable for distal bypass in patients with CLI (256,257). Kreitner et al. found that in 24 diabetic patients with CLI, 38% had pedal vessels detected by MRA that were not detected by catheter angiography (256). Such vessels treated with surgical bypass may enjoy satisfactory patency (258). The claim that MRA is more sensitive than catheter angiography for distal vessels is controversial and is affected by the quality of the comparative catheter angiogram (259,260). At least 1 study has shown MRA to be inferior to catheter angiography, particularly for patients with limb-threatening ischemia (261).

Magnetic resonance angiography has unique limitations. It tends to overestimate the degree of stenosis because of turbulence. Time-of-flight studies may overestimate occlusions owing to loss of signal from retrograde collateral flow. Metal clips can cause artifacts that mimic vessel occlusions. Similarly, some metal stents will obscure vascular flow (262). Patients with pacemakers and defibrillators and some cerebral aneurysm clips cannot be scanned safely (262,263). Magnetic resonance angiography performed with gadolinium has on rare occasions been associated with renal toxicity in patients with elevated creatinine levels (264).

Magnetic resonance angiography may be used for preoperative planning. Early studies suggested that MRA was not sufficiently accurate for preoperative planning (265). However, other studies have demonstrated agreement between preoperative plans based on MRA versus catheter angiography of at least 90%, and some centers no longer perform diagnostic catheter angiography before revascularization (253,266-268).

Magnetic resonance angiography has been used anecdotally for assessment of surgical and endovascular revascularization. Series of small numbers of patients have shown that the sensitivity and specificity of MRA compared with catheter angiography for detection of stenoses in vein or synthetic bypass grafts is 90% to 100% (269-271). For immediate postprocedure evaluation of angioplasty sites, agreement with catheter angiography is 80% to 95% (272,273). There have been no published studies that validate improved patient outcomes from postrevascularization MRA surveillance.

### 2.5.8. Contrast Angiography

#### RECOMMENDATIONS

**Class I**

1. Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated. *(Level of Evidence: B)*

2. A history of contrast reaction should be documented before the performance of contrast angiography and appropriate pretreatment administered before contrast is given. *(Level of Evidence: B)*

3. Decisions regarding the potential utility of invasive therapeutic interventions (percutaneous or surgical) in patients with lower extremity PAD should be made with a complete anatomic assessment of the affected arterial territory, including imaging of the occlusive lesion, as well as arterial inflow and outflow with angiography or a combination of angiography and noninvasive vascular techniques. *(Level of Evidence: B)*

4. Digital subtraction angiography is recommended for contrast angiographic studies because this technique allows for enhanced imaging capabilities compared with conventional unsubtracted contrast angiography. *(Level of Evidence: A)*

5. Before performance of contrast angiography, a full history and complete vascular examination should be performed to optimize decisions regarding the access site, as well as to minimize contrast dose and catheter manipulation. *(Level of Evidence: C)*

6. Selective or superselective catheter placement during lower extremity angiography is indicated because this can enhance imaging, reduce contrast dose, and improve sensitivity and specificity of the procedure. *(Level of Evidence: C)*

7. The diagnostic lower extremity arteriogram should image the iliac, femoral, and tibial bifurcations in profile without vessel overlap. *(Level of Evidence: B)*

8. When conducting a diagnostic lower extremity arteriogram in which the significance of an obstructive lesion is ambiguous, transstenotic pressure gradients and supplementary angulated views should be obtained. *(Level of Evidence: B)*

9. Patients with baseline renal insufficiency should receive hydration before undergoing contrast angiography. *(Level of Evidence: B)*

10. Follow-up clinical evaluation, including a physical examination and measurement of renal function, is recommended within 2 weeks after contrast angiography to detect the presence of delayed adverse effects, such as atheroembolism, deterioration in renal function, or access site injury (e.g., pseudoaneurysm or arteriovenous fistula). *(Level of Evidence: C)*
Class IIa

1. Noninvasive imaging modalities, including MRA, CTA, and color flow duplex imaging, may be used in advance of invasive imaging to develop an individualized diagnostic strategic plan, including assistance in selection of access sites, identification of significant lesions, and determination of the need for invasive evaluation. (Level of Evidence: B)

2. Treatment with n-acetylcysteine in advance of contrast angiography is suggested for patients with baseline renal insufficiency (creatinine greater than 2.0 mg per dL). (Level of Evidence: B)

Contrast angiography has heretofore been considered the “gold standard” for defining both normal vascular anatomy and vascular pathology. It remains the most readily available and widely used imaging technique. Images are easily displayed and interpreted by the vast majority of physicians caring for patients with vascular disease. Technical improvements in X-ray imaging equipment, including the application of digital subtraction techniques to enhance image quality and detection of abnormalities, and progressive improvements in image resolution have enabled better definition of affected vascular territories with contrast and have resulted in a better safety profile. The simultaneous miniaturization of catheters available for angiography and the development of more selective shapes has further enhanced the safety profile of this standard technique.

Although angiography remains the current “gold standard,” significant advances in duplex, magnetic resonance, and computed tomographic imaging techniques may make these newer modalities preferable to angiography for certain situations (e.g., CLI with poor inflow to the leg and below-knee vessels that are difficult to identify by digital subtraction angiography). In addition, noninvasive imaging with duplex, MRA, and/or CTA methods may allow for better preparation before initiation of an invasive procedure. Identification of a culprit lesion, preparation of the appropriate equipment, and selection of the best access sites are all facilitated by information obtained by these noninvasive imaging modalities. Thus, there is now a wide variety of practice patterns with respect to the use of noninvasive imaging modalities for therapeutic planning. At some centers, it has become the standard to obtain MRA or CTA images in advance of any invasive diagnostic studies (baring a contraindication to the particular noninvasive technique, such as a pacemaker, which precludes the use of MRA). At other centers, it is still the standard that a diagnostic angiogram is obtained with digital subtraction techniques before an intervention is planned. Detailed imaging algorithms have not yet been developed that include clinical details from the individual patient, the modalities and expertise available at a given site, and the relative costs. The goal of combining these imaging techniques will be to minimize risk and optimize outcome for the patient while maintaining economic viability for the healthcare system.

Currently, contrast angiography remains the dominant diagnostic tool used to stratify patients before intervention. When used for this purpose, complete imaging of the affected territory is usually recommended. Knowledge of inflow and outflow patterns, as well as characterization of the lesion, may affect decisions regarding therapy. From a technical standpoint, the closer the catheter is to the target vessel to be imaged, the better the image definition is and the less is the volume of contrast that is required. Accordingly, selective and superselective catheter placement is useful in optimizing image quality. This is particularly recommended in the setting of renal insufficiency or when occlusive distal vessels may not be visualized by a more proximal bolus injection of contrast. The acquisition of views from orthogonal angles, which has been the rule in coronary angiography, is less prevalent in peripheral imaging, largely because of the extensive territory to be covered in a complete diagnostic peripheral runoff angiogram (as opposed to a coronary angiogram). Nonetheless, for areas where there is doubt or uncertainty regarding the presence or absence of a significant lesion, angulated views can be useful to better delineate and define the severity of the lesion and clarify its potential contribution to the clinical syndrome. This does, however, require injection of additional contrast material and prolongs the angiographic procedure. Axial imaging techniques (e.g., MRA and CTA) may offer an advantage for visualizing some of these eccentric, ambiguous lesions, because these techniques offer a 3D view.

Digital subtraction technique provides superior definition of the vascular tree compared with unsubtracted imaging. The former eliminates much of the artifact due to bony structures and dense body tissues. Selection of the appropriate amount of contrast and application of proper image-acquisition techniques, including masking and digital enhancement, are required to optimize the accuracy of the images obtained. Improper technique or image display can cause false interpretation.

Angiography is, at present, the only universally accepted method for guiding percutaneous peripheral interventional procedures. Adjunctive hemodynamic parameters, such as pressure gradient and duplex velocity measurements, as well as use of supportive imaging modalities, such as intravascular ultrasound, angiography, and optical coherence tomography, can be useful and occasionally have been used in lieu of digital subtraction angiography to guide procedures.

Angiography has several liabilities. First, it carries with it the risks associated with any invasive procedure. Such risks include those related to vascular access (e.g., bleeding, infection, and vessel disruption). In addition, there is a small but important risk of contrast reaction; the risk of a severe reaction is approximately 0.1% (274,275). A careful history is imperative before administration of contrast agents to determine whether there is any suggestion of a previous allergic reaction or predisposition to develop such a reaction. The history of an allergic reaction may serve as a relative procedural contraindication if a patient requires the data derived from the arteriographic procedure to plan appropriate care.
Proper selection and pretreatment of such patients can mitigate, although not eliminate, the risk of significant contrast-related morbidity and mortality. The availability of alternative low-osmolality/nonionic contrast agents has reduced the number of allergic reactions.

Contrast agents are also associated with a small but important incidence of nephrotoxicity. Patients who are at increased risk of contrast nephropathy include those with severe baseline renal dysfunction, diabetes, low cardiac output state, or dehydration. Any combination of these is more problematic than an individual risk factor. Recent studies have suggested that use of low-osmolar contrast agents (e.g., iodixanol) or pretreatment with n-acetylcysteine may reduce the incidence of renal compromise (276-279). Fenoldopam does not appear to confer significant renal protective effects (280). In patients who are high risk for nephrotoxicity, data suggest that vigorous hydration before administration of contrast may serve as the most important strategy to prevent postprocedural deterioration in renal function. Because the occurrence of nephrotoxicity appears to be dose-dependent, it is also important to minimize contrast usage. This dose minimization can be accomplished by using digital subtraction techniques and placing catheters closer to the site to be imaged (selective angiography). The dose–nephrotoxicity relationship is complex and cannot be calculated precisely. Preliminary data suggest that nephrotoxicity might be further minimized by use of preprocedural hemofiltration in individuals with chronic renal failure (defined as a creatinine measurement greater than 2.0 mg per dL) (281).

Finally, complications typically associated with invasive techniques and catheter manipulation, such as atheroembolization, dissection, and inadvertent vessel-wall disruption or perforation, are all adverse events that can occur with invasive angiography. Vigilant observation and careful manipulation of guidewire and catheter location are imperative. Certain adverse events, including access-site complications, nephrotoxicity, and atheroembolism, may not be evident immediately after the procedure, and follow-up evaluation is recommended within 2 weeks after contrast angiography to detect and treat these events.

2.6. Treatment

2.6.1. Cardiovascular Risk Reduction

To reduce adverse cardiovascular events associated with lower extremity PAD, lifelong treatment should include modification or elimination of atherosclerotic risk factors, such as cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension, and promotion of daily exercise and use of a nonatherogenic diet.

2.6.1.1. Lipid-Lowering Drugs

RECOMMENDATIONS

Class I

Treatment with a hydroxymethyl glutaryl (HMG) coenzyme-A reductase inhibitor (statin) medication is indicated for all patients with PAD to achieve a target LDL cholesterol level of less than 100 mg per dL. (Level of Evidence: B)

Class IIa

1. Treatment with an HMG coenzyme-A reductase inhibitor (statin) medication to achieve a target LDL cholesterol level of less than 70 mg per dL is reasonable for patients with lower extremity PAD at very high risk of ischemic events. (Level of Evidence: B)

2. Treatment with a fibric acid derivative can be useful for patients with PAD and low HDL cholesterol, normal LDL cholesterol, and elevated triglycerides. (Level of Evidence: C)

Treatment of dyslipidemia reduces the risk of adverse cardiovascular events in patients with atherosclerosis. Cholesterol-lowering therapy with an HMG coenzyme-A reductase inhibitor (statin) reduces the risk of nonfatal MI and cardiovascular death in patients with coronary artery disease by 24% to 34% (282-284). The Heart Protection Study randomized patients with coronary artery disease, cerebrovascular disease, PAD, and/or diabetes mellitus and a total cholesterol level greater than 135 mg per dL to simvastatin or placebo (112). The study included 6748 patients with PAD, in whom there was a 25% risk reduction over 5 years of follow-up. A revision of the National Cholesterol Education Program Adult Treatment Panel III guidelines, which reviewed the totality of lipid-lowering interventional investigations, has evaluated the risk and benefit of statin therapies by population risk categories and target LDL levels (129a). In this classification system, individuals with lower extremity PAD are designated as either “high risk” or “very high risk” depending on associated risk factors. For individuals with PAD, “very high risk” can be defined as the presence of established PAD plus (a) multiple major risk factors (especially diabetes), (b) severe and poorly controlled risk factors (especially continued cigarette smoking), or (c) multiple risk factors of the metabolic syndrome (especially high triglycerides [greater than or equal to 200 mg per dL] plus non-HDL cholesterol greater than or equal to 130 mg per dL with low HDL cholesterol [greater than or equal to 40 mg per dL]).

On the basis of these findings, it is recommended that patients with PAD and an LDL cholesterol level of 100 mg per dL or greater be treated with a statin. The recommended LDL cholesterol goal is less than 100 mg per dL, but when risk is very high, an LDL cholesterol goal of less than 70 mg per dL is a therapeutic option on the basis of available clinical trial evidence. This therapeutic option may also extend to patients with lower extremity PAD who are at very high risk and who have a baseline LDL cholesterol less than 100 mg per dL.

Fibric acid derivatives increase HDL cholesterol and lower triglyceride levels. The efficacy of this class of drug in patients with PAD is not known. In patients with coronary artery disease and low HDL cholesterol levels, one study
found that gemfibrozil reduced the risk of nonfatal MI or cardiovascular death by 22% (285). Lipid-lowering therapy with niacin and binding resins such as cholestyramine reduces the progression of femoral artery atherosclerosis, but there are no data that these therapies reduce the risk of adverse cardiovascular events (286,287).

Cholesterol-lowering therapy may improve symptoms of intermittent claudication (288,289). A retrospective analysis of the 4S trial (Scandinavian Simvastatin Survival Study) found that simvastatin therapy reduced the risk of new or worsening claudication (289). A prospective trial demonstrated that atorvastatin increased the distance walked to the onset of claudication, but not the maximal walking distance, in patients with lower extremity PAD (290). Two additional single-center studies have suggested a similar benefit regarding claudication onset time with simvastatin treatment (291,292). The relative benefit of the lipid-modifying therapies for claudication symptoms remains unclear.

### 2.6.1.2. Antihypertensive Drugs

**RECOMMENDATIONS**

**Class I**

1. Antihypertensive therapy should be administered to hypertensive patients with lower extremity PAD to achieve a goal of less than 140 mm Hg systolic over 90 mm Hg diastolic (nondiabetics) or less than 130 mm Hg systolic over 80 mm Hg diastolic (diabetics and individuals with chronic renal disease) to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death. *(Level of Evidence: A)*

2. Beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated in patients with PAD. *(Level of Evidence: A)*

**Class IIa**

The use of angiotensin-converting enzyme inhibitors is reasonable for symptomatic patients with lower extremity PAD to reduce the risk of adverse cardiovascular events. *(Level of Evidence: B)*

**Class IIb**

Angiotensin-converting enzyme inhibitors may be considered for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular events. *(Level of Evidence: C)*

Treatment of high blood pressure is indicated to reduce the risk of cardiovascular events such as stroke, heart failure, and death (293). Guidelines for treatment of hypertension have been published (294). Antihypertensive therapy may decrease limb perfusion pressure and potentially exacerbate symptoms of claudication or CLI. These possibilities should be taken into consideration when administering antihypertensive drugs to patients with PAD. However, most patients are able to tolerate therapy without worsening of symptoms and should be treated appropriately to reduce the risk of adverse cardiovascular events. Concerns have been raised about the use of beta-adrenergic blockers in the treatment of patients with lower extremity PAD. Beta-blockers reduced the risk of MI and death in patients with coronary atherosclerosis (295). A meta-analysis of 11 placebo-controlled studies in patients with intermittent claudication found that beta-adrenergic blockers did not adversely affect walking capacity (296).

Angiotensin-converting enzyme inhibitors are a class of drugs used in the treatment of hypertension. Angiotensin-converting enzyme inhibitors reduce the risk of death and nonfatal cardiovascular events in patients with coronary artery disease and left ventricular dysfunction (297,298). Because the evidence base for the efficacy of ACE inhibitors in asymptomatic patients is nonexistent, recommendations for their use must be extrapolated from symptomatic populations. The Heart Outcomes Prevention Evaluation study randomized patients with coronary artery disease, cerebrovascular disease, PAD, and/or diabetes to the ACE inhibitor ramipril or placebo. The study included 4051 patients with PAD. Ramipril reduced the risk of MI, stroke, or vascular death in patients with PAD by approximately 25%, a level of efficacy comparable to that achieved in the entire study population (299). It is recommended that ACE inhibitors be considered as treatment for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular events.

### 2.6.1.3. Diabetes Therapies

**RECOMMENDATIONS**

**Class I**

Proper foot care, including use of appropriate footwear, chiropody/podiatric medicine, daily foot inspection, skin cleansing, and use of topical moisturizing creams, should be encouraged and skin lesions and ulcerations should be addressed urgently in all diabetic patients with lower extremity PAD. *(Level of Evidence: B)*

**Class IIa**

Treatment of diabetes in individuals with lower extremity PAD by administration of glucose control therapies to reduce the hemoglobin A1C to less than 7% can be effective to reduce microvascular complications and potentially improve cardiovascular outcomes. *(Level of Evidence: C)*

It is not known whether aggressive treatment of diabetes to optimize blood glucose levels decreases the risk of adverse cardiovascular events in patients with lower extremity PAD. Retrospective analysis of the Diabetes Control and Complications trial, a study of patients with type I diabetes mellitus, found that intensive insulin therapy reduced the risk of lower extremity PAD events, such as claudication, peripheral revascularization, or amputation, by 22%, but that result did not achieve statistical significance (300). In the United
Kingdom Prospective Diabetes Study, patients with type II diabetes mellitus were randomized to aggressive treatment with sulfonylureas or insulin versus conventional treatment. Patients were treated over a period of 10 years. Intensive treatment reduced the risk of MI by 16%, a finding of borderline significance, but it did not decrease the risk of death, stroke, or amputation (301). Aggressive treatment of diabetes does decrease the risk for microvascular events such as nephropathy and retinopathy (300,301). Therefore, to reduce the risk of microvascular events, pending prospective trials in patients with diabetes and lower extremity PAD, it is recommended that diabetic patients with lower extremity PAD be treated aggressively to reduce their glycosylated hemoglobin to less than 7% as per the American Diabetes Association (302).

Meticulous attention to foot care is necessary to reduce the risk of skin ulceration, necrosis, and subsequent amputation. This includes the use of appropriate footwear to avoid pressure injury, daily inspection and cleansing by the patient, the use of moisturizing cream to prevent dryness and fissuring, and chiropody. Frequent foot inspection by patients and physicians will enable early identification of foot lesions and ulcerations and facilitate prompt referral for treatment (303).

2.6.1.4. Smoking Cessation

RECOMMENDATION

Class I

Individuals with lower extremity PAD who smoke cigarettes or use other forms of tobacco should be advised by each of their clinicians to stop smoking and should be offered comprehensive smoking cessation interventions, including behavior modification therapy, nicotine replacement therapy, or bupropion. (Level of Evidence: B)

No prospective randomized trials have examined the effects of smoking cessation on cardiovascular events in patients with lower extremity PAD. Observational studies have found that the risk of death, MI, and amputation is substantially greater in those individuals with PAD who continue to smoke than in those who stop smoking (304-306). In some but not all studies, exercise time is greater in patients who discontinue smoking than in current smokers (307,308). It is recommended that efforts be made to achieve smoking cessation in patients with lower extremity PAD. Physician advice coupled with frequent follow-up achieves 1-year smoking cessation rates of approximately 5% compared with only 0.1% in those attempting to quit smoking without a physician’s intervention (309). Pharmacological interventions such as nicotine replacement therapy and bupropion achieve 1-year smoking cessation rates of approximately 16% and 30%, respectively (310). Tobacco cessation interventions are particularly critical in individuals with thromboangiitis obliterans, because it is presumed that components of tobacco may be causative in the pathogenesis of this syndrome, and continued use is associated with a particularly adverse outcome (21).

2.6.1.5. Homocysteine-Lowering Drugs

RECOMMENDATION

Class IIb

The effectiveness of the therapeutic use of folic acid and B₁₂ vitamin supplements in individuals with lower extremity PAD and homocysteine levels greater than 14 micromoles per liter is not well established. (Level of Evidence: C)

The B complex vitamins, folic acid, cobalam (B₁₂), and pyridoxine (B₆), have been used as therapy to decrease homocysteine levels. The Food and Drug Administration (FDA) has required that cereal grain products contain at least 140 micrograms of folic acid per 100 g of product. Folic acid at a dose of 400 micrograms per day will reduce plasma homocysteine levels by approximately 5 micromoles per liter (66). A meta-analysis of 12 trials that included 1114 people found that folic acid, at doses of 0.5 to 5 mg daily, decreased homocysteine concentrations by 25% and that vitamin B₁₂, at doses averaging 0.5 mg daily, decreased homocysteine levels by an additional 7% (311). Vitamin B₆ (at an average of 6.5 mg daily) had no significant additional benefit. Folic acid supplementation may exacerbate relative cobalamin deficiency, particularly in older individuals (312). Despite efficacy in reducing plasma homocysteine levels, there is currently no evidence that treatment with folic acid and/or cobalamin favorably affects vascular outcome; however, prospective trials are in progress (67,313). Treatment with B complex vitamin is generally safe, and treatment with folic acid and cobalamin can be devised to target a reduction of homocysteine levels to less than 10 micromoles per liter. However, pending the demonstration of clinical benefit from prospective trials, the therapeutic use of folate for patients with lower extremity PAD whose fasting plasma homocysteine level is greater than 14 micromoles per liter is not well established.

2.6.1.6. Antiplatelet and Antithrombotic Drugs

RECOMMENDATIONS

Class I

1. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (Level of Evidence: A)

2. Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (Level of Evidence: A)
3. Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (Level of Evidence: B)

Class III

Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD. (Level of Evidence: C)

The effect of antiplatelet therapy on cardiovascular events has been systematically reviewed by the Antithrombotic Trialists’ Collaboration (314). A meta-analysis comprising 287 studies compared the efficacy of antiplatelet therapy versus control in approximately 135,000 high-risk patients with vascular diseases manifested as acute and previous MI, acute and previous stroke, or other high-risk conditions, such as lower extremity PAD (314). Among those patients with PAD treated with antiplatelet therapy, there was a 22% odds reduction for adverse cardiovascular events, including MI, stroke, or vascular death. This analysis included 42 trials comprising 9716 patients with PAD in whom there was a 23% proportional reduction in adverse cardiovascular events. Similar benefits were realized by patients with intermittent claudication, those having peripheral angioplasty, and those having peripheral bypass graft procedures (314). There was a 23% reduction of vascular events in patients with intermittent claudication, 22% in those with peripheral arterial grafts, and 29% in those undergoing peripheral angioplasty (314). The antiplatelet therapy used in many of the lower extremity PAD trials was aspirin; however, some included ticlopidine, a thienopyridine drug, and one included picotamide, a thromboxane synthase inhibitor.

The Antithrombotic Trialists’ Collaboration meta-analysis also compared the efficacy of different doses of aspirin (314). The proportional reduction in vascular events was 32% with 75 to 150 mg daily, 26% with 160 to 325 mg daily, and 19% with 500 to 1500 mg daily, the results being relatively comparable among these dose ranges. There was a significantly smaller (13%) reduction in cardiovascular events in patients being treated with less than 75 mg of aspirin per day. The ORs for a major extracranial bleed among patients taking 75 to 150 mg of aspirin and those taking 160 to 325 mg of aspirin daily were 1.5 and 1.4, respectively (314). Higher doses of aspirin result in increased risk of gastrointestinal side effects and bleeding rates (315). One trial compared the efficacy of aspirin (325 mg daily) to the thienopyridine derivative clopidogrel (75 mg daily) in 19,185 patients with a history of MI, stroke, or PAD. Clopidogrel reduced the risk of adverse cardiovascular events by 8.7%. Among the 6452 patients with PAD, clopidogrel reduced the risk of MI, stroke, or vascular death by 23.8% more than aspirin (98). The risks of intracranial and gastrointestinal bleeding in patients randomized to aspirin were 0.49% and 2.66%, and in those randomized to clopidogrel, the risks were 0.35% and 1.99%, respectively.

It is recommended that patients with lower extremity PAD be treated with antiplatelet therapy to reduce the risk of MI, stroke, or vascular death. On the basis of the single comparative trial published to date, clopidogrel appears to be more effective than aspirin in preventing ischemic events in individuals with symptomatic PAD (98). The combination of clopidogrel plus aspirin versus aspirin alone has been examined in patients who had presented with acute coronary syndrome. Combination aspirin and clopidogrel therapy was associated with a 20% relative risk reduction for MI, stroke, or cardiovascular death (316). To date, there is no evidence to support the efficacy of combined aspirin and clopidogrel treatment versus a single antiplatelet agent in patients with lower extremity PAD.

Several studies have suggested that antiplatelet therapy may reduce the risk of progression to arterial occlusion in patients with lower extremity PAD. The Antithrombotic Trialists’ Collaboration found that antiplatelet therapy compared with no additional treatment reduced the risk of arterial occlusion over a 19-month period by 30% (317). One meta-analysis that involved 54 randomized, controlled trials in patients with intermittent claudication found that aspirin compared with placebo reduced the risk of arterial occlusion, and ticlopidine reduced the need for revascularization procedures (318).

Information regarding the efficacy of oral anticoagulants, that is, coumarin derivatives such as warfarin, in reducing adverse cardiovascular events in patients with atherosclerosis is derived primarily from studies of patients with coronary artery disease. Meta-analyses comprising 37 trials of anticoagulant therapy in more than 20,000 patients with coronary artery disease evaluated the efficacy and safety of oral anticoagulation (warfarin) alone versus the control, stratified by intensity of anticoagulation, as well as the efficacy of warfarin versus aspirin in patients with coronary artery disease (319,320).

High-intensity oral anticoagulant therapy, defined as an International Normalized Ratio (INR) of 2.8 to 4.8, was associated with a 22% odds reduction in mortality and a 43% odds reduction in MI, but this intensive anticoagulation was associated with a 4.5-fold increase in major bleeding. Moderate-intensity anticoagulation, defined as an INR of 2 to 3, was associated with a nonsignificant odds reduction of 26% for cardiovascular death and stroke and 52% for MI, but it increased bleeding by 7.7-fold. Comparison of moderate-to high-intensity oral anticoagulation versus aspirin found a 21% odds reduction in death, MI, or stroke but was associated with a 2.1-fold increased risk in major bleeding. Thus, among patients with coronary artery disease, moderate- and high-intensity oral anticoagulation with coumarin derivatives reduces the risk of MI and death but confers an increased rate of bleeding. One trial compared the efficacy of oral anticoagulants with aspirin on infrainguinal graft patency in patients with lower extremity PAD. Patients were randomized to coumarin derivatives to achieve a target INR of 3.0 to
4.5 or to aspirin 80 mg daily orally (321). A similar number of graft occlusions occurred in each treatment group, but the risk of major bleeding was increased approximately 2-fold in those treated with oral antiocoagulants. In that study, there was a nonsignificant (11%) reduction in the risk of a secondary end point that consisted of the composite of vascular death, MI, stroke, or amputation.

Meta-analyses of 7 trials of moderate-intensity oral anticoagulation plus aspirin versus aspirin alone to prevent cardiovascular events in patients with coronary artery disease found a 12% odds reduction in cardiovascular death, MI, and stroke that favored combination therapy (320). There was a 1.7-fold increased risk for major bleeding with oral anticoagulation plus aspirin versus aspirin alone. Low-intensity oral anticoagulation (INR less than 2) plus aspirin versus aspirin alone did not reduce the risk of cardiovascular events (319,320).

The combination therapy of oral anticoagulation plus aspirin may reduce the risk of cardiovascular events and is associated with an approximately 2-fold increased risk of bleeding. Taken together, there is insufficient evidence to support a recommendation for oral anticoagulation therapy with coumarin derivatives, alone or in combination with aspirin, as a means to reduce cardiovascular events in patients with PAD, and consideration for use of coumarin derivatives must be tempered by the increased risk of bleeding. For patients with lower extremity PAD in whom an additional indication for use of warfarin exists (such as individuals with lower extremity PAD and either atrial fibrillation or a prosthetic heart valve), the risk and benefit of therapy with an antiplatelet medication alone, warfarin alone, or their combination must be assessed individually.

2.6.2. Claudication

2.6.2.1. Exercise and Lower Extremity PAD Rehabilitation

RECOMMENDATIONS

Class I

1. A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. (Level of Evidence: A)

2. Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least 3 times per week for a minimum of 12 weeks. (Level of Evidence: A)

Class IIb

The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. (Level of Evidence: B)

A program of supervised exercise may be considered a primary efficacious treatment modality to alleviate claudication symptoms for all patients with intermittent claudication. Regular walking in a supervised claudication exercise program can be expected to result in an increase in the speed, distance, and duration walked, with decreased claudication symptoms at each workload or distance (322-328). These functional benefits accrue gradually and become evident over 4 to 8 weeks and increase progressively over 12 or more weeks. The biological mechanisms underlying such reproducible benefit are complex and are beyond the scope of this guideline (132). However, there is inadequate evidence to attribute this functional benefit, as is often believed, to the growth of new collaterals (angiogenesis); in contrast, clinical improvement is more likely to be due to alterations in skeletal muscle metabolism, muscle hypertrophy, improvements in endothelial function, or altered gait.

The data supporting the efficacy of supervised exercise programs to alleviate claudication symptoms are robust and are summarized in Table 17. A meta-analysis of 21 studies by Gardner and Poehlman included both nonrandomized and randomized trials of exercise training and showed that pain-free walking time improved by an average of 180% and maximal walking time increased by 120% in claudication patients who underwent exercise training (323). This meta-analysis also provided data to summarize clinical predictors of responsiveness to exercise interventions. The greatest improvements in walking ability occurred when each exercise session lasted longer than 30 minutes, when sessions took place at least 3 times per week, when the exercise modality used was walking to near-maximal pain, and when the program lasted 6 months or longer. A meta-analysis from the Cochrane Collaboration that considered only randomized, controlled trials concluded that exercise improved maximal walking ability by an average of 150% (range 74% to 230%) (329).

Supervised exercise can induce increases in maximal walking ability that exceed those attained with drug therapies, which have been estimated to result in improvements in maximal walking distance of 20% to 25% with pentoxifylline and 40% to 60% with cilostazol (337,338). Exercise-induced improvements in walking ability translate to increases in routine daily activity (199,339). In one uncontrolled study by Gardner et al., 6 months of exercise training improved treadmill walking ability, accompanied by a 31% increase in routine daily activity as measured by accelerometry (199). Self-reported physical activity increased by 62%, which confirms that patients themselves appreciated this functional improvement. Controlled studies have also demonstrated higher levels of routine daily activity in patients with claudication after exercise training (340). Such sustained increases in physical activity, if associated with improvements in cardiovascular risk factors, have the potential to reduce the risk of cardiovascular ischemic events, thereby potentially improving the poor prognosis for survival in this population (341,342).

The time course of the response to a program of exercise has not been fully established. Exercise-induced clinical benefits have been observed as early as 4 weeks and have been observed to continue to improve after 6 months of participa-
Table 17. Randomized, Controlled Trials Evaluating the Efficacy of Exercise Rehabilitation

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Duration, mo</th>
<th>Change in ACD (%)</th>
<th>Functional Assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larsen</td>
<td>1966</td>
<td>(330)</td>
<td>7</td>
<td>Daily walks</td>
<td>6</td>
<td>183†‡</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo tablet</td>
<td>6</td>
<td>–6</td>
<td></td>
</tr>
<tr>
<td>Holm</td>
<td>1973</td>
<td>(331)</td>
<td>6</td>
<td>Exercise</td>
<td>4</td>
<td>133†‡</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo tablet</td>
<td>6</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Dahllof</td>
<td>1974</td>
<td>(332)</td>
<td>11</td>
<td>Exercise</td>
<td>6</td>
<td>117†‡</td>
<td>None</td>
</tr>
<tr>
<td>Dahllof</td>
<td>1976</td>
<td>(333)</td>
<td>23</td>
<td>Exercise</td>
<td>4</td>
<td>135†‡</td>
<td>None</td>
</tr>
<tr>
<td>Lundgren</td>
<td>1989</td>
<td>(327)</td>
<td>25</td>
<td>Surgery plus exercise</td>
<td>6</td>
<td>263†‡</td>
<td>None</td>
</tr>
<tr>
<td>Creasy</td>
<td>1990</td>
<td>(334)</td>
<td>13</td>
<td>Exercise</td>
<td>6</td>
<td>442†‡§</td>
<td>None</td>
</tr>
<tr>
<td>Hiatt</td>
<td>1990</td>
<td>(326)</td>
<td>9</td>
<td>Supervised exercise</td>
<td>3</td>
<td>123†‡</td>
<td>Improved</td>
</tr>
<tr>
<td>Mannarino</td>
<td>1991</td>
<td>(335)</td>
<td>10</td>
<td>Supervised exercise</td>
<td>6</td>
<td>105†‡</td>
<td>No change</td>
</tr>
<tr>
<td>Hiatt</td>
<td>1994</td>
<td>(324)</td>
<td>10</td>
<td>Exercise plus antiplatelet</td>
<td>3</td>
<td>86†‡</td>
<td>Improved</td>
</tr>
<tr>
<td>Regensteiner</td>
<td>1997</td>
<td>(325)</td>
<td>10</td>
<td>Supervised exercise</td>
<td>3</td>
<td>74†‡</td>
<td>Improved</td>
</tr>
<tr>
<td>Patterson</td>
<td>1997</td>
<td>(336)</td>
<td>10</td>
<td>Supervised exercise</td>
<td>6</td>
<td>137†‡</td>
<td>Improved</td>
</tr>
</tbody>
</table>

*Use of questionnaire to evaluate community-based functional status.
†p less than 0.05 compared with baseline; ‡p less than 0.05 for difference between groups.
§Data given are for the 12-month follow-up point.

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).
### Table 18. Key Elements of a Therapeutic Claudication Exercise Training Program (Lower Extremity PAD Rehabilitation)

<table>
<thead>
<tr>
<th>Primary clinician role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establish the PAD diagnosis using the ABI measurement or other objective vascular laboratory evaluations</td>
</tr>
<tr>
<td>Determine that claudication is the major symptom limiting exercise</td>
</tr>
<tr>
<td>Discuss risk/benefit of claudication therapeutic alternatives, including pharmacological, percutaneous, and surgical interventions</td>
</tr>
<tr>
<td>Initiate systemic atherosclerosis risk modification</td>
</tr>
<tr>
<td>Perform treadmill stress testing</td>
</tr>
<tr>
<td>Provide formal referral to a claudication exercise rehabilitation program</td>
</tr>
</tbody>
</table>

### Exercise guidelines for claudication*

**Warm-up and cool-down period of 5 to 10 minutes each**

- **Types of exercise**
  - Treadmill and track walking are the most effective exercise for claudication
  - Resistance training has conferred benefit to individuals with other forms of cardiovascular disease, and its use, as tolerated, for general fitness is complementary to but not a substitute for walking

- **Intensity**
  - The initial workload of the treadmill is set to a speed and grade that elicit claudication symptoms within 3 to 5 minutes
  - Patients walk at this workload until they achieve claudication of moderate severity, which is then followed by a brief period of standing or sitting rest to permit symptoms to resolve

- **Duration**
  - The exercise-rest-exercise pattern should be repeated throughout the exercise session
  - The initial duration will usually include 35 minutes of intermittent walking and should be increased by 5 minutes each session until 50 minutes of intermittent walking can be accomplished

- **Frequency**
  - Treadmill or track walking 3 to 5 times per week

### Role of direct supervision

As patients improve their walking ability, the exercise workload should be increased by modifying the treadmill grade or speed (or both) to ensure that there is always the stimulus of claudication pain during the workload

As patients increase their walking ability, there is the possibility that cardiac signs and symptoms may appear (e.g., dysrhythmia, angina, or ST-segment depression). These events should prompt physician re-evaluation

---


PAD indicates peripheral arterial disease; ABI, ankle-brachial index.


---

tion (343,344). Gardner et al. reported that improvements in walking ability after 6 months of supervised exercise rehabilitation 3 times per week were sustained when patients continued to participate in an exercise maintenance program for an additional 12 months (344).

The results of these clinical investigations provided adequate scientific data to support the creation of the new current procedural terminology code (93668) in the United States for exercise rehabilitation for patients with claudication (171). The key elements of such a therapeutic claudication exercise program for patients with claudication are summarized in Table 18. Because patients with claudication often have concomitant clinical or occult coronary artery disease, hypertension, and diabetes, adverse cardiovascular and physiological responses during exercise training are possible, and this risk should be evaluated clinically before initiation of the therapeutic program. However, there is no evidence that patients with claudication need to undergo stress imaging or invasive angiographic studies before initiating a therapeutic exercise program. Such safety has been maintained, with serious adverse events rarely documented in clinical practice or in research investigations, by prudent application of an initial standard treadmill exercise test. This test should be performed with 12-lead electrocardiographic monitoring before a therapeutic exercise program is initiated, so that ischemic symptoms, ST–T-wave changes, or arrhythmias may be identified (345). Although these patients will, by definition, have claudication-limited exercise (and therefore will not achieve a true maximal exercise performance), the findings from the exercise test can be used to determine that there are no untoward cardiovascular responses at the exercise level reached. The exercise test also provides information about claudication thresholds and heart rate and blood pressure responses for establishing an exercise prescription. Patient enrollment in a medically supervised exercise program with electrocardiographic, heart rate, blood pressure, and blood glucose monitoring is encouraged. It is also prudent to use monitoring routinely during the initial exercise sessions; individual clinical responses then would determine the need for monitoring in subsequent sessions. Many cardiac rehabilitation exercise programs can accommodate patients with claudication, providing an environment conducive for “lifestyle change” that underlies long-term compliance to exercise and risk factor modification.

A typical supervised exercise program requires the performance of treadmill or track-based exercise for 45 to 60 minutes performed 3 or more times a week for a minimum of 12 weeks. Such exercise is monitored by a physical therapist, nurse, or exercise physiologist. Treadmill exercise appears to be more effective than other exercise modalities, presumably because treadmill walking most closely reproduces walking in the community setting. The initial workload of the treadmill is set to a speed and grade that elicit claudication symptoms within 3 to 5 minutes. Patients are asked to continue to walk at this workload until they achieve claudication of moderate severity. This is followed by a brief period of rest to permit symptoms to resolve. The exercise-rest-exercise cycle
training has been demonstrated to improve cardiovascular function and vitality on the SF-36 (36-item short-form health survey) questionnaire. Many patients with claudication also have reduced muscle mass (346) and a lack of muscle strength and endurance, which exacerbates their physical impairment. Resistance training, when appropriately prescribed, is generally recommended by the AHA for most individuals with other manifestations of cardiovascular disease because of its beneficial effects on strength and endurance, cardiovascular function, metabolism, coronary risk factors, and psychosocial well-being (347). Nevertheless, in patients with claudication, resistance training does not directly improve walking ability, whereas walking itself is most effective in increasing claudication-limited walking capacity (323,324,340).

Clinicians should recognize that minimal data support the efficacy of the informal “go home and walk” advice that still makes up the most typical exercise prescription for claudication (348,349). Although some patients might theoretically achieve benefit from such casual exercise prescriptions (336,350), the determinants of success and documentation of efficacy are not yet defined. In contrast, a supervised hospital- or clinic-based program, which ensures that patients are receiving a standardized exercise stimulus in a safe environment, is effective (325,351).

Supervised exercise, endovascular procedures, and limb arterial bypass surgery can each effectively provide functional benefits, and yet comparative prospective trials are few, with variable results that may depend on the population studied, length of treatment, and method of application of each intervention. In one trial, exercise training was demonstrated to be superior to angioplasty (334,352), whereas this result was not corroborated by a comparative meta-analysis (353). In other trials, surgical bypass was determined to provide superior benefits to exercise (354). There are inadequate data to compare such distinct claudication interventions effectively. It is likely that supervised exercise training can serve as a beneficial adjunct to further augment the improvements in walking that can be gained by both endovascular procedures and surgical bypass (355).

The efficacy of exercise programs to improve the functional status of patients with lower extremity PAD who undergo amputation, which affects from 5% to 10% of patients with lower extremity PAD, has not been evaluated prospectively. However, it is known that arm ergometry stress testing is an alternative for patients who cannot perform leg exercise to assess cardiovascular status, and arm ergometry exercise training has been demonstrated to improve cardiovascular endurance and upper-body strength in poorly conditioned patients (356,357).

The potential beneficial synergy of exercise training and pharmacological therapies has been incompletely evaluated (335,358-360). Although there are biological reasons that could support potentially more rapid or sustained improvements in pain-free or maximal walking distance when patients are treated concomitantly with exercise and claudication medications (e.g., cilostazol or pentoxifylline), there are currently inadequate data to support any efficacy conclusion.

In addition to the benefits of daily exercise on limb ischemic symptoms, regular exercise is associated with improved blood pressure, an improved serum lipid profile (including increased HDL values and decreased triglyceride values), and improved glycemic control. Two studies have demonstrated that these theoretical systemic benefits are achievable (361,362).

In summary, there is a strong evidence base to support a central role of structured exercise programs for all patients with claudication. Structured exercise is also likely to benefit patients who are treated with pharmacotherapies, endovascular therapies, and vascular surgical bypass. Supervised exercise can create an environment in which atherosclerosis risk factor normalization may be achieved more effectively. Supervised exercise should therefore be provided as a key component of a comprehensive claudication treatment program.

### 2.6.2.2. Medical and Pharmacological Treatment for Claudication

#### 2.6.2.2.1. Cilostazol

**RECOMMENDATIONS**

**Class I**

1. Cilostazol (100 mg orally 2 times per day) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). (*Level of Evidence: A*)

2. A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). (*Level of Evidence: A*)

Cilostazol is a phosphodiesterase type 3 inhibitor that increases cyclic adenosine monophosphate. Cilostazol has vasodilator and platelet inhibitory properties (363,364), but the precise mechanism of action in patients with intermittent claudication is not known. Cilostazol has been shown to increase plasma HDL cholesterol and decrease triglyceride concentrations (365). Cilostazol also has been reported to inhibit expression of vascular cell adhesion molecule-1, inhibit vascular smooth muscle cell proliferation, and prevent restenosis in patients with coronary artery disease who underwent percutaneous transluminal coronary angioplasty (366-368). Five prospective randomized trials of patients with intermittent claudication found that cilostazol improves maximal...
walking distance by 40% to 60% compared with placebo after 12 to 24 weeks of therapy (161,337,338,369,370). In dose-ranging trials, cilostazol administered at 100 mg twice daily was more effective than 50 mg twice daily (161,369). Cilostazol increased ABI modestly in these studies, but the hemodynamic effect could not account for the improvement in claudication (337,338,370,371). A meta-analysis of these trials indicated that cilostazol also improved walking ability and health-related quality of life (372).

The most common side effects of cilostazol include headache, diarrhea, abnormal stools, palpitations, and dizziness (370). Other phosphodiesterase inhibitors, such as milrinone and vesnarinone, are associated with increased mortality in patients with congestive heart failure and reduce systolic left ventricular function (373,374). None of the trials conducted to date have found a significant increase in mortality or major cardiovascular events in patients treated with cilostazol, and the long-term safety of this drug is under investigation.

In data that were presented to the FDA’s Cardiovascular and Renal Drugs Advisory Committee and derived from more than 2000 patients who were followed up for up to 6 months, death due to cardiovascular causes occurred in 0.6% of patients treated with cilostazol and 0.5% of patients treated with placebo. Pending more definitive information, the FDA has mandated a black-box warning that cilostazol should not be used in patients with heart failure.

2.6.2.2.2. PENTOXIFYLLINE.

RECOMMENDATIONS

Class IIb

1. Pentoxifylline (400 mg 3 times per day) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. (Level of Evidence: A)

2. The clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well established. (Level of Evidence: C)

Pentoxifylline is a methylxanthine derivative that is approved for use in patients with intermittent claudication. It is a hemorheologic agent that has been reported to decrease blood and plasma viscosity, increase erythrocyte and leukocyte deformability, inhibit neutrophil adhesion and activation, and lower plasma fibrinogen concentrations in some studies but not in others (375-379). Meta-analyses of randomized, placebo-controlled, double-blind clinical trials have found that pentoxifylline causes a marginal but statistically significant improvement in pain-free and maximal walking distance by 21 to 29 meters and 43 to 48 meters, respectively (360,380). According to 2 of the larger trials comprising 128 and 150 individuals, respectively, the average percentage increase in pain-free and maximal walking distance was 30% and 20%, respectively (381-383). One randomized, controlled trial comprising 471 patients compared pentoxifylline with cilostazol and placebo. There was no significant difference in pain-free or maximal walking distance between the placebo and pentoxifylline treatment groups, whereas cilostazol improved both pain-free and maximal walking distance (370). The recommended dose is 400 mg orally 3 times per day. Pentoxifylline does not increase the ABI at rest or after exercise (360). Adverse effects associated with pentoxifylline include sore throat, dyspepsia, nausea, and diarrhea (370). No life-threatening side effects of pentoxifylline have been reported; however, trials reported to date have been too small to assess this outcome reliably. Accordingly, pentoxifylline may be considered to treat patients with intermittent claudication; however, the anticipated outcome is likely to be of marginal clinical importance.

2.6.2.2.3. OTHER PROPOSED MEDICAL THERAPIES.

RECOMMENDATIONS

Class III

1. Oral vasodilator prostaglandins such as beraprost and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. (Level of Evidence: A)

2. Vitamin E is not recommended as a treatment for patients with intermittent claudication. (Level of Evidence: C)

3. Chelation (e.g., ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects. (Level of Evidence: A)

Vasodilator Prostaglandins. Vasodilator prostaglandins have been studied as potential therapy for treatment of patients with intermittent claudication. These drugs include prostaglandin E1 (PGE-1) and stable derivatives of prostacyclin, such as iloprost and beraprost. Vasodilator prostaglandins cause vasodilation and inhibition of platelet aggregation by activating adenyly cyclase and increasing cyclic adenosine monophosphate. Vasodilator prostaglandins are considered investigational for this indication, and none have been approved by the FDA for use in patients with PAD. Intravenous administration of PGE-1 and a PGE-1 prodrug once or twice daily for 4 to 8 weeks has been reported to increase pain-free and maximal walking distance in placebo-controlled trials (384-387). Daily intravenous administra-
tion of vasodilator prostaglandins is not practical for most patients with intermittent claudication. One placebo-controlled 6-month trial found that oral beraprost improved pain-free and maximal walking distance (388). Two randomized, controlled trials of 6 months’ duration of patients with intermittent claudication failed to demonstrate any effect on walking distance with either oral beraprost or iloprost, although cardiovascular ischemic events were reduced in the beraprost-treated group (389). Frequent adverse effects included headache, flushing, and gastrointestinal distress. Given these observations, it is unlikely that these drugs will be approved for use in patients with claudication.

**Angiogenic Growth Factors.** Angiogenic growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and hypoxia-inducible factor-1, have engendered considerable enthusiasm as potential therapeutic interventions to improve symptoms in patients with PAD. These drugs have been shown to promote collateral blood vessel formation and increase limb blood flow in experimental models of hindlimb ischemia (390,391). Angiogenic growth factors have been administered as recombinant proteins or via gene transfer with naked plasmid DNA or adenoviral vectors encoding the angiogenic growth factor (392,393). In a small phase 1, double-blind, placebo-controlled study, administration of bFGF via the femoral artery on 1 or 2 consecutive days increased calf blood flow 1 month and 6 months later (394). In a randomized, placebo-controlled study, intra-arterial administration of recombinant fibroblast growth factor–2 at a dose of 30 micrograms per kilogram on 1 occasion increased peak walking time at 90 days by 19%, although its administration on 2 occasions 30 days apart did not significantly improve peak walking time compared with placebo (395). There have been no significant adverse events reported in patients treated with recombinant fibroblast growth factor–2 compared with those receiving placebo. One study that involved the intravenous administration of bFGF to patients with claudication was terminated prematurely when 4 of 16 subjects who received bFGF developed proteinuria that exceeded 1 g per 24 hours (396). A small phase 1 study examined the safety and efficacy of intramuscular administration of an adenoviral VEGF isoform 121 and monitored patients for up to 1 year (397). Edema and rash were common early adverse events. Among 15 patients who received VEGF, there was 1 death at day 160 and 1 malignancy at day 274. A larger double-blind, randomized, placebo-controlled trial of intramuscular administration of VEGF isoform 121 in 105 patients with claudication failed to demonstrate any clinical efficacy but did provoke limb edema (398). Given the available evidence, it is premature to make any recommendations regarding the relative efficacy and safety of angiogenic growth factors for the treatment of intermittent claudication.

**Nutritional Supplements.** Several alternative (complementary) forms of therapy have been studied in patients with intermittent claudication. These include nutritional supplements such as L-arginine, ginkgo biloba, and vitamin E, as well as chelation therapy. L-Arginine is the precursor for nitric oxide that is synthesized in the endothelium by a constitutive isoform of nitric oxide synthase. Nitric oxide induces vasodilation and inhibits platelet aggregation by activating guanylyl cyclase and increasing cyclic guanosine monophosphate. Endothelium-dependent vasodilation mediated by nitric oxide is impaired in patients with atherosclerosis, including those with PAD (399). L-Arginine improves endothelium-dependent vasodilation in patients with hypercholesterolemia and atherosclerosis (386,400). One placebo-controlled trial found that intravenous administration of L-arginine, 8 g twice per day, improved pain-free and maximal walking distance after 3 weeks of treatment (386). Another placebo-controlled trial examined the efficacy of a food bar that contained 3.3 g of L-arginine (as well as antioxidant vitamins and minerals, folic acid, and B-complex vitamins) (401). After 2 weeks, there was modest improvement in pain-free and maximal walking distance in patients who ingested 2 bars per day. A larger placebo-controlled trial examining the efficacy of this food bar enriched with L-arginine has been completed, with negative results, but has not been published. Given the available findings to date, it is premature to make any recommendations regarding the efficacy of L-arginine as therapy for patients with intermittent claudication.

Carnitine is a cofactor for skeletal muscle metabolism. Patients with PAD have abnormal skeletal muscle metabolism, which includes the accumulation of acyl-coenzyme A intermediates and acylcarnitine. L-Carnitine and its congeners, propionyl-L-carnitine, increase the availability of L-carnitine for skeletal muscle and may subsequently improve exercise capacity in patients with intermittent claudication. One randomized, placebo-controlled trial found that L-carnitine, 2 g orally twice per day, improved absolute walking distance (402). Three placebo-controlled trials reported that propionyl-L-carnitine, 1 g orally twice per day, improved maximal walking distance by 54% to 73%; in one study, the effect was significant only in those patients whose baseline walking distance was less than 250 meters (403-405). There did not appear to be any serious adverse events in the patients treated with propionyl-L-carnitine compared with those treated with placebo. On the basis of these findings, propionyl-L-carnitine shows promise as a therapy to improve walking distance in patients with intermittent claudication. At this time, however, it is not an approved drug for this indication.

Ginkgo biloba is an herb that includes flavonoids and terpine trilactones, such as ginkgolides. Its purported actions include decreased red blood cell aggregation, decreased blood viscosity, and inhibition of platelet activating factor. A systematic review evaluated findings from 8 placebo-controlled trials of ginkgo biloba extract in patients with intermittent claudication (406). Patients received 120 to 160 mg per day of ginkgo biloba or placebo for 12 to 24 weeks. The weighted mean difference in pain-free walking distance was 34 meters in patients randomized to ginkgo biloba compared with those randomized to placebo. No single well-powered,
prospective, randomized, blinded trial has been performed to corroborate this meta-analysis. These findings suggest that ginkgo biloba may be considered as alternative therapy to treat patients with intermittent claudication; however, the outcome is likely to be of marginal clinical importance.

Vitamin E is a lipid soluble antioxidant that protects polyunsaturated fatty acids from oxidation. Vitamin E may improve red blood cell deformability and therefore transport through the microcirculation, because polyunsaturated fatty acids are incorporated into the erythrocyte membrane. A systematic review evaluated 5 placebo-controlled trials comprising 265 subjects that compared vitamin E with placebo in patients with intermittent claudication (407). Each of these was conducted between 1953 and 1975. The trials were small, measured different physical outcomes, and were of generally poor quality. No conclusions could be drawn regarding the efficacy of vitamin E for intermittent claudication. The Alpha-tocopherol, Beta carotene Cancer Prevention Study randomized patients to 50 mg of vitamin E (alpha-tocopherol) per day, 20 mg of beta carotene per day, both, or placebo in a 2-by-2 factorial design. Intermittent claudication was reported via the Rose questionnaire. No effect of alpha-tocopherol on claudication was observed during a mean follow-up of 3.7 years (408). Two large trials examined the efficacy of vitamin E on adverse cardiovascular events in patients with atherosclerosis, including those with PAD (112,299). There was no benefit of vitamin E compared with placebo on cardiovascular outcomes such as MI, stroke, or vascular death. Taken together, these data indicate that vitamin E is not recommended as a treatment for patients with intermittent claudication.

Chelation Therapy. Disodium ethylenediaminetetraacetic acid (EDTA) combines with polyvalent cations, such as calcium ions, and forms a soluble nonionic complex that can be excreted. It is used in the treatment of heavy metal poisoning and has been used in the treatment of patients with intermittent claudication. On the basis of the somewhat antiquated understanding of the biology of atherosclerosis, EDTA is purported to leach calcium out of atherosclerotic plaques, resulting in plaque regression and reduction in the severity of stenoses. It is administered intravenously 2 or more times per week. Two systematic reviews evaluated placebo-controlled trials of EDTA in patients with intermittent claudication and concluded that there was no evidence to support the use of EDTA in these patients (409,410). The systematic reviews included 4 trials, 3 deemed to be of good quality, that evaluated the effect of EDTA on walking distance (411-414). Overall, there were no significant changes in pain-free or maximal walking distance. One trial also obtained angiograms and found no effect of treatment with EDTA on severity of atherosclerosis (412). Potential serious adverse effects of EDTA include hypocalcemia, which may be life-threatening, renal insufficiency, proteinuria, and gastrointestinal distress. Given its lack of efficacy and important safety concerns, EDTA should not be used to treat patients with intermittent claudication.

Table 19. Indications for Revascularization in Intermittent Claudication

<table>
<thead>
<tr>
<th>Indications for Revascularization in Intermittent Claudication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before a patient with intermittent claudication is offered the option of any invasive revascularization therapy, whether endovascular or surgical, the following considerations must be taken into account:</td>
</tr>
<tr>
<td>- a predicted or observed lack of adequate response to exercise therapy and claudication pharmacotherapies</td>
</tr>
<tr>
<td>- the presence of a severe disability, with the patient either being unable to perform normal work or having very serious impairment of other activities important to the patient</td>
</tr>
<tr>
<td>- absence of other disease that would limit exercise even if the claudication was improved (e.g., angina or chronic respiratory disease)</td>
</tr>
<tr>
<td>- the anticipated natural history and prognosis of the patient</td>
</tr>
<tr>
<td>- the morphology of the lesion, which must be such that the appropriate intervention would have low risk and a high probability of initial and long-term success</td>
</tr>
</tbody>
</table>

Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

2.6.2.3. Role of Revascularization for Claudication

Because of the variability of individual limb ischemic symptoms and variable impact of these symptoms on quality of life, patients should be selected for revascularization on the basis of the severity of their symptoms; a significant disability as assessed by the patient; failure of medical therapies; lack of significant comorbid conditions; vascular anatomy suitable for the planned revascularization; and a favorable risk/benefit ratio. These recommendations have been summarized previously in an international PAD consensus statement and are summarized in Table 19 (1). Patients selected for possible revascularization may then undergo additional imaging studies as required, such as duplex ultrasound, MRA or CTA, and/or catheter angiography, to determine whether their arterial anatomy is suitable for percutaneous or surgical revascularization.

2.6.2.4. Endovascular Treatment for Claudication

RECOMMENDATIONS

Class I

1. 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 (a) there has been an inadequate response to exercise or pharmacological therapy and/or (b) there is a very favorable risk-benefit ratio (e.g., focal aortoiliac occlusive disease). (Level of Evidence: A)
Table 20. Morphological Stratification of Iliac Lesions

<table>
<thead>
<tr>
<th>TASC type A iliac lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Single stenosis less than 3 cm of the CIA or EIA (unilateral/bilateral)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC type B iliac lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Single stenosis 3 to 10 cm in length, not extending into the CFA</td>
</tr>
<tr>
<td>3. Total of 2 stenoses less than 5 cm long in the CIA and/or EIA and not extending into the CFA</td>
</tr>
<tr>
<td>4. Unilateral CIA occlusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC type C iliac lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Bilateral 5- to 10-cm-long stenosis of the CIA and/or EIA, not extending into the CFA</td>
</tr>
<tr>
<td>6. Unilateral EIA occlusion not extending into the CFA</td>
</tr>
<tr>
<td>7. Unilateral EIA stenosis extending into the CFA</td>
</tr>
<tr>
<td>8. Bilateral CIA occlusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC type D iliac lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Diffuse, multiple unilateral stenoses involving the CIA, EIA, and CFA (usually more than 10 cm long)</td>
</tr>
<tr>
<td>10. Unilateral occlusion involving both the CIA and EIA</td>
</tr>
<tr>
<td>11. Bilateral CIA occlusions</td>
</tr>
<tr>
<td>12. Diffuse disease involving the aorta and both iliac arteries</td>
</tr>
<tr>
<td>13. Iliac stenoses in a patient with an abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery</td>
</tr>
</tbody>
</table>

Endovascular procedure is the treatment of choice for type A lesions, and surgery is the procedure of choice for type D lesions. More evidence is needed to make firm recommendations about the best treatment for type B and C lesions. TASC indicates TransAtlantic Inter-Society Consensus. Adapted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

2. Endovascular intervention is recommended as the preferred revascularization technique for TASC type A (see Tables 20 and 21 and Figure 8) iliac and femoropopliteal arterial lesions. (Level of Evidence: B)

3. Translesional pressure gradients (with and without vasodilation) should be obtained to evaluate the significance of angiographic iliac arterial stenoses of 50% to 75% diameter before intervention. (Level of Evidence: C)

4. Provisional stent placement is indicated for use in the iliac arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection). (Level of Evidence: B)

5. Stenting is effective as primary therapy for common iliac artery stenosis and occlusions. (Level of Evidence: B)

6. Stenting is effective as primary therapy in external iliac artery stenoses and occlusions. (Level of Evidence: C)

Class IIa
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 dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection). (Level of Evidence: C)

Class IIb
1. The effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoral-popliteal arterial lesions (except to salvage a suboptimal result from balloon dilation) is not well-established. (Level of Evidence: A)

2. 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 dilation) is not well established. (Level of Evidence: C)

Class III
1. Endovascular intervention is not indicated if there is no significant pressure gradient across a stenosis despite flow augmentation with vasodilators. (Level of Evidence: C)

2. Primary stent placement is not recommended in the femoral, popliteal, or tibial arteries. (Level of Evidence: C)

3. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD. (Level of Evidence: C)
Endovascular techniques to treat peripheral arterial occlusive disease include PTA with balloon dilation, stents, atherectomy, laser, cutting balloons, thermal angioplasty, and fibrinolysis/fibrinectomy. Thrombolysis utilizes lytic agents that act on fibrin (thus, eliciting “fibrinolysis,” as this process is more commonly described when used with regard to the coronary circulation), and thrombectomy uses direct techniques to remove clot. (The terms “thrombolysis” and “thrombolytic” are synonymous with the terms “fibrinolysis” and “fibrinolytic,” as used in other ACC/AHA guidelines.) These interventions are discussed in Sections 2.6.3.2 and 2.6.3.3. Endovascular (and surgical) treatments can be selected on the basis of morphological features that stratify lower extremity arterial anatomy into subgroups, as displayed in Table 20 and Figure 8 (iliac lesions) and Table 21 and Figure 9 (femoropopliteal lesions).

Outcomes of PTA and stents depend on anatomic and clinical factors (Table 22). Durability of patency after PTA is greatest for lesions in the common iliac artery and decreases distally. Durability also decreases with increasing length of the stenosis/occlusion, multiple and diffuse lesions, poor-quality runoff, diabetes, renal failure, smoking, and CLI (415-430). Female gender has been reported to decrease patency of external iliac artery stents (431). Hormone replacement therapy has also been reported to decrease patency of iliac stents in women (432). Overall outcomes of PTA and stenting of native vessels are summarized in Table 22. Percutaneous transluminal angioplasty of vein bypass graft stenoses has also been reported, with 1- to 3-year patency of the treated site of approximately 60% (433-435), comparable to that for surgical repair (433). Percutaneous transluminal angioplasty of multiple vein graft stenoses has a much lower 3-year patency of only 6% (434). Therefore, patient selection is key in obtaining satisfactory outcomes.

Selection of lesions for endovascular versus conservative therapy is not well defined. Stenoses of 50% to 75% diameter by angiography may or may not be hemodynamically significant, and intravascular pressure measurements have been recommended to determine whether these lesions are significant and to predict patient improvement if the lesion is treated (439,440). Unfortunately, there is no consensus on a diagnostic transstenotic pressure criteria or on methods to meas-
mill walking distance, ABI, and pain scores (443), but these results were not durable. After 2 years of follow-up, the groups had comparable clinical outcomes (444). Most of the patients in this trial had femoral-popliteal PTA. A prospective cohort study compared 18-month outcomes of PTA, surgical bypass, and conservative treatment. Both surgery and PTA produced marked improvements in ABI, walking distance, pain scores, and functional status compared with conservative treatment. The functional gains were approximately half those reported for patients receiving hip arthroplasty and were similar to those for patients who underwent elective coronary angioplasty (445).

Several randomized trials have investigated the selection of patients for surgical or endovascular revascularization. Holm et al. reported no significant difference in 1-year primary and secondary patency in a randomized trial of PTA versus surgical bypass. Only 25% to 30% of patients were treated for CLI (446). Wilson et al. evaluated the relative efficacy and risk of PTA and surgical revascularization in 255 patients with claudication and reported comparable outcomes and risk for patients.
### Table 22. Overview of Primary Patency and Limb Salvage Rates After Endovascular Procedures for PAD of the Lower Extremities

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Lesion Type</th>
<th>Severity of Disease</th>
<th>Reference</th>
<th>No. of Limbs</th>
<th>30-Day Mortality, % (95% CI)</th>
<th>Major Complication, % (95% CI)</th>
<th>Technical Success, % (95% CI)</th>
<th>Primary Patency, % (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac PTA</td>
<td>80% stenoses, 20% occlusion</td>
<td>67% claudication, 33% critical ischemia</td>
<td>(436)</td>
<td>1473</td>
<td>1.0 (0 to 2.9)</td>
<td>4.3 (2.0 to 6.5)</td>
<td>91 (86 to 96)</td>
<td>74 (71 to 78) 66 (63 to 69) 61 (59 to 64) 58 (56 to 61)</td>
</tr>
<tr>
<td></td>
<td>Stenoses</td>
<td>Claudication</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>96</td>
<td>72 (70 to 74)</td>
<td>79 (77 to 81) 72 (70 to 74) 68 (65 to 70) 65 (62 to 68)</td>
</tr>
<tr>
<td></td>
<td>Stenoses</td>
<td>Critical ischemia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>66 (64 to 68)</td>
<td>66 (64 to 68) 60 (58 to 62) 57 (55 to 59) 54 (52 to 56)</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
<td>Claudication</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>60 (58 to 62)</td>
<td>59 (57 to 61) 51 (49 to 53) 47 (45 to 49) 44 (42 to 46)</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
<td>Critical ischemia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>67 (65 to 69)</td>
<td>60 (58 to 62) 67 (65 to 69) 64 (62 to 66) 61 (59 to 63)</td>
</tr>
<tr>
<td>Iliac stent</td>
<td>72% stenoses, 28% occlusion</td>
<td>85% claudication, 15% critical ischemia</td>
<td>(436)</td>
<td>901</td>
<td>0.8 (0.7 to 0.9)</td>
<td>5.2 (3.5 to 6.9)</td>
<td>96 (91 to 100)</td>
<td>86 (84 to 88) 79 (76 to 81) 75 (72 to 78) 74 (70 to 77)</td>
</tr>
<tr>
<td></td>
<td>Stenoses</td>
<td>Claudication</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>100</td>
<td>89 (87 to 91)</td>
<td>89 (87 to 91) 81 (78 to 83) 78 (75 to 80) 78 (75 to 80)</td>
</tr>
<tr>
<td></td>
<td>Stenoses</td>
<td>Critical ischemia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>91 (89 to 93)</td>
<td>84 (82 to 86) 80 (78 to 82) 77 (75 to 79) 77 (75 to 79)</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
<td>Claudication</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>87 (85 to 89)</td>
<td>76 (74 to 78) 70 (68 to 72) 67 (65 to 69) 67 (65 to 69)</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
<td>Critical ischemia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>72 (70 to 74)</td>
<td>67 (65 to 69) 64 (62 to 66) 61 (59 to 63) 61 (59 to 63)</td>
</tr>
<tr>
<td>Femoropopliteal PTA</td>
<td>64% stenoses, 36% occlusion</td>
<td>65% claudication, 35% critical ischemia</td>
<td>(437, 438)</td>
<td>4800/1003†</td>
<td>0.9 (0.7 to 1.1)</td>
<td>8.1 (7.3 to 8.9)</td>
<td>89 (87 to 91)</td>
<td>59 (56 to 62) 54 (51 to 57) 52 (48 to 55) 49 (45 to 52)</td>
</tr>
<tr>
<td></td>
<td>Stenoses</td>
<td>Claudication</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>95</td>
<td>90 (87 to 93)</td>
<td>90 (87 to 93) 84 (81 to 87) 77 (74 to 80) 74 (71 to 77)</td>
</tr>
<tr>
<td></td>
<td>Stenoses</td>
<td>Critical ischemia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>87</td>
<td>79 (76 to 82)</td>
<td>75 (72 to 78) 74 (71 to 75) 71 (68 to 73) 68 (65 to 70)</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
<td>Claudication</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>75</td>
<td>62 (59 to 65)</td>
<td>57 (54 to 60) 54 (51 to 55) 51 (48 to 52) 47 (44 to 49)</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
<td>Critical ischemia</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>75</td>
<td>52 (49 to 55)</td>
<td>46 (43 to 49) 43 (40 to 45) 40 (37 to 42) 35 (33 to 37)</td>
</tr>
<tr>
<td>Femoropopliteal stent</td>
<td>Stenoses and occlusions</td>
<td>80% claudication, 20% critical ischemia</td>
<td>Meta-analysis‡</td>
<td>600</td>
<td>—</td>
<td>5.9 (1.7 to 10)</td>
<td>98 (97 to 100)</td>
<td>62 (48 to 72) 52 (33 to 63) 43 (22 to 53) — —</td>
</tr>
<tr>
<td></td>
<td>Stenoses and occlusions</td>
<td>14% claudication, 86% critical ischemia</td>
<td>Meta-analysis§</td>
<td>1282</td>
<td>—</td>
<td>—</td>
<td>93 (90 to 96)</td>
<td>79 (68 to 83) 74 (65 to 81) — — — —</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ND, no difference by subgroup can be demonstrated; and PAD, peripheral arterial disease.

*All patency rates and limb salvage rates include initial technical failures.

†Mortality and complication rates are based on n equals 4800, patency rates are based on n equals 1003.

‡Based on a random-effects meta-analysis of the results from various sources, each weighted with the inverse of the variance (17-27).

§Based on a random-effects meta-regression analysis of the results from various sources, each weighted with the inverse of the variance (28-46).

treated with either technique (448). The trials of Holm et al. (448) and Wolfe et al. (446) both excluded patients with long-segment disease (greater than 6 cm and greater than 10 cm, respectively). In these trials, patients had to be considered candidates for either PTA or surgical bypass, and it is likely that patients with poor prognostic factors for PTA were not included. In the study by Holm et al., only 5% of patients considered for revascularization were actually entered into the study (446). Therefore, these results cannot be generalized to patients with poor prognostic factors for PTA. For example, patients with long-segment superficial femoral artery disease and poor runoff have had dismal outcomes with endovascular therapy (449). A cost-effectiveness analysis compared PTA and bypass surgery with exercise therapy for treatment of claudication. The cost-effectiveness of PTA was $38,000 per quality-adjusted life year, which is in the range of other accepted procedures. Bypass surgery cost-effectiveness was $311,000 per quality-adjusted life-year (450).

Effectiveness is strongly affected by the severity of patient symptoms before revascularization and severity of disease. For femoral-popliteal disease, PTA was more cost-effective than surgical bypass for the treatment of claudication (stenosis and occlusion) and for treatment of CLI (stenosis only). Surgical bypass was more cost-effective for treatment of CLI for occlusions (438). Percutaneous transluminal angioplasty would always be the preferred initial treatment if the PTA 5-year patency rate exceeded 30%. Another model of cost-effectiveness of iliac artery PTA versus supervised exercise has suggested that exercise might offer greater cost-effectiveness (as measured by dollars per meter gained) than primary iliac artery angioplasty (451). Overall, the relative clinical and health economic benefits of each claudication therapy must be considered in light of the individual clinical characteristics of each patient.

Selection of patients for iliac artery PTA or stenting has been addressed in 1 randomized trial and 1 meta-analysis of case series. The Dutch iliac stent trial compared iliac stenting as primary therapy (primary stenting) to PTA with immediate stenting (provisional stenting) for PTA failures, defined as greater than 10 mm of mean arterial pressure gradient with or without vasodilators. Forty-three percent of the PTA group required stents. Complications, 1-year patency, and clinical outcomes were similar, which indicates that provisional stenting and primary stenting are equally safe and effective (452). Another randomized trial was suggestive of superiority for primary stenting (453). In a meta-analysis, iliac artery stenting was found to have a higher technical success and long-term patency than PTA, with a similar complication rate (436). Similar to the Dutch iliac stent trial, the meta-analysis showed parallel life-table outcomes of patency after the initial technical failures of PTA, which indicates that a good initial result from iliac PTA is as durable as iliac stenting. Provisional stenting treats the initial technical failures of PTA and is more cost-effective than PTA alone (454,455); however, in routine clinical practice, most iliac lesions are treated with primary stenting.

Selection of patients for femoral-popliteal artery PTA or stenting has been assessed in 4 randomized trials and 1 meta-analysis of case series. The meta-analysis concluded that only for treatment of occlusions in patients with CLI was there a suggestion that stents were more durable than PTA (456). The 4 randomized trials have uniformly found no difference in patency, ABI, or clinical improvement when comparing stents and PTA alone (457-460). A fifth randomized trial that resulted in an FDA label for 1 stent for primary femoral/popliteal stenting similarly showed no difference in outcomes between stenting and PTA. Stenting does have a higher technical success rate (457) and may have a role in salvage of an immediate PTA failure and in treatment of recurrent stenosis after PTA (461).

Other techniques of endovascular revascularization have shown no advantages over PTA/stents. A randomized trial of atherectomy versus PTA for treatment of femoropopliteal disease showed worse 2-year patency and clinical and hemodynamic success for atherectomy (462). Another randomized trial of atherectomy versus PTA showed no difference in 6-month patency (463). A case series of atherectomy for treatment of tibial lesions had dismal results (464). Similarly, multiple randomized trials of laser angioplasty versus PTA have shown no advantage of laser therapy (465-468). Investigational randomized trials suggest that endovascular brachytherapy may reduce restenosis rates of PTA and stenting in the femoral-popliteal arteries (469-473). Techniques to be investigated in randomized trials in the peripheral circulation include fabric-covered stents (474,475) and drug-coated stents (476,477).

The use of antiplatelet agents and anticoagulants to improve the results of angioplasty and stenting is not well defined. A meta-analysis reported increased patency and a lower amputation rate with use of antiplatelet drugs after PTA (478), but a review of 11 randomized trials found no difference in preventing reocclusion after PTA using aspirin or oral anticoagulants (479).

On the basis of the above-reported outcomes of PTA/stenting and surgery, consensus recommendations for selection of patients for endovascular therapy in the management of lower-limb peripheral arterial occlusion were made by an international panel (1). The superiority of surgery versus stenting for TASC type B and C iliac lesions was confirmed in a case series, with poor runoff being the strongest prognostic factor for stenting failure (480). For femoral-popliteal lesions, Clark et al. found that AHA category 2 and 3 lesions (similar to TASC type C) had nearly identical 36-month patency (69% and 66%), whereas category 1 lesions had a 36-month patency rate of 87% (423). Selection of patients for endovascular therapy should be based on TASC anatomic classifications, as well as severity of patient symptoms, comorbid conditions, and risks of surgical revascularization. The summary consensus recommendations of TASC for indications for aortoiliac revascularization for claudication suggest endovascular procedures as the treatment of choice for type A lesions and surgical procedures as the treatment of choice for type D lesions.
2.6.2.5. Surgery for Claudication

2.6.2.5.1. Indications.

RECOMMENDATIONS

Class I
Surgical interventions are indicated for individuals with claudication symptoms who have a significant functional disability that is vocational or lifestyle limiting, who are unresponsive to exercise or pharmacotherapy, and who have a reasonable likelihood of symptomatic improvement. (Level of Evidence: B)

Class IIb
Because the presence of more aggressive atherosclerotic occlusive disease is associated with less durable results in patients younger than 50 years of age, the effectiveness of surgical intervention in this population for intermittent claudication is unclear. (Level of Evidence: B)

Class III
Surgical intervention is not indicated to prevent progression to limb-threatening ischemia in patients with intermittent claudication. (Level of Evidence: B)

Claudication usually does not progress to limb-threatening ischemia, and therefore, there is no automatic mandate to proceed to surgical intervention. Surgery is infrequently needed to treat the individual with claudication and generally should only be considered after atherosclerosis risk factors have been treated and an appropriate trial of exercise and/or claudication pharmacotherapy has been utilized. Most major vascular care centers report the use of surgical intervention in only 25% of those individuals with claudication who are referred to vascular surgeons. The indications for surgical treatment of lower extremity ischemia are defined by the severity of leg ischemic symptoms, with limb hemodynamic data serving primarily to confirm the lower extremity PAD and claudication diagnosis. Thus, intermittent claudication is considered a relative indication for surgical treatment and is usually reserved for individuals (a) who do not derive adequate functional benefit from nonsurgical therapies, (b) who have limb arterial anatomy that is favorable to obtaining a durable clinical result, and (c) in whom the cardiovascular risk of surgical revascularization is low. The 2 traditional functional indications for surgical intervention are exercise impairment sufficient to threaten the patient’s employment or to require significant alterations in the patient’s lifestyle after failure of nonsurgical or endovascular therapy. Because the impact of job and lifestyle-threatening alterations is not usually quantitated, the significance of these symptoms as an indication for surgery must be decided on a per case basis by the patient, primary clinician, and surgeon. Successful lower extremity arterial surgical revascularization, however, can effectively reduce or eliminate the symptoms of claudication.

Patients who present with symptoms of claudication before 50 years of age may have a more virulent form of atherosclerosis and have a poorer response to vascular surgical interventions, frequently requiring graft revisions or replacements (481). Olsen and associates noted a high mortality rate secondary to cardiovascular events, a high amputation rate, and an increasing disability rate in patients less than 40 years of age who required surgical intervention for claudication (482). In a study comparing the outcome of patients requiring aortobifemoral bypass for PAD who were less than 50 years of age with those who were older, Reed and colleagues noted poorer results in the younger patients (481). Younger patients had lower patency rates and required more subsequent surgical intervention than did older patients. Green and collaborators noted in a multi-institutional, prospective, randomized trial of prosthetic femoral-popliteal bypass grafting that patients younger than 65 years of age had a higher incidence of graft occlusion (483). Therefore, despite the presence of significant claudication symptoms in an age group that is often more physically active and employed, surgery for these younger patients should be avoided if possible.

2.6.2.5.2. Preoperative Evaluation.

RECOMMENDATION

Class I
A preoperative cardiovascular risk evaluation should be undertaken in those patients with lower extremity PAD in whom a major vascular surgical intervention is planned. (Level of Evidence: B)

Lower extremity PAD is associated with the presence of coronary artery disease and marks high short- and long-term coronary ischemic risk, and therefore, a preoperative cardiovascular risk evaluation should be undertaken. The specific testing strategy that might be used for a specific patient is beyond the scope of this guideline. Perioperative ischemic risk is increased for all lower extremity vascular surgical procedures (inclusive of aortic, femoral, and infrapopliteal segments). This risk is further increased in those patients with an established history of ischemic heart disease, current angina, or an abnormal electrocardiogram and may be challenging to assess in those individuals in whom a sedentary lifestyle limits assessment of functional capacity. The preoperative cardiovascular risk evaluation is summarized in more detail in the “ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery” (484).

2.6.2.5.3. Correlation of Symptoms and Lesions.

Surgical intervention must be directed at the lesions causative of the patient’s symptoms to relieve claudication. The patient’s symptoms and vascular studies must be anatomically consistent. Symptoms associated with lower extremity PAD are usually manifested in the muscle groups distal to the site of a hemodynamically significant stenosis or occlusion.
There are 3 major patterns of arterial obstruction. (a) Inflow disease refers to the presence of stenotic or occlusive lesions in the suprainguinal vessels, most commonly defined as the infrarenal aorta and iliac arteries, that limit blood flow to the common femoral artery. Inflow disease should be suspected in individuals with gluteal or thigh claudication and femoral pulse diminution or bruit. The presence of inflow disease can be easily confirmed by use of noninvasive vascular laboratory diagnostic techniques that can demonstrate evidence of aortoiliac stenoses. (b) Outflow disease represents the presence of stenotic or occlusive lesions in the lower extremity arterial tree below the inguinal ligament from the common femoral artery to the level of the infrapopliteal trifurcation. (c) Runoff disease is usually defined in the context of stenotic or occlusive lesions in the trifurcation vessels (anterior tibial, posterior tibial, and peroneal arteries) to the pedal arteries that cross the ankle. Both outflow and runoff disease can be confirmed by noninvasive vascular laboratory diagnostic studies as required to alter treatment strategies. Although the pattern of anatomic lower extremity PAD is highly variable between individuals, these terms are useful in defining therapeutic approaches.

Occlusive lesions of the infrarenal aorta and/or iliac arteries commonly lead to buttock and thigh claudication. If the stenoses or occlusions are proximal to the origins of the internal iliac arteries and are bilateral, vasculogenic erectile dysfunction may also be present in men. Although buttock and thigh claudication may represent the first exertional ischemic symptoms, continued ambulation may lead to progression of symptoms that include calf claudication.

Superficial femoral artery stenosis or occlusion is the most common lesion associated with intermittent claudication. This lesion leads to calf discomfort with ambulation and relief with rest. There are no specific thigh or foot symptoms associated with superficial femoral artery occlusive disease. Because the deep femoral artery provides collateral circulation to and reconstitution of the popliteal artery, isolated superficial femoral artery occlusion rarely is the cause of more advanced forms of ischemia. Popliteal and tibial arterial occlusions are more commonly associated with limb-threatening ischemia because of the paucity of collateral vascular pathways beyond these lesions. As isolated lesions, they are uncommonly the cause of intermittent claudication.

Patients with combined inflow and outflow disease may have broad symptoms of intermittent claudication that affect the buttock, hip, thigh, and calf.

2.6.2.5.4. SURGICAL PROCEDURES.

For individuals with claudication, initial revascularization strategies will usually rely on endovascular techniques, with surgical intervention reserved for individuals in whom arterial anatomy is not favorable for endovascular procedures. As noted in Section 2.6.2.4, comparable efficacy can often be achieved with less risk by endovascular intervention when both procedures are feasible (446-448). Once the decision to proceed with surgical intervention is made and the site and severity of occlusive lesions are defined through imaging studies, the type of revascularization must be chosen. There are several variables that must be considered by the surgeon and patient in making this choice, including general medical condition, age, gender, prior revascularization attempts, and the desired outcome, such as walking short distances or normalizing distal flow. In patients with combined inflow and outflow disease, inflow problems are corrected first. A significant improvement in inflow may diminish the symptoms of claudication to the extent that supervised exercise therapy or pharmacotherapies may be effective and, if distal revascularization is needed, reduce the likelihood of distal graft thrombosis from low flow.

2.6.2.5.4.1. Inflow Procedures: Aortoiliac Occlusive Disease

RECOMMENDATIONS

Class I
1. Aortobifemoral bypass is beneficial for patients with vocational- or lifestyle-disabling symptoms and hemodynamically significant aortoiliac disease who are acceptable surgical candidates and who are unresponsive to or unsuitable for exercise, pharmacotherapy, or endovascular repair. (Level of Evidence: B)

2. Iliac endarterectomy and aortoiliac or iliofemoral bypass in the setting of acceptable aortic inflow should be used for the surgical treatment of unilateral disease or in conjunction with femoral-iliofemoral bypass for the treatment of a patient with bilateral iliac artery occlusive disease if the patient is not a suitable candidate for aortobifemoral bypass grafting. (Level of Evidence: B)

Class IIb
Axillofemoral-femoral bypass may be considered for the surgical treatment of patients with intermittent claudication in very limited settings, such as chronic infrarenal aortic occlusion associated with symptoms of severe claudication in patients who are not candidates for aortobifemoral bypass. (Level of Evidence: B)

Class III
Axillofemoral-femoral bypass should not be used for the surgical treatment of patients with intermittent claudication except in very limited settings (see Class IIb recommendation above). (Level of Evidence: B)

There are numerous patterns of aortoiliac occlusive disease and procedures to surgically treat them (Table 23). Most commonly, patients demonstrate diffuse disease of the infrarenal aorta and iliac vessels, with the lesions of greatest hemodynamic consequence located in the iliac arteries. The most effective surgical procedure for treatment for this pattern of atherosclerotic occlusive disease and the resultant buttock and thigh claudication is aortobifemoral bypass. Through a transabdominal or retroperitoneal approach, this
Unilateral iliac stenoses or occlusions that cannot be treated effectively by angioplasty and stent placement can be treated by iliac artery endarterectomy, aortoiliac bypass, aortofemoral bypass, or iliofemoral bypass if the origin of the iliac artery is free of disease. These procedures can be performed through a small flank incision into the retroperitoneum and are usually well tolerated.

2.6.2.5.4.2. Outflow Procedures: Infrainguinal Disease.

RECOMMENDATIONS

Class I
1. Bypasses to the popliteal artery above the knee should be constructed with autogenous vein when possible. (Level of Evidence: A)

2. Bypasses to the popliteal artery below the knee should be constructed with autogenous vein when possible. (Level of Evidence: B)

Class IIa
The use of synthetic grafts to the popliteal artery below the knee is reasonable only when no autogenous vein from ipsilateral or contralateral leg or arms is available. (Level of Evidence: A)

Class IIb
1. Femoral-tibial artery bypasses constructed with autogenous vein may be considered for the treatment of claudication in rare instances for certain patients (see text). (Level of Evidence: B)

2. Because their use is associated with reduced patency rates, the effectiveness of the use of synthetic grafts to the popliteal artery above the knee is not well-established. (Level of Evidence: B)

Class III
Femoral-tibial artery bypasses with synthetic graft material should not be used for the treatment of claudication. (Level of Evidence: C)

As noted above, the superficial femoral artery and proximal popliteal artery are the most common anatomic sites of stenosis or occlusion in individuals with symptoms of intermittent claudication. Therefore, the most commonly per-
formed infrainguinal bypass for the treatment of claudication is the femoral-popliteal artery bypass (Table 24). This type of bypass can be performed under general or regional anesthesia (and, under rare circumstances, under local anesthesia), is generally well tolerated, and will reduce or may eliminate the symptoms of claudication. There are, however, specific factors that may modify the result of this procedure. The 2 major factors are the type of conduit and the site of anastomosis to the popliteal artery, whether above or below the knee.

Nearly all studies that have compared vein with prosthetic conduit for arterial reconstruction of the lower extremity have demonstrated the superior patency of vein. Four large, randomized, prospective studies summarized in Table 25 demonstrate findings consistent with the large body of evidence on the choice of graft material for the construction of bypasses to the above-knee popliteal artery (483,508-510). The superior rates of immediate and long-term patency at all time periods favor use of autogenous vein, whether in situ or reversed. In its absence, PTFE or polyester filament may be used with an expected lower but acceptable patency rate. The need for retreatment or revision is greater with synthetic material over time. With more distal anastomoses or the presence of hemodynamically significant tibial arterial occlusive disease and poor outflow, there is accelerated failure of prosthetic grafts. Therefore, the use of autogenous vein is also strongly favored for bypasses to the popliteal artery below the knee. Femoral-tibial bypass grafting with autogenous vein should rarely be necessary for the treatment of intermittent claudication because of the increased risk of amputation associated with failure of such grafts. Bypasses to the tibial arteries with prosthetic material should be avoided at all costs for the treatment of the claudicant because of very high risks of graft failure and amputation (511,512).

### 2.6.2.5.5. Follow-Up After Vascular Surgical Procedures

#### RECOMMENDATIONS

**Class I**

1. **Patients who have undergone placement of aortobifemoral bypass grafts should be followed up with periodic evaluations that record any return or progression of claudication symptoms, the presence of femoral pulses, and ABIs at rest and after exercise.**

   *(Level of Evidence: C)*

2. **Patients who have undergone placement of a lower extremity bypass with autogenous vein should undergo periodic evaluations for at least 2 years that record any claudication symptoms; a physical examination and pulse examination of the proximal, graft, and out-

<table>
<thead>
<tr>
<th>Table 24. Vascular Surgical Procedures for Outflow Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outflow Procedure</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Fem-AK popliteal vein</td>
</tr>
<tr>
<td>Fem-AK popliteal prosthetic</td>
</tr>
<tr>
<td>Fem-BK popliteal vein</td>
</tr>
<tr>
<td>Fem-BK popliteal prosthetic</td>
</tr>
<tr>
<td>Fem-Tib vein</td>
</tr>
<tr>
<td>Fem-Tib prosthetic</td>
</tr>
<tr>
<td>Composite sequential bypass</td>
</tr>
<tr>
<td>Fem-Tib blind segment bypass</td>
</tr>
<tr>
<td>Profundaplasty</td>
</tr>
</tbody>
</table>

AK indicates above the knee; BK, below the knee; Fem, femoral; and Tib, tibial.

<table>
<thead>
<tr>
<th>Table 25. Patency of Above-Knee Femoral Popliteal Bypass Grafts According to Prospective Randomized Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Author</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Johnson</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Klinkert</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>AbuRahma</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Green</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

PTFE indicates polytetrafluoroethylene; and SVG, saphenous vein graft.
flow vessels; and duplex imaging of the entire length of the graft, with measurement of peak systolic velocities and calculation of velocity ratios across all lesions. (Level of Evidence: C)

3. Patients who have undergone placement of a synthetic lower extremity bypass graft should, for at least 2 years after implantation, undergo periodic evaluations that record any return or progression of claudication symptoms; a pulse examination of the proximal, graft, and outflow vessels; and assessment of ABIs at rest and after exercise. (Level of Evidence: C)

**Inflow Procedures.** In a meta-analysis of 8123 aortobifemoral bypasses, DeVries and Hunink documented a mean 5-year patency rate of 85.8%, with a range of 85% to 89%, and a mean 10-year patency rate of 79.4%, with a range of 78% to 83% (485). Aortoiliac endarterectomy is infrequently performed today, but patencies similar to aortobifemoral grafting have been reported when patients are selected carefully and the procedure is performed appropriately. In a review by Brothers and Greenfield, the 10-year primary patency rate ranged from 48% to 77% (513).

Unilateral iliac percutaneous angioplasty and femorofemoral bypass are associated with only slightly lower patency. In large series, patencies of 78% to 92% at 1 year and 66% at 7 years have been reported (514,515). Perler and Williams noted a similar patency for femoral-femoral bypass in the setting of unilateral iliac occlusion without donor limb disease, with patencies of 73% at 1 year and 59% at 5 and 7 years (515).

Iliac endarterectomy and aortoiliac bypass for the treatment of unilateral iliac artery occlusive disease are durable procedures for the restoration of inflow. In a large review, Szilagyi and colleagues noted a 5-year patency rate of 90% (516).

Axillofemoral-femoral bypasses have significantly poorer patency than other inflow procedures. Johnson and Lee reported a 1-year patency rate of 62% and a 5-year rate of 47% in a prospective, randomized, multicenter Veterans Administration study (517).

**Outflow Procedures.** The results of femoral above-knee popliteal bypasses for each type of graft material are listed in Table 26. Similar outcomes were noted by Hunink and colleagues in an analysis of literature from 1970 to 1996 that reported patency in patients undergoing femoropopliteal bypass, as noted in Table 26 (437). Successful vascular surgical intervention will reduce or eliminate symptoms in the majority of patients.

**2.6.3. Critical Limb Ischemia and Treatment for Limb Salvage**

Critical limb ischemia differs from intermittent claudication by virtue of its natural history. Approximately 5% of patients with intermittent claudication will require a revascularization intervention for lifestyle-limiting ambulatory symptoms or progression to CLI, and only 2% will ultimately require amputation for distal ischemia. Chronic CLI is associated with a 1-year mortality rate greater than 20% (1). Nearly half of the cases will require revascularization for limb salvage. Among those who have unreconstructable disease, approximately 40% will require major amputation within 6 months of initial diagnosis. This natural history mandates a more aggressive approach to control of atherosclerosis risk factors and treatment of underlying ischemia on the part of physicians caring for this critically ill group of patients.

Critical limb ischemia occurs most frequently when 2 or more levels of the distal arterial tree are compromised by either hemodynamically significant stenoses or occlusion. Although this usually manifests in aortoiliac and femoropopliteal segments or the femoropopliteal and tibial segments, it may also occur in the setting of parallel arterial segments, such as superficial and deep femoral artery occlusions. The multiple levels of disease decrease the effectiveness of major autogenous collateral vessel flow and reduce systolic driving pressures in the periphery. As pressure is lowered in the distal arterioles, and occasionally also raised in the distal venules by inactivity and venous stasis, the pressure gradient across capillary beds is decreased, which reduces perfusion below the level required to sustain basal tissue metabolism. This results in slowly progressive tissue death and, ultimately, amputation if allowed to persist uncorrected. The most common manifestations of CLI are rest pain in the foot or toes that is sufficiently severe as to interfere with sleep and ischemic ulcers or ischemic gangrene of the foot or toes. There may be calf atrophy, dependent rubor and elevation pallor, loss of hair over the dorsum of the foot, thickening of the toenails, and shiny, scaly skin due to loss of subcutaneous tissue. These are indications of severe tissue ischemia. Therefore, any patient who presents with clinical evidence of CLI should be evaluated rapidly, with initiation of treatment as soon as is clinically feasible. Patients who are ambulatory (or who have been ambulatory immediately before this episode of CLI), have a life expectancy of more than 1 year (owing to comorbid conditions), and whose general medical condition is adequate to withstand surgical intervention should be considered for lower extremity revascularization.

<table>
<thead>
<tr>
<th>Material</th>
<th>5-Year Patency (%)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vein</td>
<td>80</td>
<td>78</td>
<td>87</td>
</tr>
<tr>
<td>PTFE above knee</td>
<td>75</td>
<td>67</td>
<td>83</td>
</tr>
<tr>
<td>PTFE below knee</td>
<td>65</td>
<td>56</td>
<td>76</td>
</tr>
</tbody>
</table>

PTFE indicates polytetrafluoroethylene.

There is a subgroup of patients with severely impaired distal perfusion who deny rest pain and have no evidence of ischemic ulcers or ischemic gangrene. They are frequently sedentary and report no symptoms of claudication or exercise intolerance. These patients are considered to have subclinical CLI (518). In the absence of indicators of ischemic deterioration of the distal limb, they require no immediate intervention. Patients with subclinical CLI, however, are at high risk for rapid distal tissue compromise and loss after even minor soft tissue trauma and should be carefully followed up with periodic examinations.

2.6.3.1. Medical and Pharmacological Treatment for CLI

RECOMMENDATION

Class III

Parenteral administration of pentoxifylline is not useful for the treatment of CLI. (Level of Evidence: B)

Medical therapies for CLI that decrease pain, promote healing of skin lesions and ulceration, and reduce the risk for amputation would be attractive alternatives to surgical reconstruction procedures. Such therapies would need to improve blood flow sufficiently to meet the resting metabolic needs of limb tissue. Conceptually, this might be accomplished by a drug that increased microcirculatory blood flow or that augmented collateral blood supply to the ischemic portion of the limb. The drug class that has undergone the most intensive investigation in this regard is vasodilator prostaglandins. More recently, phase 1 and phase 2 clinical trials have been undertaken to assess the efficacy of angiogenic growth factors. However, at this time, there is no drug approved for treatment of CLI.

2.6.3.1.1. PENTOXIFYLLINE AND CILOSTAZOL

Pentoxifylline is a xanthine derivative that has vasodilator and hemorheologic properties that might be considered helpful in patients with CLI. Two placebo-controlled trials have evaluated pentoxifylline 600 mg intravenously, twice daily, in the treatment of patients with CLI (519,520). In the first study, intravenous infusion of pentoxifylline was associated with lessened pain scores (519). In the other study, no significant benefit was realized by the patients treated with pentoxifylline (520). Cilostazol, a drug approved for the treatment of patients with intermittent claudication, has not been adequately evaluated to demonstrate efficacy in patients with CLI.

2.6.3.1.2. PROSTAGLANDINS

RECOMMENDATIONS

Class IIb

Parenteral administration of PGE-1 or iloprost for 7 to 28 days may be considered to reduce ischemic pain and facilitate ulcer healing in patients with CLI but its efficacy is likely to be limited to a small percentage of patients. (Level of Evidence: A)

Class III

Oral iloprost is not an effective therapy to reduce the risk of amputation or death in patients with CLI. (Level of Evidence: B)

Vasodilator prostaglandins, including PGE-1, iloprost, and ciprostene, have been evaluated in multiple placebo-controlled trials as potentially efficacious agents in patients with CLI who are not candidates for revascularization procedures. These drugs have been administered either intra-arterially or intravenously, either for relatively short periods (3 to 4 days) or by more long-term infusions (7 to 28 days) (1). There have been at least 8 short-term trials of parenteral administration of PGE-1 or prostacyclin in patients with CLI. The results have been inconsistent and for the most part have not demonstrated efficacy in terms of amelioration of pain or healing of ulcers (1,521-527). In addition, there have been at least 11 randomized, placebo-controlled trials of intravenous PGE-1, or iloprost, administered for 7 to 28 days (1). Prostaglandin E1 has been administered in various dosing schedules, for example, 60 to 80 micrograms over 2 to 4 hours per day and iloprost in doses of 0.5 to 2 ng per kg per min over 6 hours each day. The majority of studies have found that parenteral administration of either PGE-1 or iloprost reduced pain, as assessed by analgesic consumption, ulcer size, and/or amputation (1,528-536). The largest of these trials was conducted by the Ischemia Cronica degli Arti Inferiori study group and comprised 1560 patients with CLI. In that trial, intravenous PGE-1 administered for 28 days caused a statistically significant, albeit marginal, improvement in CLI manifested as ischemic pain and ulcer healing at 6 months (530). There were no significant reductions in the risk for amputation or mortality. One study evaluated the efficacy of oral iloprost in patients with CLI. Iloprost, administered in doses of 50 to 200 micrograms per day, did not significantly affect the primary end point of amputation or death at 1 year (537).

2.6.3.1.3. ANGIOGENIC GROWTH FACTORS

RECOMMENDATION

Class IIb

The efficacy of angiogenic growth factor therapy for treatment of CLI is not well established and is best investigated in the context of a placebo-controlled trial. (Level of Evidence: C)

As discussed previously, angiogenic growth factors have been demonstrated to improve collateral blood vessel formation in experimental models of hind limb ischemia (390,391). For this reason, they are considered as potentially efficacious treatments for patients with CLI. The angiogenic growth factors currently undergoing investigation include recombinant bFGF and gene transfer of VEGF or hypoxia-inducible factor-1a administered as plasmid DNA or with an adenovirus vector encoding the angiogenic growth factor. Initial studies of gene therapy with a VEGF plasmid DNA (phVEGF165) was accomplished via intra-arterial
administration in several nonrandomized, open-label trials (538-540). Some patients in these trials experienced improvement in blood flow, as well as angiographic and histological evidence of new blood vessel formation. A subsequent open-label trial used intramuscular gene transfer of phVEGF165 to 9 patients and reported new collateral blood vessel formation, an increase in ABI, and healing of ischemic ulcers in some of the participants (541). Larger placebo-controlled trials are in progress to evaluate the efficacy of angiogenic growth factors in patients with CLI.

2.6.3.2. Endovascular Treatments for CLI

RECOMMENDATIONS

Class I

1. For individuals with combined inflow and outflow disease with CLI, inflow lesions should be addressed first. (Level of Evidence: C)

2. For individuals with combined inflow and outflow disease in whom symptoms of CLI or infection persist after inflow revascularization, an outflow revascularization procedure should be performed. (Level of Evidence: B)

3. If it is unclear whether hemodynamically significant inflow disease exists, intra-arterial pressure measurements across suprainguinal lesions should be measured before and after the administration of a vasodilator. (Level of Evidence: C)

As defined in Section 2.4.3, the term “critical limb ischemia” identifies the clinical scenario in which resting metabolic requirements of an extremity outstrip its arterial perfusion, which places tissue viability in jeopardy. The patient presentation and clinical course with CLI may vary, depending on patient and arterial lesion characteristics, and may range from extremity pain at rest and with exertion to trophic changes that include ulceration or gangrene. Critical limb ischemia often occurs in conjunction with diabetes mellitus, chronic renal insufficiency, and other systemic disease states associated with diffuse, multisegmental, and small-vessel arterial narrowing in the extremities. Critical limb ischemia may also be precipitated by certain unique disease entities, including atheroembolism, thromboembolism, in situ thrombosis, vasculitis, and thromboangiitis obliterans.

Strategies for management of patients with CLI have evolved considerably in the past decade, in step with the dramatic advances in endovascular technology and technique. Historically, patients presenting with CLI underwent arterial bypass surgery or amputation of the affected extremity. However, as catheter, wire, balloon, and stent technology have all improved, percutaneous strategies are increasingly being used to successfully treat CLI (417,542-545). Even complex arterial lesions, such as lengthy occlusions of the iliac, femoral, and tibial arteries, can often be addressed effectively by less invasive strategies (546-551).

The optimal strategy for management of a patient with CLI must be determined on a case-by-case basis. Important issues to consider include the urgency of the clinical presentation, the presence of comorbidity, and the arterial anatomy. First, the distinction must be made between patients presenting with acute limb ischemia (described in Section 2.4.4) versus limb-salvage situations that are subacute or chronic. The former require rapid intervention via endovascular or surgical means. Therapy for the latter can be planned in a staged, or even contingent, fashion. For example, less invasive techniques can often be attempted initially, with the contingency of open surgery should the PTA fail (542). On occasion, the converse may also apply, wherein surgery is used as the first step and percutaneous revascularization applied as a salvage procedure in the event that surgery fails.

Other clinical scenarios will also dictate the initial approach to the patient with CLI. In patients presenting with late-stage or life-threatening ischemia, or in those presenting with gross infection with septic or gas gangrene, emergency amputation of the extremity may be necessary to prevent catastrophic or life-threatening circulatory collapse. The requirement for revascularization in patients undergoing limb removal will depend on whether perfusion to the amputation site is sufficient to enable healing.

The presence of patient comorbidities also influences decisions regarding optimal management in a given patient. The presence of cardiovascular or cerebrovascular disease is a major consideration in this population of patients. Patients with cardiac ischemia, cardiomyopathy, congestive heart failure, severe lung disease, or renal failure are known to be at greater risk for adverse perioperative events. It is generally accepted that in such patients, initial percutaneous revascularization, if feasible, is preferred over surgical approaches.

Details of each patient’s arterial anatomy will also guide the choice of revascularization. A significant improvement in inflow may diminish the symptoms of rest pain, but pulsatile flow to the foot is generally necessary for the treatment of ischemic ulcers or ischemic gangrene. Therefore, if infection, ischemic ulcers, or gangrenous lesions persist and the ABI is less than 0.8 after correction of inflow, an outflow procedure should be performed that bypasses all major distal stenoses and occlusions (552). The angiographic evaluation may also suggest the presence of arterial stenoses that have functional significance of which may not be clear. In this situation, measurement of transstenotic pressure gradients can guide therapy. However, in the presence of severe outflow disease, an inaccurately low pressure gradient may exist. Severe outflow disease may so limit arterial flow that gradients are not developed, and in this context, use of a pharmacological arterial vasodilator to augment flow may be useful to augment the measured gradient.

Regardless of initial treatment strategy, a key determinant of the long-term outcome is the requirement for intensive follow-up surveillance. Although no formal guidelines exist for monitoring patients after percutaneous therapy for CLI, there is general agreement that these individuals should be subjected to regular evaluation, examination of the affected limb, and noninvasive testing. Early and prompt reinterven-
tion is indicated for restenosis to maximize the chances of wound healing and to maintain the integrity of the limb.

Optimal management of patients with CLI requires the care of practitioners with knowledge of the capabilities of both percutaneous and surgical revascularization. Frequently, this is best accomplished with a multidisciplinary approach. Determination of optimal strategy in the future will likely be based on accumulating evidence and data, wherein patient and lesion substrate, functional outcome measures, and cost analyses will be standardized to enable comparison among pure endovascular, pure surgical, and combined percutaneous/surgical approaches (553). As the short- and long-term outcomes of catheter-based interventions continue to improve, it is likely that these techniques may be used in an increasing spectrum of patients presenting with CLI.

2.6.3.3. Thrombolysis for Acute and Chronic Limb Ischemia

RECOMMENDATIONS

Class I

Catheter-based thrombolysis is an effective and beneficial therapy and is indicated for patients with acute limb ischemia (Rutherford categories I and IIa) of less than 14 days’ duration. (Level of Evidence: A)

Class IIa

Mechanical thrombectomy devices can be used as adjunctive therapy for acute limb ischemia due to peripheral arterial occlusion. (Level of Evidence: B)

Class IIb

Catheter-based thrombolysis or thrombectomy may be considered for patients with acute limb ischemia (Rutherford category IIIb) of more than 14 days’ duration. (Level of Evidence: B)

Catheter-based treatment of intra-arterial thrombus has been used successfully as a treatment to recanalize acutely occluded arteries associated with acute limb ischemia. Catheter-based treatment of arterial thrombus includes localized intra-arterial infusions of thrombolytic medications and/or use of mechanical thrombectomy devices to fragment and remove the clot. Intra-arterial, local catheter-based infusions of thrombolytic agents have replaced systemic (intravenous) infusions of thrombolytic agents owing to poor efficacy and increased adverse event rates with intravenous administration of lytic drugs (554).

Randomized, controlled trials and registry reports indicate that the use of thrombolytic therapy for acute limb ischemia is effective as initial therapy. Graor and coworkers reported a series in which thrombolysis was demonstrated to be superior to surgery for salvage of failed or failing bypass grafts (555). Similar benefits of catheter-directed thrombolytic therapies have been demonstrated with differing thrombolytic agents in both native arteries and thrombosed bypass grafts (556-558). Three large, randomized, prospective clinical trials have been performed. The Rochester trial randomized patients with acute native arterial or bypass graft occlusions of less than 7 days’ duration to treatment with either urokinase or surgery (559). These patients were selected such that if revascularization was not successful, amputation would be required. Amputation-free survival favored thrombolytic therapy (75% vs. 52% for surgery, p < 0.05). Limb salvage at 12 months was identical between the 2 groups (82%), but survival at 12 months was higher for the lytic group (84% vs. 58% for surgery, p equals 0.01). This survival difference was primarily attributable to an excess of in-hospital major cardiopulmonary complications in the surgery group (49% vs. 16% in the thrombolytic group, p equals 0.001). The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial randomized patients with nonembolic occlusions who presented with new or progressive limb ischemic symptoms of up to 6 months’ duration to treatment with either urokinase or surgery (560,561). In patients with symptom onset of less than 14 days, catheter-based thrombolysis yielded a superior outcome to surgery. The amputation rate for patients treated within 14 days of the onset of symptoms was 6% for thrombolysis and 18% for surgical therapy. For patients with symptoms of greater than 14 days’ duration, surgery was more effective and durable, with less recurrent ischemia at 1 year (35% for surgery vs. 65% for lysis). The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial randomized patients with acute native arterial or bypass graft occlusions of less than 14 days’ duration to treatment with either intra-arterial urokinase or surgery (562). Six-month and 12-month amputation-free survival was similar with the 2 treatments (65% to 75%). The thrombolysis group required 40% fewer open procedures but had a higher rate of major bleeding (12.5% vs. 5.5%), primarily related to the vascular access site, which was exacerbated by concomitant heparin use. A meta-analysis comparing lysis and surgery that included these randomized trials and case series concluded that lysis improved 30-day and 6- to 12-month limb salvage and reduced mortality compared with surgery (563).

These randomized trials and case series suggest that the use of intra-arterial thrombolytic therapy for acute limb ischemia is reasonably effective and comparable to surgery. The advantage of thrombolytic therapy is that it offers a low-risk alternative to open surgery in complex patients with severe comorbidities. Other advantages of pursuing immediate angiography in patients with acute limb ischemia include delineation of the limb arterial anatomy with visualization of both inflow and runoff vessels. Finally, thrombolytic therapy has an advantage, compared with surgical embolectomy, of clearing intra-arterial thrombus from the distal runoff vessels, thereby potentially enhancing long-term patency.

The choice of thrombolytic versus surgical revascularization depends on several factors (1). Patients with profound limb ischemia may not tolerate the time necessary to perform thrombolysis. Infra-inguinal or distal arterial thrombolysis has worse outcomes than more proximal or iliofemoral lysis (561). Because of bleeding risks, thrombolysis may be con-
2.6.3.4. Surgery for CLI

RECOMMENDATIONS

Class I
1. For individuals with combined inflow and outflow disease with CLI, inflow lesions should be addressed first. (Level of Evidence: B)
2. For individuals with combined inflow and outflow disease in whom symptoms of CLI or infection persist after inflow revascularization, an outflow revascularization procedure should be performed. (Level of Evidence: B)
3. Patients who have significant necrosis of the weight-bearing portions of the foot (in ambulatory patients), an uncorrectable flexion contracture, paresis of the extremity, refractory ischemic rest pain, sepsis, or a very limited life expectancy due to comorbid conditions should be evaluated for primary amputation of the leg. (Level of Evidence: C)

Class III
Surgical and endovascular intervention is not indicated in patients with severe decrements in limb perfusion (e.g., ABI less than 0.4) in the absence of clinical symptoms of CLI. (Level of Evidence: C)

The mortality associated with distal arterial vascular surgical reconstruction in appropriately selected candidates is 0% to 6% (501,595). For major amputation of the lower extremity, the risks are significantly greater. Major amputation of the lower extremity is associated with a 30-day mortality risk of 4% to 30% and a 20% to 37% risk of significant morbidity, such as MI, stroke, and infection (596-599). The difficulties of rehabilitation and the high likelihood of inability to ambulate with a prosthesis in many older patients portend a significant negative long-term impact on the patient’s quality of life and independence (600). Therefore, as described in Section 2.6.3.2, revascularization by endovascular techniques, surgical techniques, or both should be considered the primary approach to the treatment of patients with CLI unless patient survival is very limited, the likelihood of independent ambulation is poor because of tissue necrosis or flexion contracture, or the patient’s general medical condition is poor.

The goal of surgical intervention in patients with CLI is the elimination of clinical manifestations of severe lower extremity PAD, whether rest pain, ischemic ulcers, or distal ischemic gangrene. Surgery for the treatment of severe lower extremity ischemia (as for endovascular treatment) must be based on specific goals, such as the relief of rest pain or healing of ulcers, prior revascularization attempts, the type of procedure required to accomplish the goals, and the patient’s overall ability to successfully recover from the effort. In patients with combined inflow and outflow disease, inflow problems must be corrected first.
### Table 27. Mechanical Thrombectomy Devices for the Treatment of Peripheral Arterial Occlusions

<table>
<thead>
<tr>
<th>Device and First Author</th>
<th>Year</th>
<th>n</th>
<th>Conduit, n (%)</th>
<th>Duration, n</th>
<th>MTD Success,* Adjunctive Procedures</th>
<th>Primary Patency (%)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oasis, Hopfner (143)</td>
<td>1999</td>
<td>51</td>
<td>Native: 44 (86)</td>
<td>All acute</td>
<td>Lysis: 5</td>
<td>1 month: 64</td>
<td>Hemorrhage: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 7 (14)</td>
<td></td>
<td>PTA: 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAT: 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SA: 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiojet Muller-Hulsbeck (144)</td>
<td>2000</td>
<td>112</td>
<td>Native: 99 (86)</td>
<td>All acute</td>
<td>Lysis: 20</td>
<td>6 months: 68</td>
<td>Embolization: 9.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 16 (14)</td>
<td></td>
<td>PTA: 68</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAT: 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 31 (37)</td>
<td>Complete: 51 (61)</td>
<td>PAT: 47</td>
<td>6 months: 78</td>
<td>Embolization: 2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial: 19 (23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTA: 47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAT: 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 9 (41)</td>
<td>Chronic: 21</td>
<td>PAT: 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTA: 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTA/SA: 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wagner (147)</td>
<td>1997</td>
<td>50</td>
<td>Native: 39 (78)</td>
<td>All acute</td>
<td>Lysis: 11</td>
<td>1 month: 50</td>
<td>Embolization: 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 11 (22)</td>
<td></td>
<td>PTA: 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAT: 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTA: 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 17 (61)</td>
<td>Chronic: 5</td>
<td>PTA: 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAT: 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henry (149)</td>
<td>1998</td>
<td>41</td>
<td>Native: 28 (68)</td>
<td>All acute</td>
<td>Lysis: 10</td>
<td>1 month: 50</td>
<td>Hemorrhage: 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 8 (20)</td>
<td></td>
<td>PTA: 29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other: 5</td>
<td></td>
<td>PAT: 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplatz Rilinger (150)</td>
<td>1997</td>
<td>40</td>
<td>All native</td>
<td>All acute</td>
<td>Lysis/PTA/SA: 9</td>
<td>NA</td>
<td>Device failure: 7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SA: 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTA/SA: 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadavarthy (151)</td>
<td>1994</td>
<td>14</td>
<td>Native: 2 (14)</td>
<td>All acute</td>
<td>Lysis: 4</td>
<td>6 months: 43</td>
<td>Hemorrhage: 14.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grafts: 10 (71)</td>
<td></td>
<td>PTA/SA: 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other: 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorich (152)</td>
<td>1998</td>
<td>18</td>
<td>All native</td>
<td>All acute</td>
<td>Lysis: 12</td>
<td>NA</td>
<td>Device failure: 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAT: 9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MTD indicates mechanical thrombectomy device; n, number of patients; NA, not applicable; PAT, percutaneous aspiration thrombectomy; PTA, percutaneous transluminal angioplasty; SA, Simpson atherectomy.

*Definition of success varies among studies.

2.6.3.4.1. INFLOW PROCEDURES: AORTOILIAC OCCLUSIVE DISEASE.

RECOMMENDATIONS

Class I

1. When surgery is to be undertaken, aortobifemoral bypass is recommended for patients with symptomatic, hemodynamically significant, aorto-bi-iliac disease requiring intervention. (Level of Evidence: A)

2. Iliac endarterectomy, patch angioplasty, or aortoiliac or iliolfemoral bypass in the setting of acceptable aortic inflow should be used for the treatment of unilateral disease or in conjunction with femoral-femoral bypass for the treatment of a patient with bilateral iliac artery occlusive disease if the patient is not a suitable candidate for aortobifemoral bypass grafting. (Level of Evidence: B)

3. Axillofemoral-femoral bypass is indicated for the treatment of patients with CLI who have extensive aortoiliac disease and are not candidates for other types of intervention. (Level of Evidence: B)

There are numerous patterns of aortoiliac occlusive disease and procedures to surgically treat them (Table 24). Most commonly, patients demonstrate diffuse disease of the infrarenal aorta and iliac vessels, with the lesions of greatest hemodynamic consequence located in the iliac arteries. The most effective surgical procedure for the treatment for this pattern of atherosclerotic occlusive disease is aortobifemoral bypass. Through a transabdominal or retroperitoneal approach, this bypass is constructed by sewing the proximal end of a bifurcated polyester filament or PTFE graft, usually end-to-end, to the aorta immediately below the origins of the renal arteries. The distal graft limbs are sewn to the distal common femoral arteries or onto the proximal deep femoral arteries, if the superficial femoral arteries are occluded, to provide adequate outflow for the graft limbs and improved collateral flow to the popliteal arteries.

Aortobifemoral grafting is associated with an operative mortality of 3.3% and a morbidity of 8.3% (485). Major morbidity is most commonly due to MI (0.8% to 5.2%) or renal failure (0% to 4.6%) (536,601). The expected patency of aortobifemoral bypass as the sole procedure for the treatment of CLI is excellent. A meta-analysis of major studies published after 1975 reported a limb-based 5-year primary patency rate of 87.5% and a patient-based 5-year patency of 80.4% (485). This changed little in the subsequent 5 years, with a limb-based 10-year patency rate of 81.8% and a patient-based 10-year patency of 72.1%. The site of distal anastomosis, whether to the common femoral artery when the superficial femoral artery is open or to the profunda femoris artery when the superficial femoral artery is occluded, has little impact. In a report of a large series of predominantly limb-salvage patients, 5-year patency was 89% for grafts placed to the common femoral artery and 92% for grafts placed to the profunda femoris artery (601).

If the aortoiliac lesions are confined to the area of the aortic bifurcation, localized aortoiliac endarterectomy may be considered. This procedure is effective but is uncommonly performed because few patients have such a limited manifestation of atherosclerosis. Aortoiliac endarterectomy remains an excellent surgical option but is used infrequently because of the often extensive nature of the occlusive disease in patients with CLI. Nonetheless, when the operation is indicated, the results demonstrate good patency, in the range of 48% to 77% at 10 years (513).

For patients with adequate aortic flow but stenoses or occlusions of both iliac vessels who are not considered to be acceptable candidates for aortobifemoral bypass, a somewhat less invasive approach may be appropriate. If 1 iliac artery can be made widely patent by angioplasty and stent placement, endarterectomy, or a unilateral iliolfemoral bypass, a femoral-femoral bypass can be constructed. In the absence of an inflow stenosis within the donor iliac arterial segment, this procedure can effectively improve flow to both lower extremities. Unilateral iliac stenoses or occlusions that cannot be treated effectively by angioplasty and stent placement can be treated by iliac artery endarterectomy, aortoiliac bypass, aortofemoral bypass, or iliolfemoral bypass if the origin of the iliac artery is free of disease. These procedures can be performed through a small flank incision into the retroperitoneum and are usually well tolerated.

The surgical treatment of unilateral iliac disease by aortoiliac, iliolfemoral, or femorofemoral bypass graft placement provides excellent results for the restoration of inflow into the lower extremity. Ipsilateral bypasses originating from the aorta or proximal iliac artery have a 3-year patency rate in the range of 90% (487,602). Femorofemoral bypass grafting yields a 3-year patency rate that ranges from 60% to 80% and a 5-year patency rate of 60% to 90% (514,603).

Patients with severe infrarenal aortic atherosclerosis who are at high cardiovascular or surgical risk for open aortobifemoral bypass may be treated with axillofemoral-femoral bypass. This bypass uses either polyester filament or PTFE graft material to carry blood from the axillary artery to 1 of the femoral arteries. A second femoral-femoral bypass is then constructed to provide perfusion of the contralateral extremity. If 1 iliac artery can be made widely patent by angioplasty and stent placement, endarterectomy, or a unilateral iliolfemoral bypass, a femoral-femoral bypass can be constructed. In the absence of an inflow stenosis within the donor iliac arterial segment, this procedure can effectively improve flow to both lower extremities. Unilateral iliac stenoses or occlusions that cannot be treated effectively by angioplasty and stent placement can be treated by iliac artery endarterectomy, aortoiliac bypass, aortofemoral bypass, or iliolfemoral bypass if the origin of the iliac artery is free of disease. These procedures can be performed through a small flank incision into the retroperitoneum and are usually well tolerated.

The surgical treatment of unilateral iliac disease by aortoiliac, iliolfemoral, or femorofemoral bypass graft placement provides excellent results for the restoration of inflow into the lower extremity. Ipsilateral bypasses originating from the aorta or proximal iliac artery have a 3-year patency rate in the range of 90% (487,602). Femorofemoral bypass grafting yields a 3-year patency rate that ranges from 60% to 80% and a 5-year patency rate of 60% to 90% (514,603).

Patients with severe infrarenal aortic atherosclerosis who are at high cardiovascular or surgical risk for open aortobifemoral bypass may be treated with axillofemoral-femoral bypass. This bypass uses either polyester filament or PTFE graft material to carry blood from the axillary artery to 1 of the femoral arteries. A second femoral-femoral bypass is then constructed to provide perfusion of the contralateral extremity. If 1 iliac artery can be made widely patent by angioplasty and stent placement, endarterectomy, or a unilateral iliolfemoral bypass, a femoral-femoral bypass can be constructed. In the absence of an inflow stenosis within the donor iliac arterial segment, this procedure can effectively improve flow to both lower extremities. Unilateral iliac stenoses or occlusions that cannot be treated effectively by angioplasty and stent placement can be treated by iliac artery endarterectomy, aortoiliac bypass, aortofemoral bypass, or iliolfemoral bypass if the origin of the iliac artery is free of disease. These procedures can be performed through a small flank incision into the retroperitoneum and are usually well tolerated.

The surgical treatment of unilateral iliac disease by aortoiliac, iliolfemoral, or femorofemoral bypass graft placement provides excellent results for the restoration of inflow into the lower extremity. Ipsilateral bypasses originating from the aorta or proximal iliac artery have a 3-year patency rate in the range of 90% (487,602). Femorofemoral bypass grafting yields a 3-year patency rate that ranges from 60% to 80% and a 5-year patency rate of 60% to 90% (514,603).

Patients with severe infrarenal aortic atherosclerosis who are at high cardiovascular or surgical risk for open aortobifemoral bypass may be treated with axillofemoral-femoral bypass. This bypass uses either polyester filament or PTFE graft material to carry blood from the axillary artery to 1 of the femoral arteries. A second femoral-femoral bypass is then constructed to provide perfusion of the contralateral extremity. If 1 iliac artery can be made widely patent by angioplasty and stent placement, endarterectomy, or a unilateral iliolfemoral bypass, a femoral-femoral bypass can be constructed. In the absence of an inflow stenosis within the donor iliac arterial segment, this procedure can effectively improve flow to both lower extremities. Unilateral iliac stenoses or occlusions that cannot be treated effectively by angioplasty and stent placement can be treated by iliac artery endarterectomy, aortoiliac bypass, aortofemoral bypass, or iliolfemoral bypass if the origin of the iliac artery is free of disease. These procedures can be performed through a small flank incision into the retroperitoneum and are usually well tolerated.

The surgical treatment of unilateral iliac disease by aortoiliac, iliolfemoral, or femorofemoral bypass graft placement provides excellent results for the restoration of inflow into the lower extremity. Ipsilateral bypasses originating from the aorta or proximal iliac artery have a 3-year patency rate in the range of 90% (487,602). Femorofemoral bypass grafting yields a 3-year patency rate that ranges from 60% to 80% and a 5-year patency rate of 60% to 90% (514,603).

Patients with severe infrarenal aortic atherosclerosis who are at high cardiovascular or surgical risk for open aortobifemoral bypass may be treated with axillofemoral-femoral bypass. This bypass uses either polyester filament or PTFE graft material to carry blood from the axillary artery to 1 of the femoral arteries. A second femoral-femoral bypass is then constructed to provide perfusion of the contralateral extremity. If 1 iliac artery can be made widely patent by angioplasty and stent placement, endarterectomy, or a unilateral iliolfemoral bypass, a femoral-femoral bypass can be constructed. In the absence of an inflow stenosis within the donor iliac arterial segment, this procedure can effectively improve flow to both lower extremities. Unilateral iliac stenoses or occlusions that cannot be treated effectively by angioplasty and stent placement can be treated by iliac artery endarterectomy, aortoiliac bypass, aortofemoral bypass, or iliolfemoral bypass if the origin of the iliac artery is free of disease. These procedures can be performed through a small flank incision into the retroperitoneum and are usually well tolerated.
2.6.3.4.2. Outflow Procedures: Infrainguinal Disease.

RECOMMENDATIONS

Class I
1. Bypasses to the above-knee popliteal artery should be constructed with autogenous saphenous vein when possible. (Level of Evidence: A)

2. Bypasses to the below-knee popliteal artery should be constructed with autogenous vein when possible. (Level of Evidence: A)

3. The most distal artery with continuous flow from above and without a stenosis greater than 20% should be used as the point of origin for a distal bypass. (Level of Evidence: B)

4. The tibial or pedal artery that is capable of providing continuous and uncompromised outflow to the foot should be used as the site of distal anastomosis. (Level of Evidence: B)

5. Femoral-tibial artery bypasses should be constructed with autogenous vein, including the ipsilateral greater saphenous vein, or if unavailable, other sources of vein from the leg or arm. (Level of Evidence: B)

6. Composite sequential femoropopliteal-tibial bypass and bypass to an isolated popliteal arterial segment that has collateral outflow to the foot are both acceptable methods of revascularization and should be considered when no other form of bypass with adequate autogenous conduit is possible. (Level of Evidence: B)

7. If no autogenous vein is available, a prosthetic femoral-tibial bypass, and possibly an adjunctive procedure, such as arteriovenous fistula or vein interposition or cuff, should be used when amputation is imminent. (Level of Evidence: B)

Class IIa

Prosthetic material can be used effectively for bypasses to the below-knee popliteal artery when no autogenous vein from ipsilateral or contralateral leg or arms is available. (Level of Evidence: B)

As noted above, CLI occurs because of the multisegmental nature of the occlusive disease. Lower extremity bypasses for severe ischemia may be due to the need to bypass long occlusions and multiple diseased arterial segments and thus are frequently longer and have a more distal outflow anastomosis (Table 25). The creation of an in situ or reversed greater saphenous vein bypass to a tibial vessel is the most commonly performed limb salvage procedure. This type of bypass can be performed under general or regional (or, more rarely, local) anesthesia and is generally well tolerated. There are, however, specific factors that may modify the result of this procedure. The 2 major factors are the type of conduit and the outflow tract beyond the distal anastomosis.

Nearly all studies that have compared vein with prosthetic material have demonstrated the superior patency of vein. Several large, randomized, prospective studies demonstrate that the immediate and long-term patency of bypasses to the above-knee popliteal artery favor use of autogenous vein, in situ or reversed, at all time periods (483,508-510). In its absence, PTFE or polyester filament may be used with an expected lower but acceptable patency rate for above-knee bypasses. Patency of prosthetic grafts is significantly lower once the knee joint is crossed. In a meta-analysis of reported data on 1572 patients, Hunink and colleagues noted a 5-year patency rate of 47% for prosthetic grafts to the above-knee popliteal artery and a patency rate of only 33% when grafts were brought down to the below-knee popliteal artery (437). The need for retreatment or revision is greater with synthetic material over time. With more distal anastomoses or the presence of hemodynamically significant tibial arterial occlusive disease and poor outflow, there is accelerated failure of prosthetic grafts. Therefore, bypasses to the below-knee popliteal artery or to a tibial or pedal vessel strongly favor the use of autogenous vein. Bypasses to the tibial arteries with prosthetic material should be avoided and other sources of autogenous vein sought if the ipsilateral greater saphenous vein is absent or unsuitable. Lesser saphenous vein, contralateral greater saphenous vein, arm vein, and spliced veins may be used, with an expected patency greater than prosthetic material.

When vein length is inadequate, a composite sequential graft consisting of a prosthetic graft to the above-knee popliteal artery and a jump graft of autogenous vein to the distal vessel may be used. If no other option exists, then the use of a prosthetic with an adjunctive procedure, such as arteriovenous fistula or vein interposition or cuff, may improve patency, although this has not been clearly proven. The least-diseased tibial or pedal artery with continuous flow to the foot should be used as the outflow vessel for the construction of a distal bypass, because equivalent results can be achieved with all tibial and even pedal arteries (606,607). Diabetes mellitus does not have a significant negative impact on distal revascularization (497). It is most important to achieve direct and uncompromised outflow to the foot.

The operative mortality of lower extremity revascularization in this often critically ill population of patients ranges from 1% to 6% regardless of the specific graft configuration (499,500,505,608). In a meta-analysis of reports for lower extremity revascularization composed of at least 50% of patients with CLI, there was a 70% 5-year patency rate for femorotibial grafts created with vein but only a 27% patency rate for those created with a prosthetic material (601).

2.6.3.4.3. Postsurgical Care.

RECOMMENDATIONS

Class I
1. Unless contraindicated, all patients undergoing revascularization for CLI should be placed on antiplatelet therapy (see Sections 2.4.2 and 2.6.1.6), and this treatment should be continued indefinitely. (Level of Evidence: A)

2. Patients who have undergone placement of aortofemoral bypass grafts should be followed up with
periodic evaluations that record any return or progression of ischemic symptoms, the presence of femoral pulses, and ABIs. (Level of Evidence: B)

3. If infection, ischemic ulcers, or gangrenous lesions persist and the ABI is less than 0.8 after correction of inflow, an outflow procedure should be performed that bypasses all major distal stenoses and occlusions. (Level of Evidence: A)

4. Patients who have undergone placement of a lower extremity bypass with autogenous vein should undergo for at least 2 years periodic examinations that record any return or progression of ischemic symptoms; a physical examination, with concentration on pulse examination of the proximal, graft, and outflow vessels; and duplex imaging of the entire length of the graft, with measurement of peak systolic velocities and calculation of velocity ratios across all lesions. (Level of Evidence: A)

5. Patients who have undergone placement of a synthetic lower extremity bypass graft should undergo periodic examinations that record any return of ischemic symptoms; a pulse examination of the proximal, graft, and outflow vessels; and assessment of ABIs at rest and after exercise for at least 2 years after implantation. (Level of Evidence: A)

To maximize the benefit of revascularization and to minimize the risk of cardiovascular ischemic events (MI and stroke), all postoperative patients with lower extremity PAD should receive maximal cardiovascular ischemic risk reduction therapies (as outlined in Section 2.6.1) and be maintained on an oral antiplatelet medication, usually aspirin or clopidogrel. Optimally, risk reduction therapies will be initiated preoperatively and continued for the patient’s lifetime (see Section 2.6.1). There are minimal data to suggest that anticoagulation with warfarin may prolong graft patency; most case series include small numbers of patients, and thus the overall database is inconclusive as yet (609,610). A single retrospective analysis of 293 patients who had undergone infrainguinal bypass has suggested that ACE inhibitor use might decrease mortality (611).

To maintain optimal outcomes, patients should undergo periodic graft surveillance for at least 2 years after placement. For vein grafts, duplex imaging of the donor and recipient arteries, proximal and distal anastomoses, and the entire graft length is of benefit for the detection of grafts with reduced flow secondary to intraluminal lesions. Duplex imaging is of limited benefit for the detection of lesions within synthetic grafts. Therefore, the periodic recording of ABIs is sufficient.

2.7. Algorithms

2.7.1. Diagnostic Pathway

The diagnosis of lower extremity PAD should be considered in individuals who are at risk for lower extremity PAD, as well as in those who present with lower extremity ischemic symptoms (Figure 10). Specific clinical information should be used to identify individuals who merit pursuit of an objective lower extremity PAD diagnosis by measurement of an ABI examination. Clinical data that should guide this assessment include the presence of atherosclerosis risk factors (especially age, smoking, and diabetes), clinical history (a history of atherosclerotic coronary artery, carotid artery, or renal artery disease and lower extremity symptoms), and an abnormal lower extremity pulse examination. Subsequent diagnostic testing and therapeutic interventions are dependent on presenting symptoms. Use of lower extremity symptoms and ABI data should then be used to initiate therapeutic interventions to decrease cardiovascular ischemic risk, diminish claudication symptoms, and promptly identify individuals with CLI or who are at risk for amputation.

2.7.2. Treatment Pathways

Many individuals with lower extremity PAD do not report classic symptoms of claudication or CLI, yet they remain at high risk of cardiovascular ischemic events. The algorithm shown in Figure 11 aids establishment of the lower extremity PAD diagnosis in at-risk individuals by use of (a) the ABI and exercise ABI and (b) the toe-brachial index and PVR for individuals with noncompressible pedal pulses. Establishment of the lower extremity PAD diagnosis in asymptomatic patients and individuals with atypical lower extremity symptoms should lead to use of risk factor reduction and antiplatelet medication interventions.

Classic claudication symptoms (Figure 12) markedly impair quality of life. Recognition of these symptoms should lead to confirmation of the lower extremity PAD diagnosis by use of the ABI (or occasionally other vascular diagnostic tests). The patient’s therapeutic goal is an important factor in determining whether treatment is required. Supervised exercise and pharmacotherapy are therapeutic interventions that can be applied without additional anatomic localization. For individuals with inflow disease, endovascular and surgical therapies may be particularly effective (Figure 13).

Critical limb ischemia is defined by the presence of chronic ischemic rest pain, ulcers, or gangrene caused by a severe decrease in limb perfusion. Although severe ischemia is chronic, the decrement in perfusion would lead to impending limb loss without revascularization. A history suggestive of CLI should lead to prompt confirmation of the ischemic origin, an assessment of lower extremity arterial anatomy, evaluation of limb viability and procedural benefit and risk, and consideration for revascularization by endovascular or surgical techniques (Figure 14).

Acute limb ischemia represents a vascular emergency due to the sudden decrease in lower extremity perfusion that threatens limb viability if not promptly recognized and treated. The history of sudden limb pain and signs of acute ischemia (pain, pulselessness, pallor, paresthesias, and paralysis) should lead to emergent vascular diagnostic testing to establish the ischemic cause (Figure 15). Inasmuch as an assessment of limb viability must be performed and linked to
a plan for immediate revascularization via thrombolytic, endovascular, or surgical therapies, a vascular specialty consultation should be obtained as soon as possible. The potential for limb salvage, duration of ischemia, and arterial anatomy are critical factors in determining the method of revascularization (Figure 16).

3. RENAL ARTERIAL DISEASE

3.1. Prevalence and Natural History

Renal artery stenosis (RAS) is both a common and a progressive disease in patients with atherosclerosis and is a relatively uncommon cause of hypertension (612-614). Although excellent prevalence data have been obtained in selected high-risk populations (e.g., patients with clinically evident coronary artery disease or PAD) (615-619), few studies have adequately assessed the prevalence of RAS in the general population (620). Hansen and associates studied prevalence by performing renal artery duplex ultrasound in individuals 65 years and older as part of their cardiovascular health study to determine the population-based prevalence of renovascular disease. Of 834 participants undergoing renal artery duplex ultrasound, the overall prevalence rate of significant renovascular disease was 6.8%. Renal artery disease

Figure 10. Steps toward the diagnosis of peripheral arterial disease (PAD). **Atypical” leg pain is defined by lower extremity discomfort that is exertional, but that does not consistently resolve with rest, consistently limit exercise at a reproducible distance, or meet all “Rose questionnaire” criteria. (The five “Ps” are defined by the clinical symptoms and signs that suggest potential limb jeopardy: pain, pulselessness, pallor, paresthesias, and paralysis (with polar being a sixth “P”).
Figure 11. Diagnosis and treatment of asymptomatic peripheral arterial disease (PAD) and atypical leg pain. *Duplex ultrasonography should generally be reserved for use in symptomatic patients in whom anatomic diagnostic data are required for care. †Other causes of leg pain may include lumbar disk disease, sciatica, radiculopathy, muscle strain, neuropathy, and compartment syndrome. ‡It is not yet proven that treatment of diabetes mellitus will significantly reduce PAD-specific (limb ischemic) end points. Primary treatment of diabetes mellitus should be continued according to established guidelines. #The benefit of angiotensin-converting enzyme (ACE) inhibition in individuals without claudication has not been specifically documented in prospective clinical trials but has been extrapolated from other at-risk populations. ABI indicates ankle-brachial index; HbA1C, hemoglobin A1C; JNC-7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LOE, level of evidence; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III. Adapted from Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344:1608-21 (158a). Copyright © 2001 Massachusetts Medical Society. All rights reserved.

was present in 5.5% of women, 9.1% of men, 6.9% of white participants, and 6.7% of black participants (620).

Renal artery stenosis is particularly notable in certain high-risk populations. Renal arterial disease has been documented to be present in 30% of patients undergoing screening renal artery angiography at the time of cardiac catheterization. In these cohorts, significant obstructive renal artery stenoses (i.e., greater than 50%) have been reported in 11% to 18% of patients (621-623). Prevalence studies have also demonstrated significant RAS in 22% to 59% of patients with PAD (616-619,624-630). In one necropsy study, RAS greater than 50% was found in 53% of 295 unselected, consecutive examinations (631). This high prevalence increased to 74% when a subpopulation of individuals 70 years and older was evalu-
Atherosclerotic RAS is a progressive disease. In 4 retrospective studies comprising 202 patients followed up for 12 to 60 months, temporal progression of the degree of stenosis occurred in 36% to 71% of patients, and renal artery occlusion occurred in 16% (633-636). Progression to occlusion is more common in renal arteries with more severe stenoses. When the RAS was greater than 75% at the time of diagnosis postmortem. A second autopsy series evaluated 297 patients with proven MI to document atherosclerotic RAS of greater than 75% in 12% (615). Bilateral RAS involvement is common. In 6 different studies, bilateral RAS was found in 44% of 319 patients (632). Overall, these data suggest that if 1 or more clinical clues to the presence of RAS are present, significant RAS can be found in up to 70% of such targeted populations (625). Despite the high prevalence of RAS in these atherosclerotic subgroups, it remains controversial as to which lesions are associated with important clinical sequelae.

Atherosclerotic RAS is a progressive disease. In 4 retrospective studies comprising 202 patients followed up for 12 to 60 months, temporal progression of the degree of stenosis occurred in 36% to 71% of patients, and renal artery occlusion occurred in 16% (633-636). Progression to occlusion is more common in renal arteries with more severe stenoses. When the RAS was greater than 75% at the time of diagno-
3.1.1. Clinical End Points of Renal Artery Disease

The exact contribution of atherosclerotic renal arterial disease to the development of end-stage renal disease (ESRD) is not well-defined by current data. It is unclear how many patients enter dialysis secondary to RAS. Mailloux and colleagues reviewed the causes of ESRD in 683 patients entered into their dialysis program over a 20-year period (640). Eighty-three patients (12%) had documented RAS as a cause of ESRD. Because these investigators only performed arteriography in patients in whom RAS was highly suspected, it is possible that the true incidence was underestimated.

Although the degree of global atherosclerotic risk factor control was variable in these studies, these data demonstrate that the atherosclerotic process remains dynamic and progressive in many individuals. The clinical significance of isolated anatomic progression without clinical clues or indications for intervention is still unclear.

Renal atrophy is a consequence of RAS and is associated with lesion severity and lesion progression (641,642). Several studies have documented worsening clinical out-
Figure 14. Diagnosis and treatment of critical limb ischemia. *Based on patient comorbidities. †Based on anatomy or lack of conduit. ‡Risk factor normalization: immediate smoking cessation, treat hypertension per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines; treat lipids per National Cholesterol Education Program Adult Treatment Panel III guidelines; treat diabetes mellitus (HbA1C [hemoglobin A1C] less than 7%; Class IIa). It is not yet proven that treatment of diabetes mellitus will significantly reduce peripheral arterial disease (PAD)-specific (limb ischemic) end points. Primary treatment of diabetes mellitus should be continued according to established guidelines. ABI indicates ankle-brachial index; CTA, computed tomographic angiography; ECG, electrocardiogram; MRA, magnetic resonance angiography; PVR, pulse volume recording; TBI, toe-brachial index; TEE, transesophageal echocardiography; US, ultrasound.
comes (i.e., deterioration of renal function, loss of renal mass, and lower survival rates) in patients with progressive RAS (637,641,643). One prospective study evaluated renal function in 41 patients with atherosclerotic RAS treated with medical therapy (637). At a mean follow-up of 28 months (range 6 to 102 months), 19 patients (46%) had increased serum creatinine, 12 (29%) had a 25% to 50% decline in glomerular filtration rates, and 14 (37%) had a decrease in kidney size by more than 10% (637). Investigators at Duke University demonstrated progression of RAS in patients undergoing 2 sequential cardiac catheterizations separated by 2.6 plus or minus 1.6 years (643). They observed an overall rate of RAS progression of 11.1% and a significant decline in renal function in those patients who had lesion progression.

Amongst the most clinically relevant end points for individuals with chronic renal disease is the rate of progression to renal replacement therapies. Dialysis-free survival
patients alive and free of dialysis) is inversely correlated with the severity of renal ischemia. In one study, 2-year dialysis-free survival was 97.3% for patients with unilateral RAS and 82.4% for patients with bilateral RAS but only 44.7% in patients with renovascular disease in a solitary (single) functioning kidney (641).

Patients with atherosclerotic RAS who progress to ESRD and require dialysis have high mortality rates. In one study, the mean life expectancy of individuals older than 65 with RAS who had ESRD was only 2.7 years (644). The median survival for ESRD patients with renovascular disease was 25 months, compared with 55 months for patients with ESRD due to malignant hypertension and 133 months for patients with ESRD due to polycystic kidney disease (645). This is suspected to be due to the systemic atherosclerotic burden and higher rates of cardiovascular ischemic events in those individuals with atherosclerotic RAS. Two-, 5-, and 10-year survival rates were 56%, 18%, and 5%, respectively, in individuals with atherosclerotic RAS. Prospective, randomized, controlled trials will be required to determine whether the early diagnosis of RAS will provide an opportunity for the prevention of ESRD and identify individuals at high cardiovascular risk.

The presence and severity of RAS, even before the development of ESRD, imparts a poorer prognosis. In a series of almost 4000 patients undergoing screening for RAS at the time of cardiac catheterization, the 4-year survival rates for patients with and without RAS were 57% and 89%, respectively (\(p \text{ less than } 0.001\)) (644). The 4-year survival rates for individuals with RAS of 50%, 75%, and greater than 95% were 70%, 68%, and 48%, respectively. Bilateral RAS was associated with a 47% 4-year survival compared with 59% for unilateral RAS (\(p \text{ less than } 0.001\)). In the multivariate analysis, the presence of RAS conferred a hazard ratio of 2.01 (95% CI 1.51 to 2.67, \(p \text{ less than } 0.001\)) regardless of the treatment of the underlying coronary artery disease (644). Finally, the severity of renal function impairment has been associated with reduced survival in patients with RAS (646).

In patients with serum creatinine levels less than 1.4 mg per dl, 3-year survival was 92% plus or minus 4%. For serum creatinine levels between 1.5 and 1.9 mg per dl, 3-year survival was 74% plus or minus 8%, and for creatinine greater than or equal to 2.0 mg per dl, it was only 51% plus or...
minus 8%. The relationship between the increase in serum creatinine and mortality is complex and multifactorial. Not only do the severity of RAS and the severity of systemic atherosclerosis serve as contributors to mortality, but the degree of proteinuria, parenchymal renal disease, and other comorbidities (such as diabetes mellitus) play an important role (12,647).

3.2. Clinical Clues to the Diagnosis of RAS

RECOMMENDATIONS

Class I

1. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of hypertension before the age of 30 years. (Level of Evidence: B)

2. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of severe hypertension [as defined in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report (294)] after the age of 55 years. (Level of Evidence: B)

3. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the following characteristics: (a) accelerated hypertension (sudden and persistent worsening of previously controlled hypertension); (b) resistant hypertension (defined as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic); or (c) malignant hypertension (hypertension with coexistent evidence of acute end-organ damage, i.e., acute renal failure, acutely decompensated congestive heart failure, new visual or neurological disturbance, and/or advanced [grade III to IV] retinopathy). (Level of Evidence: C)

4. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with new azotemia or worsening renal function after the administration of an ACE inhibitor or an angiotensin receptor-blocking agent (see text). (Level of Evidence: B)

5. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with an unexplained atrophic kidney or a discrepancy in size between the 2 kidneys of greater than 1.5 cm. (Level of Evidence: B)

6. The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with sudden, unexplained pulmonary edema (especially in azotemic patients). (Level of Evidence: B)

Class IIa

The performance of diagnostic studies to identify clinically significant RAS is reasonable in patients with unexplained renal failure, including individuals starting renal replacement therapy (dialysis or renal transplantation). (Level of Evidence: B)

Class IIb

1. The performance of arteriography to identify significant RAS may be reasonable in patients with multi-vessel coronary artery disease and none of the clinical clues (Figure 17) or PAD at the time of arteriography. (Level of Evidence: B)

2. The performance of diagnostic studies to identify clinically significant RAS may be reasonable in patients with unexplained congestive heart failure or refractory angina (see Section 3.5.2.4). (Level of Evidence: C)

Several clinical features raise the suspicion of RAS and provide relative indications for application of more specific diagnostic testing strategies. One such indication is the presence of an atrophic kidney (7 to 8 cm) or discrepancy in renal sizes (648). In such cases, the atrophy should be otherwise unexplained by a prior history of pyelonephritis, reflux nephropathy, trauma, and so on. When such a history is present, there is usually not an indication for additional renal diagnostic tests to define RAS. These clinical indications are outlined in Figure 17.

3.3. Pathophysiology and Disease Categories

The pathophysiology that results from RAS is mediated by the degree of renal blood flow impairment. In the acute phase, unilateral RAS causes a renin-mediated (vasoconstriction) form of hypertension, although renin increases may be moderated in the chronic phase of renal hypertension. In contrast, the effects of bilateral renal artery stenoses or stenosis to a solitary kidney are predominantly due to an increase in extracellular fluid volume. Exceptions to this include longstanding unilateral RAS and contralateral renal dysfunction (e.g., due to hypertensive nephrosclerosis or hyperfiltration injury) wherein the physiology mimics that of a patient with a single functioning kidney or those with bilateral disease. Inasmuch as renal blood flow and filtration rate are maintained, in part, by angiotensin II-induced efferent arteriolar vasoconstriction, agents that cause efferent arteriolar dilation, such as ACE inhibitors or angiotensin II receptor blockers, can cause acute renal failure. They do so by decreasing transglomerular hydrostatic pressure and thus glomerular filtration rate. In addition, because the glomerular filtration rate falls but renal blood flow changes very little, the filtration fraction decreases. Under these circumstances, blood is shunted from the afferent arteriole to the efferent arteriole because there is not an adequate hydrostatic pressure to maintain filtration. Thus, use of ACE inhibitors or angiotensin receptor-blocking medications in patients with bilateral RAS, stenosis to a solitary kidney, or uncompensated congestive heart failure in a sodium-depleted state can result in acute renal failure (649-652). This pathophysiology underlies both the caution required in the therapeutic use of angiotensin-pathway antagonists in patients with RAS.
and the diagnostic clue to RAS provided when severe hypotension or azotemia is provoked by use of these classes of medications. It should be noted that short-term changes in renal function are often multifactorial, and that clinicians have differing thresholds for defining significant new azotemia. Clinically significant azotemia has been defined as a greater than 50% rise in serum creatinine that persists or worsens after hypoperfusion states are corrected (e.g., volume depletion, nonsteroidal anti-inflammatory drug use, heart failure) (652a).

3.3.1. Atherosclerosis

Approximately 90% of all renovascular stenotic lesions are due to atherosclerosis (653). Although isolated atherosclerotic RAS may be found, it is more commonly a manifestation of systemic atherosclerosis that involves the aorta, coronary, cerebral, and peripheral arteries. Atherosclerotic RAS most often affects the aorto-ostial segment, including the proximal 1 cm of the main renal artery, that is, an intrinsic renal plaque extending to and contiguous with the aorta.

3.3.2. Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, non-inflammatory disease that most commonly affects the renal arteries and is the second most common cause of RAS (11,654-657). The most common clinical presentation is that of hypertension in a young woman, although FMD can occur in both genders at any age. Whereas atherosclerotic lesions usually involve the origin and proximal portion of the renal arteries, FMD characteristically involves the middle and distal two thirds of the main renal artery and may involve renal artery branches.

Medial fibroplasia is the histological finding in nearly 80% to 85% of all cases of FMD. This form of FMD tends to occur in 25- to 50-year-old women and often involves both renal arteries. It has a characteristic angiographic “string of
beads” appearance (Table 28). The “bead” diameter is typically larger than the adjacent, less-affected artery. Bilateral disease occurs in 60% of patients, including 10% to 15% in whom the lesions are functionally important and warrant treatment. In 25% of patients, the disease extends into the segmental arteries. Intimal fibroplasia is, by comparison, relatively rare. Its stenosis appears as a thin, discrete web. Perimedial dysplasia often affects women a decade older than those with medial fibrodysplasia. Segmental perimedial dysplasia is uncommon (658-660).

Fibromuscular dysplasia also affects other arteries, including the carotid and vertebral arteries, and less commonly, the iliac and mesenteric arteries. There appears to be an association between carotid and vertebral FMD and intracranial aneurysmal disease, with prevalence as high as 51% (661,662). However, the prevalence of cerebral aneurysms may be falsely elevated because of selection bias. When patients who presented with subarachnoid hemorrhage were excluded from the prevalence estimates, the prevalence of incidental, asymptomatic cerebral aneurysms in patients with internal carotid or vertebral artery FMD was 7.3% in one contemporary series (662).

Magnetic resonance angiography of the head should be performed in all patients with cervicocranial FMD. The prevalence of FMD in nonreferral populations is poorly elucidated, and thus, the relative efficacy of screening for FMD in nonrenal arterial beds, in the presence of renal FMD, is beyond the scope of this guideline (661,662).

### 3.3.3. Other Causes of Renal Artery Disease

Renovascular hypertension may also be caused by renal artery aneurysms. Renal artery aneurysms may require surgical or endovascular treatment to obviate risk of rupture or to diminish their contribution to a renin-mediated form of hypertension. Aneurysm rupture is of greatest concern with noncalcified aneurysms larger than 2 cm in diameter, particularly in premenopausal women because of the increased risk of aneurysm rupture during pregnancy (663,664).

The other causes of renovascular disease are myriad (663-673) and include Takayasu’s arteritis (671-673), atheroemboli, thromboemboli, William’s syndrome (669,671), neurofibromatosis (670,671), spontaneous renal artery dissection, arteriovenous malformations or fistulas, trauma (e.g., lithotripsy, direct injury, or surgery), and prior abdominal radiation therapy (665-668). Rarely, retroperitoneal fibrosis producing external compression has also been associated with RAS.

### 3.4. Diagnostic Methods

#### RECOMMENDATIONS

**Class I**

1. Duplex ultrasonography is recommended as a screening test to establish the diagnosis of RAS. *(Level of Evidence: B)*
2. Computed tomographic angiography (in individuals with normal renal function) is recommended as a

---

**Table 28. Classification of Fibromuscular Dysplasia**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Frequency</th>
<th>Pathology</th>
<th>Angiographic Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial dysplasia</td>
<td>80%</td>
<td>Alternating areas of thinned media and thickened fibromuscular ridges containing collagen; internal elastic membrane may be lost in some areas</td>
<td>“String of beads” appearance in which diameter of &quot;beading&quot; is larger than diameter of artery</td>
</tr>
<tr>
<td>Medial fibroplasia</td>
<td>10% to 15%</td>
<td>Extensive collagen deposition in outer half of media</td>
<td>“Beading” in which “beads” are smaller than diameter of artery</td>
</tr>
<tr>
<td>Medial hyperplasia</td>
<td>1% to 2%</td>
<td>True smooth muscle cell hyperplasia without fibrosis</td>
<td>Concentric smooth stenosis (similar to intimal disease)</td>
</tr>
<tr>
<td>Intimal fibroplasia</td>
<td>Less than 10%</td>
<td>Circumferential or eccentric deposition of collagen in the intima; no lipid or inflammatory component; internal elastic lamina fragmented or duplicated</td>
<td>Concentric focal band; long, smooth narrowing</td>
</tr>
<tr>
<td>Adventitial (periarterial) fibroplasia</td>
<td>Less than 1%</td>
<td>Dense collagen replaces fibrous tissue of adventitia and may extend into surrounding tissue</td>
<td>So rare that classic angiographic findings are not known</td>
</tr>
</tbody>
</table>

screening test to establish the diagnosis of RAS. (Level of Evidence: B)

3. Magnetic resonance angiography is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B)

4. When the clinical index of suspicion is high and the results of noninvasive tests are inconclusive, catheter angiography is recommended as a diagnostic test to establish the diagnosis of RAS. (Level of Evidence: B)

Class III

1. Captopril renal scintigraphy is not recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: C)

2. Selective renal vein renin measurements are not recommended as a useful screening test to establish the diagnosis of RAS. (Level of Evidence: B)

3. Plasma renin activity is not recommended as a useful screening test to establish the diagnosis of RAS. (Level of Evidence: B)

4. The captopril test (measurement of plasma renin activity after captopril administration) is not recommended as a useful screening test to establish the diagnosis of RAS. (Level of Evidence: B)

Renal artery stenosis is best diagnosed with an imaging modality. The ideal tool should evaluate both the main and accessory renal arteries, assess the hemodynamic significance of the demonstrated lesions, identify the site and severity of the stenosis, and identify associated perirenal pathology, including the presence of an AAA or renal or adrenal masses. Direct imaging modalities such as duplex ultrasound, CTA, and MRA are best suited to serve as effective diagnostic screening methods. The choice of imaging procedure will depend on the availability of the diagnostic tool, the experience and local accuracy of the chosen modality, and patient characteristics (e.g., body size, renal function, contrast allergy, and presence of prior stents or metallic objects that may serve as contraindications to MRA or CTA techniques).

3.4.1. Renal Scintigraphy

Captopril renography yields both scintigraphic images and computer-generated time-activity curves to provide information about renal size, perfusion, and excretory capacity. Typical methods to perform this examination include the oral administration of captopril 50 mg taken 60 minutes before performance of renal scintigraphic imaging with technetium-99m mercaptoacetyltriglycine or technetium-99m diethylenetriaminedipentaacetic acid. The diagnostic criteria for RAS are (a) delayed time to maximal activity (TMax greater than or equal to 11 minutes after captopril administration), (b) significant asymmetry of peak activity of each kidney, (c) marked cortical retention of the radionuclide after captopril administration, and (d) marked reduction in calculated glomerular filtration rate of the ipsilateral kidney after ACE inhibition (674). The accuracy of captopril renography in identifying patients with renovascular disease has been variable, with reported sensitivities of approximately 85% (range 45% to 94%) and specificities of approximately 93% (range 81% to 100%) (674-685).

In patients with azotemia, bilateral RAS, or RAS of a solitary functioning kidney, the sensitivity and specificity of captopril renography is poor. Many investigators have excluded from captopril testing those patients with a serum creatinine value that exceeds 2.5 to 3.0 mg per dL. In patients with a serum creatinine greater than or equal to 1.5 mg per dL and less than or equal to 3.0 mg per dL, Fommei et al. reported a reduction in the positive predictive value from 88% to 57%, whereas there was a minimum reduction in sensitivity/specificity in patients with serum creatinine of 1.5 mg per dL (678).

When captopril renography was compared with catheter angiography in a clinical practice setting, the sensitivity was only 74%, and the specificity was only 59% (686). Thus, captopril renography may not be a very useful test for screening most patients for RAS but may retain some value in the assessment of renal artery stenoses of borderline angiographic severity for which the physiological functional significance is unclear.

3.4.2. Duplex Ultrasound

Duplex (Doppler with B-mode) ultrasound, compared with angiography, has a sensitivity of 84% to 98% and a specificity of 62% to 99% for detecting RAS (687-693). An enddiastolic velocity of more than 150 cm per second predicts severe (greater than 80%) RAS (694). Other criteria used include direct peak systolic velocity greater than 18 to 200 cm per second, renal to aortic ratio greater than 3.5, rise time greater than 0.07 seconds, acceleration index less than 300 cm per second, and difference in renal or segmental resistive index greater than 0.15. These criteria have correlated with a stenosis exceeding 60% in most published series. Renal artery duplex ultrasonography is an excellent test to monitor renal artery patency after endovascular treatment or surgical revascularization of RAS (695,696). Unlike MRA, in which most stents currently cause artifacts, ultrasound transmission through a stent is not a problem. Limitations of renal artery duplex ultrasonography include its absolute dependence on operator skill, the diminished ability to visualize accessory renal arteries, and the difficulty or inability to image obese patients or patients with intervening bowel gas (696).

Renal artery duplex ultrasonography may be used to measure the renal artery resistive index (RRI). An increased RRI suggests structural abnormalities in the small blood vessels of the kidney. Such small-vessel disease has been documented in the context of longstanding hypertension associated with nephrosclerosis or glomerulosclerosis (697). There have been conflicting reports regarding the usefulness of RRI to predict individual patient response to revascularization. A retrospective study has demonstrated that an elevated resistance index greater than 0.80 predicted a lack of improvement
in blood pressure and renal function after revascularization (698). A limitation of that study was its retrospective design, lack of prespecified end points, and inclusion of a large majority of patients who received balloon angioplasty as their method of treatment. Renal angioplasty without stent placement is now generally recognized as a less optimal method of renal revascularization (699-701), and thus, the outcomes in response to renal revascularization therapy may have been underestimated in that report.

A prospective study of renal stent placement in 241 patients demonstrated that patients with an elevated RRI did have a favorable blood pressure response to intervention (702). Furthermore, serum creatinine improved 15% to 23% in patients with mild to moderate (RRI 0.7 to 0.8) and severe (RRI greater than 0.80) nephrosclerosis, respectively. Notably, only 18% of those with severe nephrosclerosis had serum creatinines greater than 2.5 mg per dL. Resistive indices may prove useful in identifying severe parenchymal disease, which might limit the value of renal revascularization. The database regarding the predictors of a beneficial clinical outcome to renal revascularization remains incomplete and will require future prospective randomized, controlled trials.

### 3.4.3. Computed Tomographic Angiography

Computed tomographic angiography produces excellent 3D images of the aorta and renal arteries. Computed tomographic angiography has a sensitivity and specificity for detecting significant RAS of 59% to 96% and 82% to 99%, respectively, compared with catheter-based contrast angiography (703-709). Current multidetector-row scanners acquire up to 16 simultaneous interweaving helices; 32- and 64-row and flat-panel scanners are in development. With current CTA techniques, sensitivity for detecting renal artery stenoses reached 91% and 92% (readers 1 and 2), and the specificity was 99% for both readers (241). Computed tomographic angiography is capable of providing high-resolution noninvasive detection of RAS while supplying associated 3D angiographic images of the aorta, renal, and visceral arteries. Computed tomographic angiography requires the administration of 100 to 150 cc of iodinated contrast and therefore is not an ideal screening method for patients with renal insufficiency because of the risk of inducing contrast nephropathy. However, as computed tomography scanner technology advances, particularly with regard to the development of scanners with increasing numbers of conventional and newer flat-panel detectors, spatial resolution will improve, scanning time will decrease, and the administered contrast load may be reduced. One advantage of CTA over the MRA technique is that metal stents may be imaged with CTA and in-stent restenosis detected.

### 3.4.4. Magnetic Resonance Angiography

Contrast-enhanced MRA is performed with gadolinium, a less-nephrotoxic contrast agent, to obtain visualization of the renal arteries and abdominal vasculature (710-716). Comparisons with catheter-based contrast angiography have indicated a range of sensitivities from 90% to 100% and specificities of 76% to 94% for detection of RAS. Many earlier flow-related artifacts are avoided almost entirely with the use of gadolinium as a contrast agent. Magnetic resonance angiography may be less effective in the assessment of patients with more subtle beading and changes of FMD because of current resolution limits balanced against the size of the distal renal artery and its branches. Occasionally, beading artifacts may appear when none exist (on angiography). However, as improvements in acquisition speed, pulse sequences, scanner technologies, and novel contrast formulations continue to evolve, many of these technical limitations may be overcome (717).

### Summary of Noninvasive Renal Artery Diagnostic Imaging Strategies

There are relative advantages and disadvantages to each of the aforementioned imaging modalities. Captopril renography has been validated in a large number of patients but is limited in value to a subset of all potential renovascular patients, and it is of limited value in patients with significant azotemia, bilateral RAS, or RAS to a single functioning kidney. Duplex renal sonography, because of the critical role of the sonographer, is accurate in experienced laboratories and is thus ideally performed in high-volume accredited laboratories. The diagnostic accuracy of these ultrasound-based examinations is further limited in patients with large body habitus or intestinal gas obscuring visualization of the entirety of the renal artery. Computed tomographic angiography currently provides higher spatial resolution than MRA and may be more readily available; however, the requirement to use iodinated contrast makes it an unattractive modality in patients with impaired renal function. Gadolinium-enhanced MRA provides excellent and less-nephrotoxic characterization of the renal arteries, surrounding vessels, renal mass, and perhaps renal function, but it remains the most costly renal artery examination. It is far less useful in patients who have had a metallic renal artery stent placed because of the inability to image inside of the stent to detect restenosis. Comparisons of contrast-enhanced 3D MRA and multidetector CTA with digital subtraction catheter angiography in a large number of arterial segments have demonstrated equally high sensitivities for detection of hemodynamically significant stenoses for MRA and computed tomography (greater than 90%), with excellent interobserver and intermodality agreement (kappa equals 0.88 to 0.90) (241).

### 3.4.5. Catheter Angiography

Renal catheter-based contrast arteriography, the longstanding “gold standard” for the diagnosis of RAS, has been largely replaced as a practical first-line modality by the previously described noninvasive imaging studies. The indications for catheter-based contrast renal angiography include (a) individuals in whom there are prespecified indications to suspect clinically important RAS (“clinical clues”) in whom defini-
tive diagnostic noninvasive images cannot be obtained and (b) individuals in whom these prespecified clinical indications and patient consent have been documented and in whom concomitant angiographic access has been obtained for peripheral angiography or coronary angiography.

Catheter-based contrast angiography is associated with a low rate of serious adverse outcomes in individuals with normal renal function. These include contrast-induced acute renal failure, contrast-related allergic reactions, atheromatous renal and distal (lower extremity) embolization, and access-related complications such as pseudoaneurysm, arteriovenous fistula, bleeding, and hematoma. However, the risk of contrast-induced acute renal failure is magnified in certain clinical groups, particularly those with diabetes and chronic kidney disease. In general, the incidence of contrast-induced acute renal failure is less than 3% in patients with neither diabetes nor chronic kidney disease; 5% to 10% in those with diabetes; 10% to 20% in those with chronic kidney disease (and greater with more advanced stages), and 20% to 50% in those with both diabetes and chronic kidney disease (717a,717b).

Iodinated contrast-related acute renal failure can be mitigated with fluids (i.e., avoiding dehydration, using preprocedure intravenous fluids to stimulate urine output) and the use of alternative imaging agents such as carbon dioxide or gadolinium. One randomized trial in diabetic patients with elevated serum creatinine (1.5 to 3.5 mg per dL) levels demonstrated that iodixanol, an iso-osmolar nonionic contrast agent, was associated with significantly fewer nephrotoxic effects than iohexol, a low-osmolar nonionic contrast agent (276). Renal protection has also been demonstrated with the use of oral acetylcysteine (600 mg 2 times per day) in a randomized, controlled trial of patients with chronic renal impairment (serum creatinine greater than 1.2 mg per dL or creatinine clearance less than 60 mL per min) undergoing coronary angiography (278). Additionally, hemofiltration performed both before and after coronary intervention in patients with chronic renal failure has been reported to materially reduce the incidence of deterioration in renal function in this patient population (281).

Given the high prevalence of RAS in individuals with coronary artery disease (621,718,719) and peripheral vascular disease (619,624-630) that warrant catheter angiography, the use of screening flush aortography (not selective renal angiography) at the time of coronary and peripheral vascular angiography has been proposed. Such studies may be appropriate (by operators skilled in the performance and evaluation of RAS using flush aortography) when individuals who will be undergoing coronary or limb angiography have clinical indicators for significant renal arterial occlusive disease. The performance of renal angiography in these individuals, in whom arterial catheterization of the aorta has been performed, provides anatomic access to the renal arteries with relatively low incremental risk (720). To date, studies have not demonstrated a measurable incremental risk to the use of nonselective renal angiography in conjunction with coronary angiography or peripheral vascular arteriography in individ-

3.4.6. Renin

3.4.6.1. Selective Renal Vein Renin Studies

Renal vein renin measurements are now performed very infrequently because of their limited clinical utility and need for invasive catheterization. The utility of the examination depends on the ability to differentiate the unilateral elevation of renin concentration from the renal vein that drains the kidney with renal artery disease from the systemic plasma renin levels and/or renal vein renin levels collected from the contralateral (normal) kidney. The test is performed with direct catheterization and collection of blood samples from within each renal vein and from the inferior vena cava cephalad and caudal to the renal veins at baseline. The test is typically repeated after stimulation of renin release by administration of either oral captopril or furosemide. To maximize the accuracy of this plasma biochemical marker of renal hypoperfusion, all medications that can affect renal secretion must be stopped, including all antihypertensive drugs, diuretics, and nonsteroidal anti-inflammatory drugs, for at least 2 weeks. In addition, the patient should be kept on a dietary sodium intake of 100 to 200 mmol per day. If it is considered unsafe to stop all antihypertensive agents, a calcium-channel blocker or alpha-1 adrenergic blocker can be used (721).

One study by Hughes et al. showed that if there was later- alization of the renal vein renin ratio of more than 1.4:1 and a duration of hypertension less than 5 years, the cure rate of hypertension after revascularization was 95% (722). Nevertheless, renal vein renin measurements have been largely supplanted by the aforementioned noninvasive imaging modalities. Renal vein renin measurements may have more utility in establishing an indication for nephrectomy in patients with renal artery occlusion than in identifying patients with RAS who may derive benefit from revascularization (721); for pediatric patients with questionably severe RAS before revascularization; or for patients with very marked aortoiliac-renal atherosclerosis, in whom revascularization could carry unusually high risk.

3.4.6.2. Plasma Renin Activity: Captopril Test

This study is performed as follows: after a baseline plasma renin level is obtained, 50 mg of captopril is given orally, and a second plasma renin level is obtained 60 minutes later. The overall sensitivity of this test is 61%, with a specificity of 86% for the detection of renal artery disease. However, this test is less accurate in patients who are volume expanded or who have chronic renal failure, bilateral renal artery disease, or disease to a solitary functioning kidney. In addition, the same principles regarding medication withdrawal apply to this test as with renal vein renin measurement. In one large study involving 540 patients, the false-negative rate for elevation of the plasma renin activity was 43% and the false-
positive rate was 34% (723). Elevated plasma renin activity may be present in approximately 15% of patients with essential hypertension. Plasma renin activity is not recommended as a useful screening test to establish the diagnosis of RAS.

3.5. Treatment of Renovascular Disease: Renal Artery Stenosis

Treatment of renal arterial disease should serve to aid in the normalization of blood pressure and to preserve renal function, and possibly to reduce risk of cardiovascular events and mortality. Both medical (pharmacological) and revascularization strategies should be considered for patients with documented renal arterial disease. The relative efficacy and safety of medical and endovascular strategies remains an area of active clinical investigation. A treatment algorithm based on the current evidence base is provided in Figure 18.

3.5.1. Medical Treatment

RECOMMENDATIONS

Class I

1. Angiotensin-converting enzyme inhibitors are effective medications for treatment of hypertension associated with unilateral RAS. (Level of Evidence: A)

2. Angiotensin receptor blockers are effective medications for treatment of hypertension associated with unilateral RAS. (Level of Evidence: B)

3. Calcium-channel blockers are effective medications for treatment of hypertension associated with unilateral RAS. (Level of Evidence: A)

4. Beta-blockers are effective medications for treatment of hypertension associated with RAS. (Level of Evidence: A)

Multiple studies have now shown that ACE inhibitors and calcium-channel blockers are effective in the treatment of hypertension in the presence of RAS (724-728). These results address primarily the treatment of hypertension, but diminution in the progression of renal disease has also been demonstrated. There is also evidence that alternative therapies, based largely on chlorothiazide, hydralazine, and beta-blockers, appear effective to achieve target blood pressures in individuals with RAS. The beneficial effects of medical therapy in these studies on the progression of atherosclerotic renal arterial disease contributed by smoking cessation, treatment of dyslipidemia, and the use of aspirin are difficult to differentiate from improvement in blood pressure control alone. In addition, although the angiotensin II receptor blockers also have an evidence base of efficacy for normalization of blood pressure in individuals with RAS, their

![Figure 18. Indications for renal revascularization. *Viable means kidney linear length greater than 7 cm. †It is recognized that renal artery surgery has proven efficacy in alleviating RAS due to atherosclerosis and fibromuscular dysplasia. Currently, however, its role is often reserved for individuals in whom less invasive percutaneous RAS interventions are not feasible. CHF indicates congestive heart failure; CRI, chronic renal insufficiency; LOE, level of evidence; PTA, percutaneous transluminal angioplasty.](image-url)
effects need to be tested further in large randomized trials. There are currently few objective clinical clues that permit selection of specific patient cohorts that would best be treated by medical therapy versus renal arterial revascularization, which remains an area of active clinical investigation. Individuals with atherosclerotic disease and hypertension should be treated according to goals of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (294).

3.5.2. Indications for Revascularization

3.5.2.1. Asymptomatic Stenosis

RECOMMENDATIONS

Class IIb

1. Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS. (Level of Evidence: C)

2. The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven. (Level of Evidence: C)

Hemodynamically significant asymptomatic (incidental) renal artery stenosis is defined as RAS in the absence of end-organ dysfunction (e.g., idiopathic pulmonary edema, stroke, visual loss, hypertension, or refractory angina) but in the presence of (a) greater than or equal to 50% to 70% diameter stenosis by visual estimation with a peak translesional gradient (measured with a less than or equal to 5-Fr catheter or pressure wire) of greater than or equal to 20 mm Hg or a mean gradient greater than or equal to 10 mm Hg, (b) any stenosis greater than or equal to 70% diameter stenosis, or (c) greater than or equal to 70% diameter stenosis by intravascular ultrasound measurement (688).

Incidental (asymptomatic) RAS found at coronary or peripheral angiography (abdominal aortography) is more common than previously suspected (Tables 29 and 30) (621-623,625,630,643,719). Screening angiography has demonstrated renal artery stenoses (defined as greater than 50% diameter stenosis) in 18% of 196 consecutive patients undergoing coronary angiography for suspected coronary artery disease (623). In patients with established coronary artery disease, the incidence of incidental, unsuspected RAS climbed to 22%. One large study examined the incidence of RAS diagnosed by screening angiography during coronary angiography and found incidental renal artery narrowing in 30% of 1235 consecutive angiograms (621). Significant unilateral RAS (greater than 50% diameter stenosis) was documented in 15% of individuals, and bilateral RAS was observed in 33% of these subjects. Multivariate predictors of the presence of high-grade renal artery disease included age, associated coronary artery disease, congestive heart failure, female gender, and PAD. Hypertension was not an associated predictive variable.

Univariate predictors of RAS in 14,152 patients undergoing abdominal aortography at the time of cardiac catheterization are summarized in Table 31 (643). A trial of screening renal angiography at the time of cardiac catheterization in 177 consecutive patients found measurable RAS in 25% of the patients, with hemodynamically significant lesions observed in 11% of this population (622). Multivariate analysis demonstrated that the extent of coronary artery disease was the strongest predictor of concomitant RAS (Table 32) (622).

The use of renal angiography screening during peripheral vascular angiography has also demonstrated a much higher than expected incidence of asymptomatic or incidental RAS (Table 30) (625,630,719). In 394 consecutive patients undergoing angiographic evaluation of clinically suspected PAD (aortoiliac and lower extremity), without the usual clinical clues to suggest RAS, 33% to 39% had significant (greater than 50% diameter stenosis) RAS (Table 33) (625). Incidental (asymptomatic) RAS was discovered in 28% of 346 patients undergoing evaluation for AAA or peripheral arterial occlusive disease.

Whereas the presence of coronary atherosclerosis predicts the presence of significant atherosclerotic renal artery disease, there is a converse ability of atherosclerotic renal arterial disease to predict the severity of coronary artery disease. Asymptomatic (incidental) RAS found at peripheral angiography screening during coronary or peripheral angiography has demonstrated an increased incidence in patients with established coronary artery disease (294).  

### Table 29. Prevalence of Incidental RAS Found at Cardiac Catheterization

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>RAS (%)</th>
<th>RAS Greater Than 50% (%)</th>
<th>Bilateral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowley</td>
<td>(643)</td>
<td>14,152</td>
<td>11.4</td>
<td>6.3</td>
<td>21</td>
</tr>
<tr>
<td>Harding</td>
<td>(621)</td>
<td>1302</td>
<td>30</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Jean</td>
<td>(623)</td>
<td>196</td>
<td>29</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Vetrovec</td>
<td>(729)</td>
<td>116</td>
<td>NR</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Conlon</td>
<td>(730)</td>
<td>3987</td>
<td>34</td>
<td>9.1</td>
<td>17</td>
</tr>
<tr>
<td>Rihal</td>
<td>(720)</td>
<td>297</td>
<td>25</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Weber-Mzell</td>
<td>(622)</td>
<td>177</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

NR indicates not reported.
raphy is strongly associated with the presence of coronary artery disease (630). The presence of asymptomatic (incidental) RAS is a strong predictor of subsequent mortality (719). Conlon and coworkers performed screening abdominal aortography on 3987 patients undergoing cardiac catheterization (730). Significant (at least 50% diameter stenosis) RAS was found in 362 patients (9.1%), and severe (at least 75% diameter stenosis) RAS was found in 191 (4.8%). Approximately one fifth (n equals 33) of patients with severe RAS had bilateral involvement. In that study, the 4-year survival rate for patients with asymptomatic, severe (at least 75% diameter stenosis) RAS incidentally discovered at cardiac catheterization was diminished to 57% compared with the 89% survival rate in patients without severe RAS (730). The presence of severe RAS was independently associated with mortality. In a multivariate model, the negative impact of incidental RAS on survival persisted even in those individuals who had undergone revascularization for coronary artery disease. As the severity of RAS increased in 3 disease severity groups (from 50% to 75%, from 75% to 95%, and greater than 95%), the 4-year patient survival rate decreased from 70% to 68% and 48%, respectively (Table 34) (730). Patients with bilateral severe (at least 75% diameter stenosis) RAS had the lowest 4-year survival rate of 47% compared with 59% for those with unilateral disease.

The tendency for RAS to progress or worsen appears unaffected by medical therapy to control blood pressure. Renal artery occlusion generally causes irreversible loss of renal excretory function, although this loss may not be evident in the elevation of serum creatinine (653). Over a 7-year period, 24,312 patients underwent cardiac catheterization, of whom 14,152 (58%) had abdominal aortograms to screen them for asymptomatic RAS (643). The likelihood of new lesions appearing or of known lesions to progress was assessed in a cohort of 1,189 patients who underwent 2 abdominal aortograms separated by at least 6 months. The average time separating the 2 angiograms was 2.6 plus or minus 1.6 years. A new RAS or RAS progression was seen in 11.1% of the patients (Table 35) (643). Progression from normal to greater than 75% stenosis in 1 or more arteries was associated with a decline in renal function and with a significantly higher serum creatinine (141 plus or minus 114 micromoles per liter) than in those patients without lesion progression (97 plus or minus 44 micromoles per liter, p equals 0.01). Lesion progression is more likely to occur in more severe stenoses (637,642). Notably, these studies were limited to individuals in whom coronary angiography was performed twice, presumably because of progressive clinical disease, and thus may not be representative of the larger population of individuals with RAS.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>RAS (%)</th>
<th>% RAS Greater Than 50% (%)</th>
<th>Bilateral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olin</td>
<td>(625)</td>
<td>318</td>
<td>NR</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>Valentine</td>
<td>(630)</td>
<td>346</td>
<td>NR</td>
<td>28</td>
<td>NR</td>
</tr>
<tr>
<td>Leertouwer</td>
<td>(719)</td>
<td>386</td>
<td>NR</td>
<td>33</td>
<td>26</td>
</tr>
</tbody>
</table>

NR indicates not reported; RAS, renal arterial stenosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>4.8 (3.9 to 5.9)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>4.5 (2.8 to 7.2)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2.6 (2.2 to 3.0)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2.3 (2.0 to 2.7)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.3 (2.0 to 2.6)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Ejection fraction less than 30%</td>
<td>1.5 (1.2 to 1.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.5 (1.3 to 1.7)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.4 (1.2 to 1.6)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1.2 (1.0 to 1.4)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CI, confidence interval; OR, odds ratio; RAS, renal arterial disease.

There are no well-controlled prospective, randomized investigations to measure the relative risk and benefit of endovascular interventions (or associated medical therapies) in individuals with asymptomatic renal artery disease, and thus the role of such interventions remains controversial. Recommendations regarding the role of percutaneous revascularization of asymptomatic renal disease are made largely on the basis of expert opinion and are not based on evidence that treatment of asymptomatic RAS improves any renal or systemic outcome, including renal preservation, blood pressure, or cardiovascular morbidity or mortality. Therefore, these recommendations are still considered controversial and must be individualized for the patient by each treating physician. The recommendations will likely be modified once controlled prospective data become available.

### 3.5.2.2. Hypertension

**RECOMMENDATIONS**

**Class IIa**

Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication. *(Level of Evidence: B)*

Control of hypertension is an important component of all atherosclerosis risk reduction. Most hypertension is not due to RAS (essential hypertension) and routine evaluation for RAS is not indicated. However, there are clinical clues that can be useful in identifying the small subset of individuals in whom directed evaluation for renal artery disease may be useful (see Section 3.2 and Figure 17). It should be noted that “resistant hypertension” is defined as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic *(from p. 2570 of Chobanian et al., 294).*

Renovascular hypertension remains the most common form of correctable hypertension. Percutaneous techniques have largely replaced surgical revascularization for atherosclerotic renovascular hypertension *(731).* The DRASTIC trial *(Dutch Renal Artery Stenosis Intervention Cooperative)* was an attempt to determine the efficacy of medical therapy compared with percutaneous transluminal renal angioplasty for blood pressure control in renovascular hypertension *(732).* There was an advantage for the percutaneous transluminal renal angioplasty group at 3 months. The intention-to-treat analysis at 1 year was limited in this study by the high proportion *(greater than 40%)* of patients who were assigned to the “medical treatment” cohort who crossed over to percutaneous transluminal renal angioplasty, thus potentially underestimating the benefit of percutaneous transluminal renal angioplasty. In addition, the percutaneous technique applied in this trial did not consistently utilize stents. Another

### Table 32. Multivariate Logistic Regression of Univariate Predictors of Renal Arterial Stenosis in Patients Undergoing Cardiac Catheterization for Suspected Coronary Artery Disease (CAD)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression Coefficient</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of CAD</td>
<td>0.801</td>
<td>2.227</td>
<td>1.204 to 4.119</td>
<td>0.011</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>-0.04</td>
<td>0.961</td>
<td>0.925 to 0.998</td>
<td>0.038</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.025</td>
<td>1.026</td>
<td>0.996 to 1.057</td>
<td>0.078</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01</td>
<td>0.99</td>
<td>0.917 to 1.069</td>
<td>0.802</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.091</td>
<td>1.095</td>
<td>0.570 to 2.071</td>
<td>0.781</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.


### Table 33. Prevalence of RAS in Individuals With Systemic Atherosclerotic Syndromes*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>AAA (n=108)</th>
<th>AOD (n=21)</th>
<th>PAD (n=189)</th>
<th>RAS (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with greater than 50% stenosis</td>
<td>41 (38%)</td>
<td>7 (33%)</td>
<td>74 (39%)</td>
<td>53 (70%)†</td>
</tr>
</tbody>
</table>

*Significant renal arterial stenosis (RAS) was defined as greater than 50% stenosis.

†p<0.01 versus other 3 groups.

AAA indicates abdominal aortic aneurysm; AOD, aortic occlusive disease; n, total sample size; and PAD, peripheral arterial disease.

hemodynamically significant stenosis defined as (a) 50% to 70% diameter stenosis by visual estimation with a peak translesional gradient (measured with a 5F or smaller catheter or pressure wire) of at least 20 mm Hg or a mean gradient of at least 10 mm Hg; (b) any stenosis of at least 70% diameter; or (c) greater than or equal to 70% diameter stenosis by intravascular ultrasound measurement (718).

It has been assumed that the outcome variability of the current investigational database is attributable to both the heterogeneity of patient selection criteria for inclusion in these clinical trials and the lack of standard reporting criteria. One trial demonstrated that patients with the highest baseline systolic blood pressures had the greatest decrease in systolic pressure, but the variables of age, sex, race, severity of stenosis, number of vessels treated, baseline diastolic pressure, or baseline serum creatinine did not correlate with blood pressure improvement after renal stent placement (13). Another multivariate logistic regression analysis demonstrated that 2 variables, bilateral RAS (OR equals 4.6, \( p \) equals 0.009) and mean arterial pressure greater than 110 mm Hg (OR equals 2.9, \( p \) equals 0.003), predicted a beneficial blood pressure response after renal artery stent placement (736). No difference has been demonstrated in the blood pressure response after stent placement in older (75 years and older) versus younger (less than 75 years) patients or in women versus men (740,741).

The current evidence base suggests that patients with severe atherosclerotic RAS and accelerated, resistant, and malignant hypertension may expect to receive some clinical benefit, including improved blood pressure control, the need for fewer medications, or both. However, “cure” of hypertension is rare, improvement in blood pressure response after stent placement in older (75 years and older) versus younger (less than 75 years) patients or in women versus men (740,741).

3.5.2.3. Preservation of Renal Function

RECOMMENDATIONS

Class Ia
Percutaneous revascularization is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney. (Level of Evidence: B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1.9 (1.5 to 2.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Increased age</td>
<td>1.6 (1.4 to 1.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.3 (1.2 to 1.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Time between angiograms, yr</td>
<td>1.3 (1.2 to 1.4)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and OR, odds ratio.

Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS. (Level of Evidence: C)

Atherosclerotic RAS is an important cause of or contributor to renal failure (632,740,742,743). It is unclear how many patients enter dialysis secondary to RAS. In one study, patients with renovascular disease as the cause of their renal failure had survival rates of 56% at 2 years (640). As individuals with progressive worsening renal function are evaluated for reversible etiologies (including RAS), it should be noted that the National Kidney Foundation defines chronic kidney disease as a decrease in estimated glomerular filtration rate to less than 60 mL/min per 1.73 m² (modified Modification of Diet in Renal Disease formula) that persists for at least 3 months. Moreover, it may be inappropriate for many patients with new end-stage renal disease to be considered as candidates for evaluation for RAS when significant intrinsic kidney disease is a major contributor to renal failure.

Revascularization is effective in stabilizing or improving renal function in patients with symptomatic atherosclerotic RAS (701,744-748). Several trials have documented that renal artery stent placement improves or stabilizes renal function in patients with atherosclerotic RAS (749-752). Significant improvement in renal function up to 1 year after unilateral renal artery stent placement was demonstrated by Leeroutouwer and coworkers (701). They demonstrated that the glomerular filtration rate in the revascularized kidney improved significantly but that overall glomerular filtration rate from both kidneys did not change (721). Prospective randomized trials of stenting for unilateral RAS in an effort to preserve renal function are needed.

Harden and colleagues (750) reported a series of 32 patients (33 kidneys) with unexplained renal insufficiency and hemodynamically significant RAS who underwent stent placement. The majority of patients had bilateral or unilateral solitary RAS, although unilateral disease was present in 7 patients. Improvement and stabilization of renal function were demonstrated by plotting the slope of serial reciprocal serum creatinine values. This study was limited by a relatively short median follow-up of only 8 months. The authors concluded that stent placement slowed the progression of RAS (750). Ultimately, large-scale prospective, controlled trials better defining the role, thresholds, and patient subsets that warrant revascularization in the setting of chronic kidney disease need to be performed.

Improvement of renal function was demonstrated in 33 patients undergoing successful renal artery stent placement for bilateral or unilateral solitary RAS (greater than or equal to 70%) with a baseline serum creatinine between 1.5 and 4.0 mg per dL (751). When reciprocal creatinine plots were used, all patients at baseline had deteriorating renal function manifested by the negative calculated renal function slope. Follow-up data at greater than or equal to 8 months were available in 25 patients, all of whom had either a positive or less-negative reciprocal slope of the creatinine, which indi-
cated improvement and stabilization of renal function. This small study also demonstrated preserved renal mass by ultrasound measurements.

Using a serum creatinine value greater than or equal to 1.5 mg per dL and a negative slope of the reciprocal of the serum creatinine in the preceding 12 months, Rocha-Singh et al. documented reversal of declining renal function with stent placement; this benefit was sustained over 30 months (752). The improvement in renal function was associated with lower blood pressure and fewer medication requirements. These authors concluded that renal stent revascularization should be considered a valid therapeutic option for the long-term treatment of ischemic nephropathy.

Several factors may argue against renal revascularization or predict poorer outcomes. These include the presence of proteinuria greater than 1 g every 24 hours, renal atrophy, severe renal parenchymal disease, and severe diffuse intrarenal arteriolar disease. In addition, several studies have shown that renal function can deteriorate after renal artery angioplasty, especially in patients with stable renal function prior to the intervention (752a,752b). Thus, the risks and benefits of renal revascularization must be carefully evaluated in each individual.

The adverse consequences of renal atheroembolization at the time of surgical revascularization have been documented (753). Similar potentially severe atheroembolization may be provoked by renal percutaneous revascularization methods (754). The contribution of procedure-related renal artery atheroembolization to decrements in renal function after revascularization can be difficult to quantitate and distinguish from the nephrotoxic effects of iodinated contrast, particularly in patients with initially elevated serum creatinine and limited renal reserve. These potential limitations emphasize the need for preprocedural volume expansion and strict use of contrast-sparing techniques (e.g., highly diluted contrast), the use of alternative agents (e.g., carbon dioxide or gadolinium), preprocedure oral acetylcysteine administration, and high levels of operator experience when revascularization is performed in individuals with renal insufficiency. In a preliminary study, Henry and coworkers used embolic protection devices during percutaneous renal revascularization and demonstrated atheroembolic debris in all 32 arteries treated (755). The value of embolic protection devices is being tested in clinical trials to determine whether these devices can decrease (or increase) the frequency of clinically important atheroemboli to the kidneys. Ultimately, large-scale prospective, controlled trials better defining the role, thresholds, and patient subsets that warrant revascularization in the setting of chronic kidney disease need to be performed.

3.5.2.4. Impact of RAS on Congestive Heart Failure and Unstable Angina

RECOMMENDATIONS

Class I

Percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (see text). (Level of Evidence: B)

Class IIa

Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina (see text). (Level of Evidence: B)

Alterations in circulatory homeostasis can be prominent in individuals with significant RAS and may provoke exacerbations of coronary ischemia and/or congestive heart failure due to peripheral arterial vasoconstriction, direct effects of angiotensin II on the myocardium, and/or volume overload. Renovascular disease may also complicate the long-term management of cardiac patients (e.g., those with hypertension or left ventricular systolic dysfunction) by preventing administration of angiotensin antagonist therapies.

Individuals with RAS may experience sudden-onset or “flash” pulmonary edema (756-761). Patients with hemodynamically severe bilateral or solitary RAS may manifest a volume-overload state because they lack normal renal function to respond to pressure natriuresis (762,763). Patients with unilateral renal stenosis may also experience pulmonary edema due to increased left ventricular afterload secondary to angiotensin-mediated vasoconstriction. Unilateral RAS may contribute to the development of unstable coronary syndromes by causing sudden increases in myocardial oxygen demand in patients with coronary disease secondary to peripheral vasoconstriction; this mechanism is distinct from the usual assumption underlying other mechanisms of acute coronary syndromes (e.g., plaque rupture or progressive atherosclerosis) (764,765).

This pathophysiology underpins the potential therapeutic benefit of renal artery stent placement in the treatment of some manifestations of congestive heart failure or unstable coronary syndromes (766,767). These patients were characterized by having at least 1 renal artery with a hemodynamically significant stenosis and established coronary artery disease. Successful renal stent placement resulted in a significant decrease in blood pressure and control of anginal symptoms in 88% of all patients (42 of 48). Some patients underwent both coronary and renal intervention, whereas others had only renal artery stent placement because their coronary atherosclerotic lesions were unsuitable for revascularization. Outcomes were assessed acutely and at 8 months with the Canadian Cardiovascular Society angina classification and the New York Heart Association functional classification. There was no incremental therapeutic advantage gained for the group that underwent coronary intervention with renal stent placement compared with the group that underwent renal stent placement alone.

These potential benefits of renal revascularization for individuals with severe angina or with exacerbations of heart failure have been observed in small prospective case series but have not been evaluated in prospective, randomized clinical trials. In addition, the individuals enrolled in these interventional case series were carefully selected and are not rep-
representative of the majority of patients with “accelerated angina” or with “recurrent congestive heart failure.” Angina is known to accelerate via many mechanisms that are unrelated to renal hemodynamics (e.g., simple progressive coronary atherosclerosis and instability of coronary plaque), and these mechanisms are predominant. Thus, clinicians are cautioned to carefully explore these other mechanisms before presuming that renal artery disease is the major mechanism underlying the exacerbation of coronary symptoms. Similarly, heart failure is frequently caused by nonatherosclerotic mechanisms, and exacerbations of heart failure symptoms are multifactorial (e.g., due to progressive remodeling, progressive coronary disease, dietary changes, or medical noncompliance). The recommendations in the present guideline are intended to apply to individuals in whom these nonrenal factors have been explored and in whom there are clinical indications to suggest the presence of RAS (e.g., systemic atherosclerosis).

In summary, the potential physiological benefits of renal stent placement include reperfusion of the ischemic kidney(s), resulting in a reduction in the stimulus to renin production, which decreases angiotensin and aldosterone production, thereby decreasing peripheral arterial vasoconstriction and the tendency to develop an expanded extracellular fluid volume. Improvement in renal perfusion enhances glomerular filtration and therefore promotes natriuresis. Finally, in patients with a solitary kidney or bilateral RAS, the ability of the patient to tolerate long-term administration of angiotensin antagonist medications may be facilitated by relief of a hemodynamic renal artery obstruction.

3.5.3. Catheter-Based Interventions

RECOMMENDATIONS

Class I

1. Renal stent placement is indicated for ostial atherosclerotic RAS lesions that meet the clinical criteria for intervention. (Level of Evidence: B)

2. Balloon angioplasty with bailout stent placement if necessary is recommended for FMD lesions. (Level of Evidence: B)

Percutaneous transluminal renal balloon angioplasty is the treatment of choice for symptomatic RAS caused by FMD (744,768-770). However, in atherosclerotic RAS, balloon angioplasty alone is associated with a lower procedural success rate and a higher restenosis rate (745,771-777). Aorto-ostial stenoses represent the most common atherosclerotic lesions and are prone to vascular recoil due to confluent plaque that extends from the wall of the aorta into the ostium of the renal artery. These atherosclerotic aorto-ostial lesions are generally considered unsuitable for treatment by balloon angioplasty alone (769,770,778).

Stent placement has consistently proven superior to balloon angioplasty in the treatment of renal artery atherosclerotic lesions. Balloon angioplasty was compared with stent placement in atherosclerotic RAS by Dorros and coworkers (779). Quantitative vascular angiography and translesional pressure gradients were measured in 18 patients who served as their own controls. Stents were significantly more effective than balloon angioplasty in these atherosclerotic renal artery lesions (Table 37) (779).

The superiority of renal stent placement over balloon angioplasty was confirmed in a randomized, controlled trial in hypertensive patients by van de Ven and coworkers (700). A total of 42 patients and 51 arteries were randomized to balloon angioplasty (with bailout stenting), and 42 patients and 52 arteries were randomized to receive primary stent therapy. Procedure success and long-term patency markedly favored the stent group (Table 38) (700). Over the course of the study, 12 (29%) patients in the balloon group crossed over to the stent group. This large percentage of crossover patients confounded the analysis of the clinical end point at 1 year.

The authors calculated that a renal bailout (provisional) stent strategy would avoid a stent during the initial procedure 40% of the time. However, 45% of the patients would ultimately require a second procedure with a stent and also would incur additional complications that would make the strategy of primary stent placement more efficient. For the balloon group to achieve a 90% patency rate at 6 months, 62% of all patients would ultimately require a stent, and 57% of all patients would need a second or third procedure. To obtain a 90% 6-month patency rate in the primary stent group, only 12% would need a second procedure. This randomized, controlled trial clearly demonstrated the superiority of renal stents over balloons in hypertensive patients with atherosclerotic RAS for procedure success, late patency, and cost-effectiveness (700).

A meta-analysis of 10 renal stent studies performed between 1991 and 1997 demonstrated procedural success rates greater than or equal to 96% with a procedure-related mortality rate of less than 1% (780). The average restenosis rate, evaluated between 6 and 12 months after the procedure, was 16%. A second meta-analysis, comparing renal stent

---

Table 37. Renal Artery Intervention: The Posttreatment Efficacy of Primary Balloon Versus Stent Interventions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Balloon</th>
<th>Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis (%)</td>
<td>82 plus or minus 12</td>
<td>29 plus or minus 14</td>
<td>3 plus or minus 6*</td>
</tr>
<tr>
<td>Mean gradient, mm Hg</td>
<td>50 plus or minus 22</td>
<td>8 plus or minus 6</td>
<td>1 plus or minus 3*</td>
</tr>
<tr>
<td>Peak gradient, mm Hg</td>
<td>94 plus or minus 33</td>
<td>23 plus or minus 19</td>
<td>1 plus or minus 3*</td>
</tr>
</tbody>
</table>

*p less than 0.05.

Two series have addressed the long-term durability and patency of renal stents (733, 735). In those series, the 5-year primary patency rates of renal stents were 79% and 84.5%, and the secondary patency rates were 92.4% and 98%. Almost all occurrences of stent restenosis occurred during the first year after stent implantation, with restenosis later than 2 years an unusual occurrence.

3.5.4. Surgery for RAS

RECOMMENDATIONS

Class I
1. Vascular surgical reconstruction is indicated for patients with fibromuscular dysplastic RAS with clinical indications for intervention (same as for PTA), especially those exhibiting complex disease that extends into the segmental arteries and those having macroaneurysms. (Level of Evidence: B)

2. Vascular surgical reconstruction is indicated for patients with atherosclerotic RAS and clinical indications for intervention, especially those with multiple small renal arteries or early primary branching of the main renal artery. (Level of Evidence: B)

3. Vascular surgical reconstruction is indicated for patients with atherosclerotic RAS in combination with pararenal aortic reconstructions (in treatment of aortic aneurysms or severe aortoiliac occlusive disease). (Level of Evidence: C)

### Table 38. Balloon Versus Stent: Randomized, Controlled Trial

<table>
<thead>
<tr>
<th></th>
<th>Balloon (n=51)</th>
<th>Stent (n=52)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure success</td>
<td>63%</td>
<td>90%</td>
<td>Less than 0.05</td>
</tr>
<tr>
<td>Restenosis</td>
<td>48%</td>
<td>14%</td>
<td>Less than 0.05</td>
</tr>
</tbody>
</table>


### Table 39. Renal Stent Placement Procedural Outcomes

<table>
<thead>
<tr>
<th>First Author</th>
<th>Date</th>
<th>Reference</th>
<th>Arteries (n)</th>
<th>Success* (%)</th>
<th>Restenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1997</td>
<td>(738)</td>
<td>133</td>
<td>99</td>
<td>18.8</td>
</tr>
<tr>
<td>Blum</td>
<td>1997</td>
<td>(733)</td>
<td>74</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td>Tuttle</td>
<td>1998</td>
<td>(734)</td>
<td>148</td>
<td>98</td>
<td>14</td>
</tr>
<tr>
<td>Henry</td>
<td>1999</td>
<td>(735)</td>
<td>209</td>
<td>99</td>
<td>11.4</td>
</tr>
<tr>
<td>van de Ven</td>
<td>1999</td>
<td>(700)</td>
<td>43</td>
<td>90</td>
<td>14</td>
</tr>
<tr>
<td>Rocha-Singh</td>
<td>1999</td>
<td>(736)</td>
<td>180</td>
<td>97</td>
<td>12</td>
</tr>
<tr>
<td>Lederman</td>
<td>2001</td>
<td>(739)</td>
<td>358</td>
<td>100</td>
<td>21</td>
</tr>
</tbody>
</table>

*Definitions of procedural success vary in each study. n indicates number of patients.
3.5.4.1. Fibromuscular Dysplasia

Operative therapy for treatment of FMD, be it performed in situ or ex vivo, is undertaken in 2 basic modes with either (a) an aortorenal bypass or (b) a nonanatomic bypass (781,782). In situ revascularizations are preferred in that disruption of preexisting collateral vessels does not accompany this type of reconstructive procedure. However, ex vivo revascularizations are appropriate in certain patients with complex disease, especially that which affects multiple segmental vessels or that is associated with macroaneurysmal disease of these smaller arteries (783).

Age and the status of the aorta become important determinants of the type of in situ operation. In patients less than 21 years of age, vein grafts are avoided because of the potential for late aneurysmal degeneration (784). Internal iliac artery grafts are favored in younger patients and in occasional older patients. Vein grafts are favored in most patients 21 years and older in whom the aorta is relatively normal. In patients with no suitable vein, synthetic conduits of PTFE or polyester filament may be used, but these materials are not favored over autologous grafts in younger individuals.

In patients with an aorta encased in scar tissue from previous surgery or in whom clamping of the aorta would be hazardous because of severe ventricular dysfunction, a nonanatomic revascularization, in the form of a hepatorenal, splenorenal, or iliofemoral reconstruction, would be appropriate (785). A normal, undiseased celiac artery is necessary for the performance of a hepatorenal or splenorenal bypass.

A secondary nephrectomy may be necessary to provide adequate blood pressure control in those patients whose primary operation has failed when attempts at re-revascularization have been unsuccessful (3,12). In rare circumstances, a kidney will initially appear to be hypoplastic or will exhibit irreparable ischemic atrophy. When the contralateral kidney appears normal, a primary nephrectomy may be performed. Dysplastic renal artery stenoses in pediatric-aged patients are usually treated by open surgery, although balloon angioplasty or transcatheter alcohol ablation of the renal parenchyma beyond isolated intrarenal webs may be successfully used in select patients (786-788).

3.5.4.2. Arteriosclerotic Renal Artery Occlusive Disease

Unilateral isolated nonostial RAS in the case of normal renal function is usually treated by percutaneous balloon angioplasty with stenting in lieu of operative therapy (789-791), although with abnormal renal function, surgical treatment may be performed in select patients (782,792,793). Unilateral and bilateral ostial stenoses account for most arteriosclerotic renovascular disease. In the case of unilateral disease and normal renal function, either balloon angioplasty or operative therapy provides acceptable results, although less-invasive endovascular therapy is usually the preferred modality. If restenosis after PTA is severe enough to warrant surgical operation, it can result in secondary nephrectomy (794).

Operative therapy, when undertaken for arteriosclerotic renovascular disease, must consider the status of the aorta. A nonanatomic bypass is appropriate in the case of a hostile aorta due to intrinsic disease that is nontreatable without inordinate patient risks or in instances of very poor cardiac function where aortic cross-clamping would be hazardous. In patients who require open surgical treatment of AAAs or severe aortoiliac occlusive disease, a concomitant aortic reconstruction and an aortorenal bypass or endarterectomy may be performed (782,792,795-797). These latter 2 options also exist in the case of a normal aorta, with an aortorenal bypass favored in treatment of single renal artery disease and aortorenal endarterectomy favored for treatment of multiple renal arteries to the same kidney, as well as in treatment of bilateral disease.

Nonanatomic bypass is an important means of renal revascularization in select patients, provided that flow within the donor artery is normal. When hepatic or splenic bypasses are created, no significant celiac artery stenoses should be present. For iliofemoral bypasses, no pressure gradients across the aorta or proximal iliac arteries should be present, lest they impair graft flow.

Aortorenal bypass is the most common open surgical means of treating arteriosclerotic renovascular disease (782,795). Reversed saphenous vein is the favored conduit when small renal arteries are being bypassed or multiple vessel reconstructions are being performed. For reconstruction of a large poststenotic renal artery, especially when the graft originates from a concurrently placed synthetic aortic prosthesis, use of a PTFE or polyester filament graft is acceptable.

Aortorenal endarterectomy is preferred by many surgeons, especially when undertaken in concert with an aortic reconstructive operation (797). This form of renal revascularization is generally considered more technically demanding than a nonanatomic bypass or a conventional bypass (796). It is often performed through an axial aortotomy that extends from the level of the superior mesenteric artery to the infrarenal aorta or through the transected aorta at the time of the aortic reconstruction. The axial transaortic approach has particular applicability for treatment of bilateral and multiple renal artery ostial stenoses, as well as when coexistent celiac and superior mesenteric arterial stenoses need to be treated. A direct renal arteriotomy and endarterectomy has certain advantages for treatment of complex disease that extends into early branchings of the renal artery, but it is performed much less often than transaortic endarterectomy.

Secondary nephrectomy should only be done after reconstructive failures are deemed impossible to salvage with reoperation (798,799). Irreparable ischemic atrophy or injury in some patients may be a consequence of advanced arteriosclerotic occlusive disease. It is most likely to exist when (a) radionuclide scan evidence exists that the kidney contributes less than 10% of the total renal function, (b) the kidney length is less than 5 cm, or (c) there is evidence of exten-
sive cortical infarction. In such circumstances, especially if the serum creatinine is less than 3 mg per dL, a primary nephrectomy may be appropriate. Renal revascularizations are unlikely to improve either blood pressure control or renal function in these patients.

Primary nephrectomy is performed in select patients in whom operative or catheter-based procedures are not possible, and only when a benefit, especially regarding blood pressure control, is expected after removal of the kidney (800,801). The technique of primary intracapsular nephrectomy is the same as with secondary nephrectomy.

3.5.4.3. Results of Operative Therapy

Renal preservation and maintenance of renal function are important in the assessment of clinical experiences. Nephrectomy will usually not offer as much benefit as revascularization. Even when nephrectomy provides good results, it leaves the patient at considerable risk if contralateral disease occurs later. Improved renal function after revascularization is well recognized and is most likely to occur among patients exhibiting arteriosclerotic disease with a relatively sudden onset of renal function impairment.

Surgical treatment of renovascular hypertension affords good clinical outcomes (802-806). The risk of surgery increases in patients who require concomitant aortic reconstruction, in patients with renal insufficiency, and when aortic grafts are used as a source of the bypass graft. The need for reoperation has been reported in 5% to 15% of patients, with survival in 65% to 81% of patients (802-806). Differences among most individual experiences reflect variations in the prevalence of different renovascular disease categories. Arterial fibrodysplastic renovascular hypertension (Table 40) is more likely to benefit from surgical revascularization than is arteriosclerotic renovascular hypertension (Table 41). This is probably a reflection of coexistent essential hypertension in older patients with arteriosclerotic disease. Arteriosclerotic renovascular hypertension occurs in 2 subgroups of patients: (a) those with focal renal artery disease whose only clinical manifestation of arteriosclerosis is secondary hypertension and (b) those with clinically overt extrarenal arteriosclerosis that affects the coronary artery, carotid artery, aorta, or extremity vessels. The severity and duration of hypertension, age, and gender in these 2 subgroups are similar, yet the surgical outcome regarding amelioration of hypertension is worse in patients with overt extrarenal arteriosclerotic disease.

Surgery was compared with balloon angioplasty for renal artery revascularization in a randomized clinical trial in hypertensive patients with atherosclerotic RAS (731). At the 2-year follow-up interval, the surgery group had a higher primary patency rate than the balloon angioplasty group (95% vs. 75%, p equals 0.05); however, there was no difference in the secondary patency rate between the groups (balloon 90% vs. surgery 97%, p equals 0.61). The clinical end points of hypertension control and renal function preservation were not different for angioplasty or surgery. Major complications were seen in twice as many surgical patients (34%) as balloon angioplasty patients (17%). The authors concluded that in patients with RAS who were candidates for either surgery or balloon angioplasty, balloon angioplasty should be the first choice of therapy. One retrospective trial comparing outcomes and costs associated with endovascular and surgical revascularization described similar clinical outcomes but a nearly 6-fold greater initial cost for surgery (807).

4. MESENTERIC ARTERIAL DISEASE

All diseases and conditions that affect the arteries have been reported in the arteries that supply the intestines, including atherosclerosis, arteritis, aneurysms, arterial infections, FMD, dissections, arterial emboli, and thrombosis. The evidence and recommendations in this section of the guideline are directed at the various causes and treatment of the most common vascular problem affecting the intestines, ischemia. Because there are major differences in presentation, the sections are divided into acute and chronic intestinal ischemia. Acute intestinal ischemia is most frequently caused by arterial obstruction but also occurs in the absence of intestinal arterial obstruction (e.g., nonocclusive mesenteric ischemia seen in low flow states). Chronic intestinal ischemia is always the result of arterial obstruction. Regardless of cause, intestinal ischemia is rare. This means that there are no randomized or controlled trials of diagnosis or therapy for intestinal ischemia, acute or chronic, regardless of cause. There are important gaps in our knowledge of the natural history of intestinal ischemia, especially with regard to the number of persons with asymptomatic intestinal arterial obstructions who eventually become symptomatic. Despite this, the condition and the primary diagnoses responsible for most cases have been known for decades. Numerous series documenting the results of surgical treatment have been reported, and recently, the clinical course of a number of patients’ case series treated by percutaneous intervention has also been documented. These largely retrospective clinical reviews form the basis for our knowledge of and recommendations for treatment of intestinal ischemia.

4.1. Acute Intestinal Ischemia

4.1.1. Acute Intestinal Ischemia Caused by Arterial Obstruction

4.1.1.1. Etiology

Acute obstructive intestinal ischemia occurs when the intestinal arteries are suddenly blocked to a degree that all or part of the intestine has insufficient perfusion for viability. The many possible causes include embolism from cardiac or proximal arterial sources (including arterial debris dislodged during percutaneous interventions) and arterial thrombosis, either of arteries chronically stenosed by atherosclerosis or as a result of a hypercoagulable state or an acute arterial dissection (807-812).
Regardless of the cause, patients with acute intestinal ischemia have severe abdominal pain that is initially out of proportion to any physical findings that may be present. This is because peritoneal irritation that leads to abdominal tenderness takes hours to develop, and distention, rigidity, guarding, and systemic symptoms of vascular collapse may take days to manifest and are best correlated with intestinal perforation.

4.1.1.2. Diagnosis

RECOMMENDATIONS

Class I

1. Patients with acute abdominal pain out of proportion to physical findings and who have a history of cardiovascular disease should be suspected of having acute intestinal ischemia. *(Level of Evidence: B)*

### Table 40. Surgical Revascularization of Fibrodysplastic Renovascular Hypertension in Adults

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of Patients</th>
<th>Operative Outcome (%)</th>
<th>Surgical Mortality (30-Day) Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Michigan</td>
<td>144</td>
<td>55 39 6 0</td>
<td></td>
</tr>
<tr>
<td>Baylor College of Medicine</td>
<td>113</td>
<td>43 24 33 0</td>
<td></td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>92</td>
<td>58 31 11 Unstated</td>
<td></td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>77</td>
<td>66 32 1.3 0</td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>63</td>
<td>66 24 10 Unstated</td>
<td></td>
</tr>
<tr>
<td>University Hospital Leiden, the Netherlands</td>
<td>53</td>
<td>53 34 13 2</td>
<td></td>
</tr>
<tr>
<td>Vanderbilt University</td>
<td>44</td>
<td>72 24 4 2.3</td>
<td></td>
</tr>
<tr>
<td>Columbia University</td>
<td>42</td>
<td>76 14 10 Unstated</td>
<td></td>
</tr>
<tr>
<td>Bowman Gray</td>
<td>40</td>
<td>33 57 10 0</td>
<td></td>
</tr>
<tr>
<td>University of Lund, Malmo, Sweden</td>
<td>40</td>
<td>66 24 10 0</td>
<td></td>
</tr>
</tbody>
</table>


### Table 41. Surgical Revascularization of Arteriosclerotic Renovascular Hypertension in Adults

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of Patients</th>
<th>Operative Outcome (%)</th>
<th>Surgical Mortality (30-Day) Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor College of Medicine</td>
<td>360</td>
<td>34 31 35 2.5</td>
<td></td>
</tr>
<tr>
<td>Bowman Gray</td>
<td>152</td>
<td>15 75 10 1.3</td>
<td></td>
</tr>
<tr>
<td>University of Michigan</td>
<td>135</td>
<td>29 52 19 4.4</td>
<td></td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>84</td>
<td>39 23 38 2.4</td>
<td></td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>78</td>
<td>40 51 9 2</td>
<td></td>
</tr>
<tr>
<td>Columbia University</td>
<td>67</td>
<td>58 21 21 Unstated</td>
<td></td>
</tr>
<tr>
<td>University of Lund, Malmo, Sweden</td>
<td>66</td>
<td>49 24 27 0.9</td>
<td></td>
</tr>
<tr>
<td>Hospital Aiguelongue, Montpellier, France</td>
<td>65</td>
<td>45 40 15 1.1</td>
<td></td>
</tr>
<tr>
<td>Vanderbilt University</td>
<td>63</td>
<td>50 45 5 9</td>
<td></td>
</tr>
</tbody>
</table>

2. Patients who develop acute abdominal pain after arterial interventions in which catheters traverse the visceral aorta or any proximal arteries or who have arrhythmias (such as atrial fibrillation) or recent MI should be suspected of having acute intestinal ischemia. *(Level of Evidence: C)*

**Class III**

*In contrast to chronic intestinal ischemia, duplex sonography of the abdomen is not an appropriate diagnostic tool for suspected acute intestinal ischemia.* *(Level of Evidence: C)*

**Clinical Presentation.** Approximately two thirds of patients with acute intestinal ischemia are women, with a median age of 70 years. Most patients have a history of pre-existing cardiovascular disease (807-810). Abdominal pain is always present; its nature, location, and duration are variable, but most commonly, the pain is anterior, periumbilical, and sufficiently severe that medical attention is sought immediately. Initially, signs of peritoneal irritation are absent, which is classically referred to as “pain out of proportion to physical findings.”

**Laboratory Findings.** Laboratory evaluation most frequently shows leukocytosis and lactic acidosis, and amylase is elevated in approximately 50% of patients; approximately 25% of patients have occult blood in the stool. Abdominal radiographs most frequently show some dilated loops of intestine. There are no specific laboratory or plain radiograph findings for acute intestinal ischemia.

**Ultrasound.** Because duplex ultrasound scanning is capable of identifying occlusive lesions of the intestinal arteries, this test is theoretically attractive for diagnosis of acute intestinal ischemia. In practice, it is not very helpful. This is because duplex scanning of the deeply located intestinal arteries is technically demanding, requiring ideal conditions for success (e.g., fasting patients and early morning examinations to avoid excessive intestinal gas). The abdominal distention and fluid frequently present with acute ischemia precludes successful scanning in most patients. Because of the need for emergent treatment in acute ischemia and the time required to attempt duplex scanning, this test is contraindicated.

**Computed Tomographic Scanning.** Computed tomographic scans are frequently performed in patients with acute abdominal pain. Computed tomographic findings suggestive of intestinal ischemia include atherosclerotic disease of intestinal arteries and obvious thrombosis of proximal intestinal arteries, as well as intestinal distention, intestinal wall thickening, intraabdominal fluid, and intestinal perforation. These findings may also be present in patients without intestinal ischemia. Computed tomographic findings suggestive of intestinal ischemia include pneumatosis intestinalis and portal venous air, both of which are late findings. Because computed tomographic scanning for evaluation of abdominal pain requires administration of intravenous iodinated contrast material, which may affect later arteriography, this test is not the best initial examination for suspected acute intestinal ischemia, although it is frequently performed before consideration of the mesenteric ischemia diagnosis.

**Arteriography.** Arteriography is the most helpful diagnostic test in patients suspected of having acute intestinal ischemia; however, its use is controversial because of the time required for its performance in the emergency setting. In patients suspected of having intestinal ischemia, arteriography can be diagnostic and can differentiate occlusive from nonocclusive ischemia. Furthermore, catheter-directed therapy of arterial occlusions with intra-arterial vasodilators, thrombolysis, or mechanical thrombectomy devices is possible in some patients with acute ischemia. If surgical treatment is required, knowledge of the extent and nature of intestinal arterial lesions is helpful.

The decision for arteriography is probably best individualized in patients suspected of having acute intestinal ischemia. For those with a very acute presentation, a high likelihood of arterial obstruction, and suspected bowel infarction, immediate laparotomy by a surgeon capable of intestinal revascularization is the best approach. In patients with acute onset in whom angiography can be performed rapidly and without delay, this is a reasonable approach. For those with a more delayed presentation or a high likelihood of nonocclusive ischemia, initial arteriography is indicated. In these cases, the advantages of the additional information provided by arteriography outweigh the time required for its performance.

### 4.1.1.3. Natural History

All series of acute intestinal ischemia patients include some who had a history of chronic abdominal pain and weight loss. The frequency with which chronic intestinal ischemia caused by arterial obstruction becomes acute intestinal ischemia (presumably by thrombosis) is unknown.

The natural history of acute intestinal ischemia caused by obstruction of intestinal arteries in the absence of treatment is nearly always fatal. Intestinal ischemia leads to infarction, perforation, peritonitis, and death in the vast majority of patients. A few exceptions occur in which the ischemic injury may be confined to the mucosal layer of the intestine, or in which the gradual development of collateral circulation may result in resolution of the ischemia before infarction. Although such patients are well recognized, they are rare compared with those who do not recover. The exact percentage is unknown (808,809,813-818). The focus of treatment in patients with acute mesenteric ischemia is to provide an aggressive and rapid diagnosis to minimize the amount of ischemic bowel that will progress to infarction, while rapidly instituting appropriate therapy.
4.1.1.4. Surgical Treatment

RECOMMENDATION

Class I
Surgical treatment of acute obstructive intestinal ischemia includes revascularization, resection of necrotic bowel, and, when appropriate, a “second look” operation 24 to 48 hours after the revascularization. (Level of Evidence: B)

Despite treatment, acute intestinal ischemia caused by arterial obstruction is most often fatal. Various surgical series show both that treatment outcome has changed little during the past several decades and that mortality averages approximately 70% (808,809,813-817). The reason for this grim prognosis is found in the time course of the signs and symptoms of the disease. Because patients present initially with abdominal pain and few findings, diagnosis is often delayed. By the time the diagnosis is obvious because of abdominal distention, perforation, shock, and so on, ischemia is far advanced, and survival is doubtful, despite treatment.

Surgical treatment consists of laparotomy, revascularization of the ischemic intestine either by embolectomy or bypass grafting, assessment of the viability of the intestine after revascularization, resection of nonviable intestine, and intensive care. Frequently, some intestine is clearly viable, some is clearly nonviable, and some is questionable. No intraoperative diagnostic test has yet been described that is superior to the clinical judgment of experienced surgeons in determining intestinal viability (819). Scheduled “second look” operations, 24 to 48 hours after the initial procedure, are the best way to avoid both excessive resection of potentially viable bowel and failure to resect nonviable intestine.

4.1.1.5. Endovascular Treatment

RECOMMENDATION

Class IIb
Percutaneous interventions (including transcatheter lytic therapy, balloon angioplasty, and stenting) are appropriate in selected patients with acute intestinal ischemia caused by arterial obstructions. Patients so treated may still require laparotomy. (Level of Evidence: C)

Acute intestinal ischemia caused by arterial obstructions is most frequently the result of occlusion of the proximal portion of the superior mesenteric artery either by thrombosis at the site of atherosclerosis or by localized arterial embolism. It is reasonable to consider the role of lytic therapy, balloon angioplasty/stenting, or both as definitive treatment, especially in view of the dismal results associated with standard surgical therapy.

Several isolated reports of percutaneous interventional treatment of superior mesenteric artery obstruction producing acute intestinal ischemia have been published (820-822).

Because most patients with acute intestinal ischemia have at least some nonviable intestine at the time of presentation, most will still require laparotomy and surgical assessment of the intestinal viability. This approach may be required even if percutaneous therapy is successful in relieving the obstruction. However, re-establishment of flow to infarcted bowel may cause a sudden systemic release of endotoxins, which may be associated with the sudden onset of disseminated intravascular coagulation, adult respiratory distress syndrome, and sudden cardiovascular collapse. Therefore, in the presence of infarcted bowel or markedly elevated lactic acid levels, initial percutaneous treatment should be weighed against surgical options in which control of the venous outflow (and the endotoxins) from the infarcted bowel segment can be achieved.

Although only a few cases have been reported, further exploration of this approach to acute ischemia seems appropriate. Percutaneous treatment of the arterial obstruction greatly reduces the magnitude of the surgical procedure that is required, and the high mortality associated with the standard approach means that investigation of alternative approaches is appropriate.

4.1.2. Acute Nonocclusive Intestinal Ischemia

4.1.2.1. Etiology

RECOMMENDATIONS

Class I
1. Nonocclusive intestinal ischemia should be suspected in patients with low flow states or shock, especially cardiogenic shock, who develop abdominal pain. (Level of Evidence: B)
2. Nonocclusive intestinal ischemia should be suspected in patients receiving vasoconstrictor substances and medications (e.g., cocaine, ergots, vasopressin, or noradrenaline/norepinephrine) who develop abdominal pain. (Level of Evidence: B)
3. Nonocclusive intestinal ischemia should be suspected in patients who develop abdominal pain after coarctation repair or after surgical revascularization for intestinal ischemia caused by arterial obstruction. (Level of Evidence: B)

Acute intestinal ischemia sufficient to produce infarction also occurs in the absence of fixed arterial obstruction. The most frequent setting is severe systemic illness with systemic shock, usually as a result of reduced cardiac output (808,823-827). In this situation, the intestinal ischemia has been shown to be the result of severe and prolonged intestinal arterial vasospasm. Before modern intensive care and vasodilator treatment of congestive heart failure, nonocclusive intestinal ischemia was quite common. With the advent of this therapy, it has become rare.

Intestinal vasospasm sufficient to produce ischemia/infarction also occurs as a result of cocaine ingestion and ergot poisoning (828,829). Therapeutic drugs may produce intestinal
ischemia from vasospasm, especially when vasopressors are used in high doses to treat circulatory shock.

Intestinal ischemia can also occur as a result of mesenteric arterial spasm after repair of aortic coarctation (830) and occasionally occurs after revascularization procedures for chronic mesenteric ischemia (825). The mechanism of this apparently paradoxical spasm is unknown.

4.1.2.2. Diagnosis

RECOMMENDATION

Class I

Arteriography is indicated in patients suspected of having nonocclusive intestinal ischemia whose condition does not improve rapidly with treatment of their underlying disease. (Level of Evidence: B)

Nonocclusive mesenteric ischemia should be suspected whenever patients with circulatory shock, especially cardiogenic shock, develop abdominal pain and/or distention. Because such patients are seriously ill, often with a decreased level of consciousness, diagnosis may be delayed.

In modern practice, nearly all ergot poisoning is the result of use/misuse of therapeutic ergot preparations intended to treat migraine headaches. The diagnosis of nonocclusive intestinal ischemia should be suspected in persons using cocaine or amphetamines who have abdominal pain.

There are no physical findings or laboratory tests specific for nonocclusive intestinal ischemia. Arteriography is the “gold standard” study. It can demonstrate the characteristic mesenteric arterial vasospasm and allow direct intra-arterial instillation of vasodilator medications (824,826,829).

4.1.2.3. Treatment

RECOMMENDATIONS

Class I

1. Treatment of the underlying shock state is the most important initial step in treatment of nonocclusive intestinal ischemia. (Level of Evidence: C)

2. Laparotomy and resection of nonviable bowel is indicated in patients with nonocclusive intestinal ischemia who have persistent symptoms despite treatment. (Level of Evidence: B)

Class IIa

Transcatheter administration of vasodilator medications into the area of vasospasm is indicated in patients with nonocclusive intestinal ischemia who do not respond to systemic supportive treatment and in patients with intestinal ischemia due to cocaine or ergot poisoning. (Level of Evidence: B)

Initial treatment of nonocclusive intestinal ischemia should be directed at treatment of the underlying shock state. The most intensive hemodynamic monitoring possible, including appropriate fluid/pharmacological therapy to improve cardiac output/peripheral perfusion, is the most reliable way to relieve the inappropriate vasospasm.

Administration of vasodilators by percutaneously placed catheters at the site of inappropriate vasospasm has been associated with relief of vasospasm/ischemic symptoms in multiple patients (823). Because of the complete absence of any controlled trials, it is not possible to determine whether the improvement that occurred was the result of the systemic or local effects of the vasodilators or the result of simultaneous treatment of the systemic condition.

Transcatheter administration of vasodilators is especially appropriate in nonocclusive mesenteric ischemia caused by drugs such as ergot or cocaine, in which systemic shock may not coexist (831). Abdominal symptoms/findings that persist after relief of intestinal arterial vasospasm are an indication for laparotomy/resection of necrotic intestine.

There are few level I or II data on treatments for acute mesenteric ischemia caused by mesenteric venous thromboses, internal or external hernias, vasculitides, or aortic dissections, and therefore, a formal discussion of these causes is not included in this document.

4.2. Chronic Intestinal Ischemia

4.2.1. Etiology

Although atherosclerotic disease of the celiac and mesenteric vessels is common, the clinical presentation of chronic intestinal ischemia is rare. It is nearly uniformly caused by atherosclerosis (832). Other rare causes include Buergers’ disease (812,833), fibromuscular dysplasia/dissection, and aortic dissection, but these are very rare causes of an already rare syndrome. The celiac, superior mesenteric, and inferior mesenteric arteries are all extensively interconnected, to a degree that means that in usual circumstances, proximal occlusion by atherosclerosis of any one is well tolerated (832). Although classic clinical approaches to the diagnosis of intestinal ischemia have often suggested that this syndrome requires occlusion or stenosis of at least 2 of the 3 intestinal arteries, this is not entirely true (833,834). Well-documented cases of intestinal ischemia occur as a result of single-vessel disease, virtually always of the superior mesenteric artery. Patients in whom some of the normal collateral intestinal arterial connections have been interrupted by previous surgery are especially vulnerable to single-vessel occlusions.

Patients with chronic intestinal ischemia are most often female (70%) and classically complain of severe abdominal pain induced by eating. The pattern of pain is quite variable, however, and the relationship to food is not always clear, at least by history. What is clear is that patients voluntarily vastly reduce their food intake, so that weight loss occurs, and this may be profound. Vomiting, diarrhea, and constipation are all present in a minority of patients. A majority have a history of cardiovascular disease, and 30% to 50% have had previous operations for atherosclerotic disease (most frequently coronary and lower extremity bypass) (835,836).
4.2.2. Diagnosis

RECOMMENDATIONS

Class I
1. Chronic intestinal ischemia should be suspected in patients with abdominal pain and weight loss without other explanation, especially those with cardiovascular disease. (Level of Evidence: B)
2. Duplex ultrasound, CTA, and gadolinium-enhanced MRA are useful initial tests for supporting the clinical diagnosis of chronic intestinal ischemia. (Level of Evidence: B)
3. Diagnostic angiography, including lateral aortography, should be obtained in patients suspected of having chronic intestinal ischemia for whom noninvasive imaging is unavailable or indeterminate. (Level of Evidence: B)

Clinical Presentation

Because there are many common causes of abdominal pain and weight loss, and because chronic intestinal ischemia is rare, diagnosis is delayed in most patients. Many patients in whom the diagnosis is made have been symptomatic for months or even years and have undergone the gamut of abdominal diagnostic procedures, including contrast X-ray studies, endoscopy, and multiple scans. The profound weight loss that occurs suggests a diagnosis of malignancy, which leads to further imaging studies.

Laboratory Testing

Although multiple tests of intestinal absorption and others have been proposed for diagnosis of chronic intestinal ischemia, none has proven worthwhile. At present, there are no laboratory abnormalities that are diagnostic.

Duplex Scanning

The atherosclerotic lesions that typically produce intestinal arterial obstruction are usually located at the origin of the vessels from the aorta and are actually protruding aortic plaques in most (833). This feature makes the lesions suitable for diagnosis by duplex ultrasound. Duplex scanning of visceral vessels is technically difficult but can be accomplished in more than 85% of subjects in the elective setting. The test has an overall accuracy of approximately 90% for detection of greater than 70% diameter stenoses or occlusions of the celiac and superior mesenteric arteries when performed in highly experienced laboratories (837-839). Although the expected increase in intestinal arterial flow that results from food ingestion can be detected and quantified by duplex scanning, this information has not added to the diagnostic accuracy of the test for establishing whether abdominal symptoms that are present are the result of intestinal ischemia (840).

Computed Tomography/MRA

Both contrast-enhanced CTA and gadolinium-enhanced MRA are well suited for visualizing the typical atherosclerotic lesions at the origins of the intestinal arteries that are implicated in most cases of chronic intestinal ischemia. These techniques are presently less suited for visualizing the more distal intestinal arteries and for diagnosis of some of the more unusual causes of intestinal ischemia.

Arteriography

Arteriograms provide definitive diagnosis of intestinal arterial lesions. Lateral aortography is best suited for display of the typical origin lesions, which may not be apparent on frontal projections. The presence of an enlarged “arc of Riolan” (an enlarged collateral vessel connecting the left colic branch of the inferior mesenteric artery with the superior mesenteric artery) is an arteriographic sign of proximal mesenteric arterial obstruction that is visible on anteroposterior aortograms. Selective arteriography of the intestinal vessels may fail to visualize the typical atherosclerotic origin lesions because the selective catheter may be positioned beyond them in the affected vessel.

Approach to Diagnosis

Although multiple diagnostic techniques are available to demonstrate diseased intestinal vessels, such lesions are actually quite common, whereas symptomatic intestinal ischemia is rare. At present, there are no diagnostic tests that establish the diagnosis definitively. Rather, it is the combination of the typical clinical presentation of abdominal pain and weight loss, with other evidence of cardiovascular disease, and the finding of intestinal arterial obstruction in the absence of other obvious cause of the symptoms that should lead to consideration of the diagnosis.

4.2.3. Natural History

Significant atherosclerotic obstruction of the intestinal arteries is present in 6% to 10% of unselected autopsies and in 14% to 24% of patients undergoing abdominal arteriography. The fact that nearly all such patients have no symptoms of intestinal ischemia is a reflection of the extensive collateral connections present among the intestinal arteries (832). Only one study (841) has addressed the issue of how many patients with asymptomatic intestinal arterial lesions ultimately develop intestinal ischemia. Of 980 abdominal aortograms, there were 15 patients who had severe stenosis or occlusions of all 3 intestinal vessels, of whom 4 developed symptomatic intestinal ischemia with a mean follow-up of 2.6 years. No patients who had fewer than 3 severely affected vessels developed symptoms (841). Development of symptomatic intestinal ischemia in patients with asymptomatic intestinal arterial obstruction after abdominal surgery for other reasons has been described (842). The presumed mechanism is division of vital collateral-
als during the surgical procedure. This sequence of events has been most frequently recognized after abdominal vascular surgery (e.g., aortic aneurysm or renal artery repair). The frequency with which this complication occurs is unknown. The natural history of symptomatic chronic intestinal ischemia is known in part. An unknown percentage of patients progress to acute intestinal ischemia, and the remainder have progressive weight loss with ultimate death from inanition. Although it is reasonable to postulate that some of the affected patients must experience spontaneous recovery, no such case has been documented in the literature.

4.2.4. Interventional Treatment

RECOMMENDATION

Class I
Percutaneous endovascular treatment of intestinal arterial stenosis is indicated in patients with chronic intestinal ischemia. *(Level of Evidence: B)*

Percutaneous treatment of symptomatic intestinal ischemia was first reported in 1980 (843). Since then, a large number of reports in the literature have documented that percutaneous interventional treatment of intestinal arterial obstructions is possible with a high technical success rate and few complications in properly selected cases (844-849). Most procedures have been performed to treat intestinal arterial stenoses, with few attempting to treat occlusions. To date, there have been no prospective therapeutic trials, and follow-up information is limited; that which exists indicates that elimination of the arterial obstruction is reliably followed by relief of symptoms and weight gain. Several reports of concurrent series treated by angioplasty/stenting or surgery indicate that recurrences after percutaneous procedures have been more frequent than after open surgery, but many of the recurrences can be managed by percutaneous interventions (850). The results of several series are listed in Table 42. The reported recurrence rates mandate careful follow-up of patients treated with angioplasty and stents. As with open surgery, recurrent symptoms have nearly always indicated recurrent arterial obstruction.

4.2.5. Surgical Treatment

RECOMMENDATIONS

Class I
Surgical treatment of chronic intestinal ischemia is indicated in patients with chronic intestinal ischemia. *(Level of Evidence: B)*

Class IIb
Revascularization of asymptomatic intestinal arterial obstructions may be considered for patients undergoing aortic/renal artery surgery for other indications. *(Level of Evidence: B)*

Class III
Surgical revascularization is not indicated for patients with asymptomatic intestinal arterial obstructions, except in patients undergoing aortic/renal artery surgery for other indications. *(Level of Evidence: B)*

4.2.4. Interventional Treatment

RECOMMENDATION

Class I
Percutaneous endovascular treatment of intestinal arterial stenosis is indicated in patients with chronic intestinal ischemia. *(Level of Evidence: B)*

Percutaneous treatment of symptomatic intestinal ischemia was first reported in 1980 (843). Since then, a large number of reports in the literature have documented that percutaneous interventional treatment of intestinal arterial obstructions is possible with a high technical success rate and few complications in properly selected cases (844-849). Most procedures have been performed to treat intestinal arterial stenoses, with few attempting to treat occlusions. To date, there have been no prospective therapeutic trials, and follow-up information is limited; that which exists indicates that elimination of the arterial obstruction is reliably followed by relief of symptoms and weight gain. Several reports of concurrent series treated by angioplasty/stenting or surgery indicate that recurrences after percutaneous procedures have been more frequent than after open surgery, but many of the recurrences can be managed by percutaneous interventions (850). The results of several series are listed in Table 42. The reported recurrence rates mandate careful follow-up of patients treated with angioplasty and stents. As with open surgery, recurrent symptoms have nearly always indicated recurrent arterial obstruction.

5. ANEURYSMS OF THE ABDOMINAL AORTA, ITS BRANCH VESSELS, AND THE LOWER EXTREMITIES

Although their causes may be diverse, arterial aneurysms share many of the same atherosclerotic risk factors and pose

---

**Table 42. Single-Institution Comparisons of Mesenteric Angioplasty/Stenting Versus Surgery**

<table>
<thead>
<tr>
<th>First Author and Procedure</th>
<th>Year</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Successfully Revascularized (%)</th>
<th>30-Day Mortality (%)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasirajan* Angioplasty</td>
<td>2001</td>
<td>(850)</td>
<td>28</td>
<td>93</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>85</td>
<td>98</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Rose† Angioplasty/stenting</td>
<td>1995</td>
<td>(850a)</td>
<td>8</td>
<td>80</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>9</td>
<td>100</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Bowser‡ Angioplasty/stenting</td>
<td>2002</td>
<td>(850b)</td>
<td>18</td>
<td>88</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>22</td>
<td>100</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

*Surgical controls were historic; mean postprocedure follow-up was 3 years for both groups.
†Mean follow-up for surgery was 3 years; for angioplasty/stenting, 9 months.
‡Mean follow-up was 14 months.
similar threats to life, limb, and vital organ function as occlusive arterial disease. Like occlusive disease, the presence of most common aneurysms can be suspected on the basis of an attentive physical examination and subsequently confirmed by noninvasive, widely available imaging studies. Just as important, there are now a variety of therapeutic options that include both traditional open surgery and endovascular techniques such that relatively few large aneurysms should merely be observed until morbid events occur. For all of these reasons, current guidelines for the diagnosis and management of arterial aneurysms may be useful to clinicians irrespective of their primary care or specialty training.

5.1. Definition

According to some sources, the diagnosis of AAA should be determined by formulas that adjust for age or body surface area or by calculating the ratio between normal and dilated aortic segments (859-863). Generally, however, an AAA is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The size of the aorta can be measured in any plane that is perpendicular to the vessel axis, but in practice, the anteroposterior diameter is measured most easily and reproducibly. Accordingly, most screening studies define AAA in this manner (859).

There is abundant information concerning normal diameters of the abdominal aorta and its branches in healthy adults, which indicates enlargement with age and body size and larger diameters in men than in women (Table 43) (864-866). A diameter of 2.7 cm represents the 95th percentile for the nonaneurysmal infrarenal aorta in men 65 to 83 years of age (867), and 2.9 cm exceeds the upper limit of normal irrespective of age, gender, or body surface area (868). Women have slightly smaller normal aortic diameters than men (862), and although this difference in baseline aortic diameter between women and men is not great enough to influence the minimum size of 3.0 cm that customarily is used to define a small AAA, it may influence recommendations for the size at which larger aneurysms should be repaired.

5.2. Abdominal Aortic and Iliac Aneurysms

5.2.1. Prevalence

The prevalence of AAA varies with a number of demographic factors (Table 44), including advancing age, family history, male gender, and tobacco use. A necropsy study in Malmo, Sweden, where autopsies are performed after nearly all hospital deaths, revealed that the incidence of AAAs larger than 3.0 cm in diameter increased at ages over 50 years, reaching a maximum prevalence of 5.9% in men 80 to 85 years of age and 4.5% for women over 90 years of age (868). Most population-based ultrasound screening surveys have been performed among white men and women, particularly those of Northern European and Scandinavian ancestry. A variety of threshold diameters have been used in these investigations, which makes it difficult to establish consistent estimates of prevalence. In general, the prevalence of AAAs 2.9 to 4.9 cm in diameter ranges from 1.3% for men aged 45 to 54 years to up to 12.5% for men 75 to 84 years of age. Comparable prevalence figures for women are 0% and 5.2%, respectively.

Race also appears to influence the prevalence of AAAs and iliac aneurysms. These aneurysms are rarely encountered in population-based screening studies in Japan, where the prevalence of traditional risk factors for atherosclerosis is lower than in white populations (876,877). In a United Kingdom community in which 14% of the population was of Asian descent, a review of medical records identified 233 cases of AAA, none of which occurred in the Asian population (878).

5.2.1.1. Generalized Arteriomegaly

Generalized arteriomegaly reflects a systemic alteration of the elastic component of the arterial wall, which results in dilation and elongation of many arteries. Patients with localized AAA are relatively unlikely to have generalized arteriomegaly (879), but the familial pattern of generalized arteriomegaly is similar. In one series, there was a family history of aneurysms in 10% (4/40) of patients with peripheral aneurysms, in 22% (19/86) of patients with AAA, and in 36% (5/14) of patients with generalized arteriomegaly (880).

5.2.2. Etiology

Most aortic and peripheral aneurysms represent a manifestation of aortic medial degeneration, which has complex biological mechanisms. Traditional views held that most aneurysms were caused by degenerative atherosclerotic disease, but other data (see Section 5.2.2.3) suggest that many aneurysms form in response to altered tissue metalloproteinases that diminish the integrity of the arterial wall.

5.2.2.1. Hereditary Risk Factors

A genetic predisposition to AAA formation has been suggested by studies of familial incidence, and an analysis of 313 pedigrees confirms the importance of familial factors (881). In a series of 542 patients undergoing AAA repair during a 9-year period, 15% had first-degree relatives with aneurysms compared with 2% of a control group of similar age and gender (p < 0.001) (882). Other series have found first-degree relatives similarly affected in up to 28% of cases (883). A family history of AAAs is particularly relevant for male siblings of male probands, in whom the relative risk for AAA is as high as 18 (881), which suggests a single dominant gene effect (Table 45). Among the offspring of patients with ruptured AAA, 21% of sons older than 45 years and 4% of daughters older than 42 years had aortic enlargement to a diameter of at least 3.0 cm (884). First-degree male relatives of patients with AAA have 2 to 4 times the normal risk for AAA. Female first-degree relatives appear to be at similar risk, but the data are less certain. One study found that patients with familial aneurysms were more often female than those without (35% vs. 14%) (885). Familial aneurysms
do not expand more rapidly than nonfamilial AAA, nor are they differently located, but they may develop at an earlier age (see Section 5.2.4.6) (886).

Polycystic kidney disease, an autosomal dominant disease that affects 0.5 million people, and 8% to 10% of long-term hemodialysis cases in the United States have been associated with abdominal aneurysms (891,892). The association of cardiovascular lesions with polycystic kidney disease suggests involvement of the extracellular matrix in this disorder, but the main cause of aortic aneurysms is degenerative. Patients with renal disease may be prone to aortic aneurysm because of hypertension and connective tissue disorders, and yet an independent association between AAA and autosomal-dominant polycystic kidney disease is unproven.

5.2.2.2. Atherosclerotic Risk Factors

RECOMMENDATIONS

Class I

1. In patients with AAAs, blood pressure and fasting serum lipid values should be monitored and controlled as recommended for patients with atherosclerotic disease. (*Level of Evidence: C*)

2. Patients with aneurysms or a family history of aneurysms should be advised to stop smoking and be offered smoking cessation interventions, including behavior modification, nicotine replacement, or bupropion. (*Level of Evidence: B*)

It is widely recognized that patients with AAAs have a significantly higher prevalence of smoking, hypertension, MI, heart failure, and carotid artery and/or lower extremity PAD than do age- and gender-matched controls. The lipoprotein(a) serum level, an indicator of atherosclerosis, is elevated in patients with AAA independent of cardiovascular risk factors and the extent of atherosclerosis, whereas patients with dissecting thoracic aortic aneurysms have levels comparable to those of healthy individuals (893).

Thoracic aortic atheromata detected by transesophageal echocardiography may independently predict AAA (894). In a study of 364 patients, 14% of those with thoracic atheromata had AAAs compared with only 1.4% of those without (OR 11.4, *p* < 0.0001). Another indicator of generalized atherosclerosis, common carotid arterial intima-media thickness, was 0.98 plus or minus 0.34 mm in patients with occlusive arterial disease compared with 0.91 plus or minus 0.20 mm in patients with AAAs (an age- and gender-adjust-

---

### Table 43. Dimensions of Normal Arteries

<table>
<thead>
<tr>
<th>First Author and Procedure</th>
<th>Females</th>
<th>Males</th>
<th>Assessment Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Diameter, cm, Range</td>
<td>Standard Deviation, cm, Range</td>
<td>Mean Diameter, cm, Range</td>
</tr>
<tr>
<td>Abdominal aorta, supraceliac</td>
<td>2.10 to 2.31</td>
<td>0.27</td>
<td>2.50 to 2.72</td>
</tr>
<tr>
<td>Abdominal aorta, suprarenal</td>
<td>1.86 to 1.88</td>
<td>0.09 to 0.21</td>
<td>1.98 to 2.27</td>
</tr>
<tr>
<td>Abdominal aorta, infrarenal</td>
<td>1.66 to 2.16</td>
<td>0.22 to 0.32</td>
<td>1.99 to 2.39</td>
</tr>
<tr>
<td>Abdominal aorta, infrarenal</td>
<td>1.19 to 1.87</td>
<td>0.09 to 0.34</td>
<td>1.41 to 2.05</td>
</tr>
<tr>
<td>Celiac</td>
<td>0.53</td>
<td>0.03</td>
<td>0.53</td>
</tr>
<tr>
<td>Superior mesenteric</td>
<td>0.63</td>
<td>0.04</td>
<td>0.63</td>
</tr>
<tr>
<td>Common iliac</td>
<td>0.97 to 1.02</td>
<td>0.15 to 0.19</td>
<td>1.17 to 1.23</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>0.54</td>
<td>0.15</td>
<td>0.54</td>
</tr>
<tr>
<td>Common femoral</td>
<td>0.78 to 0.85</td>
<td>0.07 to 0.11</td>
<td>0.78 to 1.12</td>
</tr>
<tr>
<td>Popliteal</td>
<td>NA</td>
<td>NA</td>
<td>0.9</td>
</tr>
<tr>
<td>Posterior tibial</td>
<td>NA</td>
<td>NA</td>
<td>0.3</td>
</tr>
</tbody>
</table>

IV indicates intravenous; and NA, not available.

<table>
<thead>
<tr>
<th>Country/Study</th>
<th>First Author</th>
<th>Reference</th>
<th>Number Screened</th>
<th>Age, y</th>
<th>Criteria</th>
<th>% Prevalence/ Gender</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Australia</td>
<td>Jamrozik</td>
<td>(869)</td>
<td>12203</td>
<td>65 to 69</td>
<td>Larger than 3.0 cm</td>
<td>4.8/Male</td>
<td>Higher risk: Current or ex-smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80 to 83</td>
<td>Larger than 3.0 cm</td>
<td>10.8/Male</td>
<td>Established PAD, CAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65 to 83</td>
<td>Larger than 5.0 cm</td>
<td>0.69/Male</td>
<td>Waist-hip ratio larger than 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower risk: Mediterranean born versus Australian born (OR 0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regular vigorous exercise</td>
</tr>
<tr>
<td>Veterans Affairs Cooperative</td>
<td>Lederle</td>
<td>(870)</td>
<td>126,196*</td>
<td>50 to 79</td>
<td>Larger than 4.0 cm</td>
<td>1.3/Male and female</td>
<td>Higher risk: Increased age per 7 years (OR 1.7)</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smoking history (OR 5.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Family history (OR 1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Established atherosclerosis (OR 1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower risk: Female (OR 0.18; 2.7% of total)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black race (OR 0.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes mellitus (OR 0.50)</td>
</tr>
<tr>
<td>Norway</td>
<td>Singh</td>
<td>(871)</td>
<td>6386</td>
<td>25 to 84</td>
<td>Larger than 2.9 cm</td>
<td>8.9/Male; 2.2/female</td>
<td>Higher risk: Increased age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45 to 54</td>
<td>Larger than 2.9 cm</td>
<td>1.9/Male; 0.7/female</td>
<td>Smoker older than 40 y vs. never-smoker (OR 8.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55 to 64</td>
<td>Larger than 2.9 cm</td>
<td>6.0/Male; 0.5/female</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65 to 74</td>
<td>Larger than 2.9 cm</td>
<td>12.8/Male; 2.8/female</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75 to 84</td>
<td>Larger than 2.9 cm</td>
<td>19.5/Male; 1.9/female</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55 to 64</td>
<td>Larger than 3.9 cm</td>
<td>1.1/Male; 0.1/female</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65 to 74</td>
<td>Larger than 3.9 cm</td>
<td>4.1/Male; 0.2/female</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75 to 84</td>
<td>Larger than 3.9 cm</td>
<td>8.6/Male; 1.0/female</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Pleumeekers</td>
<td>(872)</td>
<td>5283†</td>
<td>Older than 54</td>
<td>Larger than 3.6 cm or</td>
<td>2.8/Male; 0.5/female</td>
<td>Higher risk: Smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>distal dilation greater than 49%</td>
<td></td>
<td>High serum cholesterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Older than 54</td>
<td>1.6/Male; 0.3/female</td>
<td>Established cardiovascular disease</td>
</tr>
<tr>
<td>Belgium</td>
<td>Vazquez</td>
<td>(873)</td>
<td>716‡</td>
<td>65 and 75</td>
<td>Larger than 3 cm</td>
<td>3.8/Male</td>
<td>Higher risk: Arterial hypertension (p less than 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 4 cm</td>
<td>0.3/Male</td>
<td>Prior CABG (p less than 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smoker (p less than 0.06)</td>
</tr>
</tbody>
</table>

Continued on Next Page

**Notes:**
- * = Includes all ages.
- † = Includes patients with secondary causes.
- ‡ = Includes patients with primary causes.
### Table 44. Continued

<table>
<thead>
<tr>
<th>Country/Study</th>
<th>First Author</th>
<th>Reference</th>
<th>Number Screened</th>
<th>Age, y</th>
<th>Criteria</th>
<th>% Prevalence/Gender</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>Boll</td>
<td>(874)</td>
<td>2419§</td>
<td>60 to 80</td>
<td>Larger than 2.9 cm</td>
<td>8.1/Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 4.9 cm</td>
<td>1.7/Male</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Wilmink¶</td>
<td>(875)</td>
<td>426</td>
<td>65 to 74</td>
<td>Larger than 4.0 cm or 5 mm larger than SRA</td>
<td>5.4/Male</td>
<td></td>
</tr>
<tr>
<td>Oxford</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65 to 74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 4.0 cm</td>
<td>2.3/Male</td>
<td></td>
</tr>
<tr>
<td>Liverpool</td>
<td></td>
<td></td>
<td>4232</td>
<td>65</td>
<td>Larger than 2.5 cm</td>
<td>8.4/Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 4.0 cm</td>
<td>1.3/Male</td>
<td></td>
</tr>
<tr>
<td>Gloucestershire</td>
<td></td>
<td></td>
<td>2669</td>
<td>65 to 75</td>
<td>Larger than 2.9 cm</td>
<td>8.4/Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 4.0 cm</td>
<td>3.0/Male</td>
<td></td>
</tr>
<tr>
<td>Birmingham</td>
<td></td>
<td></td>
<td>5394</td>
<td>65 to 80</td>
<td>Larger than 2.9 cm</td>
<td>7.6/Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65 to 80</td>
<td>1.3/Female</td>
<td></td>
</tr>
<tr>
<td>Chichester</td>
<td></td>
<td></td>
<td>628</td>
<td>65 to 79</td>
<td>Larger than 2.9 cm</td>
<td>6.7/Male</td>
<td></td>
</tr>
<tr>
<td>Northumberland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntingdon</td>
<td></td>
<td></td>
<td>7493</td>
<td>Older than 49</td>
<td>Larger than 2.9 cm</td>
<td>5.2/Male</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Takei</td>
<td>(876)</td>
<td>348</td>
<td>60 to 79</td>
<td>—</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Adachi</td>
<td>(877)</td>
<td>1591</td>
<td>—</td>
<td>—</td>
<td>0.3/Male</td>
<td></td>
</tr>
</tbody>
</table>

*52745 plus prior report of 73451.
†Of 10215 eligible.
‡Of 1764 eligible.
§Of 2914 eligible.
¶This portion of table adapted from Wilmink and Quick (875).
CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; OR, odds ratio; SRA, suprarenal aneurysm.
Table 45. Prevalence in Families of Patients With Abdominal Aortic Aneurysms (AAAs)

<table>
<thead>
<tr>
<th>Country</th>
<th>First Author</th>
<th>Reference</th>
<th>Study Group</th>
<th>Screened With Ultrasound</th>
<th>Age, y (Gender)</th>
<th>Criteria</th>
<th>Incidence/Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>Adams</td>
<td>(887)</td>
<td>Relatives of 100 patients with known AAA</td>
<td>76 of 110 eligible</td>
<td>Older than 50</td>
<td>Larger than 4.0 cm</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Older than 50</td>
<td>2.5 to 3.9 cm</td>
<td>21% of male first-degree relatives;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27% of sons; 17% of brothers;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4% of sisters; 0% of daughters</td>
</tr>
<tr>
<td>Sweden</td>
<td>Bengtsson</td>
<td>(884)</td>
<td>Offspring of patients who died of ruptured AAA</td>
<td>62 of 90 eligible</td>
<td>45 to 75 (males)</td>
<td>Larger than 2.9 cm</td>
<td>21% of sons</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45 to 80 (female)</td>
<td>Larger than 2.9 cm</td>
<td>4% of daughters</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45 to 80 (female)</td>
<td>Larger than 5.0 cm</td>
<td>3% (1 male aged 53 y)</td>
</tr>
<tr>
<td>Ireland</td>
<td>Fitzgerald</td>
<td>(888)</td>
<td>Siblings of patients with known AAA</td>
<td>125 of 234 eligible</td>
<td>Older than 80</td>
<td>3.1 to 6.8 cm</td>
<td>22% of brothers; 3% of sisters</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Van Der Graf</td>
<td>(889)</td>
<td>Brothers of patients having elective surgery for AAA</td>
<td>210 of 571 eligible</td>
<td>Older than 50</td>
<td>New AAA</td>
<td>12.30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Older than 50</td>
<td>Larger than 4.9 cm</td>
<td>3.80%</td>
</tr>
<tr>
<td>Finland</td>
<td>Jaakkola</td>
<td>(890)</td>
<td>Families of patients with surgery for AAA</td>
<td>123 of 172 eligible</td>
<td>41 to 82</td>
<td>Larger than 2.9 cm or history of repair or rupture</td>
<td>10% of brothers; 3% of sisters</td>
</tr>
<tr>
<td>United States</td>
<td>Webster</td>
<td>(883)</td>
<td>First-degree relatives of patients with surgery for AAA</td>
<td>103 of 202 eligible</td>
<td>Older than 55</td>
<td>Larger than 3.0 cm or I/S diameter ratio greater than 1.5</td>
<td>16% of first-degree relatives; 25% of men; 6.9% of women</td>
</tr>
</tbody>
</table>
ed mean difference of 0.18 mm; 95% CI 0.08 to 0.28 mm) (895). The difference remained 0.11 mm (95% CI 0.01 to 0.21 mm) after adjustments for other cardiovascular risk factors. The smaller common carotid intimal-medial thickness in patients with AAAs than in patients with occlusive disease is independent of other determinants of intimal-medial thickness and probably reflects other pathophysiological mechanisms, such as hypertension.

5.2.2.3. Collagenase, Elastase, Metalloproteases

The striking histological feature of aortic aneurysms is destruction of the media and elastic tissue. Excessive proteolytic enzyme activity in the aortic wall may promote deterioration of structural matrix proteins, such as elastin and collagen (896). Smooth muscle cells derived from patients with AAAs display increased migration, perhaps related to overproduction of the matrix metalloproteinase MMP-2, which may lead to extracellular matrix remodeling and medial disruption (897). Abnormal biochemical elastolytic and active proteolytic activity has also been identified in aneurysmal aortas (898). An abnormal accumulation of macrophages (899) and elevated levels of cytokines (900) indicate that an inflammatory process may contribute to their pathogenesis. Cultured smooth muscle cells from aneurysmal aortas produce elevated levels of the plasminogen activators urokinase plasminogen activator and tissue plasminogen activator (901), which could increase proteolysis. In aggregate, the data suggest a major role for matrix metalloproteinases and their inhibitors in the loss of aortic wall structural integrity that leads to AAA formation and expansion.

Chronic obstructive pulmonary disease (COPD) and AAA share several risk factors. In 240 patients with thoracic aneurysms or AAAs, forced expiratory volume/forced vital capacity and carbon monoxide diffusion capacity were lower than in a control group (p < 0.01) (902). The proportion with airway obstruction (forced expiratory volume in 1 second less than 70% of normal) was higher in the AAA group (100 of 240, or 42%) than in those without overt cardiovascular disease (51 of 223, or 23%) or in patients with coronary artery disease matched for age, gender, smoking, and other atherosclerotic risk factors (43 of 238, or 18%). By multiple logistic regression analysis, the presence of AAA (OR 2.928, 95% CI 1.722 to 4.979) and male gender (OR 1.622, 95% CI 1.055 to 2.493) were most strongly associated with COPD.

The association between AAA and COPD has been attributed to elastin degradation caused by tobacco smoking. Among 4404 men 65 to 73 years of age with a 4.2% prevalence of AAA, 7.7% of those with COPD had aortic aneurysms (903). The overall mean annual expansion rate was 2.7 mm per year irrespective of COPD, but it was 4.7 mm per year among patients treated with corticosteroid agents compared with 2.6 mm per year among those who were not treated (p < 0.05). There was a negative correlation between the forced expiratory volume in 1 second and concentrations of serum elastin peptide and plasma elastase–alpha 1–antitrypsin complexes in patients with COPD, and the concentration of serum elastin peptide, therapy with beta-agonist bronchodilator medication, and forced expiratory volume in 1 second correlated with the degree of expansion. The high prevalence of AAA among patients with COPD might therefore be related more to medication use and coexisting diseases than to a common pathogenic mechanism.

Uregulation of genes involved in oxidative stress (e.g., heme oxygenase, inducible nitric oxide synthase, 12-lipoxygenase, and heart cytochrome c oxidase subunit VIa) and the downregulation of antioxidant genes (e.g., superoxide dismutase, reduced nicotinamide adenine dinucleotide-cytochrome b-5 reductase, and glutathione S-transferase) may play a role in the progression of AAAs (904). In patients with small, asymptomatic AAAs, prolonged administration of doxycycline was associated with reduced plasma matrix metalloproteinase (MMP-9) levels (905), but further studies are needed to evaluate the long-term effects of doxycycline on the rate and extent of aneurysm growth and the potential use of plasma MMP-9 levels as a biomarker of aneurysm disease progression.

The HMG coenzyme-A reductase inhibitors (statins) reduce the expression of matrix metalloproteinases independently of their cholesterol-lowering effect. One such agent (cerivastatin, 0.001 to 0.1 micromoles per liter) significantly reduced tissue levels of both total and active MMP-9 (p < 0.001) (906). Cerivastatin suppressed MMP-9 production by inhibiting the activation of neutrophils and macrophages. It remains to be determined whether statin therapy could be useful for prevention or treatment of AAA.

5.2.2.4. Congenital Aneurysms

Over the course of normal aging, degenerative changes occur throughout most of the length of the aorta, which leads to a mild form of cystic medial necrosis. Although physiological, this process develops more rapidly in patients with bicuspid aortic valves and during pregnancy, and very markedly in the Marfan syndrome, in which more than 11% of patients sustain dissections of the aorta. The mechanisms by which the medial layer of the aorta is subject to accelerated degeneration are a topic of molecular genetic investigation. Gsell (in 1928) and Erdheim (in 1929) first described cystic medial necrosis, which is associated with histological evidence of severe elastic fiber degeneration, necrosis of muscle cells, and cystic spaces filled with mucoid material (907, 908). This is most often encountered in the ascending aorta between the aortic valve and the innominate artery, although similar changes can also occur in the remainder of the aorta. The Marfan syndrome, an inherited disorder characterized by dolichostenomelia, ligamentous redundancy, ectopia lentis, ascending aortic dilatation, and incompetency of the aortic and/or mitral valve (909), is frequently associated with cystic medial necrosis of the aorta. The syndrome is linked to an autosomal dominant anomaly in fibrillin type 1 (910), a structural protein that directs and orients elastin in the develop-
opining aorta (911-917). The Marfanoid aorta has markedly abnormal elastic properties and increased pulse wave velocities, with progressive stiffening and dilatation (918). Single-gene mutations have been identified that cause aneurysm formation in the Marfan syndrome and in Ehlers-Danlos syndrome type IV (919), but polygenic factors are probably involved in many cases.

Abnormalities associated with the Marfan syndrome typically affect the entire length of the aorta, although dissection most often involves the thoracic portion (920). Histologically, 10% to 21% of aortic dissections and 43% of all dissections in patients with Marfan syndrome have severe degeneration of the medial layer; more than 50% of the wall area shows features of cystic necrosis. Although most often encountered in the ascending aorta, cystic medial necrosis may occur in the abdominal aorta as well. Cystic medial degeneration may also be associated with other connective tissue disorders, such as the Ehlers-Danlos syndrome.

5.2.2.5. Inflammatory Aneurysms

Inflammatory AAAs represent a unique clinical entity, typically consisting of an AAA that is associated with an unusually thickened aneurysm wall, shiny white perianeurysmal fibrosis, and intense adherence of adjacent intra-abdominal structures. This entity was first described in 1972 by Walker et al. and has since been described by Rasmussen and Hallett as an extreme manifestation of inflammation present in all aortic aneurysms (921). Abnormal accumulation of macrophages and cytokines in aneurysmal aortic tissue supports an association with inflammation (899,900). In a case-control study, there were no distinctions between patients with inflammatory aneurysms and those without inflammatory aneurysms with respect to risk factors, treatment requirements, or prognosis, but patients with inflammatory aneurysms were more often symptomatic and had a higher erythrocyte sedimentation rate, larger aneurysm diameter, and more retroperitoneal inflammatory reaction (922). In another series of 355 patients undergoing surgical repair of AAA, 5.6% had inflammatory clinical features and 11% had histological evidence of inflammation (923), but the early and late results of surgery were no different between the 2 groups.

The triad of chronic abdominal pain, weight loss, and elevated erythrocyte sedimentation rate in a patient with AAA is highly suggestive of an inflammatory aneurysm. Inflammatory aortic or iliac aneurysms were present in 4.5% of the 2816 patients who underwent elective AAA repair at the Mayo Clinic from 1955 to 1985 (924). More than 90% of the patients with inflammatory aneurysms were smokers, and clinical evidence of peripheral arterial occlusive disease and coronary artery disease was found in 27% and 39%, respectively. Additional aneurysms were discovered in half of these patients, including iliac aneurysms in 55, thoracic or thoracoabdominal aneurysms in 17, femoral aneurysms in 16, and popliteal aneurysms in 10. Excretory urographic findings of medial ureteral displacement or obstruction suggested the diagnosis of inflammatory AAA in 31% of the cases. Compared with patients with noninflammatory atherosclerotic aneurysms, those with inflammatory aneurysms were more likely to have symptoms (66% vs. 20%, p less than 0.0001), weight loss (20.5% vs. 10%, p less than 0.05), a higher erythrocyte sedimentation rate (73% vs. 33%, p less than 0.0001), and a higher operative mortality rate (7.9% vs. 2.4%, p less than 0.002).

5.2.2.6. Infectious Aneurysms

Primary infection of the aortic wall is a rare cause of aneurysms, which are more often saccular than fusiform. Infectious, or “mycotic,” aneurysms may arise secondarily from infection of pre-existent aneurysm (925). Staphylococcus and Salmonella are the most frequent pathogens that cause primary aortic infections (926), and tuberculosis has been described in association with aortic pseudoaneurysms (927).

An infectious etiology also has been postulated for conventional atherosclerotic aneurysms. Antibodies against Chlamydia pneumoniae have been detected by polymerase chain reactions in conjunction with atherosclerosis and expanding AAA (928), but it has not been possible to document that C pneumoniae antigens react with anti-C pneumoniae membrane proteins. Sixty-six percent of specimens from atherosclerotic arteries collected during various peripheral arterial operations (including AAA repair in 28 patients) revealed severe atherosclerosis and positive immunohistochemical staining for specific antibodies against C pneumoniae (929). Because there were no differences in cardiovascular risk factors, the prevalence of coronary heart disease or previous vascular surgery, or inflammatory serum markers between patients with and without C pneumoniae antibodies, this organism has been considered a concomitant phenomenon rather than a causative factor for atherosclerosis.

Although secondary prevention benefits of antibiotic therapy have been demonstrated in some studies, negative studies have also emerged. In a randomized study, 92 subjects with small AAAs received the macrolide antibiotic roxithromycin (300 mg orally daily for 28 days) or a matching placebo. The mean expansion rate of the AAA during the first year of observation in the intervention group (1.6 mm) was reduced by 44% compared with the placebo group (2.8 mm, p equals 0.02). During the second year, however, the difference favoring roxithromycin was only 5% (930). When adjusted for smoking, diastolic blood pressure, and the immunoglobulin A level, roxithromycin treatment and the antibiotic aneurysms have also been described in association with aortic pseudoaneurysms (927).
5.2.3. Natural History

The natural history of arterial aneurysms is distinguished by gradual and/or sporadic expansion in their diameter and by the accumulation of mural thrombus caused by turbulent blood flow at their periphery. These features contribute to the 3 most common complications of aneurysms, that is, rupture, thromboembolic ischemic events, and the compression or erosion of adjacent structures, which often are quite specific to their location.

5.2.3.1. Aortic Aneurysm Rupture

RECOMMENDATIONS

Class I
1. Patients with infrarenal or juxtarenal AAAs measuring 5.5 cm or larger should undergo repair to eliminate the risk of rupture. (Level of Evidence: B)
2. Patients with infrarenal or juxtarenal AAAs measuring 4.0 to 5.4 cm in diameter should be monitored by ultrasound or computed tomographic scans every 6 to 12 months to detect expansion. (Level of Evidence: A)

Class IIa
1. Repair can be beneficial in patients with infrarenal or juxtarenal AAAs 5.0 to 5.4 cm in diameter. (Level of Evidence: B)
2. Repair is probably indicated in patients with suprarenal or type IV thoracoabdominal aortic aneurysms larger than 5.5 to 6.0 cm. (Level of Evidence: B)
3. In patients with AAAs smaller than 4.0 cm in diameter, monitoring by ultrasound examination every 2 to 3 years is reasonable. (Level of Evidence: B)

Class III
Intervention is not recommended for asymptomatic infrarenal or juxtarenal AAAs if they measure less than 5.0 cm in diameter in men or less than 4.5 cm in diameter in women. (Level of Evidence: A)

Rupture is the most widely recognized complication of arterial aneurysms and primarily is associated with those involving the abdominal aorta, the common iliac arteries, and the visceral arteries. Before the introduction of B-mode ultrasonography in the 1970s and computed tomographic scanning in the 1980s, the expansion rate of aortic, iliac, and visceral aneurysms could only be determined by standard plain-film roentgenograms in the presence of mural calcification. Modern imaging techniques, which now have been further supplemented by magnetic resonance imaging/MRA, currently permit more accurate estimates of expansion rates that can be used to monitor the growth of aneurysms and to select patients for preemptive intervention before rupture occurs. Growth rates have been most widely documented for aortic aneurysms, several examples of which are presented in Table 46. These data confirm similar observations (931,932) that large aneurysms tend to expand more rapidly than small aneurysms and thus require closer surveillance. According to the available information, average annual expansion rates are approximately 1 to 4 mm for aortic aneurysms measuring less than 4.0 cm in diameter at the time of their discovery, 4 to 5 mm for those measuring 4.0 to 6.0 cm in diameter, and as much as 7 to 8 mm for larger aneurysms (933,934). An observed rate of expansion that exceeds these figures usually is considered to represent a “growth spurt” that may justify early elective aneurysm repair.

High operative mortality rates alone do not fully reflect the catastrophic nature of ruptured aortic aneurysms. Given the number of patients who do not survive even to reach the operating room, the overall mortality rate for this complication may be as high as 90% (942-944). In a classic report, Szilagyi et al. (945) were among the first to recognize that the risk for spontaneous rupture was a direct function of aneurysm size. Others have since discovered that additional factors also may influence the rupture rate, such as hypertension (946,947), COPD and/or tobacco abuse (946-949), female gender (882,947), and a family history of aortic aneurysms, particularly when a woman with an aortic aneurysm is present in the proband (882). Nevertheless, aneurysm size remains the single most important predictor not only for aneurysm rupture, but also for unrelated death from other cardiopulmonary events (932,950).

Table 47 contains representative data regarding aneurysm rupture rates and long-term patient survival rates according to the baseline diameter of AAAs at the time of their discovery. These data suggest that the eventual risk for rupture is approximately 20% for aneurysms that measure larger than 5.0 cm in diameter, 40% for those measuring at least 6.0 cm in diameter, and higher than 50% for aneurysms that exceed 7.0 cm in diameter. Taylor and Porter interpreted earlier data to indicate that the annual rupture rates for aneurysms of these sizes were in the range of 4%, 7%, and 20%, respectively (938). Conversely, the rupture rate for truly small aneurysms that are less than 4.0 cm in diameter is quite low, perhaps because aged patients with such small aneurysms ordinarily do not survive long enough for this complication to occur. Watson et al. found that more patients with small aneurysms died of other causes than ever required surgical treatment for enlarging aneurysms (951). Bengtsson et al. have recommended only 1 annual follow-up scan for aneurysms less than 3.5 cm in diameter because the unrelated mortality rate in such patients is so high that relatively few live long enough to incur sufficient aneurysm growth to warrant elective surgical treatment (931). Prospective nonrandomized studies have indicated that small aneurysms may be safely monitored by annual or semiannual imaging scans, with a low risk for rupture, provided elective repair is advised once a diameter of at least 5.0 cm has been documented (952,953). Katz et al. concluded from a Markov predictive model that early intervention to repair aneurysms that measure 4.0 cm in diameter could be justified if operative mortality rates were 4.6% or lower, but their estimates were
confounded by the low reported rupture rate for untreated aneurysms of this size (954).

5.2.3.1.1. RANDOMIZED TRIALS. Prospective randomized trials comparing early intervention versus expectant observation for infrarenal AAAs measuring 4.0 to 5.4 cm in diameter have been conducted in the United Kingdom (UK) and by the U.S. Department of Veterans Affairs (VA) during the past decade (947,961-963). By protocol, elective surgical treatment was not offered to patients who were allocated to the nonoperative cohort in each trial until their aneurysms exceeded 5.4 cm in size on serial imaging studies. Selected data from both investigations are summarized in Table 48, with updated information from the UK trial at a mean follow-up interval of 8 years (963) compared with 4.6 years when its findings first were disclosed in 1998. Not surprisingly, the principal demographic difference between the 2 trials is the fact that whereas women composed 17% of patients in the UK study, they represented only 0.8% of the VA population. Thirty-day operative mortality rates (UK 5.4%; VA 2.1%) were competitive with those from other multicenter studies (see Table 49). Endografts were used in 27 patients in the surgical limb of the UK trial (4.8%) but in just 2 patients in the VA trial.

At a mean of 4.9 years of follow-up, early aneurysm repair had produced no significant benefits with respect to the incidence of either aneurysm-related deaths or deaths due to all causes in the VA trial. These are the same conclusions that originally were reached at a mean follow-up of 4.6 years in the UK trial (960). Although the UK surgical cohort now has a lower overall mortality rate than the nonoperative cohort (\( p \) equals 0.03) at a mean follow-up of 8 years, this finding has been attributed in part to a higher rate of smoking cessation in the early-surgery group (963). The annual rupture rate was negligible (0.6%) for observed aneurysms in the VA trial and was 3.2% in the UK trial. Rupture was more likely to occur in women in the UK trial (OR 4.0; 95% CI 2.0 to 7.9; \( p \) less than 0.001), accounting for 14% of all deaths in women compared with 4.6% of all deaths in men \( (p \) less than 0.001). Aneurysm size at the time of randomization did not influence the risk for rupture in the UK trial or the long-term mortality rate in either trial, but this may reflect the promptness with which intervention was performed whenever aneurysms reached a diameter of at least 5.5 cm. More than 60% of the patients in the nonoperative limb of each of these trials currently have undergone aneurysm repair because of documented enlargement, including 81% of the patients whose aneurysms were 5.0 to 5.4 cm in diameter when they were recruited into the VA trial.

Collectively, these 2 randomized trials provide a wealth of information that otherwise has not been available. For instance, the finding that rupture has been significantly more likely to occur among women in the nonoperative cohort of the UK trial adds further perspective to the lingering controversy concerning whether the indications for elective aneurysm repair should be slightly more liberal in women than in men because of the smaller size of the normal aorta in women. On the basis of the data regarding gender differences in the UK trial, a guidelines subcommittee of the American Association for Vascular Surgery and the Society for Vascular Surgery now has recommended that a diameter of 4.5 to 5.0 cm is an appropriate threshold for elective repair

---

Table 46. Annual Rates of Expansion for Abdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Initial Aneurysm Diameter</th>
<th>Mean Annual Expansion, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevitt</td>
<td>(935)</td>
<td>1989</td>
<td>103</td>
<td>3.5 to 5 cm</td>
<td>2.1</td>
</tr>
<tr>
<td>Cronenwett</td>
<td>(936)</td>
<td>1990</td>
<td>73</td>
<td>Smaller than 6 cm</td>
<td>4 to 5</td>
</tr>
<tr>
<td>Bengtsson</td>
<td>(937)</td>
<td>1993</td>
<td>155</td>
<td>Smaller than 4 cm</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than or equal to 4 cm</td>
<td>5.3</td>
</tr>
<tr>
<td>Collective reviews</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor</td>
<td>(938)</td>
<td>1986</td>
<td>—</td>
<td>Larger than or equal to 5 cm</td>
<td>5</td>
</tr>
<tr>
<td>Hollier</td>
<td>(939)</td>
<td>1992</td>
<td>—</td>
<td>3 to 3.9 cm</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 to 5.9 cm</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 6 cm</td>
<td>7.5</td>
</tr>
<tr>
<td>Hallin</td>
<td>(940)</td>
<td>2001</td>
<td>—</td>
<td>Smaller than 4 cm</td>
<td>2 to 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 to 5 cm</td>
<td>3 to 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 5 cm</td>
<td>3 to 7</td>
</tr>
<tr>
<td>Randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veterans Affairs</td>
<td>(941)</td>
<td>2002</td>
<td>—</td>
<td>4 to 5.5 cm</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Collective reviews

- Taylor (938) 1986
- Hollier (939) 1992
- Hallin (940) 2001
- Veterans Affairs (941) 2002

Collective reviews

- Taylor (938) 1986
- Hollier (939) 1992
- Hallin (940) 2001
- Veterans Affairs (941) 2002
Table 47. Rupture and Survival Rates for Patients With Abdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Baseline Aneurysm Diameter</th>
<th>Follow-Up Interval</th>
<th>Aneurysm Rupture Rate (%)</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szilagyi</td>
<td>(945)</td>
<td>1966</td>
<td>82</td>
<td>Less than or equal to 6 cm</td>
<td>Mean 34 mo</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 6 cm</td>
<td>Mean 17 mo</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>Hertzer</td>
<td>(955)</td>
<td>1987</td>
<td>24</td>
<td>Smaller than 6 cm</td>
<td>5 y</td>
<td>20</td>
<td>38 Overall</td>
</tr>
<tr>
<td>Nevitt</td>
<td>(955)</td>
<td>1989</td>
<td>130</td>
<td>At least 6 cm</td>
<td>5 y</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Bengtsson</td>
<td>(937)</td>
<td>1993</td>
<td>155</td>
<td>Median 4 cm</td>
<td>Median 3.4 y</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Perko</td>
<td>(956)</td>
<td>1993</td>
<td>63</td>
<td>Smaller than 6 cm</td>
<td>less than 5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Galland</td>
<td>(957)</td>
<td>1998</td>
<td>267</td>
<td>At least 6 cm</td>
<td>10 to 15</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jones</td>
<td>(958)</td>
<td>1998</td>
<td>25</td>
<td>Smaller than 4 cm</td>
<td>5 y</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 to 5.5 cm</td>
<td>5 y</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>Scott</td>
<td>(953)</td>
<td>1998</td>
<td>32</td>
<td>Smaller than 6 cm</td>
<td>3 y</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At least 6 cm</td>
<td>3 y</td>
<td>41</td>
<td>NA</td>
</tr>
<tr>
<td>Conway</td>
<td>(950)</td>
<td>2001</td>
<td>23</td>
<td>3.5 to 5.9 cm</td>
<td>5 y</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 to 7 cm</td>
<td>10 y</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 7 cm</td>
<td>10 y</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Biancari</td>
<td>(959)</td>
<td>2002</td>
<td>41</td>
<td>2.5 to 4 cm</td>
<td>Median 7.3 y</td>
<td>7.3</td>
<td>59</td>
</tr>
</tbody>
</table>

Collective reviews

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Baseline Aneurysm Diameter</th>
<th>Follow-Up Interval</th>
<th>Aneurysm Rupture Rate (%)</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor</td>
<td>(938)</td>
<td>1986</td>
<td></td>
<td>5 cm</td>
<td>NA</td>
<td>4.1 per year</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.7 cm</td>
<td>NA</td>
<td>6.6 per year</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 cm</td>
<td>NA</td>
<td>19 per year</td>
<td>NA</td>
</tr>
<tr>
<td>Hollier</td>
<td>(939)</td>
<td>1992</td>
<td>349</td>
<td>Smaller than 5 cm</td>
<td>5 y</td>
<td>4.6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 5 cm</td>
<td>5 y</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td>Hallin</td>
<td>(940)</td>
<td>2001</td>
<td>54048</td>
<td>Smaller than 4 cm</td>
<td>4 y</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 4 cm</td>
<td>4 y</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Larger than 5 cm</td>
<td>4 y</td>
<td>22</td>
<td>NA</td>
</tr>
</tbody>
</table>

Randomized trials

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Baseline Aneurysm Diameter</th>
<th>Follow-Up Interval</th>
<th>Aneurysm Rupture Rate (%)</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK Small Aneurysm Trial (nonoperated cohort)</td>
<td>(960)</td>
<td>1998</td>
<td>213</td>
<td>4 to 4.4 cm</td>
<td>Mean 4.6 y</td>
<td>NA</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.5 to 4.8 cm</td>
<td>Mean 4.6 y</td>
<td>NA</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.9 to 5.5 cm</td>
<td>Mean 4.6 y</td>
<td>NA</td>
<td>64%</td>
</tr>
<tr>
<td>UK Small Aneurysm Trial (nonoperated cohort)</td>
<td>(961)</td>
<td>1999</td>
<td>NA</td>
<td>3 to 3.9 cm</td>
<td>7 y</td>
<td>2.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 to 5.5 cm</td>
<td>7 y</td>
<td>4.6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At least 5.6 cm</td>
<td>7 y</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA indicates not available; UK, United Kingdom.
Table 48. Outcomes of Early Elective Repair Versus Nonoperative Surveillance of Asymptomatic Abdominal Aortic Aneurysms*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, n</td>
<td>1090</td>
<td>1136</td>
</tr>
<tr>
<td>Early elective repair, n</td>
<td>563</td>
<td>569</td>
</tr>
<tr>
<td>Open</td>
<td>536</td>
<td>567</td>
</tr>
<tr>
<td>Endovascular</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Nonoperative surveillance, n</td>
<td>527</td>
<td>567</td>
</tr>
<tr>
<td>Men</td>
<td>902</td>
<td>1127</td>
</tr>
<tr>
<td>Women</td>
<td>188</td>
<td>9</td>
</tr>
<tr>
<td>Age 69 plus or minus 4 years</td>
<td>68 plus or minus 6 years</td>
<td></td>
</tr>
<tr>
<td>Operative mortality rate</td>
<td>5.4% (30 days)</td>
<td>2.1% (30 days); 2.7% (in-hospital)</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>Range 6 to 10; mean 8</td>
<td>Range 3.5 to 8.0; mean 4.9</td>
</tr>
<tr>
<td>Survival rate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical cohort</td>
<td>57</td>
<td>75</td>
</tr>
<tr>
<td>Nonoperative cohort</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>(p equals 0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm rupture rate</td>
<td>3.2% annually</td>
<td>0.6% annually</td>
</tr>
<tr>
<td>(nonoperative cohorts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>OR 1.0 (reference set)</td>
<td>NA</td>
</tr>
<tr>
<td>Women</td>
<td>OR 4.0</td>
<td>NA</td>
</tr>
<tr>
<td>95% CI 2.0 to 7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p less than 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eventual aneurysm repair, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical cohort</td>
<td>520 (92)</td>
<td>527 (93)</td>
</tr>
<tr>
<td>Nonoperative cohort</td>
<td>327 (62)</td>
<td>349 (62)</td>
</tr>
<tr>
<td>Influence of aneurysm diameter (nonoperative cohorts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0 to 4.4 cm: 57%</td>
<td>4.0 to 4.4 cm: 79%</td>
<td></td>
</tr>
<tr>
<td>4.5 to 4.8 cm: 54%</td>
<td>4.5 to 4.9 cm: 78%</td>
<td></td>
</tr>
<tr>
<td>4.9 to 5.5 cm: 43%</td>
<td>5.0 to 5.4 cm: 68%</td>
<td></td>
</tr>
<tr>
<td>Eventual repair rate</td>
<td>NA</td>
<td>4.0 to 4.4 cm: 27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 to 4.9 cm: 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0 to 5.4 cm: 81%</td>
</tr>
</tbody>
</table>

NA indicates not available.
*Results of 2 prospective randomized trials conducted in the United Kingdom (960, 963) and by the United States Department of Veterans Affairs (941).
<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic intact: 329</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 860</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Hertzer</td>
<td>(955)</td>
<td>1987 (1978-1982)</td>
<td>246</td>
<td>4.4</td>
</tr>
<tr>
<td>Reigel</td>
<td>(1063)</td>
<td>1987</td>
<td>499</td>
<td>2.8</td>
</tr>
<tr>
<td>Golden</td>
<td>(1065)</td>
<td>1990</td>
<td>500</td>
<td>1.6</td>
</tr>
<tr>
<td>Sicard</td>
<td>(1071)</td>
<td>1995</td>
<td>145</td>
<td>1.4</td>
</tr>
<tr>
<td>Lloyd</td>
<td>(1079)</td>
<td>1996 (1980-1995)</td>
<td>1000</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women: 92</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 582</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Aune</td>
<td>(1058)</td>
<td>2001 (1985-1999)</td>
<td>Age less than 66 y: 118</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 66 y and older: 333</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 451</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Menard</td>
<td>(1080)</td>
<td>2003 (1990-2000)</td>
<td>Low risk: 444</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk: 128</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 572</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Small Aneurysm Trial (surgical cohort)</td>
<td>(960)</td>
<td>1998</td>
<td>563</td>
<td>5.8</td>
</tr>
<tr>
<td>Lederle (U.S. Veterans Affairs Small Aneurysm Trial; surgical cohort)</td>
<td>(941)</td>
<td>2002</td>
<td>569</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Collective reviews</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ernst</td>
<td>(1081)</td>
<td>1993 (1981-1992)</td>
<td>6488</td>
<td>4.0</td>
</tr>
<tr>
<td>Zarins</td>
<td>(973)</td>
<td>1997 (1987-1992)</td>
<td>2162</td>
<td>2.1</td>
</tr>
<tr>
<td>Blankensteijn</td>
<td>(1074)</td>
<td>1998 (1985-1997)</td>
<td>2162</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective population: 692</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective hospital: 1677</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective population: 21 409</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective hospital: 12 019</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subset analyses: 1857</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td><strong>Regional or multicentered studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston (Canadian Aneurysm Group)</td>
<td>(1082)</td>
<td>1988</td>
<td>Elective: 541</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic intact: 125</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 666</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Richardson (Kentucky Medicare)</td>
<td>(1083)</td>
<td>1991</td>
<td>136</td>
<td>5.9</td>
</tr>
<tr>
<td>Johnston (Canadian Aneurysm Group)</td>
<td>(1085)</td>
<td>1994</td>
<td>Men: 545</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women: 134</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 679</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Kantonen (Finland Vascular Registry)</td>
<td>(1089)</td>
<td>1997</td>
<td>929</td>
<td>5.1</td>
</tr>
<tr>
<td>Koskas (French AURC Vascular Registry)</td>
<td>(1057)</td>
<td>1997</td>
<td>1107</td>
<td>4.8</td>
</tr>
<tr>
<td>Manheim (California statewide)</td>
<td>(1091)</td>
<td>1998 (1982-1994)</td>
<td>35 130</td>
<td>7.6</td>
</tr>
<tr>
<td>Dardik (Maryland statewide)</td>
<td>(1092)</td>
<td>1999 (1990-1995)</td>
<td>2335</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>U.S. hospital databases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawrence (National Hospital Discharge Survey)</td>
<td>(1075)</td>
<td>1999 (1994)</td>
<td>32 387</td>
<td>8.4</td>
</tr>
<tr>
<td>Heller (National Hospital Discharge Survey)</td>
<td>(1076)</td>
<td>2000 (1979-1997)</td>
<td>358 521</td>
<td>5.6</td>
</tr>
<tr>
<td>Huber (Nationwide Inpatient Sample)</td>
<td>(1096)</td>
<td>2001 (1994-1996)</td>
<td>16 450</td>
<td>4.2</td>
</tr>
<tr>
<td>Dimick (Nationwide Inpatient Sample)</td>
<td>(1078)</td>
<td>2002 (1996-1997)</td>
<td>13 887</td>
<td>3.8</td>
</tr>
</tbody>
</table>

AURC indicates Association for Academic Research in Vascular Surgery; UK, United Kingdom.
5.2.4.1. Symptomatic Aortic or Iliac Aneurysms

Popliteal aneurysms also have signs of venous insufficiency commonly, approximately 20% of patients who have large iliac aneurysms are situated deep in the pelvis. Approximately one third to one half of common iliac aneurysms are bilateral, and 50% to 85% are asymptomatic at the time of their discovery (965,966). According to a collective review of 3 clinical series, aneurysm rupture usually occurs at a diameter of 5.0 cm or larger, whereas common iliac aneurysms that are less than 3.0 cm in diameter almost never rupture (966). Therefore, isolated common iliac aneurysms that are smaller than 3.0 cm probably can be monitored safely with serial noninvasive imaging. Contrast-enhanced computed tomographic scans or magnetic resonance imaging studies appear to be better suited for this purpose than ultrasonography because many common iliac aneurysms are situated deep in the pelvis.

5.2.3.3. Local Compression or Erosion

Exceptionally large or inflammatory aortic aneurysms occasionally can be associated with early satiety or gastric outlet symptoms on the basis of duodenal compression. More catastrophically and just as infrequently, an aortic aneurysm may cause either sudden upper gastrointestinal bleeding on the basis of a primary aortoenteric fistula or acute congestive heart failure on the basis of an aortocaval fistula. Far more commonly, approximately 20% of patients who have large popliteal aneurysms also have signs of venous insufficiency in the lower leg on the basis of compression of the adjacent popliteal veins (967,968).

5.2.4. Diagnosis

5.2.4.1. Symptomatic Aortic or Iliac Aneurysms

RECOMMENDATIONS

Class I

1. In patients with the clinical triad of abdominal and/or back pain, a pulsatile abdominal mass, and hypotension, immediate surgical evaluation is indicated. (Level of Evidence: B)

2. In patients with symptomatic aortic aneurysms, repair is indicated regardless of diameter. (Level of Evidence: C)

Most AAAs are asymptomatic and are discovered incidentally on routine physical examination or on an abdominal roentgenogram (969) or an ultrasound scan that has been performed for other indications. Younger patients are more likely to be symptomatic at the time of diagnosis (970). Pain is the most frequent complaint in patients with symptomatic AAAs and usually is located in the hypogastrum or the lower part of the back. Pain is typically steady, lasting for hours to days at a time, and has a gnawing quality. In contrast to musculoskeletal back pain, aneurysm pain is not affected by movement, although patients may be more comfortable in certain positions, such as with the knees flexed. Expansion and impending rupture are heralded by the development of new or worsening pain, characteristically constant, severe, and located in the back or lower part of the abdomen, sometimes with radiation into the groin, buttocks, or legs. Rupture is associated with abrupt onset of back pain, abdominal pain, and tenderness. Unless they are hypotensive because of blood loss, many patients with ruptured aneurysms have a palpable, pulsatile abdominal mass. It must be remembered, however, that the pathognomonic triad of abdominal/back pain, pulsatile abdominal mass, and hypotension occurs in only about one third of cases (971). The symptoms of a ruptured aneurysm may mimic those of renal colic, diverticulitis, or a gastrointestinal hemorrhage, thus leading to a misdiagnosis that can cost valuable time.

Hemorrhagic shock may ensue rapidly and is manifested by hypotension, vasocnstriction, mottled skin, diaphoresis, mental obtundation, and oliguria. and terminally, by arrhythmias and cardiac arrest. In a few patients who survive with contained ruptures, the retroperitoneal hematoma may be accompanied by ecchymosis in the flanks (Grey-Turner sign) and groin. Free rupture into the peritoneal cavity produces obvious abdominal distention and often is rapidly fatal, whereas rupture into the duodenum is manifested by massive gastrointestinal hemorrhage.

5.2.4.2. Asymptomatic Aortic or Iliac Aneurysms

Patients with even small AAAs have a high prevalence of risk factors for and clinical manifestations of atherosclerotic cardiovascular disease. A longitudinal cohort study involving 4734 men and women older than 65 years of age in 4 US communities correlated abdominal aortic diameter by ultrasonography with incidental cardiovascular disease, mortality, and repair or rupture during a mean follow-up period of 4.5 years (972). The prevalence of aneurysms was 8.8%, of which 88% were at least 3.5 cm in size. The rates of total mortality (65 vs. 33 per 1000 person-years), cardiovascular mortality (34 vs. 14 per 1000 person-years), and incidental cardiovascular disease (47 vs. 31 per 1000 person-years) were higher in participants who had aneurysms than in those who did not. After adjustment for age, risk factors, and the presence of other cardiovascular disease, the respective relative risks were 1.32, 1.36, and 1.57, respec-
tively. In comparison, the rates of repair and rupture were low in this series.

Elective surgical repair improves the survival rate for patients with large aneurysms (945), and approximately 50,000 operations are performed annually for this condition in the United States, with operative mortality rates that are reported to be as low as 2% in some centers (973). Even before the results of randomized trials were available, however, it generally was accepted that watchful waiting with serial imaging was a better long-term treatment strategy than early surgical repair for aneurysms less than 5.0 cm in diameter (939). Up to 13% of patients with aortic aneurysms have multiple aneurysms elsewhere (974), and 25% to 28% of those with thoracic aortic aneurysms have concomitant AAAs (975,976). Accordingly, patients in whom an aortic aneurysm is discovered at either level should undergo an appropriate examination of the entire aorta to detect aneurysms in other locations.

5.2.4.3. Physical Examination

A comprehensive physical examination should include palpation of the abdomen and the lower extremity arteries in an attempt to detect widened pulses that suggest the presence of aneurysms. Palpation of AAAs is safe and has not been reported to precipitate rupture. Perhaps the best evidence regarding the accuracy of abdominal palpation comes from 15 studies of patients who were not previously known to have AAAs but were screened with both an abdominal examination and ultrasound scans (977). The pooled sensitivity of abdominal palpation increased significantly with aortic diameter (p less than 0.001), ranging from 29% for AAAs of 3.0 to 3.9 cm to 50% for AAAs of 4.0 to 4.9 cm and 76% for AAAs measuring 5.0 cm or more by ultrasonography. The positive and negative likelihood ratios were 12.0 (95% CI 7.4 to 19.5) and 0.72 (95% CI 0.65 to 0.81), respectively, for AAAs that were 3.0 cm or larger and 15.6 (95% CI 8.6 to 28.5) and 0.51 (95% CI 0.38 to 0.67) for AAAs that were larger than 4.0 cm. The positive predictive value of palpation was 43% for AAAs that were documented to be at least 3.0 cm in diameter. Intuition and limited data suggest that abdominal obesity reduces the sensitivity of palpation. In summary, careful abdominal palpation is moderately sensitive for the detection of AAAs that are large enough to be referred for surgical intervention, but the physical examination alone may not be sufficiently reliable for the detection of smaller AAAs, especially if rupture already is suspected.

In a 3-year retrospective study of 198 patients with AAAs that was conducted by Alcorn et al. (860) in a general hospital setting, 48% of the aneurysms had been discovered clinically, 37% represented incidental findings during radiographic investigation of another condition, and 15% were encountered during unrelated abdominal operations. Of those that initially were detected by radiography, 38% were palpable on subsequent physical examination. The average size of the AAAs that were discovered clinically (6.5 plus or minus 1.3 cm) was larger than those that were found by radiography (5.47 plus or minus 1.4 cm, p less than 0.001) or at operation (5.4 plus or minus 1.5 cm, p equals 0.039). Not surprisingly, the average size of palpable AAAs was larger than that of nonpalpable AAAs (6.4 plus or minus 1.2 cm vs. 4.9 plus or minus 1.4 cm, p less than 0.001).

5.2.4.4. Incidental Radiological Findings

5.2.4.4.1. Plain Films. It is not the current standard of care to use plain radiographic studies for follow-up surveillance of AAAs, but 15% to as many as 85% of these aneurysms initially are discovered because of curvilinear aortic wall calcification that represents an incidental finding on a plain abdominal film that was obtained for other purposes. The plain film also may demonstrate a soft tissue mass with obliteration of the psoas margin and/or disruption of mural calcification with extension into a periaortic soft tissue mass, occasionally suggesting that the aneurysm has ruptured. In addition, smaller calcified rings sometimes suggest the presence of visceral artery aneurysms (978-981).

5.2.4.4.2. Ultrasound and Other Scans. Asymptomatic AAAs also may be discovered incidentally on ultrasound, computed tomography, and nuclear scans that have been performed for unrelated indications; conversely, computed tomography or ultrasound may demonstrate incidental nonvascular lesions during AAA evaluation, notably malignancy (982-991). The existence of incidental findings is not surprising given the advanced age of many patients undergoing imaging studies. Phillips and King reported that 3.1% of male urologic patients (65 to 80 years of age) undergoing urinary tract ultrasonography were documented to have unsuspected aortic aneurysms; with deliberate augmentation of the scan to include the aorta (i.e., opportunistic screening), the incidence rose to 9.1%, a figure that appeared to exceed random discovery rates (985). Akkersdijk et al. found that incidental aneurysms with a diameter of at least 3.0 cm, or 1.5 times the diameter of the proximal aorta, were present in 4.9% of 1687 patients older than 50 years who underwent some form of abdominal ultrasonography, comprising 8.8% of men, 2.1% of women, and 11% of men over 60 years of age (988). Because the symptoms of expanding aneurysms can mimic urologic symptoms, additional scanning to include the aorta may be especially prudent in some specific clinical situations (991).

5.2.4.4.3. Opportunistic Screening. In the paradigm of “opportunistic” screening, abdominal ultrasound studies that primarily have been performed to obtain information regarding disease states other than aortic aneurysms (e.g., a urologic evaluation) are extended to include an examination of the nearby abdominal aorta (985,988,992-994). Studies in this area of interest have reported the prevalence of incidental aortic aneurysms to range from 6.5% to 12%, but these studies have not been rigorously controlled for age or other high-risk factors, such as tobacco use or a family history of aneurysms. Some believe that unlike a dedicated screening
program, opportunistic screening can be done at little additional cost because most of the expense of the aortic imaging is borne by the baseline ultrasound scan. However, Wolf et al. noted that the addition of an aortic ultrasound scan to other unrelated studies in the vascular laboratory prolongs each examination by 5 minutes per patient and requires 83 minutes of scanning time for each aortic aneurysm that is detected (36 minutes per male smoker), at a cost of $240 to $553 per patient (994). In fact, this happens to be in the cost range of conventional population-based ultrasound screening (873). Furthermore, at least 1 investigation has indicated that opportunistic screening successfully demonstrates the aorta in only 89% of patients (less than the expected rate for most dedicated screening programs), perhaps because of inadequate patient preparation or operator skill (994). Therefore, because the ultrasound scan represents only a small fraction of the total expense that is associated with the detection and treatment of aortic aneurysms, the cost savings of opportunistic screening may be quite small in the general population in which the prevalence of such aneurysms is low.

There are multiple strategies for utilizing ultrasonography in a screening program for AAAs. Together with the data that already are available with respect to the prevalence rate of these aneurysms in various populations, the publication of 2 large randomized trials regarding aneurysm size and its influence on surgical indications may encourage computer modeling to determine the benefit, risks, and cost-effectiveness of ultrasound screening in targeted patient populations (947,961-963). This kind of information might also influence the decisions to be made by third-party payers.

5.2.4.4. Unlimited Arteriography. Catheter-based arteriography is not used as a primary diagnostic modality for aortic aneurysms, especially since mural thrombus makes it impossible to determine the true size of the aneurysm with the diameter of the contrast column. Arteriography instead is reserved to answer specific anatomic questions before endovascular management or, increasingly less frequently, before open AAA repair. However, several incidental findings during unrelated arteriographic studies may suggest the presence of an AAA, such as mural calcification, slow and/or turbulent flow, a widened interior lumen that is paradoxically smooth because of laminated thrombus and occlusions of its branch vessels (e.g., the inferior mesenteric and lumbar arteries), “draping” of the superior mesenteric artery over the contour of the aneurysm, and a thickened aortic wall or soft tissue mass (995).

5.2.4.5. Diagnostic Imaging

5.2.4.5.1. Ultrasonography. B-mode or real-time ultrasound is excellent for imaging many aortic aneurysms because it has no risk to the patient and is less expensive than computed tomographic scanning (996-999). Its accuracy for measuring the aortic diameter below the level of the renal arteries approaches that of direct intraoperative measurements (997-999). In comparison, the accuracy of duplex ultrasound can be operator-dependent, and therefore, its results may vary between or even within centers, especially with small AAAs (1000,1001). This variability can be decreased with appropriate quality control and credentialing, but duplex scanning is more frequently used to evaluate the femoral or popliteal arteries to distinguish aneurysms from other vascular and nonvascular masses in these particular anatomic areas (1002-1008).

Infrarenal Aortic Aneurysms. Ultrasound scanning has been used in large screening and surveillance programs for both the initial assessment and subsequent follow-up of small aneurysms that are not repaired immediately. Multiple studies have suggested that ultrasound is an appropriate means to determine the presence or absence of an infrarenal aortic aneurysm in more than 95% of candidates (870,1009,1010). The maximum anteroposterior aortic diameter usually is determined after overnight fasting to aid visualization (859,1009). Ultrasonography should be performed in the plane perpendicular to the arterial axis, because oblique measurements tend to overestimate the true size of the aorta (863) and represent one source for potential variability.

Diagnostic specificity for the presence of an aneurysm is nearly 100% (859,873,1011), with sensitivity ranging from 92% to 99% (859,873,1011). The reproducibility and intraobserver variability of ultrasound measurements are quite satisfactory and are similar to those for computed tomographic scanning (961,1011,1012), although intraobserver correlation appears to be better near the aortic bifurcation than in the proximal infrarenal aorta (1011). Thus, ultrasonography is an excellent tool for screening and surveillance, both for individual patients and for screening programs. Modalities such as computed tomographic or MRA scanning usually are reserved for anatomic mapping before aneurysm repair because they are more expensive than ultrasound scanning and have some risk related to contrast and radiation.

Suprarenal Aortic and Iliac Aneurysms. Despite its utility in establishing the size of infrarenal aortic aneurysms, ultrasonography usually does not provide dependable imaging of aneurysms that extend close to the origins of the renal arteries or into the suprarenal segment of the abdominal aorta (969,996,998,1013-1015). In one prospective study, the upper and lower limits of AAAs were accurately demonstrated by ultrasound in only 47% and 41% of cases, respectively (1015). In another prospective study of 79 patients with AAAs, ultrasound reliably determined the length of the infrarenal aortic “neck” in only 20% of inflammatory aneurysms and 28% of noninflammatory aneurysms. Furthermore, standard B-mode ultrasound is suboptimal for imaging the common and internal iliac artery segments in the context of aneurysm disease, and duplex scanning is able to detect iliac artery involvement only about 50% of the time. A spiral computed tomographic scan of the abdomen and pelvis with 3D reconstruction in special instances is superior to ultrasonography for this purpose (1016).
5.2.4.5.2. Contrast-Enhanced Spiral Computed Tomographic Scanning. For many years, transcatheter arteriography, including intra-arterial digital subtraction arteriography, was the “gold standard” for the preoperative assessment of AAAs. Early studies reported a high radiation dose and contrast load with computed tomography compared with digital subtraction arteriography (1017), but computed tomography provided additional information about adjacent veins and soft tissue and eventually supplanted digital subtraction arteriography as the preoperative study of choice. Because of improved techniques, their relatively noninvasive nature, and their cost advantage over transcatheter angiography, CTA and MRA have emerged as current “gold standards” in the preoperative and postoperative evaluation of AAAs (1018). In comparison, arteriography may be warranted to optimally define collateral or variant artery anatomy, such as the arterial supply to a horseshoe kidney, or the location and severity of occlusive disease or associated aneurysms in the visceral, renal, iliac, or peripheral arteries (997,1019). The decision to use either CTA or MRA is often locale-specific. Operator proficiency and the availability of suitable equipment and protocols may determine which modality is preferred.

Preoperative Aortic Aneurysm Assessment. The preoperative assessment of AAAs before open or endovascular repair includes defining the maximum transverse diameter and the relation of the aneurysm to the renal arteries. The length of normal-caliber aorta below the renal arteries before the aneurysm is commonly referred to as the infrarenal neck of the aneurysm. The length of this segment of normal caliber aorta as well as its diameter and angulation are particularly important when endovascular aneurysm repair is contemplated. In addition, preoperative imaging should demonstrate iliac or hypogastric aneurysms, serious occlusive disease in the iliac or renal arteries, the presence of vascular abnormalities (e.g., accessory renal arteries, duplicate vena cavae, or a retro-aortic left renal vein), or nonvascular soft tissue anomalies, such as horseshoe kidney (1020,1021). If endovascular AAA repair is under consideration, it is even more important to obtain precise measurements regarding the diameter and length of the proximal neck and the tortuosity of the aorta and the iliac arteries. Contrast-enhanced computed tomographic scanning provides baseline information in all of these areas. In select cases, contrast arteriography may be necessary in defining complicated arterial anatomy before endovascular aneurysm repair.

For accurate imaging of the length and diameter of the infrarenal AAA neck, narrow collimation (i.e., 3 mm or less) should be used (997,1021-1023). Because narrow collimation limits the aortic length that can be scanned and slows reconstruction time, typical computed tomography protocols call for narrow collimation around the renal arteries to define the superior extent of the aneurysm, combined with 10-mm collimation for the rest of the abdomen and pelvis (997). New multidetector computed tomography instrumentation promises to improve accuracy by being able to acquire more images in a faster time, with a single breath hold and less contrast medium (239). Recent helical computed tomographic techniques and protocols with 3D reconstruction displays should position computed tomography as a possible sole imaging modality for either open or endovascular AAA repair in the future (1024).

5.2.4.5.3. Magnetic Resonance Scanning. The presence of heavy mural calcification is sometimes important, because it may alter the planned repair. Computed tomography can accurately demonstrate vascular calcification, but it requires ionizing radiation and relatively large volumes of iodinated contrast. The presence of mural calcification can preclude successful computed tomographic evaluation of the peripheral arteries, so either adjunct arteriography or MRA may be needed. Magnetic resonance angiography presently has the disadvantage of being a slower scanning procedure than computed tomography and usually is not appropriate for use in patients who are claustrophobic or have metal implants. However, the coronal acquisition mode of current magnetic resonance techniques may expand its applications in the future.

Early MRA protocols depended on 3D time-of-flight imaging, which has a high signal-to-noise ratio but requires multiple slices and long imaging time because of in-plane flow saturation. Time-of-flight imaging is performed perpendicular to flow. The development of breath-held dynamic contrast-enhanced MRA has broadened the applicability of magnetic resonance by allowing rapid acquisition of images in any plane independent of flow (1025-1028). By imaging on the first pass during a breath hold, vascular signals can be obtained before leakage of contrast into the surrounding soft tissues, yielding an angiogram with high signal-to-noise ratio and enhanced detail. Images can be synchronized or subtracted for further enhancement (1028,1029). Similar protocols can be used to enhance contrast between the vessels and the background fatty tissue and have proven to be better than 3D time of flight for imaging the aortic branch vessels and the iliac arteries (1030).

In an early, blinded comparison of MRA versus conventional arteriography before elective aortic aneurysm repair, MRA was thought to be superior for defining the proximal extent of the AAA and for depicting venous anatomy, intraluminal thrombus, and coexistent iliac aneurysms (998). Subsequent improvement in magnetic resonance technique has yielded more accurate imaging of the renal arteries (209,981), a feature that eventually may make MRA as useful as spiral computed tomographic scanning for preoperative assessment before endovascular AAA repair (1012,1025,1031). In conclusion, the rapid development of both CTA and MRA makes their respective use for preoperative AAA assessment in large part dependent on local experience and the availability of the latest scanner. There presently is no consensus to indicate the superiority of either technique.
5.2.4.6. Screening High-Risk Populations

RECOMMENDATIONS

Class I

Men 60 years of age or older who are either the siblings or offspring of patients with AAAs should undergo physical examination and ultrasound screening for detection of aortic aneurysms. (Level of Evidence: B)

Class IIa

Men who are 65 to 75 years of age who have ever smoked should undergo a physical examination and 1-time ultrasound screening for detection of AAAs. (Level of Evidence: B)

Aortic diameter can be measured accurately by ultrasound imaging in more than 97% of subjects (1032,1033). Screening by this method has the potential to reduce the incidence of aortic rupture and has increasingly become the focus of population-based screening programs that have examined the efficacy of targeted AAA detection strategies. The effectiveness of ultrasound screening studies has been evaluated in several countries, with specific targeting of high-risk groups, such as those with hypertension, coronary disease, or tobacco use. A study of screening for AAAs in 3000 of 6058 males aged 64 to 81 years was underpowered to demonstrate a reduction in mortality through selective rescreening or surgical intervention for AAAs (1034). In a cohort of 52 745 military veterans aged 50 to 79 years who had no history of aneurysms, AAAs measuring 4.0 cm or larger in diameter were detected by ultrasound screening in 613 participants (1.2%). When this cohort was combined with a similar cohort of 73 451 veterans in the same age range, the ORs for major risk factors were as follows: 1.71 per 7 years of age, 0.18 for female gender, 0.53 for black race, 1.94 for family history of AAA, 5.07 for smoking, 0.52 for diabetes, and 1.66 for atherosclerotic diseases. The excess prevalence associated with smoking accounted for 75% of all AAAs 4.0 cm or larger in the combined population of 126 196 veterans. The risk factor associations for smaller AAAs (3.0 to 3.9 cm) were similar but less robust (870). According to one estimate, if the risk for AAA were based on age alone, it would be necessary to examine over half of the elderly male population to obtain 80% of the total potential benefit among men. If age and smoking were included, the proportion needed to screen would fall to 35%. Even if other risk factors, such as coronary disease or hyperlipidemia, were included, it still would be necessary to screen 15% to 20% of the population, and the cost would be prohibitive (1035).

In another population-based study, 67 800 men aged 65 to 74 years were randomly allocated to receive an invitation for an abdominal ultrasound scan (1036). Men in whom aortic aneurysms at least 3.0 cm in diameter were detected underwent repeat scans for a mean of 4.1 years. Surgical treatment was considered when the diameter reached 5.5 cm, if expansion occurred at a rate of more than 1 cm per year, or if symptoms occurred. More than 27 000 (80%) of the 33 839 men in the invited group agreed to screening, and 1333 aneurysms were detected. There were 65 aneurysm-related deaths (absolute risk 0.19%) in the invited group and 113 (0.33%) in the control group (risk reduction 42%; 95% CI 22% to 58%; p equals 0.0002), including a 53% reduction of risk (95% CI 30% to 64%) among those who actually underwent screening. The 30-day mortality rate was 6% (24 of 414) after elective aneurysm repair compared with 37% (30 of 81) after emergency operations. During the 4 years in which this trial was conducted, there were 47 fewer deaths related to AAAs in the screening group than in the control group, but the additional costs incurred were 2.2 million British pounds (approximately 3.5 million US dollars). After an adjustment for censoring and a discount of 6%, the mean additional cost of screening was 63£ or $98 (95% CI 53.31£ to 73£ or $84 to $116) per patient. The hazard ratio for AAA was 0.58 (95% CI 0.42 to 0.78). Over 4 years, the mean incremental cost-effectiveness ratio for screening was 28 400£ or $45 000 per life-year gained, a figure that is equivalent to approximately 36 000£ or $57 000 per quality-adjusted life-year. After 10 years, this figure was estimated to decline to approximately 8000£ or $12 500 per life-year gained (1037).

These values of cost-effectiveness for AAA screening are at the margin of acceptability according to most current health services thresholds. Over a longer period, however, cost-effectiveness is expected to improve substantially, decreasing to about one fourth of the 4-year figure at 10 years. How to set policy in relation to these values depends on national and regional health standards. A Canadian cohort analysis that used a multiprovince life-table model determined that the most cost-effective rate at which latent AAAs should be detected is 20% per year, which corresponds to a screening interval of 5 years by abdominal ultrasonography for patients over 50 years of age (1038), but the aortic dimensions at which intervention was recommended were larger than those that recently have been used in influential randomized trials (962,963). In Finland, 74% (238 of 322) of first-degree relatives of 150 consecutive AAA patients were screened at a central university hospital to evaluate the effectiveness and costs of treatment (1039). Outcomes were assessed with the national discharge registry and from survival analysis of AAA patients who underwent elective or emergency surgery. The incremental effectiveness in life-years gained by the screening of male siblings was 92 years, with an incremental cost-effectiveness ratio of 33 000 Finnish marks or $6200. Given these data, screening of male siblings of AAA patients was recommended because it appeared to be associated with improved survival at low cost.

Selected screening of populations with a high prevalence of AAA (e.g., males 60 years or older who have a family history of AAA, in whom the prevalence is approximately 18%, or men who smoke) and the use of a limited ultrasound scan are more cost-effective than conventional abdominal imaging of unselected populations. In a small pilot study, the average time required to perform a limited screening scan was...
one sixth that of a conventional study (4 vs. 24 minutes), with comparable accuracy for the diagnosis of AAA alone (1040). Reducing the cost of screening tests from $259, which represents the approximate Medicare reimbursement for conventional abdominal ultrasound imaging, to $40 for the limited scan would improve cost-effectiveness.

A meta-analysis of the currently published international data that might support the use of screening programs to detect AAA has been completed recently and was summarized by the United States Preventive Services Task Force (USPSTF). This summary provides a concise focus on the potential benefit and harm that might be associated with such targeted AAA screening programs, balancing detection efficacy, interventional risk reduction, and cost-effectiveness (1041). A version prepared for the Agency for Healthcare Research and Quality in February 2005 is available online at www.ahrq.gov/clinic/serfiles.htm. The USPSTF meta-analysis supports the concept that screening for AAA and surgical repair of large AAAs (5.5 cm or more) in men aged 65 to 75 years who have ever smoked (inclusive of both current and former smokers) leads to decreased AAA-specific mortality when abdominal ultrasonography is performed in a setting with adequate quality assurance (i.e., in an accredited facility with credentialed technologists). It is notable that the data do not support the application of AAA screening for men who have never smoked or for women. The USPSTF analysis balanced the efficacy of AAA detection and potential diminution of AAA-associated death by surgical repair with the potential psychological harm and increased morbidity and mortality of AAA surgery performed in low risk populations.

There are important caveats to be applied to any screening recommendations. These include the need for the screening intervention to be performed in individuals whose life expectancy is adequately long for benefit to accrue (thus, decreasing benefit is gained in more elderly populations with ages greater than 75 years) and that the use of endovascular repair (vs. open surgical) aortic repair is likely no more beneficial in the long-term risk-benefit calculation, because there are inadequate data to demonstrate that use of endovascular techniques would be associated with any greater benefit than with operative repair. Finally, AAA screening has not been proven to be linked to an improvement in all-cause mortality, even when AAA-associated death is diminished. These limitations may have significant impact on the willingness of screening candidates to participate in this screening pathway. Finally, the USPSTF analysis suggested that screening performed as per the Multicentre Aneurysm Screening Study (MASS) would be associated with a cost-effectiveness ratio for population-based AAA screening (compared with no screening) in the range of $14 000 to $20 000 per quality-adjusted life-year. Although this estimate is promising, additional data are required to confirm that these estimates are accurate over longer periods of time in actual (vs. clinical trial) practice (1042).

### 5.2.5. Observational Management

#### 5.2.5.1. Blood Pressure Control and Beta-Blockade

**RECOMMENDATIONS**

**Class I**

Perioperative administration of beta-adrenergic blocking agents, in the absence of contraindications, is indicated to reduce the risk of adverse cardiac events and mortality in patients with coronary artery disease undergoing surgical repair of atherosclerotic aortic aneurysms. *(Level of Evidence: A)*

**Class IIb**

Beta-adrenergic blocking agents may be considered to reduce the rate of aneurysm expansion in patients with aortic aneurysms. *(Level of Evidence: B)*

Preclinical models of aneurysm progression have suggested that beta-adrenergic antagonist agents may reduce the risk of aneurysm development and expansion. Brophy et al. (1043) demonstrated that propranolol delays the development of aneurysms in a mouse model that is prone to spontaneous aortic aneurysms. In that model, drug efficacy appeared to be independent of reductions in blood pressure or diminution of the force of left ventricular ejection (dp/dt) and may have resulted from actions on the connective tissue structure of the aortic wall. In another animal model in which AAAs were induced both in normotensive and in genetically hypertensive rats by perfusion of the isolated infrarenal aorta with elastase for 2 hours, the aneurysms were significantly larger in hypertensive rats, with a mean expansion rate (mm per day) that was nearly twice that of normotensive animals (1044). In comparison, the aneurysms in the study by Brophy et al. were significantly smaller in hypertensive propranolol-treated rats than in placebo-treated controls (p less than 0.05).

Retrospective clinical studies have suggested that beta-adrenergic antagonist agents might reduce the risk of aneurysm expansion and rupture (1045), but these data have been inconsistent. In one small retrospective analysis, the mean aneurysm growth rate was 0.17 cm per year in treated patients versus 0.44 cm per year in untreated patients (1046). Eight percent of the patients in the beta-blockade group exhibited a growth rate that exceeded the mean for the overall study population, compared with 53% of the patients who received no treatment. The mean rate of aneurysm expansion was slower in treated patients, a difference that was most pronounced in those with large aneurysms. Lindholdt et al. reported another study of 54 patients who had small AAAs who were randomized to receive 40 mg of propranolol twice daily or placebo and were followed up for 2 years (1047). Sixty percent of the subjects in the propranolol group and 25% of those in the placebo group ultimately withdrew from this trial, with many subjects in the propranolol group reporting problems with dyspnea. Reductions in pulmonary function, ABI, and quality of life were also observed in the pro-
pranolol group compared with 4.2% in the placebo group (risk reduction 1.6; 95% CI 1.02 to 2.51). However, the relative risk of aneurysm expansion at an annual rate of more than 2 mm in the placebo group was 1.17 (95% CI 0.74 to 1.85) by intention-to-treat analysis and 2.44 (95% CI 0.88 to 6.77) according to on-treatment analysis. Only 22% of the treated patients continued to take propranolol for the full 2 years. In another trial, asymptomatic patients with AAAs measuring 3.0 to 5.0 cm in diameter were randomized in a double-blind fashion to receive either propranolol (n equals 276) or placebo (n equals 272) and then observed for a mean of 2.5 years (601). Forty-two percent of the patients in the propranolol group discontinued their medication compared with 27% of those in the placebo group (p equals 0.0002). The annual aneurysm growth rate was similar for the propranolol (0.22 cm per year) and placebo (0.26 cm per year, p equals 0.11) groups. There was a slight trend towards more elective surgical intervention in the placebo group (27% vs. 20%, p equals 0.11), but there was no difference in mortality rates (propranolol 12%, placebo 9%; p equals 0.36). Patients in the propranolol group had significantly poorer quality-of-life scores. Finally, one prospective randomized trial found that the expansion rate of AAAs was not attenuated by use of beta-adrenergic blockers (601).

Long-term prophylactic beta-blockade appears to be effective in slowing the rate of aortic dilation and decreasing the incidence of aortic complications in some patients with Marfan syndrome by reducing the heart rate and the impulse (i.e., the rate of pressure change in the aortic root) of left ventricular ejection. An open-label, randomized trial of propranolol (mean dose 212 plus or minus 68 mg daily) in adolescent and adult patients with classic Marfan syndrome determined that the rate of aortic root dilation was significantly lower in the treatment group than in the control group (0.023 vs. 0.084 cm per year, p less than 0.001) (1048). Clinical end points were reached in 5 patients in the treatment group and 9 in the control group. The Kaplan-Meier survival curve for the treatment group differed significantly from that for the control group during the middle years of the trial and remained better for the treatment group throughout the study. It is not clear whether these observations apply to aneurysms in the abdominal aorta, because patients with Marfan syndrome develop aneurysms less commonly in this location than in the thoracic aorta.

Aside from their effects on aneurysm size, the perioperative administration of beta-blockers may reduce the risk of adverse cardiac events and death in patients with cardiac risk factors who undergo AAA repair and other noncardiac vascular surgery (1049-1051).

5.2.5.2. Follow-Up Surveillance

A number of prospective nonrandomized studies that were reported before the disclosures from the UK Small Aneurysm Trial and the VA Aneurysm Detection and Management (ADAM) Trial suggested annual ultrasound surveillance for aneurysms measuring less than 4.0 cm in diameter and ultrasound scans every 6 months for those 4.0 to 4.9 cm in diameter, with a recommendation for elective aneurysm repair in appropriate surgical candidates whenever an AAA reached a size of at least 5.0 cm. One such study of 99 patients documented a mean expansion rate of 2.2 mm in the first year of observation, 2.8 mm in the second year, and 1.8 mm in the third year for aneurysms that initially were smaller than 4.0 cm. The corresponding growth rates for aneurysms measuring 4.0 to 4.9 cm were 2.7, 4.2, and 2.2 mm, respectively (1052). Given the usual slow rate of expansion for truly small aneurysms, however, Grimshaw et al. and Santilli et al. have recommended that those measuring less than 4.0 cm in diameter can be followed up safely with ultrasound scans every 2 to 3 years (933,934).

The available evidence does not support a lower size threshold for the endovascular repair of AAAs than for conventional surgical repair (1053,1054). No recommendations currently are available for patients whose aortic diameter is ectatic but less than 3.0 cm in diameter and thus not truly aneurysmal. Screening of 12,500 people at a university-affiliated VA medical center yielded 223 patients whose aortic diameters were 2.5 to 2.9 cm (1055). On the basis of serial ultrasound imaging over 7 years, these ectatic aortas expanded slowly, rupture did not occur, and criteria for operative repair were infrequently met. No risk factors linked to the development of aneurysms were identified on multivariate analysis. Therefore, in patients with ectatic but noneurysmal aortas, repeat ultrasound imaging was recommended no more often than 5 years after the initial study. Because of the potential for late dissection or aneurysm in other areas of the aorta, however, patients with Marfan syndrome should undergo serial imaging of the aorta indefinitely after surgical repair of aneurysmal disease or dissection.

5.2.6. Open Aortic Aneurysm Repair

The management of patients who have AAAs that are large enough to represent a predictable risk for fatal rupture often is guided by several considerations. First, the survival rate of this patient population generally is acknowledged to be significantly lower than that for a normal population of the same age (1056-1059), and Aune has reported that unfavorable late survival is particularly evident among patients who are 65 years of age or younger at the time that their aortic aneurysms are discovered (1058). Second, it has long been recognized that coronary artery disease and its consequences represent the leading causes of late death in these patients, superseding even the mortality rate that can be attributed directly to unoperated aneurysms (945,1060). Therefore, in addition to their importance regarding early surgical risk, these observations have long-term implications with respect to the identification and treatment of underlying coronary disease before the elective repair of aortic aneurysms. Finally, the emergence of new technology for transfemoral endovascular repair of AAAs with a variety of commercially available, FDA-approved stent grafts now provides an alter-
native to open surgical treatment in patients with aneurysms that warrant repair on the basis of their size or expansion rate. Thus, the contemporary clinician is faced with an array of choices in the management of aortic aneurysms, each of which must be tailored to the individual patient.

5.2.6.1. Infrarenal AAAs

5.2.6.1.1. Preoperative Cardiac Evaluation. A number of studies have demonstrated that the perioperative and long-term mortality rates in conjunction with open aortic aneurysm repair are highest among patients who have symptomatic coronary disease (i.e., class III to IV angina pectoris or congestive heart failure), intermediate in those who have chronic stable angina and/or a history of remote MI, and lowest among those who have no indication of coronary disease whatsoever (955,1061-1064). Glance constructed a Markov predictive model in which patients at high cardiac risk underwent coronary arteriography, those at intermediate risk received noninvasive assessment with dipyridamole-thallium scanning, and those at low risk proceeded directly to aneurysm repair (1064). The conclusion of this exercise was that selective screening “may improve 5-year survival and be cost effective.” Several large clinical series have been reported in which a similar clinical approach has been used (1065-1068). According to these reports, the mortality rate for open aortic aneurysm repair can be reduced to less than 2% in a setting in which approximately 5% to 15% of patients undergo preliminary coronary artery intervention (1069). However, the role of coronary artery revascularization in the context of contemporary medical management appears to be less than has been traditionally assumed. Intensive medical therapy and coronary revascularization (including percutaneous coronary intervention and coronary artery bypass grafting), when offered to individuals anticipated to undergo lower extremity or AAA revascularization surgery, resulted in equal postoperative rates of cardiovascular ischemic events in a prospective investigation (1069). A comprehensive discussion of this topic may be found in a previous guidelines document sponsored by the ACC/AHA (484).

5.2.6.1.2. Open Surgical Approaches. Open aortic aneurysm repair can be performed by a midline transabdominal approach or an extraperitoneal incision in the left flank, and Darling et al. have recommended that the flank approach also be used to gain expeditious suprarenal aortic control for ruptured infrarenal aneurysms (1070). There is no clear consensus, however, regarding the superiority of either of these incisions on the basis of prospectively randomized studies. Sicard et al. found that the extraperitoneal approach was associated with fewer postoperative complications, a shorter length of stay, and lower hospital charges (1071). Other randomized institutional trials (1072,1073) have failed to demonstrate any material advantage to the routine use of the extraperitoneal approach and have suggested that it may result in a higher incidence of muscular atony, incisional her-
only slightly less than 10% (1108,1109). These findings also are supported by data from the NHDS (1075,1076) and the Nationwide Inpatient Sample (1077). Nevertheless, the mortality rate for elective operations is so much lower than for ruptured aneurysms that octogenarians should not be dismissed as surgical candidates merely on the basis of their age, provided their aneurysms are sufficiently large by contemporary standards to justify intervention (1108-1110).

**Gender.** Patient gender did not influence early mortality or late survival rates in series of approximately 600 patients from the Canadian Aneurysm Group (1102) or the Cleveland Clinic (1060), but this experience is far from universal. According to larger, population-based data sets in Michigan (1086); Maryland (1092); and Ontario, Canada (1088), the mortality rate for elective aneurysm repair may be as much as 50% higher among women and appears to be higher than in men for ruptured aneurysm repair (1076,1099,1100).

**Race.** Patient race has not been found to be an independent predictor of early mortality after elective aneurysm repair in the VA system (1111), but another large database from the NHDS suggests that the elective mortality rate is significantly higher among blacks (1076). Similarly, Dardik et al. found that the elective mortality rate for blacks (6.7%) was higher than the comparable figure for other races (3.2%, \( p \) equals 0.046) in the state of Maryland during the early 1990s (1092).

**Organ-Specific Risk Factors.** Reports (1068,1076,1077) have confirmed the conclusions of countless previous studies that the mortality rate for elective aneurysm repair is closely related to the presence of preoperative cardiac risk factors and the severity of pre-existing renal impairment. In comparison, COPD is associated with increased morbidity, the need for prolonged ventilatory support, and longer lengths of stay in the hospital but has been shown not to be a predictor of operative mortality (949).

**Volume/Outcome Relationship.** During the past 15 years, a growing number of studies have demonstrated an inverse relationship between the mortality rate for aortic aneurysm repair and both the annual hospital volume and the experience of individual surgeons with these procedures.

### Table 50: Operative Mortality Rates for Open Repair of Ruptured Abdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darling</td>
<td>(1070)</td>
<td>1996 (1988-1995)</td>
<td>104</td>
<td>28</td>
</tr>
<tr>
<td>Noel</td>
<td>(1100)</td>
<td>2001 (1980-1998)</td>
<td>413</td>
<td>37</td>
</tr>
<tr>
<td><strong>Collective reviews</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor</td>
<td>(938)</td>
<td>1987</td>
<td>5 Reports</td>
<td>42</td>
</tr>
<tr>
<td>Ernst</td>
<td>(1081)</td>
<td>1993 (1981-1992)</td>
<td>1731</td>
<td>49</td>
</tr>
<tr>
<td>Zarins</td>
<td>(973)</td>
<td>1997 (1988-1996)</td>
<td>1618</td>
<td>42</td>
</tr>
<tr>
<td><strong>Regional or multicentered studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston (Canadian Aneurysm Group)</td>
<td>(1102)</td>
<td>1994</td>
<td>147</td>
<td>50</td>
</tr>
<tr>
<td>Kantonen (Finland Vascular Registry)</td>
<td>(1089)</td>
<td>1997</td>
<td>454</td>
<td>46</td>
</tr>
<tr>
<td>Axelrod (Veterans Affairs)</td>
<td>(949)</td>
<td>2001</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td><strong>U.S. hospital databases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawrence (National Hospital Discharge Survey)</td>
<td>(1075)</td>
<td>1999 (1994)</td>
<td>6623</td>
<td>68</td>
</tr>
<tr>
<td>Heller (National Hospital Discharge Survey)</td>
<td>(1076)</td>
<td>2000 (1979-1997)</td>
<td>67751</td>
<td>46</td>
</tr>
<tr>
<td>Dimick (National Inpatient Sample)</td>
<td>(1078)</td>
<td>2002</td>
<td>13887</td>
<td>47</td>
</tr>
</tbody>
</table>
Representative data showing these relationships for intact and ruptured aneurysms are summarized in Table 51. Other studies have reconfirmed these observations with respect to hospital volume (1094,1114), surgeon experience (1089), or both (1112). Manheim et al. (1091) and Dimick et al. (1078) have estimated that the operative mortality rate for elective aneurysm repair is reduced by approximately 50% in high-volume hospitals in the United States, and Wen et al. (1088) have calculated that there is a 6% reduction in the relative odds for death with every 10 additional elective cases that are added to the annual hospital volume in Ontario, Canada. Pearce et al. (1093) discovered that a doubling of the annual surgeon volume was associated with an 11% reduction in the relative risk for death after aortic aneurysm repair in Florida, and Dardik et al. (1092) have determined that hospital charges are significantly lower in conjunction with the repair of either intact or ruptured aortic aneurysms by high-volume surgeons in Maryland.

5.2.6.1.4. Late Survival Rates. Representative late survival rates after open surgical repair of intact and ruptured AAAs are summarized in Table 52. Five-year survival rates after intact aneurysm repair generally have ranged from 60% to 75%, with 10-year survival rates of approximately 40% to 50%. Several other studies (1085,1095,1102,1114,1115) have determined that the long-term mortality rate is substantially higher after ruptured aneurysm repair even among operative survivors, possibly because some of these patients may have serious medical comorbidities that discouraged earlier elective intervention for their aneurysms. Several risk factors have been shown to be significant in more than 1 of these studies, including advanced age, ischemic heart disease manifested by congestive heart failure or electrocardiographic evidence of myocardial ischemia, an elevated serum creatinine level, COPD, and cerebrovascular disease (1057,1068,1085,1102,1114,1116).

5.2.6.1.5. Late Graft Complications. Late graft complications (e.g., aortic pseudoaneurysms, graft infections and/or enteric fistulas, and graft limb occlusions) are exceedingly unusual after open aortic aneurysm repair. Hallett et al. (1120) reported graft-related complications in only 9.4% of a population-based series of 307 patients who underwent open aneurysm repair at the Mayo Clinic between 1957 and 1990, which included anastomotic pseudoaneurysms in 3.0%, graft thrombosis in 2.0%, enteric fistulas in 1.6%, and graft infections in 1.3%. In another long-term study that included a substantial number of aortofemoral grafts, Biancari et al. (959) calculated survival rates free from graft complications of 94% at 5 years, 88% at 10 years, and 74% at 15 years. Only 2.9% of the patients in that series developed aortic pseudoaneurysms, and the higher rates of distal anastomotic pseudoaneurysms (8.7%) and graft limb occlusions (5.3%) that occurred in the series almost certainly were related to the fact that the majority (55%) of the replacement grafts extended below the inguinal ligament. Hertzer et al. (1068) reported a modern series of 1135 open aneurysm procedures that were collected from 1989 through 1998, were performed with monofilament suture material, and included relatively few aortofemoral grafts (5%). Only 0.4% of these patients have required reoperations for graft complications.

5.2.6.2. Juxtarenal, Pararenal, and Suprarenal Aortic Aneurysms

Aneurysms involving the upper abdominal aorta generally are classified according to their relationship to the renal arteries. Juxtarenal aneurysms arise distal to the renal arteries but in very close proximity to them; pararenal aneurysms involve the origin of 1 or both renal arteries; suprarenal aneurysms encompass the visceral aortic segment containing the superior mesenteric and celiac arteries, and specifically are termed type IV thoracoabdominal aneurysms if they extend upward to the crus of the diaphragm (1121). Open repair of juxtarenal or pararenal aortic aneurysms may be accomplished through a midline transabdominal incision with or without medial visceral rotation of the spleen, the pancreas, and sometimes the left kidney, depending on the preference of the surgeon. These aneurysms also can be repaired with a thoracoretroperitoneal approach, which almost always is necessary for type IV thoracoabdominal aneurysms. Irrespective of the incision that is used for their exposure, the principal technical consideration that is common to most of these aneurysms is that they require a period of aortic cross-clamping above the renal arteries.

5.2.6.2.1. Early Mortality and Complication Rates Juxtarenal Aortic Aneurysms. Juxtarenal aneurysms represent the only exception to the requirement for suprarenal aortic cross-clamping, because some of these aneurysms are associated with an adequate cuff of relatively normal aorta for proximal control just below the renal arteries. This is not always evident on preoperative imaging because of angulation of the aorta or superimposition of the aneurysm over the infrarenal cuff (1121). Even when suprarenal cross-clamping is required, it is only for the period of time that is necessary to construct the proximal anastomosis of the replacement graft near the uninvolved renal arteries. This feature undoubtedly accounts for the observation that operative mortality and morbidity rates for juxtarenal aortic aneurysms are higher than those for standard infrarenal aneurysms but lower than those for aneurysms that extend above the renal arteries. Taylor et al. encountered no postoperative deaths after juxtarenal aneurysm repair, but 7% of their patients experienced at least transient renal failure (1013). In a series of 53 juxtarenal aneurysms and 376 infrarenal aneurysms, Ayari et al. reported early mortality rates of 11% and 3% (p < 0.01) and morbidity rates of 51% and 26% (p < 0.01), respectively (1122). Faggioli et al. described a series of 50 juxtarenal or pararenal aneurysms in which the operative mortality rate of 12% was significantly worse (p < 0.02) than the comparable figure for all infrarenal aneurysm procedures that were done at the same center (1123).
<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Overall Mortality Rate (%)</th>
<th>Hospital</th>
<th>Annual Volume</th>
<th>Surgeon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intact aneurysms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hertzer (Northeastern Ohio)</td>
<td>(1101)</td>
<td>1984 (1978-1981)</td>
<td>840</td>
<td>6.50</td>
<td>NA</td>
<td>Low: 4.7%; medium: 16%; high: 2.9% ($p$ less than 0.001)</td>
<td></td>
</tr>
<tr>
<td>Amundsen (Norway)</td>
<td>(1113)</td>
<td>1990</td>
<td>279</td>
<td>NA</td>
<td>Low: 11%; high: 4.8% ($p$ equals 0.05)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Hannan (New York statewide)</td>
<td>(1084)</td>
<td>1992 (1982-1987)</td>
<td>6042</td>
<td>7.60</td>
<td>Low: 12%; medium: 6.8%; high: 5.6%</td>
<td>Low: 11%; medium: 7.3%; high: 5.6%</td>
<td></td>
</tr>
<tr>
<td>Katz (Michigan statewide)</td>
<td>(1086)</td>
<td>1994 (1980-1990)</td>
<td>8185</td>
<td>7.50</td>
<td>Low: 8.9% High: 6.2% ($p$ less than 0.001)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kazmers (Veterans Affairs)</td>
<td>(1087)</td>
<td>1996 (1991-1993)</td>
<td>3419</td>
<td>4.90</td>
<td>Low: 6.7% High: 4.2% ($p$ less than 0.05)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Dardik (Maryland statewide)</td>
<td>(1092)</td>
<td>1999 (1990-1995)</td>
<td>2335</td>
<td>3.50</td>
<td>Low: 4.3% medium: 4.2% high: 2.5% ($p$ equals 0.08)</td>
<td>Very low: 9.9%; low: 4.9%; medium: 2.8%; high: 2.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Ruptured aneurysms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amundsen (Norway)</td>
<td>(1113)</td>
<td>1990</td>
<td>165</td>
<td>NA</td>
<td>Low: 73% high: 52% ($p$ equals 0.03)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Katz (Michigan statewide)</td>
<td>(1086)</td>
<td>1994 (1980-1990)</td>
<td>1829</td>
<td>50</td>
<td>Low: 54% high: 46% ($p$ equals 0.0026)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Dardik (Maryland statewide)</td>
<td>(1092)</td>
<td>1999 (1990-1995)</td>
<td>527</td>
<td>47</td>
<td>Low: 46% medium: 49% high: 47% ($p$ equals NS)</td>
<td>Low: 51% medium: 47% high: 36% ($p$ equals 0.05)</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates not available; NS, not significant.
Table 52. Late Survival Rates After Open Aortic Abdominal Aneurysm Repair

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Survival Rates</th>
<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
<th>10 Years</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intact aneurysms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford</td>
<td>(1061)</td>
<td>1981</td>
<td>816</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hertzer</td>
<td>(955)</td>
<td>1987</td>
<td>236</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallett</td>
<td>(1056)</td>
<td>1993</td>
<td>130</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stonebridge</td>
<td>(1117)</td>
<td>1993</td>
<td>311</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soisalon-Soininen</td>
<td>(1114)</td>
<td>1995</td>
<td>706</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho</td>
<td>(1115)</td>
<td>1998</td>
<td>116</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aune</td>
<td>(1058)</td>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Younger than age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 y: 118</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 y or older: 333</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total: 451</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biancari</td>
<td>(959)</td>
<td>2002</td>
<td>208</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hertzer</td>
<td>(1068)</td>
<td>2002</td>
<td>1135</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menard</td>
<td>(1080)</td>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low risk: 444</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: 128</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total: 572</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collective reviews or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multicenter studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ernst (collective review)</td>
<td>(1081)</td>
<td>1993</td>
<td>3226</td>
<td></td>
<td>92%</td>
<td>67%</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston (Canadian Aneurysm Group)</td>
<td>(1085)</td>
<td>1994</td>
<td>680</td>
<td></td>
<td>91%</td>
<td>81%</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feinglass (Veterans Affairs)</td>
<td>(1116)</td>
<td>1995</td>
<td>280</td>
<td></td>
<td>89%</td>
<td>64%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koskus (French AURC)</td>
<td>(1057)</td>
<td>1997</td>
<td>794</td>
<td></td>
<td>94%</td>
<td>84%</td>
<td>67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norman (collective review)</td>
<td>(1118)</td>
<td>2001</td>
<td>32 Reports</td>
<td></td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ruptured aneurysms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stonebridge</td>
<td>(1117)</td>
<td>1993</td>
<td>227</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soisalon-Soininen</td>
<td>(1114)</td>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho</td>
<td>(1115)</td>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evans</td>
<td>(1119)</td>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collective reviews or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multicenter studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston (Canadian aneurysm study)</td>
<td>(1102)</td>
<td>1994</td>
<td>147</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AURC indicates Association for Academic Research in Vascular Surgery.
Pararenal/Suprarenal and Type IV Thoracoabdominal Aortic Aneurysms. Selected but representative data regarding the operative mortality and complication rates for all upper AAAs involving the renal arteries are presented in Table 53. In aggregate, the mortality for elective repair of type IV thoracoabdominal aneurysms is approximately twice as high as that for pararenal or “low” suprarenal aneurysms. All of these aneurysms share the requirement for suprarenal aortic cross-clamping and usually for additional reconstruction of the left renal artery, either by reimplantation or with the use of an independent renal artery graft that originates from the aortic prosthesis. Accordingly, a period of renal ischemia is unavoidable unless continuous kidney perfusion is used, and for this reason, postoperative renal insufficiency is the most common organ-specific complication that is generic to the repair of any aortic aneurysm arising at or above the level of the renal arteries. A transient elevation in the serum creatinine can be expected in 20% to 30% of these patients, with temporary hemodialysis support being necessary in 3% to 15%. Fortunately, however, permanent renal failure generally has been reported in fewer than 5% of patients. The risk of spinal cord ischemia with paraplegia is less than 5% for type IV thoracoabdominal aneurysms but otherwise is distinctly uncommon.

The operative mortality rate for aneurysms that involve the upper abdominal aorta has been shown to be related to patient age and the presence of coronary artery disease (1123), as well as to whether the aneurysm extends to the level of the diaphragm and/or requires urgent rather than elective surgical treatment (1133). The risk for postoperative renal insufficiency can be correlated with the severity of intrinsic renal artery disease and the extent of revascularization that is necessary to correct it, particularly when both renal arteries require additional reconstruction (1124,1125).

5.2.6.2.2. LATE SURVIVAL RATES. According to the data that are available, the late survival rate after repair of juxtarenal, pararenal, or suprarenal aortic aneurysms may be slightly lower than after operations for infrarenal aortic aneurysms. Schwartz et al. (1131) and Martin et al. (1133) have reported 5-year survival rates of 50%, whereas the 5-year survival rate was only 40% in the series described by Faggioli et al. (1123).

5.2.7. Endovascular Aortic Aneurysm Repair

5.2.7.1. Introduction

The technique of transfemoral catheter-based repair of infrarenal AAAs was first reported by Parodi et al., originally as an alternative for the management of patients whose medical comorbidities made them poor candidates for conventional surgical treatment (1134). A variety of proprietary stent grafts and delivery systems now have been used for more than a decade throughout the world, 4 of which presently have market approval by the FDA and remain commercially available in the United States. Open exposure of the common femoral arteries conventionally is used for sheath placement in most patients, and extraperitoneal incisions occasionally are necessary to construct temporary access conduits to 1 or both iliac arteries if the external iliac arteries are too small or tortuous for transfemoral cannulation. Endovascular AAA repair can avoid a major transabdominal procedure, can be performed under regional or even local anesthesia, and clearly represents a major advance in the management of patients with AAA who have severe cardiopulmonary disease or other risk factors, such as advanced age, morbid obesity, or a hostile abdomen from multiple previous operations. Once its feasibility had been demonstrated in such patients, however, endovascular repair also has been offered at many centers to low- or average-risk patients who have no particular contraindications to conventional surgical treatment. This has resulted in a distinct shift in the paradigm for management of infrarenal aortic aneurysms in some geographic areas during a relatively short period of time. According to statewide data from New York, for example, 53% of patients who underwent AAA repair received endografts in 2002 compared with 40% in 2001 (1135).

Driven by necessity and a competitive medical marketplace, the design of aortic stent grafts has passed through several iterations. Most contemporary stent grafts are supported by a metallic skeleton that is secured to the fabric of the graft during the manufacturing process to maintain linear stability once the device has been implanted and to avoid kinking that can result in graft limb occlusion with unsupported grafts. To better accommodate the aortoiliac anatomy and facilitate graft deployment, the majority of modern endografts also are modular in construction. Thus, the aortic stem and a contiguous iliac limb are inserted through 1 femoral artery, with the opposite iliac limb then being positioned by a separate delivery system through the contralateral femoral artery. The absence of an adequate length of relatively normal aorta below the renal arteries historically has excluded patients from consideration for endovascular repair because of the high risk for proximal attachment failure, graft migration, and endoleak.

In an attempt to overcome the risk of distal migration and proximal attachment failure, a growing number of new devices now incorporate barbed hooks that are sufficiently strong to secure the metallic frame of the stent graft to the visceral segment of the aorta above the renal arteries. Better graft stability with a transrenal attachment will likely improve results but does not necessarily mean that patients with aneurysms with shorter necks can be treated, because the proximal seal of the endovascular graft continues to be infrarenal in all currently approved devices. In aggregate, modular externally supported bifurcation endografts are more widely applicable, less prone to migrate from their sites of attachment, and more likely to remain patent than was the case with the first generation of unsupported endografts only a few years ago. Some aspects of endovascular aneurysm repair remain problematic, however, and will require further refinements in the future. In addition to the vexing problem of metal fatigue (1136,1137), these include anatomic limita-
Table 53. Operative Mortality and Postoperative Complication Rates for Open Repair of Pararenal, Suprarenal, and Type IV Thoracoabdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Mortality Rate (%)</th>
<th>Postoperative Complication Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td>Pararenal or suprarenal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qvarfordt</td>
<td>(1124)</td>
<td>1986</td>
<td>77</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Nypaver</td>
<td>(1125)</td>
<td>1993 (1985-1992)</td>
<td>53</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Faggioli</td>
<td>(1123)</td>
<td>1998</td>
<td>50</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Jean-Claude</td>
<td>(1126)</td>
<td>1999 (1977-1997)</td>
<td>257</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Anagnostopoulos</td>
<td>(1127)</td>
<td>2001 (1986-1999)</td>
<td>65</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Type IV thoracoabdominal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford</td>
<td>(1121)</td>
<td>1986 (1960-1985)</td>
<td>145</td>
<td>4.8</td>
<td>Dialysis: 5.5</td>
</tr>
<tr>
<td>Svensson</td>
<td>(1129)</td>
<td>1993 (1960-1991)</td>
<td>346</td>
<td>5.8</td>
<td>Total: 22</td>
</tr>
<tr>
<td>Coselli</td>
<td>(1130)</td>
<td>1995 (1984-1993)</td>
<td>35</td>
<td>14 (reoperations)</td>
<td>None permanent</td>
</tr>
<tr>
<td>Schwartz</td>
<td>(1131)</td>
<td>1996 (1977-1994)</td>
<td>58</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates not available.
5.2.7.1.1. Anatomic Limitations. Even with suprarenal fixation of its metallic exoskeleton, the fabric component of an endograft obviously cannot be permitted to overlap the origins of the renal arteries. Accordingly, at least 1 cm of proximal aortic cuff (1.5 cm for commercially available grafts) presently is optimal for elective endograft repair below the renal arteries. For devices without a suprarenal fixation device, the optimum infrarenal aortic diameter at the time of this writing is 25 mm or less, and for devices with a suprarenal fixation component, it is 28 mm or less. Because of the inflexibility of externally supported grafts, this segment of the aorta must not be severely angulated. This requirement may impose a gender bias in patient selection, because in addition to the fact that their small external iliac arteries often present problems with respect to vascular access, women also appear to have a higher prevalence of short, angulated aneurysm necks than men (1138,1139). Considering all of these criteria, Carpenter et al. reported that a disproportionate number of women were excluded from endograft repair because of anatomic limitations (60% of women vs. 30% of men; p equals 0.0009) (1140). Becker et al. (1141) also found that significantly fewer women qualified for endovascular aneurysm repair (26% of women vs. 41% of men), and Mathison et al. (1142) were forced to abandon more attempted endograft procedures in women (17%) than in men (2.1%; p less than 0.01). Wolf et al. described comparable eligibility rates for endograft repair in women (49%) and in men (57%), but the women in that series had a higher incidence of intraoperative complications than men (31% vs. 13%, p less than 0.05) and required more adjunctive arterial reconstructions (42% vs. 21%, p less than 0.05) to correct those complications (1143).

5.2.7.1.2. Intrac sac Endoleaks. Endoleaks represent sources of continued blood flow into the excluded aneurysm sac and are of such importance that they justified a consensus conference of experts on endovascular aneurysm repair in 2000 (1144). Type I endoleaks are caused by incompetent proximal or distal attachment sites, produce high intrasac pressure that can lead to rupture, and should be repaired with intraluminal extender cuffs or conversion to an open procedure as soon as they are discovered. Type II endoleaks are the result of retrograde flow from branch vessels (e.g., lumbar arteries and the inferior mesenteric artery), occur in as many as 40% of patients at some point in time after endograft implantation, and often may be corrected by selective arterial catheterization and therapeutic embolization. More than half of all type II endoleaks will seal spontaneously, however, and although isolated examples of aneurysm rupture on the basis of persistent type II endoleaks have been reported (1145,1146), they do not yet appear to influence the risk for rupture during 18 to 36 months of surveillance in large series of patients (1147,1148). If an intervention is necessary for the few type II endoleaks that persist or are associated with aneurysm expansion, therapeutic embolization of feeding branches through a translumbar approach to the aneurysm sac has been successful. Type III endoleaks are caused by midgraft defects from fabric tears or the junctional disruption of modular graft components, especially if these components become buckled as the excluded aneurysm sac shrinks and foreshortens. Type III endoleaks are considered to have the same potential for delayed aneurysm rupture as type I endoleaks and therefore should be repaired promptly at the time of their discovery. Type IV endoleaks are the result of high graft porosity and diffuse leakage through its interstices, usually occur within 30 days of implantation, and are rare compared with the frequency of other endoleaks. Finally, the term “endotension” has been applied to those circumstances in which the excluded sac continues to enlarge and appears to remain pressurized despite the absence of any visible endoleaks on contrast-enhanced computed tomographic scans.

In summary, it is largely because of the uncertainties related to intrasac endoleaks that clinical investigators and the FDA consider follow-up imaging to be mandatory every 6 to 12 months for any patient whose aortic aneurysm is treated with an endovascular stent graft (1144,1149). If persistent endoleaks or continued aneurysm expansion is demonstrated, further studies are necessary to determine the cause. Perhaps the most active area of current interest in this regard is related to the management of type II endoleaks, largely because of the frequency with which they occur and both the inconvenience and expense of their treatment. According to European collaborators registry on stent-graft techniques for abdominal aortic aneurysm repair (EUROSTAR) data for follow-up intervals as long as 6 years, the presence of type II endoleaks has not been associated with a significant incidence of any adverse clinical events other than the secondary interventions that are performed at the discretion of the attending physicians (1150). Similar findings have led Steinmetz et al. to conclude that selective intervention should be considered only for type II endoleaks that have persisted for at least 6 months on serial noninvasive imaging (1151).

5.2.7.1.3. Graft Occlusion. Occlusion of the iliac limbs of bifurcation endografts was not uncommon with early devices, occurring in 10% of some series (1152). After finding that further intraluminal stenting was necessary to eliminate torsion or kinking in 36% of all unsupported grafts, Amesur et al. adopted the use of routine intraoperative intravascular ultrasonography to identify these potential problems and to correct them before thrombosis occurred (1153). Graft occlusion may become a less frequent complication in the future, because the stability of a metallic skeleton tends to prevent the kinds of graft distortion that can lead to subsequent thrombosis. Although Baum et al. encountered limb kinking in a total of 12% of grafts in their series, they were able to document this finding in only 5% of externally supported grafts compared with 44% of unsupported grafts (1154). In a multicenter study of 242 unsupported bifurcation endografts that were implanted from 1995 through 1998,
Fairman et al. reported an overall primary patency rate of 62% at a mean follow-up interval of 31 months (1155). The primary-assisted and secondary patency rates for this series were 94% and 97%, however, because of successful intraoperative (28%) or postoperative (12%) graft limb interventions that were necessary in 40% of the 242 patients.

5.2.7.1.4. AORTIC NECK EXPANSION. Endograft migration from the proximal attachment site has been reported in a wide range of 1.5% to 16% of patients (1024,1156,1157). One of the factors that could lead to graft migration or delayed type I endoleaks is further expansion of the proximal aorta, a finding that Makaroun et al. have documented by serial imaging studies in 13% of patients at 1 year after endovascular aneurysm repair, in 21% at 2 years, and in 19% at 3 years (1158). According to Matsumura et al., the mean increase in aortic neck diameter after endografting is 0.7 plus or minus 2.1 mm at 1 year and 0.9 plus or minus 1.9 mm at 2 years (1159). Even when device diameters are purposefully oversized by as much as 20% in an attempt to accommodate future aortic neck expansion, Conners et al. have found that endograft migration still can occur (1157). The implications of these observations are a source of some concern, but the maximum follow-up period of approximately 3 years for most reported endograft series is too short for their influence on late clinical outcomes to be known.

5.2.7.2. Preoperative Cardiac Evaluation

The preoperative cardiac evaluation before endovascular aneurysm repair may be dictated by patient selection, because severe cardiac disease already will have been documented in many patients who are treated at centers where endografting is restricted to high-risk cases. Perhaps for this reason, relatively little published information is available on this topic. In an unselected series of 83 endovascular and 63 open repairs in patients who had an identical number of Eagle Criteria risk factors, de Virgilio et al. found no differences in the incidence of postoperative cardiac events (6% and 4.8%, respectively) or mortality rates (3.6% and 4.8%, respectively) (1160). Among patients who received endografts, the only predictors of cardiac events were a history of congestive heart failure (p equals 0.005) or the presence of a Q wave on the preoperative electrocardiogram. More recently, Aziz et al. have reported that perioperative cardiac events were associated with certain Eagle risk factors, such as age 70 years or older (p equals 0.026) and a history of either MI (p equals 0.024) or congestive heart failure (p equals 0.001), after aortic endografting in 365 patients (1161). Moreover, the lack of preoperative beta-blockade was associated with a higher risk for perioperative events in this nonrandomized series (p equals 0.007).

At least one study appears to confirm the intuitive impression that endografting should have less cardiac risk than a major transabdominal operation. In a concurrent series of 71 open and 49 endovascular aneurysm repairs, Cuypers et al. found that endovascular procedures were associated with a higher intraoperative cardiac index (p less than 0.01) and a lower intraoperative stroke work index (p equals 0.04) than open procedures (1162). Although the number of adverse cardiac events was comparable, postoperative electrocardiograms and transesophageal echocardiograms revealed significantly more evidence of myocardial ischemia after open operations (57% vs. 33% after endograft repair; p equals 0.01). On the basis of admittedly incomplete data, elective endovascular aortic aneurysm repair in unselected patients probably should be considered as an “intermediate or low surgical risk procedure” according to the previous ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery (484).

5.2.7.3. Early Mortality and Complication Rates

Table 54 contains representative data regarding the procedural mortality rate for endovascular aneurysm repair, the incidence of early endoleaks, and the risk for immediate conversion to an open operation. This information has been collected from case series, from FDA- and industry-sponsored device trials in the United States, and from EUROSTAR, a cooperative archive for endograft data that are submitted voluntarily by nearly 60 participating centers. The study periods for the references that are cited in Table 54 help to identify the generation of devices that were under investigation, and they also provide points of reference during an era in which rapid advances in technology tend to make the preceding iteration of stent grafts and delivery systems obsolete as soon as new devices are introduced. With the exception of the specific device trials, most of these reports describe results with a wide variety of proprietary endografts, each of which appears to be associated with a declining complication rate after sufficient experience has been accumulated with its use at individual centers (1141,1163-1166). Data regarding volume/outcome relationships are not yet available for endovascular aneurysm repair.

The early mortality rate for endograft repair generally has been less than 3%, but May et al. (1165) have shown this to be substantially lower than the mortality rate for a concurrent series of open procedures. The comparative safety of endograft repair is difficult to assess, however, because it often is difficult to determine from published reports whether aortic stent grafts were offered only to high-risk surgical patients or to a mix of high-, average-, and low-risk patients. Using a scoring system for perioperative risks that ranged from zero (low) to 3 (high) in a large series of 305 patients, Becker et al. (1141) calculated the mortality rates for endovascular repair to be 2.5%, 0.8%, 3.4%, and 6.5%, respectively. Several EUROSTAR studies have demonstrated that both early mortality rates and nonfatal complication rates were significantly higher among patients who were deemed to be unfit for open repair or general anesthesia (1163,1166,1192), as well as among those who needed adjunctive procedures in addition to the placement of an aortic stent graft (1163). Walker et al. also found significant differences between mortality rates for endovascular repair in high- and low-risk patients.
Table 54. Representative Early Results for Endovascular Repair of Infrarenal Aortic Abdominal Aneurysms

<table>
<thead>
<tr>
<th>First Author (Study/Sponsor)</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Immediate Open Conversion (%)</th>
<th>Postoperative Complication Rates (%)</th>
<th>Procedural Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum</td>
<td>(1167)</td>
<td>1997 (1994-1996)</td>
<td>295</td>
<td>1.7</td>
<td>8.1 NA</td>
<td>0.7</td>
</tr>
<tr>
<td>Zarins</td>
<td>(1171)</td>
<td>2000 (1996-2000)</td>
<td>149</td>
<td>1.30</td>
<td>36 18 1.3</td>
<td>NA 1.3</td>
</tr>
<tr>
<td>Becker</td>
<td>(1141)</td>
<td>2001 (1994-2001)</td>
<td>305</td>
<td>1.30</td>
<td>23 17 2.6</td>
<td>NA</td>
</tr>
<tr>
<td>Fairman</td>
<td>(1173)</td>
<td>2001 (1998-1999)</td>
<td>75</td>
<td>None</td>
<td>44 20 0</td>
<td>NA</td>
</tr>
<tr>
<td>Holzenbein</td>
<td>(1174)</td>
<td>2001</td>
<td>173</td>
<td>1.2</td>
<td>4.6 (Type I) NA</td>
<td>2.8</td>
</tr>
<tr>
<td>Howell</td>
<td>(1175)</td>
<td>2001</td>
<td>215</td>
<td>None</td>
<td>42 11 0</td>
<td>NA</td>
</tr>
<tr>
<td>Mathison</td>
<td>(1142)</td>
<td>2001 (1994-2000)</td>
<td>305</td>
<td>1.3</td>
<td>23 NA 2.6</td>
<td>NA</td>
</tr>
<tr>
<td>May</td>
<td>(1165)</td>
<td>2001 (1995-1998)</td>
<td>Endo: 148, Open: 135</td>
<td>0.7</td>
<td>6.8 5.4 2.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Sicard</td>
<td>(1176)</td>
<td>2001 (1997-2000)</td>
<td>Endo: 260, Open: 210</td>
<td>0.8</td>
<td>13 3 1.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Abraham</td>
<td>(1146)</td>
<td>2002 (1998-2001)</td>
<td>116</td>
<td>None</td>
<td>15 11 0.9</td>
<td>NA</td>
</tr>
<tr>
<td>Sampram</td>
<td>(1178)</td>
<td>2003 (1996-2002)</td>
<td>703</td>
<td>NA</td>
<td>NA NA 1.7</td>
<td>NA</td>
</tr>
<tr>
<td>Shames</td>
<td>(1180)</td>
<td>2003 (1999-2001)</td>
<td>302 Men 42 Women</td>
<td>0.5 14</td>
<td>NA NA 2.3</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continued on Next Page
### Table 54. Continued

<table>
<thead>
<tr>
<th>First Author (Study/Sponsor)</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Immediate Open Conversion (%)</th>
<th>Postoperative Complication Rates (%)</th>
<th>Procedural Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore (Endovascular Technologies)</td>
<td>(1181)</td>
<td>1996 (1993-1994)</td>
<td>46</td>
<td>15</td>
<td>44 (44)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Coppi (Stentor, Mintec)</td>
<td>(1182)</td>
<td>1998 (1995-1996)</td>
<td>66</td>
<td>6.10</td>
<td>6.1 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Matsumura (Endovascular Technologies)</td>
<td>(1159)</td>
<td>1998 (1993-1995)</td>
<td>68</td>
<td>13</td>
<td>47 (47)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Becquemin (Vanguard, Boston Scientific)</td>
<td>(1183)</td>
<td>1999 (1996-1997)</td>
<td>75</td>
<td>None</td>
<td>31 (31)</td>
<td>9.3 (9.3)</td>
</tr>
<tr>
<td>Zarins (AneuRx, Medronic)</td>
<td>(1184)</td>
<td>1999 (1996-1997)</td>
<td>Endo: 190 Open: 60</td>
<td>None</td>
<td>21 (21)</td>
<td>8.9 (8.9)</td>
</tr>
<tr>
<td>Zarins (AneuRx, Medronic)</td>
<td>(1185)</td>
<td>2000 (1997-1998)</td>
<td>425</td>
<td>1.20</td>
<td>Centers: 38; core lab: 50</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Beebe (Vanguard, Boston Scientific)</td>
<td>(1186)</td>
<td>2001 (1997-1998)</td>
<td>Endo: 268 Open: 98</td>
<td>1.90</td>
<td>5.70 (5.7)</td>
<td>2.7 (2.7)</td>
</tr>
<tr>
<td>Greenberg (Zenith, Cook)</td>
<td>(1156)</td>
<td>2001 (1995-2000)</td>
<td>528</td>
<td>0.80</td>
<td>16 (16)</td>
<td>5.5 (5.5)</td>
</tr>
<tr>
<td>Faries (Talent, Medtronic/AVE-Worldmedical)</td>
<td>(1187)</td>
<td>2002 (1999-2001)</td>
<td>368</td>
<td>1.10</td>
<td>12 (12)</td>
<td>4.8 (4.8)</td>
</tr>
<tr>
<td>Matsumura (Excluder; WL Gore &amp; Associates)</td>
<td>(1188)</td>
<td>2003 (2000-2002)</td>
<td>Endo: 235 Open: 99</td>
<td>None</td>
<td>22 (22)</td>
<td>17 (17)</td>
</tr>
<tr>
<td><strong>EUROSTAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buth</td>
<td>(1163)</td>
<td>2000 (1994-1999)</td>
<td>1554</td>
<td>1.70</td>
<td>16 (16)</td>
<td>0.9 (0.9)</td>
</tr>
<tr>
<td>Harris</td>
<td>(1189)</td>
<td>2000 (1996-2000)</td>
<td>2464</td>
<td>1.30</td>
<td>17 (17)</td>
<td>8.3 (8.3)</td>
</tr>
<tr>
<td>Vallabhaneni</td>
<td>(1190)</td>
<td>2001 (1994-2000)</td>
<td>2812</td>
<td>NA</td>
<td>NA</td>
<td>NA (NA)</td>
</tr>
<tr>
<td>Buth</td>
<td>(1166)</td>
<td>2002 (1996-2001)</td>
<td>3075</td>
<td>1.70</td>
<td>17 (17)</td>
<td>NA (NA)</td>
</tr>
<tr>
<td>Peppelenbosch</td>
<td>(1191)</td>
<td>2004 (1996-2002)</td>
<td>1962 (4.0 cm to 5.4 cm)</td>
<td>1.1</td>
<td>3.7 (Type I)</td>
<td>NA (NA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1528 (5.5 cm to 6.4 cm)</td>
<td>1.4</td>
<td>6.8 (Type I)</td>
<td>NA (NA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>902 (over 6.4 cm)</td>
<td>2.3</td>
<td>9.9 (Type I)</td>
<td>NA (NA)</td>
</tr>
</tbody>
</table>

EUROSTAR indicates European collaborators registry on stent-graft techniques for abdominal aortic aneurysm repair; NA, not available.
patients (16% vs. 3.7%, \( p = 0.02 \)) (1193). Consequently, the perceived margin of safety for endovascular aneurysm repair in truly high-risk candidates may be slightly overestimated by results from nonuniform patient populations. Irrespective of case mix, however, the comparatively low early mortality rate for endograft repair of aortic aneurysms in New York State deserves close attention. According to data reported by Anderson et al., the mortality rate for endograft procedures was significantly lower than for open procedures in New York during both 2001 (1.1% vs. 3.6%, \( p = 0.0018 \)) and 2002 (0.8% vs. 4.2%, \( p < 0.0001 \)) (1135).

Immediate conversion to an open operation presently is necessary in only 1% of patients, and approximately half of all early endoleaks appear to resolve spontaneously within a period of 30 days. Several reports have indicated that endovascular procedures have fewer early complications than open operations, require less intensive care, and are associated with correspondingly shorter lengths of stay in the hospital (1194-1196). Nevertheless, these and other studies (1197-1199) also have suggested that the total costs of endovascular repair probably exceed those for open repair, especially when the expense of subsequent follow-up imaging, further intervention, and secondary hospital admissions is added to the base cost ($6000 to $12 000 US) of most endografts. Despite its shorter length of stay and an earlier return to normal activity, aortic endografting does not appear to be associated with superior late functional outcome or longer quality-adjusted life expectancy than open surgical treatment (1200,1201).

5.2.7.4. Late Survival and Complication Rates

Representative data regarding late survival rate and the incidence of aneurysm rupture, delayed or persistent endoleaks, and endograft reinterventions are provided in Table 55. The follow-up interval is 3 years or less for much of the information in Table 55, and the methods that were used to calculate outcomes (i.e., crude vs. cumulative) are inconsistent. In addition, according to a 1999 report (1202), only 45% of the expected 18-month follow-up results for the first 899 aortic endografts in the EUROSTAR experience had been submitted to its central registry office. The current acquisition rate for this database is not known.

5.2.7.4.1. Survival Rates. Intermediate-term survival rates after endovascular aortic aneurysm repair primarily are influenced by antecedent risk factors, being lowest in series for which high surgical risk was a criterion for patient selection (1164,1170). Again using their scoring system (0 to 3) for stratifying incremental risk, Becker et al. (1141) calculated actuarial 1-year survival rates of 98%, 94%, 87%, and 81%, respectively. On the basis of EUROSTAR data, Buth et al. found that the cumulative 3-year survival rate was significantly lower for patients who had been deemed unfit for open repair or for general anesthesia than for the remainder of the registry population (68% vs. 83%, \( p = 0.0001 \)) (1166).
### Table 55. Representative Late Results for Endograft Repair of Infrarenal Abdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>First Author (Study/Sponsor)</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Aneurysm Rupture</th>
<th>Late Endoleaks</th>
<th>Endograft Reinterventions</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stelter</td>
<td>(1152)</td>
<td>1997 (1994-1997)</td>
<td>201</td>
<td>None</td>
<td>9.50%</td>
<td>11% Endo: 7.4% (median, 29 mo)</td>
<td>NA</td>
</tr>
<tr>
<td>Amesur</td>
<td>(1169)</td>
<td>1999 (1996-1998)</td>
<td>54</td>
<td>None</td>
<td>13%</td>
<td>NA Endo: 17%</td>
<td>NA</td>
</tr>
<tr>
<td>Amesur</td>
<td>(1153)</td>
<td>2000 (1996-1999)</td>
<td>130 Limbs</td>
<td>NA</td>
<td>NA</td>
<td>None Endo: 36% of limbs</td>
<td>NA</td>
</tr>
<tr>
<td>Baum</td>
<td>(1154)</td>
<td>2000</td>
<td>Unsupported: 27 limbs; supported: 122 limbs</td>
<td>NA</td>
<td>NA</td>
<td>Unsupported: 44%; supported: 5% (p less than .001)</td>
<td>NA</td>
</tr>
<tr>
<td>Chuter</td>
<td>(1164)</td>
<td>2000 (1996-1999)</td>
<td>High risk: 116</td>
<td>0.9%</td>
<td>7.8%</td>
<td>15% Endo: 82%; open: 96% (1 y)</td>
<td>82% (Mean, 16 mo)</td>
</tr>
<tr>
<td>Zarins</td>
<td>(1147)</td>
<td>2000 (1996-2000)</td>
<td>149</td>
<td>None</td>
<td>NA</td>
<td>Total 17% (median, 11 mo)</td>
<td>90%</td>
</tr>
<tr>
<td>Becker</td>
<td>(1141)</td>
<td>2001 (1994-2001)</td>
<td>305</td>
<td>0.7%</td>
<td>NA</td>
<td>Total 9.8% (5 y)</td>
<td>NA</td>
</tr>
<tr>
<td>Holzenbein</td>
<td>(1174)</td>
<td>2001</td>
<td>173</td>
<td>0.6%</td>
<td>NA</td>
<td>Total 22% (median, 18 mo)</td>
<td>NA</td>
</tr>
<tr>
<td>Howell</td>
<td>(1175)</td>
<td>2001</td>
<td>215</td>
<td>None</td>
<td>12%</td>
<td>Total 10% (maximum, 2 y)</td>
<td>NA</td>
</tr>
<tr>
<td>May</td>
<td>(1165)</td>
<td>2001 (1995-1998)</td>
<td>Endo: 148; open: 135</td>
<td>1.4%</td>
<td>5.4%</td>
<td>4.7% Endo: 96%; open: 85% (3 y)</td>
<td>85% (16 mo)</td>
</tr>
<tr>
<td>Ohki</td>
<td>(1203)</td>
<td>2001 (1992-2000)</td>
<td>239</td>
<td>0.8%</td>
<td>8.8%</td>
<td>5.9%</td>
<td>3.8% Endo: 91%; open: 86% (3 y)</td>
</tr>
<tr>
<td>Sicard</td>
<td>(1176)</td>
<td>2001 (1997-2000)</td>
<td>Endo: 260; open: 210</td>
<td>None</td>
<td>4.2%</td>
<td>2.7% Endo: 91%; open: NA (mean, 10 mo)</td>
<td>86% (3 y)</td>
</tr>
<tr>
<td>Abraham</td>
<td>(1146)</td>
<td>2002 (1998-2001)</td>
<td>116</td>
<td>0.9%</td>
<td>4.3%</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Datillo</td>
<td>(1177)</td>
<td>2002 (1994-2000)</td>
<td>362</td>
<td>0.8%</td>
<td>NA</td>
<td>11%</td>
<td>2.2% Late conversion</td>
</tr>
<tr>
<td>Sampram</td>
<td>(1178)</td>
<td>2003 (1996-2002)</td>
<td>703</td>
<td>0.4%</td>
<td>23%</td>
<td>15% (Total)</td>
<td>70% (3 y)</td>
</tr>
<tr>
<td>Ouriel</td>
<td>(1204)</td>
<td>2003 (1996-2002)</td>
<td>416 (Size less than 5.5 cm)</td>
<td>0.2%</td>
<td>1.4% (Type I)</td>
<td>NA</td>
<td>1.4% Conversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>284 (Size 5.5 cm or more)</td>
<td>0.7%</td>
<td>6.4%(Type I)</td>
<td>NA</td>
<td>8.2% Conversion</td>
</tr>
<tr>
<td>Ouriel</td>
<td>(1179)</td>
<td>2003 (1996-2002)</td>
<td>606 Men; 98 women</td>
<td>Men: 0.3%; women: 1.0%</td>
<td>Men: 30%; women: 35% (12 mo)</td>
<td>Men: 24%; women: 21% (total)</td>
<td>Men: 80%; women: 78% (24 mo)</td>
</tr>
<tr>
<td>Shames</td>
<td>(1180)</td>
<td>2003 (1999-2001)</td>
<td>203 Men; 42 women</td>
<td>None</td>
<td>Men: 11%; women: 21%</td>
<td>Men: 9%; women: 29% (total)</td>
<td>Men: 95%; women: 90% (mean, 11 mo)</td>
</tr>
</tbody>
</table>

*Continued on Next Page*
<table>
<thead>
<tr>
<th>First Author (Study/Sponsor)</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>No. of Patients</th>
<th>Aneurysm Rupture</th>
<th>Late Endoleaks</th>
<th>Endograft Reinterventions</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becquemin (Vanguard; Boston Scientific)</td>
<td>(1183)</td>
<td>1999 (1996-1997)</td>
<td>75</td>
<td>1.3%</td>
<td>6.70%</td>
<td>24%</td>
<td>4%</td>
</tr>
<tr>
<td>Zarins (AneuRx; Medtronic)</td>
<td>(1184)</td>
<td>1999 (1996-1997)</td>
<td>Endo: 190; open: 60</td>
<td>None</td>
<td>9.00%</td>
<td>5.9%</td>
<td>2%</td>
</tr>
<tr>
<td>Zarins (AneuRx; Medtronic)</td>
<td>(1185)</td>
<td>2000 (1996-1999)</td>
<td>1046</td>
<td>0.7% (mean, 16 mo)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zarins (AneuRx; Medtronic)</td>
<td>(1171)</td>
<td>2000 (1997-1998)</td>
<td>398</td>
<td>0.3%</td>
<td>13% (Centers) 20% (core lab)</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Zarins (AneuRx; Medtronic)</td>
<td>(1148)</td>
<td>2001 (1996-1999)</td>
<td>1192</td>
<td>0.8%</td>
<td>NA</td>
<td>Total 12%; cumulative (3 y)</td>
<td>86% (3 y)</td>
</tr>
<tr>
<td>Faries (Talent; Medtronic/AVE-Worldmedical)</td>
<td>(1187)</td>
<td>2002 (1999-2001)</td>
<td>368</td>
<td>0.5%</td>
<td>4.8% (12 mo)</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Zarins (AneuRx; Medtronic)</td>
<td>(1137)</td>
<td>2003 (1996-1999)</td>
<td>1193</td>
<td>1.3%</td>
<td>14%</td>
<td>NA</td>
<td>4.1% Late conversion</td>
</tr>
<tr>
<td><strong>EUROSTAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuypers (endoleak study)</td>
<td>(1202)</td>
<td>1999 (1994-1998)</td>
<td>899</td>
<td>NA</td>
<td>26% total 10% persistent</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cuypers (conversion study)</td>
<td>(1205)</td>
<td>2000 (1994-1999)</td>
<td>1871</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.6% overall conversion</td>
</tr>
<tr>
<td>Harris</td>
<td>(1189)</td>
<td>2000 (1996-2000)</td>
<td>2464</td>
<td>1% annual</td>
<td>15%</td>
<td>NA</td>
<td>2.1% annual conversion</td>
</tr>
<tr>
<td>Laheij</td>
<td>(1206)</td>
<td>2000 (1996-1999)</td>
<td>1023</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.1% annual conversion</td>
</tr>
<tr>
<td>Vallabhaneni</td>
<td>(1190)</td>
<td>2001 (1994-2000)</td>
<td>2464</td>
<td>0.01% annual</td>
<td>NA</td>
<td>NA</td>
<td>3.1% conversion</td>
</tr>
<tr>
<td>Buth</td>
<td>(1166)</td>
<td>2002 (1996-2001)</td>
<td>3075</td>
<td>0.7%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Harris</td>
<td>(1150)</td>
<td>2004 (1996-2003)</td>
<td>4242</td>
<td>1.4%</td>
<td>30% total 10% persistent</td>
<td>Total 22% cumulative (5 y)</td>
<td>80% (5 y)</td>
</tr>
<tr>
<td>Peppelenbosch</td>
<td>(1191)</td>
<td>2004 (1996-2002)</td>
<td>1962 (4.0 to 5.4 cm); 1528 (5.5 to 6.4 cm); 902 (over 6.4 cm)</td>
<td>0.4%; 0.6%; 1.8%;</td>
<td>5.3% (Type I); 4.9% (Type I); 10% (Type I)</td>
<td>NA</td>
<td>6.8% conversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endo indicates endovascular repair; EUROSTAR indicates European collaborators registry on stent-graft techniques for abdominal aortic aneurysm repair; NA, not available.
Ouriel and associates have made several observations regarding late complication rates in a large series of 703 patients who underwent endovascular repair of AAAs with either investigational or commercially available stent grafts at a single center during a 6-year period of study beginning in 1996 (1204). First, certain complications (i.e., graft limb occlusions, fabric tears, and type II endoleaks) appeared to occur more commonly with some grafts than with others and therefore may be device-specific (1204). Second, endograft repair of aneurysms that were larger than 5.4 cm in diameter was associated with a higher incidence of type I endoleaks (6.4% vs. 1.4%, p equals 0.011), device migration (13% vs. 4.4%, p equals 0.006), and conversion to open surgical repair (8.2% vs. 1.4%, p equals 0.031) than was the case with smaller aneurysms. Patients with larger aneurysms also had a lower survival rate (71% vs. 86%, p less than 0.001) and a higher risk for aneurysm-related death (6.1% vs. 2.6%, p equals 0.011) at 24 months of follow-up (1212). Finally, although there were no gender differences in the overall incidence of secondary interventions, graft limb occlusions occurred more frequently in women than in men (11% vs. 3.3%, p equals 0.022) (1179).

Others have reported similar data with respect to aneurysm size and patient gender. Peppelenbosch et al. found that EUROSTAR patients with aneurysms larger than 5.4 cm in diameter were more likely to be older and to have more preoperative risk factors, early complications, and late unrelated deaths than patients with smaller aneurysms (1191). In addition, large aneurysms often were associated with arterial anatomy (such as angulated or ectatic infrarenal necks and iliac aneurysms) that was less favorable for endograft repair and probably contributed to the significantly higher overall incidence of type I endoleaks, conversion to open surgical repair, and late rupture and/or aneurysm-related deaths that were documented in the group of patients who had large aneurysms. In another study of endograft repair in 245 patients (42 women), Shames et al. also determined that graft limb occlusions were more common among women (12% vs. 2.5%, p equals 0.05) (1180). Unlike Ouriel and associates (1179), however, these investigators found that women also had a higher incidence of all technical complications (17% vs. 8.3%, p less than 0.05) and secondary procedures (29% vs. 9.0%, p equals 0.001).

**5.2.7.4.3. Technical Success Rates.** The technical success rate is a useful way to express endograft results because it condenses a number of events into a single outcome value that ordinarily is calculated with the life-table method. Table 56 summarizes the early and intermediate-term technical success rates from 16 previous reports. These data reconfirm that longer follow-up will be necessary to determine the relative merit of endovascular repair compared with open operations for AAAs. In comparison, the technical success rate for endograft repair of isolated iliac aneurysms appears to be quite favorable according to the scant follow-up information that is available. Scheinert et al. described a series of 53 such aneurysms in 48 patients with successful endograft deploy-

ment in 98%, no persistent or secondary endoleaks, and patency rates of 95% and 88% at 3 and 4 years of follow-up, respectively (1213).

### 5.2.8. Prevention of Aortic Aneurysm Rupture

Aside from their infrequent other complications (e.g., peripheral or visceral embolism, aortocaval or primary aortoenteric fistula), the single most compelling reason to repair AAAs is to prevent fatal rupture. The first step in this process is to identify the presence of these aneurysms, beginning with a thorough physical examination or their recognition as an incidental finding on unrelated abdominal imaging studies. This is especially important in certain high-prevalence populations, such as those with known popliteal aneurysms or a family history of aortic aneurysms. The next step is to establish, on the basis of ultrasonography or computed tomography/magnetic resonance scanning, whether a particular aortic aneurysm already is large enough to warrant intervention or instead should be placed under periodic surveillance to determine its rate of expansion. Brown et al. have shown in a prospective but nonrandomized study that observation alone is a safe approach until an aneurysm undergoes a growth spurt or attains a threshold diameter of 5.0 cm (952). The success of watchful waiting is predicated on patient cooperation, however. In a similar study of 101 patients with aneurysms measuring less than 5.0 cm in diameter, Valentine et al. encountered no ruptures among patients who complied with their follow-up program compared with a 10% rupture rate among those who did not (1217). If continued surveillance is recommended, measures should be taken to control hypertension and to discourage smoking, because these risk factors are associated with accelerated rates of aneurysm growth (936,961). Ultimately, once an infrarenal aortic aneurysm reaches an appropriate size for graft replacement, a choice must be made between a traditional open operation or endovascular repair. Like all other aspects of aneurysm management, this decision requires a balanced judgment of relative risks.

#### 5.2.8.1. Management Overview

**RECOMMENDATIONS**

**Class I**

1. **Open repair of infrarenal AAAs and/or common iliac aneurysms is indicated in patients who are good or average surgical candidates. (Level of Evidence: B)**

2. **Periodic long-term surveillance imaging should be performed to monitor for an endoleak, to document shrinkage or stability of the excluded aneurysm sac, and to determine the need for further intervention in patients who have undergone endovascular repair of infrarenal aortic and/or iliac aneurysms. (Level of Evidence: B)**
Table 56. Technical Success Rates for Endograft Repair of Infrarenal Abdominal Aortic Aneurysms

<table>
<thead>
<tr>
<th>Author</th>
<th>Device/Vendor</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>n</th>
<th>Criteria for Technical Success</th>
<th>Technical Success Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blum</td>
<td></td>
<td>(1167)</td>
<td>1997 (1994-1996)</td>
<td>154</td>
<td>Successful deployment</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td></td>
</tr>
<tr>
<td>Stelter</td>
<td></td>
<td>(1152)</td>
<td>1997 (1994-1997)</td>
<td>201</td>
<td>NA</td>
<td>89%</td>
</tr>
<tr>
<td>Coppi</td>
<td></td>
<td>(1182)</td>
<td>1998 (1995-1996)</td>
<td>66</td>
<td>Successful deployment</td>
<td>86% (30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No deaths</td>
<td></td>
</tr>
<tr>
<td>Hausegger</td>
<td></td>
<td>(1214)</td>
<td>1999</td>
<td>30</td>
<td>Successful deployment</td>
<td>83% primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td>93% secondary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Open: 107</td>
<td>No re-intervention</td>
<td>94% (1 year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td></td>
</tr>
<tr>
<td>Howell</td>
<td></td>
<td>(1215)</td>
<td>2000</td>
<td>56</td>
<td>NA</td>
<td>83% primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85% secondary (6 months)</td>
</tr>
<tr>
<td>Blum</td>
<td></td>
<td>(1172)</td>
<td>2001 (1994-2001)</td>
<td>111</td>
<td>Successful deployment</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>96%</td>
</tr>
<tr>
<td>Ohki</td>
<td></td>
<td>(1203)</td>
<td>2001 (1992-2000)</td>
<td>239</td>
<td>Successful deployment</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td></td>
</tr>
<tr>
<td>Device Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zarins</td>
<td>AneuRx™/Medtronic</td>
<td>(1184)</td>
<td>1999</td>
<td>190</td>
<td>Successful deployment</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No endoleaks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No deaths</td>
<td></td>
</tr>
<tr>
<td>Zarins</td>
<td>AneuRx™/Medtronic</td>
<td>(1171)</td>
<td>2000 (1997-1998)</td>
<td>398</td>
<td>Survival free of aneurysm</td>
<td>88% (18 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rupture, open conversion, or re-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>intervention for endoleaks or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>graft thrombosis</td>
<td></td>
</tr>
</tbody>
</table>

Continued on Next Page
Table 56. Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Device/Vendor</th>
<th>Reference</th>
<th>Year (Study Period)</th>
<th>n</th>
<th>Criteria for Technical Success</th>
<th>Technical Success Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early</td>
</tr>
<tr>
<td>Beebe</td>
<td>Vanguard™/Boston Scientific</td>
<td>(1186)</td>
<td>2001</td>
<td>240</td>
<td>Successful deployment</td>
<td>89% (30 days)</td>
</tr>
<tr>
<td>Criado</td>
<td>Talent™/Medtronic World Medical</td>
<td>(1216)</td>
<td>2001 (1997-2001)</td>
<td>High risk: 127 Low risk: 151</td>
<td>Successful deployment No endoleaks</td>
<td>86% (96% at 30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuypers</td>
<td></td>
<td>(1202)</td>
<td>1999 (1994-1998)</td>
<td>899</td>
<td>Endoleak-free survival</td>
<td>79% (18 months, cumulative)</td>
</tr>
<tr>
<td>Buth</td>
<td></td>
<td>(1163)</td>
<td>2000 (1994-1999)</td>
<td>1,554</td>
<td>Successful deployment No endoleaks</td>
<td>72% (30 days)</td>
</tr>
<tr>
<td>Laheij</td>
<td></td>
<td>(1206)</td>
<td>2000 (1996-1999)</td>
<td>1,023</td>
<td>Freedom from any secondary intervention</td>
<td>1 yr: 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 yrs: 67%</td>
</tr>
</tbody>
</table>

EUROSTAR indicates European collaborators registry on stent-graft techniques for abdominal aortic aneurysm repair; n, number of patients; NA, not available.
Class IIa
Endovascular repair of infrarenal aortic and/or common iliac aneurysms is reasonable in patients at high risk of complications from open operations because of cardiopulmonary or other associated diseases. (Level of Evidence: B)

Class IIb
Endovascular repair of infrarenal aortic and/or common iliac aneurysms may be considered in patients at low or average surgical risk. (Level of Evidence: B)

An overview of the management of AAAs is depicted in Figure 19. This algorithm incorporates the results of the randomized UK and VA trials and takes into account the relatively limited information that yet is available regarding the long-term outcome of endograft repair for infrarenal aneurysms. It must be conceded from the outset that there could be honest scientific disagreement regarding a few of the recommended pathways that are illustrated in this algorithm. Some clinicians may be convinced that infrarenal aneurysms should continue to be repaired at a size of only 5.0 cm or larger, whereas others could believe that the conclusions of the UK and VA trials are not directly applicable to aortic aneurysms that involve the renal arteries and that these aneurysms should be even larger than 5.5 cm in diameter before elective surgical treatment is advised, to warrant its additional risks. In addition, there undoubtedly are many who believe that the present technology of endovascular repair is at a state of development that justifies its general use in low- and average-risk patients and in those who appear to be at high risk for conventional open operations. There is nothing unfavorable about its early safety to discourage this opinion. As an example from northern California and Nevada, proctored endovascular aneurysm repair was undertaken at 22 community hospitals in a series of 257 patients, only 29% of whom had medical contraindications to conventional operations, with 2 immediate open conversions and a 30-day mortality rate of 1.2% (1218). However, this report shares the current liability of many studies concerning aortic stent grafts. The mean follow-up period for these patients was only 9.6 months, during which another 8% of them required reintervention.

5.3. Visceral Artery Aneurysms

RECOMMENDATIONS

Class I
Open repair or catheter-based intervention is indicated for visceral aneurysms measuring 2.0 cm in diameter or larger in women beyond childbearing age and in men. (Level of Evidence: B)

Visceral aneurysms are insidious because they usually cannot be detected by physical examination, are easily overlooked on plain roentgenograms unless mural calcification is present, and occur so infrequently that they may not be fully appreciated during incidental computed tomography/magnetic resonance imaging scanning. Not surprisingly, therefore, several studies have indicated that approximately half of all visceral artery aneurysms present with rupture (Table 57). In comparison, spontaneous rupture appears to be an unusual event for renal artery aneurysms, possibly because exceptionally large renal artery aneurysms may be discovered on the basis of nonacute symptoms, such as hypertension or hematuria. Although rare under any circumstances, both visceral and renal artery aneurysms most commonly occur in multiparous women (1219, 1220). Furthermore, some studies have suggested that the incidence of splenic artery aneurysms is particularly high among patients who have portal hypertension or a history of previous liver transplantation (1221-1223). The mortality rate for surgical repair of ruptured visceral aneurysms is sufficiently ominous (25% or higher) that patients who have these risk factors probably should be investigated for visceral artery aneurysms in the presence of unexplained abdominal symptoms.

5.3.1. Splenic Artery Aneurysms

Splenic artery aneurysms historically have been considered to be the most common visceral artery aneurysms (Table 58), but an increasing incidence of hepatic artery pseudoaneurysms has been described in relation to percutaneous and laparoscopic biliary procedures, as well as improved imaging techniques (1229, 1230). Most splenic artery aneurysms are asymptomatic at the time they are recognized as an incidental finding during some type of abdominal imaging, but approximately 20% of patients present with either chronic upper abdominal pain or acute rupture (Table 59). An increasing number of splenic artery aneurysms also are being discovered in women undergoing ultrasound evaluations during pregnancy. The mortality rate for ruptured splenic artery aneurysms in patients who are not pregnant ranges from 10% to 25%, but the risk of maternal death from rupture during pregnancy has been estimated to be as high as 70%, with a fetal mortality rate of more than 90% (1231). The natural history of splenic artery aneurysms followed up through pregnancy is unknown because no large series of such patients has been collected. Nevertheless, the literature contains many case reports of pregnant women who were known to have splenic artery aneurysms that were at least 2.0 cm in diameter and that eventually ruptured during their pregnancies.

5.3.2. Superior Mesenteric Artery Aneurysms

Superior mesenteric artery aneurysms represent only 6% to 7% of all visceral aneurysms (1226, 1229). Stone et al. have
Figure 19. Management of abdominal aortic aneurysms. CT indicates computed tomography; MR, magnetic resonance imaging.
described the largest series of superior mesenteric aneurysms, comprising just 21 patients who were collected from 2 large institutions during a 19-year study period (1226). Men and those patients with noncalcified aneurysms appeared to have the highest risk for rupture. Interestingly, no ruptured aneurysms happened to occur among patients who were receiving beta-blockade. The operative mortality rate for ruptured aneurysms was 38%, but there were no deaths after elective intervention (e.g., ligation, catheter embolization, or prosthetic replacement grafting) in 8 patients. None of the patients who underwent elective ligation or catheter embolization developed intestinal ischemia. This probably implies that these patients were selected very carefully on the basis of the collateral circulation that was demonstrated by their initial arteriograms, but it could also suggest that revascularization after ligation or catheter embolization sometimes can be deferred unless there is clinical evidence of ischemia. Five patients in this series who had small (diameter of 1.0 to 2.4 cm) aneurysms have been followed up with computed tomographic or ultrasound scans for 2 to 147 months without complications.

### Table 58. Site of Visceral Artery Aneurysms

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenic</td>
<td>60</td>
</tr>
<tr>
<td>Hepatic</td>
<td>20</td>
</tr>
<tr>
<td>Superior mesenteric</td>
<td>6</td>
</tr>
<tr>
<td>Celiac</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
</tr>
</tbody>
</table>

Reprinted from Semin Vasc Surg, 8, Hallett JW, Jr., Splenic artery aneurysms, 321-6, Copyright 1995, with permission from Elsevier (1229).

### Table 59. Demographics of Splenic Artery Aneurysms (n=100)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>87:13</td>
</tr>
<tr>
<td>Women:men</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>58.2 (16 to 81)</td>
</tr>
<tr>
<td>Mean number of pregnancies</td>
<td>4.5 (1 to 16)</td>
</tr>
<tr>
<td>Aneurysm size (cm)</td>
<td>2.1 (0.6 to 30)</td>
</tr>
<tr>
<td>Symptoms (%)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>83</td>
</tr>
<tr>
<td>Chronic</td>
<td>13</td>
</tr>
<tr>
<td>Rupture</td>
<td>4</td>
</tr>
</tbody>
</table>

n indicates number of patients.

Reprinted from Semin Vasc Surg, 8, Hallett JW, Jr., Splenic artery aneurysms, 321-6, Copyright 1995, with permission from Elsevier (1229).
5.3.3. Management Options

An array of open surgical and laparoscopic approaches has been reported for visceral artery aneurysms, with varying mortality rates depending on the clinical setting. Percutaneous catheter-based therapy with coil embolization leading to thrombosis of visceral aneurysms has been described for elective patients and for those who present with acute rupture. The technical success rate for these nonsurgical options ranges from 67% to 100%, with few fatalities or complications (850,1232,1233). One concern that should be recognized related to the catheter-based management of visceral artery aneurysms is the limited ability to assess the end organ after aneurysm treatment. This is in contrast to open surgical visceral artery aneurysm repair, in which the end organ may be visualized and assessed, a point that appears to be especially important in the treatment of mesenteric artery aneurysms, for which there is potential risk for bowel ischemia. Therefore, patients undergoing catheter-based intervention for visceral artery aneurysms should be watched closely after the procedure for the development of abdominal pain in the setting of mesenteric or splenic artery aneurysms and flank pain in the setting of renal artery aneurysms.

5.4. Lower Extremity Aneurysms

5.4.1. Etiology

As illustrated in Figures 20 and 21, the diameters of peripheral arteries increase approximately 20% to 25% between the ages of 20 and 70 years (865,1234). Coexistent AAAs have been reported in 85% of patients with femoral aneurysms (1235) and in 62% of those with popliteal aneurysms (1236), whereas femoral or popliteal aneurysms are present in 3% to 7% of patients who have AAAs. It is not known whether these patients are specifically prone to diffuse aneurysm disease because of genetic or other factors or whether certain aneurysms are associated with generalized arterial ectasia elsewhere (1237-1239). The possibility that arterial aneurysm disease is a generalized process in the vascular system is supported by studies showing defective mechanical properties in the walls of distant arteries that usually do not undergo dilatation (1240,1241). When dilatation of the peripheral arteries was described in patients with AAAs more than a decade ago, the normal diameters of the studied regional arteries were unknown (1242,1243).

In an angiographic study in which arterial luminal diameters were measured, dilatation in the iliac artery was identified in patients with AAA, but the peripheral arteries in the leg were not affected (1244). The tunica media of the femoral and popliteal arteries consists largely of smooth muscle cells. The mechanical properties (and thus the integrity) of arterial
walls are based on the matrix components, elastin and collagen, whereas smooth muscle cells have the potential to modulate wall mechanics. Therefore, the systemic implications of an aortic aneurysm may be different in central arteries than in peripheral arteries. In another investigation by Sandgren et al., ultrasound measurements of the anteroposterior diameters of the peripheral arteries of the right legs of 183 consecutive patients who were referred for elective repair of AAA revealed 8 common femoral aneurysms and 4 popliteal aneurysms, all in men (879). Of those in whom femoral and popliteal aneurysms were identified, occlusive PAD was present in 46% and 49%, respectively. After exclusion of those with either peripheral aneurysms or occlusive disease, no dilating diathesis was found in the limb vessels of the remaining patients with AAA.

5.4.2. Natural History

Unlike AAAs, the natural history of extremity-artery aneurysms is not one of expansion and rupture but one of thromboembolism or thrombosis.

RECOMMENDATION

Class I

In patients with femoral or popliteal aneurysms, ultrasound (or computed tomography or magnetic resonance) imaging is recommended to exclude contralateral femoral or popliteal aneurysms and AAA. (Level of Evidence: B)

5.4.2.1 Popliteal Artery Aneurysms

Popliteal aneurysms account for 70% of all aneurysms in the lower extremities and have an estimated incidence of 0.1% to 2.8% (1245,1246). Approximately 5% of small aortic aneurysms are discovered because of lower extremity ischemia caused by distal embolization of mural thrombus (1247). However, thromboembolic complications are much more common with popliteal aneurysms, which also may be associated with arteriomegaly involving the common femoral and superficial femoral arteries. Before the introduction of modern arterial bypass grafting, Gifford et al. reported a series of 69 patients with 100 popliteal aneurysms, of which 45% were bilateral and 65% were symptomatic (1248). Only 21% of these aneurysms were treated surgically. Very few (7%) of the remaining aneurysms eventually ruptured, but 21% ultimately were associated with ischemic complications, and 23% of the 69 patients required amputations.

Although rupture has continued to be distinctly unusual in some studies, the data in Table 60 confirm many of the other observations that were made by Gifford et al. (1248). The vast majority of popliteal aneurysms occur in men, and approximately half are bilateral. Approximately half of popliteal aneurysms also are associated with other aneurysms, principally involving the abdominal aorta. At least 40% of popliteal aneurysms are symptomatic on discovery because of thrombosis-in-situ of the popliteal artery or distal emboli to the calf or foot. According to a collective review of the literature that was conducted by Dawson et al. (1249), these complications still occur in 36% of patients whose popliteal aneurysms are merely placed under observation, a figure that is remarkably similar to the late complication rate of 34% that was reported by Gifford and his associates more than 40 years earlier. Furthermore, Dawson et al. also found that the cumulative incidence of ischemic complications was as high as 70% during 5 to 10 years of follow-up for popliteal aneurysms that were evaluated at their own center (1250,1251).

According to data reported by Roggo et al., as many as 50% of previously asymptomatic popliteal aneurysms may be expected to become symptomatic within 2 years after their discovery and 75% within 5 years (1254) (Figure 22). Symptomatic popliteal aneurysms generally exceed 2.0 cm in diameter, often contain a substantial amount of mural thrombus on B-mode ultrasound imaging, and frequently are associated with distal tibioperoneal arterial occlusions that suggest previous emboli (1252,1253,1255). Probably because of prior emboli with thrombosis of downstream outflow vessels, Poirier et al. reported that 56% of patients continued to experience distal ischemia despite surgical repair of symptomatic popliteal aneurysms, and 19% eventually required amputation (1256).

The unfavorable consequences of popliteal aneurysms suggest that even asymptomatic popliteal aneurysms with good distal runoff should be repaired electively, although there is a lack of prospective studies to support an unqualified recommendation in this regard, especially for aneurysms measuring less than 2.0 cm in diameter. In fact, there is a published consensus that small popliteal aneurysms rarely become symptomatic and that elective surgical intervention should be considered only for those measuring at least 2.0 cm in diameter (1245,1254,1255). Stiegler et al. have reported a series of 46 patients who had 65 popliteal artery aneurysms with a mean diameter of 1.9 cm (range 0.8 to 4.0 cm); the aneurysms were occluded at the time of their discovery in only 8 patients (mean diameter 2.4 cm, range 1.4 to 4.0 cm) (1257). Thirty-six patients with 46 aneurysms were observed over a period of 2.5 years. The total complication rate was 6.5%, with a higher incidence in patients whose aneurysms were larger than 2.0 cm in diameter (14% vs. 3.1%). Complications also appeared to occur more frequently (14% vs. 0%) in the 19 patients who were treated with platelet-inhibitor drugs than in 16 others who received coumarin anticoagulation. The mean increase in diameter during follow-up was 1.5 mm per year for aneurysms larger than 2.0 cm versus 0.7 mm per year for smaller aneurysms. In another regional survey of 19 vascular surgeons who contributed data for 200 popliteal aneurysms in 137 patients during a 4-year period of study, Varga et al. determined that 31% of small, untreated aneurysms eventually required surgical intervention because of the onset of new symptoms or expansion to a diameter that exceeded 2.0 cm while under surveillance (968).
### Table 60. Presentation and Complication Rates for Popliteal Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients and/or Aneurysms</th>
<th>Bilateral Popliteal or Other Aneurysms</th>
<th>Previous Symptoms Before Presentation</th>
<th>Initial Surgical Treatment</th>
<th>Complications With Observation Alone</th>
<th>Related Amputation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gifford</td>
<td>(1248)</td>
<td>1953</td>
<td>69/100 (66 men)</td>
<td>45% bilateral; 25% other</td>
<td>45% (34% ischemic; 12% ruptured)</td>
<td>21%</td>
<td>34% (21% ischemic; 7% ruptured)</td>
<td>23% (7% early; 16% late)</td>
</tr>
<tr>
<td>Dawson</td>
<td>(1250)</td>
<td>1991</td>
<td>50/71</td>
<td>42% bilateral; 32% other</td>
<td>NA</td>
<td>65%</td>
<td>54%</td>
<td>NA</td>
</tr>
<tr>
<td>Carpenter</td>
<td>(967)</td>
<td>1994</td>
<td>33/54</td>
<td>62% bilateral; 61% other</td>
<td>61% (39% ischemic)</td>
<td>83%</td>
<td>NA</td>
<td>11%</td>
</tr>
<tr>
<td>Dawson</td>
<td>(1251)</td>
<td>1994</td>
<td>42/42</td>
<td>NA</td>
<td>All asymptomatic</td>
<td>None</td>
<td>60%</td>
<td>7%</td>
</tr>
<tr>
<td>Lowell</td>
<td>(1252)</td>
<td>1994</td>
<td>106/161 (103 men)</td>
<td>52% bilateral</td>
<td>42%</td>
<td>31%</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Schroder</td>
<td>(1253)</td>
<td>1996</td>
<td>217/349</td>
<td>61% bilateral</td>
<td>45%</td>
<td>63%</td>
<td>47%</td>
<td>NA</td>
</tr>
<tr>
<td>Duffy</td>
<td>(1245)</td>
<td>1998</td>
<td>24/40 (23 men)</td>
<td>66% bilateral</td>
<td>58%</td>
<td>75%</td>
<td>None (smaller than 2 cm)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Collective reviews</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dawson</td>
<td>(1249)</td>
<td>1997</td>
<td>1673/2445 (95% men)</td>
<td>50% bilateral; 37% other</td>
<td>67%</td>
<td>NA</td>
<td>36%</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA indicates not available.
deep femoral aneurysms appears to be higher than that of other lower extremity aneurysms, occurring in one third of the cases reported by Cutler and Darling (1260). Other complications are related to expansion, such as femoral nerve compression, venous occlusion with phlegmasia cerulea dolens, and acute leg ischemia secondary to thrombosis or embolization (1260-1264).

5.4.3. Management

RECOMMENDATIONS

Class I

1. Patients with a palpable popliteal mass should undergo an ultrasound examination to exclude popliteal aneurysm. (Level of Evidence: B)

2. Patients with popliteal aneurysms 2.0 cm in diameter or larger should undergo repair to reduce the risk of thromboembolic complications and limb loss. (Level of Evidence: B)

3. Patients with anastomotic pseudoaneurysms or symptomatic femoral artery aneurysms should undergo repair. (Level of Evidence: A)

Class IIa

1. Surveillance by annual ultrasound imaging is suggested for patients with asymptomatic femoral artery true aneurysms smaller than 3.0 cm in diameter. (Level of Evidence: C)

2. In patients with acute ischemia and popliteal artery aneurysms and absent runoff, catheter-directed thrombolysis or mechanical thrombectomy (or both) is suggested to restore distal runoff and resolve emboli. (Level of Evidence: B)

3. In patients with asymptomatic enlargement of the popliteal arteries twice the normal diameter for age and gender, annual ultrasound monitoring is reasonable. (Level of Evidence: C)
4. In patients with femoral or popliteal artery aneurysms, administration of antiplatelet medication may be beneficial. (Level of Evidence: C)

5.4.3.1. Popliteal Aneurysms

A popliteal mass should be studied by duplex ultrasonography to distinguish an aneurysm from other soft-tissue lesions, such as a synovial (Baker’s) cyst, especially if the patient has a history of other arterial aneurysms involving the contralateral lower extremity or the abdominal aorta. Nonoperative observation with periodic noninvasive surveillance may be appropriate if the aneurysm measures less than 2.0 cm in diameter or contains no thrombus or if the patient is at high surgical risk or has limited longevity because of medical comorbidities. If symptoms develop or the aneurysm enlarges on follow-up duplex scans, the risk of thromboembolic complications and limb loss then must be weighed against whatever factors originally may have influenced the decision to postpone surgical treatment. Farina et al. were unable to identify any controlled trials regarding clinical management in their review of 29 studies comprising 1673 patients with 2445 popliteal arterial aneurysms (1265).

In the setting of acute ischemia related to popliteal artery aneurysm thrombosis or thromboembolism, catheter-directed thrombolytic therapy is useful to re-establish patency of the popliteal and tibial trunks to allow for more effective definitive aneurysm treatment and limb salvage. Largely on the basis of previous and often unrecognized emboli, one of the obstacles to a successful surgical outcome is the absence of adequate arterial outflow in the calf and foot. Because limb salvage rates can be correlated directly with the number of available runoff vessels, as much thrombus as possible must be cleared from the tibioperoneal and plantar arteries in conjunction with bypass grafting to exclude the popliteal aneurysm from the circulation. In the past, this has been done strictly with thromboembolectomy balloon catheters in the operating room, often after preoperative arteriograms or MRA scans have failed to determine whether a target vessel for revascularization even is present. Some series now have been reported, however, in which preoperative intra-arterial thrombolytic therapy has been a valuable adjunct for restoring runoff in the presence of recent thromboembolic events (881,882,1251,1252). Failure to attain runoff with catheter-directed thrombolysis suggests that atheroemboli are involved and/or that a fasciotomy should be considered because of high muscular compartment pressures that may be contributing to the occlusion of otherwise normal outflow vessels.


![Figure 23.](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.105.9.607)

cessful if saphenous vein is used as the conduit and fasciotomy is performed.

The algorithm presented in Figure 24 summarizes the management options for either symptomatic or asymptomatic popliteal aneurysms. In the presence of mural thrombus, the diameter of a popliteal aneurysm will appear to be smaller on an arteriogram than its true diameter on duplex or computed tomographic imaging, but the value of an arteriogram is to determine the adequacy of tibioperoneal outflow and whether the use of catheter-directed thrombolytic therapy should be considered to restore runoff. The decision to proceed with elective surgical treatment in the absence of limb-threatening ischemia is not predicated on aneurysm size alone. It must also take into account the overall clinical situation, the severity of symptoms in the leg, and the surgical or endovascular facilities that are available.

5.4.3.2. Femoral Aneurysms

The cause of femoral artery aneurysms may be arterial degeneration (i.e., true aneurysms) or false aneurysms related to previous vascular reconstructions or arterial injury. Femoral artery pseudoaneurysm represents a pulsatile mass that is contained by incomplete elements of the arterial wall and surrounding subcutaneous/fibrous tissue and may result from disruption of a previous femoral suture line, femoral artery access for a catheter-based procedure, or injury resulting from puncture due to self-administered drug abuse. Regardless of the cause, a pulsatile groin mass should be evaluated by duplex ultrasound and/or contrast-enhanced computed tomographic scan. The clinical presentation of true femoral artery aneurysms is summarized in Table 62 (1272). Most reports encourage a policy of elective surgical treatment for symptomatic patients if their operative risk is low and if the patient has a reasonable life expectancy. In 2 series, however, nonoperative observation has been used twice as often as elective intervention for asymptomatic femoral aneurysms and appears to be associated with a relatively low risk for complications during follow-up periods of 28 to 52 months (1115,1156). Therefore, the stable femoral artery aneurysm presents a therapeutic dilemma, because its complication rate appears to be substantially lower than that for

Figure 24. Diagnostic and treatment algorithm for popliteal mass. CT indicates computed tomography.
Table 61. Graft Patency and Limb Salvage Rates for Popliteal Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Follow-Up (y)</th>
<th>No. of Patients</th>
<th>Symptoms</th>
<th>Patency (%)</th>
<th>Graft Material</th>
<th>Limb Salvage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Anton</td>
<td>(1266)</td>
<td>5</td>
<td>123</td>
<td>–</td>
<td>82</td>
<td>57</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>56</td>
<td>82</td>
<td>48</td>
<td>94</td>
<td>27</td>
</tr>
<tr>
<td>Carpenter</td>
<td>(967)</td>
<td>5</td>
<td>54</td>
<td>71</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cole</td>
<td>(1267)</td>
<td>3</td>
<td>59</td>
<td>88</td>
<td>94</td>
<td>81</td>
<td>–</td>
</tr>
<tr>
<td>Dawson</td>
<td>(1250)</td>
<td>5</td>
<td>46</td>
<td>75</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>64</td>
<td>–</td>
<td>–</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>Duffy</td>
<td>(1245)</td>
<td>3</td>
<td>30</td>
<td>84</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Farina</td>
<td>(1265)</td>
<td>5</td>
<td>50</td>
<td>62</td>
<td>80</td>
<td>65</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inahara</td>
<td>(1268)</td>
<td>10</td>
<td>40</td>
<td>76</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lilly</td>
<td>(1268a)</td>
<td>5</td>
<td>48</td>
<td>74</td>
<td>91</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>Reilly</td>
<td>(1269)</td>
<td>5</td>
<td>167</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>77</td>
</tr>
<tr>
<td>Roggo</td>
<td>(1254)</td>
<td>5</td>
<td>252</td>
<td>69</td>
<td>85</td>
<td>61</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>87</td>
</tr>
<tr>
<td>Schellack</td>
<td>(1270)</td>
<td>5</td>
<td>95</td>
<td>75</td>
<td>93</td>
<td>66</td>
<td>92</td>
</tr>
<tr>
<td>Schroder</td>
<td>(1253)</td>
<td>4</td>
<td>221</td>
<td>–</td>
<td>89</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Szilagyi</td>
<td>(1255)</td>
<td>5</td>
<td>50</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>28</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Towne</td>
<td>(1271)</td>
<td>5</td>
<td>115</td>
<td>53</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*A indicates 34% polyester fiber and 74% polytetrafluorethylene (PTFE); B, 33% polyester fiber and 64% PTFE.
SV indicates saphenous vein.
### Table 62. Clinical Presentation of Femoral Aneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Aneurysms (n)</th>
<th>Males:Females</th>
<th>Bilateral (%)</th>
<th>AAA/PAA Associated (%)</th>
<th>Asymptomatic (%)</th>
<th>Presenting Symptoms</th>
<th>Complications at Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutler</td>
<td>(1260)</td>
<td>45</td>
<td>63</td>
<td>40:5</td>
<td>47</td>
<td>51/27</td>
<td>29</td>
<td>Local: 29%</td>
<td>Acute thrombosis: 16%; chronic thrombosis: 16%; rupture: 14%</td>
</tr>
<tr>
<td>Adiseshiah</td>
<td>(1273)</td>
<td>16</td>
<td>27</td>
<td>15:1</td>
<td>62</td>
<td>25/31</td>
<td>70</td>
<td></td>
<td>Embolization: 4%; thrombosis: 7%; rupture: 15%</td>
</tr>
<tr>
<td>Baird</td>
<td>(1274)</td>
<td>30</td>
<td>36</td>
<td>30:0</td>
<td>20</td>
<td>40/17</td>
<td>27</td>
<td>Local: 23%; ischemic: 50%</td>
<td>Acute thrombosis/embolization: 13%; rupture: 0%</td>
</tr>
<tr>
<td>Graham</td>
<td>(1235)</td>
<td>100</td>
<td>172</td>
<td>100:0</td>
<td>72</td>
<td>85/44</td>
<td>40</td>
<td>Local pain: 11%; mass: 16%; venous: 8%; ischemic: 42%</td>
<td>Embolization: 8%; acute thrombosis: 1%; chronic thrombosis: 1%; rupture: 2%</td>
</tr>
<tr>
<td>Sapienza</td>
<td>(1275)</td>
<td>22</td>
<td>31</td>
<td>21:1</td>
<td>41</td>
<td>50/—</td>
<td>64</td>
<td>Local: 5%; ischemic: 35%</td>
<td></td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; FAA, femoral artery aneurysm; PAA, popliteal artery aneurysm.

popliteal aneurysms of similar size. A wide range of normal dimensions (see Figure 20) makes it difficult to determine an arbitrary size at which true femoral aneurysms should be repaired. By convention, femoral aneurysms measuring 3.0 cm or larger appear most likely to cause compressive symptoms and therefore also are most likely to be treated surgically. Although the presence of mural thrombus conceivably could represent a risk for distal emboli unless elective repair is performed, the actual magnitude of this risk is unknown.

Anastomotic pseudoaneurysms occur with an incidence of 2% to 5%, are encountered most commonly as a late complication of synthetic aortofemoral bypass grafting, inevitably continue to enlarge if left untreated, and may require arteriography before repair. Infected femoral pseudoaneurysms may occur as the result of arterial puncture during drug abuse and must be treated by extensive operative debridement, often in conjunction with either autogenous in situ reconstruction or extra-anatomic bypass grafts to avoid CLI. Skin erosion or expanding rupture into adjacent soft tissue obviously is an unstable situation for which urgent surgical repair is necessary regardless of the cause of the femoral artery aneurysm or pseudoaneurysm.

5.4.3.3. Catheter-Related Femoral Artery Pseudoaneurysms

RECOMMENDATIONS

Class I

1. Patients with suspected femoral pseudoaneurysms should be evaluated by duplex ultrasonography. (Level of Evidence: B)

2. Initial treatment with ultrasound-guided compression or thrombin injection is recommended in patients with large and/or symptomatic femoral artery pseudoaneurysms. (Level of Evidence: B)

A pseudoaneurysm is a pulsatile hematoma that communicates with an artery through a defect in the arterial wall. Femoral pseudoaneurysms are well-recognized complications of arterial catheterization, occurring after 0.1% to 0.2% of diagnostic angiograms and after 3.5% to 5.5% of interventional procedures. Puncture-site pseudoaneurysms are most commonly associated with longer procedures, the use of larger-diameter delivery-sheath sizes catheters, systemic anticoagulation, and difficult arterial access. Some studies have suggested that more than 60% of catheter-related femoral pseudoaneurysms are overlooked on the basis of the physical examination alone. Therefore, although a pulsatile mass is an obvious indication that a pseudoaneurysm may be present, a diagnostic duplex scan should be obtained whenever the diagnosis is even suspected.

In the absence of antithrombotic therapy, several studies have indicated that catheter-related pseudoaneurysms that are less than 2.0 cm in diameter tend to heal spontaneously and usually require no treatment. Collectively, 61% of the small pseudoaneurysms in the 9 series that are summarized in Table 63 resolved within 7 to 52 days of observation, and only 11% ultimately required surgical intervention. Figure 25 illustrates the spontaneous closure rate of selected pseudoaneurysms that were not repaired immediately, 90% of which resolved within 2 months. Accordingly, small asymptomatic pseudoaneurysms probably can be managed conservatively.

Table 63. Spontaneous Thrombosis of Femoral Pseudoaneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Spontaneous Closure (n)</th>
<th>Surgery (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feld</td>
<td>(1276)</td>
<td>17</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fellmeth</td>
<td>(1277)</td>
<td>35</td>
<td>4</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Johns</td>
<td>(1278)</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>7 to 42 days to close</td>
</tr>
<tr>
<td>Kazmers</td>
<td>(1279)</td>
<td>53</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Kresowik</td>
<td>(1280)</td>
<td>7</td>
<td>7</td>
<td>—</td>
<td>Less than 28 days to close</td>
</tr>
<tr>
<td>Samuels</td>
<td>(1281)</td>
<td>11</td>
<td>11</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Schaub</td>
<td>(1282)</td>
<td>54</td>
<td>50</td>
<td>—</td>
<td>Approximately 52 days to close</td>
</tr>
<tr>
<td>Toursarkissian</td>
<td>(1283)</td>
<td>147</td>
<td>86%</td>
<td>14%</td>
<td>Approximately 23 days to close</td>
</tr>
<tr>
<td>Weatherford</td>
<td>(1284)</td>
<td>27</td>
<td>7</td>
<td>10</td>
<td>Median 40 days to close</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>357</td>
<td>217</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Fractional percentage</td>
<td></td>
<td></td>
<td>61%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>
unless they are still present on a follow-up duplex scan 2 months later.

At the opposite extreme, large pseudoaneurysms can rupture into the retroperitoneal space or the upper thigh or cause venous thrombosis or painful neuropathy by compressing the adjacent femoral vein or the femoral nerve. Urgent surgical repair clearly is necessary if any of these serious complications occur, and until recently, it was the mainstay of treatment for most catheter-related femoral artery injuries. Many reports now have demonstrated, however, that the majority of uncomplicated pseudoaneurysms can be managed nonoperatively with either ultrasound-guided compression therapy or the injection of miniscule amounts of thrombin directly into the pseudoaneurysm cavity. Problems with ultrasound-guided compression therapy include pain at the site of compression, long compression times, and incomplete closure, each of which is more problematic with large pseudoaneurysms. Table 64 contains information from 17 series of patients who underwent ultrasound-guided compression therapy with a primary success rate of 86% and surgical treatment in only 4.9%. Recurrences usually responded to further compression and most frequently were associated with pseudoaneurysms that exceeded 4.0 cm in size in patients who had required larger-diameter delivery sheaths or periprocedural anticoagulation.

Pseudoaneurysms ranging in size from 1.5 to more than 7.5 cm may be successfully obliterated by the injection of thrombin, 100 to 3000 international units, under ultrasound guidance. Table 65 contains data from 7 institutional series in which thrombin injection was performed for catheter-related femoral pseudoaneurysms. In aggregate, the success rate was 93%, and only 4.1% of the patients needed operations. Thrombin injection can be complicated by distal arterial thromboembolism in less than 2% of cases and rarely by pul-

![Figure 25. Spontaneous closure rates of selected pseudoaneurysms. AVF indicates arteriovenous fistula; PSA, pseudoaneurysm. Reprinted from J Vasc Surg, 25, Toursarkissian B, Allen BT, Petinec D, et al. Spontaneous closure of selected iatrogenic pseudoaneurysms and arteriovenous fistulae, 803-8, Copyright 1997, with permission from Elsevier (1283).]

Table 64. Ultrasound-Guided Compression of Femoral Pseudoaneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Patients (n)</th>
<th>Closure (n)</th>
<th>Surgery (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatterjee</td>
<td>(1285)</td>
<td>38</td>
<td>37</td>
<td>1</td>
<td>FemoStop used</td>
</tr>
<tr>
<td>Coghlan</td>
<td>(1286)</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cox</td>
<td>(1287)</td>
<td>100</td>
<td>94</td>
<td>2</td>
<td>10 recurrences, 1 to 35 days</td>
</tr>
<tr>
<td>Dean</td>
<td>(1288)</td>
<td>77</td>
<td>56</td>
<td>14</td>
<td>Size less than 4 cm; twice as successful at closure</td>
</tr>
<tr>
<td>Feld</td>
<td>(1276)</td>
<td>15</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fellmeth</td>
<td>(1277)</td>
<td>29</td>
<td>27</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hajarizadeh</td>
<td>(1289)</td>
<td>57</td>
<td>54</td>
<td>2</td>
<td>2 recurrences 2 to 10 days</td>
</tr>
<tr>
<td>Hertz</td>
<td>(1290)</td>
<td>41</td>
<td>36</td>
<td>3</td>
<td>Large catheter sheath size problematic</td>
</tr>
<tr>
<td>Kazmers</td>
<td>(1279)</td>
<td>33</td>
<td>25</td>
<td>3</td>
<td>2 pseudoaneurysm ruptures</td>
</tr>
<tr>
<td>Kumins</td>
<td>(1291)</td>
<td>60</td>
<td>52</td>
<td>—</td>
<td>7 recurrences</td>
</tr>
<tr>
<td>Langella</td>
<td>(1292)</td>
<td>36</td>
<td>27</td>
<td>—</td>
<td>3 recurrences</td>
</tr>
<tr>
<td>Paulson</td>
<td>(1293)</td>
<td>48</td>
<td>37</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Perkins</td>
<td>(1294)</td>
<td>13</td>
<td>10</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Schaub</td>
<td>(1282)</td>
<td>124</td>
<td>104</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sorrell</td>
<td>(1295)</td>
<td>11</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Steinkamp</td>
<td>(1296)</td>
<td>98</td>
<td>96</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Weatherford</td>
<td>(1284)</td>
<td>11</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Pulmonary embolism. The recurrence rate is approximately 5% after an initial injection, but recurrent pseudoaneurysms can be safely reinjected with a high rate of success (1297-1299). According to a multicenter registry of patients who have been treated with this technique, thrombin injection ultimately has provided successful treatment for 98% of pseudoaneurysms and appears to represent an improvement over ultrasound-guided compression therapy (1300,1301). One study has been reported in which thrombin injection was compared concurrently with ultrasound-guided compression therapy (1306).

### Table 65. Thrombin Injection Closure of Femoral Pseudoaneurysms

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Patients (n)</th>
<th>Thrombin Dose (U)</th>
<th>Closure (n)</th>
<th>Surgery (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes</td>
<td>(1303)</td>
<td>9</td>
<td>1000 to 2000</td>
<td>8</td>
<td>0</td>
<td>1 recurrence at 4 days</td>
</tr>
<tr>
<td>Kang</td>
<td>(1304)</td>
<td>21</td>
<td>500 to 1000</td>
<td>20</td>
<td>1</td>
<td>94% overall success rate</td>
</tr>
<tr>
<td>La Perna</td>
<td>(1299)</td>
<td>70</td>
<td>1000</td>
<td>66</td>
<td>2</td>
<td>Success maintained in patients using antithrombotic medications</td>
</tr>
<tr>
<td>Liau</td>
<td>(1305)</td>
<td>5</td>
<td>1000</td>
<td>5</td>
<td>0</td>
<td>98% overall success rate</td>
</tr>
<tr>
<td>Mohler</td>
<td>(1300)</td>
<td>91</td>
<td>500 to 1000</td>
<td>87</td>
<td>0</td>
<td>Second injection required for 3 patients</td>
</tr>
<tr>
<td>Reeder</td>
<td>(1306)</td>
<td>26</td>
<td>50 to 450</td>
<td>25</td>
<td>0</td>
<td>1 recurrence at 4 days</td>
</tr>
<tr>
<td>Sacket</td>
<td>(1307)</td>
<td>30</td>
<td>100 to 2000</td>
<td>27</td>
<td>3</td>
<td>94% overall success rate</td>
</tr>
<tr>
<td>Taylor</td>
<td>(1308)</td>
<td>29</td>
<td>600</td>
<td>27</td>
<td>1</td>
<td>98% overall success rate</td>
</tr>
</tbody>
</table>

**Figure 26.** Diagnostic and treatment algorithm for femoral pseudoaneurysm. AV indicates arteriovenous.
therapy (1302). Thrombin injection took less time and was associated with lower vascular laboratory costs, but the overall hospital costs were equivalent in both groups of patients.

The algorithm illustrated in Figure 26 presents an approach to the management of catheter-related femoral artery pseudoaneurysms that is consistent with the current literature on this topic.

**STAFF**

*American College of Cardiology*

Tom Arend, Interim Chief Staff Officer
Marie Temple, Specialist, Knowledge Development

*American Heart Association*

Joseph Allen, MS, Research Analyst, Knowledge Development
Deborah Steinbach, MA, Managing Editor, Knowledge Development
Peg Christiansen, Librarian, Knowledge Development

**American Heart Association**

M. Cass Wheeler, Chief Executive Officer
Rose Marie Robertson, MD, FACC, FAHA, Chief Science Officer
Kathryn A. Taubert, PhD, FAHA, Senior Science Advisor
### APPENDIX 1. ACC/AHA Writing Committee to Develop Guidelines on Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Research Grant</th>
<th>Speakers Bureau/ Honoraria</th>
<th>Stock Ownership</th>
<th>Consultant</th>
<th>Advisory Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Curtis W. Bakal</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Berlex Labs, Abbott Labs</td>
</tr>
<tr>
<td>Dr Mark A. Creager</td>
<td>Eli Lilly Otsuka Pharmaceuticals Pfizer Vasogen</td>
<td>Bristol Myers Squibb/ Sanofi Partnership Otsuka Pharmaceuticals</td>
<td>None</td>
<td>Northport Domain None</td>
<td>Bristol Myers Squibb/ Sanofi Genvec Geozyme</td>
</tr>
<tr>
<td>Dr Jonathan L. Halperin</td>
<td>None</td>
<td>AstraZeneca, LP Bristol Myers Squibb/ Sanofi Partnership</td>
<td>None</td>
<td>AstraZeneca, LP Bayer AG Boehringer Ingelheim Bristol Myers Squibb/ Sanofi Partnership</td>
<td>AstraZeneca, LP</td>
</tr>
<tr>
<td>Dr Ziv J. Haskal</td>
<td>Bard/Impra Boston Scientific Cook Cordis Endovascular Genentech IntraTherapeutics W. L. Gore</td>
<td>TransVascular W. L. Gore</td>
<td>None</td>
<td>Bard/Impra Endosurgery Ethicon Omnisonics TransVascular</td>
<td>TransVascular</td>
</tr>
<tr>
<td>Dr Norman R. Hertzler</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Loren F. Hiratzka</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Alan T. Hirsch</td>
<td>Alteon AstraZeneca Pharmaceuticals Bristol Myers Squibb/ Sanofi Aventis Partnership Kos Pharmaceuticals Otsuka America Pharmaceuticals</td>
<td>None</td>
<td>None</td>
<td>Sonosite Vasogen</td>
<td>None</td>
</tr>
<tr>
<td>Dr William R.C. Murphy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Jeffrey W. Olin</td>
<td>Bristol Myers Squibb/ Sanofi Partnership Vasogen</td>
<td>None</td>
<td>None</td>
<td>Aventis Bristol Myers Squibb/ Sanofi Partnership Otsuka Vasogen</td>
<td>Abbott Aventis Bristol Myers Squibb/ Sanofi Partnership Genzyme</td>
</tr>
</tbody>
</table>

*Continued on Next Page*
### APPENDIX 1. Continued

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Research Grant</th>
<th>Speakers Bureau/ Honoraria</th>
<th>Stock Ownership</th>
<th>Consultant</th>
<th>Advisory Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Jules B. Puschett</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr David Sacks</td>
<td>None</td>
<td>None</td>
<td>Angiotech</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr James C. Stanley</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Lloyd M. Taylor, Jr</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Christopher J. White</td>
<td>None</td>
<td>Eli Lilly</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr John White</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Rodney A. White</td>
<td>AVE Bard Boston Scientific Cordis J &amp; J EndoLogix EndoSonics Medtronic</td>
<td>Multiple relationships with commercial entities that arise and are met as needed</td>
<td>Several biomedical companies</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

This table represents the relationships of committee members with industry that were disclosed at the initial writing committee meeting in November 2002 and that were updated in conjunction with all meetings and conference calls of the writing committee. It does not necessarily reflect relationships with industry at the time of publication.
### APPENDIX 2. External Peer Reviewers for the ACC/AHA 2005 Guideline Update for Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic)*

<table>
<thead>
<tr>
<th>Peer Reviewer Name*</th>
<th>Representation</th>
<th>Research Grant</th>
<th>Speakers Bureau/ Honoraria</th>
<th>Stock Ownership</th>
<th>Consultant/ Advisory Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Joshua A. Beckman</td>
<td>Content Reviewer – ACC PVD Committee</td>
<td>None</td>
<td>Merck</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr James F. Benenati</td>
<td>Official Reviewer – AHA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Ralph G. Brindis</td>
<td>Official Reviewer – ACC BOT</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Alan S. Brown</td>
<td>Official Reviewer – ACC BOG</td>
<td>AstraZeneca Merck Schering Plough Pfizer</td>
<td>Merck Schering Plough Pfizer</td>
<td>None</td>
<td>AstraZeneca Merck Schering Plough</td>
</tr>
<tr>
<td>Rita C. Clark</td>
<td>Organizational Reviewer – SVN</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr John P. Cooke</td>
<td>Content Reviewer – Individual</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Robert T. Eberhardt</td>
<td>Official Reviewer – AHA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Brian S. Funaki</td>
<td>Content Reviewer – AHA Committee on PV Imaging and Intervention</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Bruce Gray</td>
<td>Organizational Reviewer – SVMB</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Karen Hayden, MSN</td>
<td>Organizational Reviewer – SVN</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr William R. Hiatt</td>
<td>Organizational Reviewer – TASC</td>
<td>None</td>
<td>BMS/Sanofi Otsuka</td>
<td>None</td>
<td>BMS/Sanofi Signature</td>
</tr>
<tr>
<td>Dr David Holmes, Jr</td>
<td>Content Reviewer – ACC BOG</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Sharon A. Hunt</td>
<td>Organizational Reviewer – ACC/AHA TF on PGL</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Michael R. Jaff</td>
<td>Organizational Reviewer – SVMB</td>
<td>None</td>
<td>OtsukaBMS/Sanofi</td>
<td>None</td>
<td>Cordis Endovascular</td>
</tr>
<tr>
<td>Dr Matthew S. Johnson</td>
<td>Content Reviewer – AHA Committee on PV Imaging and Intervention</td>
<td>Bard Access Systems Boston Scientific</td>
<td>None</td>
<td>None</td>
<td>Boston Scientific</td>
</tr>
<tr>
<td>Dr John A. Kaufman</td>
<td>Content Reviewer – AHA Atherosclerosis PVD Steering Committee</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Morton Kern</td>
<td>Content Reviewer – AHA Diag and Interv Cardiac Cath Cmte</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Lloyd Klein</td>
<td>Content Reviewer – AHA Diag and Interv Cardiac Cath Cmte</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
</tbody>
</table>

*Continued on Next Page*
<table>
<thead>
<tr>
<th>Peer Reviewer Name*</th>
<th>Representation</th>
<th>Research Grant</th>
<th>Speakers Bureau/ Honoraria</th>
<th>Stock Ownership</th>
<th>Consultant/ Advisory Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Frank Lederle</td>
<td>Content Reviewer – Individual Review</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Jonathan Lindner</td>
<td>Official Reviewer – ACCF TF on CECD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Mary M. McDermott</td>
<td>Content Reviewer – AHA Athero PVD PVD Steering Committee</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Alan Matsumoto</td>
<td>Content Reviewer – AHA Committee on PV Imaging and Intervention</td>
<td>None</td>
<td>Genentech</td>
<td>None</td>
<td>Cordis Endovascular Medtronic W. L. Gore</td>
</tr>
<tr>
<td>Dr Roxana Mehran</td>
<td>Content Reviewer – Individual Review</td>
<td>Boston Scientific Cordis Medtronic</td>
<td>The Medicines Company Tyco/Mallinckrodt</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Emile R. Mohler III</td>
<td>Content Reviewer – Individual Review</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Roberta Oka, RN</td>
<td>Content Reviewer – AHA Atherosclerosis PVD Steering Committee</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Joseph P. Ornato</td>
<td>Official Reviewer – ACC/AHA TF on PGL, Lead Reviewer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Genentech Meridian Revivant Wyeth</td>
</tr>
<tr>
<td>Dr Kenneth Ouriel</td>
<td>Content Reviewer – ACC PVD Committee</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
<tr>
<td>Dr William Pearce</td>
<td>Official Reviewer – AHA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Carolyn A. Robinson</td>
<td>Organizational Reviewer – SVN</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Robert D. Safian</td>
<td>Organizational Reviewer – SCAI</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Boston Scientific Cordis/Johnson &amp; Johnson eV3 Medtronic</td>
</tr>
<tr>
<td>Dr Sonia I. Skarlatos</td>
<td>Organizational Reviewer – NHLBI</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Kimberly A. Skelding</td>
<td>Content Reviewer – AHA Diag and Interv Cardiac Cath Cmte</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Vincenza Snow</td>
<td>Organizational Reviewer – ACP/ASIM</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dr Thomas L. Whitsett</td>
<td>Organizational Reviewer – SVMB</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication. Participation in the peer review process does not imply endorsement of the document.

*Names are listed in alphabetical order.

ACCF indicates American College of Cardiology Foundation; ACP, American College of Physicians; AHA Diag and Interv Cardiac Cath Cmte, AHA Diagnostic and Interventional Cardiac Catheterization Committee; ASIM, American Society of Internal Medicine; BOG, Board of Governors; BOT, Board of Trustees; NHLBI, National Heart, Lung, and Blood Institute; PV, peripheral vein; PVD, peripheral vascular disease; SCAI, Society for Cardiovascular Angiography and Interventions; SVMB, Society of Vascular Medicine and Biology; SVN, Society for Vascular Nursing; TBD, to be determined; TF on CECD, Task Force on Clinical Expert Consensus Documents; and TF on PGL, Task Force on Practice Guidelines.
APPENDIX 3. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>ankle-brachial index</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk in Communities study</td>
</tr>
<tr>
<td>bFGF</td>
<td>basic fibroblast growth factor</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CLIP</td>
<td>critical limb ischemia</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomographic angiography</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRASTIC</td>
<td>Dutch Renal Artery Stenosis Intervention Cooperative</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
<tr>
<td>EUROSTAR</td>
<td>EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FMD</td>
<td>fibromuscular dysplasia</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
</tr>
<tr>
<td>HMG</td>
<td>hydroxymethyl glutaryl</td>
</tr>
<tr>
<td>ICAVL</td>
<td>Intersocietal Commission for Accreditation of Vascular Laboratories</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinases</td>
</tr>
<tr>
<td>MRA</td>
<td>magnetic resonance angiography</td>
</tr>
<tr>
<td>NHDS</td>
<td>National Hospital Discharge Survey</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>p</td>
<td>statistical significance</td>
</tr>
<tr>
<td>PAD</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td>PARTNERS</td>
<td>PAD Awareness, Risk and Treatment: New Resources for Survival (study)</td>
</tr>
<tr>
<td>PGE-1</td>
<td>prostaglandin E1</td>
</tr>
<tr>
<td>phVEGF165</td>
<td>vascular endothelial growth factor plasma DNA</td>
</tr>
<tr>
<td>PTA</td>
<td>percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>PTFE</td>
<td>polytetrafluoroethylene</td>
</tr>
<tr>
<td>PVR</td>
<td>pulse volume recording</td>
</tr>
<tr>
<td>RAS</td>
<td>renal artery stenosis</td>
</tr>
<tr>
<td>RRI</td>
<td>resistive index</td>
</tr>
<tr>
<td>ROS</td>
<td>review of symptoms</td>
</tr>
<tr>
<td>TASC</td>
<td>TransAtlantic Inter-Society Consensus Working Group</td>
</tr>
<tr>
<td>TBI</td>
<td>toe-brachial index</td>
</tr>
<tr>
<td>3D</td>
<td>3-dimensional</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USPSTF</td>
<td>United States Preventive Services Task Force</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affairs</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
</tbody>
</table>
References


120. Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. Int J Epidemiol 1988;17:248-54.


424. Kinney TB, Rose SC. Intraarterial pressure measurements during angiographic evaluation of peripheral vascular disease: techniques, interpretation, applications, and limitations. AJR Am J
Roentgenol 1996;166:277-84.
476. Duda SH, Poerner TC, Wiesinger B, et al. Drug-eluting stents:


582. Duda SH, Tepe G, Luz O, et al. Peripheral artery occlusion: treatment with abciximab plus urokinase versus with urokinase alone—a randomized pilot trial (the PROMPT Study). Platelet Receptor Antibodies in Order to Manage Peripheral Artery...


740. Harjai K, Khosla S, Shaw D, et al. Effect of gender on outcomes following renal artery stent placement for renovascular hyperten-


977. Lederle FA, Simel DL. The rational clinical examination: does this patient have abdominal aortic aneurysm? JAMA 1999;281:77-82.


980. JANOWER ML. Ruptured arteriosclerotic aneurysms of the abdominal aorta: roentgenographic findings on plain films. N


1051. Auerbach AD, Goldman L. Beta-blockers and reduction of cardiac events in noncardiac surgery: scientific JAMA 2002;287:1435-44.


1097. Panettone JM, Lassonde J, Laurendeau F. Ruptured abdominal aortic aneurysm: impact of comorbidity and postoperative com-


1205. Hirsch et al. 2005 e651


1291. Kumins NH, Landau DS, Montalvo J, et al. Expanded indications for the treatment of postcatheterization femoral pseudoa-

Circulation. 2006;113:e463-e654
doi: 10.1161/CIRCULATIONAHA.106.174526
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/11/e463.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/