

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

A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery,* Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease)

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

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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 Inter-Society 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.

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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 pathophysi-

ological 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 blockade, “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, pre-operative 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 1 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 “Size of Treatment Effect”

	Class I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	Class IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	Class IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	Class III <i>Risk ≥ Benefit</i> <i>No additional studies needed</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
Level A <i>Multiple (3-5) population risk strata evaluated*</i> <i>General consistency of direction and magnitude of effect</i>	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
Level B <i>Limited (2-3) population risk strata evaluated*</i>	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Limited evidence from single randomized trial or non-randomized studies
Level C <i>Very limited (1-2) population risk strata evaluated*</i>	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care

Suggested phrases for writing recommendations †

should be recommended	is reasonable	may/might be considered	is not recommended
is indicated	can be useful/effective/ beneficial	may/might be reasonable	is not indicated
is useful/effective/beneficial	is probably recommended or indicated	usefulness/effectiveness is unknown /unclear/uncertain or not well established	should not
			is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, 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 abnormal 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 vas-

cular 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 (conduit 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 obliterative 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 thrombo-genic 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. Individuals at Risk for Lower Extremity Peripheral Arterial Disease

Age less than 50 years, with diabetes and one other atherosclerosis risk factor (smoking, dyslipidemia, hypertension, or hyperhomocysteinemia)
Age 50 to 69 years and history of smoking or diabetes
Age 70 years and older
Leg symptoms with exertion (suggestive of claudication) or ischemic rest pain
Abnormal lower extremity pulse examination
Known atherosclerotic coronary, carotid, or renal artery disease

Section 2.1.1) 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).

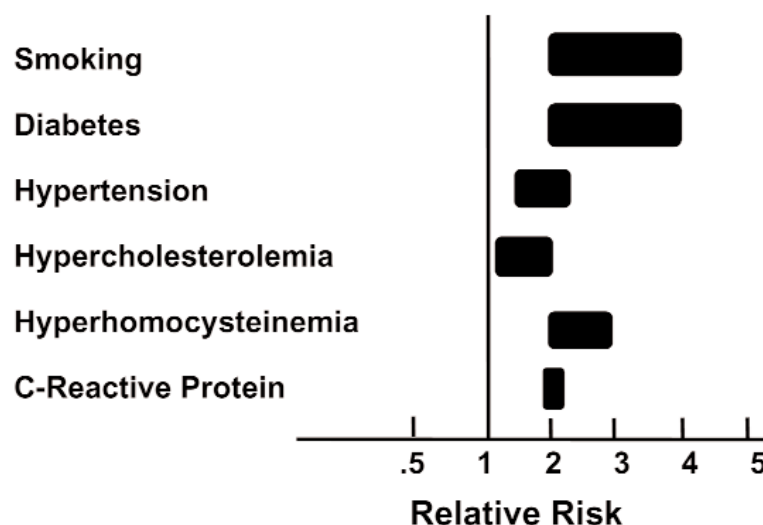


Figure 1. Risk of developing lower extremity PAD. The range for each risk factor is estimated from epidemiological studies (see text). The relative risks take into consideration current smokers versus former smokers and nonsmokers, presence versus absence of diabetes and hypertension, and highest versus 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 intermit-

tent 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

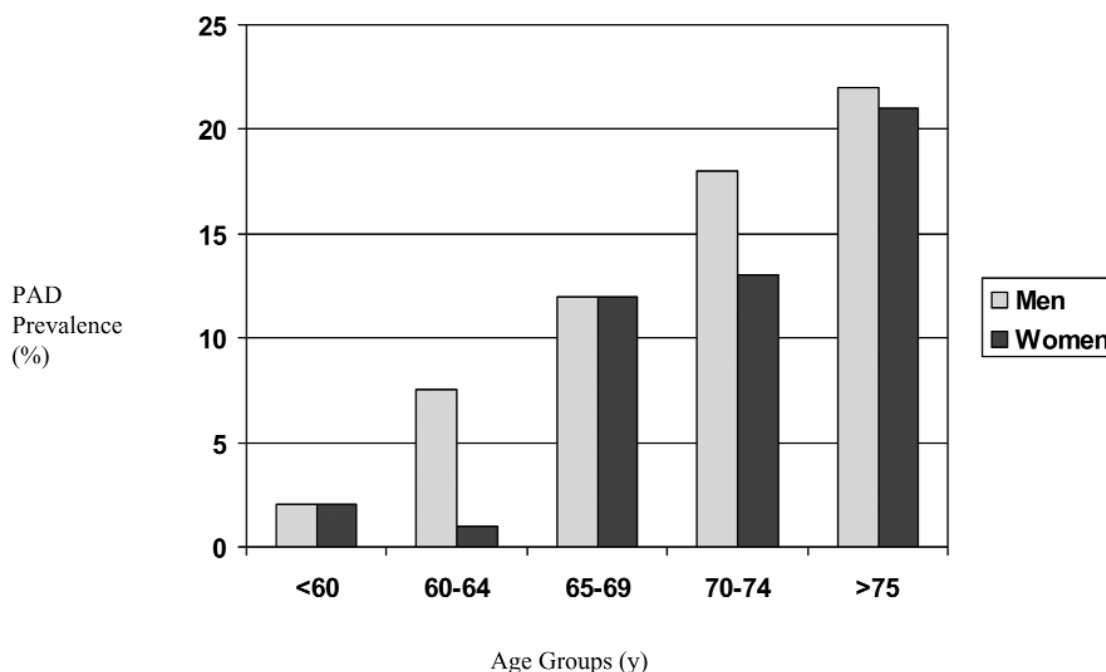


Figure 2. Prevalence of peripheral arterial disease (PAD) by age. Reprinted with permission from Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;71:510-5 (77).

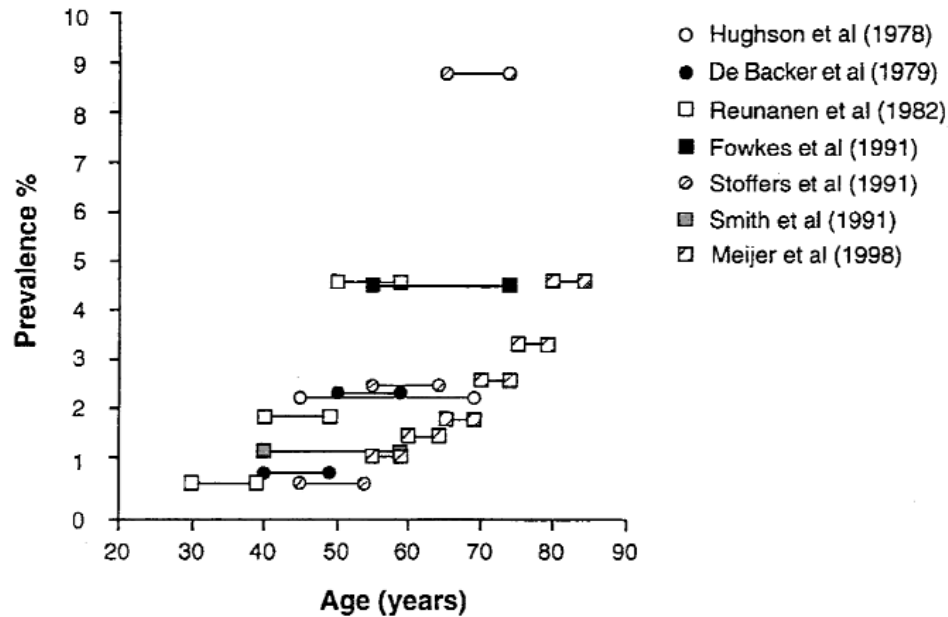


Figure 3. Prevalence of intermittent claudication in various studies. Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier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

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

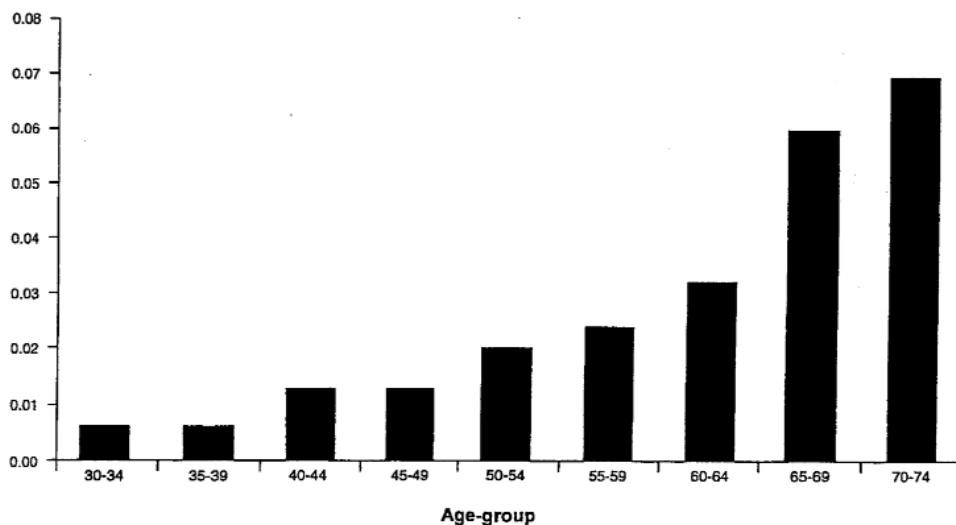


Figure 4. Mean prevalence of intermittent claudication in large population studies. Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission 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

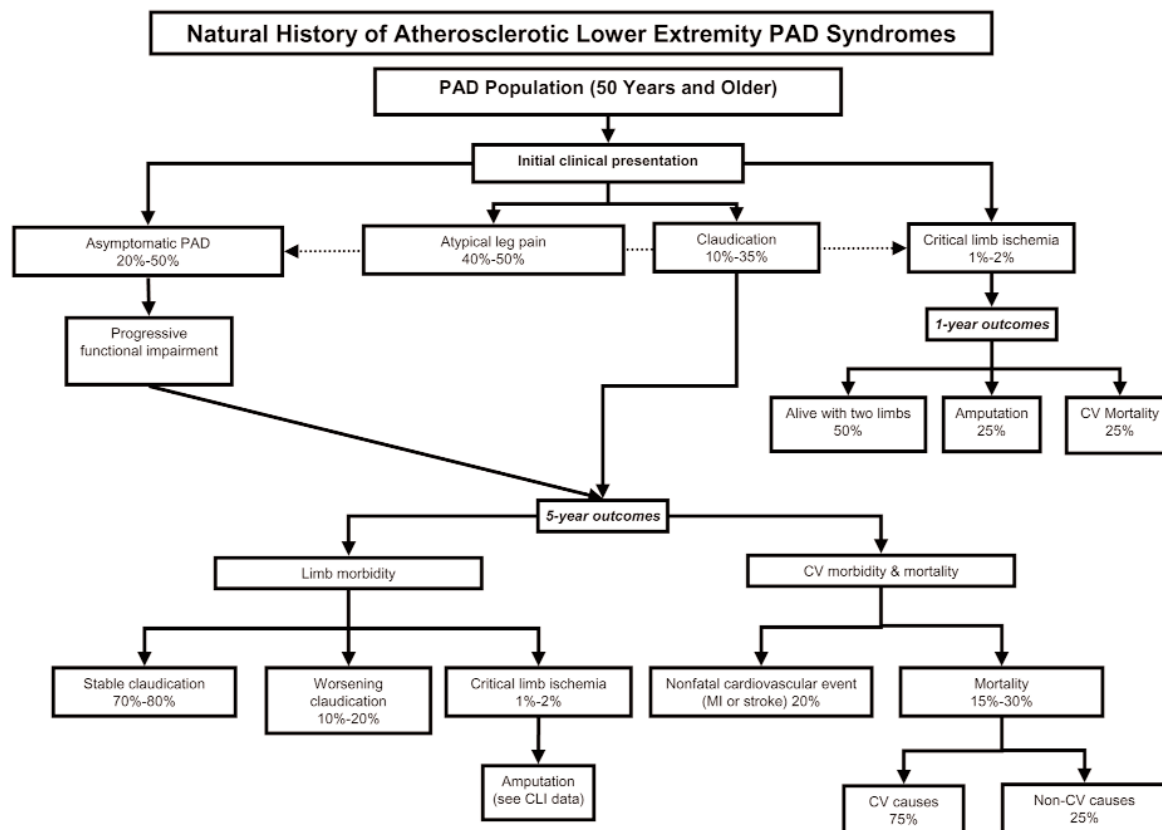


Figure 5. The natural history of atherosclerotic lower extremity peripheral arterial disease (PAD). Individuals with atherosclerotic lower extremity PAD may be: (a) asymptomatic (without identified ischemic leg symptoms, albeit with a functional impairment); (b) present with leg symptoms (classic claudication 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).

cerebrovascular disease in patients with lower extremity PAD (35,92,94). The relative prevalence of coronary and cerebral atherosclerosis depends on the criteria used to establish the diagnosis. Among patients presenting with lower extremity PAD, approximately one third to one half have evidence of coronary artery disease based on clinical history and electrocardiogram and two thirds based on an abnormal stress test. Significant coronary artery disease of at least 1 coronary artery has been reported in up to 60% to 80% of those with lower extremity PAD (62,95-98). Approximately 12% to 25% of patients with lower extremity PAD have hemodynamically significant carotid artery stenoses detected by duplex ultrasound (99-101). In one study, approximately one third of individuals with significant carotid artery stenosis had symptoms of cerebrovascular ischemia (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.

2.2.2. 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 incidence of transient ischemic attack and stroke (103). The annual mortality rate derived from epidemiological studies of patients with lower extremity PAD is 4% to 6% and is highest in those with the most severe disease (106,109-111).

In more contemporary published clinical trials, the annual mortality rate of patients with lower extremity PAD is lower; the combined event rate for MI, stroke, and vascular death is approximately 4% to 5% per year and increases to 6% per year if revascularization is included. Lower event rates in clinical trial populations is likely due to both referral bias and the higher standard of care inherent to the clinical trial environment (98,112,113). The 1-year mortality rate in patients with CLI is approximately 25% and may be as high as 45% in those who have undergone amputation (106,114-117).

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: B)*
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, post-occlusive reactive hyperemia, and pulse-reappearance half-time) (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-

viduals 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 high 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

reported by McDermott et al. from a cross-sectional study of 460 individuals with lower extremity PAD and 130 without lower extremity PAD that provided a comprehensive classification of limb symptoms at rest and with exertion. In all cohorts, including individuals with lower extremity PAD but no limb symptoms either at rest or with exertion, decreased functional status was documented (124). Newman et al. evaluated the 5888 individuals in the Cardiovascular Health Study to corroborate that lower extremity PAD and leg pain are coprevalent, that the standard Rose questionnaire underestimates the presence of leg symptoms, and that more sensitive survey tools can better identify the functional impairment experienced by these individuals (125). Overall, current data document that lower extremity PAD is common, that the traditional term “asymptomatic” may inaccurately imply that limb function is normal, and that lower extremity PAD is invariably and independently associated with impaired lower extremity functioning.

Thus, most individuals with lower extremity PAD do not have classic (typical) claudication but may have more subtle impairments of lower extremity function. For these individuals with asymptomatic lower extremity PAD, there is currently no evidence that additional vascular laboratory diagnostic tests (e.g., segmental pressure studies, duplex ultrasound, magnetic resonance angiography [MRA], or contrast angiography) provide incremental information that can improve outcomes. Similarly, there are no data that suggest that limb arterial revascularization of these patients is associated with any net improvement in limb function or limb symptoms. As well, no clinical investigations have heretofore been performed to evaluate the relative benefit of pharmacological interventions on leg function in patients with lower extremity PAD but without classic symptoms of claudication.

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

tool to a population at risk. The most cost-effective tool for lower extremity PAD detection is the ABI, which has been used in numerous field surveys and cross-sectional practice surveys, as cited in this guideline.

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

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

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Table 4. Differential Diagnosis of Intermittent Claudication

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

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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 impending 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-

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

Factors that reduce blood flow to the microvascular bed:
Diabetes
Severe renal failure
Severely decreased cardiac output (severe heart failure or shock)
Vasospastic diseases or concomitant conditions (e.g., Raynaud's phenomenon, prolonged cold exposure)
Smoking and tobacco use
Factors that increase demand for blood flow to the microvascular bed:
Infection (e.g., cellulitis, osteomyelitis)
Skin breakdown or traumatic injury

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 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-à-vis proximal vs. combined revascularization of multilevel disease)
Assessment of individual patient endovascular or operative risk

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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 A _{1c} , 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)

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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. Such 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 8. Differential Diagnosis of Common Foot and Leg Ulcers

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

PAD indicates peripheral arterial disease.

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Table 9. Foot Physical Examination and Differential Diagnosis of Neuropathic and Neuroischemic Ulcers

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

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anticoagulant medications, intravenous prostanooids, rheologic agents, and maintenance of the limb in a dependent position. However, none of these clinical interventions has been evaluated adequately or proven to offer predictable improvements in limb outcomes in prospective clinical trials. Passage of time will sometimes be associated with adequate improvements in the arterial supply-demand balance to permit improvement in symptoms. For example, collateral vessels may form to enable resolution of CLI and reduction in pain. Treatment of infection may decrease the metabolic demands that impede wound healing, and use of non-weight-bearing orthotics may diminish the contribution of repeated trauma to skin breakdown. Investigation of angiogenic therapies, via administration of gene or protein, to enhance collateral blood flow has offered promise as a potential strategy to treat CLI (see Section 2.6.3.1.2). However, these are not yet proven interventions and are not available as established therapies.

Importance of Collaboration Between Primary Care and Vascular Specialty Care in the Treatment of CLI

In the absence of revascularization, most patients with CLI are expected to require amputation within 6 months. Therefore, timely referral to a vascular specialist is indicated to expedite treatment, prevent further deterioration, and reverse the ischemic process. Such a referral, along with continued interactive long-term care collaboration, is essential if all potential options for limb salvage are to be considered and understood by the patient.

For example, patients with ulcers, gangrene, or lower extremity rest pain (i.e., CLI) require full evaluation of the anatomic basis of the ischemia. Detailed arterial mapping requires vascular expertise to (a) identify the etiology of the ischemia and (b) define the options available for revascularization.

Patients with CLI often have concomitant severe coronary artery disease or cerebrovascular disease. This suggests an indication for performance of investigations to define potentially severe coronary artery disease or extracranial carotid

artery disease and revascularization of these circulations. The evaluation of the risk, benefit, and optimal timing of revascularization of multiple arterial circulations is among the most complex in medical decision making. It can be chal-

Table 10. Etiologic Classification of Foot and Leg Ulcers

Venous obstruction and insufficiency
Arterial etiologies
Larger arteries
Atherosclerotic lower extremity PAD
Thromboemboli, atheroemboli
Thromboangiitis 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 B ₁₂ deficiency
Drugs
Artifactual or factitious

PAD indicates peripheral arterial disease.

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lenging to stage coronary or carotid revascularization procedures in individuals with CLI and a jeopardized limb who do not present with recent coronary or cerebrovascular ischemic symptoms. The diagnostic evaluation and treatment (whether percutaneous or surgical) of coronary or cerebrovascular disease to treat asymptomatic disease in CLI patients may lead to delay in performance of limb revascularization and may theoretically increase the risk of limb loss. Limited data suggest that individuals who present with low to moderate risk and who can tolerate administration of beta-blockers perioperatively do not benefit from dobutamine stress echocardiography and an extensive cardiovascular risk reduction investigation (142). Proof that preprocedural (coronary and carotid) revascularization lowers short-term cardiovascular ischemic risk of limb revascularization interventions is not yet available.

2.4.4. Acute Limb Ischemia

RECOMMENDATIONS

Class I

Patients with acute limb ischemia and a salvageable extremity should undergo an emergent evaluation that defines the anatomic level of occlusion and that leads to prompt endovascular or surgical revascularization. (Level of Evidence: B)

Class III

Patients with acute limb ischemia and a nonviable extremity should not undergo an evaluation to define vascular anatomy or efforts to attempt revascularization. (Level of Evidence: B)

Acute limb ischemia arises when a rapid or sudden decrease in limb perfusion threatens tissue viability. This form of CLI may be the first manifestation of arterial disease in a previously asymptomatic patient or may occur as an acute event that causes symptomatic deterioration in a patient with antecedent lower extremity PAD and intermittent claudication. Although the progression of PAD from intermittent claudication to CLI may occur gradually, it may also reflect the cumulative effect of multiple acute local thrombotic events that progressively increase the intensity of ischemia. The classification of acute ischemic syndromes had been modified over time with the Society for Vascular Surgery/International Society for Cardiac Vascular Surgery (SVS/ISCVS) reporting standards being used frequently (143). Although attempts have been made to define various levels of ischemia, it is frequently not possible to precisely delineate the status of the patient with an acutely ischemic limb, because many of the classification schemes are based on subjective clinical criteria and not discrete end points. Table 11 displays the SVS/ISCVS classification scheme and provides the most useful clinical method to describe this entity.

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.

Table 11. Clinical Categories of Acute Limb Ischemia

Category	Description/ Prognosis	Sensory Loss	Muscle Weakness	Arterial Doppler Signals	Venous Doppler Signals
Viable	Not immediately threatened	None	None	Audible	Audible
Threatened marginally	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
Threatened immediately	Salvageable with immediate revascularization	More than toes; associated with rest pain	Mild, moderate	(Usually) inaudible	Audible
Irreversible	Major tissue loss or permanent nerve damage	Profound, anesthetic	Profound paralysis (rigor)	Inaudible	Inaudible

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The clinical history should determine the onset and course of ischemia and any background information pertaining to origin, differential diagnosis, and concurrent disease. Symptoms in acute limb ischemia relate primarily to pain and dysfunction. The pattern of onset may have etiological implications (i.e., embolism tends to present more abruptly than thrombosis), whereas the character and distribution of pain may aid the differential diagnosis. The limb pain associated with severe acute limb ischemia may be similar in intensity to the rest pain of chronic severe ischemia. However, 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 gen-

erally 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

Table 12. Surveillance Program for Aortoiliac and Infringuinal Transluminal Angioplasty

Patients undergoing aortoiliac and infringuinal 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
- Resting and, if possible, 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; PAD, peripheral arterial disease; and PTA, percutaneous transluminal angioplasty.
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(angiography) is then indicated when noninvasive methods suggest hemodynamically significant lesions (e.g., greater than 50% stenosis) (151,152). Some patients with failing lower extremity grafts due to stenosis documented by duplex ultrasound may proceed to operative repair without angiography.

Whereas autogenous vein grafts generally become compromised within their midportion and at anastomotic sites, prosthetic grafts fail more frequently as a result of impaired native vessel outflow or poor arterial inflow (153). Accordingly, the benefit of surveillance with duplex ultrasound is less well established for prosthetic grafts.

Postprocedure surveillance after percutaneous or endovascular procedures is less well studied, and standards are less well established. Regular visits, with assessment of interval change in symptoms, vascular examination, and ABI measurement are considered the standard of care. Postexercise

Table 13. Surveillance Program for Infringuinal 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
- 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.
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Table 14. Surveillance Program for Infringuinal Prosthetic Grafts

Patients undergoing prosthetic femoropopliteal or femorotibial bypass for claudication or limb-threatening ischemia should be entered into a graft surveillance program that consists of:

- Interval history (new symptoms)
- Vascular examination of the leg with palpation of proximal and outflow vessel pulses
- Measurement of ABIs at rest and, if possible, after exercise testing

Surveillance programs should be performed in the immediate postoperative period and at regular intervals (timing of surveillance and efficacy have not been ideally defined) for at least 2 years

ABI indicates ankle-brachial index.
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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 interventional 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

Diagnostic Tool*	Benefits	Limitations
Ankle-brachial indices (ABIs)	A quick and cost-effective way to establish or refute the lower extremity PAD diagnosis (see text)	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
Toe-brachial indices	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	Requires small cuffs and careful technique to preserve accuracy
Segmental pressure examination	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	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
Pulse volume recording	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	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
Continuous-wave Doppler ultrasound	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	“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)
Duplex ultrasound	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	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

Continued on Next Page

Table 15. *Continued*

Diagnostic Tool*	Benefits	Limitations
Toe-tip exercise testing, with pre-exercise and postexercise ABIs	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	Provides qualitative (rather than quantitative) exercise diagnostic results Lower workload may not elicit symptoms in all individuals with claudication
Treadmill exercise testing, with and without pre-exercise and postexercise ABIs	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 Useful to measure the objective functional response to claudication therapeutic interventions	Requires use of a motorized treadmill, with or without continuous electrocardiogram monitoring, as well as staff familiar with exercise testing protocols
Magnetic resonance angiography (MRA)	Useful to assess PAD anatomy and presence of significant stenoses Useful to select patients who are candidates for endovascular or surgical revascularization	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)
Computed tomographic angiography (CTA)	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	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
Contrast angiography	Definitive method for anatomic evaluation of PAD when revascularization is planned	Invasive evaluation is associated with risk of bleeding, infection, vascular access complications (e.g., dissection or hematoma), athero-embolization, 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

*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

Clinical Presentation	Noninvasive Vascular Test
Asymptomatic lower extremity PAD	ABI
Claudication	ABI, PVR, or segmental pressures Duplex ultrasound Exercise test with ABI to assess functional status
Possible pseudoclaudication	Exercise test with ABI
Postoperative vein graft follow-up	Duplex ultrasound
Femoral pseudoaneurysm; iliac or popliteal aneurysm	Duplex ultrasound
Suspected aortic aneurysm; serial AAA follow-up	Abdominal ultrasound, CTA, or MRA
Candidate for revascularization	Duplex ultrasound, MRA, or CTA

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.

Adapted from Primary Cardiology, 2nd ed., Braunwald E, Goldman L, eds., "Recognition and management of peripheral arterial disease," Hirsch AT, 659-71, Philadelphia, Pa: WB Saunders, Copyright 2003, with permission from Elsevier (155a).

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

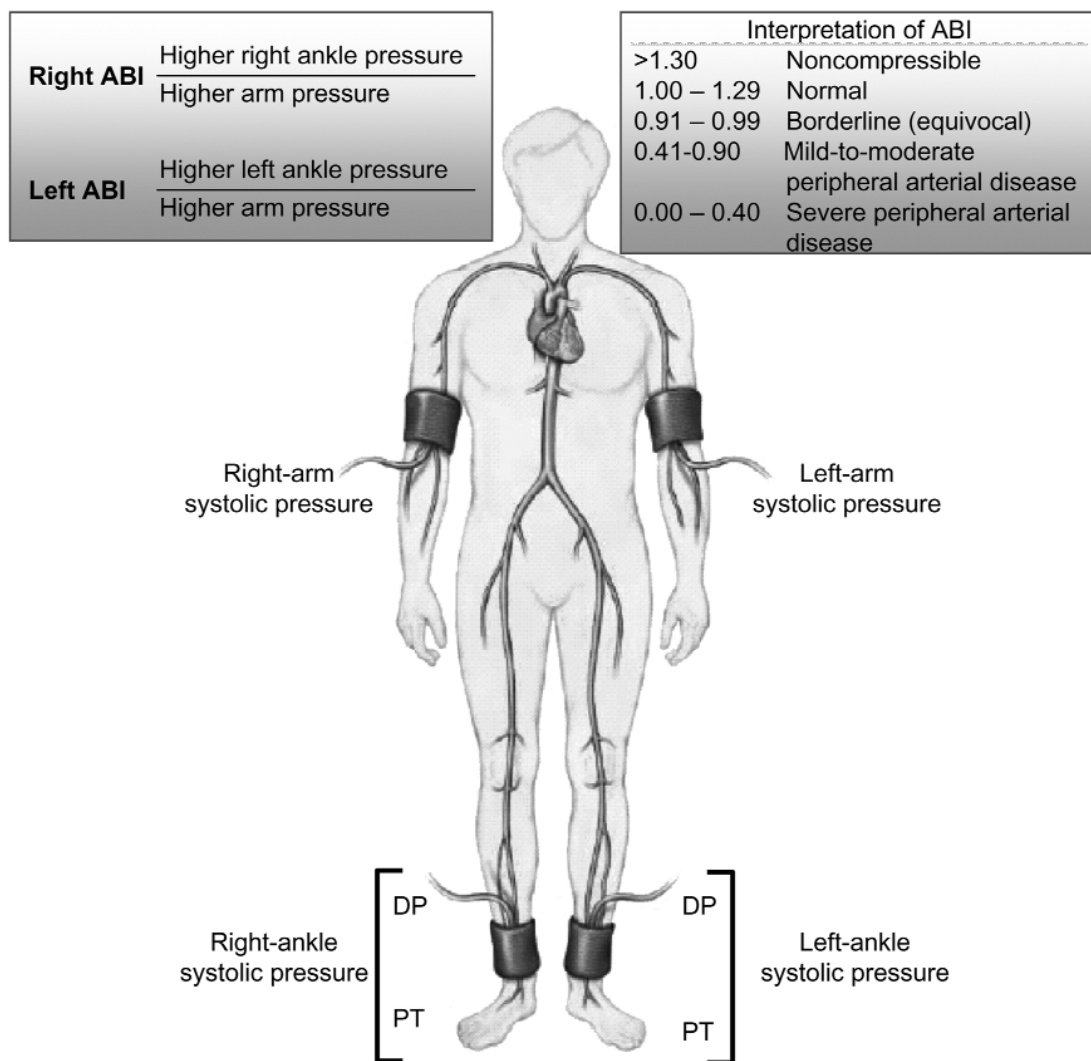


Figure 6. Ankle-brachial index. DP indicates dorsalis pedis; and PT, posterior tibial artery. Adapted with permission from Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;344:1608-21 (158a). Copyright © 2001 Massachusetts Medical Society. All rights reserved.

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 artifactually 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 upstroke 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.

$$\text{Pulsatility Index} = \frac{V_{\max} - V_{\min}}{V_{\text{mean}}}$$

Figure 7. Pulsatility index. V_{\max} indicates peak systolic velocity; V_{\min} , minimum diastolic velocity; V_{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 gray-scale 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

- 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)**
- 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)**
- 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 specific 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 tolerated 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 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 lymphocele, 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 presence of significant stenosis in patients with lower extremity PAD. (Level of Evidence: B)**
2. **Computed tomographic angiography of the extremities may be considered as a substitute for MRA for those patients with contraindications to MRA. (Level of Evidence: B)**

Computed tomographic angiography of the extremities has been used in preliminary studies to diagnose the 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 infrainguinal 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: A)**

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 (barring 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, angioscopy, 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 close 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 A_{1C} 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 syn-

drome, 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, cobalamin (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 anticoagulants. 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

First Author	Year	Reference	No. of Patients	Intervention	Duration, mo	Change in ACD (%)	Functional Assessment*
Larsen Treatment group Control group	1966	(330)	7 7	Daily walks Placebo tablet	6	183 ^{††} -6	None
Holm Treatment group Control group	1973	(331)	6 6	Exercise Placebo tablet	4	133 ^{††} NC	None
Dahllof Treatment group Control group	1974	(332)	11 11	Exercise Placebo tablet	6	117 ^{††} NC	None
Dahllof Treatment group Control group	1976	23 (333)	8 10	Exercise Placebo tablet	4	135 ^{††} 75 [†]	None
Lundgren Treatment group 1	1989	(327)	25	Surgery plus exercise	6	263 ^{††}	None
Treatment group 2 Treatment group 3			25 25	Surgery Exercise		173 ^{††} 151 ^{††}	
Creasy Treatment group 1 Treatment group 2	1990	(334)	13 20	Exercise Angioplasty	6	442 ^{††§} 57	None
Hiatt Treatment group Control group	1990	(326)	9 10	Supervised exercise Control	3	123 ^{††} 20	Improved No change
Mannarino Treatment group 1	1991	(335)	10	Exercise plus antiplatelet	6	105 ^{††}	None
Treatment group 2 Treatment group 3			10 10	Exercise Antiplatelet		86 ^{††} 38 [†]	
Hiatt Treatment group 1 Treatment group 2 Control	1994	(324)	9 8 10	Supervised exercise Strength training Control	3	74 ^{††} 36 [†] -1	Improved No change No change
Regensteiner Treatment group 1 Treatment group 2	1997	(325)	10 10	Supervised exercise Home exercise	3	137 ^{††} 5	Improved No change
Patterson Treatment group 1 Treatment group 2	1997	(336)	19 19	Supervised exercise Home exercise	6	195 ^{††} 83 [†]	Improved Improved

*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)

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

*These general guidelines should be individualized and based on the results of treadmill stress testing and the clinical status of the patient. A full discussion of the exercise precautions for persons with concomitant diseases can be found elsewhere for diabetes (Ruderman N, Devlin JT, Schneider S, Kriska A. Handbook of Exercise in Diabetes. Alexandria, Va: American Diabetes Association; 2002) (362a), hypertension (ACSM's Guidelines for Exercise Testing and Prescription. In: Franklin BA, ed. Baltimore, Md: Lippincott Williams & Wilkins; 2000) (362b), and coronary artery disease (Guidelines for Cardiac Rehabilitation and Secondary Prevention/American Association of Cardiovascular and Pulmonary Rehabilitation. Champaign, Ill: Human Kinetics; 1999) (362c).

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

Adapted with permission from Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Medical progress: exercise training for claudication. N Engl J Med 2002;347:1941-51 (362d). Copyright © 2002 Massachusetts Medical Society. All Rights Reserved.

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 an 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

is repeated several times during the hour of supervision. Such a program requires that patients be reassessed as they continue the program so that the workload, modified by treadmill grade or speed (or both), can be increased to allow patients to achieve increased pain-free and maximal walking distances until program completion. Typical benefits of such a program include a more than 100% improvement in peak exercise performance (322-326,329), significant improvements in walking speed and distance noted with the Walking Impairment Questionnaire and improvements in physical 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 sig-

nificant 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 IIb

1. **The effectiveness of L-arginine for patients with intermittent claudication is not well established. (Level of Evidence: B)**
2. **The effectiveness of propionyl-L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. (Level of Evidence: B)**
3. **The effectiveness of ginkgo biloba to improve walking distance for patients with intermittent claudication is marginal and not well established. (Level of Evidence: B)**

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 adenylyl 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 pro-drug 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 congener, 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

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:

- a predicted or observed lack of adequate response to exercise therapy and claudication pharmacotherapies
- 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
- absence of other disease that would limit exercise even if the claudication was improved (e.g., angina or chronic respiratory disease)
- the anticipated natural history and prognosis of the patient
- 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

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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

TASC type A iliac lesions:

1. Single stenosis less than 3 cm of the CIA or EIA (unilateral/bilateral)

TASC type B iliac lesions:

2. Single stenosis 3 to 10 cm in length, not extending into the CFA
3. Total of 2 stenoses less than 5 cm long in the CIA and/or EIA and not extending into the CFA
4. Unilateral CIA occlusion

TASC type C iliac lesions:

5. Bilateral 5- to 10-cm-long stenosis of the CIA and/or EIA, not extending into the CFA
6. Unilateral EIA occlusion not extending into the CFA
7. Unilateral EIA stenosis extending into the CFA
8. Bilateral CIA occlusion

TASC type D iliac lesions:

9. Diffuse, multiple unilateral stenoses involving the CIA, EIA, and CFA (usually more than 10 cm long)
10. Unilateral occlusion involving both the CIA and EIA
11. Bilateral EIA occlusions
12. Diffuse disease involving the aorta and both iliac arteries
13. Iliac stenoses in a patient with an abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery

Endovascular procedure is the treatment of choice for type A lesions, and surgery is the procedure of choice for type D lesions.

CFA indicates common femoral artery; CIA, common iliac artery; EIA, external iliac artery; TASC, TransAtlantic Inter-Society Consensus.

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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

Table 21. Morphological Stratification of Femoropopliteal Lesions

TASC type A femoropopliteal lesions:

1. Single stenosis less than 3 cm of the superficial femoral artery or popliteal artery

TASC type B femoropopliteal lesions:

2. Single stenosis 3 to 10 cm in length, not involving the distal popliteal artery
3. Heavily calcified stenoses up to 3 cm in length
4. Multiple lesions, each less than 3 cm (stenoses or occlusions)
5. Single or multiple lesions in the absence of continuous tibial runoff to improve inflow for distal surgical bypass

TASC type C femoropopliteal lesions:

6. Single stenosis or occlusion longer than 5 cm
7. Multiple stenoses or occlusions, each 3 to 5 cm in length, with or without heavy calcification

TASC type D femoropopliteal lesions:

8. Complete common femoral artery or superficial femoral artery occlusions or complete popliteal and proximal trifurcation occlusions

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).

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*)

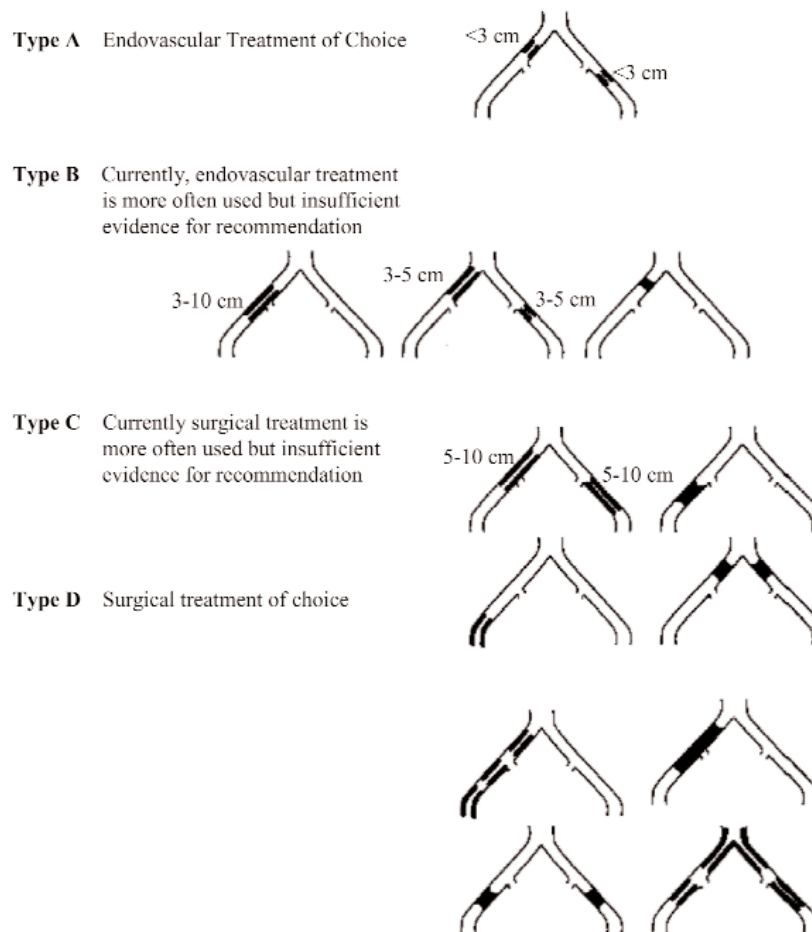


Figure 8. Summary of preferred options in interventional management of iliac lesions. Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

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-

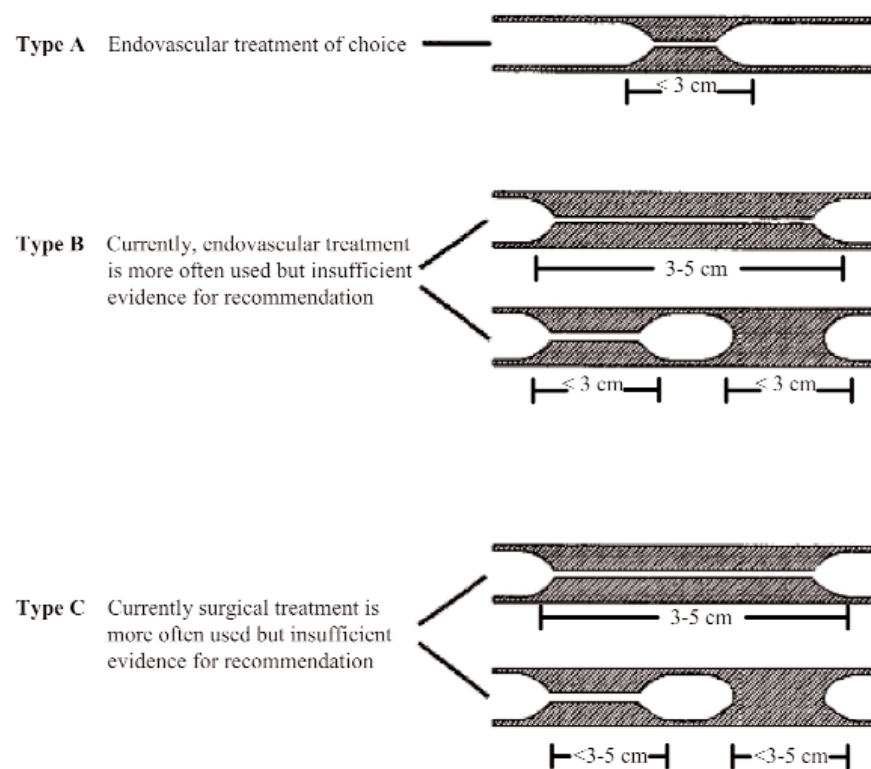


Figure 9. Summary of preferred options for interventional treatment of femoropopliteal lesions. Reprinted from J Vasc Surg, 31, Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (PAD), S1-S296, Copyright 2000, with permission from Elsevier (1).

ure these pressures (441,442). One criterion would utilize a mean gradient of 10 mm Hg before or after vasodilators; another has suggested use of a mean gradient of 5 mm Hg, or 10, 15, or 20 mm Hg peak systolic; and a third criteria would use a 15% peak systolic pressure gradient after administration of a vasodilator (425,439-441). Pressure measurements may be obtained with 2 separate pressure transducers or by obtaining pullback pressures with a single transducer. Pressures obtained with the catheter positioned across the stenosis may artifactually increase the pressure gradient by reducing the residual lumen with the catheter. Endovascular treatment of a stenosis that lacks a pressure gradient is not indicated. No studies have been performed to assess the safety and efficacy of treating asymptomatic but hemodynamically significant lesions to prevent progression of disease (prophylactic angioplasty), and therefore this strategy is not recommended.

Selection of patients for endovascular versus conservative (medical) therapy has been evaluated in several trials. A small randomized trial of PTA versus supervised exercise found that PTA improved the ABI more than exercise at 15 months, but claudication and walking distance were better in the exercise group (352). Another randomized trial of PTA versus exercise advice found that at 6 months, PTA yielded significantly better results for claudication symptoms, tread-

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 for treatment of iliac and femoral-popliteal disease. Sixty percent of patients were treated for CLI (446). Wolf *et al.* similarly reported no significant difference in 4-year primary patency, ABI, health status, and patient survival in a randomized trial of PTA versus surgical bypass. Only 25% to 30% of patients were treated for CLI (447).

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

Procedure	Lesion Type	Severity of Disease	Reference	No. of Limbs	30-Day Mortality, % (95% CI)	Major Complication, % (95% CI)	Technical Success, % (95% CI)	Primary Patency, % (95% CI)*				
								1 y	2 y	3 y	4 y	5 y
Iliac PTA	80% stenoses, 20% occlusion	67% claudication, 33% critical ischemia	(436)	1473	1.0 (0 to 2.9)	4.3 (2.0 to 6.5)	91 (86 to 96)	74 (71 to 76)	66 (63 to 68)	61 (59 to 64)	58 (56 to 61)	—
								79	72	68	65	—
	Stenoses	Claudication			ND	ND	96					—
	Stenoses	Critical ischemia			ND	ND	ND					—
	Occlusion	Claudication			ND	ND	80					—
Iliac stent	72% stenoses, 28% occlusion	85% claudication, 15% critical ischemia	(436)	901	0.8 (0.7 to 0.9)	5.2 (3.5 to 6.9)	96 (91 to 100)	86 (84 to 89)	79 (76 to 81)	75 (72 to 78)	74 (69 to 78)	—
								91	84	80	77	—
	Stenoses	Claudication			ND	ND	100					—
	Stenoses	Critical ischemia			ND	ND	ND					—
	Occlusion	Claudication			ND	ND	80					—
Femoropopliteal PTA	64% stenoses, 36% occlusion	65% claudication, 35% critical ischemia	(437, 438)	4800/1003†	0.9 (0.7 to 1.1)	8.1 (7.3 to 8.9)	89 (87 to 91)	59 (56 to 62)	54 (51 to 57)	52 (48 to 55)	49 (45 to 52)	45 (41 to 49)
								95	90	87	75	68
	Stenoses	Claudication			ND	ND	95					—
	Stenoses	Critical ischemia			ND	ND	90					—
	Occlusion	Claudication			ND	ND	87					—
Femoropopliteal stent	Stenoses and occlusions	80% claudication, 20% critical ischemia	Meta-analysis‡	600	—	5.9 (1.7 to 10)	98 (97 to 100)	62 (48 to 80)	52 (33 to 83)	43 (22 to 86)	—	—
								79 (68 to 90)	74 (65 to 83)	—	—	—
	Stenoses and occlusions	14% claudication, 86% critical ischemia	Meta-analysis§	1282	—	—	—	93 (90 to 96)	79 (68 to 90)	74 (65 to 83)	—	—

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).

Reprinted from Kandarpa K, Becker BJ, Humink M, et al. J Vasc Interv Radiol 2001;12:683-95 (438a).

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 B and 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 in general 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-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)**

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

Table 23. Vascular Surgical Procedures for Inflow Improvement

Inflow Procedure	Operative Mortality (%)	Expected Patency Rate (%)	References
Aortobifemoral bypass	3.3	87.5 (5 years)	(485)
Aortoiliac or aortofemoral bypass	1 to 2	85 to 90 (5 years)	(486-488)
Iliac endarterectomy	0	79 to 90 (5 years)	(489-491)
Femorofemoral bypass	6	71 (5 years)	(492)
Axillofemoral bypass	6	49 to 80 (3 years)	(493, 494)
Axillofemoral-femoral bypass	4.9	63 to 67.7 (5 years)	(495, 496)

bypass is constructed by sewing the proximal end of a bifurcated polyester filament or polytetrafluoroethylene (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.

As noted above, results of aortobifemoral bypass grafting are uniformly better in patients who present with symptoms at age 50 years or greater. Diabetes, a well-known risk factor for progressive atherosclerotic occlusive disease, does not adversely impact the surgical treatment of aortoiliac disease.

Faries and associates, in a study of 504 patients undergoing aortobifemoral bypass grafting, noted that diabetes was not a risk factor for the need for subsequent surgical revision or more distal revascularization procedures (497).

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.

A less invasive approach may be appropriate for patients with adequate aortic flow but stenoses or occlusions of both iliac vessels. Such patients may not be considered acceptable candidates for aortobifemoral bypass owing to comorbid cardiovascular disease. If endovascular treatment of 1 iliac artery is feasible and patency can be achieved with this less invasive approach, a subsequent endarterectomy, unilateral iliofemoral bypass, or femoral-femoral bypass can be constructed. In the absence of an inflow stenosis within the donor iliac arterial segment, this procedure can effectively provide flow to both lower extremities and eliminate the symptoms of claudication.

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 utilizes 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. Because of lower patency rates, such bypasses are reserved for those who have no alternatives for revascularization. The procedure is uncommonly performed for claudication.

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: Infringuinal 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-

Table 24. Vascular Surgical Procedures for Outflow Improvement

Outflow Procedure	Operative Mortality (%)	Expected Patency Rate (%)	References
Fem-AK popliteal vein	1.3 to 6.3	66 (5 years)	(437,498,499)
Fem-AK popliteal prosthetic	1.3 to 6.3	50 (5 years)	(483,508-510)
Fem-BK popliteal vein	1.3 to 6.3	66 (5 years)	(498,499)
Fem-BK popliteal prosthetic	1.3 to 6.3	33 (5 years)	(437,498,499)
Fem-Tib vein	1.3 to 6.3	74 to 80 (5 years)	(500a)
Fem-Tib prosthetic	1.3 to 6.3	25 (3 years)	(502)
Composite sequential bypass	0 to 4	28 to 40 (5 years)	(503,504)
Fem-Tib blind segment bypass	2.7 to 3.2	64 to 67 (2 years)	(505)
Profundaplasty	0 to 3	49 to 50 (3 years)	(506,507)

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

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 25. Patency of Above-Knee Femoral Popliteal Bypass Grafts According to Prospective Randomized Trials

First Author	Reference	Graft Material	No. of Patients	% Patency (Years)				
				2	5	5 Assisted	6	6 Assisted
Johnson	(509)	SVG	226	81	73			
		PTFE	265	69	39			
Klinkert	(510)	SVG	75		75.6	79.7		
		PTFE	76		51.9	57.2		
AbuRahma	(508)	SVG	43				76	83
		PTFE	43				68	68
Green	(483)	PTFE			43		68	
		Polyester fiber		45		68		

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 femoral-femoral 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 femoral-popliteal 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

Table 26. Patency of Bypass Grafts Placed for Treatment of Claudication

Material	5-Year Patency (%)	
	Mean	Range
Vein	80	78 to 87
PTFE above knee	75	67 to 83
PTFE below knee	65	56 to 76

PTFE indicates polytetrafluoroethylene.

Reprinted with permission from Hunink MG, Wong JB, Donaldson MC, et al. Patency results of percutaneous and surgical revascularization for femoropopliteal arterial disease. *Med Decis Making*. 1994;14:71-81 (437).

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 femoral-popliteal segments or the femoral-popliteal 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 forefoot and toes that is sufficiently severe as to interfere with sleep and ischemic ulcers or ischemic gangrene of the forefoot 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.

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 hemorrheologic 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 ciprostone, 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-1 α administered as plasmid DNA or with an adenovirus vector encoding the angiogenic growth factor. Initial studies of gene transfer 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 the 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 IIb) 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 less than 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-

traindicated in some patients. Contraindications have been summarized, although these recommendations are based on common practice and are not necessarily supported by published studies. Because of comorbidities, surgery may be contraindicated in some patients.

Most of the literature supporting the use of thrombolysis has used urokinase as the lytic drug. Other drugs that have been studied include pro-urokinase (not currently available), alteplase, reteplase, tenecteplase, and streptokinase. Streptokinase has been largely abandoned owing to lower efficacy and increased bleeding complications compared with urokinase (564,565). The optimal dosage and concentration of alteplase, reteplase, and tenecteplase and the optimal dose of adjunctive heparin are still under investigation. Alteplase has been reported to be as effective as or more effective than urokinase, with similar or higher bleeding rates (557,566-572). Reteplase has been studied in small series with outcomes similar to urokinase (573,574), with the best dosage and concentration still under investigation (575). The results of a pilot study with tenecteplase have been reported (576). Although a number of comparative trials have been published, there is no single agent that has consistently demonstrated superiority (577-579). One randomized trial (577) demonstrated more rapid thrombus dissolution with tissue plasminogen activator than with urokinase (577-579).

Small series have reported the results of combined thrombolytic and intravenous antiplatelet therapy (glycoprotein IIb/IIIa platelet inhibitors) and have suggested that the combination may increase lysis effectiveness, decrease time to complete lysis, and possibly increase bleeding (557,580-583). The risk/benefit and cost/benefit ratio of these strategies, compared with catheter-directed thrombolysis or thrombectomy alone, remain to be demonstrated in larger comparative trials. Nonrandomized trials and small series have also reported on the use of mechanical thrombectomy devices, which may avert the need for thrombolysis or permit the use of decreased doses of thrombolytic drugs (Table 27) (584,585). Mechanical thrombectomy was used in 21 patients (22 vessels [limbs]) who presented to the hospital within 2 weeks of the development of limb-threatening ischemia. Fifty-two percent had contraindications to thrombolytics, and 57% had severe comorbidities. All of the target vessels were occluded with thrombus on the initial angiogram. Procedural success was achieved in 20 limbs (91%). Acute limb salvage was achieved in 18 (95%) of 19 limbs in the 18 survivors, and 6-month limb salvage was achieved in 16 (89%) of 18 limbs in the 17 survivors. The authors concluded that rheolytic thrombectomy was effective in restoring immediate blood flow in acute limb-threatening ischemia, especially in high-risk surgical patients and patients with contraindications to thrombolytic therapy (584).

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

Device and First Author (Reference No.)	Year	n	Conduit, n (%)	Duration, n	MTD Success,* n (%)	Adjunctive Procedures	Primary Patency (%)	Complications (%)
Oasis, Hopfner (143)	1999	51	Native: 44 (86) Grafts: 7 (14)	All acute	6 (11.8)	Lysis: 5 PTA: 20 PAT: 15 SA: 3	1 month: 64 6 months: 54	Hemorrhage: 8 Emboli: 4.8 Acute occlusion: 3 Amputation: 17.7 Mortality: 8
Angiojet Muller-Hulsbeck (144)	2000	112	Native: 99 (86) Grafts: 16 (14)	All acute	79 (71)	Lysis: 20 PTA: 68 PAT: 11	6 months: 68 2 years: 60 3 years: 58	Embolization: 9.8 Dissection: 8 Perforation: 3.6 Amputation: 1.8 Mortality: 7
Kasirajan (145)	2001	83	Native: 52 (63) Grafts: 31 (37)	Acute: 62 Chronic: 21	Complete: 51 (61) Partial: 19 (23)	Lysis: 50 PTA: 47	3 months: 90 6 months: 78	Hemorrhage: 10.5 Emboli: 2.3 Dissection: 3.5 Perforation: 2.3 Amputation: 11.6 Mortality: 9.3
Schava (146)	1998	22	Native: 13 (59) Grafts: 9 (41)	All acute	21 (95)	PTA: 21	NA	Hemorrhage: 10 Embolism: 9 Dissection: 5 Occlusion: 18 Amputation: 5 Mortality: 14
Wagner (147)	1997	50	Native: 39 (78) Grafts: 11 (22)	All acute	26 (52)	Lysis: 15 PTA: 34 PAT: 9	1 year : 69	Hemorrhage: 6 Emboli: 6 Dissection: 6 Perforation: 6 Amputation: 8 Mortality: 0
Hydrolyser Reekers (148)	1996	28	Native: 11 (39) Grafts: 17 (61)	Acute: 23 Chronic: 5	23 (82)	Lysis: 11 PTA: 20 PAT: 2	1 month: 50	Embolization: 18 Hemorrhage: 0 Acute occlusion: 10 Amputation: 11 Mortality: 0
Henry (149)	1998	41	Native: 28 (68) Grafts: 8 (20) Other: 5	All acute	34 (83)	Lysis: 10 PTA: 29 PAT: 17	1 month: 73	Acute occlusion: 12 Emboli: 2.4 Amputation: 0 Mortality: 0
Amplatz Rilinger (150)	1997	40	All native	All acute	30 (75)	Lysis/PTA/ SA: 9	NA	Hemorrhage: 2.5 Device failure: 7.5 Emboli: 0 Amputation: 5 Mortality: 0
Tadavarthy (151)	1994	14	Native: 2 (14) Grafts: 10 (71) Other: 2	Acute: 9 Chronic: 5	10 (71)	Lysis: 4 PTA/SA: 11	6 months: 43	Hemorrhage: 14.3 Emboli: 14 Device failure: 7 Amputation: 0 Mortality: 0
Gorich (152)	1998	18	All native	All acute	14 (78)	Lysis: 12 PAT: 9	NA	Hemorrhage: 6 Device failure: 6 Amputation: 6

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.

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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 iliofemoral 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 iliofemoral 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 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.

The surgical treatment of unilateral iliac disease by aortoiliac, iliofemoral, 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. Because this graft is based on the axillary artery, preoperative assessment of bilateral arm blood pressures, duplex ultrasound flow assessments, and/or imaging of the aortic arch and great vessels to the origin of the donor vessel should be obtained.

Axillofemoral and axillobifemoral grafts are significantly inferior to aortobifemoral bypass grafts or aortoiliac endarterectomy for the treatment of severe diffuse aortoiliac disease. The 5-year patency rate for axillofemoral grafts ranges from 19% to 50% (173,604). The results of axillobifemoral bypass are somewhat better, with 5-year patency rates ranging from 50% to 76% (605).

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 conduit for arterial reconstruction of the lower extremity 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 aortobifemoral 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

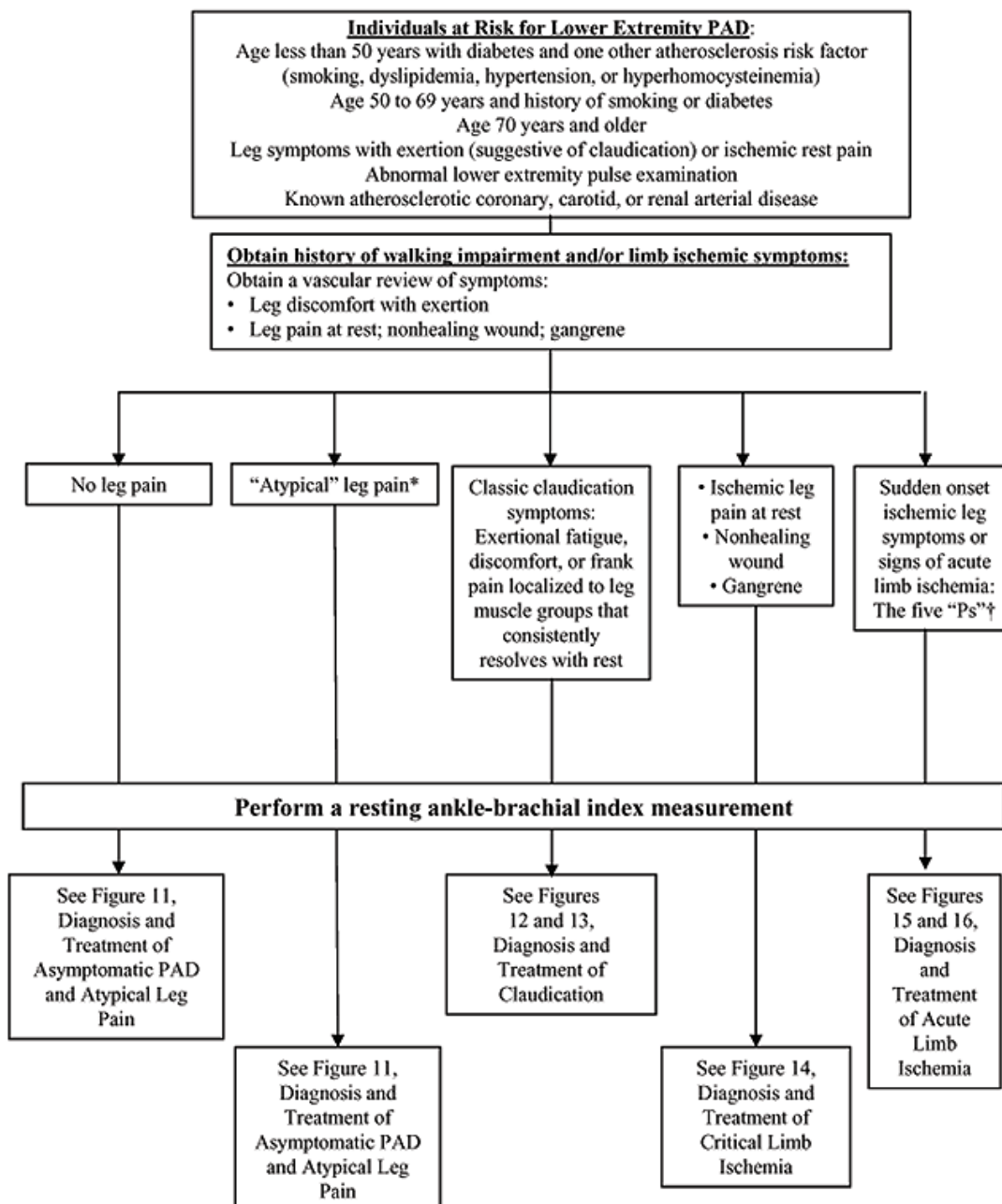


Figure 10. Steps toward the diagnosis of peripheral arterial disease (PAD). **"Atypical" leg pain is defined by lower extremity discomfort that is exertional, but that does not consistently resolve with rest, consistently limit exercise at a reproducible distance, or meet all "Rose questionnaire" criteria. †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").

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 rel-

atively 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

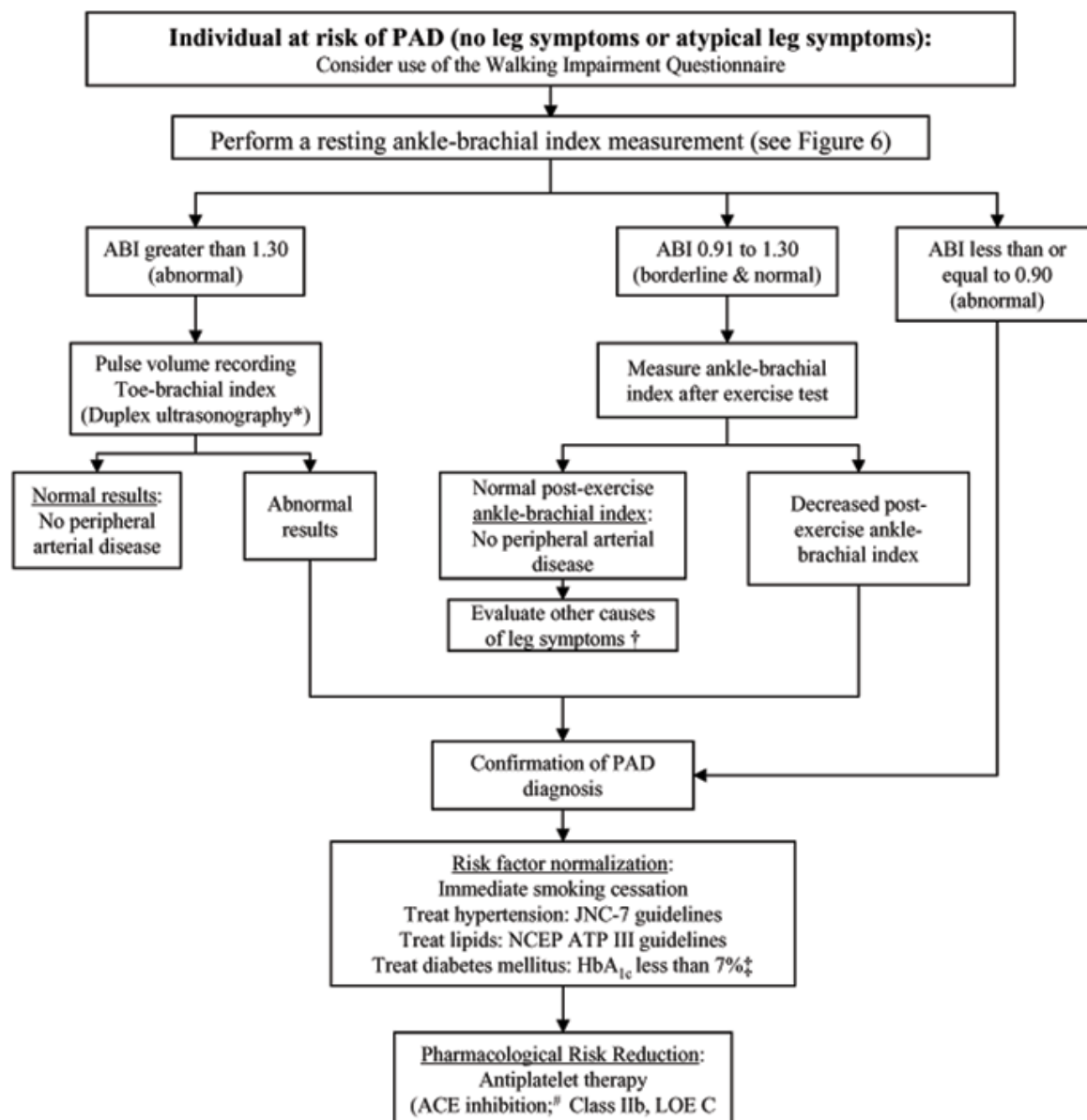


Figure 11. Diagnosis and treatment of asymptomatic peripheral arterial disease (PAD) and atypical leg pain. *Duplex ultrasonography should generally be reserved for use in symptomatic patients in whom anatomic diagnostic data are required for care. †Other causes of leg pain may include lumbar disk disease, 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; HbA_{1c}, hemoglobin A_{1c}; 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-

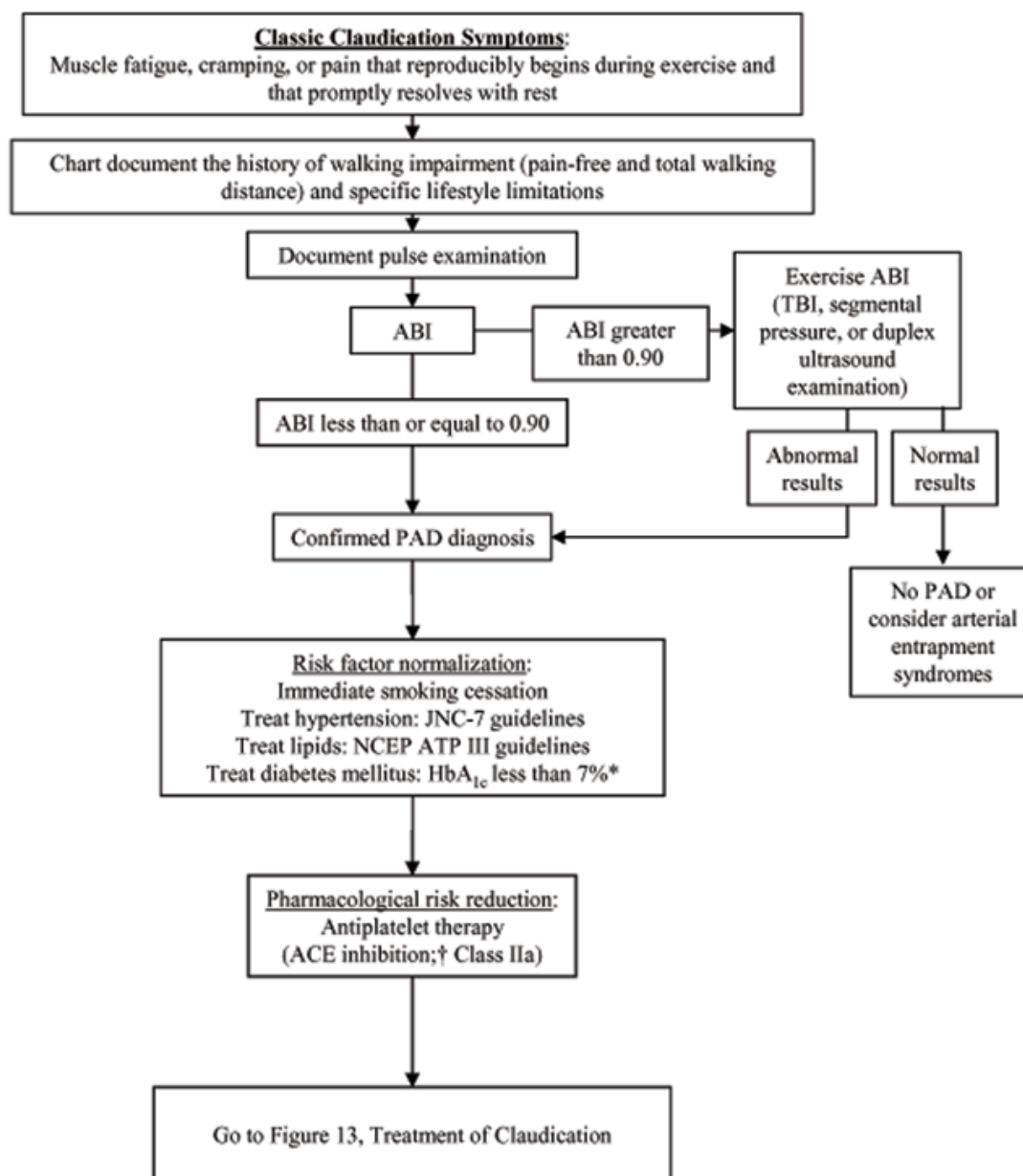


Figure 12. Diagnosis of claudication and systemic risk treatment. *It is not yet proven that treatment of diabetes mellitus will significantly reduce peripheral arterial disease (PAD)-specific (limb ischemic) endpoints. Primary treatment of diabetes mellitus should be continued according to established 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; HbA_{1c}, hemoglobin A_{1c}; JNC-7, Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LOE, level of evidence; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

ated 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-

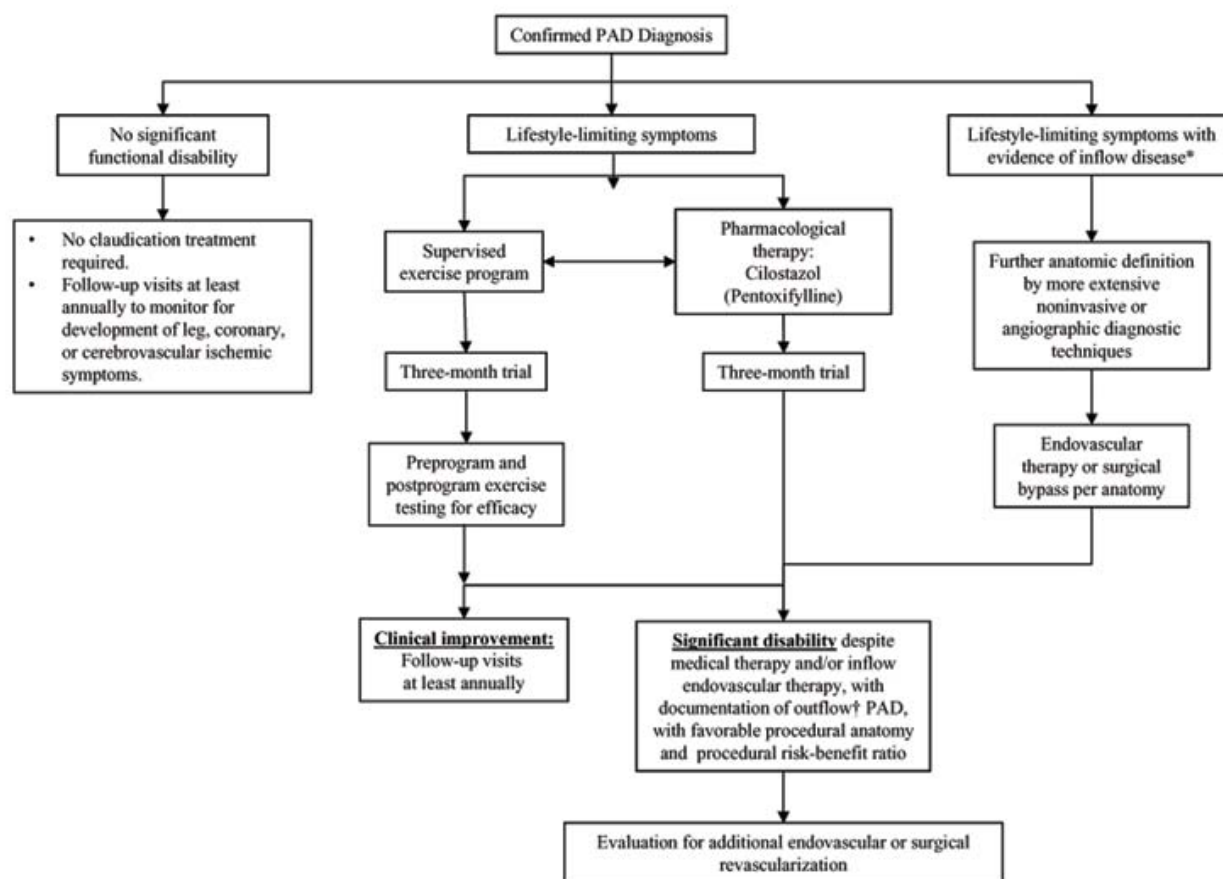


Figure 13. Treatment of claudication. *Inflow disease should be suspected in individuals with gluteal or thigh claudication and femoral pulse diminution or bruit and should be confirmed by noninvasive vascular laboratory diagnostic evidence of aortoiliac stenoses. †Outflow disease represents femoropopliteal and infrapopliteal stenoses, (the presence of occlusive lesions in the lower extremity arterial tree below the inguinal ligament from the common femoral artery to the pedal vessels). PAD indicates peripheral arterial disease.

sis, occlusion occurred in 39% of cases over a 12- to 60-month follow-up period (635).

Several prospective natural history studies have described the progression of RAS. In a series published by Dean and coworkers, RAS progressed in 29% (10 of 35) of patients and resulted in total occlusion in 11% of patients during a mean follow-up of 28 months (range 6 to 102 months) (637). Over a 3-year period, Zierler and associates found that 48% of patients had progression of RAS from less than 60% to greater than or equal to 60% stenosis (638). The renal arteries that progressed to occlusion were each characterized by a stenosis greater than or equal to 60% at baseline (study entry). Progression of RAS occurred at an average rate of approximately 7% per year. Using sonography, Caps et al. monitored 295 kidneys in 170 patients for a mean of 33 months (639). Disease progression, based on sonographic determination, was 35% at 3 years and 51% at 5 years. Nine renal artery occlusions (3%) occurred over the course of the study. All occlusions developed in patients with greater than 60% stenosis in the study that preceded the occlusion. Occlusion occurred most often in patients with diabetes, high-grade stenoses, and severe hypertension (639).

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-

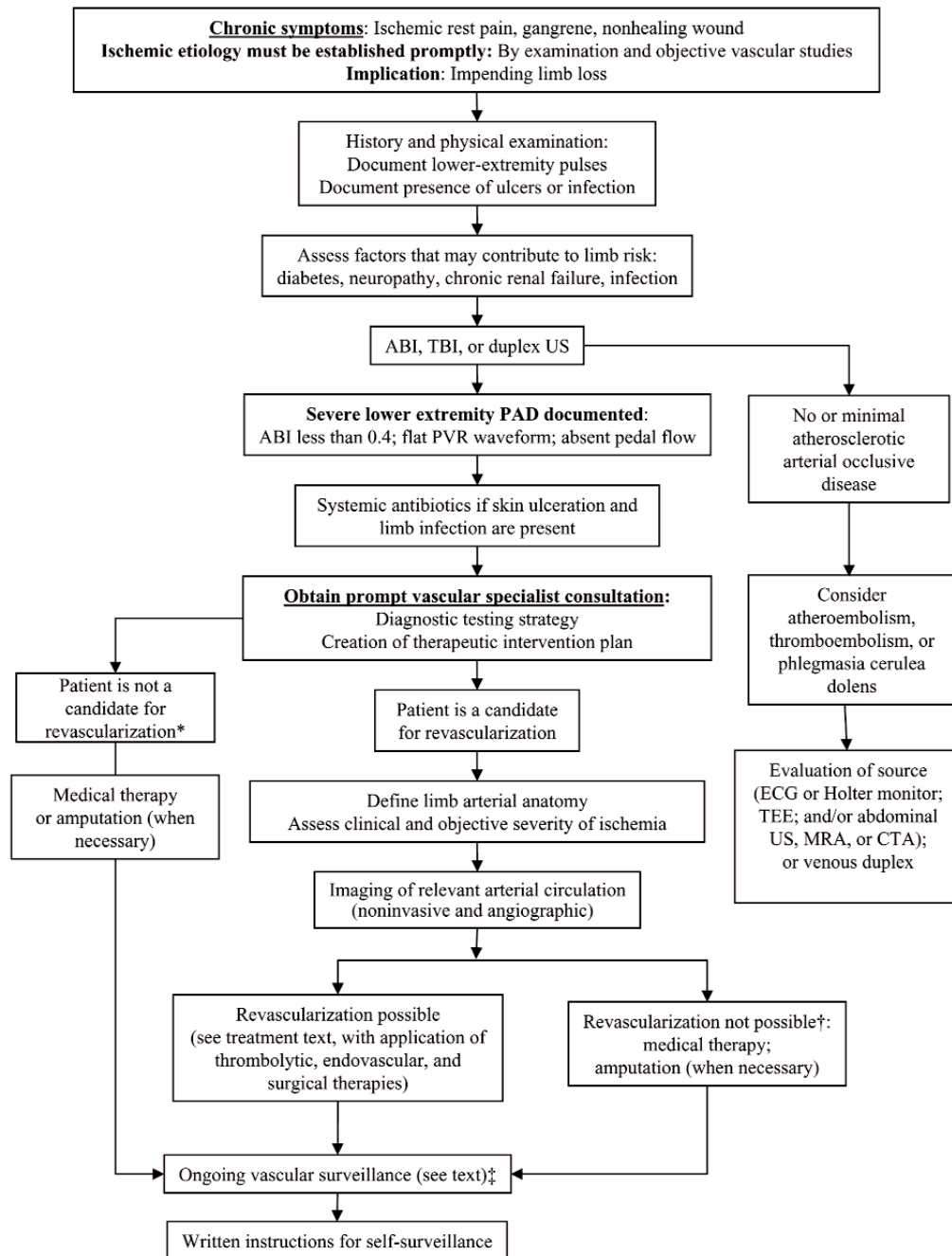


Figure 14. Diagnosis and treatment of critical limb ischemia. *Based on patient comorbidities. †Based on anatomy or lack of conduit. ‡Risk factor normalization: immediate smoking cessation, treat hypertension per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines; treat lipids per National Cholesterol Education Program Adult Treatment Panel III guidelines; treat diabetes mellitus (HbA_{1c} [hemoglobin A_{1c}] 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.

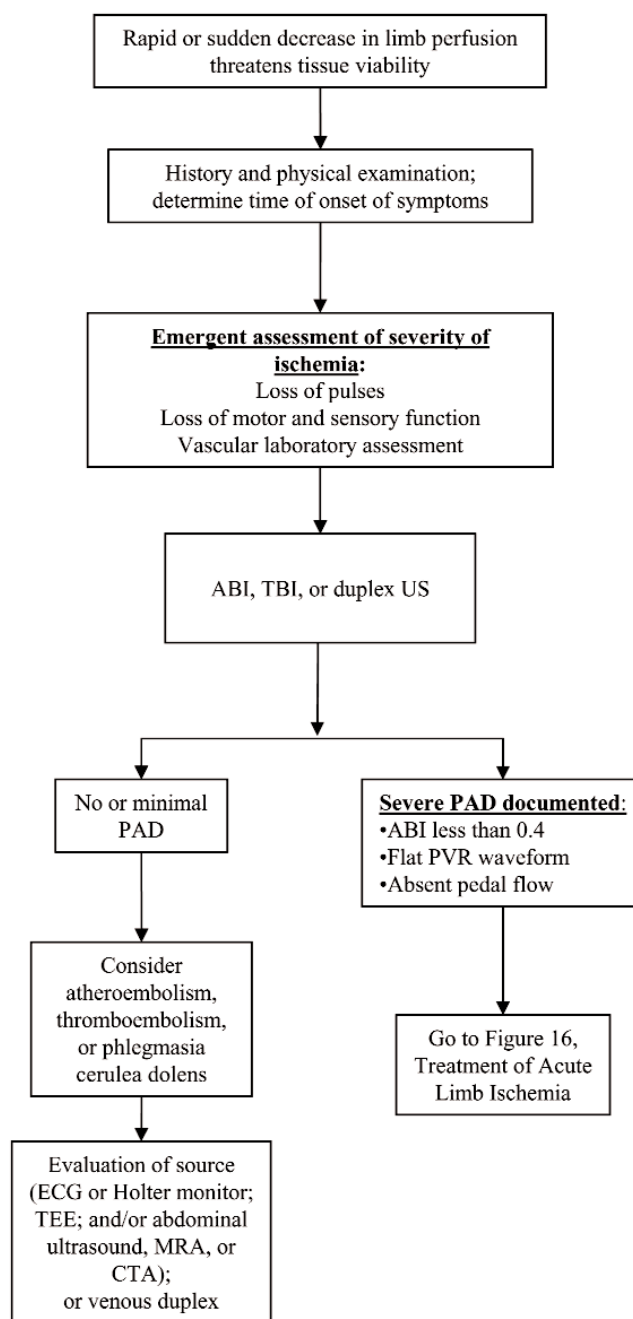


Figure 15. Diagnosis of acute limb ischemia. ABI indicates ankle-brachial index; CTA, computed tomographic angiography; ECG, electrocardiogram; MRA, magnetic resonance angiography; PVR, pulse volume recording; TBI, toe-brachial index; TEE, transesophageal echocardiography; US, ultrasound. Adapted from J Vasc Surg, 26, Rutherford RB, Baker JD, Ernst C, et al., Recommended standards for reports dealing with lower extremity ischemia: revised version, 517-38, Copyright 1997, with permission from Elsevier (518).

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

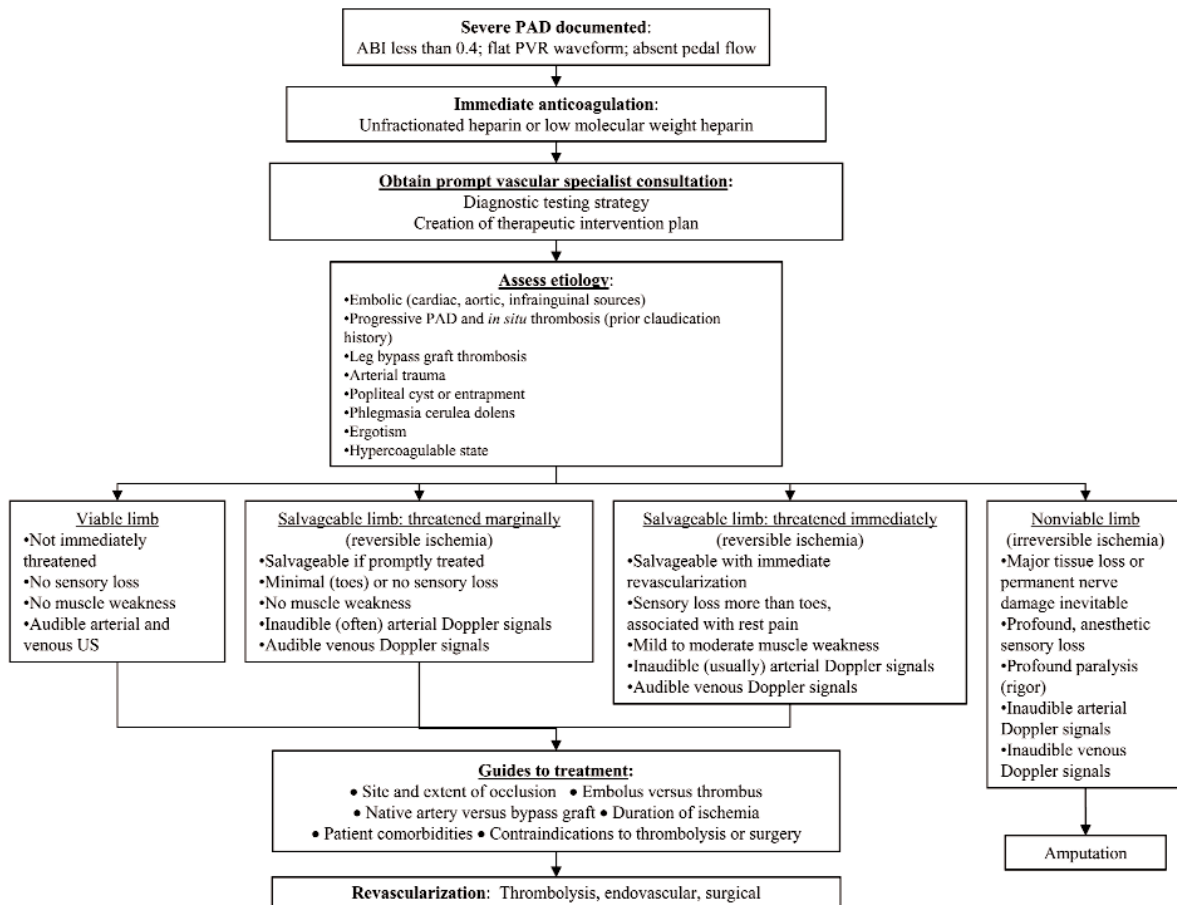


Figure 16. Treatment of acute limb ischemia. PAD indicates peripheral arterial disease; PVR, pulse volume recording; US, ultrasonography. Adapted from J Vasc Surg, 26, Rutherford RB, Baker JD, Ernst C, et al., Recommended standards for reports dealing with lower extremity ischemia: revised version, 517-38, Copyright 1997, with permission from Elsevier (518).

(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 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 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 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 start-

ing 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 multivessel 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 decompensated 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

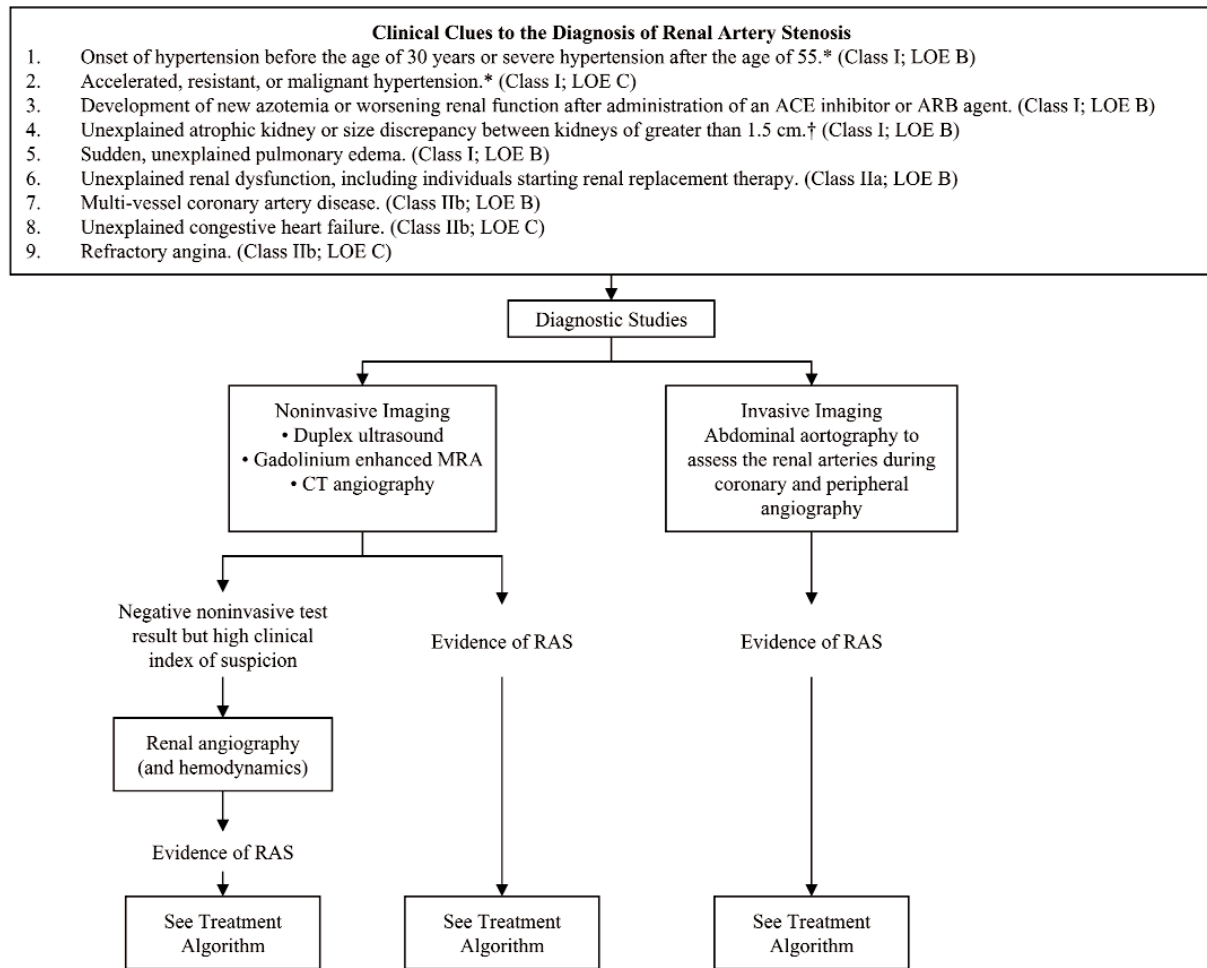


Figure 17. Clinical clues to the diagnosis of renal artery stenosis (RAS). *For definition of hypertension, please see Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report. JAMA 2003;289:2560-72 (294). †For example, atrophic kidney due to chronic pyelonephritis is not an indication for RAS evaluation. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocking agent; CT, computed tomography; LOE, level of evidence; MRA, magnetic resonance angiography.

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

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

Reprinted with permission from Begelman SM, Olin JW. Fibromuscular dysplasia. *Curr Opin Rheumatol* 2000;12:41-7 (11).

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 mercaptoacetyl triglycine or technetium-99m diethylenetriaminepentaacetic acid. The diagnostic criteria for RAS are (a) delayed time to maximal activity (T_{Max} 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 end-diastolic 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-

uals in whom indications for these procedures exist. Controlled studies demonstrating the benefit of identifying these lesions need to be performed.

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 renin 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 lateralization 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

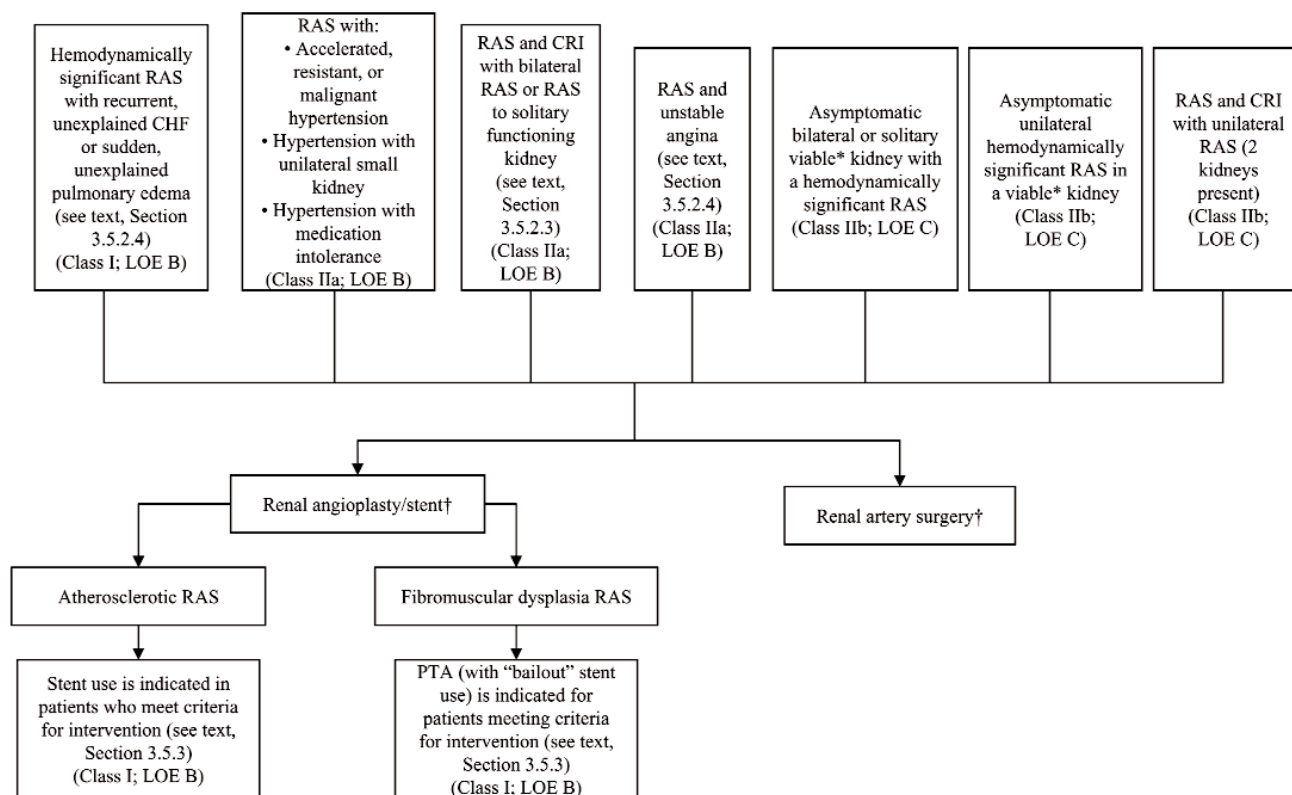


Figure 18. Indications for renal revascularization. *Viable means kidney linear length greater than 7 cm. †It is recognized that renal artery surgery has proven efficacy in alleviating RAS due to atherosclerosis and fibromuscular dysplasia. Currently, however, its role is often reserved for individuals 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.

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 demon-

strated 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 artery disease to predict the severity of coronary artery disease. Asymptomatic (incidental) RAS found at peripheral angiog-

Table 29. Prevalence of Incidental RAS Found at Cardiac Catheterization

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

NR indicates not reported.

Table 30. Prevalence of Incidental RAS Found at Abdominal Aortography

First Author	Reference	No. of Patients	RAS (%)	% RAS Greater Than 50% (%)	Bilateral (%)
Olin	(625)	318	NR	38	13
Valentine	(630)	346	NR	28	NR
Leertouwer	(719)	386	NR	33	26

NR indicates not reported; RAS, renal arterial stenosis.

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 1189 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 31. Univariate Predictors of RAS in Individuals Undergoing Cardiac Catheterization

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

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

Reprinted with permission from Crowley JJ, Santos RM, Peter RH, *et al.* Progression of renal artery stenosis in patients undergoing cardiac catheterization. *Am Heart J.* 1998;136:913-8 (643).

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

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

CI indicates confidence interval.

Reprinted with permission from Weber-Mzell D, Kotanko P, Schumacher M, et al. Coronary anatomy predicts presence or absence of renal artery stenosis: a prospective study in patients undergoing cardiac catheterization for suspected coronary artery disease. *Eur Heart J*. 2002;23:1684-91 (622).

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

	AAA (n=108)	AOD (n=21)	Infrainguinal PAD (n=189)	RAS (n=76)
All patients with greater than 50% stenosis	41 (38%)	7 (33%)	74 (39%)	53 (70%)†

*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.

Adapted with permission from Olin JW, Melia M, Young JR, et al. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med*. 1990;88(1N):46N-51N (625).

Table 34. Four-Year Survival for Individuals With Incidental (Asymptomatic) RAS as Documented at Cardiac Catheterization

Severity of Incidental RAS	Four-Year Survival (%)
No RAS	90
50% to 75%	70
75% to 95%	68
Greater than 95%	48

RAS indicates renal arterial stenosis.

Reprinted with permission from Conlon PJ, Little MA, Pieper K, et al. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int.* 2001;60:1490-7 (730).

criticism of the DRASTIC trial is that there was no proof of hemodynamic significance of stenoses of 50% to 70%. Therefore, some patients may have been treated with renal revascularization for nonhemodynamically significant stenoses. This would decrease the overall benefit for the treatment group. Since publication of this trial, stent placement has emerged as a superior technique to balloon angioplasty alone for the treatment of atherosclerotic ostial RAS. In a meta-analysis comparing the clinical benefits of balloon angioplasty and stent therapy, stent therapy demonstrated a better blood pressure response and a lower restenosis rate (699).

The single randomized, controlled trial that compared renal stent placement with balloon treatment alone demonstrated procedural superiority for primary stent placement (700). The burden of reintervention in the percutaneous transluminal renal angioplasty group (48%) compared with that of the stent group (14%) also supported the cost efficacy of stent placement during the primary procedure. The reduced restenosis with stenting compared with angioplasty alone seen in this study was not associated with differences in either hypertension or renal function benefit. A number of studies have confirmed the high technical success rates (95% or higher) for primary renal stent placement (733-739).

As noted above, the indications for renal artery revascularization presume the presence of clinical indications with a

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 control is common, and a moderate fraction of individuals do not achieve measurable benefit (Table 36).

3.5.2.3. Preservation of Renal Function

RECOMMENDATIONS

Class IIa

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 35. Multivariate Analysis of Risk Factors Associated With Progression of Renal Arterial Stenosis

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

CI indicates confidence interval; and OR, odds ratio.

Reprinted with permission from Crowley JJ, Santos RM, Peter RH, et al. Progression of renal artery stenosis in patients undergoing cardiac catheterization. *Am Heart J.* 1998;136:913-8 (643).

Table 36. Clinical Benefit (Net Cure and/or Improvement in Blood Pressure Response) to Renal Artery Stenting

First Author	Reference	No. of Patients	Arteries	Cure (%)	Improvement (%)	Benefit (%)
Dorros	(737)	76	92	7	52	59
Blum	(733)	68	74	16	62	78
White	(738)	100	133	NR	76	76
Tuttle	(734)	129	148	2	55	57
Henry	(735)	210	244	19	61	78
Rocha-Singh	(736)	150	180	6	50	56
Lederman	(739)	261	NR	Less than 1	70	70

NR indicates not reported.

Class IIb

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 Leertouwer 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 non-compliance). 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

	Baseline	Balloon	Stent
Stenosis (%)	82 plus or minus 12	29 plus or minus 14	3 plus or minus 6*
Mean gradient, mm Hg	50 plus or minus 22	8 plus or minus 6	1 plus or minus 3*
Peak gradient, mm Hg	94 plus or minus 33	23 plus or minus 19	1 plus or minus 3*

**p* less than 0.05.

Reprinted with permission from Dorros G, Jaff M, Mathiak L, et al. Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. *Circulation*. 1998;98:642-7 (779).

Table 38. Balloon Versus Stent: Randomized, Controlled Trial

	Balloon (n=51)	Stent (n=52)	p Value
Procedure success	63%	90%	Less than 0.05
Restenosis	48%	14%	Less than 0.05

van de Ven PJ, Kaatee R, Beutler JJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet*. 1999;353:282-6. (700). Reprinted with permission from Elsevier.

placement and balloon angioplasty, for atherosclerotic RAS was performed by Leertouwer and colleagues (700). They confirmed a significantly higher procedural success rate for stents (98%) than for balloon angioplasty (77%; *p* less than 0.001) and a lower restenosis rate for stents (17%) than for balloon angioplasty (26%; *p* less than 0.001). A survey of the literature suggests that restenosis rates for renal stenting are often lower (Table 39).

Renal resistive index has been suggested as a marker for selecting patients likely to respond to intervention. However, there are conflicting data regarding the ability of the RRI to predict treatment response. A retrospective study in which most patients were treated by balloon angioplasty alone by Radermacher and coworkers (698) suggested that an elevated resistance index greater than 0.80 was associated with a low probability of improved blood pressure control or renal function preservation after revascularization. This study has been criticized for its retrospective nature without use of pre-specified end points and for its reliance on the use of balloon angioplasty as the primary method of treatment. These data have been challenged recently by a prospective uncontrolled study of renal stent placement in 241 patients by Zeller and associates (702). These investigators clearly demonstrated that patients with an elevated RRI were also able to achieve a favorable blood pressure response and renal functional improvement after renal arterial intervention.

For renal artery atherosclerotic lesions, the larger the post-stent minimal lumen diameter, as measured by quantitative vascular angiography, the better the late stent patency (738). Similar to coronary stents, larger diameter renal arteries have lower restenosis rates than smaller diameter vessels (698,

736). 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

- Vascular surgical reconstruction is indicated for patients with fibromuscular dysplastic RAS with clinical indications for interventions (same as for PTA), especially those exhibiting complex disease that extends into the segmental arteries and those having macroaneurysms. (Level of Evidence: B)**
- 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)**
- 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 39. Renal Stent Placement Procedural Outcomes

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

*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 iliorenal 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 hepatorenal or splenorenal bypasses are created, no significant celiac artery stenoses should be present. For iliorenal 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).

Table 40. Surgical Revascularization of Fibrodysplastic Renovascular Hypertension in Adults

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

Adapted with permission from Stanley JC. The evolution of surgery for renovascular occlusive disease. *Cardiovasc Surg.* 1994;2:195-202 (781).

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 41. Surgical Revascularization of Arteriosclerotic Renovascular Hypertension in Adults

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

Adapted with permission from Stanley JC. The evolution of surgery for renovascular occlusive disease. *Cardiovasc Surg.* 1994;2:195-202 (781).

- 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 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

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

diac 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 Buerger's 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 Riolo” (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)

Surgical treatment of chronic intestinal ischemia is accomplished by endarterectomy or bypass grafting, with the majority of surgeons preferring the latter approach (836,851-858). The overall operative mortality and durability of revascularization in chronic cases described by multiple contemporary reports are listed in Table 42. Long-term patency and relief of symptoms are the rule, with few recurrences; however, long-term follow-up is mandatory. Essentially all symptomatic recurrences are the result of recurrent stenosis or occlusion of visceral arteries or the reconstructions.

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

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

*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 Malmö, 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 less than 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

Table 43. Dimensions of Normal Arteries

First Author and Procedure	Females		Males		Assessment Method
	Mean Diameter, cm, Range	Standard Deviation, cm, Range	Mean Diameter, cm, Range	Standard Deviation, cm, Range	
Abdominal aorta, supraceliac	2.10 to 2.31	0.27	2.50 to 2.72	0.24 to 0.35	Computed tomography
Abdominal aorta, suprarenal	1.86 to 1.88	0.09 to 0.21	1.98 to 2.27	0.19 to 0.23	Computed tomography
Abdominal aorta, infrarenal	1.66 to 2.16	0.22 to 0.32	1.99 to 2.39	0.30 to 0.39	Computed tomography, IV arteriography
Abdominal aorta, infrarenal	1.19 to 1.87	0.09 to 0.34	1.41 to 2.05	0.04 to 0.37	B-mode ultrasound, computed tomography, IV arteriography
Celiac	0.53	0.03	0.53	0.03	B-mode ultrasound
Superior mesenteric	0.63	0.04	0.63	0.04	B-mode ultrasound
Common iliac	0.97 to 1.02	0.15 to 0.19	1.17 to 1.23	0.20	Computed tomography
Internal iliac	0.54	0.15	0.54	0.15	Arteriography
Common femoral	0.78 to 0.85	0.07 to 0.11	0.78 to 1.12	0.09 to 0.30	Computed tomography, B- or M-mode ultrasound
Popliteal	NA	NA	0.9	0.2	B-mode ultrasound
Posterior tibial	NA	NA	0.3	0.01	M-mode ultrasound

IV indicates intravenous; and NA, not available.

Adapted from J Vasc Surg, 13, Johnston KW, Rutherford RB, Tilson MD, et al. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery, 452-58, Copyright © 1991, with permission from Elsevier (863).

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

- 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)**

- 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* less than 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 44. Prevalence of Abdominal Aortic Aneurysms in Population-Based Screening Studies

Country/Study	First Author	Reference	Number Screened	Age, y	Criteria	% Prevalence/ Gender	Relative Risk
Western Australia	Jamrozik	(869)	12 203	65 to 69 80 to 83 65 to 83	Larger than 3.0 cm Larger than 3.0 cm Larger than 5.0 cm	4.8/Male 10.8/Male 0.69/Male	Higher risk: Current or ex-smokers Established PAD, CAD Waist-hip ratio larger than 0.9 Lower risk: Mediterranean born versus Australian born (OR 0.6) Regular vigorous exercise
Veterans Affairs Cooperative Study	Lederle	(870)	126 196*	50 to 79 50 to 79 50 to 79	Larger than 4.0 cm Larger than 4.9 cm Larger than 5.4 cm	1.3/Male and female 0.45/Male and female 0.27/Male and female	Higher risk: Increased age per 7 years (OR 1.7) Smoking history (OR 5.17) Family history (OR 1.9) Established atherosclerosis (OR 1.6) Lower risk: Female (OR 0.18; 2.7% of total) Black race (OR 0.59) Diabetes mellitus (OR 0.50)
Norway	Singh	(871)	6386	25 to 84 45 to 54 55 to 64 65 to 74 75 to 84 55 to 64 65 to 74 75 to 84	Larger than 2.9 cm Larger than 2.9 cm Larger than 3.9 cm	8.9/Male; 2.2/female 1.9/Male; 0/female 6.0/Male; 1.1/female 12.8/Male; 2.8 female 18.5/Male; 4.8/female 1.1/Male; 0.1/female 4.1/Male; 0.7/female 8.6/Male; 1.0/female	Higher risk: Increased age Smoker older than 40 y vs. never-smoker (OR 8.0)
The Netherlands	Pleumeekers	(872)	5283†	Older than 54 Older than 54	3.4 to 3.6 cm or distal dilation greater than 49% Larger than 4.0 cm	2.8/Male; 0.5/female 1.6/Male; 0.3/female	Higher risk: Smoker High serum cholesterol Established cardiovascular disease
Belgium	Vazquez	(873)	716‡	65 and 75	Larger than 3 cm Larger than 4 cm	3.8/Male 0.3/Male	Higher risk: Arterial hypertension (<i>p</i> less than 0.05) Prior CABG (<i>p</i> less than 0.01) Smoker (<i>p</i> less than 0.06)

Continued on Next Page

Table 44. Continued

Country/Study	First Author	Reference	Number Screened	Age, y	Criteria	% Prevalence/ Gender	Relative Risk
The Netherlands	Boll	(874)	2419§	60 to 80	Larger than 2.9 cm Larger than 4.9 cm	8.1/Male 1.7/Male	
United Kingdom Oxford	Wilmink¶	(875)	426	65 to 74	Larger than 4.0 cm or 5 mm larger than SRA	5.4/Male	
Liverpool				65 to 74	Larger than 4.0 cm	2.3/Male	
Gloucestershire			4232	Older than 55	Larger than 3.0 cm	2.9/Male	
Birmingham			2669	65	Larger than 2.5 cm Larger than 4.0 cm	8.4/Male 1.3/Male	
Chichester			5394	65 to 75	Larger than 2.9 cm Larger than 4.0 cm	8.4/Male 3.0/Male	
Northumberland			628	65 to 80	Larger than 2.9 cm	7.6/Male 1.3/Female	
Huntingdon			7493	65 to 80	Larger than 2.9 cm	6.7/Male	
Japan	Takei	(876)	348	Older than 49	Larger than 2.9 cm	5.2/Male	
Japan	Adachi	(877)	1591	60 to 79	—	0	
				—	—	0.3/Male	

*52 745 plus prior report of 73 451.

†Of 10 215 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)

Country	First Author	Reference	Study Group	Screened With Ultrasound	Age, y (Gender)	Criteria	Incidence/Risk Factor
United Kingdom	Adams	(887)	Relatives of 100 patients with known AAA	76 of 110 eligible	Older than 50	Larger than 4.0 cm	0
					Older than 50	2.5 to 3.9 cm	21% of male first-degree relatives; 27% of sons; 17% of brothers; 4% of sisters; 0% of daughters
Sweden	Bengtsson	(884)	Offspring of patients who died of ruptured AAA	62 of 90 eligible	45 to 75 (males)	Larger than 2.9 cm	21% of sons
					45 to 80 (female)	Larger than 2.9 cm	4% of daughters
					45 to 80 (female)	Larger than 5.0 cm	3% (1 male aged 53 y)
Ireland	Fitzgerald	(888)	Siblings of patients with known AAA	125 of 234 eligible	Older than 80	3.1 to 6.8 cm	22% of brothers; 3% of sisters
Netherlands	Van Der Graf	(889)	Brothers of patients having elective surgery for AAA	210 of 571 eligible	Older than 50	New AAA	12.30%
					Older than 50	Larger than 4.9 cm	3.80%
Finland	Jaakkola	(890)	Families of patients with surgery for AAA	123 of 172 eligible	41 to 82	Larger than 2.9 cm or history of repair or rupture	10% of brothers; 3% of sisters
United States	Webster	(883)	First-degree relatives of patients with surgery for AAA	103 of 202 eligible	Older than 55	Larger than 3.0 cm or I/S diameter ratio greater than 1.5	16% of first-degree relatives; 25% of men; 6.9% of women

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 diffusing capacity were lower than in a control group (p less than 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 less than 0.05). There was a negative correlation between the forced expiratory volume in 1 second and concentrations of serum elastin peptide and plasma elas-

tase- α 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.

Upregulation 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 less than 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 devel-

oping 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 with noninflammatory 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 initial size of the aneurysm were related to AAA expansion. Logistic regression analysis confirmed a significant difference in expansion rates exceeding 2 mm annually between the intervention and placebo groups (OR 0.09, 95% CI 0.01 to 0.83). The results of larger prospective, human antibiotic intervention trials may help to establish whether or not there is a causal link between C pneumoniae infection and atherosclerotic aortic aneurysms.

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

Table 46. Annual Rates of Expansion for Abdominal Aortic Aneurysms

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

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 47. Rupture and Survival Rates for Patients With Abdominal Aortic Aneurysms

First Author	Reference	Year	No. of Patients	Baseline Aneurysm Diameter	Follow-Up Interval	Aneurysm Rupture Rate (%)	Survival Rate (%)
Case series							
Szilagyi	(945)	1966	82	Less than or equal to 6 cm	Mean 34 mo	19	45
Hertzer	(955)	1987	141	Larger than 6 cm	Mean 17 mo	43	10
			24	Smaller than 6 cm	5 y	20	38 Overall
			18	At least 6 cm	5 y	69	
Nevitt	(935)	1989	130	Smaller than 5 cm	5 y	0	NA
			46	At least 5 cm	5 y	25	NA
Bengtsson	(937)	1993	155	Median 4 cm	Median 3.4 y	14	30
Perko	(956)	1993	63	Smaller than 6 cm		less than 5	NA
				At least 6 cm		10 to 15	NA
Galland	(957)	1998	267	Smaller than 4 cm	5 y	4	NA
				4 to 5.5 cm	5 y	21	NA
Jones	(958)	1998	25	5 to 5.9 cm	3 y	28	NA
			32	At least 6 cm	3 y	41	NA
Scott	(953)	1998	218	3 to 4.4 cm	7 y	2.1 per year and/or operation	NA
				4.5 to 5.9 cm	7 y	10 per year and/or operation	NA
Conway	(950)	2001	23	5.5 to 5.9 cm	10 y	22	39
			62	6 to 7 cm	10 y	34	32
			21	Larger than 7 cm	10 y	52	5
Biancari	(959)	2002	41	2.5 to 4 cm	Median 7.3 y	7.3	59
Collective reviews							
Taylor	(938)	1986		5 cm	NA	4.1 per year	NA
				5.7 cm	NA	6.6 per year	NA
				7 cm	NA	19 per year	NA
Hollier	(939)	1992	349	Smaller than 5 cm	5 y	4.6	NA
			90	Larger than 5 cm	5 y	30	NA
Hallin	(940)	2001	54 048	Smaller than 4 cm	4 y	2	NA
				4 to 5 cm	4 y	10	NA
				Larger than 5 cm	4 y	22	NA
Randomized trials							
UK Small Aneurysm Trial (nonoperated cohort)	(960)	1998	213	4 to 4.4 cm	Mean 4.6 y	NA	75%
			169	4.5 to 4.8 cm	Mean 4.6 y	NA	72%
			145	4.9 to 5.5 cm	Mean 4.6 y	NA	64%
UK Small Aneurysm Trial (nonoperated cohort)	(961)	1999	NA	3 to 3.9 cm	7 y	2.1	NA
			NA	4 to 5.5 cm	7 y	4.6	NA
			NA	At least 5.6 cm	7 y	20	NA

NA indicates not available; UK, United Kingdom.

Table 48. Outcomes of Early Elective Repair Versus Nonoperative Surveillance of Asymptomatic Abdominal Aortic Aneurysms*

	UK Trial (2002)	VA Trial (2002)
Total patients, n	1090	1136
Early elective repair, n	563	569
Open	536	567
Endovascular	27	2
Nonoperative surveillance, n	527	567
Men	902	1127
Women	188	9
Age	69 plus or minus 4 years	68 plus or minus 6 years
Operative mortality rate (surgical cohorts)	5.4% (30 days)	2.1% (30 days); 2.7% (in-hospital)
Follow-up period, y	Range 6 to 10; mean 8	Range 3.5 to 8.0; mean 4.9
Survival rate, %		
Surgical cohort	57	75
Nonoperative cohort	52	78
	(<i>p</i> equals 0.03)	
Aneurysm rupture rate (nonoperative cohorts)	3.2% annually	0.6% annually
Men	OR 1.0 (reference set)	NA
Women	OR 4.0 95% CI 2.0 to 7.9 (<i>p</i> less than 0.001)	NA
Eventual aneurysm repair, n (%)		
Surgical cohort	520 (92)	527 (93)
Nonoperative cohort	327 (62)	349 (62)
Influence of aneurysm diameter (nonoperative cohorts)		
Survival rate	4.0 to 4.4 cm: 57% 4.5 to 4.8 cm: 54% 4.9 to 5.5 cm: 43%	4.0 to 4.4 cm: 79% 4.5 to 4.9 cm: 78% 5.0 to 5.4 cm: 68%
Eventual repair rate	NA	4.0 to 4.4 cm: 27% 4.5 to 4.9 cm: 53% 5.0 to 5.4 cm: 81%

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 49. Operative Mortality Rates for Open Repair of Intact Abdominal Aneurysms

First Author	Reference	Year (Study Period)	No. of Patients	Mortality Rate (%)
Case series				
Crawford	(1061)	1981 (1955-1980)	Asymptomatic: 531	3.8
			Symptomatic intact: 329	6.4
			Total: 860	4.8
Hertzer	(955)	1987 (1978-1982)	246	4.4
Reigel	(1063)	1987	499	2.8
Golden	(1065)	1990	500	1.6
Sicard	(1071)	1995	145	1.4
Lloyd	(1079)	1996 (1980-1995)	1000	2.4
Starr	(1060)	1996 (1983-1989)	Men: 490	5.1
			Women: 92	4.3
			Total: 582	5.0
Aune	(1058)	2001 (1985-1999)	Age less than 66 y: 118	1.7
			Age 66 y and older: 333	6.0
			Total: 451	4.9
Hertzer	(1068)	2002 (1989-1998)	1135	1.2
Menard	(1080)	2003 (1990-2000)	Low risk: 444	0.0
			High risk: 128	4.7
			Total: 572	1.0
Randomized trials				
UK Small Aneurysm Trial (surgical cohort)	(960)	1998	563	5.8
Lederle (U.S. Veterans Affairs Small Aneurysm Trial; surgical cohort)	(941)	2002	569	2.7
Collective reviews				
Ernst	(1081)	1993 (1981-1992)	6488	4.0
Zarins	(973)	1997 (1987-1992)	2162	2.1
Blankensteijn	(1074)	1998 (1985-1997)	Prospective population: 692	8.2
			Prospective hospital: 1677	7.4
			Retrospective population: 21 409	3.8
			Retrospective hospital: 12 019	3.8
			Subset analyses: 1857	3.5
Regional or multicentered studies				
Johnston (Canadian Aneurysm Group)	(1082)	1988	Elective: 541	3.9
			Symptomatic intact: 125	7.2
			Total: 666	4.5
Richardson (Kentucky Medicare)	(1083)	1991	136	5.9
Hannan (New York statewide)	(1084)	1992 (1982-1987)	6042	7.6
Johnston (Canadian Aneurysm Group)	(1085)	1994	Men: 545	4.4
			Women: 134	5.2
			Total: 679	4.6
Katz (Michigan statewide)	(1086)	1994 (1980-1990)	8185	7.5
Kazmers (Veterans Affairs)	(1087)	1996 (1991-1993)	3419	4.9
Wen (Ontario Aneurysm Study)	(1088)	1996 (1988-1992)	5492	3.8
Kantonen (Finland Vascular Registry)	(1089)	1997	929	5.1
Koskas (French AURC)	(1057)	1997 (1989)	1107	4.8
Bradbury (Edinburgh Vascular Registry)	(1090)	1998 (1976-1996)	492	6.1
Manheim (California statewide)	(1091)	1998 (1982-1994)	35 130	7.6
Dardik (Maryland statewide)	(1092)	1999 (1990-1995)	2335	3.5
Pearce (Florida statewide)	(1093)	1999 (1992-1996)	13 415	5.7
Sollano (New York statewide)	(1094)	1999 (1990-1995)	9847	5.5
Kazmers (Veterans Affairs)	(1095)	2001 (1991-1995)	5833	4.5
Axelrod (Veterans Affairs)	(949)	2001 (1997-1998)	1001	3.7
U.S. hospital databases				
Lawrence (National Hospital Discharge Survey)	(1075)	1999 (1994)	32 387	8.4
Heller (National Hospital Discharge Survey)	(1076)	2000 (1979-1997)	358 521	5.6
Huber (Nationwide Inpatient Sample)	(1096)	2001 (1994-1996)	16 450	4.2
Dimick (Nationwide Inpatient Sample)	(1078)	2002 (1996-1997)	13 887	3.8

AURC indicates Association for Academic Research in Vascular Surgery; UK, United Kingdom.

of asymptomatic infrarenal aortic aneurysms in women (964).

No randomized trial has yet addressed the size at which suprarenal, pararenal, or type IV thoracoabdominal aortic aneurysms should be repaired to prevent rupture. Because of their higher risk for postoperative death, renal insufficiency, and other surgical complications, however, there has been a consensus that elective intervention should be considered for these aneurysms at a slightly larger diameter than for infrarenal aortic aneurysms.

5.2.3.2. Common Iliac Aneurysms

Isolated common iliac aneurysms are unusual in the absence of a proximal aortic aneurysm, and comparatively little information is available with respect to their natural history. 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 hypogastrium 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, vasoconstriction, 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 non-vascular 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.

5.2.4.4.4. UNRELATED 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 rescreeing 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 expan-

sion 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 (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-

propranolol group. The mortality rate was 17% in the propranolol 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 nonaneurysmal 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-

nias, and wound discomfort than a standard transabdominal incision (1073).

5.2.6.1.3. **EARLY MORTALITY AND COMPLICATION RATES.** In a collective review of nearly 40 000 reported cases, Blankensteijn et al. concluded that the operative mortality rate for elective open aortic aneurysm repair varied according to whether the individual case series were prospective or retrospective in design and whether they were population-based or hospital-based (1074). Such factors undoubtedly account for some of the variability in the representative early outcomes that are summarized in Table 49. Mortality rates from single centers generally were in the range of 4% to 5% during the 1980s, whereas information that has been published during the 1990s contains several series in which the mortality rate has declined to less than 2%. In comparison, regional or multicenter studies in the United States and elsewhere generally have been associated with slightly higher mortality rates, ranging from 5% to 7%. Exceptionally large databases, such as the National Hospital Discharge Survey (NHDS) and the Nationwide Inpatient Sample, are intriguing because of their potential sample size but often require considerable editing to distinguish between infrarenal and suprarenal aortic aneurysms, both of which are classified under the same ICD-9 (International Classification of Diseases, 9th Revision) code. Lawrence et al. (1075) used the NHDS to calculate an operative mortality rate of 8.4% for 32 387 patients in 1994, but as indicated in Table 49, conflicting results can be generated from the NHDS and the Nationwide Inpatient Sample during similar periods of study (1075-1078). In comparison, the operative mortality rate for open repair of ruptured AAAs is uniformly grim, ranging from 40% to 70% regardless of whether it has been reported from single-center case series, collective reviews, regional or multicenter studies, or large national databases (Table 50).

The clinical variables that significantly influence the mortality rate for ruptured aneurysm repair generally reflect a sudden loss of blood volume, as well as the physiological resilience of individual patients to withstand such a catastrophe. These include a low initial hematocrit, hypotension that requires resuscitation, cardiac arrest, a high APACHE (Acute Physiological And Chronic Health Evaluation) score, and advanced age (1097,1100,1101,1103-1105). In comparison, certain patient demographics and organ-specific factors take precedence over hemodynamic instability in the determination of the surgical risk for elective repair of intact aneurysms. Some of these considerations are listed below.

Age. Not surprisingly, higher patient age has been shown to be directly related to higher operative mortality rates in typical case series (1058,1060), collective reviews (1106), regional or statewide audits (1086,1092), and the UK Small Aneurysm Trial (1107). Although the operative mortality rate for urgent repair of ruptured aortic aneurysms is no higher among octogenarians than in younger patients (1099,1108), the results of 2 relatively large series indicate that the mortality rate for elective aneurysm repair in octogenarians is

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

First Author	Reference	Year (Study Period)	No. of Patients	Mortality Rate (%)
Case series				
Johansen	(943)	1991 (1980-1989)	180	69
Panneton	(1097)	1995 (1980-1992)	112	49
Seiwert	(1098)	1995 (1986-1993)	119	45
Darling	(1070)	1996 (1988-1995)	104	28
Barry	(1099)	1998 (1982-1993)	258	43
Noel	(1100)	2001 (1980-1998)	413	37
Collective reviews				
Taylor	(938)	1987	5 Reports	42
Hollier	(939)	1992 (1985-1991)	1040	48
Ernst	(1081)	1993 (1981-1992)	1731	49
Zarins	(973)	1997 (1988-1996)	1618	42
Regional or multicentered studies				
Hertzer (Northeastern Ohio)	(1101)	1984 (1978-1981)	213	33
Johnston (Canadian Aneurysm Group)	(1102)	1994	147	50
Katz (Michigan statewide)	(1086)	1994 (1980-1990)	1829	50
Kazmers (Veterans Affairs)	(1087)	1996 (1991-1993)	268	47
Wen (Ontario Aneurysm Study)	(1088)	1996 (1988-1992)	1203	40
Kantonen (Finland Vascular Registry)	(1089)	1997	454	46
Bradbury (Edinburgh Vascular Registry)	(1090)	1998 (1976-1996)	673	37
Manheim (California statewide)	(1091)	1998 (1982-1994)	7327	48
Axelrod (Veterans Affairs)	(949)	2001	52	31
Kazmers (Veterans Affairs)	(1095)	2001 (1991-1995)	427	46
U.S. hospital databases				
Lawrence (National Hospital Discharge Survey)	(1075)	1999 (1994)	6623	68
Heller (National Hospital Discharge Survey)	(1076)	2000 (1979-1997)	67 751	46
Dimick (National Inpatient Sample)	(1078)	2002	13 887	47

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 (1094,1111), 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 (1057,1068,1085,1095,1102,1116).

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. Hertzner 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 less than 0.01) and morbidity rates of 51% and 26% (p less than 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 less than 0.02) than the comparable figure for all infrarenal aneurysm procedures that were done at the same center (1123).

Table 51. Volume/Outcome Relationships for Open Aortic Abdominal Aneurysm Repair

First Author	Reference	Year (Study Period)	No. of Patients	Overall Mortality Rate (%)	Annual Volume	
					Hospital	Surgeon
Intact aneurysms Hertzer (Northeastern Ohio)	(1101)	1984 (1978-1981)	840	6.50	NA	Low: 4.7%; medium: 16%; high: 2.9% (<i>p</i> less than 0.001)
	(1113)	1990	279	NA	Low: 11%; high: 4.8% (<i>p</i> equals 0.05)	NA
Hannan (New York statewide)	(1084)	1992 (1982-1987)	6042	7.60	Low: 12%; medium: 6.8%; high: 5.6%	Low: 11%; medium: 7.3%; high: 5.6%
Katz (Michigan statewide)	(1086)	1994 (1980-1990)	8185	7.50	Low: 8.9% High: 6.2% (<i>p</i> less than 0.001)	NA
Kazmers (Veterans Affairs)	(1087)	1996 (1991-1993)	3419	4.90	Low: 6.7%; high: 4.2% (<i>p</i> less than 0.05)	NA
Dardik (Maryland statewide)	(1092)	1999 (1990-1995)	2335	3.50	Low: 4.3%; medium: 4.2%; high: 2.5% (<i>p</i> equals 0.08)	Very low: 9.9%; low: 4.9%; medium: 2.8%; high: 2.9%
Ruptured aneurysms Hertzer (Northeastern Ohio)	(1101)	1984 (1978-1981)	213	33	NA	Low: 32%; medium: 39%; high: 27% (<i>p</i> equals NS)
Amundsen (Norway)	(1113)	1990	165	NA	Low: 73%; high: 52% (<i>p</i> equals 0.03)	NA
Katz (Michigan statewide)	(1086)	1994 (1980-1990)	1829	50	Low: 54%; high: 46% (<i>p</i> equals 0.0026)	NA
Dardik (Maryland statewide)	(1092)	1999 (1990-1995)	527	47	Low: 46%; medium: 49%; high: 47% (<i>p</i> equals NS)	Low: 51%; medium: 47%; high: 36% (<i>p</i> equals 0.05)

NA indicates not available; NS, not significant.

Table 52. Late Survival Rates After Open Aortic Abdominal Aneurysm Repair

First Author	Reference	Year	No. of Patients	Survival Rates				
				1 Year	3 Years	5 Years	10 Years	Other
Intact aneurysms								
Case series								
Crawford	(1061)	1981	816			63%	38%	15 y: 18%
Hertzner	(955)	1987	236			72%		
Hallett	(1056)	1993	130			61%		
Stonebridge	(1117)	1993	311					8 y: 45%
Soisalon-Soininen	(1114)	1995	706			67%		
Cho	(1115)	1998	116	97%		74%		
Aune	(1058)	2001	Younger than age 66 y: 118 66 y or older: 333 Total: 451				43% 8 y: 69%	
Biancari	(959)	2002	208					
Hertzner	(1068)	2002	1135		67%	39%		
Menard	(1080)	2003	Low risk: 444 High risk: 128 Total: 572	94%	68% 74% 46%	75%	49%	
Collective reviews or multicenter studies								
Ernst (collective review)	(1081)	1993	3226	92%		67%	40%	
Johnston (Canadian Aneurysm Group)	(1085)	1994	680	91%	81%	68%		6 y: 60%
Feinglass (Veterans Affairs)	(1116)	1995	280	89%		64%		
		1995	280	89%		64%		
Koskus (French AURC)	(1057)	1997	794	94%	84%	67%		
Norman (collective review)	(1118)	2001	32 Reports		70%			
Ruptured aneurysms								
Case series								
Stonebridge	(1117)	1993	227				8 y: 40%	
Soisalon-Soininen	(1114)	1995	Operative survivors: 364		60%			
Cho	(1115)	1998	Operative survivors: 116	86%		64%	33%	
Evans	(1119)	1999	Operative survivors: 115	88%		59%	26%	
Collective reviews or multicenter studies								
Johnston (Canadian aneurysm study)	(1102)	1994	147				6 y: 22%	

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 long 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

First Author	Reference	Year (Study Period)	No. of Patients	Mortality Rate (%)	Postoperative Complication Rates (%)		
					Renal	Paraplegia	Other
Pararenal or suprarenal Quarfordt	(1124)	1986	77	1.3	Transient: 23 Dialysis: 2.5	NA	5
Nypaver	(1125)	1993 (1985-1992)	53	3.8	Transient: 23 Dialysis: 5.7	NA	NA
Faggioli	(1123)	1998	50	12	NA	NA	NA
Jean-Claude	(1126)	1999 (1977-1997)	257	5.8	Transient: 30 Sustained: 9.3 Dialysis: 7.0	0.4	31
Anagnostopoulos	(1127)	2001 (1986-1999)	65	0	Total: 42 Dialysis: 9.2 Permanent: 1.5	0	NA
Type IV thoracoabdominal Crawford	(1121)	1986 (1960-1985)	145	4.8	Dialysis: 5.5	2.1	NA
Cox	(1128)	1992 (1966-1991)	42	Total: 31 Elective: 12 Urgent: 55	NA	Total: 11 Elective: 4.3 Urgent: 20	NA
Svensson	(1129)	1993 (1960-1991)	346	5.8	Total: 22	4.3	NA
Coselli	(1130)	1995 (1984-1993)	35	14 (reoperations)	None permanent	2.9	NA
Schwartz	(1131)	1996 (1977-1994)	58	5.3	Transient: 31 Sustained: 28 Dialysis: 8.8 Permanent: 1.9	1.8	42
Dunning	(1132)	1999 (1995-1998)	26	12	Dialysis: 3.8	3.8	42
Martin	(1133)	2000 (1989-1998)	165	Total: 11 Elective: 7.2 Urgent: 22	Transient: 19 Dialysis: 14 Permanent: 3.0	3.6	56

NA indicates not available.

tions, intrasac endoleaks, graft occlusion, and aortic neck expansion.

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. INTRASAC 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 in 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, Connors 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 preoperative 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

Table 54. Representative Early Results for Endovascular Repair of Infrarenal Aortic Abdominal Aneurysms

First Author (Study/Sponsor)	Reference	Year (Study Period)	No. of Patients	Immediate Open Conversion (%)	Postoperative Complication Rates (%)		
					Total	Persistent	Procedural Mortality Rate (%)
Case series							
Blum	(1167)	1997 (1994-1996)	295	1.7	8.1	NA	0.7
Stelter	(1152)	1997 (1994-1997)	201	2	9	NA	3.5
May	(1168)	1998 (1992-1996)	Endo: 108 Open: 195	12	14	11	5.6 5.6
Amesur	(1169)	1999 (1996-1998)	54	NA	39	13	NA
Becquemin	(1170)	2000 (1995-1999)	Endo: 73 Open: 195	None	23	9.6	2.7 2.8
Chuter	(1164)	2000 (1996-1999)	High risk: 116	None	NA	10	1.7
Zarins	(1171)	2000 (1996-2000)	149	1.30	36	18	1.3
Blum	(1172)	2001 (1994-2001)	1994-1996: 111 1996-1997: 159 1998-2001: 28	3.6 0.6 None	14 3.1 11	NA NA NA	Total: 8.1
Becker	(1141)	2001 (1994-2001)	305	1.30	23	17	2.6
Fairman	(1173)	2001 (1998-1999)	75	None	44	20	0
Holzenbein	(1174)	2001	173	1.2	4.6 (Type I)	NA	2.8
Howell	(1175)	2001	215	None	42	11	0
Mathison	(1142)	2001 (1994-2000)	305	1.3	23	NA	2.6
May	(1165)	2001 (1995-1998)	Endo: 148 Open: 135	0.7	6.8	5.4	2.7 5.9
Sicard	(1176)	2001 (1997-2000)	Endo: 260 Open: 210	0.8	13	3	1.9 2.9
Abraham	(1146)	2002 (1998-2001)	116	None	15	11	0.9
Dattilo	(1177)	2002 (1994-2000)	362	1.40	NA	NA	1.5
Sampram	(1178)	2003 (1996-2002)	703	NA	NA	NA	1.7
Ouriel	(1179)	2003 (1996-2002)	606 Men 98 Women	NA NA	NA NA	NA NA	1.3 3.1
Shames	(1180)	2003 (1999-2001)	302 Men 42 Women	0.5 14	NA NA	NA NA	1.5 2.3
Anderson (New York State)	(1135)	2004 (2000-2002)	Endo: 1706 Open: 3063	NA	NA	NA	1.1 4.0

Continued on Next Page

Table 54. Continued

First Author (Study/Sponsor)	Reference	Year (Study Period)	No. of Patients	Immediate Open Conversion (%)	Postoperative Complication Rates (%)		
					Total	Persistent	Procedural Mortality Rate (%)
Device trials							
Moore (Endovascular Technologies)	(1181)	1996 (1993-1994)	46	15	44	21	0
Coppi (Stentor, Mintec)	(1182)	1998 (1995-1996)	66	6.10	6.1	3	1.5
Matsumura (Endovascular Technologies)	(1159)	1998 (1993-1995)	68	13	47	24	0
Becquemini (Vanguard, Boston Scientific)	(1183)	1999 (1996-1997)	75	None	31	9.3	0
Zarins (AneuRx, Medtronic)	(1184)	1999 (1996-1997)	Endo: 190 Open: 60	None	21	8.9	2.6 0
Zarins (AneuRx, Medtronic)	(1185)	2000 (1997-1998)	425	1.20	Centers: 38; core lab: 50	13	1.4
Beebe (Vanguard, Boston Scientific)	(1186)	2001 (1997-1998)	Endo: 268 Open: 98	1.90	5.70	2.7	1.5 3.1
Greenberg (Zenith, Cook)	(1156)	2001 (1995-2000)	528	0.80	16	5.5	0.2
Faries (Talent, Medtronic/AVE-Worldmedical)	(1187)	2002 (1999-2001)	368	1.10	12	4.8	1.9
Matsumura (Excluder; WL Gore & Associates)	(1188)	2003 (2000-2002)	Endo: 235 Open: 99	None	22	17	0.9 0
EUROSTAR							
Buth	(1163)	2000 (1994-1999)	1554	1.70	16	0.9	2.6
Harris	(1189)	2000 (1996-2000)	2464	1.30	17	8.3	3.2
Vallabhaneni	(1190)	2001 (1994-2000)	2812	NA	NA	NA	2.9
Buth	(1166)	2002 (1996-2001)	3075	1.70	17	NA	2.5
Peppelenbosch	(1191)	2004 (1996-2002)	1962 (4.0 cm to 5.4 cm) 1528 (5.5 cm to 6.4 cm) 902 (over 6.4 cm)	1.1 1.4 2.3	3.7 (Type I) 6.8 (Type I) 9.9 (Type I)	NA NA NA	1.6 2.6 4.1

EUROSTAR indicates European collaborators registry on stent-graft techniques for abdominal aortic aneurysm repair; NA, not available.

patients (16% vs. 3.7%, p equals 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 equals 0.0018) and 2002 (0.8% vs. 4.2%, p less than 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 equals 0.0001) (1166).

5.2.7.4.2. ENDOGRAFT-RELATED COMPLICATIONS. Secondary interventions are common after endovascular aortic aneurysm repair and often are performed within months for limb ischemia, within 1 year for endoleaks, and after 2 years or more for graft migration (1207). Aneurysm rupture is a rare event in most series, possibly because of the recognized importance of serial computed tomography scanning to detect continued aneurysm expansion. Delayed rupture has occurred at a rate of 1% per year in the EUROSTAR population; has been significantly associated with the presence of type I or type III endoleaks, graft migration, or postoperative endograft kinking; and has a postoperative mortality rate of 58% (1189,1190). Persistent and/or delayed endoleaks occur in a wide range of approximately 5% to more than 20% of patients and are the indication for most reinterventions after endografting. Becker et al. documented endoleaks in 23% of their series (1141). Nearly half (43%) of these required intervention, whereas the remainder either resolved spontaneously (24%) or remain untreated (31%). Holzenbein et al. also reported reinterventions in 22% of their series, of which 46% were performed within 1 year of the index procedure and 74% within 2 years (1174). Ninety percent of these reinterventions were necessary to control endoleaks, whereas the remaining 10% were done to restore endograft patency. Some sources in the United States have found that graft-related complications appear to occur with greater frequency after specific devices that previously were used only in the setting of clinical trials receive market approval by the FDA. The proposed explanation for this finding is that the stringent anatomic criteria that were necessary for inclusion in the clinical trials, especially those concerning the allowable length, diameter, and angulation of the proximal infrarenal neck, may be interpreted more liberally once these devices become commercially available (1208,1209).

Zarins et al. have described further aneurysm enlargement after endograft repair in 46 (12%) of the 383 patients who entered the phase II AneuRx clinical trial from 1997 through 1998 (1210). Not surprisingly, patients with aneurysm enlargement were more likely to undergo secondary interventions (21 [46%] of 46 patients) than those with either no change (33 [17%] of 199 patients) or a reduction in postendograft aneurysm size (16 [12%] of 138 patients; p equals 0.0001). Open surgical conversion was performed in a total of 18 (4.7%) of the 383 patients, including 9 (20%) of the 46 patients who had experienced aneurysm enlargement after their original endograft procedures (p less than 0.0001). The postoperative mortality rate after open conversion was 33% in these 9 patients. According to EUROSTAR data, the annual incidence of late endograft conversion to an open operation is 2.1%, with a postoperative mortality rate of 24% (1189,1190). Overall, the crude rate of device-related complications submitted to the EUROSTAR registry declined from 22% in 1994 to 7.3% in 2000. Nevertheless, patients who had these complications were nearly 14 times more likely to require conversion procedures and were 2.4 times more likely to die than patients who did not have device-related complications (1211).

Table 55. Representative Late Results for Endograft Repair of Infraarenal Abdominal Aneurysms

First Author (Study/Sponsor)	Reference	Year (Study Period)	No. of Patients	Aneurysm Rupture	Late Endoleaks	Endograft Reinterventions		Survival Rate
						Endo	Open	
Case series								
Stelter	(1152)	1997 (1994-1997)	201	None	9.50%	11%	10%	NA
May	(1168)	1998 (1992-1996)	Endo: 108 open: 195	None	6.30%	Total 7.4% (median, 29 mo)	NA	
Amesur	(1169)	1999 (1996-1998)	54	None	13%	17%	None	NA
Amesur	(1153)	2000 (1996-1999)	130 Limbs	NA	NA	36% of limbs	None	NA
Becquemin	(1170)	2000 (1995-1999)	Endo: 73; open: 107	4.1%	NA	Total 21% cumulative (1 y)		Endo: 82%; open: 96% (1 y)
Baum	(1154)	2000	Unsupported: 27 limbs; supported: 122 limbs	NA	NA	Unsupported: 44%; supported: 5% (<i>p</i> less than .001)	NA	NA
Chuter	(1164)	2000 (1996-1999)	High risk: 116	0.9%	7.8%	15%	2.6%	82% (Mean, 16 mo)
Zarins	(1147)	2000 (1996-2000)	149	None		Total 17% (median, 11 mo)		90%
Becker	(1141)	2001 (1994-2001)	305	0.7%	NA	Total 9.8%	70% (5 y)	
Holzenbein	(1174)	2001	173	0.6%	NA	Total 22% (median, 18 mo)	NA	
Howell	(1175)	2001	215	None	12%	Total 10% (maximum, 2 y)	94% 2.7%	Endo: 96%; open: 85% (3 y)
May	(1165)	2001 (1995-1998)	Endo: 148; open: 135	1.4%	5.4%	5.9%	3.8%	78% (Mean, 16 mo)
Ohki	(1203)	2001 (1992-2000)	239	0.8%	8.8%	2.7%	1.2%	Endo: 91%; open: 86% (3 y)
Sicard	(1176)	2001 (1997-2000)	Endo: 260; open: 210	None	4.2%	2.6%	2.6%	NA (mean, 10 mo)
Abraham	(1146)	2002 (1998-2001)	116	0.9%	4.3%	11%	2.2% Late conversion	NA
Datillo	(1177)	2002 (1994-2000)	362	0.8%	NA	15% (Total)	70% (3 y)	
Sampram	(1178)	2003 (1996-2002)	703	0.4%	23%	NA	1.4% Conversion	86% (24 mo)
Ouriel	(1204)	2003 (1996-2002)	416 (Size less than 5.5 cm) 284 (Size 5.5 cm or more)	0.2%	1.4%(Type I)	NA	8.2% Conversion	71% (24 mo)
Ouriel	(1179)	2003 (1996-2002)	606 Men; 98 women	Men: 0.3%; women: 1.0%	Men: 30%; women: 35% (12 mo)	Men: 24%; women: 21% (total)		Men: 80%; women 78% (24 mo)
Shames	(1180)	2003 (1999-2001)	203 Men; 42 women	None	Men: 11%; women: 21%	Men: 9%; women: 29% (total)		Men: 95%; women: 90% (mean, 11 mo)

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Table 55. Continued

First Author (Study/Sponsor)	Reference	Year (Study Period)	No. of Patients	Aneurysm Rupture	Late Endoleaks	Endograft Reinterventions		Survival Rate
						Endo	Open	
Device trials								
Becquemini (Vanguard; Boston Scientific)	(1183)	1999 (1996-1997)	75	1.3%	6.70%	24%	4%	86% (25 mo)
Zarins (AneuRx; Medtronic)	(1184)	1999 (1996-1997)	Endo: 190; open: 60	None	9.00%	5.9%	None	Endo: 96%; open: 97% (1 y)
Zarins (AneuRx; Medtronic)	(1185)	2000 (1996-1999)	1046	0.7% (mean, 16 mo)	NA	NA	NA	NA
Zarins (AneuRx; Medtronic)	(1171)	2000 (1997-1998)	398	0.3%	13% (Centers 20% (core lab)	4%	2%	95% (18 mo)
Beebe (Vanguard; Boston Scientific)	(1186)	2001 (1997-1998)	Endo: 268; open: 98	None	16% Cumulative (24 mo)	Total 31%; cumulative (24 mo)		Endo: 85%; open: 80% (24 mo)
Zarins (AneuRx; Medtronic)	(1148)	2001 (1996-1999)	1192	0.8%	NA	Total 12%; cumulative (3 y)		86% (3 y)
Faries (Talent; Medtronic/AVE-Worldmedical)	(1187)	2002 (1999-2001)	368	0.5%	4.8% (12 mo)	3%	3%	89% (7.3 mo)
Matsumura (Excluder; WL Gore)	(1188)	2003 (2000-2002)	Endo: 235; open: 99	None	20% (24 mo)	11%	1.7%	Endo: 87%; open: 93% (24 mo)
Zarins (AneuRx; Medtronic)	(1137)	2003 (1996-1999)	1193	1.3%	14%	NA	4.1% Late conversion	62% (4 y)
EUROSTAR								
Cuypers (endoleak study)	(1202)	1999 (1994-1998)	899	NA	26% total 10% persistent	NA	NA	88% (18 mo)
Cuypers (conversion study)	(1205)	2000 (1994-1999)	1871	NA	NA	NA	2.6% overall conversion	NA
Harris	(1189)	2000 (1996-2000)	2464	1% annual	15%	NA	2.1% annual conversion	75% (4 y)
Laheij	(1206)	2000 (1996-1999)	1023	NA	NA	14%	4%	NA
Vallabhaneni	(1190)	2001 (1994-2000)	2464	0.01% annual	NA	NA	2.1% annual conversion	NA
Buth	(1166)	2002 (1996-2001)	3075	0.7%	NA	NA	3.1% conversion	No risk: 88%; high risk: 75% (2 y)
Harris	(1150)	2004 (1996-2003)	4242	1.4%	30% total 10% persistent		Total 22% cumulative (5 y)	80% (5 y)
Peppelenbosch	(1191)	2004 (1996-2002)	1962 (4.0 to 5.4 cm); 1528 (5.5 to 6.4 cm); 902 (over 6.4 cm)	0.4% 0.6% 1.8%	5.3% (Type I) 4.9% (Type I) 10% (Type I)	NA NA NA	6.6% conversion 6.8% conversion 14% conversion	84% (5 y) 70% (5 y) 62% (5 y)

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

Author Device/Vendor	Reference	Year (Study Period)	n	Criteria for Technical Success	Technical Success Rates	
					Early	Late
Case Series						
Blum	(1167)	1997 (1994-1996)	154	Successful deployment No endoleaks	87%	
Stelter	(1152)	1997 (1994-1997)	201	NA	89%	
Coppi	(1182)	1998 (1995-1996)	66	Successful deployment No endoleaks No deaths	86% (30 days)	
Hausegger	(1214)	1999	30	Successful deployment No endoleaks	83% primary 93% secondary	
Becquemin	(1170)	2000 (1995-1999)	Endo: 73 Open: 107	No endoleaks No re-intervention		74% ($p=.001$) 94% (1 year)
Chuter	(1164)	2000 (1996-1999)	High risk: 116	Successful deployment No endoleaks	86% (2 weeks)	
Howell	(1215)	2000	56	NA		83% primary 85% secondary (6 months)
Blum	(1172)	2001 (1994-2001)	111 (1994-1996) 159 (1996-1997) 28 (1998-2001)	Successful deployment No endoleaks	82%	
Ohki	(1203)	2001 (1992-2000)	239	Successful deployment No endoleaks	89%	
Device Trials						
Zarins AneuRx™ /Medtronic	(1184)	1999 (1996-1997)	190	Successful deployment No endoleaks No deaths	77%	
Zarins AneuRx™/ Medtronic	(1171)	2000 (1997-1998)	398	Survival free of aneurysm rupture, open conversion, or re- intervention for endoleaks or graft thrombosis		88% (18 months)

Continued on Next Page

Table 56. Continued

Author Device/Vendor	Reference	Year (Study Period)	n	Criteria for Technical Success	Technical Success Rates	
					Early	Late
Device Trials (<i>Continued</i>) Beebe Vanguard™/ Boston Scientific	(1186)	2001	240	Successful deployment No endoleaks Graft patent No deaths	89% (30 days)	
	(1216)	2001 (1997-2001)	High risk: 127 Low risk: 151	Successful deployment No endoleaks	86% (96% at 30 days) 88% (97% at 30 days)	
Criado Talent™/ Medtronic World Medical	(1202)	1999 (1994-1998)	899	Endoleak-free survival		79% (18 months, cumulative)
EUROSTAR Cuypers	(1163)	2000 (1994-1999)	1,554	Successful deployment No endoleaks No deaths	72% (30 days)	
Buth	(1206)	2000 (1996-1999)	1,023	Freedom from any secondary intervention		1 yr: 89% 3 yrs: 67% 4 yrs: 62%
Laheij						

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 of childbearing age who are not pregnant and in patients of either gender undergoing liver transplantation. (Level of Evidence: B)

Class IIa

Open repair or catheter-based intervention is probably indicated for visceral aneurysms 2.0 cm in diame-

ter 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

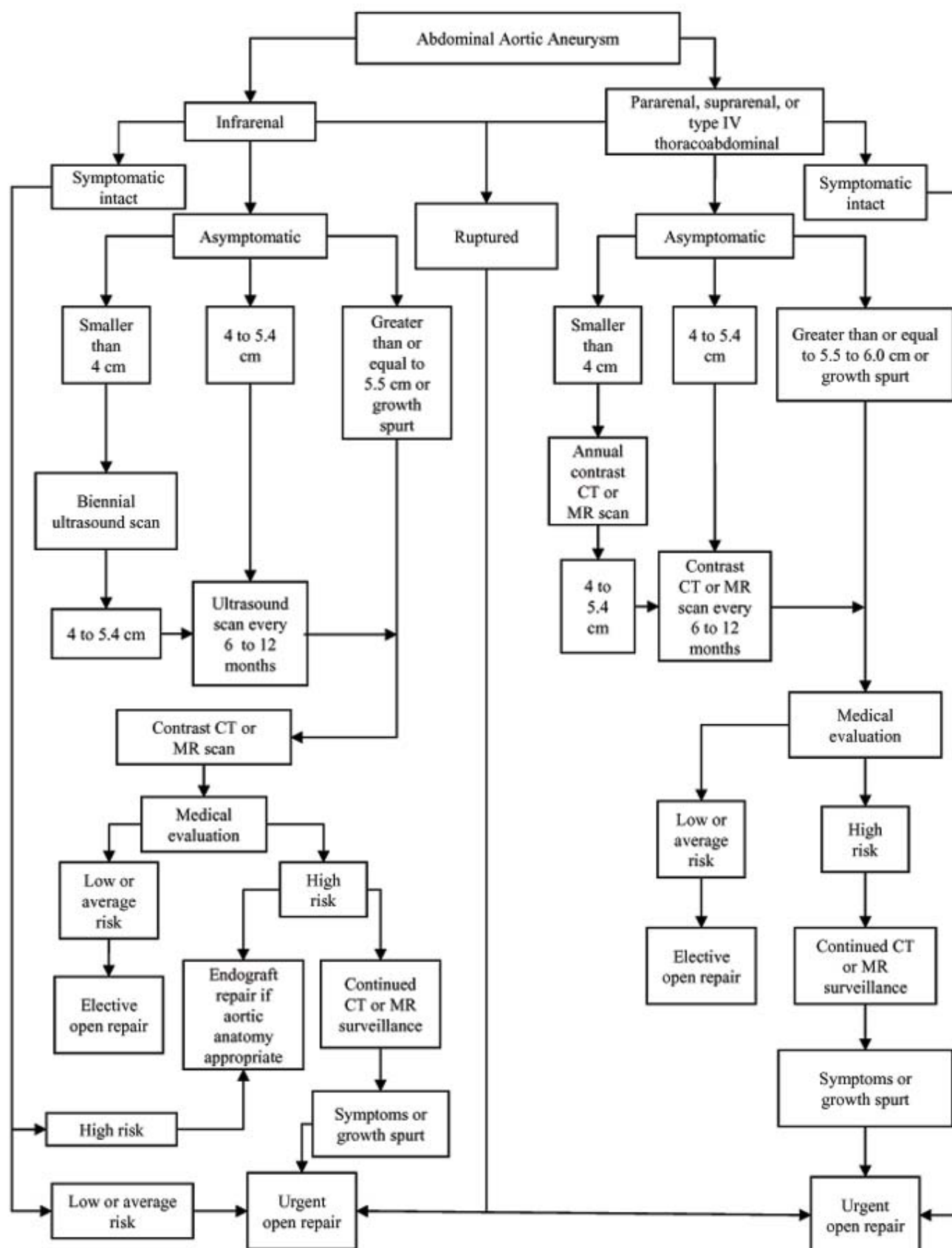


Figure 19. Management of abdominal aortic aneurysms. CT indicates computed tomography; MR, magnetic resonance imaging.

Table 57. Presentation and Mortality Rates for Visceral Artery Aneurysms

First Author	Reference	Year	Patients and/or Aneurysms, n	Symptomatic and/or Ruptured on Presentation	Initial Treatment	Complications With Observation Alone	Mortality Rate (%)
All visceral Carneci	(1224)	2000	31 (20 Women)	74%	Open: 25; Endo: 9	NA	3
Carr	(1225)	2001	26/34	Ruptured: 42%	Open: 19	14% Rupture	Total: 12; ruptured: 25
Splenic Trastek Lee	(1219) (1223)	1982 1999	100 (87 Women) 34 (21 Women)	17%; Ruptured: 3% Ruptured: 44%	Open: 81 Open: 34	None at 7.4 y NA	1 Elective: 0; ruptured: 40
Superior mesenteric Stone	(1226)	2002	21 (7 Women)	52%; Ruptured: 38% (50% of men)	Open: 13; Endo: 3	None (mean size 1.8 cm)	Elective: 0; ruptured: 38
Renal Tham Henriksson	(1227) (1228)	1983 1985	83/89 21/34 (16 Women)	None None	Open: 14 Open: 8	None None	0 0

Endo indicates endovascular repair; NA, not available.

Table 58. Site of Visceral Artery Aneurysms

Aneurysm	%
Splenic	60
Hepatic	20
Superior mesenteric	6
Celiac	4
Others	10

Reprinted from Semin Vasc Surg, 8, Hallett JW, Jr., Splenic artery aneurysms, 321-6, Copyright 1995, with permission from Elsevier (1229).

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 59. Demographics of Splenic Artery Aneurysms (n=100)

Characteristic	Value (Range)
Gender	87:13
Women:men	
Mean age (years)	58.2 (16 to 81)
Mean number of pregnancies	4.5 (1 to 16)
Aneurysm size (cm)	2.1 (0.6 to 30)
Symptoms (%)	
Asymptomatic	83
Chronic	13
Rupture	4

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).

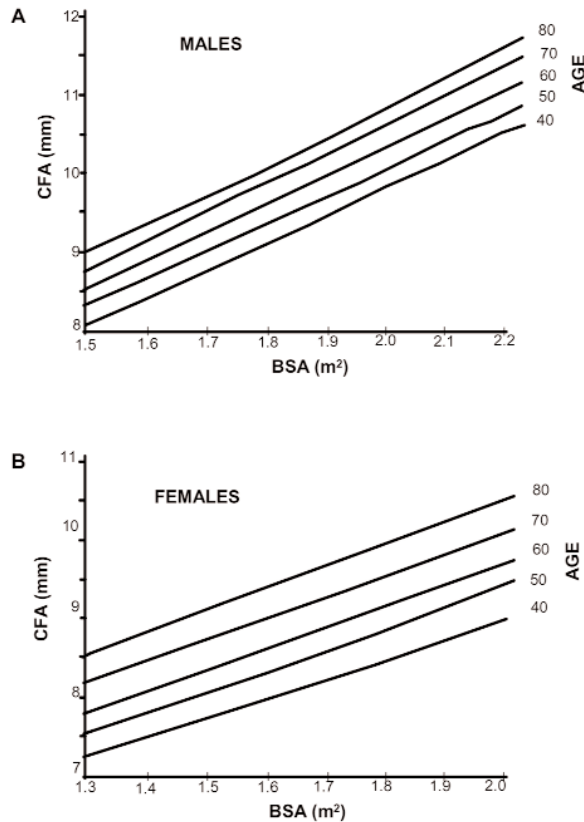


Figure 20. Predicted diameter of common femoral artery (CFA) in male and female subjects. Select appropriate curve for age marked on right and follow curve to appropriate body surface area (BSA) on horizontal axis. Predicted diameter is shown on vertical axis. Reprinted from *J Vasc Surg*, 29, Sandgren T, Sonesson B, Ahlgren R, et al., The diameter of the common femoral artery in healthy human: influence of sex, age, and body size, 503-10, with permission from Elsevier (1234).

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

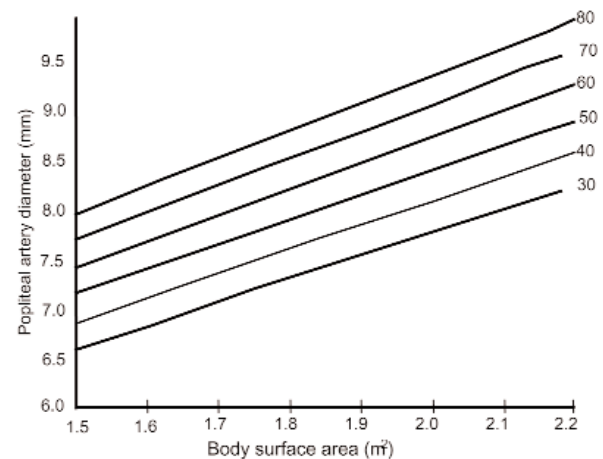


Figure 21. Predicted diameter of popliteal artery in males. To use this nomogram, select the appropriate age curve marked on the right and follow the curve to the appropriate body surface area (BSA) on the horizontal axis. The vertical axis shows the predicted diameter. Sandgren T, Sonesson B, Ahlgren AR, et al. Factors predicting the diameter of the popliteal artery in healthy humans. *J Vasc Surg*. 1998;28:284-9, with permission from Elsevier (865).

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 dis-

covery 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

First Author	Reference	Year	No. of Patients and/or Aneurysms	Bilateral Popliteal or Other Aneurysms	Previous Symptoms Before Presentation	Initial Surgical Treatment	Complications With Observation Alone	Related Amputation Rate
Case series Gifford	(1248)	1953	69/100 (66 men)	45% bilateral; 25% other	65% (34% ischemic; 12% ruptured)	21%	34% (21% ischemic; 7% ruptured)	23% (7% early; 16% late)
Dawson	(1250)	1991	50/71	42% bilateral; 32% other	NA	65%	54%	NA
Carpenter	(967)	1994	33/54	62% bilateral; 61% other	61% (39% ischemic)	83%	NA	11%
Dawson	(1251)	1994	42/42	NA	All asymptomatic	None	60%	7%
Lowell	(1252)	1994	106/161 (103 men)	52% bilateral	42%	31%	22%	7%
Schroder	(1253)	1996	217/349	61% bilateral	45%	63%	47%	NA
Duffy	(1245)	1998	24/40 (23 men)	66% bilateral	58%	75%	None (smaller than 2 cm)	None
Collective reviews Dawson	(1249)	1997	1673/2445 (95% men)	50% bilateral; 37% other	67%	NA	36%	NA

NA indicates not available.

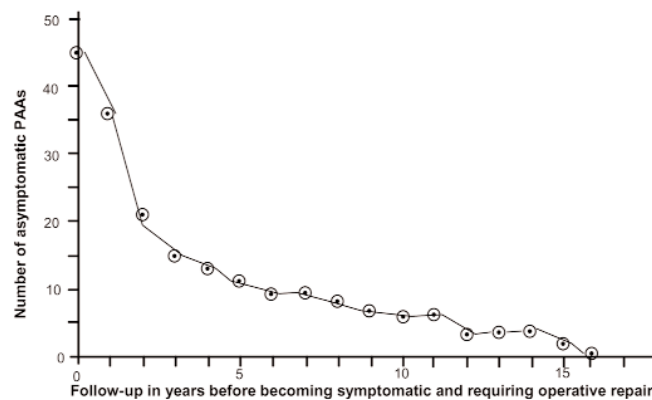


Figure 22. Follow-up evaluation of asymptomatic popliteal artery aneurysm (PAAs). Reprinted from Roggo A, Brunner U, Ottinger LW. The continuing challenge of aneurysms of the popliteal artery. *Surg Gynecol Obstet.* 1993;177:565-72 (1254).

Thrombosis of popliteal arterial aneurysms accounts for approximately 10% of acute arterial occlusions in elderly men. Commonly mistaken for an embolic event, the diagnosis is often made intraoperatively at the time of an attempted embolectomy (518,1258). Severe ischemia usually occurs because thrombosis occurs suddenly in the absence of collateral enhancement and because the popliteal artery is the sole axial artery traversing the knee. Given that half of all popliteal aneurysms are bilateral, the presence of a prominent popliteal pulse in the opposite leg may be a valuable clue to the underlying etiology of the acute ischemia. Once suspected, ultrasound imaging is the most rapid means to confirm the diagnosis. In a series of 33 patients with 54 popliteal artery aneurysms that were followed up over 62 months, thrombosis occurred in 39%, most often in larger aneurysms (967).

5.4.2.2 Femoral Artery Aneurysms

Femoral artery aneurysms may be discovered incidentally as a pulsatile mass in the thigh, or they may present with distal ischemia, and even more rarely, with rupture and bleeding. In a series of 13 aneurysms of the superficial femoral artery reported by Jarrett et al., 11 (85%) occurred in men, 9 (69%) were associated with aortic or iliac aneurysms, and 7 (54%) were contiguous with common femoral or popliteal aneurysms (1259). Six patients (46%) presented with distal ischemia and 4 (31%) with a thigh mass, whereas the remaining 3 (23%) were discovered during investigations for other vascular conditions. None of these aneurysms had ruptured. Aneurysms of the deep femoral artery usually are found in conjunction with an adjacent aneurysm of the common femoral artery, but isolated aneurysms of the deep femoral artery account for just 0.5% of peripheral aneurysms and for only 1% to 2.6% of femoral aneurysms (1260,1261). Twenty percent of patients with deep femoral aneurysms in 1 series had 3 or more peripheral aneurysms. The rate of rupture of

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)

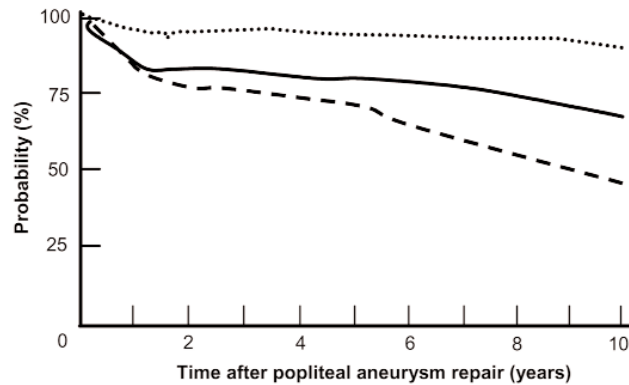


Figure 23. Long-term graft patency, limb salvage, and patient survival after popliteal aneurysm repair. — indicates long-term graft patency; limb salvage; and - - - - patient survival. From Dawson RB, Sie RB, van Bockel JH. Atherosclerotic popliteal aneurysm. Br J Surg. 1997;84:293-9. ©John Wiley & Sons Limited. Reproduced with permission (1249).

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 thromboembolism 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.

The data illustrated in Figure 23 document the 10-year graft patency, limb salvage, and patient survival rates for a series of popliteal aneurysm repairs described by Dawson et al. (1249). The survival rate was lower than that for the general population because of the medical comorbidities in such patients. Nevertheless, these data indicate that it is possible to achieve limb salvage rates exceeding 90% at 10 years when the operation is done for asymptomatic aneurysms, with graft patency rates that are as high as 80% after operations for symptomatic aneurysms. According to information collected from 14 other reports (1249), the choice of the bypass conduit may influence late results (Table 61). Saphenous vein grafts were associated with superior long-term patency and limb salvage rates compared with either polyester filament or PTFE grafts in 6 of these reports, and in several others, PTFE grafts were approximately twice as likely as polyester filament grafts to remain patent. Furthermore, in the absence of adequate runoff, surgical repair of popliteal artery aneurysms is more likely to be suc-

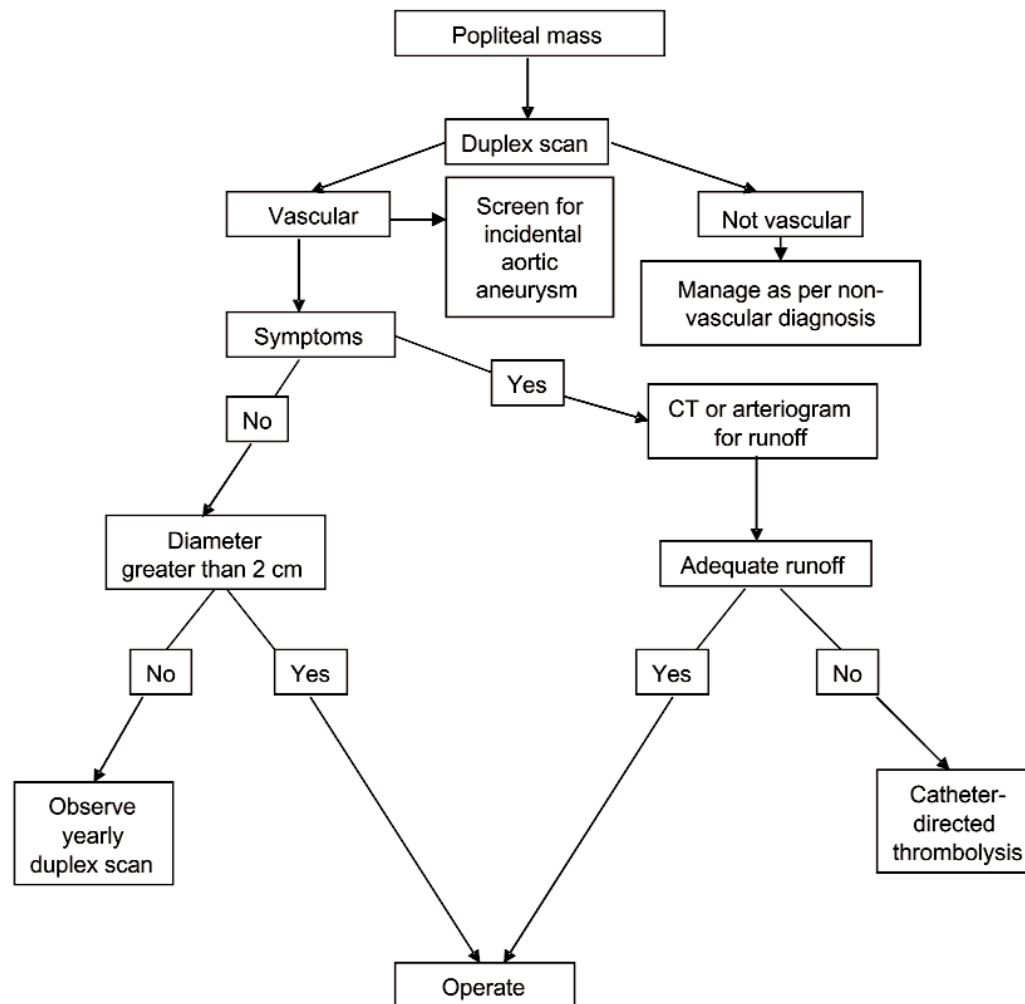


Figure 24. Diagnostic and treatment algorithm for popliteal mass. CT indicates computed tomography.

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 relat-

ed 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

Table 61. Graft Patency and Limb Salvage Rates for Popliteal Aneurysms

First Author	Reference	Follow-Up (y)	No. of Patients	Patency (%)						Limb Salvage (%)			
				Total	Symptoms		Graft Material		Total	Symptoms		Graft Material	
					Asymptomatic	Symptomatic	SV	Others*		Asymptomatic	Symptomatic	SV	Others
Anton	(1266)	5	123	—	82	57	94	43	83	93	82	98	75
		10		56	82	48	94	27	83	93	79	98	66
Carpenter	(967)	5	54	71	—	—	—	—	90	—	—	—	—
Cole	(1267)	3	59	88	94	81	—	—	—	—	—	—	—
Dawson	(1250)	5	46	75	—	—	—	—	—	—	—	—	—
		10		64	—	—	84	41	95	—	—	100	88
Duffy	(1245)	3	30	84	—	—	—	—	96	—	—	—	0
Farina	(1265)	5	50	62	80	65	100	60 A	94	—	—	—	—
		10		62	—	—	—	—	—	—	—	—	—
Inahara	(1268)	10	40	76	—	—	—	—	—	—	—	—	—
Lilly	(1268a)	5	48	74	91	54	—	—	—	—	—	—	—
Reilly	(1269)	5	167	—	—	—	77	30	—	—	—	—	—
Roggo	(1254)	5	252	69	85	61	81	40 B	94	98	92	97	88
		10		—	—	—	—	—	87	96	81	94	74
Schellack	(1270)	5	95	75	93	66	92	55	94	100	91	—	—
Schroder	(1253)	4	221	—	89	—	—	—	—	100	—	—	0
Szilagyi	(1255)	5	50	60	—	—	—	—	—	—	—	—	—
		10		28	—	—	—	—	—	—	—	—	—
Towne	(1271)	5	115	53	—	—	—	—	—	—	—	—	—

*A indicates 34% polyester fiber and 74 % polytetrafluorethylene (PTFE); B, 33% polyester fiber and 64% PTFE.

SV indicates saphenous vein.

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Table 62. Clinical Presentation of Femoral Aneurysms

First Author	Reference	No. of Patients	Aneurysms (n)	Males:Females	Bilateral (%)	AAA/PAA Associated (%)	Asymptomatic (%)	Presenting Symptoms	Complications at Presentation
Cutler	(1260)	45	63	40:5	47	51/27	29	Local: 29%	Acute thrombosis: 16%; chronic thrombosis: 16%; rupture: 14%
Adisesiah	(1273)	16	27	15:1	62	25/31	70		Embolization: 4%; thrombosis: 7%; rupture: 15%
Baird	(1274)	30	36	30:0	20	40/17	27	Local: 23%; ischemic: 50%	Acute thrombosis/embolization: 13%; rupture: 0%
Graham	(1235)	100	172	100:0	72	85/44	40	Local pain: 11%; mass: 16%; venous: 8%; ischemic: 42%	Embolization: 8%; acute thrombosis: 1%; chronic thrombosis: 1%; rupture: 2%
Sapienza	(1275)	22	31	21:1	41	50/—	64	Local: 5%; ischemic: 35%	

AAA indicates abdominal aortic aneurysm; FAA, femoral artery aneurysm; PAA, popliteal artery aneurysm.
Reprinted from Vascular Surgery (5th ed), Graham L, Femoral and popliteal aneurysms, 1345-56, copyright 2000, with permission from Elsevier (1272).

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)**

Class IIa

1. **Surgical repair is reasonable in patients with femoral artery pseudoaneurysms 2.0 cm in diameter or larger that persist or recur after ultrasound-guided compression or thrombin injection. (Level of Evidence: B)**
2. **Re-evaluation by ultrasound 1 month after the original injury can be useful in patients with asymptomatic femoral artery pseudoaneurysms smaller than 2.0 cm in diameter. (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

First Author	Reference	No. of Patients	Spontaneous Closure (n)	Surgery (n)	Comments
Feld	(1276)	17	3	2	
Fellmeth	(1277)	35	4	—	
Johns	(1278)	6	5	2	7 to 42 days to close
Kazmers	(1279)	53	4	3	
Kresowik	(1280)	7	7	—	Less than 28 days to close
Samuels	(1281)	11	11	—	
Schaub	(1282)	54	50	—	Approximately 52 days to close
Toursarkissian	(1283)	147	86%	14%	Approximately 23 days to close
Weatherford	(1284)	27	7	10	Median 40 days to close
Total		357	217	38	
Fractional percentage			61%	11%	

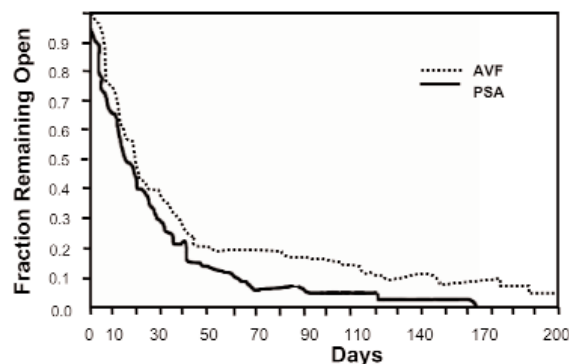


Figure 25. Spontaneous closure rates of selected pseudoaneurysms. AVF indicates arteriovenous fistula; PSA, pseudoaneurysm. Reprinted from J Vasc Surg, 25, Toursarkissian B, Allen BT, Petinec D, et al. Spontaneous closure of selected iatrogenic pseudoaneurysms and arteriovenous fistulae, 803-8, Copyright 1997, with permission from Elsevier (1283).

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 complica-

tions 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-

Table 64. Ultrasound-Guided Compression of Femoral Pseudoaneurysms

First Author	Reference	Patients (n)	Closure (n)	Surgery (n)	Comments
Chatterjee	(1285)	38	37	1	FemoStop used
Coghlan	(1286)	10	9	1	
Cox	(1287)	100	94	2	10 recurrences, 1 to 35 days
Dean	(1288)	77	56	14	Size less than 4 cm; twice as successful at closure
Feld	(1276)	15	10	2	
Fellmeth	(1277)	29	27	—	
Hajarizadeh	(1289)	57	54	2	2 recurrences 2 to 10 days
Hertz	(1290)	41	36	3	Large catheter sheath size problematic
Kazmers	(1279)	33	25	3	2 pseudoaneurysm ruptures
Kumins	(1291)	60	52	—	7 recurrences
Langella	(1292)	36	27	—	3 recurrences
Paulson	(1293)	48	37	—	
Perkins	(1294)	13	10	—	
Schaub	(1282)	124	104	5	
Sorrell	(1295)	11	10	1	
Steinkamp	(1296)	98	96	2	
Weatherford	(1284)	11	8	3	

Table 65. Thrombin Injection Closure of Femoral Pseudoaneurysms

First Author	Reference	Patients (n)	Thrombin Dose (U)	Closure (n)	Surgery (n)	Comments
Hughes	(1303)	9	1000 to 2000	8	0	1 recurrence at 4 days
Kang	(1304)	21	500 to 1000	20	1	
La Perna	(1299)	70	1000	66	2	94% overall success rate Success maintained in patients using antithrombotic medications
Liau	(1305)	5	1000	5	0	
Mohler	(1300)	91	500 to 1000	87	0	98% overall success rate Second injection required for 3 patients
Reeder	(1306)	26	50 to 450	25	0	1 recurrence at 4 days
Sacket	(1307)	30	100 to 2000	27	3	
Taylor	(1308)	29	600	27	1	

monary 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 ul-

mately 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

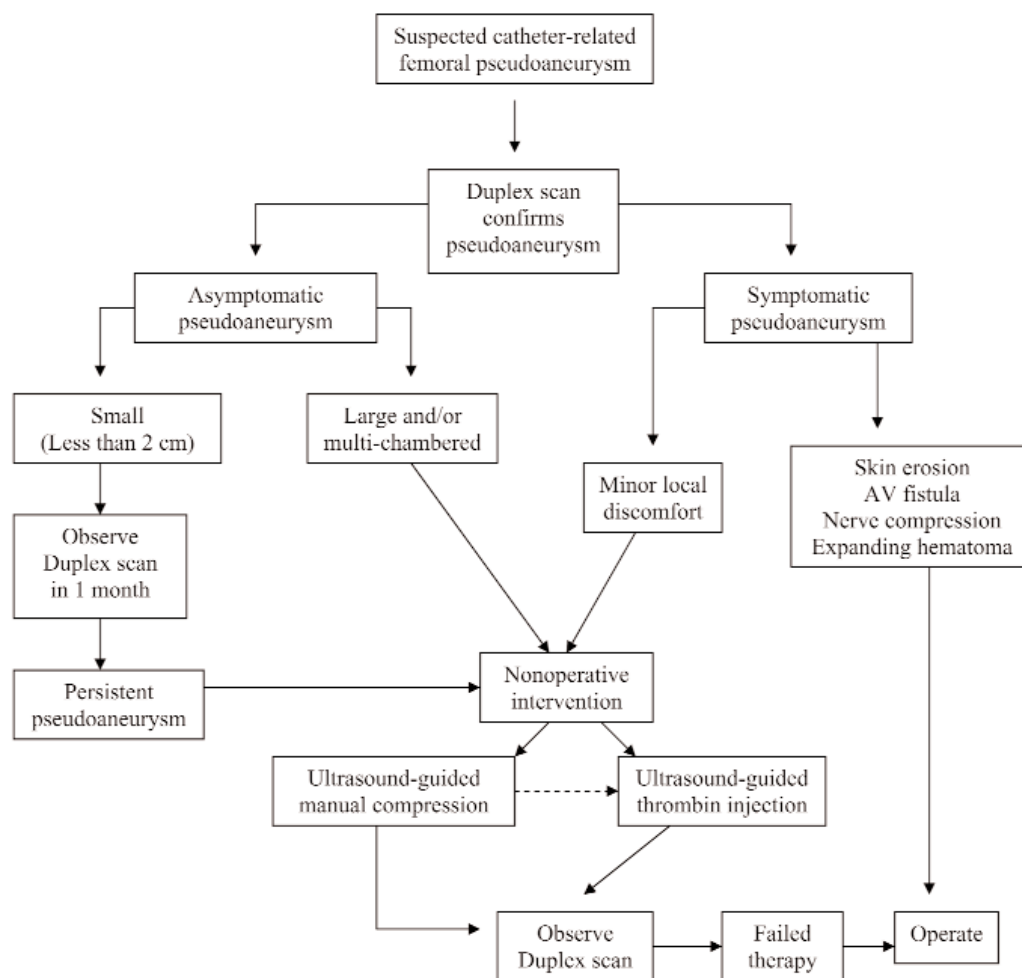


Figure 26. Diagnostic and treatment algorithm for femoral pseudoaneurysm. AV indicates arteriovenous.

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.

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APPENDIX 1. ACC/AHA Writing Committee to Develop Guidelines on Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic)

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APPENDIX 1. Continued

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Dr John White	None	None	None	None	None
Dr Rodney A. White	AVE Bard Baxter Cordis J & J EndoLogix EndoSonics Medtronic	Multiple relationships with commercial entities that arise and are met as needed	Several biomedical companies	None	None

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)*

Peer Reviewer Name*	Representation	Research Grant	Speakers Bureau/Honoraria	Stock Ownership	Consultant/Advisory Board
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Dr James F. Benenati	Official Reviewer – AHA	None	None	None	None
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Dr Alan S. Brown	Official Reviewer – ACC BOG	AstraZeneca Merck Merck Schering Plough Pfizer Smith Kline Beecham	Merck Merck Schering Plough Pfizer	None	AstraZeneca Merck Merck Schering Plough
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Dr John P. Cooke	Content Reviewer – Individual	None	None	None	None
Dr Robert T. Eberhardt	Official Reviewer – AHA	None	None	None	None
Dr Brian S. Funaki	Content Reviewer – AHA Committee on PV Imaging and Intervention	None	None	None	None
Dr Bruce Gray	Organizational Reviewer – SVM/B	None	None	None	None
Karen Hayden, MSN	Organizational Reviewer – SVN	None	None	None	None
Dr William R. Hiatt	Organizational Reviewer – TASC	None	BMS/Sanofi Otsuka	None	BMS/Sanofi Signature
Dr David Holmes, Jr	Content Reviewer – ACC BOG	None	None	None	None
Dr Sharon A. Hunt	Organizational Reviewer – ACC/AHA TF on PGL	None	None	None	None
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Dr Matthew S. Johnson	Content Reviewer – AHA Committee on PV Imaging and Intervention	Bard Access Systems Boston Scientific	None	None	Boston Scientific
Dr John A. Kaufman	Content Reviewer – AHA Atherosclerosis PVD Steering Committee	None	None	None	None
Dr Morton Kern	Content Reviewer – AHA Diag and Interv Cath Cmt	None	None	None	None
Dr Lloyd Klein	Content Reviewer – AHA Diag and Interv Cath Cmt	TBD	TBD	TBD	TBD

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APPENDIX 2. Continued

Peer Reviewer Name*	Representation	Research Grant	Speakers Bureau/Honoraria	Stock Ownership	Consultant/Advisory Board
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Dr Alan Matsumoto	Content Reviewer – AHA Committee on PV Imaging and Intervention	None	Genentech	None	Cordis Endovascular Medtronic W. L. Gore
Dr Roxana Mehran	Content Reviewer – Individual Review	Boston Scientific Cordis Medtronic	The Medicines Company Tyco/Mallinckrodt	None	None
Dr Emile R. Mohler III	Content Reviewer – Individual Review	None	None	None	None
Roberta Oka, RN	Content Reviewer – AHA Atherosclerosis PVD Steering Committee	None	None	None	None
Dr Joseph P. Ornato	Official Reviewer – ACC/AHA TF on PGL, Lead Reviewer	None	None	None	Genentech Meridian Revivant Wyeth
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Dr Sonia I. Skarlatos	Organizational Reviewer – NHLBI	None	None	None	None
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*Names are listed in alphabetical order.

ACCF indicates American College of Cardiology Foundation; ACP, American College of Physicians; AHA Diag and Interv Cardiac Cath Cmtc, 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

ABI	= ankle-brachial index	NHDS	= National Hospital Discharge Survey
ACC	= American College of Cardiology	OR	= odds ratio
ACE	= angiotensin-converting enzyme	p	= statistical significance
AHA	= American Heart Association	PAD	= peripheral arterial disease
ARIC	= Atherosclerosis Risk in Communities study	PARTNERS	= PAD Awareness, Risk and Treatment: New Resources for Survival (study)
bFGF	= basic fibroblast growth factor	PGE-1	= prostaglandin E1
CI	= confidence interval	phVEGF165	= vascular endothelial growth factor plasma DNA
CLI	= critical limb ischemia	PTA	= percutaneous transluminal angioplasty
COPD	= chronic obstructive pulmonary disease	PTFE	= polytetrafluoroethylene
CTA	= computed tomographic angiography	PVR	= pulse volume recording
DNA	= deoxyribonucleic acid	RAS	= renal artery stenosis
DRASTIC	= Dutch Renal Artery Stenosis Intervention Cooperative	RRI	= resistive index
EDTA	= ethylenediaminetetraacetic acid	ROS	= review of symptoms
ESRD	= end-stage renal disease	SVS/ISCVS	= Society for Vascular Surgery/ International Society for Cardiac Vascular Surgery
EUROSTAR	= EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair	TASC	= TransAtlantic Inter-Society Consensus Working Group
FDA	= Food and Drug Administration	TBI	= toe-brachial index
FMD	= fibromuscular dysplasia	3D	= 3-dimensional
HDL	= high-density lipoprotein	UK	= United Kingdom
HMG	= hydroxymethyl glutaryl	US	= United States
ICAVL	= Intersocietal Commission for Accreditation of Vascular Laboratories	USPSTF	= United States Preventive Services Task Force
INR	= international normalized ratio	VA	= Veterans Affairs
LDL	= low-density lipoprotein	VEGF	= vascular endothelial growth factor
MI	= myocardial infarction		
MMP	= matrix metalloproteinases		
MRA	= magnetic resonance angiography		

References

- Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000;31(1 pt 2):S1-S296.
- Ross R. Cellular and molecular studies of atherosclerosis. *Atherosclerosis* 1997;131(suppl):S3-4.
- Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992;135:331-40.
- Ridker PM, Cushman M, Stampfer MJ, et al. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998;97:425-8.
- Taylor LM Jr, DeFrang RD, Harris EJ Jr, et al. The association of elevated plasma homocyst(e)ine with progression of symptomatic peripheral arterial disease. *J Vasc Surg* 1991;13:128-36.
- Robinson PN, Booms P. The molecular pathogenesis of the Marfan syndrome. *Cell Mol Life Sci* 2001;58:1698-707.
- Pyeritz RE. The Marfan syndrome. *Annu Rev Med* 2000;51:481-510.
- Parfitt J, Chalmers RT, Wolfe JH. Visceral aneurysms in Ehlers-Danlos syndrome: case report and review of the literature. *J Vasc Surg* 2000;31:1248-51.
- Pope FM, Burrows NP. Ehlers-Danlos syndrome has varied molecular mechanisms. *J Med Genet* 1997;34:400-10.
- Bergqvist D. Ehlers-Danlos type IV syndrome: a review from a vascular arterial point of view. *Eur J Surg* 1996;162:163-70.
- Begelman SM, Olin JW. Fibromuscular dysplasia. *Curr Opin Rheumatol* 2000;12:41-7.
- Luscher TF, Lie JT, Stanson AW, et al. Arterial fibromuscular dysplasia. *Mayo Clin Proc* 1987;62:931-52.
- Gonzalez-Gay MA, Garcia-Porrua C. Epidemiology of the vasculitides. *Rheum Dis Clin North Am* 2001;27:729-49.
- Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. *J Clin Pathol* 2002;55:481-6.
- Salvarani C, Cantini F, Boiardi L, et al. Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med* 2002;347:261-71.
- Cid MC, Font C, Coll-Vinent B, et al. Large vessel vasculitides. *Curr Opin Rheumatol* 1998;10:18-28.
- Langford CA, Sneller MC. New developments in the treatment of Wegener's granulomatosis, polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. *Curr Opin Rheumatol* 1997;9:26-30.
- Barron KS. Kawasaki disease: etiology, pathogenesis, and treatment. *Cleve Clin J Med* 2002;69 suppl 2:SII69-78.
- Gedalia A. Kawasaki disease: an update. *Curr Rheumatol Rep* 2002;4:25-9.
- Newburger JW, Burns JC. Kawasaki disease. *Vasc Med* 1999;4:187-202.
- Olin JW. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med* 2000;343:864-9.
- Szuba A, Cooke JP. Thromboangiitis obliterans: an update on Buerger's disease. *West J Med* 1998;168:255-60.
- Aqel MB, Olin JW. Thromboangiitis obliterans (Buerger's disease). *Vasc Med* 1997;2:61-6.
- Lee R. Factor V Leiden: a clinical review. *Am J Med Sci* 2001;322:88-102.
- Kottke-Marchant K. Genetic polymorphisms associated with venous and arterial thrombosis: an overview. *Arch Pathol Lab Med* 2002;126:295-304.
- Segal JB, McNamara RL, Miller MR, et al. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. *Cochrane Database Syst Rev* 2001;(1):CD001938.
- Hirsh J, Anand SS, Halperin JL, et al. Guide to anticoagulant therapy: heparin: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;103:2994-3018.
- Lillicrap D. The genetics of venous and arterial thromboembolism. *Curr Atheroscler Rep* 2001;3:209-15.
- Dormandy J, Heeck L, Vig S. Acute limb ischemia. *Semin Vasc Surg* 1999;12:148-53.
- Fraenkel L. Raynaud's phenomenon: epidemiology and risk factors. *Curr Rheumatol Rep* 2002;4:123-8.
- Edwards JM, Porter JM. Upper extremity arterial disease: etiologic considerations and differential diagnosis. *Semin Vasc Surg* 1998;11:60-6.
- Belch J. Raynaud's phenomenon. *Cardiovasc Res* 1997;33:25-30.
- Belch JJ, Ho M. Pharmacotherapy of Raynaud's phenomenon. *Drugs* 1996;52:682-95.
- Criqui MH, Fronek A, Klauber MR, et al. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985;71:516-22.
- Criqui MH, Denenberg JO, Langer RD, et al. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. *Vasc Med* 1997;2:221-6.
- Price JF, Mowbray PI, Lee AJ, et al. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J* 1999;20:344-53.
- Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc* 1985;33:13-8.
- Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality. The Whitehall Study. *Circulation* 1990;82:1925-31.
- Bowlin SJ, Medalie JH, Flocke SA, et al. Epidemiology of intermittent claudication in middle-aged men. *Am J Epidemiol* 1994;140:418-30.
- Meijer WT, Hoes AW, Rutgers D, et al. Peripheral arterial disease in the elderly: the Rotterdam Study. *Arterioscler Thromb Vasc Biol* 1998;18:185-92.
- Cole CW, Hill GB, Farzad E, et al. Cigarette smoking and peripheral arterial occlusive disease. *Surgery* 1993;114:753-6; discussion 756-7.
- Powell JT, Edwards RJ, Worrell PC, et al. Risk factors associated with the development of peripheral arterial disease in smokers: a case-control study. *Atherosclerosis* 1997;129:41-8.
- Kannel WB, Shurtleff D. The Framingham Study: cigarettes and the development of intermittent claudication. *Geriatrics* 1973;28:61-8.
- Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. *Circulation* 1993;88:837-45.
- Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995;91:1472-9.
- Beks PJ, Mackaay AJ, de Neeling JN, et al. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. *Diabetologia* 1995;38:86-96.
- Katsilambros NL, Tsapogas PC, Arvanitis MP, et al. Risk factors for lower extremity arterial disease in non-insulin-dependent diabetic persons. *Diabet Med* 1996;13:243-6.

48. Bowers BL, Valentine RJ, Myers SI, et al. The natural history of patients with claudication with toe pressures of 40 mm Hg or less. *J Vasc Surg* 1993;18:506-11.
49. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 1989;3:273-7.
50. Dormandy JA, Murray GD. The fate of the claudicant—a prospective study of 1969 claudicants. *Eur J Vasc Surg* 1991;5:131-3.
51. Most RS, Sinnock P. The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* 1983;6:87-91.
52. Murabito JM, Evans JC, Nieto K, et al. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *Am Heart J* 2002;143:961-5.
53. Ingolfsson IO, Sigurdsson G, Sigvaldason H, et al. A marked decline in the prevalence and incidence of intermittent claudication in Icelandic men 1968-1986: a strong relationship to smoking and serum cholesterol—the Reykjavik Study. *J Clin Epidemiol* 1994;47:1237-43.
54. Murabito JM, D'Agostino RB, Silbershatz H, et al. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation* 1997;96:44-9.
55. Bainton D, Sweetnam P, Baker I, et al. Peripheral vascular disease: consequence for survival and association with risk factors in the Speedwell prospective heart disease study. *Br Heart J* 1994;72:128-32.
56. Sanderson KJ, van Rij AM, Wade CR, et al. Lipid peroxidation of circulating low density lipoproteins with age, smoking and in peripheral vascular disease. *Atherosclerosis* 1995;118:45-51. Erratum in: *Atherosclerosis* 1996;121:295.
57. Horby J, Grande P, Vestergaard A, et al. High density lipoprotein cholesterol and arteriography in intermittent claudication. *Eur J Vasc Surg* 1989;3:333-7.
58. Bradby GV, Valente AJ, Walton KW. Serum high-density lipoproteins in peripheral vascular disease. *Lancet* 1978;2:1271-4.
59. Greenhalgh RM, Rosengarten DS, Mervart I, et al. Serum lipids and lipoproteins in peripheral vascular disease. *Lancet* 1971;2:947-50.
60. Harris LM, Armstrong D, Browne R, et al. Premature peripheral vascular disease: clinical profile and abnormal lipid peroxidation. *Cardiovasc Surg* 1998;6:188-93.
61. Mowat BF, Skinner ER, Wilson HM, et al. Alterations in plasma lipids, lipoproteins and high density lipoprotein subfractions in peripheral arterial disease. *Atherosclerosis* 1997;131:161-6.
62. Mendelson G, Aronow WS, Ahn C. Prevalence of coronary artery disease, atherothrombotic brain infarction, and peripheral arterial disease: associated risk factors in older Hispanics in an academic hospital-based geriatrics practice. *J Am Geriatr Soc* 1998;46:481-3.
63. Novo S, Avellone G, Di Garbo V, et al. Prevalence of risk factors in patients with peripheral arterial disease: a clinical and epidemiological evaluation. *Int Angiol* 1992;11:218-29.
64. Hooi JD, Stoffers HE, Kester AD, et al. Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. *Peripheral Arterial Occlusive Disease. Scand J Prim Health Care* 1998;16:177-82.
65. Reunanen A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. *Acta Med Scand* 1982;211:249-56.
66. Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *JAMA* 1995;274:1049-57.
67. Graham IM, Daly LE, Refsum HM, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. *JAMA* 1997;277:1775-81.
68. Robinson K, Arheart K, Refsum H, et al. Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. European COMAC Group. *Circulation* 1998;97:437-43. Erratum in: *Circulation* 1999;99:983.
69. Hoogeveen EK, Kostense PJ, Beks PJ, et al. Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non-insulin-dependent diabetes mellitus: a population-based study. *Arterioscler Thromb Vasc Biol* 1998;18:133-8.
70. Aronow WS, Ahn C. Association between plasma homocysteine and peripheral arterial disease in older persons. *Coron Artery Dis* 1998;9:49-50.
71. Currie IC, Wilson YG, Scott J, et al. Homocysteine: an independent risk factor for the failure of vascular intervention. *Br J Surg* 1996;83:1238-41.
72. Molgaard J, Malinow MR, Lassvik C, et al. Hyperhomocyst(e)inaemia: an independent risk factor for intermittent claudication. *J Intern Med* 1992;231:273-9.
73. Taylor LM Jr, Moneta GL, Sexton GJ, et al. Prospective blinded study of the relationship between plasma homocysteine and progression of symptomatic peripheral arterial disease. *J Vasc Surg* 1999;29:8-19; discussion 19-21.
74. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA* 2002;288:980-7.
75. Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 1995;26:386-91.
76. Kannel WB, Skinner JJ Jr, Schwartz MJ, et al. Intermittent claudication: incidence in the Framingham Study. *Circulation* 1970;41:875-83.
77. Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;71:510-5.
78. Kannel WB. The demographics of claudication and the aging of the American population. *Vasc Med* 1996;1:60-4.
79. Hiatt WR, Marshall JA, Baxter J, et al. Diagnostic methods for peripheral arterial disease in the San Luis Valley Diabetes Study. *J Clin Epidemiol* 1990;43:597-606.
80. Fowkes FG, Housley E, Cawood EH, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;20:384-92.
81. Aronow WS. Prevalence of atherothrombotic brain infarction, coronary artery disease and peripheral arterial disease in elderly blacks, Hispanics and whites. *Am J Cardiol* 1992;70:1212-3.
82. Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women > or = 62 years of age. *Am J Cardiol* 1994;74:64-5.
83. Cofan F, Nunez I, Gilabert R, et al. Increased prevalence of carotid and femoral atherosclerosis in renal transplant recipients. *Transplant Proc* 2001;33:1254-6.
84. Erdoes LS, Hunter GC, Venerus BJ, et al. Prospective evaluation of peripheral vascular disease in heart transplant recipients. *J Vasc Surg* 1995;22:434-40; discussion 440-2.

85. Hirsch AT, Halverson SL, Treat-Jacobson D, et al. The Minnesota Regional Peripheral Arterial Disease Screening Program: toward a definition of community standards of care. *Vasc Med* 2001;6:87-96.
86. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001;286:1317-24.
87. Coni N, Tennison B, Troup M. Prevalence of lower extremity arterial disease among elderly people in the community. *Br J Gen Pract* 1992;42:149-52.
88. Gallotta G, Iazzetta N, Milan G, et al. Prevalence of peripheral arterial disease in an elderly rural population of southern Italy. *Gerontology* 1997;43:289-95.
89. Cheng SW, Ting AC, Lau H, et al. Epidemiology of atherosclerotic peripheral arterial occlusive disease in Hong Kong. *World J Surg* 1999;23:202-6.
90. Binaghi F, Fronteddu PF, Cannas F, et al. Prevalence of peripheral arterial occlusive disease and associated risk factors in a sample of southern Sardinian population. *Int Angiol* 1994;13:233-45.
91. Al Zahrani HA, Al Bar HM, Bahnassi A, et al. The distribution of peripheral arterial disease in a defined population of elderly high-risk Saudi patients. *Int Angiol* 1997;16:123-8.
92. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. *J Am Geriatr Soc* 1999;47:1255-6.
93. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996;94:3026-49. Erratum in: *Circulation* 2000;102:1074.
94. Stoffers HE, Rinkens PE, Kester AD, et al. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *Int J Epidemiol* 1996;25:282-90.
95. Dormandy J, Mahir M, Ascady G, et al. Fate of the patient with chronic leg ischaemia: a review article. *J Cardiovasc Surg (Torino)* 1989;30:50-7.
96. Golomb B, Criqui MH, Budens W. Epidemiology. In: Creager MA, ed. *Management of Peripheral Arterial Disease*. London, UK: ReMEDICA Pub; 2000:1-18.
97. Valentine RJ, Grayburn PA, Eichhorn EJ, et al. Coronary artery disease is highly prevalent among patients with premature peripheral vascular disease. *J Vasc Surg* 1994;19:668-74.
98. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329-39.
99. Klop RB, Eikelboom BC, Taks AC. Screening of the internal carotid arteries in patients with peripheral vascular disease by colour-flow duplex scanning. *Eur J Vasc Surg* 1991;5:41-5.
100. Alexandrova NA, Gibson WC, Norris JW, et al. Carotid artery stenosis in peripheral vascular disease. *J Vasc Surg* 1996;23:645-9.
101. Cheng SW, Wu LL, Ting AC, et al. Screening for asymptomatic carotid stenosis in patients with peripheral vascular disease: a prospective study and risk factor analysis. *Cardiovasc Surg* 1999;7:303-9.
102. Long TH, Criqui MH, Vasilevskis EE, et al. The correlation between the severity of peripheral arterial disease and carotid occlusive disease. *Vasc Med* 1999;4:135-42.
103. Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996;25:1172-81.
104. Kornitzer M, Dramaix M, Sobolski J, et al. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology* 1995;46:211-9.
105. Newman AB, Sutton-Tyrrell K, Vogt MT, et al. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. *JAMA* 1993;270:487-9.
106. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326:381-6.
107. Vogt MT, Cauley JA, Newman AB, et al. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 1993;270:465-9.
108. Zheng ZJ, Sharrett AR, Chambless LE, et al. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis* 1997;131:115-25.
109. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991;87:119-28.
110. McDermott MM, Feinglass J, Slavensky R, et al. The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. *J Gen Intern Med* 1994;9:445-9.
111. Howell MA, Colgan MP, Seeger RW, et al. Relationship of severity of lower limb peripheral vascular disease to mortality and morbidity: a six-year follow-up study. *J Vasc Surg* 1989;9:691-6; discussion 696-7.
112. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22. Summary for patients in *Curr Cardiol Rep* 2002;4:486-7.
113. Yusuf S, Dagenais G, Pogue J, et al. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:154-60.
114. Luther M. The influence of arterial reconstructive surgery on the outcome of critical leg ischaemia. *Eur J Vasc Surg* 1994;8:682-9.
115. Ebskov B. Relative mortality and long term survival for the non-diabetic lower limb amputee with vascular insufficiency. *Prosthet Orthot Int* 1999;23:209-16.
116. Kazmers A, Perkins AJ, Jacobs LA. Major lower extremity amputation in Veterans Affairs medical centers. *Ann Vasc Surg* 2000;14:216-22.
117. Dormandy J, Heeck L, Vig S. The fate of patients with critical leg ischemia. *Semin Vasc Surg* 1999;12:142-7.
118. Muluk SC, Muluk VS, Kelley ME, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. *J Vasc Surg* 2001;33:251-7; discussion 257-8.
119. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962; 27:645-58.
120. Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. *Int J Epidemiol* 1988;17:248-54.
121. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992;45:1101-9.
122. Criqui MH, Denenberg JO, Bird CE, et al. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med*

- 1996;1:65-71.
123. McDermott MM, Ferrucci L, Simonsick EM, et al. The ankle brachial index and change in lower extremity functioning over time: the Women's Health and Aging Study. *J Am Geriatr Soc* 2002;50:238-46.
124. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001;286:1599-606.
125. Newman AB, Naydeck BL, Sutton-Tyrrell K, et al. The role of comorbidity in the assessment of intermittent claudication in older adults. *J Clin Epidemiol* 2001;54:294-300.
126. Hooi JD, Kester AD, Stoffers HE, et al. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol* 2001;153:666-72.
127. Criqui MH, Denenberg JO. The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease. *Vasc Med* 1998;3:241-5.
128. Simons PC, Algra A, Eikelboom BC, et al. Carotid artery stenosis in patients with peripheral arterial disease: the SMART study. SMART study group. *J Vasc Surg* 1999;30:519-25.
129. House AK, Bell R, House J, et al. Asymptomatic carotid artery stenosis associated with peripheral vascular disease: a prospective study. *Cardiovasc Surg* 1999;7:44-9.
- 129a. Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004;110:227-39.
130. Joint National Committee on Prevention, Detection Evaluation and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, Md: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1997. Publication No. 98-4080.
131. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, Md: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health; 2002. Publication No. 02-5215. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>. Accessed July 16, 2005.
132. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. *N Engl J Med* 2002;347:1941-51.
133. Feinglass J, McCarthy WJ, Slavensky R, et al. Effect of lower extremity blood pressure on physical functioning in patients who have intermittent claudication. The Chicago Claudication Outcomes Research Group. *J Vasc Surg* 1996;24:503-11; discussion 511-2.
134. Breek JC, Hamming JF, De Vries J, et al. The impact of walking impairment, cardiovascular risk factors, and comorbidity on quality of life in patients with intermittent claudication. *J Vasc Surg* 2002;36:94-9.
135. Aquino R, Johnnides C, Makaroun M, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. *J Vasc Surg* 2001;34:962-70.
136. Mukherjee D, Lingam P, Chetcuti S, et al. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). *Circulation* 2002;106:1909-12.
137. Grundy SM, Pasternak R, Greenland P, et al. AHA/ACC scientific statement: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol* 1999;34:1348-59.
138. Chan AW, Bhatt DL, Chew DP, et al. Early and sustained survival benefit associated with statin therapy at the time of percutaneous coronary intervention. *Circulation* 2002;105:691-6.
139. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med* 1998;158:1357-64.
140. Second European Consensus Document on chronic critical leg ischemia. *Circulation* 1991;84(4 suppl):IV1-26.
141. Vale PR, Isner JM, Rosenfield K. Therapeutic angiogenesis in critical limb and myocardial ischemia. *J Interv Cardiol* 2001;14:511-28.
142. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA* 2001;285:1865-73.
143. Mercer KG, Berridge DC. Saddle embolus—the need for intensive investigation and critical evaluation: a case report. *Vasc Surg* 2001;35:63-5.
144. Ha JW, Chung N, Chang BC, et al. Aortic saddle embolism. *Clin Cardiol* 1999;22:229-30.
145. Green RM, Ouriel K, Ricotta JJ, et al. Revision of failed infrainguinal bypass graft: principles of management. *Surgery* 1986;100:646-54.
146. Bartlett ST, Olinde AJ, Flinn WR, et al. The reoperative potential of infrainguinal bypass: long-term limb and patient survival. *J Vasc Surg* 1987;5:170-9.
147. Belkin M, Donaldson MC, Whittemore AD, et al. Observations on the use of thrombolytic agents for thrombotic occlusion of infrainguinal vein grafts. *J Vasc Surg* 1990;11:289-94; discussion 295-6.
148. Kinney EV, Bandyk DF, Mewissen MW, et al. Monitoring functional patency of percutaneous transluminal angioplasty. *Arch Surg* 1991;126:743-7.
149. Schmidtke I, Roth FJ. Repeated percutaneous transluminal catheter-treatment: primary results. *Int Angiol* 1985;4:87-91.
150. Brewster DC, LaSalle AJ, Robison JG, et al. Femoropopliteal graft failures: clinical consequences and success of secondary reconstructions. *Arch Surg* 1983;118:1043-7.
151. Moody P, de Cossart LM, Douglas HM, et al. Asymptomatic strictures in femoro-popliteal vein grafts. *Eur J Vasc Surg* 1989;3:389-92.
152. Decrinis M, Doder S, Stark G, et al. A prospective evaluation of sensitivity and specificity of the ankle/brachial index in the follow-up of superficial femoral artery occlusions treated by angioplasty. *Clin Investig* 1994;72:592-7.
153. Sanchez LA, Suggs WD, Veith FJ, et al. Is surveillance to detect failing polytetrafluoroethylene bypasses worthwhile? Twelve-year experience with ninety-one grafts. *J Vasc Surg* 1993;18:981-9; discussion 989-90.
154. Buth J, Disselhoff B, Sommeling C, et al. Color-flow duplex criteria for grading stenosis in infrainguinal vein grafts. *J Vasc Surg* 1991;14:716-26; discussion 726-8.
155. Idu MM, Blankenstein JD, de Gier P, et al. Impact of a color-flow duplex surveillance program on infrainguinal vein graft patency: a five-year experience. *J Vasc Surg* 1993;17:42-52; discussion 52-3.

- 155a. Hirsch AT. Recognition and management of peripheral arterial disease. In: Eugene Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Saunders, 2003:659-71.
156. Lijmer JG, Hunink MG, van den Dungen JJ, et al. ROC analysis of noninvasive tests for peripheral arterial disease. *Ultrasound Med Biol* 1996;22:391-8.
157. Feigelson HS, Criqui MH, Fronek A, et al. Screening for peripheral arterial disease: the sensitivity, specificity, and predictive value of noninvasive tests in a defined population. *Am J Epidemiol* 1994;140:526-34.
158. Nassoura ZE, Ivatury RR, Simon RJ, et al. A reassessment of Doppler pressure indices in the detection of arterial lesions in proximity penetrating injuries of extremities: a prospective study. *Am J Emerg Med* 1996;14:151-6.
- 158a. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;344:1608-21.
159. Baker JD, Dix DE. Variability of Doppler ankle pressures with arterial occlusive disease: an evaluation of ankle index and brachial-ankle pressure gradient. *Surgery* 1981;89:134-7.
160. Carter SA. Clinical measurement of systolic pressures in limbs with arterial occlusive disease. *JAMA* 1969;207(10):1869-74.
161. Strandness DE Jr, Dalman RL, Panian S, et al. Effect of cilostazol in patients with intermittent claudication: a randomized, double-blind, placebo-controlled study. *Vasc Endovascular Surg* 2002;36:83-91.
162. Yao ST. Haemodynamic studies in peripheral arterial disease. *Br J Surg* 1970;57:761-6.
163. Ouriel K, Zarins CK. Doppler ankle pressure: an evaluation of three methods of expression. *Arch Surg* 1982;117:1297-1300.
164. Jenes R, Gaardsting O, Hougaard Jensen K, et al. Fate in intermittent claudication: outcome and risk factors. *Br Med J (Clin Res Ed)* 1986;293:1137-40.
165. McLafferty RB, Moneta GL, Taylor LM Jr, et al. Ability of ankle-brachial index to detect lower-extremity atherosclerotic disease progression. *Arch Surg* 1997;132:836-40; discussion 840-1.
166. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation* 2004;109:733-9.
167. Sikkink CJ, van Asten WN, van't Hof MA, et al. Decreased ankle/brachial indices in relation to morbidity and mortality in patients with peripheral arterial disease. *Vasc Med* 1997;2:169-73.
168. Mohler ER 3rd, Treat-Jacobson D, Reilly MP, et al. Utility and barriers to performance of the ankle-brachial index in primary care practice. *Vasc Med* 2004;9:253-60.
169. Orchard TJ, Strandness DE Jr. Assessment of peripheral vascular disease in diabetes: report and recommendations of an international workshop sponsored by the American Diabetes Association and the American Heart Association September 18-20, 1992 New Orleans, Louisiana. *Circulation* 1993;88:819-28.
170. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26:3333-41.
171. American Medical Association. *Current Procedural Terminology (CPT)*. Chicago, Ill: American Medical Association; 2001.
172. Heintz SE, Bone GE, Slaymaker EE, et al. Value of arterial pressure measurements in the proximal and distal part of the thigh in arterial occlusive disease. *Surg Gynecol Obstet* 1978;146:337-43.
173. Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. *Am J Surg* 1979;138:211-8.
174. Carter SA. Indirect systolic pressures and pulse waves in arterial occlusive diseases of the lower extremities. *Circulation* 1968;37:624-37.
175. Carter SA. Clinical measurement of systolic pressures in limbs with arterial occlusive disease. *JAMA* 1969;207:1869-74.
176. Carter SA, Tate RB. Value of toe pulse waves in addition to systolic pressures in the assessment of the severity of peripheral arterial disease and critical limb ischemia. *J Vasc Surg* 1996;24:258-65.
177. Carter SA, Tate RB. The value of toe pulse waves in determination of risks for limb amputation and death in patients with peripheral arterial disease and skin ulcers or gangrene. *J Vasc Surg* 2001;33:708-14.
178. Brooks B, Dean R, Patel S, et al. TBI or not TBI: that is the question. Is it better to measure toe pressure than ankle pressure in diabetic patients? *Diabet Med* 2001;18:528-32.
179. Ramsey DE, Manke DA, Sumner DS. Toe blood pressure: a valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *J Cardiovasc Surg (Torino)* 1983;24:43-8.
180. Raines JK. The pulse volume recorder in peripheral arterial disease. In: Bernstein EF, ed. *Noninvasive Diagnostic Techniques in Vascular Disease*. St. Louis, Mo: Mosby; 1985:513-44.
181. Jorgensen JJ, Strandness E, Gjølberg T. Measurements of common femoral artery flow velocity in the evaluation of aortoiliac atherosclerosis: comparisons between pulsatility index, pressures measurements and pulse-volume recordings. *Acta Chir Scand* 1988;154:261-6.
182. Symes JF, Graham AM, Mousseau M. Doppler waveform analysis versus segmental pressure and pulse-volume recording: assessment of occlusive disease in the lower extremity. *Can J Surg* 1984;27:345-7.
183. Clifford PC, Morgan AP, Thomas WE, et al. Monitoring arterial surgery: a comparison of pulse volume recording and electromagnetic flowmetering in aortofemoral reconstruction. *J Cardiovasc Surg (Torino)* 1986;27:262-7.
184. Kaufman JL, Fitzgerald KM, Shah DM, et al. The fate of extremities with flat lower calf pulse volume recordings. *J Cardiovasc Surg (Torino)* 1989;30:216-9.
185. Gale SS, Scissons RP, Salles-Cunha SX, et al. Lower extremity arterial evaluation: are segmental arterial blood pressures worthwhile? *J Vasc Surg* 1998;27:831-8; discussion 838-9.
186. Gosling RG, Dunbar G, King DH, et al. The quantitative analysis of occlusive peripheral arterial disease by a non-intrusive ultrasonic technique. *Angiology* 1971;22:52-5.
187. Johnston KW, Taraschuk I. Validation of the role of pulsatility index in quantitation of the severity of peripheral arterial occlusive disease. *Am J Surg* 1976;131:295-7.
188. Thiele BL, Hutchinson KJ, Greene FM, et al. Pulsed Doppler waveform patterns produced by smooth stenosis in the dog thoracic aorta. In: Taylor DM, Stevens AL, eds. *Blood Flow, Theory and Practice*. San Diego, Calif: Academic Press; 1983:85-104.
189. Bascom PA, Johnston KW, Cobbald RS, et al. Defining the limitations of measurements from Doppler spectral recordings. *J Vasc Surg* 1996;24:34-44; discussion 44-5.
190. Thiele BL, Bandyk DF, Zierler RE, et al. A systematic approach to the assessment of aortoiliac disease. *Arch Surg* 1983;118:477-81.
191. Johnston KW, Kassam M, Cobbald RS. Relationship between Doppler pulsatility index and direct femoral pressure measurements in the diagnosis of aortoiliac occlusive disease. *Ultrasound Med Biol* 1983;9:271-81.
192. Gardner AW, Skinner JS, Cantwell BW, et al. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991;23:402-8.
193. Hiatt WR, Nawaz D, Regensteiner JG, et al. The evaluation of exercise performance in patients with peripheral vascular disease.

- J Cardiopulm Rehabil 1988;8:525-32.
194. Nagle FJ, Balke B, Naughton JP. Gradational step tests for assessing work capacity. *J Appl Physiol* 1965;20:745-8.
195. Sumner DS, Strandness DE Jr. The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication. *Surgery* 1969;65:763-71.
196. Raines JK, Darling RC, Buth J, et al. Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities. *Surgery* 1976;79:21-9.
197. McPhail IR, Spittell PC, Weston SA, et al. Intermittent claudication: an objective office-based assessment. *J Am Coll Cardiol* 2001;37:1381-5.
198. Greig C, Butler F, Skelton D, et al. Treadmill walking in old age may not reproduce the real life situation. *J Am Geriatr Soc* 1993;41:15-8.
199. Gardner AW, Katzell LI, Sorkin JD, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc* 2001;49:755-62.
200. Simonsick EM, Gardner AW, Poehlman ET. Assessment of physical function and exercise tolerance in older adults: reproducibility and comparability of five measures. *Aging (Milano)* 2000;12:274-80.
201. Moneta GL, Yeager RA, Lee RW, et al. Noninvasive localization of arterial occlusive disease: a comparison of segmental Doppler pressures and arterial duplex mapping. *J Vasc Surg* 1993;17:578-82.
202. Pinto F, Lencioni R, Napoli V, et al. Peripheral ischemic occlusive arterial disease: comparison of color Doppler sonography and angiography. *J Ultrasound Med* 1996;15:697-704; quiz 705-6.
203. Sacks D, Robinson ML, Marinelli DL, et al. Peripheral arterial Doppler ultrasonography: diagnostic criteria. *J Ultrasound Med* 1992;11:95-103.
204. de Smet AA, Ermers EJ, Kitslaar PJ. Duplex velocity characteristics of aortoiliac stenoses. *J Vasc Surg* 1996;23:628-36.
205. Fletcher JP, Kershaw LZ, Chan A, et al. Noninvasive imaging of the superficial femoral artery using ultrasound Duplex scanning. *J Cardiovasc Surg (Torino)* 1990;31:364-7.
206. Ranke C, Creutzig A, Alexander K. Duplex scanning of the peripheral arteries: correlation of the peak velocity ratio with angiographic diameter reduction. *Ultrasound Med Biol* 1992;18:433-40.
207. Whelan JF, Barry MH, Moir JD. Color flow Doppler ultrasonography: comparison with peripheral arteriography for the investigation of peripheral vascular disease. *J Clin Ultrasound* 1992;20:369-74.
208. Davies AH, Willcox JH, Magee TR, et al. Colour duplex in assessing the infrainguinal arteries in patients with claudication. *Cardiovasc Surg* 1995;3:211-2.
209. Currie IC, Jones AJ, Wakeley CJ, et al. Non-invasive aortoiliac assessment. *Eur J Vasc Endovasc Surg* 1995;9:24-8.
210. van der Heijden FH, Legemate DA, van Leeuwen MS, et al. Value of duplex scanning in the selection of patients for percutaneous transluminal angioplasty. *Eur J Vasc Surg* 1993;7:71-6.
211. de Vries SO, Hunink MG, Polak JF. Summary receiver operating characteristic curves as a technique for meta-analysis of the diagnostic performance of duplex ultrasonography in peripheral arterial disease. *Acad Radiol* 1996;3:361-9.
212. Allard L, Cloutier G, Durand LG, et al. Limitations of ultrasonic duplex scanning for diagnosing lower limb arterial stenoses in the presence of adjacent segment disease. *J Vasc Surg* 1994;19:650-7.
213. Edwards JM, Coldwell DM, Goldman ML, et al. The role of duplex scanning in the selection of patients for transluminal angioplasty. *J Vasc Surg* 1991;13:69-74.
214. Proia RR, Walsh DB, Nelson PR, et al. Early results of infra-genicular revascularization based solely on duplex arteriography. *J Vasc Surg* 2001;33:1165-70.
215. Ligush J Jr, Reavis SW, Preisser JS, et al. Duplex ultrasound scanning defines operative strategies for patients with limb-threatening ischemia. *J Vasc Surg* 1998;28:482-90; discussion 490-1.
216. Ascher E, Mazzariol F, Hingorani A, et al. The use of duplex ultrasound arterial mapping as an alternative to conventional arteriography for primary and secondary infrapopliteal bypasses. *Surg Gynecol Obstet* 1999;178:162-5.
217. Wain RA, Berdejo GL, Delvalle WN, et al. Can duplex scan arterial mapping replace contrast arteriography as the test of choice before infrainguinal revascularization? *J Vasc Surg* 1999;29:100-7; discussion 107-9.
218. Larch E, Minar E, Ahmadi R, et al. Value of color duplex sonography for evaluation of tibio-peroneal arteries in patients with femoropopliteal obstruction: a prospective comparison with anterograde intraarterial digital subtraction angiography. *J Vasc Surg* 1997;25:629-36.
219. Mattos MA, van Bemmelen PS, Hodgson KJ, et al. Does correction of stenoses identified with color duplex scanning improve infrainguinal graft patency? *J Vasc Surg* 1993;17:54-64; discussion 64-6.
220. Mills JL, Harris EJ, Taylor LM Jr, et al. The importance of routine surveillance of distal bypass grafts with duplex scanning: a study of 379 reversed vein grafts. *J Vasc Surg* 1990;12:379-86; discussion 387-9.
221. Laborde AL, Synn AY, Worsey MJ, et al. A prospective comparison of ankle/brachial indices and color duplex imaging in surveillance of the in situ saphenous vein bypass. *J Cardiovasc Surg (Torino)* 1992;33:420-5.
222. Taylor PR, Tyrrell MR, Crofton M, et al. Colour flow imaging in the detection of femoro-distal graft and native artery stenosis: improved criteria. *Eur J Vasc Surg* 1992;6:232-6.
223. Bandyk DF, Schmitt DD, Seabrook GR, et al. Monitoring functional patency of in situ saphenous vein bypasses: the impact of a surveillance protocol and elective revision. *J Vasc Surg* 1989;9:286-96.
224. Golledge J, Beattie DK, Greenhalgh RM, et al. Have the results of infrainguinal bypass improved with the widespread utilisation of postoperative surveillance? *Eur J Vasc Endovasc Surg* 1996;11:388-92.
225. Lundell A, Lindblad B, Bergqvist D, et al. Femoropopliteal-cru-ral graft patency is improved by an intensive surveillance program: a prospective randomized study. *J Vasc Surg* 1995;21:26-33; discussion 33-4.
226. Ihlberg L, Luther M, Tiera E, et al. The utility of duplex scanning in infrainguinal vein graft surveillance: results from a randomised controlled study. *Eur J Vasc Endovasc Surg* 1998;16:19-27.
227. Lalak NJ, Hanel KC, Hunt J, et al. Duplex scan surveillance of infrainguinal prosthetic bypass grafts. *J Vasc Surg* 1994;20:637-41.
228. Dunlop P, Sayers RD, Naylor AR, et al. The effect of a surveillance programme on the patency of synthetic infrainguinal bypass grafts. *Eur J Vasc Endovasc Surg* 1996;11:441-5.
229. Calligaro KD, Musser DJ, Chen AY, et al. Duplex ultrasonography to diagnose failing arterial prosthetic grafts. *Surgery* 1996;120:455-9.
230. Woodburn KR, Murtagh A, Breslin P, et al. Insonation and impedance analysis in graft surveillance. *Br J Surg* 1995;82:1222-5.
231. Sacks D, Robinson ML, Marinelli DL, et al. Evaluation of the peripheral arteries with duplex US after angioplasty. *Radiology*

- 1990;176:39-44.
232. Sacks D, Robinson ML, Summers TA, et al. The value of duplex sonography after peripheral artery angioplasty in predicting subacute restenosis. *AJR Am J Roentgenol* 1994;162:179-83.
233. Spijkerboer AM, Nass PC, de Valois JC, et al. Iliac artery stenoses after percutaneous transluminal angioplasty: follow-up with duplex ultrasonography. *J Vasc Surg* 1996;23:691-7.
234. Spijkerboer AM, Nass PC, de Valois JC, et al. Evaluation of femoropopliteal arteries with duplex ultrasound after angioplasty. Can we predict results at one year? *Eur J Vasc Endovasc Surg* 1996;12:418-23.
235. Mewissen MW, Kinney EV, Bandyk DF, et al. The role of duplex scanning versus angiography in predicting outcome after balloon angioplasty in the femoropopliteal artery. *J Vasc Surg* 1992;15:860-5; discussion 865-6.
236. Miller BV, Sharp WJ, Shamma AR, et al. Surveillance for recurrent stenosis after endovascular procedures: a prospective study. *Arch Surg* 1991;126:867-71; discussion 871-2.
237. Vroegindeweij D, Kemper FJ, Tielbeek AV, et al. Recurrence of stenoses following balloon angioplasty and Simpson atherectomy of the femoro-popliteal segment: a randomised comparative 1-year follow-up study using colour flow duplex. *Eur J Vasc Surg* 1992;6:164-71.
238. Vroegindeweij D, Tielbeek AV, Buth J, et al. Patterns of recurrent disease after recanalization of femoropopliteal artery occlusions. *Cardiovasc Intervent Radiol* 1997;20:257-62.
239. Rubin GD, Shiau MC, Leung AN, et al. Aorta and iliac arteries: single versus multiple detector-row helical CT angiography. *Radiology* 2000;215:670-6.
240. Martin ML, Tay KH, Flak B, et al. Multidetector CT angiography of the aortoiliac system and lower extremities: a prospective comparison with digital subtraction angiography. *AJR Am J Roentgenol* 2003;180:1085-91.
241. Willmann JK, Wildermuth S, Pfammatter T, et al. Aortoiliac and renal arteries: prospective intraindividual comparison of contrast-enhanced three-dimensional MR angiography and multi-detector row CT angiography. *Radiology* 2003;226:798-811.
242. Willmann JK, Mayer D, Banyai M, et al. Evaluation of peripheral arterial bypass grafts with multi-detector row CT angiography: comparison with duplex US and digital subtraction angiography. *Radiology* 2003;229:465-74.
243. Ofer A, Nitecki SS, Linn S, et al. Multidetector CT angiography of peripheral vascular disease: a prospective comparison with intraarterial digital subtraction angiography. *AJR Am J Roentgenol* 2003;180:719-24.
244. Ota H, Takase K, Igarashi K, et al. MDCT compared with digital subtraction angiography for assessment of lower extremity arterial occlusive disease: importance of reviewing cross-sectional images. *AJR Am J Roentgenol* 2004;182:201-9.
245. Rieker O, Duber C, Schmiedt W, et al. Prospective comparison of CT angiography of the legs with intraarterial digital subtraction angiography. *AJR Am J Roentgenol* 1996;166:269-76.
246. Tins B, Oxtoby J, Patel S. Comparison of CT angiography with conventional arterial angiography in aortoiliac occlusive disease. *Br J Radiol* 2001;74:219-25.
247. Rubin GD, Schmidt AJ, Logan LJ, et al. Multi-detector row CT angiography of lower extremity arterial inflow and runoff: initial experience. *Radiology* 2001;221:146-58.
248. Catalano C, Fraioli F, Laghi A, et al. Infrarenal aortic and lower-extremity arterial disease: diagnostic performance of multi-detector row CT angiography. *Radiology* 2004;231:555-63.
249. Beregi JP, Djabbari M, Desmoucelle F, et al. Popliteal vascular disease: evaluation with spiral CT angiography. *Radiology* 1997;203:477-83.
250. Adriaensen ME, Kock MC, Stijnen T, et al. Peripheral arterial disease: therapeutic confidence of CT versus digital subtraction angiography and effects on additional imaging recommendations. *Radiology* 2004;233:385-91.
251. Rofsky NM, Adelman MA. MR angiography in the evaluation of atherosclerotic peripheral vascular disease. *Radiology* 2000;214:325-38.
252. Baum RA, Rutter CM, Sunshine JH, et al. Multicenter trial to evaluate vascular magnetic resonance angiography of the lower extremity. American College of Radiology Rapid Technology Assessment Group. *JAMA* 1995;274:875-80.
253. Nelemans PJ, Leiner T, de Vet HC, et al. Peripheral arterial disease: meta-analysis of the diagnostic performance of MR angiography. *Radiology* 2000;217:105-14.
254. Khilnani NM, Winchester PA, Prince MR, et al. Peripheral vascular disease: combined 3D bolus chase and dynamic 2D MR angiography compared with x-ray angiography for treatment planning. *Radiology* 2002;224:63-74.
255. Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US—a meta-analysis. *Radiology* 2000;216:67-77.
256. Kreitner KF, Kalden P, Neufang A, et al. Diabetes and peripheral arterial occlusive disease: prospective comparison of contrast-enhanced three-dimensional MR angiography with conventional digital subtraction angiography. *AJR Am J Roentgenol* 2000;174:171-9.
257. Owen RS, Carpenter JP, Baum RA, et al. Magnetic resonance imaging of angiographically occult runoff vessels in peripheral arterial occlusive disease. *N Engl J Med* 1992;326:1577-81.
258. Dorweiler B, Neufang A, Kreitner KF, et al. Magnetic resonance angiography unmasks reliable target vessels for pedal bypass grafting in patients with diabetes mellitus. *J Vasc Surg* 2002;35:766-72.
259. Hartnell G. MR angiography compared with digital subtraction angiography. *AJR Am J Roentgenol* 2000;175:1188-9.
260. Oser RF, Picus D, Hicks ME, et al. Accuracy of DSA in the evaluation of patency of infrapopliteal vessels. *J Vasc Interv Radiol* 1995;6:589-94.
261. Leyendecker JR, Elsass KD, Johnson SP, et al. The role of infrapopliteal MR angiography in patients undergoing optimal contrast angiography for chronic limb-threatening ischemia. *J Vasc Interv Radiol* 1998;9:545-51.
262. Maintz D, Tombach B, Juergens KU, et al. Revealing in-stent stenoses of the iliac arteries: comparison of multidetector CT with MR angiography and digital radiographic angiography in a Phantom model. *AJR Am J Roentgenol* 2002;179:1319-22.
263. Lee VS, Martin DJ, Krinsky GA, et al. Gadolinium-enhanced MR angiography: artifacts and pitfalls. *AJR Am J Roentgenol* 2000;175:197-205.
264. Sam AD 2nd, Morasch MD, Collins J, et al. Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. *J Vasc Surg* 2003;38:313-8.
265. Hilfiker PR, Quick HH, Debatin JF. Plain and covered stent-grafts: in vitro evaluation of characteristics at three-dimensional MR angiography. *Radiology* 1999;211:693-7.
266. Snidow JJ, Harris VJ, Trerotola SO, et al. Interpretations and treatment decisions based on MR angiography versus conventional arteriography in symptomatic lower extremity ischemia. *J Vasc Interv Radiol* 1995;6:595-603.
267. Cambria RP, Kaufman JA, L'Italien GJ, et al. Magnetic resonance

- angiography in the management of lower extremity arterial occlusive disease: a prospective study. *J Vasc Surg* 1997;25:380-9.
268. Hoch JR, Tullis MJ, Kennell TW, et al. Use of magnetic resonance angiography for the preoperative evaluation of patients with infrainguinal arterial occlusive disease. *J Vasc Surg* 1996;23:792-800; discussion 801.
269. Huber TS, Back MR, Ballinger RJ, et al. Utility of magnetic resonance arteriography for distal lower extremity revascularization. *J Vasc Surg* 1997;26:415-23; discussion 423-4.
270. Loewe C, Cejna M, Lammer J, et al. Contrast-enhanced magnetic resonance angiography in the evaluation of peripheral bypass grafts. *Eur Radiol* 2000;10:725-32.
271. Dorenbeck U, Seitz J, Volk M, et al. Evaluation of arterial bypass grafts of the pelvic and lower extremities with gadolinium-enhanced magnetic resonance angiography: comparison with digital subtraction angiography. *Invest Radiol* 2002;37:60-4.
272. Bertschinger K, Cassina PC, Debatin JF, et al. Surveillance of peripheral arterial bypass grafts with three-dimensional MR angiography: comparison with digital subtraction angiography. *AJR Am J Roentgenol* 2001;176:215-20.
273. Davis CP, Schopke WD, Seifert B, et al. MR angiography of patients with peripheral arterial disease before and after transluminal angioplasty. *AJR Am J Roentgenol* 1997;168:1027-34.
274. Bettmann MA, Heeren T, Greenfield A, et al. Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. *Radiology* 1997;203:611-20.
275. Waugh JR, Sacharias N. Arteriographic complications in the DSA era. *Radiology* 1992;182:243-6.
276. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;348:491-9.
277. Baker CS, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol* 2003;41:2114-8.
278. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA* 2003;289:553-8.
279. Isenbarger DW, Kent SM, O'Malley PG. Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy. *Am J Cardiol* 2003;92:1454-8.
280. Stone GW, McCullough PA, Tumlin JA, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003;290:2284-91.
281. Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003;349:1333-40.
282. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) *Lancet* 1994;344:1383-9.
283. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
284. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349-57.
285. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8.
286. Blankenhorn DH, Azen SP, Crawford DW, et al. Effects of colestipol-niacin therapy on human femoral atherosclerosis. *Circulation* 1991;83:438-47.
287. Duffield RG, Lewis B, Miller NE, et al. Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis: a randomised controlled trial. *Lancet* 1983;2:639-42.
288. Buchwald H, Bourdages HR, Campos CT, et al. Impact of cholesterol reduction on peripheral arterial disease in the Program on the Surgical Control of the Hyperlipidemias (POSCH). *Surgery* 1996;120:672-9.
289. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). *Am J Cardiol* 1998;81:333-5.
290. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;108:1481-6.
291. Aronow WS, Nayak D, Woodworth S, et al. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol* 2003;92:711-2.
292. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;114:359-64.
293. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA* 1997;277:739-45.
294. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72. Erratum in: *JAMA* 2003;290:197.
295. Hennekens CH, Albert CM, Godfried SL, et al. Adjunctive drug therapy of acute myocardial infarction—evidence from clinical trials. *N Engl J Med* 1996;335:1660-7.
296. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease: a meta-analysis of randomized controlled trials. *Arch Intern Med* 1991;151:1769-76.
297. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
298. Gustafsson F, Torp-Pedersen C, Kober L, et al. Effect of angiotensin converting enzyme inhibition after acute myocardial infarction in patients with arterial hypertension. TRACE Study Group, Trandolapril Cardiac Event. *J Hypertens* 1997;15:793-8.
299. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-53. Errata in: *N Engl J Med* 2000;342:1376; *N Engl J Med* 2000;342:748.
300. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;75:894-903.
301. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective

- Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837-53. Erratum in: *Lancet* 1999;354:602.
302. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2003;26 suppl 1:S33-50. Erratum in: *Diabetes Care* 2003;26:972.
303. Donohoe ME, Fletton JA, Hook A, et al. Improving foot care for people with diabetes mellitus—a randomized controlled trial of an integrated care approach. *Diabet Med* 2000;17:581-7.
304. Faulkner KW, House AK, Castleden WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. *Med J Aust* 1983;1:217-9.
305. Lassila R, Lepantalo M. Cigarette smoking and the outcome after lower limb arterial surgery. *Acta Chir Scand* 1988;154:635-40.
306. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta Med Scand* 1987;221:253-60.
307. Quick CR, Cotton LT. The measured effect of stopping smoking on intermittent claudication. *Br J Surg* 1982;69 suppl:S24-6.
308. Gardner AW. The effect of cigarette smoking on exercise capacity in patients with intermittent claudication. *Vasc Med* 1996;1:181-6.
309. Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smoking. *Arch Intern Med* 1995;155:1933-41.
310. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685-91.
311. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998;316:894-8.
312. Omenn GS, Beresford SA, Motulsky AG. Preventing coronary heart disease: B vitamins and homocysteine. *Circulation* 1998;97:421-4.
313. Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B6 reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. *J Cardiovasc Risk* 1998;5:249-55.
314. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. Erratum in: *BMJ* 2002;324:141.
315. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993;35:219-26.
316. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. Errata in: *N Engl J Med* 2001;345:1716; *N Engl J Med* 2001;345:1506.
317. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81-106. Erratum in: *BMJ* 1994;308:1540.
318. Girolami B, Bernardi E, Prins MH, et al. Antithrombotic drugs in the primary medical management of intermittent claudication: a meta-analysis. *Thromb Haemost* 1999;81:715-22.
319. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999;282:2058-67. Erratum in: *JAMA* 2000;284:45.
320. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol* 2003;41(4 suppl S):62S-69S. 3
321. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;355:346-51. Erratum in: *Lancet* 2000;355:1104.
322. Regensteiner JG. Exercise in the treatment of claudication: assessment and treatment of functional impairment. *Vasc Med* 1997;2:238-42.
323. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA* 1995;274:975-80.
324. Hiatt WR, Wolfel EE, Meier RH, et al. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease: implications for the mechanism of the training response. *Circulation* 1994;90:1866-74.
325. Regensteiner JG, Meyer TJ, Krupski WC, et al. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology* 1997;48:291-300.
326. Hiatt WR, Regensteiner JG, Hargarten ME, et al. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990;81:602-9.
327. Lundgren F, Dahllof AG, Schersten T, et al. Muscle enzyme adaptation in patients with peripheral arterial insufficiency: spontaneous adaptation, effect of different treatments and consequences on walking performance. *Clin Sci (Lond)* 1989;77:485-93.
328. Hirsch AT, Ekers MA. A comprehensive vascular medical therapeutic approach to peripheral arterial disease: the foundation of effective vascular rehabilitation. In: Fahey VA, ed. *Vascular Nursing*. 3rd ed. Philadelphia, Pa: WB Saunders; 1999:188-211.
329. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2000;CD000990.
330. Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. *Lancet* 1966;2:1093-6.
331. Holm J, Dahllof AG, Bjorntorp P, et al. Enzyme studies in muscles of patients with intermittent claudication: effect of training. *Scand J Clin Lab Invest Suppl* 1973;128:201-5.
332. Dahllof AG, Bjorntorp P, Holm J, et al. Metabolic activity of skeletal muscle in patients with peripheral arterial insufficiency. *Eur J Clin Invest* 1974;4:9-15.
333. Dahllof AG, Holm J, Schersten T, et al. Peripheral arterial insufficiency, effect of physical training on walking tolerance, calf blood flow, and blood flow resistance. *Scand J Rehabil Med* 1976;8:19-26.
334. Creasy TS, McMillan PJ, Fletcher EW, et al. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. *Eur J Vasc Surg* 1990;4:135-40.
335. Mannarino E, Pasqualini L, Innocente S, et al. Physical training and antiplatelet treatment in stage II peripheral arterial occlusive disease: alone or combined? *Angiology* 1991;42:513-21.
336. Patterson RB, Pinto B, Marcus B, et al. Value of a supervised exercise program for the therapy of arterial claudication. *J Vasc Surg* 1997;25:312-8; discussion 318-9.
337. Dawson DL, Cutler BS, Meissner MH, et al. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. *Circulation* 1998;98:678-86.
338. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg* 1998;27:267-74; discussion 274-5.
339. Clifford PC, Davies PW, Hayne JA, et al. Intermittent claudica-

- tion: is a supervised exercise class worth while? *Br Med J* 1980; 280:1503-5.
340. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg* 1996;23:104-15.
341. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
342. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413-46. Erratum in *Arch Intern Med* 1998;158:573.
343. Gibellini R, Fanello M, Bardile AF, et al. Exercise training in intermittent claudication. *Int Angiol* 2000;19:8-13.
344. Gardner AW, Katzel LI, Sorkin JD, et al. Effects of long-term exercise rehabilitation on claudication distances in patients with peripheral arterial disease: a randomized controlled trial. *J Cardiopulm Rehabil* 2002;22:192-8.
345. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. 4th ed. Roitman JL, ed. Baltimore, Md: Lippincott, Williams, and Wilkins; 2001.
346. Ryan AS, Katzel LI, Gardner AW. Determinants of peak V(O₂) in peripheral arterial occlusive disease patients. *J Gerontol A Biol Sci Med Sci* 2000;55:B302-6.
347. Pollock ML, Franklin BA, Balady GJ, et al. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* 2000;101:828-33.
348. Coffman JD. Intermittent claudication—be conservative. *N Engl J Med* 1991;325:577-8.
349. Radack K, Wyderski RJ. Conservative management of intermittent claudication. *Ann Intern Med* 1990;113:135-46.
350. Savage P, Ricci MA, Lynn M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. *J Cardiopulm Rehabil* 2001;21:152-7.
351. Degischer S, Labs KH, Hochstrasser J, et al. Physical training for intermittent claudication: a comparison of structured rehabilitation versus home-based training. *Vasc Med* 2002;7:109-15.
352. Perkins JM, Collin J, Creasy TS, et al. Exercise training versus angioplasty for stable claudication: long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg* 1996;11:409-13.
353. Chong PF, Gollidge J, Greenhalgh RM, et al. Exercise therapy or angioplasty? A summation analysis. *Eur J Vasc Endovasc Surg* 2000;20:4-12.
354. Gelin J, Jivegard L, Taft C, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg* 2001;22:107-13.
355. Lundgren F, Dahllof AG, Lundholm K, et al. Intermittent claudication—surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg* 1989;209:346-55.
356. Priebe M, Davidoff G, Lampman RM. Exercise testing and training in patients with peripheral vascular disease and lower extremity amputation. *West J Med* 1991;154:598-601.
357. Walker RD, Nawaz S, Wilkinson CH, et al. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg* 2000;31:662-9.
358. Belcaro G, Nicolaides AN, Agus G, et al. PGE(1) treatment of severe intermittent claudication (short-term versus long-term, associated with exercise)—efficacy and costs in a 20-week, randomized trial. *Angiology* 2000;51(8 pt 2):S15-26.
359. Diehm C, Kuhn A, Strauss R, et al. Effects of regular physical training in a supervised class and additional intravenous prostaglandin E1 and naftidrofuryl infusion therapy in patients with intermittent claudication—a controlled study. *Vasa Suppl* 1989;28:26-30.
360. Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or naftrolyl: a meta-analysis. *Arch Intern Med* 1999;159:337-45.
361. Hall JA, Barnard J. The effects of an intensive 26-day program of diet and exercise on patients with peripheral vascular disease. *J Cardiac Rehabil* 1982;2:569-74.
362. Rosfors S, Bygdeman S, Arnetz BB, et al. Longterm neuroendocrine and metabolic effects of physical training in intermittent claudication. *Scand J Rehabil Med* 1989;21:7-11.
- 362a. Ruderman N, Devlin JT, Schneider S, Kriska A. Handbook of Exercise in Diabetes. Alexandria, VA: American Diabetes Association, 2002.
- 362b. ACSM's Guidelines for Exercise Testing and Prescription. In: Franklin BA, ed. Baltimore, MD: Lippincott, Williams, & Wilkins, 2000.
- 362c. Guidelines for Cardiac Rehabilitation and Secondary Prevention/American Association of Cardiovascular and Pulmonary Rehabilitation. Champaign, IL: Human Kinetics, 1999.
- 362d. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Medical progress: exercise training for claudication. *N Engl J Med* 2002;347:1941-51.
363. Igawa T, Tani T, Chijiwa T, et al. Potentiation of anti-platelet aggregating activity of cilostazol with vascular endothelial cells. *Thromb Res* 1990;57:617-23.
364. Woo SK, Kang WK, Kwon KI. Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002;71:246-52.
365. Elam MB, Heckman J, Crouse JR, et al. Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. *Arterioscler Thromb Vasc Biol* 1998;18:1942-7.
366. Otsuki M, Saito H, Xu X, et al. Cilostazol represses vascular cell adhesion molecule-1 gene transcription via inhibiting NF-kappaB binding to its recognition sequence. *Atherosclerosis* 2001; 158:121-8.
367. Tsuchikane E, Fukuhara A, Kobayashi T, et al. Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty. *Circulation* 1999;100:21-6.
368. Takahashi S, Oida K, Fujiwara R, et al. Effect of cilostazol, a cyclic AMP phosphodiesterase inhibitor, on the proliferation of rat aortic smooth muscle cells in culture. *J Cardiovasc Pharmacol* 1992;20:900-6.
369. Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med* 1999;159:2041-50.
370. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilosta-

- zol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000;109:523-30.
371. Mohler ER 3rd, Beebe HG, Salles-Cuhna S, et al. Effects of cilostazol on resting ankle pressures and exercise-induced ischemia in patients with intermittent claudication. *Vasc Med* 2001;6:151-6.
372. Regensteiner JG, Ware JE Jr, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 2002;50:1939-46.
373. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991;325:1468-75.
374. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med* 1998;339:1810-6.
375. Strano A, Davi G, Avellone G, et al. Double-blind, crossover study of the clinical efficacy and the hemorheological effects of pentoxifylline in patients with occlusive arterial disease of the lower limbs. *Angiology* 1984;35:459-66.
376. Rao KM, Simel DL, Cohen HJ, et al. Effects of pentoxifylline administration on blood viscosity and leukocyte cytoskeletal function in patients with intermittent claudication. *J Lab Clin Med* 1990;115:738-44.
377. Schratzberger P, Dunzendorfer S, Reinisch N, et al. Mediator-dependent effects of pentoxifylline on endothelium for transmigration of neutrophils. *Immunopharmacology* 1999;41:65-75.
378. Dawson DL, Zheng Q, Worthy SA, et al. Failure of pentoxifylline or cilostazol to improve blood and plasma viscosity, fibrinogen, and erythrocyte deformability in claudication. *Angiology* 2002;53:509-20.
379. Franzini E, Sellak H, Babin-Chevaye C, et al. Effects of pentoxifylline on the adherence of polymorphonuclear neutrophils to oxidant-stimulated human endothelial cells: involvement of cyclic AMP. *J Cardiovasc Pharmacol* 1995;25 suppl 2:S92-5.
380. Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. *CMAJ* 1996;155:1053-9.
381. Lindgarde F, Jernes R, Bjorkman H, et al. Conservative drug treatment in patients with moderately severe chronic occlusive peripheral arterial disease. Scandinavian Study Group. *Circulation* 1989;80:1549-56.
382. Porter JM, Cutler BS, Lee BY, et al. Pentoxifylline efficacy in the treatment of intermittent claudication: multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. *Am Heart J* 1982;104:66-72.
383. Lindgarde F, Labs KH, Rossner M. The pentoxifylline experience: exercise testing reconsidered. *Vasc Med* 1996;1:145-54.
384. Belch JJ, Bell PR, Creissen D, et al. Randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AS-013, a prostaglandin E1 prodrug, in patients with intermittent claudication. *Circulation* 1997;95:2298-302.
385. Diehm C, Balzer K, Bisler H, et al. Efficacy of a new prostaglandin E1 regimen in outpatients with severe intermittent claudication: results of a multicenter placebo-controlled double-blind trial. *J Vasc Surg* 1997;25:537-44.
386. Boger RH, Bode-Boger SM, Thiele W, et al. Restoring vascular nitric oxide formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. *J Am Coll Cardiol* 1998;32:1336-44.
387. Mangiafico RA, Messina R, Attina T, et al. Impact of a 4-week treatment with prostaglandin E1 on health-related quality of life of patients with intermittent claudication. *Angiology* 2000;51:441-9.
388. Lievre M, Morand S, Besse B, et al. Oral Beraprost sodium, a prostaglandin I(2) analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. Beraprost et Claudication Intermittente (BERCI) Research Group. *Circulation* 2000;102:426-31.
389. Mohler ER 3rd, Hiatt WR, Olin JW, et al. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I2 analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003;41:1679-86.
390. Yang HT, Deschenes MR, Ogilvie RW, et al. Basic fibroblast growth factor increases collateral blood flow in rats with femoral arterial ligation. *Circ Res* 1996;79:62-9.
391. Takeshita S, Zheng LP, Brogi E, et al. Therapeutic angiogenesis: a single intraarterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model. *J Clin Invest* 1994;93:662-70.
392. Tsurumi Y, Takeshita S, Chen D, et al. Direct intramuscular gene transfer of naked DNA encoding vascular endothelial growth factor augments collateral development and tissue perfusion. *Circulation* 1996;94:3281-90.
393. Ohara N, Koyama H, Miyata T, et al. Adenovirus-mediated ex vivo gene transfer of basic fibroblast growth factor promotes collateral development in a rabbit model of hind limb ischemia. *Gene Ther* 2001;8:837-45.
394. Lazarous DF, Unger EF, Epstein SE, et al. Basic fibroblast growth factor in patients with intermittent claudication: results of a phase I trial. *J Am Coll Cardiol* 2000;36:1239-44.
395. Lederman RJ, Mendelsohn FO, Anderson RD, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. *Lancet* 2002;359:2053-8.
396. Cooper LT Jr, Hiatt WR, Creager MA, et al. Proteinuria in a placebo-controlled study of basic fibroblast growth factor for intermittent claudication. *Vasc Med* 2001;6:235-9.
397. Rajagopalan S, Trachtenberg J, Mohler E, et al. Phase I study of direct administration of a replication deficient adenovirus vector containing the vascular endothelial growth factor cDNA (CI-1023) to patients with claudication. *Am J Cardiol* 2002;90:512-6.
398. Rajagopalan S, Mohler ER 3rd, Lederman RJ, et al. Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. *Circulation* 2003;108:1933-8.
399. Cooke JP, Creager MA. Hypercholesterolemia, atherosclerosis, and the NO synthase pathway. In: Vallance PJ, Webb DJ, eds. *Vascular Endothelium in Human Physiology and Pathophysiology*. Amsterdam, the Netherlands: Harwood Academic Publishers, 2000:147-70.
400. Creager MA, Gallagher SJ, Girdard XJ, et al. L-arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. *J Clin Invest* 1992;90:1248-53.
401. Maxwell AJ, Anderson BE, Cooke JP. Nutritional therapy for peripheral arterial disease: a double-blind, placebo-controlled, randomized trial of HeartBar. *Vasc Med* 2000;5:11-9.
402. Brevetti G, Chiariello M, Ferulano G, et al. Increases in walking distance in patients with peripheral vascular disease treated with

- L-carnitine: a double-blind, cross-over study. *Circulation* 1988; 77:767-73.
403. Brevetti G, Diehm C, Lambert D. European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999;34:1618-24.
404. Brevetti G, Perna S, Sabba C, et al. Propionyl-L-carnitine in intermittent claudication: double-blind, placebo-controlled, dose titration, multicenter study. *J Am Coll Cardiol* 1995;26:1411-6.
405. Hiatt WR, Regensteiner JG, Creager MA, et al. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. *Am J Med* 2001;110:616-22.
406. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000;108:276-81.
407. Kleijnen J, Mackerras D. Vitamin E for intermittent claudication. *Cochrane Database Syst Rev* 2000;(2):CD000987.
408. Tornwall ME, Virtamo J, Haukka JK, et al. The effect of alpha-tocopherol and beta-carotene supplementation on symptoms and progression of intermittent claudication in a controlled trial. *Atherosclerosis* 1999;147:193-7.
409. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. *Circulation* 1997;96:1031-3.
410. Villarruz MV, Dans A, Tan F. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev* 2002; CD002785.
411. Olszewer E, Sabbag FC, Carter JP. A pilot double-blind study of sodium-magnesium EDTA in peripheral vascular disease. *J Natl Med Assoc* 1990;82:173-7.
412. Sloth-Nielsen J, Guldager B, Mouritzen C, et al. Arteriographic findings in EDTA chelation therapy on peripheral arteriosclerosis. *Surg Gynecol Obstet* 1991;162:122-5.
413. van Rij AM, Solomon C, Packer SG, et al. Chelation therapy for intermittent claudication: a double-blind, randomized, controlled trial. *Circulation* 1994;90:1194-9.
414. Guldager B, Jernes R, Jorgensen SJ, et al. EDTA treatment of intermittent claudication—a double-blind, placebo-controlled study. *J Intern Med* 1992;231:261-7.
415. Johnston KW, Rae M, Hogg-Johnston SA, et al. 5-year results of a prospective study of percutaneous transluminal angioplasty. *Ann Surg* 1987;206:403-13.
416. Lofberg AM, Karacagil S, Ljungman C, et al. Percutaneous transluminal angioplasty of the femoropopliteal arteries in limbs with chronic critical lower limb ischemia. *J Vasc Surg* 2001;34:114-21.
417. Jansen T, Manninen H, Tulla H, et al. The final outcome of primary infrainguinal percutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. *J Vasc Interv Radiol* 2002;13:455-63.
418. Powell RJ, Fillinger M, Walsh DB, et al. Predicting outcome of angioplasty and selective stenting of multisegment iliac artery occlusive disease. *J Vasc Surg* 2000;32:564-9.
419. Laborde JC, Palmaz JC, Rivera FJ, et al. Influence of anatomic distribution of atherosclerosis on the outcome of revascularization with iliac stent placement. *J Vasc Interv Radiol* 1995;6:513-21.
420. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty: factors influencing long-term success. *Circulation* 1991; 83(2 suppl):I70-80.
421. Stokes KR, Strunk HM, Campbell DR, et al. Five-year results of iliac and femoropopliteal angioplasty in diabetic patients. *Radiology* 1990;174(3 pt 2):977-82.
422. Johnston KW. Iliac arteries: reanalysis of results of balloon angioplasty. *Radiology* 1993;186:207-12.
423. Clark TW, Groffsky JL, Soulen MC. Predictors of long-term patency after femoropopliteal angioplasty: results from the STAR registry. *J Vasc Interv Radiol* 2001;12:923-33.
424. Beck AH, Muhe A, Ostheim W, et al. Long-term results of percutaneous transluminal angioplasty: a study of 4750 dilatations and local lyses. *Eur J Vasc Surg* 1989;3:245-52.
425. Palmaz JC, Laborde JC, Rivera FJ, et al. Stenting of the iliac arteries with the Palmaz stent: experience from a multicenter trial. *Cardiovasc Intervent Radiol* 1992;15:291-7.
426. Soder HK, Manninen HI, Jaakkola P, et al. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. *J Vasc Interv Radiol* 2000;11:1021-31.
427. Sapoval MR, Chatellier G, Long AL, et al. Self-expandable stents for the treatment of iliac artery obstructive lesions: long-term success and prognostic factors. *AJR Am J Roentgenol* 1996;166:1173-9.
428. Bakal CW, Sprayregen S, Scheinbaum K, et al. Percutaneous transluminal angioplasty of the infrapopliteal arteries: results in 53 patients. *AJR Am J Roentgenol* 1990;154:171-4.
429. Brown KT, Moore ED, Getrajdman GI, et al. Infrapopliteal angioplasty: long-term follow-up. *J Vasc Interv Radiol* 1993;4:139-44.
430. Bull PG, Mendel H, Hold M, et al. Distal popliteal and tibio-peroneal transluminal angioplasty: long-term follow-up. *J Vasc Interv Radiol* 1992;3:45-53.
431. Timaran CH, Stevens SL, Freeman MB, et al. External iliac and common iliac artery angioplasty and stenting in men and women. *J Vasc Surg* 2001;34:440-6.
432. Timaran CH, Stevens SL, Grandas OH, et al. Influence of hormone replacement therapy on the outcome of iliac angioplasty and stenting. *J Vasc Surg* 2001;33(2 suppl):S85-92.
433. Avino AJ, Bandyk DF, Gonsalves AJ, et al. Surgical and endovascular intervention for infrainguinal vein graft stenosis. *J Vasc Surg* 1999;29:60-70; discussion 70-1.
434. Whitemore AD, Donaldson MC, Polak JF, et al. Limitations of balloon angioplasty for vein graft stenosis. *J Vasc Surg* 1991; 14:340-5.
435. Goh RH, Sniderman KW, Kalman PG. Long-term follow-up of management of failing in situ saphenous vein bypass grafts using endovascular intervention techniques. *J Vasc Interv Radiol* 2000;11:705-12.
436. Bosch JL, Hunink MG. Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. *Radiology* 1997;204:87-96. Erratum in: *Radiology* 1997;205:584.
437. Hunink MG, Wong JB, Donaldson MC, et al. Patency results of percutaneous and surgical revascularization for femoropopliteal arterial disease. *Med Decis Making* 1994;14:71-81.
438. Hunink MG, Wong JB, Donaldson MC, et al. Revascularization for femoropopliteal disease: a decision and cost-effectiveness analysis. *JAMA* 1995;274:165-71.
- 438a. Kandarpa K, Becker BJ, Hunink M, et al. *J Vasc Interv Radiol* 2001;12:683-95.
439. Udoff EJ, Barth KH, Harrington DP, et al. Hemodynamic significance of iliac artery stenosis: pressure measurements during angiography. *Radiology* 1979;132:289-93.
440. Tetteroo E, van Engelen AD, Spithoven JH, et al. Stent placement after iliac angioplasty: comparison of hemodynamic and angiographic criteria. Dutch Iliac Stent Trial Study Group. *Radiology* 1996;201:155-9.
441. 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.
442. Bonn J. Percutaneous vascular intervention: value of hemodynamic measurements. *Radiology* 1996;201:18-20.
443. Whyman MR, Fowkes FG, Kerracher EM, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. *Eur J Vasc Endovasc Surg* 1996;12:167-72.
444. Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. *J Vasc Surg* 1997;26:551-7.
445. Feinglass J, McCarthy WJ, Slavensky R, et al. Functional status and walking ability after lower extremity bypass grafting or angioplasty for intermittent claudication: results from a prospective outcomes study. *J Vasc Surg* 2000;31(1 pt 1):93-103.
446. Holm J, Arfvidsson B, Jivegard L, et al. Chronic lower limb ischaemia. A prospective randomised controlled study comparing the 1-year results of vascular surgery and percutaneous transluminal angioplasty (PTA). *Eur J Vasc Surg* 1991;5:517-22.
447. Wolf GL, Wilson SE, Cross AP, et al. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. *J Vasc Interv Radiol* 1993;4:639-48.
448. Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis: report of a prospective randomized trial in a selected group of patients. *J Vasc Surg* 1989;9:1-9.
449. Gray BH, Sullivan TM, Childs MB, et al. High incidence of restenosis/reocclusion of stents in the percutaneous treatment of long-segment superficial femoral artery disease after suboptimal angioplasty. *J Vasc Surg* 1997;25:74-83.
450. de Vries SO, Visser K, de Vries JA, et al. Intermittent claudication: cost-effectiveness of revascularization versus exercise therapy. *Radiology* 2002;222:25-36.
451. Treesak C, Kasemsup V, Treat-Jacobson D, et al. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. *Vasc Med* 2004;9:279-85.
452. Tetteroo E, van der Graaf Y, Bosch JL, et al. Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. *Lancet* 1998;351:1153-9.
453. Richter GM, Roeren T, Noeldge G, et al. [Initial long-term results of a randomized 5-year study: iliac stent implantation versus PTA] *Vasa Suppl* 1992;35:192-3.
454. Bosch JL, Tetteroo E, Mali WP, et al. Iliac arterial occlusive disease: cost-effectiveness analysis of stent placement versus percutaneous transluminal angioplasty. Dutch Iliac Stent Trial Study Group. *Radiology* 1998;208:641-8.
455. Bosch JL, Haaring C, Meyerovitz MF, et al. Cost-effectiveness of percutaneous treatment of iliac artery occlusive disease in the United States. *AJR Am J Roentgenol* 2000;175:517-21.
456. Muradin GS, Bosch JL, Stijnen T, et al. Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. *Radiology* 2001;221:137-45.
457. Cejna M, Thurnher S, Illiasch H, et al. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. *J Vasc Interv Radiol* 2001;12:23-31.
458. Grimm J, Muller-Hulsbeck S, Jahnke T, et al. Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. *J Vasc Interv Radiol* 2001;12:935-42.
459. Vroegindewij D, Vos LD, Tielbeek AV, et al. Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: a comparative randomized study. *Cardiovasc Intervent Radiol* 1997;20:420-5.
460. Zdanowski Z, Albrechtsson U, Lundin A, et al. Percutaneous transluminal angioplasty with or without stenting for femoropopliteal occlusions? A randomized controlled study. *Int Angiol* 1999;18:251-5.
461. Schillinger M, Mlekusch W, Haumer M, et al. Angioplasty and elective stenting of de novo versus recurrent femoropopliteal lesions: 1-year follow-up. *J Endovasc Ther* 2003;10:288-97.
462. Vroegindewij D, Tielbeek AV, Buth J, et al. Directional atherectomy versus balloon angioplasty in segmental femoropopliteal artery disease: two-year follow-up with color-flow duplex scanning. *J Vasc Surg* 1995;21:255-68; discussion 268-9.
463. Nakamura S, Conroy RM, Gordon IL, et al. A randomized trial of transcatheter extraction atherectomy in femoral arteries: intravascular ultrasound observations. *J Clin Ultrasound* 1995;23:461-71.
464. Jahnke T, Link J, Muller-Hulsbeck S, et al. Treatment of infrapopliteal occlusive disease by high-speed rotational atherectomy: initial and mid-term results. *J Vasc Interv Radiol* 2001;12:221-6.
465. Belli AM, Cumberland DC, Procter AE, et al. Follow-up of conventional angioplasty versus laser thermal angioplasty for total femoropopliteal artery occlusions: results of a randomized trial. *J Vasc Interv Radiol* 1991;2:485-8.
466. Fisher CM, Fletcher JP, May J, et al. No additional benefit from laser in balloon angioplasty of the superficial femoral artery. *Eur J Vasc Endovasc Surg* 1996;11:349-52.
467. Jeans WD, Murphy P, Hughes AO, et al. Randomized trial of laser-assisted passage through occluded femoro-popliteal arteries. *Br J Radiol* 1990;63:19-21.
468. Lammer J, Pilger E, Decrinis M, et al. Pulsed excimer laser versus continuous-wave Nd:YAG laser versus conventional angioplasty of peripheral arterial occlusions: prospective, controlled, randomised trial. *Lancet* 1992;340:1183-8.
469. Minar E, Pokrajac B, Maca T, et al. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: results of a prospective randomized study. *Circulation* 2000;102:2694-9.
470. Waksman R, Laird JR, Jurkovitz CT, et al. Intravascular radiation therapy after balloon angioplasty of narrowed femoropopliteal arteries to prevent restenosis: results of the PARIS feasibility clinical trial. *J Vasc Interv Radiol* 2001;12:915-21.
471. Sidawy AN, Weiswasser JM, Waksman R. Peripheral vascular brachytherapy. *J Vasc Surg* 2002;35:1041-7.
472. Zehnder T, von Briel C, Baumgartner I, et al. Endovascular brachytherapy after percutaneous transluminal angioplasty of recurrent femoropopliteal obstructions. *J Endovasc Ther* 2003;10:304-11.
473. Krueger K, Landwehr P, Bendel M, et al. Endovascular gamma irradiation of femoropopliteal de novo stenoses immediately after PTA: interim results of prospective randomized controlled trial. *Radiology* 2002;224:519-28.
474. Jahnke T, Andresen R, Muller-Hulsbeck S, et al. Hemobahn stent-grafts for treatment of femoropopliteal arterial obstructions: midterm results of a prospective trial. *J Vasc Interv Radiol* 2003;14:41-51.
475. Saxon RR, Coffman JM, Gooding JM, et al. Long-term results of ePTFE stent-graft versus angioplasty in the femoropopliteal artery: single center experience from a prospective, randomized trial. *J Vasc Interv Radiol* 2003;14:303-11.
476. Duda SH, Poerner TC, Wiesinger B, et al. Drug-eluting stents:

- potential applications for peripheral arterial occlusive disease. *J Vasc Interv Radiol* 2003;14:291-301.
477. Duda SH, Pusich B, Richter G, et al. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results. *Circulation* 2002;106:1505-9.
 478. Girolami B, Bernardi E, Prins MH, et al. Antiplatelet therapy and other interventions after revascularisation procedures in patients with peripheral arterial disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2000;19:370-80.
 479. Watson HR, Bergqvist D. Antithrombotic agents after peripheral transluminal angioplasty: a review of the studies, methods and evidence for their use. *Eur J Vasc Endovasc Surg* 2000;19:445-50.
 480. Timaran CH, Prault TL, Stevens SL, et al. Iliac artery stenting versus surgical reconstruction for TASC (TransAtlantic Inter-Society Consensus) type B and type C iliac lesions. *J Vasc Surg* 2003;38:272-8.
 481. Reed AB, Conte MS, Donaldson MC, et al. The impact of patient age and aortic size on the results of aortobifemoral bypass grafting. *J Vasc Surg* 2003;37:1219-25.
 482. Olsen PS, Gustafsen J, Rasmussen L, et al. Long-term results after arterial surgery for arteriosclerosis of the lower limbs in young adults. *Eur J Vasc Surg* 1988;2:15-8.
 483. Green RM, Abbott WM, Matsumoto T, et al. Prosthetic above-knee femoropopliteal bypass grafting: five-year results of a randomized trial. *J Vasc Surg* 2000;31:417-25.
 484. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;105:1257-67.
 485. de Vries SO, Hunink MG. Results of aortic bifurcation grafts for aortoiliac occlusive disease: a meta-analysis. *J Vasc Surg* 1997;26:558-69.
 486. van der Vliet JA, Scharn DM, de Waard JW, et al. Unilateral vascular reconstruction for iliac obstructive disease. *J Vasc Surg* 1994;19:610-4.
 487. Ricco JB. Unilateral iliac artery occlusive disease: a randomized multicenter trial examining direct revascularization versus crossover bypass. *Association Universitaire de Recherche en Chirurgie. Ann Vasc Surg* 1992;6:209-19.
 488. Raptis S, Faris I, Miller J, et al. The fate of the aortofemoral graft. *Eur J Vasc Endovasc Surg* 1995;9:97-102.
 489. Oskam J, van den Dungen JJ, Boontje AH. Thromboendarterectomy for obstructive disease of the common iliac artery. *Cardiovasc Surg* 1996;4:356-9.
 490. Pretre R, Katchaturian G, Bednarkiewicz M, et al. Aortoiliac endarterectomy: a 9-year experience. *Thorac Cardiovasc Surg* 1992;40:152-4.
 491. Radoux JM, Maiza D, Coffin O. Long-term outcome of 121 iliofemoral endarterectomy procedures. *Ann Vasc Surg* 2001;15:163-70.
 492. Mingoli A, Sapienza P, Feldhaus RJ, et al. Comparison of femorofemoral and aortofemoral bypass for aortoiliac occlusive disease. *J Cardiovasc Surg (Torino)* 2001;42:381-7.
 493. Mohan CR, Sharp WJ, Hoballah JJ, et al. A comparative evaluation of externally supported polytetrafluoroethylene axillofemoral and axillounifemoral bypass grafts. *J Vasc Surg* 1995;21:801-8; discussion 808-9.
 494. Harrington ME, Harrington EB, Haimov M, et al. Axillofemoral bypass: compromised bypass for compromised patients. *J Vasc Surg* 1994;20:195-201.
 495. Onohara T, Komori K, Kume M, et al. Multivariate analysis of long-term results after an axillobifemoral and aortobifemoral bypass in patients with aortoiliac occlusive disease. *J Cardiovasc Surg (Torino)* 2000;41:905-10.
 496. Martin D, Katz SG. Axillofemoral bypass for aortoiliac occlusive disease. *Surg Gynecol Obstet* 2000;180:100-3.
 497. Faries PL, LoGerfo FW, Hook SC, et al. The impact of diabetes on arterial reconstructions for multilevel arterial occlusive disease. *Surg Gynecol Obstet* 2001;181:251-5.
 498. Archie JP Jr. Femoropopliteal bypass with either adequate ipsilateral reversed saphenous vein or obligatory polytetrafluoroethylene. *Ann Vasc Surg* 1994;8:475-84.
 499. Nicoloff AD, Taylor LM Jr, McLafferty RB, et al. Patient recovery after infrainguinal bypass grafting for limb salvage. *J Vasc Surg* 1998;27:256-63; discussion 264-6.
 500. Gentile AT, Lee RW, Moneta GL, et al. Results of bypass to the popliteal and tibial arteries with alternative sources of autogenous vein. *J Vasc Surg* 1996;23:272-9; discussion 279-80.
 - 500a. Allen BT, Reilly JM, Rubin BG, et al. Femoropopliteal bypass for claudication: vein vs. PTFE. *Ann Vasc Surg* 1996;10:178-85.
 501. Taylor LM Jr, Edwards JM, Porter JM. Present status of reversed vein bypass grafting: five-year results of a modern series. *J Vasc Surg* 1990;11:193-205; discussion 205-6.
 502. Schweiger H, Klein P, Lang W. Tibial bypass grafting for limb salvage with ringed polytetrafluoroethylene prostheses: results of primary and secondary procedures. *J Vasc Surg* 1993;18:867-74.
 503. Londrey GL, Ramsey DE, Hodgson KJ, et al. Infrapopliteal bypass for severe ischemia: comparison of autogenous vein, composite, and prosthetic grafts. *J Vasc Surg* 1991;13:631-6.
 504. McCarthy WJ, Pearce WH, Flinn WR, et al. Long-term evaluation of composite sequential bypass for limb-threatening ischemia. *J Vasc Surg* 1992;15:761-9; discussion 769-70.
 505. Desai TR, Meyerson SL, Skelly CL, et al. Patency and limb salvage after infrainguinal bypass with severely compromised ("blind") outflow. *Arch Surg* 2001;136:635-42.
 506. Towne JB, Bernhard VM, Rollins DL, et al. Profundaplasty in perspective: limitations in the long-term management of limb ischemia. *Surgery* 1981;90:1037-46.
 507. Kalman PG, Johnston KW, Walker PM. The current role of isolated profundaplasty. *J Cardiovasc Surg (Torino)* 1990;31:107-11.
 508. AbuRahma AF, Robinson PA, Holt SM. Prospective controlled study of polytetrafluoroethylene versus saphenous vein in claudicant patients with bilateral above knee femoropopliteal bypasses. *Surgery* 1999;126:594-601; discussion 601-2.
 509. Johnson WC, Lee KK. A comparative evaluation of polytetrafluoroethylene, umbilical vein, and saphenous vein bypass grafts for femoral-popliteal above-knee revascularization: a prospective randomized Department of Veterans Affairs cooperative study. *J Vasc Surg* 2000;32:268-77.
 510. Klinkert P, Schepers A, Burger DH, et al. Vein versus polytetrafluoroethylene in above-knee femoropopliteal bypass grafting: five-year results of a randomized controlled trial. *J Vasc Surg* 2003;37:149-55.
 511. Baldwin ZK, Pearce BJ, Curi MA, et al. Limb salvage after infrainguinal bypass graft failure. *J Vasc Surg* 2004;39:951-7.
 512. Veith FJ, Gupta SK, Ascer E, et al. Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. *J Vasc Surg* 1986;3:104-14.
 513. Brothers TE, Greenfield LJ. Long-term results of aortoiliac reconstruction. *J Vasc Interv Radiol* 1990;1:49-55.

514. Criado E, Burnham SJ, Tinsley EA Jr, et al. Femorofemoral bypass graft: analysis of patency and factors influencing long-term outcome. *J Vasc Surg* 1993;18:495-504; discussion 504-5.
515. Perler BA, Williams GM. Does donor iliac artery percutaneous transluminal angioplasty or stent placement influence the results of femorofemoral bypass? Analysis of 70 consecutive cases with long-term follow-up. *J Vasc Surg* 1996;24:363-9; discussion 369-70.
516. Szilagyi DE, Elliott JP Jr, Smith RF, et al. A thirty-year survey of the reconstructive surgical treatment of aortoiliac occlusive disease. *J Vasc Surg* 1986;3:421-36.
517. Johnson WC, Lee KK. Comparative evaluation of externally supported Dacron and polytetrafluoroethylene prosthetic bypasses for femorofemoral and axillofemoral arterial reconstructions. Veterans Affairs Cooperative Study #141. *J Vasc Surg* 1999;30:1077-83.
518. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26:517-38. Erratum in: *J Vasc Surg* 2001;33:805.
519. Intravenous pentoxifylline for the treatment of chronic critical limb ischaemia. The European Study Group. *Eur J Vasc Endovasc Surg* 1995;9:426-36.
520. Efficacy and clinical tolerance of parenteral pentoxifylline in the treatment of critical lower limb ischemia: a placebo controlled multicenter study. Norwegian Pentoxifylline Multicenter Trial Group. *Int Angiol* 1996;15:75-80.
521. Nizankowski R, Krolkowski W, Bielawicz J, et al. Prostacyclin for ischemic ulcers in peripheral arterial disease: a random assignment, placebo controlled study. *Thromb Res* 1985;37:21-8.
522. Negus D, Irving JD, Friedgood A. Intra-arterial prostacyclin compared to Praxilene in the management of severe lower limb ischaemia: a double blind trial. *J Cardiovasc Surg (Torino)* 1987;28:196-9.
523. Eklund AE, Eriksson G, Olsson AG. A controlled study showing significant short term effect of prostaglandin E1 in healing of ischaemic ulcers of the lower limb in man. *Prostaglandins Leukot Med* 1982;8:265-71.
524. Schuler JJ, Flanagan DP, Holcroft JW, et al. Efficacy of prostaglandin E1 in the treatment of lower extremity ischemic ulcers secondary to peripheral vascular occlusive disease: results of a prospective randomized, double-blind, multicenter clinical trial. *J Vasc Surg* 1984;1:160-70.
525. Telles GS, Campbell WB, Wood RF, et al. Prostaglandin E1 in severe lower limb ischaemia: a double-blind controlled trial. *Br J Surg* 1984;71:506-8.
526. Belch JJ, McKay A, McArdle B, et al. Epoprostenol (prostacyclin) and severe arterial disease: a double-blind trial. *Lancet* 1983;1:315-7.
527. Cronenwett JL, Zelenock GB, Whitehouse WM Jr, et al. Prostacyclin treatment of ischemic ulcers and rest pain in unreconstructible peripheral arterial occlusive disease. *Surgery* 1986;100:369-75.
528. Trubestein G, Diehm C, Gruss JD, et al. Prostaglandin E1 in chronic arterial disease—a multicenter study. *Vasa Suppl* 1987;17:39-43.
529. The effect of ciprostone in patients with peripheral vascular disease (PVD) characterized by ischemic ulcers. The Ciprostone Study Group. *J Clin Pharmacol* 1991;31:81-7.
530. Prostanoids for chronic critical leg ischemia. A randomized, controlled, open-label trial with prostaglandin E1. The ICAI Study Group. *Ischemia Cronica degli Arti Inferiori. Ann Intern Med* 1999;130:412-21.
531. Trubestein G, von Bary S, Breddin K, et al. Intravenous prostaglandin E1 versus pentoxifylline therapy in chronic arterial occlusive disease—a controlled randomised multicenter study. *Vasa Suppl* 1989;28:44-9.
532. Balzer K, Bechara G, Bisler H, et al. Reduction of ischaemic rest pain in advanced peripheral arterial occlusive disease: a double blind placebo controlled trial with iloprost. *Int Angiol* 1991;10:229-32.
533. Diehm C, Abri O, Baitsch G, et al. [Iloprost, a stable prostacyclin derivative, in stage 4 arterial occlusive disease: a placebo-controlled multicenter study] *Dtsch Med Wochenschr* 1989;114:783-8.
534. Norgren L, Alwmark A, Angqvist KA, et al. A stable prostacyclin analogue (iloprost) in the treatment of ischaemic ulcers of the lower limb: a Scandinavian-Polish placebo controlled, randomised multicenter study. *Eur J Vasc Surg* 1990;4:463-7.
535. Brock FE, Abri O, Baitsch G, et al. [Iloprost in the treatment of ischemic tissue lesions in diabetics: results of a placebo-controlled multicenter study with a stable prostacyclin derivative] *Schweiz Med Wochenschr* 1990;120:1477-82.
536. Treatment of limb threatening ischaemia with intravenous iloprost: a randomised double-blind placebo controlled study. U.K. Severe Limb Ischaemia Study Group. *Eur J Vasc Surg* 1991;5:511-6.
537. Two randomised and placebo-controlled studies of an oral prostacyclin analogue (Iloprost) in severe leg ischaemia. The Oral Iloprost in severe Leg Ischaemia Study Group. *Eur J Vasc Endovasc Surg* 2000;20:358-62.
538. Isner JM, Walsh K, Symes J, et al. Arterial gene therapy for therapeutic angiogenesis in patients with peripheral artery disease. *Circulation* 1995;91:2687-92.
539. Isner JM, Pieczek A, Schainfeld R, et al. Clinical evidence of angiogenesis after arterial gene transfer of phVEGF165 in patient with ischaemic limb. *Lancet* 1996;348:370-4.
540. Isner JM. Arterial gene transfer of naked DNA for therapeutic angiogenesis: early clinical results. *Adv Drug Deliv Rev* 1998;30(1-3):185-97.
541. Baumgartner I, Pieczek A, Manor O, et al. Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation* 1998;97:1114-23.
542. Nasr MK, McCarthy RJ, Hardman J, et al. The increasing role of percutaneous transluminal angioplasty in the primary management of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2002;23:398-403.
543. Isner JM, Rosenfield K. Redefining the treatment of peripheral artery disease: role of percutaneous revascularization. *Circulation* 1993;88(4 pt 1):1534-57.
544. Durham JR, Horowitz JD, Wright JG, et al. Percutaneous transluminal angioplasty of tibial arteries for limb salvage in the high-risk diabetic patient. *Ann Vasc Surg* 1994;8:48-53.
545. Isner JM, Pieczek A, Rosenfield K. Images in cardiovascular medicine: untreated gangrene in patients with peripheral artery disease. *Circulation* 1994;89:482-3.
546. Gray BH, Laird JR, Ansel GM, et al. Complex endovascular treatment for critical limb ischemia in poor surgical candidates: a pilot study. *J Endovasc Ther* 2002;9:599-604.
547. Faglia E, Mantero M, Caminiti M, et al. Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. *J Intern Med* 2002;252:225-32.

548. Ingle H, Nasim A, Bolia A, et al. Subintimal angioplasty of isolated infragenicular vessels in lower limb ischemia: long-term results. *J Endovasc Ther* 2002;9:411-6. Erratum in: *J Endovasc Ther* 2002;9:A-6.
549. Gordon IL, Conroy RM, Arefi M, et al. Three-year outcome of endovascular treatment of superficial femoral artery occlusion. *Arch Surg* 2001;136:221-8.
550. Spence LD, Hartnell GG, Reinking G, et al. Diabetic versus non-diabetic limb-threatening ischemia: outcome of percutaneous iliac intervention. *AJR Am J Roentgenol* 1999;172:1335-41.
551. Marzelle J, Fichelle JM, Cormier F, et al. Outcome of infringuinal endovascular revascularization procedures for limb-threatening ischemia. *Ann Vasc Surg* 1995;9 suppl:S24-31.
552. Bernstein EF, Rhodes GA, Stuart SH, et al. Toe pulse reappearance time in prediction of aortofemoral bypass success. *Ann Surg* 1981;193:201-5.
553. Bakal CW, Cynamon J, Sprayregen S. Infrapopliteal percutaneous transluminal angioplasty: what we know. *Radiology* 1996;200:36-43.
554. Berridge DC, Gregson RH, Hopkinson BR, et al. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis. *Br J Surg* 1991;78:988-95.
555. Graor RA, Risius B, Young JR, et al. Thrombolysis of peripheral arterial bypass grafts: surgical thrombectomy compared with thrombolysis: a preliminary report. *J Vasc Surg* 1988;7:347-55.
556. Ouriel K, Kandarpa K, Schuerr DM, et al. Prourokinase versus urokinase for recanalization of peripheral occlusions, safety and efficacy: the PURPOSE trial. *J Vasc Interv Radiol* 1999;10:1083-91.
557. Mahler F, Schneider E, Hess H; Steering Committee. Study on Local Thrombolysis. Recombinant tissue plasminogen activator versus urokinase for local thrombolysis of femoropopliteal occlusions: a prospective, randomized multicenter trial. *J Endovasc Ther* 2001;8:638-47.
558. Khosla S, Jain P, Manda R, et al. Acute and long-term results after intra-arterial thrombolysis of occluded lower extremity bypass grafts using recombinant tissue plasminogen activator for acute limb-threatening ischemia. *Am J Ther* 2003;10:3-6.
559. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg* 1994;19:1021-30.
560. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg* 1994;220:251-66; discussion 266-8.
561. Weaver FA, Comerota AJ, Youngblood M, et al. Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: results of a prospective randomized trial. The STILE Investigators. Surgery versus Thrombolysis for Ischemia of the Lower Extremity. *J Vasc Surg* 1996;24:513-21; discussion 521-3.
562. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med* 1998;338:1105-11.
563. Diffin DC, Kandarpa K. Assessment of peripheral intraarterial thrombolysis versus surgical revascularization in acute lower-limb ischemia: a review of limb-salvage and mortality statistics. *J Vasc Interv Radiol* 1996;7:57-63.
564. van Breda A, Katzen BT, Deutsch AS. Urokinase versus streptokinase in local thrombolysis. *Radiology* 1987;165:109-11.
565. Traugher PD, Cook PS, Micklos TJ, et al. Intraarterial fibrinolytic therapy for popliteal and tibial artery obstruction: comparison of streptokinase and urokinase. *AJR Am J Roentgenol* 1987;149:453-6.
566. Arepally A, Hofmann LV, Kim HS, et al. Weight-based rt-PA thrombolysis protocol for acute native arterial and bypass graft occlusions. *J Vasc Interv Radiol* 2002;13:45-50.
567. Swischuk JL, Fox PF, Young K, et al. Transcatheter intraarterial infusion of rt-PA for acute lower limb ischemia: results and complications. *J Vasc Interv Radiol* 2001;12:423-30.
568. Semba CP, Murphy TP, Bakal CW, et al. Thrombolytic therapy with use of alteplase (rt-PA) in peripheral arterial occlusive disease: review of the clinical literature. The Advisory Panel. *J Vasc Interv Radiol* 2000;11(2 pt 1):149-61.
569. Shortell CK, Queiroz R, Johansson M, et al. Safety and efficacy of limited-dose tissue plasminogen activator in acute vascular occlusion. *J Vasc Surg* 2001;34:854-9.
570. Braithwaite BD, Buckenham TM, Galland RB, et al. Prospective randomized trial of high-dose bolus versus low-dose tissue plasminogen activator infusion in the management of acute limb ischaemia. Thrombolysis Study Group. *Br J Surg* 1997;84:646-50.
571. Ouriel K, Gray B, Clair DG, et al. Complications associated with the use of urokinase and recombinant tissue plasminogen activator for catheter-directed peripheral arterial and venous thrombolysis. *J Vasc Interv Radiol* 2000;11:295-8.
572. Schweizer J, Altmann E, Stosslein F, et al. Comparison of tissue plasminogen activator and urokinase in the local infiltration thrombolysis of peripheral arterial occlusions. *Eur J Radiol* 1996;22:129-32.
573. Ouriel K, Katzen B, Mewissen M, et al. Reteplase in the treatment of peripheral arterial and venous occlusions: a pilot study. *J Vasc Interv Radiol* 2000;11:849-54.
574. Davidian MM, Powell A, Benenati JF, et al. Initial results of reteplase in the treatment of acute lower extremity arterial occlusions. *J Vasc Interv Radiol* 2000;11:289-94.
575. Castaneda F, Swischuk JL, Li R, et al. Declining-dose study of reteplase treatment for lower extremity arterial occlusions. *J Vasc Interv Radiol* 2002;13:1093-8.
576. Burkart DJ, Borsa JJ, Anthony JP, et al. Thrombolysis of occluded peripheral arteries and veins with tenecteplase: a pilot study. *J Vasc Interv Radiol* 2002;13:1099-102.
577. Meyerovitz MF, Goldhaber SZ, Reagan K, et al. Recombinant tissue-type plasminogen activator versus urokinase in peripheral arterial and graft occlusions: a randomized trial. *Radiology* 1990;175:75-8.
578. Cina CS, Goh RH, Chan J, et al. Intraarterial catheter-directed thrombolysis: urokinase versus tissue plasminogen activator. *Ann Vasc Surg* 1999;13:571-5.
579. Sugimoto K, Hofmann LV, Razavi MK, et al. The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. *J Vasc Surg* 2003;37:512-7.
580. Drescher P, McGuckin J, Rilling WS, et al. Catheter-directed thrombolytic therapy in peripheral artery occlusions: combining reteplase and abciximab. *AJR Am J Roentgenol* 2003;180:1385-91.
581. Burkart DJ, Borsa JJ, Anthony JP, et al. Thrombolysis of acute peripheral arterial and venous occlusions with tenecteplase and eptifibatide: a pilot study. *J Vasc Interv Radiol* 2003;14:729-33.
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

- Thrombosis. *Radiology* 2001;221:689-96.
583. Yoon HC, Miller FJ Jr. Using a peptide inhibitor of the glycoprotein IIb/IIIa platelet receptor: initial experience in patients with acute peripheral arterial occlusions. *AJR Am J Roentgenol* 2002;178:617-22.
 584. Silva JA, Ramee SR, Collins TJ, et al. Rheolytic thrombectomy in the treatment of acute limb-threatening ischemia: immediate results and six-month follow-up of the multicenter AngioJet registry. *Possis Peripheral AngioJet Study AngioJet Investigators. Cathet Cardiovasc Diagn* 1998;45:386-93.
 585. Kasirajan K, Haskal ZJ, Ouriel K. The use of mechanical thrombectomy devices in the management of acute peripheral arterial occlusive disease. *J Vasc Interv Radiol* 2001;12:405-11.
 586. Hopfner W, Vicol C, Bohndorf K, et al. Shredding embolectomy thrombectomy catheter for treatment of acute lower-limb ischemia. *Ann Vasc Surg* 1999;13:426-35.
 587. Muller-Hulsbeck S, Kalinowski M, Heller M, et al. Rheolytic hydrodynamic thrombectomy for percutaneous treatment of acutely occluded infra-aortic native arteries and bypass grafts: midterm follow-up results. *Invest Radiol* 2000;35:131-40.
 588. Kasirajan K, Gray B, Beavers FP, et al. Rheolytic thrombectomy in the management of acute and subacute limb-threatening ischemia. *J Vasc Interv Radiol* 2001;12:413-21.
 589. Wagner HJ, Muller-Hulsbeck S, Pitton MB, et al. Rapid thrombectomy with a hydrodynamic catheter: results from a prospective, multicenter trial. *Radiology* 1997;205:675-81.
 590. Reekers JA, Kromhout JG, Spithoven HG, et al. Arterial thrombosis below the inguinal ligament: percutaneous treatment with a thrombosuction catheter. *Radiology* 1996;198:49-53.
 591. Henry M, Amor M, Henry I, et al. The Hydrolyser thrombectomy catheter: a single-center experience. *J Endovasc Surg* 1998;5:24-31.
 592. Rilinger N, Gorich J, Scharrer-Pamler R, et al. Short-term results with use of the Amplatz thrombectomy device in the treatment of acute lower limb occlusions. *J Vasc Interv Radiol* 1997;8:343-8.
 593. Tadavarthy SM, Murray PD, Inampudi S, et al. Mechanical thrombectomy with the Amplatz device: human experience. *J Vasc Interv Radiol* 1994;5:715-24.
 594. Gorich J, Rilinger N, Sokiranski R, et al. Mechanical thrombolysis of acute occlusion of both the superficial and the deep femoral arteries using a thrombectomy device. *AJR Am J Roentgenol* 1998;170:1177-80.
 - 594a. Haskal ZJ. Mechanical thrombectomy devices for the treatment of peripheral arterial occlusions. *Rev Cardiovasc Med* 2002;3 Suppl 2:S45-S52.
 595. Schneider JR, Besso SR, Walsh DB, et al. Femorofemoral versus aortobifemoral bypass: outcome and hemodynamic results. *J Vasc Surg* 1994;19:43-55; discussion 55-7.
 596. Hobson RW 2nd, Lynch TG, Jamil Z, et al. Results of revascularization and amputation in severe lower extremity ischemia: a five-year clinical experience. *J Vasc Surg* 1985;2:174-85.
 597. Schina MJ Jr, Atnip RG, Healy DA, et al. Relative risks of limb revascularization and amputation in the modern era. *Cardiovasc Surg* 1994;2:754-9.
 598. Dawson I, Keller BP, Brand R, et al. Late outcomes of limb loss after failed infrainguinal bypass. *J Vasc Surg* 1995;21:613-22.
 599. Moller BN, Solund K, Hansen SL. Wound infection after lower extremity amputation because of ischemia. *Arch Orthop Trauma Surg* 1985;104:262-4.
 600. Cutson TM, Bongiorno DR. Rehabilitation of the older lower limb amputee: a brief review. *J Am Geriatr Soc* 1996;44:1388-93.
 601. Propanolol Aneurysm Trial Investigators. Propanolol for small abdominal aortic aneurysms: results of a randomized trial. *J Vasc Surg* 2002;35:72-9.
 602. Kalman PG, Hosang M, Johnston KW, et al. Unilateral iliac disease: the role of iliofemoral bypass. *J Vasc Surg* 1987;6:139-43.
 603. Ng RL, Gillies TE, Davies AH, et al. Iliofemoral versus femorofemoral bypass: a 6-year audit. *Br J Surg* 1992;79:1011-3.
 604. Naylor AR, Ah-See AK, Engeset J. Axillofemoral bypass as a limb salvage procedure in high risk patients with aortoiliac disease. *Br J Surg* 1990;77:659-61.
 605. Ascer E, Veith FJ, Gupta SK, et al. Comparison of axilofemoral and axillobifemoral bypass operations. *Surgery* 1985;97:169-75.
 606. Shah DM, Darling RC 3rd, Chang BB, et al. Is long vein bypass from groin to ankle a durable procedure? An analysis of a ten-year experience. *J Vasc Surg* 1992;15:402-7; discussion 407-8.
 607. Pomposelli FB Jr, Maccaccio EJ, Gibbons GW, et al. Dorsalis pedis arterial bypass: durable limb salvage for foot ischemia in patients with diabetes mellitus. *J Vasc Surg* 1995;21:375-84.
 608. Roddy SP, Darling RC 3rd, Ozsvath KJ, et al. Composite sequential arterial reconstruction for limb salvage. *J Vasc Surg* 2002;36:325-9.
 609. Johnson WC, Williford WO; Department of Veterans Affairs Cooperative Study #362. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg* 2002;35:413-21.
 610. Hamdan AD, Rayan SS, Hook SC, et al. Bypasses to tibial vessels using polytetrafluoroethylene as the solo conduit in a predominantly diabetic population. *Vasc Endovascular Surg* 2002;36:59-63.
 611. Henke PK, Blackburn S, Proctor MC, et al. Patients undergoing infrainguinal bypass to treat atherosclerotic vascular disease are underprescribed cardioprotective medications: effect on graft patency, limb salvage, and mortality. *J Vasc Surg* 2004;39:357-65.
 612. Holley KE, Hunt JC, Brown AL Jr, et al. Renal artery stenosis: a clinical-pathologic study in normotensive and hypertensive patients. *Am J Med* 1964;37:14-22.
 613. Dustan HP, Humphries AW, Dewolfe VG, et al. Normal arterial pressure in patients with renal arterial stenosis. *JAMA* 1964;187:1028-9.
 614. Scoble JE. The epidemiology and clinical manifestations of atherosclerotic renal disease. In: Novick AC, Scoble JE, Hamilton G, eds. *Renal Vascular Disease*. London, UK: WB Saunders Co, Ltd; 1996:303-14.
 615. Uzu T, Inoue T, Fujii T, et al. Prevalence and predictors of renal artery stenosis in patients with myocardial infarction. *Am J Kidney Dis* 1997;29:733-8.
 616. Wilms G, Marchal G, Peene P, et al. The angiographic incidence of renal artery stenosis in the arteriosclerotic population. *Eur J Radiol* 1990;10:195-7.
 617. Choudhri AH, Cleland JG, Rowlands PC, et al. Unsuspected renal artery stenosis in peripheral vascular disease. *BMJ* 1990;301:1197-8.
 618. Swartbol P, Thorvinger BO, Parsson H, et al. Renal artery stenosis in patients with peripheral vascular disease and its correlation to hypertension: a retrospective study. *Int Angiol* 1992;11:195-9.
 619. Missouri CG, Papavassiliou MB, Khaw K, et al. High prevalence of carotid artery disease in patients with atheromatous renal artery stenosis. *Nephrol Dial Transplant* 1998;13:945-8.
 620. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg* 2002;36:443-51.
 621. Harding MB, Smith LR, Himmelstein SI, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing

- routine cardiac catheterization. *J Am Soc Nephrol* 1992;2:1608-16.
622. Weber-Mzell D, Kotanko P, Schumacher M, et al. Coronary anatomy predicts presence or absence of renal artery stenosis: a prospective study in patients undergoing cardiac catheterization for suspected coronary artery disease. *Eur Heart J* 2002;23:1684-91.
623. Jean WJ, al-Bitar I, Zwicke DL, et al. High incidence of renal artery stenosis in patients with coronary artery disease. *Cathet Cardiovasc Diagn* 1994;32:8-10.
624. Missouris CG, Buckenham T, Cappuccio FP, et al. Renal artery stenosis: a common and important problem in patients with peripheral vascular disease. *Am J Med* 1994;96:10-4.
625. Olin JW, Melia M, Young JR, et al. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med* 1990;88(1N):46N-51N.
626. Louie J, Isaacson JA, Zierler RE, et al. Prevalence of carotid and lower extremity arterial disease in patients with renal artery stenosis. *Am J Hypertens* 1994;7:436-9.
627. Zierler RE, Bergelin RO, Polissar NL, et al. Carotid and lower extremity arterial disease in patients with renal artery atherosclerosis. *Arch Intern Med* 1998;158:761-7.
628. Rossi GP, Rossi A, Zanin L, et al. Excess prevalence of extracranial carotid artery lesions in renovascular hypertension. *Am J Hypertens* 1992;5:8-15.
629. Metcalfe W, Reid AW, Geddes CC. Prevalence of angiographic atherosclerotic renal artery disease and its relationship to the anatomical extent of peripheral vascular atherosclerosis. *Nephrol Dial Transplant* 1999;14:105-8.
630. Valentine RJ, Clagett GP, Miller GL, et al. The coronary risk of unsuspected renal artery stenosis. *J Vasc Surg* 1993;18:433-9; discussion 439-40.
631. Schwartz CJ, White TA. Stenosis of renal artery: an unselected necropsy study. *Br Med J* 1964;5422:1415-21.
632. Rimmer JM, Gennari FJ. Atherosclerotic renovascular disease and progressive renal failure. *Ann Intern Med* 1993;118:712-9.
633. Wollenweber J, Sheps SG, Davis GD. Clinical course of atherosclerotic renovascular disease. *Am J Cardiol* 1968;21:60-71.
634. Meaney TF, Dustan HP, McCormack LJ. Natural history of renal arterial disease. *Radiology* 1968;91:881-7.
635. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. *Urol Clin North Am* 1984;11:383-92.
636. Tollefson DF, Ernst CB. Natural history of atherosclerotic renal artery stenosis associated with aortic disease. *J Vasc Surg* 1991;14:327-31.
637. Dean RH, Kieffer RW, Smith BM, et al. Renovascular hypertension: anatomic and renal function changes during drug therapy. *Arch Surg* 1981;116:1408-15.
638. Zierler RE, Bergelin RO, Davidson RC, et al. A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. *Am J Hypertens* 1996;9:1055-61.
639. Caps MT, Perissinotto C, Zierler RE, et al. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation* 1998;98:2866-72.
640. Mailloux LU, Napolitano B, Bellucci AG, et al. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am J Kidney Dis* 1994;24:622-9.
641. Guzman RP, Zierler RE, Isaacson JA, et al. Renal atrophy and arterial stenosis. A prospective study with duplex ultrasound. *Hypertension* 1994;23:346-50.
642. Caps MT, Zierler RE, Polissar NL, et al. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. *Kidney Int* 1998;53:735-42.
643. Crowley JJ, Santos RM, Peter RH, et al. Progression of renal artery stenosis in patients undergoing cardiac catheterization. *Am Heart J* 1998;136:913-8.
644. Eggers PW, Connerton R, McMullan M. The Medicare experience with end-stage renal disease: trends in incidence, prevalence, and survival. *Health Care Financ Rev* 1984;5:69-88.
645. Mailloux LU, Bellucci AG, Mossey RT, et al. Predictors of survival in patients undergoing dialysis. *Am J Med* 1988;84:855-62.
646. Dorros G, Jaff M, Mathiak L, et al. Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. *Circulation* 1998;98:642-7.
647. Wright JR, Shurab AE, Cheung C, et al. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am J Kidney Dis* 2002;39:1153-61.
648. Gifford RW Jr, McCormack LJ, Poutasse EF. The atrophic kidney: its role in hypertension. *Mayo Clin Proc* 1965;40:834-52.
649. Packer M, Lee WH, Medina N, et al. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 1987;106:346-54.
650. Textor SC. Renal failure related to angiotensin-converting enzyme inhibitors. *Semin Nephrol* 1997;17:67-76.
651. Watson ML, Bell GM, Muir AL, et al. Captopril/diuretic combinations in severe renovascular disease: a cautionary note. *Lancet* 1983;2:404-5.
652. Hricik DE, Browning PJ, Kopelman R, et al. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. *N Engl J Med* 1983;308:373-6.
- 652a. Bakris GL, Weir MR. Angiotensin converting enzyme inhibitor-associated elevations in serum creatinine. *Arch Int Med* 2000;160:685-93.
653. Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med* 2001;344:431-42.
654. Luscher TF, Keller HM, Imhof HG, et al. Fibromuscular hyperplasia: extension of the disease and therapeutic outcome: results of the University Hospital Zurich Cooperative Study on Fibromuscular Hyperplasia. *Nephron* 1986;44 suppl 1:109-14.
655. Archibald GR, Beckmann CF, Libertino JA. Focal renal artery stenosis caused by fibromuscular dysplasia: treatment by percutaneous transluminal angioplasty. *AJR Am J Roentgenol* 1988;151:593-6.
656. Cluzel P, Raynaud A, Beyssen B, et al. Stenoses of renal branch arteries in fibromuscular dysplasia: results of percutaneous transluminal angioplasty. *Radiology* 1994;193:227-32.
657. Mounier-Vehier C, Haulon S, Devos P, et al. Renal atrophy outcome after revascularization in fibromuscular dysplasia disease. *J Endovasc Ther* 2002;9:605-13.
658. Stanley JC, Gewertz BL, Bove EL, et al. Arterial fibrodysplasia: histopathologic character and current etiologic concepts. *Arch Surg* 1975;110:561-6.
659. Stanley JC, Wakefield TW. Arterial fibrodysplasia. In: Rutherford RB, ed. *Vascular Surgery* 6th ed. Philadelphia, Pa: Saunders; 2004:387-408.
660. Messina LM, Stanley JC. Renal artery fibrodysplasia and renovascular hypertension. In: Rutherford RB, ed. *Vascular Surgery* 6th ed. Philadelphia, Pa: Saunders; 2004:1650-64.
661. Mettinger KL. Fibromuscular dysplasia and the brain. II. Current concept of the disease. *Stroke* 1982;13:53-8.
662. Cloft HJ, Kallmes DF, Kallmes MH, et al. Prevalence of cerebral aneurysms in patients with fibromuscular dysplasia: a reassess-

- ment. *J Neurosurg* 1998;88:436-40.
663. Abud O, Chechile GE, Sole-Balcells F. Aneurysm and arteriovenous malformation. In: Novick AC, Scoble JE, Hamilton G, eds. *Renal Vascular Disease*. London, UK: WB Saunders Co, Ltd; 1996:35-46.
664. Novick AC. Renal artery aneurysms and arteriovenous malformation. In: Novick AC, Straffon RA, eds. *Vascular Problems in Urologic Surgery*. Philadelphia, Pa: WB Saunders; 1982:189-204.
665. Poutasse EF. Renal artery aneurysms. *J Urol* 1975;113:443-9.
666. McCready RA, Hyde GL, Bivins BA, et al. Radiation-induced arterial injuries. *Surgery* 1983;93:306-12.
667. Guthaner DF, Schmitz L. Percutaneous transluminal angioplasty of radiation-induced arterial stenoses. *Radiology* 1982;144:77-8.
668. Andros G, Schneider PA, Harris RW, et al. Management of arterial occlusive disease following radiation therapy. *Cardiovasc Surg* 1996;4:135-42.
669. Ingelfinger JR, Newburger JW. Spectrum of renal anomalies in patients with Williams syndrome. *J Pediatr* 1991;119:771-3.
670. Booth C, Preston R, Clark G, et al. Management of renal vascular disease in neurofibromatosis type 1 and the role of percutaneous transluminal angioplasty. *Nephrol Dial Transplant* 2002;17:1235-40.
671. Courtel JV, Soto B, Niaudet P, et al. Percutaneous transluminal angioplasty of renal artery stenosis in children. *Pediatr Radiol* 1998;28:59-63.
672. Tyagi S, Singh B, Kaul UA, et al. Balloon angioplasty for renovascular hypertension in Takayasu's arteritis. *Am Heart J* 1993;125(5 pt 1):1386-93.
673. Teoh MK. Takayasu's arteritis with renovascular hypertension: results of surgical treatment. *Cardiovasc Surg* 1999;7:626-32.
674. Prigent A, Cosgriff P, Gates GF, et al. Consensus report on quality control of quantitative measurements of renal function obtained from the renogram: International Consensus Committee from the Scientific Committee of Radionuclides in Nephrourology. *Semin Nucl Med* 1999;29:146-59.
675. Nally JV Jr, Clarke HS Jr, Grecos GP, et al. Effect of captopril on 99mTc-diethylenetriaminepentaacetic acid renograms in two-kidney, one clip hypertension. *Hypertension* 1986;8:685-93.
676. Setaro JF, Saddler MC, Chen CC, et al. Simplified captopril renography in diagnosis and treatment of renal artery stenosis. *Hypertension* 1991;18:289-98.
677. Dondi M. Captopril renal scintigraphy with 99mTc-mercaptoacetyltriglycine (99mTc-MAG3) for detecting renal artery stenosis. *Am J Hypertens* 1991;4(12 pt 2):737S-740S.
678. Fommei E, Ghione S, Hilson AJ, et al. Captopril radionuclide test in renovascular hypertension: a European multicentre study. European Multicentre Study Group. *Eur J Nucl Med* 1993;20:617-23.
679. Geyskes GG, Oei HY, Puylaert CB, et al. Renography with captopril. Changes in a patient with hypertension and unilateral renal artery stenosis. *Arch Intern Med* 1986;146:1705-8.
680. Sfakianakis GN, Bourgoignie JJ, Jaffe D, et al. Single-dose captopril scintigraphy in the diagnosis of renovascular hypertension. *J Nucl Med* 1987;28:1383-92.
681. Erbsloh-Moller B, Dumas A, Roth D, et al. Furosemide-131I-hippuran renography after angiotensin-converting enzyme inhibition for the diagnosis of renovascular hypertension. *Am J Med* 1991;90:23-9.
682. Mann SJ, Pickering TG, Sos TA, et al. Captopril renography in the diagnosis of renal artery stenosis: accuracy and limitations. *Am J Med* 1991;90:30-40.
683. Elliott WJ, Martin WB, Murphy MB. Comparison of two noninvasive screening tests for renovascular hypertension. *Arch Intern Med* 1993;153:755-64.
684. van Jaarsveld BC, Krijnen P, Derkx FH, et al. The place of renal scintigraphy in the diagnosis of renal artery stenosis: fifteen years of clinical experience. *Arch Intern Med* 1997;157:1226-34.
685. Mittal BR, Kumar P, Arora P, et al. Role of captopril renography in the diagnosis of renovascular hypertension. *Am J Kidney Dis* 1996;28:209-13.
686. Huot SJ, Hansson JH, Dey H, et al. Utility of captopril renal scans for detecting renal artery stenosis. *Arch Intern Med* 2002;162:1981-4.
687. Carman TL, Olin JW. Diagnosis of renal artery stenosis: what is the optimal diagnostic test? *Curr Interv Cardiol Rep* 2000;2:111-8.
688. Olin JW. Role of duplex ultrasonography in screening for significant renal artery disease. *Urol Clin North Am* 1994;21:215-26.
689. Hoffmann U, Edwards JM, Carter S, et al. Role of duplex scanning for the detection of atherosclerotic renal artery disease. *Kidney Int* 1991;39:1232-9.
690. Kohler TR, Zierler RE, Martin RL, et al. Noninvasive diagnosis of renal artery stenosis by ultrasonic duplex scanning. *J Vasc Surg* 1986;4:450-6.
691. Taylor DC, Kettler MD, Moneta GL, et al. Duplex ultrasound scanning in the diagnosis of renal artery stenosis: a prospective evaluation. *J Vasc Surg* 1988;7:363-9.
692. Wilcox CS. Ischemic nephropathy: noninvasive testing. *Semin Nephrol* 1996;16:43-52.
693. Carman TL, Olin JW, Czum J. Noninvasive imaging of the renal arteries. *Urol Clin North Am* 2001;28:815-26.
694. Olin JW, Piedmonte MR, Young JR, et al. The utility of duplex ultrasound scanning of the renal arteries for diagnosing significant renal artery stenosis. *Ann Intern Med* 1995;122:833-8.
695. Hudspeth DA, Hansen KJ, Reavis SW, et al. Renal duplex sonography after treatment of renovascular disease. *J Vasc Surg* 1993;18:381-8; discussion 389-90.
696. Hansen KJ, Tribble RW, Reavis SW, et al. Renal duplex sonography: evaluation of clinical utility. *J Vasc Surg* 1990;12:227-36.
697. Kim SH, Kim WH, Choi BI, et al. Duplex Doppler US in patients with medical renal disease: resistive index vs serum creatinine level. *Clin Radiol* 1992;45:85-7.
698. Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001;344:410-7.
699. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* 2000;216:78-85.
700. van de Ven PJ, Kaatee R, Beutler JJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet* 1999;353:282-6.
701. Leertouwer TC, Derkx FH, Pattynama PM, et al. Functional effects of renal artery stent placement on treated and contralateral kidneys. *Kidney Int* 2002;62:574-9.
702. Zeller T, Muller C, Frank U, et al. Stent angioplasty of severe atherosclerotic ostial renal artery stenosis in patients with diabetes mellitus and nephrosclerosis. *Catheter Cardiovasc Interv* 2003;58:510-5.
703. Beregi JP, Elkohen M, Deklunder G, et al. Helical CT angiography compared with arteriography in the detection of renal artery stenosis. *AJR Am J Roentgenol* 1996;167:495-501.
704. Halpern EJ, Rutter CM, Gardiner GA Jr, et al. Comparison of Doppler US and CT angiography for evaluation of renal artery stenosis. *Acad Radiol* 1998;5:524-32.
705. Johnson PT, Halpern EJ, Kuszyk BS, et al. Renal artery stenosis: CT angiography—comparison of real-time volume-rendering and

- maximum intensity projection algorithms. *Radiology* 1999; 211:337-43.
706. Kim TS, Chung JW, Park JH, et al. Renal artery evaluation: comparison of spiral CT angiography to intra-arterial DSA. *J Vasc Interv Radiol* 1998;9:553-9.
707. Rubin GD, Dake MD, Napel S, et al. Spiral CT of renal artery stenosis: comparison of three-dimensional rendering techniques. *Radiology* 1994;190:181-9.
708. Kawashima A, Sandler CM, Ernst RD, et al. CT evaluation of renovascular disease. *Radiographics* 2000;20:1321-40.
709. Lufft V, Hoogstraat-Lufft L, Fels LM, et al. Contrast media nephropathy: intravenous CT angiography versus intraarterial digital subtraction angiography in renal artery stenosis: a prospective randomized trial. *Am J Kidney Dis* 2002;40:236-42.
710. Saloner D. Determinants of image appearance in contrast-enhanced magnetic resonance angiography: a review. *Invest Radiol* 1998;33:488-95.
711. Leung DA, Hoffmann U, Pfammatter T, et al. Magnetic resonance angiography versus duplex sonography for diagnosing renovascular disease. *Hypertension* 1999;33:726-31.
712. Loubeyre P, Trollet P, Cahen R, et al. MR angiography of renal artery stenosis: value of the combination of three-dimensional time-of-flight and three-dimensional phase-contrast MR angiography sequences. *AJR Am J Roentgenol* 1996;167:489-94.
713. Prince MR, Schoenberg SO, Ward JS, et al. Hemodynamically significant atherosclerotic renal artery stenosis: MR angiographic features. *Radiology* 1997;205:128-36.
714. Hany TF, Debatin JF, Leung DA, et al. Evaluation of the aortoiliac and renal arteries: comparison of breath-hold, contrast-enhanced, three-dimensional MR angiography with conventional catheter angiography. *Radiology* 1997;204:357-62.
715. Sueyoshi E, Sakamoto I, Matsuoka Y, et al. Aortoiliac and lower extremity arteries: comparison of three-dimensional dynamic contrast-enhanced subtraction MR angiography and conventional angiography. *Radiology* 1999;210:683-8.
716. Tan KT, van Beek EJ, Brown PW, et al. Magnetic resonance angiography for the diagnosis of renal artery stenosis: a meta-analysis. *Clin Radiol* 2002;57:617-24.
717. Mitsuzaki K, Yamashita Y, Sakaguchi T, et al. Abdomen, pelvis, and extremities: diagnostic accuracy of dynamic contrast-enhanced turbo MR angiography compared with conventional angiography-initial experience. *Radiology* 2000;216:909-15.
- 717a. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;105:2259-64.
- 717b. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* 1989;320:143-9.
718. Rundback JH, Sacks D, Kent KC, et al. Guidelines for the reporting of renal artery revascularization in clinical trials. American Heart Association. *Circulation* 2002;106:1572-85.
719. Leertouwer TC, Pattynama PM, van den Berg-Huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? *Kidney Int* 2001;59:1480-3.
720. Rihal CS, Textor SC, Breen JF, et al. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. *Mayo Clin Proc* 2002;77:309-16.
721. Rossi GP, Cesari M, Chiesura-Corona M, et al. Renal vein renin measurements accurately identify renovascular hypertension caused by total occlusion of the renal artery. *J Hypertens* 2002;20:975-84.
722. Hughes JS, Dove HG, Gifford RW Jr, et al. Duration of blood pressure elevation in accurately predicting surgical cure of renovascular hypertension. *Am Heart J* 1981;101:408-13.
723. Maxwell MH, Rudnick MR, Waks AU. New approaches to the diagnosis of renovascular hypertension. *Adv Nephrol Necker Hosp* 1985;14:285-304.
724. Plouin PF, Chatellier G, Darne B, et al. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. *Hypertension* 1998;31:823-9.
725. Webster J, Marshall F, Abdalla M, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. *J Hum Hypertens* 1998;12:329-35.
726. Nordmann AJ, Woo K, Parkes R, et al. Balloon angioplasty or medical therapy for hypertensive patients with atherosclerotic renal artery stenosis? A meta-analysis of randomized controlled trials. *Am J Med* 2003;114:44-50.
727. Plouin PF. Stable patients with atherosclerotic renal artery stenosis should be treated first with medical management. *Am J Kidney Dis* 2003;42:851-7.
728. Hollenberg NK. Medical therapy of renovascular hypertension: efficacy and safety of captopril in 269 patients. *Cardiovasc Rev Repl* 1983;4:852-76.
729. Vetrovec GW, Landwehr DM, Edwards VL. Incidence of renal artery stenosis in hypertensive patients undergoing coronary angiography. *J Interv Cardiol* 1989;2:69-76.
730. Conlon PJ, Little MA, Pieper K, et al. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int* 2001;60:1490-7.
731. Weibull H, Bergqvist D, Bergentz SE, et al. Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: a prospective randomized study. *J Vasc Surg* 1993;18:841-50; discussion 850-2.
732. van Jaarsveld BC, Krijnen P, Pieterman H, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med* 2000;342:1007-14.
733. Blum U, Krumme B, Flugel P, et al. Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty. *N Engl J Med* 1997;336:459-65.
734. Tuttle KR, Chouinard RF, Webber JT, et al. Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. *Am J Kidney Dis* 1998;32:611-22.
735. Henry M, Amor M, Henry I, et al. Stents in the treatment of renal artery stenosis: long-term follow-up. *J Endovasc Surg* 1999;6:42-51.
736. Rocha-Singh KJ, Mishkel GJ, Katholi RE, et al. Clinical predictors of improved long-term blood pressure control after successful stenting of hypertensive patients with obstructive renal artery atherosclerosis. *Catheter Cardiovasc Interv* 1999;47:167-72.
737. Dorros G, Jaff M, Jain A, et al. Follow-up of primary Palmaz-Schatz stent placement for atherosclerotic renal artery stenosis. *Am J Cardiol* 1995;75:1051-5.
738. White CJ, Ramee SR, Collins TJ, et al. Renal artery stent placement: utility in lesions difficult to treat with balloon angioplasty. *J Am Coll Cardiol* 1997;30:1445-50.
739. Lederman RJ, Mendelsohn FO, Santos R, et al. Primary renal artery stenting: characteristics and outcomes after 363 procedures. *Am Heart J* 2001;142:314-23.
740. Harjai K, Khosla S, Shaw D, et al. Effect of gender on outcomes following renal artery stent placement for renovascular hyperten-

- sion. *Cathet Cardiovasc Diagn* 1997;42:381-6.
741. Bloch MJ, Trost DA, Whitmer J, et al. Ostial renal artery stent placement in patients 75 years of age or older. *Am J Hypertens* 2001;14:983-8.
742. Tuttle KR. Ischemic nephropathy. *Curr Opin Nephrol Hypertens* 2001;10:167-73.
743. Tuttle KR. Toward more rational management of ischemic nephropathy: the need for clinical evidence. *Am J Kidney Dis* 2000;36:863-5.
744. Airolidi F, Palatresi S, Marana I, et al. Angioplasty of atherosclerotic and fibromuscular renal artery stenosis: time course and predicting factors of the effects on renal function. *Am J Hypertens* 2000;13:1210-7.
745. Losinno F, Zuccala A, Busato F, et al. Renal artery angioplasty for renovascular hypertension and preservation of renal function: long-term angiographic and clinical follow-up. *AJR Am J Roentgenol* 1994;162:853-7.
746. Geroulakos G, Abel P. Effect of renal-artery stenting on progression of renovascular renal failure. *Lancet* 1997;349(9068):1840.
747. Dorros G, Jaff M, Mathiak L, et al. Multicenter Palmaz stent renal artery stenosis revascularization registry report: four-year follow-up of 1,058 successful patients. *Catheter Cardiovasc Interv* 2002;55:182-8.
748. Ying CY, Tift CP, Gavras H, et al. Renal revascularization in the azotemic hypertensive patient resistant to therapy. *N Engl J Med* 1984;311:1070-5.
749. Hirshberg B, Sasson T, Grinblat I, et al. Prolonged renal dysfunction secondary to renal-artery stenosis in the elderly—it is never too late. *Nephrol Dial Transplant* 1998;13:982-4.
750. Harden PN, MacLeod MJ, Rodger RS, et al. Effect of renal-artery stenting on progression of renovascular renal failure. *Lancet* 1997;349:1133-6.
751. Watson PS, Hadjipetrou P, Cox SV, et al. Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. *Circulation* 2000;102:1671-7.
752. Rocha-Singh KJ, Ahuja RK, Sung CH, et al. Long-term renal function preservation after renal artery stenting in patients with progressive ischemic nephropathy. *Catheter Cardiovasc Interv* 2002;57:135-41.
- 752a. Muray S, Martin M, Amoedo ML, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis* 2002;39:60-6.
- 752b. Beutler JJ, Van Ampting JM, van de Ven PJ, et al. Long-term effects of arterial stenting on kidney function for patients with ostial atherosclerotic renal artery stenosis and renal insufficiency. *J Am Soc Nephrol* 2001;12: 1475-81.
753. Krishnamurthi V, Novick AC, Myles JL. Atheroembolic renal disease: effect on morbidity and survival after revascularization for atherosclerotic renal artery stenosis. *J Urol* 1999;161:1093-6.
754. Scolari F, Tardanico R, Zani R, et al. Cholesterol crystal embolism: a recognizable cause of renal disease. *Am J Kidney Dis* 2000;36:1089-109.
755. Henry M, Klonaris C, Henry I, et al. Protected renal stenting with the PercuSurge GuardWire device: a pilot study. *J Endovasc Ther* 2001;8:227-37.
756. Pickering TG, Herman L, Devereux RB, et al. Recurrent pulmonary oedema in hypertension due to bilateral renal artery stenosis: treatment by angioplasty or surgical revascularisation. *Lancet* 1988;2:551-2.
757. Messina LM, Zelenock GB, Yao KA, et al. Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. *J Vasc Surg* 1992;15:73-80; discussion 80-2.
758. Weatherford DA, Freeman MB, Regester RF, et al. Surgical management of flash pulmonary edema secondary to renovascular hypertension. *Surg Gynecol Obstet* 1997;174:160-3.
759. Mansoor S, Shah A, Scoble JE. 'Flash pulmonary oedema'—a diagnosis for both the cardiologist and the nephrologist? *Nephrol Dial Transplant* 2001;16:1311-3.
760. Planken II, Rietveld AP. Rapid onset pulmonary edema (flash edema) in renal artery stenosis. *Neth J Med* 1998;52:116-9.
761. Gray BH, Olin JW, Childs MB, et al. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. *Vasc Med* 2002;7:275-9.
762. Azizi M, Lavergne T, Day M, et al. Renal artery stenosis and congestive heart failure. *Lancet* 1993;342(8866):302.
763. Missouri CG, Buckenham T, Vallance PJ, et al. Renal artery stenosis masquerading as congestive heart failure. *Lancet* 1993; 341:1521-2.
764. Tami LF, McElderry MW, al-Adli NM, et al. Renal artery stenosis presenting as crescendo angina pectoris. *Cathet Cardiovasc Diagn* 1995;35:252-6.
765. Gross CM, Kramer J, Waigand J, et al. Ostial renal artery stent placement for atherosclerotic renal artery stenosis in patients with coronary artery disease. *Cathet Cardiovasc Diagn* 1998;45:1-8.
766. Bloch MJ, Trost DW, Pickering TG, et al. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *Am J Hypertens* 1999;12(1 pt 1):1-7.
767. Khosla S, White CJ, Collins TJ, et al. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. *Am J Cardiol* 1997;80:363-6.
768. Tegtmeier CJ, Selby JB, Hartwell GD, et al. Results and complications of angioplasty in fibromuscular disease. *Circulation* 1991;83(2 suppl):I155-61.
769. Brawn LA, Ramsay LE. Is "improvement" real with percutaneous transluminal angioplasty in the management of renovascular hypertension? *Lancet* 1987;2:1313-6.
770. Cicuto KP, McLean GK, Oleaga JA, et al. Renal artery stenosis: anatomic classification for percutaneous transluminal angioplasty. *AJR Am J Roentgenol* 1981;137:599-601.
771. Ramsay LE, Waller PC. Blood pressure response to percutaneous transluminal angioplasty for renovascular hypertension: an overview of published series. *BMJ* 1990;300:569-72.
772. Ives NJ, Wheatley K, Stowe RL, et al. Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials. *Nephrol Dial Transplant* 2003;18:298-304.
773. Sos TA, Pickering TG, Sniderman K, et al. Percutaneous transluminal renal angioplasty in renovascular hypertension due to atheroma or fibromuscular dysplasia. *N Engl J Med* 1983; 309:274-9.
774. Libertino JA, Beckmann CF. Surgery and percutaneous angioplasty in the management of renovascular hypertension. *Urol Clin North Am* 1994;21:235-43.
775. Canzanello VJ, Millan VG, Spiegel JE, et al. Percutaneous transluminal renal angioplasty in management of atherosclerotic renovascular hypertension: results in 100 patients. *Hypertension* 1989;13:163-72.
776. Klinge J, Mali WP, Puijlaert CB, et al. Percutaneous transluminal renal angioplasty: initial and long-term results. *Radiology* 1989;171:501-6.

777. Plouin PF, Darne B, Chatellier G, et al. Restenosis after a first percutaneous transluminal renal angioplasty. *Hypertension* 1993;21:89-96.
778. Martin LG, Cork RD, Kaufman SL. Long-term results of angioplasty in 110 patients with renal artery stenosis. *J Vasc Interv Radiol* 1992;3:619-26.
779. Dorros G, Prince C, Mathiak L. Stenting of a renal artery stenosis achieves better relief of the obstructive lesion than balloon angioplasty. *Cathet Cardiovasc Diagn* 1993;29:191-8.
780. Isles CG, Robertson S, Hill D. Management of renovascular disease: a review of renal artery stenting in ten studies. *QJM* 1999;92:159-67.
781. Stanley JC. The evolution of surgery for renovascular occlusive disease. *Cardiovasc Surg* 1994;2:195-202.
782. Stanley JC. David M. Hume memorial lecture. Surgical treatment of renovascular hypertension. *Surg Gynecol Obstet* 1997;174:102-10.
783. van Bockel JH, van Schilfgaarde R, Felthuis W, et al. Long-term results of in situ and extracorporeal surgery for renovascular hypertension caused by fibrodysplasia. *J Vasc Surg* 1987;6:355-64.
784. Stanley JC, Ernst CB, Fry WJ. Fate of 100 aortorenal vein grafts: characteristics of late graft expansion, aneurysmal dilatation, and stenosis. *Surgery* 1973;74:931-44.
785. Khauli RB, Novick AC, Ziegelbaum M. Splenorenal bypass in the treatment of renal artery stenosis: experience with sixty-nine cases. *J Vasc Surg* 1985;2:547-51.
786. Stanley JC, Fry WJ. Renovascular hypertension secondary to arterial fibrodysplasia in adults: criteria for operation and results of surgical therapy. *Arch Surg* 1975;110:922-8.
787. Novick AC, Straffon RA, Stewart BH, et al. Surgical treatment of renovascular hypertension in the pediatric patient. *J Urol* 1978;119:794-9.
788. Berkowitz HD, O'Neill JA Jr. Renovascular hypertension in children. Surgical repair with special reference to the use of reinforced vein grafts. *J Vasc Surg* 1989;9:46-55.
789. Palmaz JC. The current status of vascular intervention in ischemic nephropathy. *J Vasc Interv Radiol* 1998;9:539-43.
790. Martin LG, Rees CR, O'Bryant T. Percutaneous angioplasty of the renal arteries. In: Rutherford RB, ed. *Vascular Surgery* 5th ed. Philadelphia, Pa: WB Saunders; 2000:1611-39.
791. Slonim SM, Dake MD. Radiographic evaluation and treatment of renovascular disease. In: Strandness DE Jr, VanBreda A, eds. *Surgical & Interventional Therapy*. New York: Churchill Livingstone; 1994:721-41.
792. Hansen KJ, Thomason RB, Craven TE, et al. Surgical management of dialysis-dependent ischemic nephropathy. *J Vasc Surg* 1995;21:197-209; discussion 209-11.
793. Hansen KJ, Starr SM, Sands RE, et al. Contemporary surgical management of renovascular disease. *J Vasc Surg* 1992;16:319-30; discussion 330-1.
794. Wong JM, Hansen KJ, Oskin TC, et al. Surgery after failed percutaneous renal artery angioplasty. *J Vasc Surg* 1999;30:468-82.
795. Cambria RP, Brewster DC, L'Italien G, et al. Simultaneous aortic and renal artery reconstruction: evolution of an eighteen-year experience. *J Vasc Surg* 1995;21:916-24; discussion 925.
796. Dougherty MJ, Hallett JW Jr, Naessens J, et al. Renal endarterectomy vs. bypass for combined aortic and renal reconstruction: is there a difference in clinical outcome? *Ann Vasc Surg* 1995;9:87-94.
797. Stoney RJ, Messina LM, Goldstone J, et al. Renal endarterectomy through the transected aorta: a new technique for combined aortorenal atherosclerosis—a preliminary report. *J Vasc Surg* 1989;9:224-33. Erratum in: *J Vasc Surg* 1989;10:19.
798. Stanley JC, Whitehouse WM Jr, Zelenock GB, et al. Reoperation for complications of renal artery reconstructive surgery undertaken for treatment of renovascular hypertension. *J Vasc Surg* 1985;2:133-44.
799. Hansen KJ, Deitch JS, Oskin TC, et al. Renal artery repair: consequence of operative failures. *Ann Surg* 1998;227:678-89; discussion 689-90.
800. Whitehouse WM Jr, Kazmers A, Zelenock GB, et al. Chronic total renal artery occlusion: effects of treatment on secondary hypertension and renal function. *Surgery* 1981;89:753-63.
801. Oskin TC, Hansen KJ, Deitch JS, et al. Chronic renal artery occlusion: nephrectomy versus revascularization. *J Vasc Surg* 1999;29:140-9.
802. Novick AC. Surgical correction of renovascular hypertension. *Surg Clin North Am* 1988;68:1007-25.
803. Cambria RP, Brewster DC, L'Italien GJ, et al. The durability of different reconstructive techniques for atherosclerotic renal artery disease. *J Vasc Surg* 1994;20:76-85; discussion 86-7.
804. Novick AC, Ziegelbaum M, Vidt DG, et al. Trends in surgical revascularization for renal artery disease: ten years' experience. *JAMA* 1987;257:498-501.
805. Libertino JA, Bosco PJ, Ying CY, et al. Renal revascularization to preserve and restore renal function. *J Urol* 1992;147:1485-7.
806. Clair DG, Belkin M, Whitemore AD, et al. Safety and efficacy of transaortic renal endarterectomy as an adjunct to aortic surgery. *J Vasc Surg* 1995;21:926-33; discussion 934.
807. Xue F, Bettmann MA, Langdon DR, et al. Outcome and cost comparison of percutaneous transluminal renal angioplasty, renal arterial stent placement, and renal arterial bypass grafting. *Radiology* 1999;212:378-84.
808. Ottinger LW, Austen WG. A study of 136 patients with mesenteric infarction. *Surg Gynecol Obstet* 1967;124:251-61.
809. Hertzner NR, Beven EG, Humphries AW. Acute intestinal ischemia. *Am Surg* 1978;44:744-9.
810. Bergan JJ. Recognition and treatment of intestinal ischemia. *Surg Clin North Am* 1967;47:109-26.
811. Krupski WC, Effeney DJ, Ehrenfeld WK. Spontaneous dissection of the superior mesenteric artery. *J Vasc Surg* 1985;2:731-4.
812. Wolf EA Jr, Sumner DS, Strandness DE Jr. Disease of the mesenteric circulation in patients with thromboangiitis obliterans. *Vasc Surg* 1972;6:218-23.
813. Slater H, Elliott DW. Primary mesenteric infarction. *Surg Gynecol Obstet* 1972;123:309-11.
814. Singh RP, Shah RC, Lee ST. Acute mesenteric vascular occlusion: a review of thirty-two patients. *Surgery* 1975;78:613-7.
815. Smith JS Jr, Patterson LT. Acute mesenteric infarction. *Am Surg* 1976;42:562-7.
816. Kairaluoma MI, Karkola P, Heikkinen D, et al. Mesenteric infarction. *Surg Gynecol Obstet* 1977;133:188-93.
817. Sachs SM, Morton JH, Schwartz SI. Acute mesenteric ischemia. *Surgery* 1982;92:646-53.
818. Levy PJ, Krausz MM, Manny J. Acute mesenteric ischemia: improved results—a retrospective analysis of ninety-two patients. *Surgery* 1990;107:372-80.
819. Bulkley GB, Zuidema GD, Hamilton SR, et al. Intraoperative determination of small intestinal viability following ischemic injury: a prospective, controlled trial of two adjuvant methods (Doppler and fluorescein) compared with standard clinical judgment. *Ann Surg* 1981;193:628-37.
820. Gallego AM, Ramirez P, Rodriguez JM, et al. Role of urokinase in the superior mesenteric artery embolism. *Surgery* 1996;120:111-3.

821. McBride KD, Gaines PA. Thrombolysis of a partially occluding superior mesenteric artery thromboembolus by infusion of streptokinase. *Cardiovasc Intervent Radiol* 1994;17:164-6.
822. Schoenbaum SW, Pena C, Koenigsberg P, et al. Superior mesenteric artery embolism: treatment with intraarterial urokinase. *J Vasc Interv Radiol* 1992;3:485-90.
823. Boley SJ, Sprayregen S, Siegelman SS, et al. Initial results from an aggressive roentgenological and surgical approach to acute mesenteric ischemia. *Surgery* 1977;82:848-55.
824. Kawauchi M, Tada Y, Asano K, et al. Angiographic demonstration of mesenteric arterial changes in postcoarctectomy syndrome. *Surgery* 1985;98:602-4.
825. Gewertz BL, Zarins CK. Postoperative vasospasm after antegrade mesenteric revascularization: a report of three cases. *J Vasc Surg* 1991;14:382-5.
826. Siegelman SS, Sprayregen S, Boley SJ. Angiographic diagnosis of mesenteric arterial vasoconstriction. *Radiology* 1974;112:533-42.
827. Ende N. Infarction of the bowel in cardiac failure. *N Engl J Med* 1958;258:879-81.
828. Greene FL, Ariyan S, Stansel HC Jr. Mesenteric and peripheral vascular ischemia secondary to ergotism. *Surgery* 1977;81:176-9.
829. Nalbandian H, Sheth N, Dietrich R, et al. Intestinal ischemia caused by cocaine ingestion: report of two cases. *Surgery* 1985;97:374-6.
830. Cheatham JE Jr, Williams GR, Thompson WM, et al. Coarctation: a review of 80 children and adolescents. *Surg Gynecol Obstet* 1979;138:889-93.
831. Merhoff GC, Porter JM. Ergot intoxication: historical review and description of unusual clinical manifestations. *Ann Surg* 1974;180:773-9.
832. Fisher DF Jr, Fry WJ. Collateral mesenteric circulation. *Surg Gynecol Obstet* 1987;164:487-92.
833. Mikkelsen WP. Intestinal angina: its surgical significance. *Surg Gynecol Obstet* 1957;94:262-7; discussion, 267-9.
834. Buchardt Hansen HJ. Abdominal angina: results of arterial reconstruction in 12 patients. *Acta Chir Scand* 1976;142:319-25.
835. Hollier LH, Bernatz PE, Pairolero PC, et al. Surgical management of chronic intestinal ischemia: a reappraisal. *Surgery* 1981;90:940-6.
836. Johnston KW, Lindsay TF, Walker PM, et al. Mesenteric arterial bypass grafts: early and late results and suggested surgical approach for chronic and acute mesenteric ischemia. *Surgery* 1995;118:1-7.
837. Moneta GL, Yeager RA, Dalman R, et al. Duplex ultrasound criteria for diagnosis of splanchnic artery stenosis or occlusion. *J Vasc Surg* 1991;14:511-8; discussion 518-20.
838. Moneta GL, Lee RW, Yeager RA, et al. Mesenteric duplex scanning: a blinded prospective study. *J Vasc Surg* 1993;17:79-84; discussion 85-6.
839. Zwolak RM, Fillinger MF, Walsh DB, et al. Mesenteric and celiac duplex scanning: a validation study. *J Vasc Surg* 1998;27:1078-87; discussion 1088.
840. Gentile AT, Moneta GL, Lee RW, et al. Usefulness of fasting and postprandial duplex ultrasound examinations for predicting high-grade superior mesenteric artery stenosis. *Surg Gynecol Obstet* 1995;169:476-9.
841. Thomas JH, Blake K, Pierce GE, et al. The clinical course of asymptomatic mesenteric arterial stenosis. *J Vasc Surg* 1998;27:840-4.
842. Connolly JE, Stemmer EA. Intestinal gangrene as the result of mesenteric arterial steal. *Surg Gynecol Obstet* 1973;126:197-204.
843. Furrer J, Gruntzig A, Kugelmeier J, et al. Treatment of abdominal angina with percutaneous dilatation of an arteria mesenterica superior stenosis: preliminary communication. *Cardiovasc Intervent Radiol* 1980;3:43-4.
844. Golden DA, Ring EJ, McLean GK, et al. Percutaneous transluminal angioplasty in the treatment of abdominal angina. *AJR Am J Roentgenol* 1982;139:247-9.
845. Odurny A, Sniderman KW, Colapinto RF. Intestinal angina: percutaneous transluminal angioplasty of the celiac and superior mesenteric arteries. *Radiology* 1988;167:59-62.
846. Roberts L Jr, Wertman DA Jr, Mills SR, et al. Transluminal angioplasty of the superior mesenteric artery: an alternative to surgical revascularization. *AJR Am J Roentgenol* 1983;141:1039-42.
847. Levy PJ, Haskell L, Gordon RL. Percutaneous transluminal angioplasty of splanchnic arteries: an alternative method to elective revascularisation in chronic visceral ischaemia. *Eur J Radiol* 1987;7:239-42.
848. McShane MD, Proctor A, Spencer P, et al. Mesenteric angioplasty for chronic intestinal ischaemia. *Eur J Vasc Surg* 1992;6:333-6.
849. Allen RC, Martin GH, Rees CR, et al. Mesenteric angioplasty in the treatment of chronic intestinal ischemia. *J Vasc Surg* 1996;24:415-21; discussion 421-3.
850. Kasirajan K, O'Hara PJ, Gray BH, et al. Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. *J Vasc Surg* 2001;33:63-71.
- 850a. Rose SC, Quigley TM, Raker EJ. Revascularization for chronic mesenteric ischemia: comparison off operative arterial bypass grafting and percutaneous transluminal angioplasty. *J Vasc Interv Radiol* 1995;6:339-49.
- 850b. Bowser AN. Revascularization for chronic mesenteric ischemia: comparison of endovascular and open surgical intervention (Government Rep. No. CI02-4). University of South Florida, Jan. 17, 2002.
851. Jimenez JG, Huber TS, Ozaki CK, et al. Durability of antegrade synthetic aortomesenteric bypass for chronic mesenteric ischemia. *J Vasc Surg* 2002;35:1078-84. Erratum in: *J Vasc Surg* 2002;36:548.
852. Park WM, Cherry KJ Jr, Chua HK, et al. Current results of open revascularization for chronic mesenteric ischemia: a standard for comparison. *J Vasc Surg* 2002;35:853-9.
853. Cunningham CG, Reilly LM, Rapp JH, et al. Chronic visceral ischemia. Three decades of progress. *Ann Surg* 1991;214:276-87; discussion 287-8.
854. Kieny R, Batellier J, Kretz JG. Aortic reimplantation of the superior mesenteric artery for atherosclerotic lesions of the visceral arteries: sixty cases. *Ann Vasc Surg* 1990;4:122-5.
855. Foley MI, Moneta GL, Abou-Zamzam AM Jr, et al. Revascularization of the superior mesenteric artery alone for treatment of intestinal ischemia. *J Vasc Surg* 2000;32:37-47.
856. Beebe HG, MacFarlane S, Raker EJ. Supraceliac aortomesenteric bypass for intestinal ischemia. *J Vasc Surg* 1987;5:749-54.
857. Rapp JH, Reilly LM, Qvarfordt PG, et al. Durability of endarterectomy and antegrade grafts in the treatment of chronic visceral ischemia. *J Vasc Surg* 1986;3:799-806.
858. Moawad J, McKinsey JF, Wyble CW, et al. Current results of surgical therapy for chronic mesenteric ischemia. *Arch Surg* 1997;132:613-8; discussion 618-9.
859. Ebaugh JL, Garcia ND, Matsumura JS. Screening and surveillance for abdominal aortic aneurysms: who needs it and when. *Semin Vasc Surg* 2001;14:193-9.
860. Alcorn HG, Wolfson SK Jr, Sutton-Tyrrell K, et al. Risk factors for abdominal aortic aneurysms in older adults enrolled in The Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*

- 1996;16:963-70.
861. Pedersen OM, Aslaksen A, Vik-Mo H. Ultrasound measurement of the luminal diameter of the abdominal aorta and iliac arteries in patients without vascular disease. *J Vasc Surg* 1993;17:596-601.
862. Lanne T, Sandgren T, Sonesson B. A dynamic view on the diameter of abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1998;15:308-12.
863. Johnston KW, Rutherford RB, Tilson MD, et al. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery *J Vasc Surg* 1991;13:452-8.
864. Pearce WH, Slaughter MS, LeMaire S, et al. Aortic diameter as a function of age, gender, and body surface area. *Surgery* 1993;114:691-7.
865. Sandgren T, Sonesson B, Ahlgren AR, et al. Factors predicting the diameter of the popliteal artery in healthy humans. *J Vasc Surg* 1998;28:284-9.
866. Sonesson B, Lanne T, Hansen F, et al. Infrarenal aortic diameter in the healthy person. *Eur J Vasc Surg* 1994;8:89-95.
867. Lawrence-Brown MM, Norman PE, Jamrozik K, et al. Initial results of ultrasound screening for aneurysm of the abdominal aorta in Western Australia: relevance for endoluminal treatment of aneurysm disease. *Cardiovasc Surg* 2001;9:234-40.
868. Bengtsson H, Sonesson B, Bergqvist D. Incidence and prevalence of abdominal aortic aneurysms, estimated by necropsy studies and population screening by ultrasound. *Ann N Y Acad Sci* 1996;800:1-24.
869. Jamrozik K, Norman PE, Spencer CA, et al. Screening for abdominal aortic aneurysm: lessons from a population-based study. *Med J Aust* 2000;173:345-50.
870. Lederle FA, Johnson GR, Wilson SE, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000;160:1425-30.
871. Singh K, Bonna KH, Jacobsen BK, et al. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromso Study. *Am J Epidemiol* 2001;154:236-44.
872. Pleumeekers HJ, Hoes AW, van der Does E, et al. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. *Am J Epidemiol* 1995;142:1291-9.
873. Vazquez C, Sakalihasan N, D'Harcour JB, et al. Routine ultrasound screening for abdominal aortic aneurysm among 65- and 75-year-old men in a city of 200,000 inhabitants. *Ann Vasc Surg* 1998;12:544-9.
874. Boll AP, Verbeek AL, van de Lisdonk EH, et al. High prevalence of abdominal aortic aneurysm in a primary care screening programme. *Br J Surg* 1998;85:1090-4.
875. Wilmink AB, Quick CR. Epidemiology and potential for prevention of abdominal aortic aneurysm. *Br J Surg* 1998;85:155-62.
876. Takei H, Ishikawa S, Otaki A, et al. Screening for abdominal aortic aneurysm and occlusive peripheral vascular disease in Japanese residents. *Surg Today* 1995;25:608-11.
877. Adachi K, Iwasawa T, Ono T. Screening for abdominal aortic aneurysms during a basic medical checkup in residents of a Japanese rural community. *Surg Today* 2000;30:594-9.
878. Spark JL, Baker JL, Vowden P, et al. Epidemiology of abdominal aortic aneurysms in the Asian community. *Br J Surg* 2001;88:382-4.
879. Sandgren T, Sonesson B, Ryden-Ahlgren, Lanne T. Arterial dimensions in the lower extremities of patients with abdominal aortic aneurysms—no indications of a generalized dilating diathesis. *J Vasc Surg* 2001;34:1079-84.
880. Lawrence PF, Wallis C, Dobrin PB, et al. Peripheral aneurysms and arteriomegaly: is there a familial pattern? *J Vasc Surg* 1998;28:599-605.
881. Verloes A, Sakalihasan N, Koulischer L, et al. Aneurysms of the abdominal aorta: familial and genetic aspects in three hundred thirteen pedigrees. *J Vasc Surg* 1995;21:646-55.
882. Darling RC 3rd, Brewster DC, Darling RC, et al. Are familial abdominal aortic aneurysms different? *J Vasc Surg* 1989;10:39-43.
883. Webster MW, Ferrell RE, St Jean PL, et al. Ultrasound screening of first-degree relatives of patients with an abdominal aortic aneurysm. *J Vasc Surg* 1991;13:9-13; discussion 13-4.
884. Bengtsson H, Sonesson B, Lanne T, et al. Prevalence of abdominal aortic aneurysm in the offspring of patients dying from aneurysm rupture. *Br J Surg* 1992;79:1142-3.
885. Hirose H, Tilson MD. Abdominal aortic aneurysm as an autoimmune disease. *Ann N Y Acad Sci* 2001;947:416-8.
886. Lindholt JS, Jorgensen B, Fasting H, et al. Plasma levels of plasmin-antiplasmin-complexes are predictive for small abdominal aortic aneurysms expanding to operation-recommendable sizes. *J Vasc Surg* 2001;34:611-5.
887. Adams DC, Tulloh BR, Galloway SW, et al. Familial abdominal aortic aneurysm: prevalence and implications for screening. *Eur J Vasc Surg* 1993;7:709-12.
888. Fitzgerald P, Ramsbottom D, Burke P, et al. Abdominal aortic aneurysm in the Irish population: a familial screening study. *Br J Surg* 1995;82:483-6.
889. van der Graaf Y, Akkersdijk GJ, Hak E, et al. Results of aortic screening in the brothers of patients who had elective aortic aneurysm repair. *Br J Surg* 1998;85:778-80.
890. Jaakkola P, Kuivaniemi H, Partanen K, et al. Familial abdominal aortic aneurysms: screening of 71 families. *Eur J Surg* 1996;162:611-7.
891. Leier CV, Baker PB, Kilman JW, et al. Cardiovascular abnormalities associated with adult polycystic kidney disease. *Ann Intern Med* 1984;100:683-8.
892. Torra R, Nicolau C, Badenas C, et al. Abdominal aortic aneurysms and autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1996;7:2483-6.
893. McConathy WJ, Alaupovic P, Woolcock N, et al. Lipids and apolipoprotein profiles in men with aneurysmal and stenosing aorto-iliac atherosclerosis. *Eur J Vasc Surg* 1989;3:511-4.
894. Schillinger M, Domanovits H, Ignatescu M, et al. Lipoprotein (a) in patients with aortic aneurysmal disease. *J Vasc Surg* 2002;36:25-30.
895. Simons PC, Algra A, Bots ML, et al. Common carotid intima-media thickness in patients with peripheral arterial disease or abdominal aortic aneurysm: the SMART study. Second Manifestations of ARterial disease. *Atherosclerosis* 1999;146:243-8.
896. Davies MJ. Aortic aneurysm formation: lessons from human studies and experimental models. *Circulation* 1998;98:193-5.
897. Goodall S, Porter KE, Bell PR, et al. Enhanced invasive properties exhibited by smooth muscle cells are associated with elevated production of MMP-2 in patients with aortic aneurysms. *Eur J Vasc Endovasc Surg* 2002;24:72-80.
898. Reilly JM, Brophy CM, Tilson MD. Characterization of an elastase from aneurysmal aorta which degrades intact aortic elastin. *Ann Vasc Surg* 1992;6:499-502.
899. Anidjar S, Dobrin PB, Eichorst M, et al. Correlation of inflammatory infiltrate with the enlargement of experimental aortic

- aneurysms. *J Vasc Surg* 1992;16:139-47.
900. Pearce WH, Koch AE. Cellular components and features of immune response in abdominal aortic aneurysms. *Ann N Y Acad Sci* 1996;800:175-85.
901. Louwrens HD, Kwaan HC, Pearce WH, et al. Plasminogen activator and plasminogen activator inhibitor expression by normal and aneurysmal human aortic smooth muscle cells in culture. *Eur J Vasc Endovasc Surg* 1995;10:289-93.
902. Sakamaki F, Oya H, Nagaya N, et al. Higher prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm. *J Vasc Surg* 2002;36:35-40.
903. Lindholt JS, Heickendorff L, Antonsen S, et al. Natural history of abdominal aortic aneurysm with and without coexisting chronic obstructive pulmonary disease. *J Vasc Surg* 1998;28:226-33.
904. Yajima N, Masuda M, Miyazaki M, et al. Oxidative stress is involved in the development of experimental abdominal aortic aneurysm: a study of the transcription profile with complementary DNA microarray. *J Vasc Surg* 2002;36:379-85.
905. Baxter BT, Pearce WH, Waltke EA, et al. Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: report of a prospective (Phase II) multicenter study. *J Vasc Surg* 2002;36:1-12.
906. Nagashima H, Aoka Y, Sakomura Y, et al. A 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, cerivastatin, suppresses production of matrix metalloproteinase-9 in human abdominal aortic aneurysm wall. *J Vasc Surg* 2002;36:158-63.
907. Gsell O. Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur. *Virchows Arch Pathol Anat Physiol Klin Med* 1928:1-36.
908. Erdheim J. Medionecrosis aortae idiopathica (cystica). *Virchows Arch Pathol Anat Physiol Klin Med* 1929:454-79.
909. Marfan AB. Un cas de déformation congénitale des quatre membres plus prononcée aux extrémités caractérisée par l'allongement des os avec un certain degré d'amincissement. *Bull Mém Soc Méd Hôp* 1896;13:220-6.
910. Jondeau G, Delorme G, Guiti C. [Marfan syndrome] *Rev Prat*. 2002;52:1089-93.
911. Hollister DW, Godfrey M, Sakai LY, et al. Immunohistologic abnormalities of the microfibrillar-fiber system in the Marfan syndrome. *N Engl J Med* 1990;323:152-9.
912. Dietz HC, Cutting GR, Pyeritz RE, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337-9.
913. Lee B, Godfrey M, Vitale E, et al. Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes. *Nature* 1991;352:330-4.
914. Tsipouras P, Del Mastro R, Sarfarazi M, et al. Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5. The International Marfan Syndrome Collaborative Study. *N Engl J Med* 1992;326:905-9.
915. Francke U, Furthmayr H. Marfan's syndrome and other disorders of fibrillin. *N Engl J Med* 1994;330:1384-5.
916. Kainulainen K, Savolainen A, Palotie A, et al. Marfan syndrome: exclusion of genetic linkage to five genes coding for connective tissue components in the long arm of chromosome 2. *Hum Genet* 1990;84:233-6.
917. Maslen CL, Corson GM, Maddox BK, et al. Partial sequence of a candidate gene for the Marfan syndrome. *Nature* 1991;352:334-7.
918. Jeremy RW, Huang H, Hwa J, et al. Relation between age, arterial distensibility, and aortic dilatation in the Marfan syndrome. *Am J Cardiol* 1994;74:369-73.
919. Pepin M, Schwarze U, Superti-Furga A, et al. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000;342:673-80. Erratum in: *N Engl J Med* 2001;344:392.
920. Francke U, Berg MA, Tynan K, et al. A Gly1127Ser mutation in an EGF-like domain of the fibrillin-1 gene is a risk factor for ascending aortic aneurysm and dissection. *Am J Hum Genet* 1995;56:1287-96.
921. Rasmussen TE, Hallett JW Jr. Inflammatory aortic aneurysms: a clinical review with new perspectives in pathogenesis. *Ann Surg* 1997;225:155-64.
922. Bonamigo TP, Bianco C, Becker M, et al. Inflammatory aneurysms of infra-renal abdominal aorta: a case-control study. *Minerva Cardioangiol* 2002;50:253-8.
923. Cavallaro A, Sapienza P, di Marzo L, et al. [Inflammatory aneurysm of the abdominal aorta: study of 355 patients with aortic aneurysm] *Recenti Prog Med* 2001;92:269-73. Italian.
924. Pennell RC, Hollier LH, Lie JT, et al. Inflammatory abdominal aortic aneurysms: a thirty-year *J Vasc Surg* 1985;2:859-69.
925. Munshi IA, Rhee SW, Pane T, et al. Clostridium septicum mycotic aortic aneurysm. *Surg Gynecol Obstet* 2002;184:54-5.
926. Fiessinger JN, Paul JF. [Inflammatory and infectious aortitis] *Rev Prat*. 2002;52:1094-9.
927. Hagino RT, Clagett GP, Valentine RJ. A case of Pott's disease of the spine eroding into the suprarenal aorta. *J Vasc Surg* 1996;24:482-6.
928. Vammen S, Vorum H, Ostergaard L, et al. Immunoblotting analysis of abdominal aortic aneurysms using antibodies against Chlamydia pneumoniae recombinant MOMP. *Eur J Vasc Endovasc Surg* 2002;24:81-5.
929. Loehe F, Bittmann I, Weilbach C, et al. Chlamydia pneumoniae in atherosclerotic lesions of patients undergoing vascular surgery. *Ann Vasc Surg* 2002;16:467-73.
930. Vammen S, Lindholt JS, Ostergaard L, et al. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. *Br J Surg* 2001;88:1066-72. Erratum in: *Br J Surg* 2002;89:120-1.
931. Bengtsson H, Nilsson P, Bergqvist D. Natural history of abdominal aortic aneurysm detected by screening. *Br J Surg* 1993;80:718-20.
932. Englund R, Hudson P, Hanel K, et al. Expansion rates of small abdominal aortic aneurysms. *Aust N Z J Surg* 1998;68:21-4.
933. Grimshaw GM, Thompson JM, Hamer JD. A statistical analysis of the growth of small abdominal aortic aneurysms. *Eur J Vasc Surg* 1994;8:741-6.
934. Santilli SM, Littooy FN, Cambria RA, et al. Expansion rates and outcomes for the 3.0-cm to the 3.9-cm infrarenal abdominal aortic aneurysm. *J Vasc Surg* 2002;35:666-71.
935. Nevitt MP, Ballard DJ, Hallett JW Jr. Prognosis of abdominal aortic aneurysms. A population-based study. *N Engl J Med* 1989;321:1009-14.
936. Cronenwett JL, Sargent SK, Wall MH, et al. Variables that affect the expansion rate and outcome of small abdominal aortic aneurysms. *J Vasc Surg* 1990;11:260-8; discussion 268-9.
937. Bengtsson H, Bergqvist D, Ekberg O, et al. Expansion pattern and risk of rupture of abdominal aortic aneurysms that were not operated on. *Eur J Surg* 1993;159:461-7.
938. Taylor LM Jr, Porter JM. Basic data related to clinical decision-making in abdominal aortic aneurysms. *Ann Vasc Surg* 1987;1:502-4.
939. Hollier LH, Taylor LM, Ochsner J. Recommended indications for operative treatment of abdominal aortic aneurysms: report of a

- subcommittee of the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery *J Vasc Surg* 1992;15:1046-56.
940. Hallin A, Bergqvist D, Holmberg L. Literature review of surgical management of abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2001;22:197-204.
941. Lederle FA, Wilson SE, Johnson GR, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002;346:1437-44.
942. Mealy K, Salman A. The true incidence of ruptured abdominal aortic aneurysms. *Eur J Vasc Surg* 1988;2:405-8.
943. Johansen K, Kohler TR, Nicholls SC, et al. Ruptured abdominal aortic aneurysm: the Harborview experience. *J Vasc Surg* 1991;13:240-5; discussion 245-7.
944. Heikkinen M, Salenius J, Zeitlin R, et al. The fate of AAA patients referred electively to vascular surgical unit. *Scand J Surg* 2002;91:345-52.
945. Szilagyi DE, Smith RF, DeRusso FJ, et al. Contribution of abdominal aortic aneurysmectomy to prolongation of life. *Ann Surg* 1966;164:678-99.
946. Cronenwett JL, Murphy TF, Zelenock GB, et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. *Surgery* 1985;98:472-83.
947. Powell JT, Brown LC. The natural history of abdominal aortic aneurysms and their risk of rupture. *Acta Chir Belg* 2001;101:11-6.
948. Chang JB, Stein TA, Liu JP, et al. Risk factors associated with rapid growth of small abdominal aortic aneurysms. *Surgery* 1997;121:117-22.
949. Axelrod DA, Henke PK, Wakefield TW, et al. Impact of chronic obstructive pulmonary disease on elective and emergency abdominal aortic aneurysm repair. *J Vasc Surg* 2001;33:72-6.
950. Conway KP, Byrne J, Townsend M, et al. Prognosis of patients turned down for conventional abdominal aortic aneurysm repair in the endovascular and sonographic era: Szilagyi revisited? *J Vasc Surg* 2001;33:752-7.
951. Watson CJ, Walton J, Shaw E, et al. What is the long-term outcome for patients with very small abdominal aortic aneurysms? *Eur J Vasc Endovasc Surg* 1997;14:299-304.
952. Brown PM, Pattenden R, Gutelius JR. The selective management of small abdominal aortic aneurysms: the Kingston study. *J Vasc Surg* 1992;15:21-5; discussion 25-7.
953. Scott RA, Tisi PV, Ashton HA, et al. Abdominal aortic aneurysm rupture rates: a 7-year follow-up of the entire abdominal aortic aneurysm population detected by screening. *J Vasc Surg* 1998;28:124-8.
954. Katz DA, Littenberg B, Cronenwett JL. Management of small abdominal aortic aneurysms: early surgery vs watchful waiting. *JAMA* 1992;268:2678-86.
955. Hertzner NR, Young JR, Beven EG, et al. Late results of coronary bypass in patients with infrarenal aortic aneurysms. The Cleveland Clinic Study. *Ann Surg* 1987;205:360-7.
956. Perko MJ, Schroeder TV, Olsen PS, et al. Natural history of abdominal aortic aneurysm: a survey of 63 patients treated non-operatively. *Ann Vasc Surg* 1993;7:113-6.
957. Galland RB, Whiteley MS, Magee TR. The fate of patients undergoing surveillance of small abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1998;16:104-9.
958. Jones L, Pressdee DJ, Lamont PM, et al. A phase contrast (PC) rephase/dephase sequence of magnetic resonance angiography (MRA): a new technique for imaging distal run-off in the pre-operative evaluation of peripheral vascular disease. *Clin Radiol* 1998;53:333-7.
959. Biancari F, Ylonen K, Anttila V, et al. Durability of open repair of infrarenal abdominal aortic aneurysm: a 15-year follow-up study. *J Vasc Surg* 2002;35:87-93.
960. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet* 1998;352:1649-55.
961. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann Surg* 1999;230:289-96; discussion 296-7.
962. Lederle FA, Johnson GR, Wilson SE, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *JAMA* 2002;287:2968-72.
963. United Kingdom Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002;346:1445-52.
964. Brewster DC, Cronenwett JL, Hallett JW Jr, et al. Guidelines for the treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery *J Vasc Surg* 2003;37:1106-17.
965. Krupski WC, Selzman CH, Florida R, et al. Contemporary management of isolated iliac aneurysms. *J Vasc Surg* 1998;28:1-11; discussion 11-3.
966. Kasirajan V, Hertzner NR, Beven EG, et al. Management of isolated common iliac artery aneurysms. *Cardiovasc Surg* 1998;6:171-7.
967. Carpenter JP, Barker CF, Roberts B, et al. Popliteal artery aneurysms: current management and outcome. *J Vasc Surg* 1994;19:65-72; discussion 72-3.
968. Varga ZA, Locke-Edmunds JC, Baird RN. A multicenter study of popliteal aneurysms. Joint Vascular Research Group. *J Vasc Surg* 1994;20:171-7.
969. Vowden P, Wilkinson D, Ausubsky JR, et al. A comparison of three imaging techniques in the assessment of an abdominal aortic aneurysm. *J Cardiovasc Surg (Torino)* 1989;30:891-6.
970. Muluk SC, Gertler JP, Brewster DC, et al. Presentation and patterns of aortic aneurysms in young patients. *J Vasc Surg* 1994;20:880-6; discussion 887-8.
971. Kiell CS, Ernst CB. Advances in management of abdominal aortic aneurysm. *Adv Surg* 1993;26:73-98.
972. Newman AB, Arnold AM, Burke GL, et al. Cardiovascular disease and mortality in older adults with small abdominal aortic aneurysms detected by ultrasonography: the cardiovascular health study. *Ann Intern Med* 2001;134:182-90.
973. Zarins CK, Harris EJ Jr. Operative repair for aortic aneurysms: the gold standard. *J Endovasc Surg* 1997;4:232-41.
974. Crawford ES, Cohen ES. Aortic aneurysm: a multifocal disease. Presidential address. *Arch Surg* 1982;117:1393-400.
975. Bickerstaff LK, Pairorero PC, Hollier LH, et al. Thoracic aortic aneurysms: a population-based study. *Surgery* 1982;92:1103-8.
976. Pressler V, McNamara JJ. Aneurysm of the thoracic aorta: review of 260 cases. *J Thorac Cardiovasc Surg* 1985;89:50-4.
977. Lederle FA, Simel DL. The rational clinical examination: does this patient have abdominal aortic aneurysm? *JAMA* 1999;281:77-82.
978. May AG, DeWeese JA, Frank I, et al. Surgical treatment of abdominal aortic aneurysms. *Surgery* 1968;63:711-21.
979. Nichols GB, Schilling PJ. Pseudo-retroperitoneal gas in rupture of aneurysm of abdominal aorta. *Am J Roentgenol Radium Ther Nucl Med* 1975;125:134-7.
980. JANOWER ML. Ruptured arteriosclerotic aneurysms of the abdominal aorta: roentgenographic findings on plain films. *N*

- Engl J Med 1961;265:12-5.
981. Littooy FN, Steffan G, Greisler HP, et al. Use of sequential B-mode ultrasonography to manage abdominal aortic aneurysms. Arch Surg 1989;124:419-21.
982. Hara AK, Johnson CD, MacCarty RL, et al. Incidental extra-colonic findings at CT colonography. Radiology 2000;215:353-7.
983. Flanigan RC, McKay TC, Olson M, et al. Limited efficacy of preoperative computed tomographic scanning for the evaluation of lymph node metastasis in patients before radical prostatectomy. Urology 1996;48:428-32.
984. Aoyagi K, Watanabe N, Yukihiro M, et al. Incidental detection of arterial aneurysms with Tc-99m human serum albumin. Clin Nucl Med 1996;21:485-6.
985. Phillips SM, King D. The role of ultrasound to detect aortic aneurysms in "urological" patients. Eur J Vasc Surg 1993;7:298-300.
986. Howe SF, Taylor RJ, Halloran BG, et al. Management of synchronous renal cell carcinoma and aortic disease. Surg Gynecol Obstet 1995;170:231-4.
987. Kumar A, Pham DH, Meindok H, et al. Diagnosis of bleeding mycotic iliac aneurysm on technetium-99m renal scan. J Nucl Med 1992;33:1548-9.
988. Akkersdijk GJ, Puylaert JB, de Vries AC. Abdominal aortic aneurysm as an incidental finding in abdominal ultrasonography. Br J Surg 1991;78:1261-3.
989. Thompson GT. Incidental findings on gallbladder sonography. Can Assoc Radiol J 1987;38:40-1.
990. Moreno AJ, Brown JM, Spicer MJ, et al. Ruptured abdominal aortic aneurysm identified incidental to bone scintigraphy. Eur J Nucl Med 1983;8:546-8.
991. Hautumm B, Grauel H. Aortic aneurysm in urology. Int Urol Nephrol 1982;14:3-11.
992. Spittell PC, Ehram JE, Anderson L, et al. Screening for abdominal aortic aneurysm during transthoracic echocardiography in a hypertensive patient population. J Am Soc Echocardiogr 1997;10:722-7.
993. Derbyshire ND, Lindsell DR, Collin J, et al. Opportunistic screening for abdominal aortic aneurysm. J Med Screen 1994;1:220-2.
994. Wolf YG, Otis SM, Schwend RB, et al. Screening for abdominal aortic aneurysms during lower extremity arterial evaluation in the vascular laboratory. J Vasc Surg 1995;22:417-21; discussion 421-3.
995. Rosch J, Keller FS, Porter JM, et al. Value of angiography in the management of abdominal aortic aneurysm. Cardiovasc Radiol 1978;1:83-94.
996. Bandyk DF. Preoperative imaging of aortic aneurysms: conventional and digital subtraction angiography, computed tomography scanning, and magnetic resonance imaging. Surg Clin North Am 1989;69:721-35.
997. Siegel CL, Cohan RH. CT of abdominal aortic aneurysms. AJR Am J Roentgenol 1994;163:17-29.
998. Turnipseed WD, Acher CW, Detmer DE, et al. Digital subtraction angiography and B-mode ultrasonography for abdominal and peripheral aneurysms. Surgery 1982;92:619-26.
999. Maloney JD, Pairolero PC, Smith SF Jr, et al. Ultrasound evaluation of abdominal aortic aneurysms. Circulation 1977;56(3 suppl):II80-5.
1000. Ellis M, Powell JT, Greenhalgh RM. Limitations of ultrasonography in surveillance of small abdominal aortic aneurysms. Br J Surg 1991;78:614-6.
1001. Andrews SM, Cumming R, Macsweeney ST, et al. Assessment of feasibility for endovascular prosthetic tube correction of aortic aneurysm. Br J Surg 1995;82:917-9.
1002. Diwan A, Sarkar R, Stanley JC, et al. Incidence of femoral and popliteal artery aneurysms in patients with abdominal aortic aneurysms. J Vasc Surg 2000;31:863-9.
1003. Helvie MA, Rubin JM, Silver TM, et al. The distinction between femoral artery pseudoaneurysms and other causes of groin masses: value of duplex Doppler sonography. AJR Am J Roentgenol 1988;150:1177-80.
1004. Bluth EI, Merritt CR, Sullivan MA. Gray-scale ultrasound evaluation of the lower extremities. JAMA 1982;247:3127-9.
1005. Hirsch JH, Thiele BL, Carter SS, et al. Aortic and lower extremity arterial aneurysms. J Clin Ultrasound 1981;9:29-31.
1006. Neiman HL, Yao JS, Silver TM. Gray-scale ultrasound diagnosis of peripheral arterial aneurysms. Radiology 1979;130:413-6.
1007. Collins GJ Jr, Rich NM, Phillips J, et al. Ultrasound diagnosis of popliteal arterial aneurysms. Am Surg 1976;42:853-8.
1008. Atallah C, al Hassan HK, Neglen P. Superficial femoral artery aneurysm—an uncommon site of aneurysm formation. Eur J Vasc Endovasc Surg 1995;10:502-4.
1009. Lindholt JS, Henneberg EW, Fasting H, et al. Hospital based screening of 65-73 year old men for abdominal aortic aneurysms in the county of Viborg, Denmark. J Med Screen 1996;3:43-6.
1010. Pleumeekers HJ, Hoes AW, Hofman A, et al. Selecting subjects for ultrasonographic screening for aneurysms of the abdominal aorta: four different strategies. Int J Epidemiol 1999;28:682-6.
1011. Lindholt JS, Vammen S, Juul S, et al. The validity of ultrasonographic scanning as screening method for abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 1999;17:472-5.
1012. Nasim A, Thompson MM, Sayers RD, et al. Role of magnetic resonance angiography for assessment of abdominal aortic aneurysm before endoluminal repair. Br J Surg 1998;85:641-4.
1013. Taylor SM, Mills JL, Fujitani RM. The juxtarenal abdominal aortic aneurysm: a more common problem than previously realized? Arch Surg 1994;129:734-7.
1014. Tennant WG, Hartnell GG, Baird RN, et al. Radiologic investigation of abdominal aortic aneurysm disease: comparison of three modalities in staging and the detection of inflammatory change. J Vasc Surg 1993;17:703-9.
1015. Lamah M, Darke S. Value of routine computed tomography in the preoperative assessment of abdominal aneurysm replacement. World J Surg 1999;23:1076-80; discussion 1080-1.
1016. Fillinger MF. Imaging of the thoracic and thoracoabdominal aorta. Semin Vasc Surg 2000;13:247-63.
1017. Errington ML, Ferguson JM, Gillespie IN, et al. Complete preoperative imaging assessment of abdominal aortic aneurysm with spiral CT angiography. Clin Radiol 1997;52:369-77.
1018. Rubin GD, Armerding MD, Dake MD, et al. Cost identification of abdominal aortic aneurysm imaging by using time and motion analyses. Radiology 2000;215:63-70.
1019. Galt SW, Pearce WH. Preoperative assessment of abdominal aortic aneurysms: noninvasive imaging versus routine arteriography. Semin Vasc Surg 1995;8:103-7.
1020. Coulam CH, Rubin GD. Acute aortic abnormalities. Semin Roentgenol 2001;36:148-64.
1021. Papanicolaou N, Wittenberg J, Ferrucci JT Jr, et al. Preoperative evaluation of abdominal aortic aneurysms by computed tomography. AJR Am J Roentgenol 1986;146:711-5.
1022. Vicaretti M, Young N, Jenkins J, et al. Helical computed tomography in the assessment of abdominal aortic pathology. Australas Radiol 1997;41:125-31.
1023. Eriksson I, Forsberg JO, Hemmingsson A, et al. Preoperative evaluation of abdominal aortic aneurysms: is there a need for

- aortography? *Acta Chir Scand* 1981;147:533-7.
1024. Broeders IA, Blankensteijn JD. Preoperative imaging of the aortoiliac anatomy in endovascular aneurysm surgery. *Semin Vasc Surg* 1999;12:306-14.
1025. Ludman CN, Yusuf SW, Whitaker SC, et al. Feasibility of using dynamic contrast-enhanced magnetic resonance angiography as the sole imaging modality prior to endovascular repair of abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2000;19:524-30.
1026. Hovsepian DM, Siegel BA, Kimbiris G, et al. Tc-99m sulfur colloid scintigraphy for detecting perigraft flow following endovascular aortic aneurysm repair: a feasibility study. *Cardiovasc Intervent Radiol* 1999;22:447-51.
1027. Hanson SR, Kotze HF, Pieters H, et al. Analysis of indium-111 platelet kinetics and imaging in patients with aortic grafts and abdominal aortic aneurysms. *Arteriosclerosis* 1990;10:1037-44.
1028. Prince MR, Yucel EK, Kaufman JA, et al. Dynamic gadolinium-enhanced three-dimensional abdominal MR arteriography. *J Magn Reson Imaging* 1993;3:877-81.
1029. Frayne R, Grist TM, Swan JS, et al. 3D MR DSA: effects of injection protocol and image masking. *J Magn Reson Imaging* 2000;12:476-87.
1030. Yamashita Y, Mitsuzaki K, Tang Y, et al. Gadolinium-enhanced breath-hold three-dimensional time-of-flight MR angiography of the abdominal and pelvic vessels: the value of ultrafast MP-RAGE sequences. *J Magn Reson Imaging* 1997;7:623-8.
1031. Thurnher SA, Dorffner R, Thurnher MM, et al. Evaluation of abdominal aortic aneurysm for stent-graft placement: comparison of gadolinium-enhanced MR angiography versus helical CT angiography and digital subtraction angiography. *Radiology* 1997;205:341-52.
1032. Scott RA, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. *Br J Surg* 1991;78:1122-5.
1033. Grimshaw GM, Thompson JM. The abnormal aorta: a statistical definition and strategy for monitoring change. *Eur J Vasc Endovasc Surg* 1995;10:95-100.
1034. Scott RA, Vardulaki KA, Walker NM, et al. The long-term benefits of a single scan for abdominal aortic aneurysm (AAA) at age 65. *Eur J Vasc Endovasc Surg* 2001;21:535-40.
1035. Cole CW, Hill GB, Millar WJ, et al. Selective screening for abdominal aortic aneurysm. *Chronic Dis Can.* 1996;17:51-5.
1036. Multicentre Aneurysm Screening Study Group. Multicentre aneurysm screening study (MASS): cost effectiveness analysis of screening for abdominal aortic aneurysms based on four year results from randomised controlled trial. *BMJ* 2002;325:1135.
1037. Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002;360:1531-9.
1038. Connelly JB, Hill GB, Millar WJ. The detection and management of abdominal aortic aneurysm: a cost-effectiveness analysis. *Clin Invest Med* 2002;25:127-33.
1039. Soisalon-Soininen S, Rissanen P, Pentikainen T, et al. Cost-effectiveness of screening for familial abdominal aortic aneurysms. *Vasa* 2001;30:262-70.
1040. Lee TY, Korn P, Heller JA, et al. The cost-effectiveness of a "quick-screen" program for abdominal aortic aneurysms. *Surgery* 2002;132:399-407.
1041. Fleming C, Whitlock EP, Beil TL, et al. Screening for abdominal aortic aneurysm: a best-evidence systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2005;142:203-11.
1042. Meenan RT, Fleming C, Whitlock EP, et al. Cost-Effectiveness Analyses of Population-Based Screening for Abdominal Aortic Aneurysm. Evidence Synthesis. AHRQ Publication No. 05-0569-C, February 2005. Agency for Healthcare Research and Quality, Rockville, Md. Available at: <http://www.ahrq.gov/clinic/uspstf05/aaascr/aaacost.htm>. Accessed July 16, 2005.
1043. Brophy C, Tilson JE, Tilson MD. Propranolol delays the formation of aneurysms in the male blotchy mouse. *J Surg Res* 1988;44:687-9.
1044. Ricci MA, Slaiby JM, Gadowski GR, et al. Effects of hypertension and propranolol upon aneurysm expansion in the Anidjar/Dobrin aneurysm model. *Ann N Y Acad Sci* 1996;800:89-96.
1045. Leach SD, Toole AL, Stern H, et al. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. *Arch Surg* 1988;123:606-9.
1046. Gadowski GR, Pilcher DB, Ricci MA. Abdominal aortic aneurysm expansion rate: effect of size and beta-adrenergic blockade. *J Vasc Surg* 1994;19:727-31.
1047. Lindholt JS, Henneberg EW, Juul S, et al. Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. *Int Angiol* 1999;18:52-7.
1048. Shores J, Berger KR, Murphy EA, et al. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335-41.
1049. Kertai MD, Boersma E, Westerhout CM, et al. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 2004;28:343-52.
1050. Fleisher LA, Eagle KA. Clinical practice: lowering cardiac risk in noncardiac surgery. *N Engl J Med* 2001;345:1677-82.
1051. Auerbach AD, Goldman L. Beta-blockers and reduction of cardiac events in noncardiac surgery: scientific JAMA 2002; 287:1435-44.
1052. Cook TA, Galland RB. A prospective study to define the optimum rescreening interval for small abdominal aortic aneurysm. *Cardiovasc Surg* 1996;4:441-4.
1053. Finlayson SR, Birkmeyer JD, Fillinger MF, et al. Should endovascular surgery lower the threshold for repair of abdominal aortic aneurysms? *J Vasc Surg* 1999;29:973-85.
1054. Thompson RW. Detection and management of small aortic aneurysms. *N Engl J Med* 2002;346:1484-6.
1055. d'Audiffret A, Santilli S, Tretinyak A, et al. Fate of the ectatic infrarenal aorta: expansion rates and outcomes. *Ann Vasc Surg* 2002;16:534-6.
1056. Hallett JW Jr, Naessens JM, Ballard DJ. Early and late outcome of surgical repair for small abdominal aortic aneurysms: a population-based analysis. *J Vasc Surg* 1993;18:684-91.
1057. Koskas F, Kieffer E. Long-term survival after elective repair of infrarenal abdominal aortic aneurysm: results of a prospective multicentric study. Association for Academic Research in Vascular Surgery (AURC). *Ann Vasc Surg* 1997;11:473-81.
1058. Aune S. Risk factors and operative results of patients aged less than 66 years operated on for asymptomatic abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2001;22:240-3.
1059. Brady AR, Fowkes FG, Thompson SG, et al. Aortic aneurysm diameter and risk of cardiovascular mortality. *Arterioscler Thromb Vasc Biol* 2001;21:1203-7.
1060. Starr JE, Hertzner NR, Mascha EJ, et al. Influence of gender on cardiac risk and survival in patients with infrarenal aortic aneurysms. *J Vasc Surg* 1996;23:870-80.

1061. Crawford ES, Saleh SA, Babb JW 3rd, et al. Infrarenal abdominal aortic aneurysm: factors influencing survival after operation performed over a 25-year period. *Ann Surg* 1981;193:699-709.
1062. Hollier LH, Plate G, O'Brien PC, et al. Late survival after abdominal aortic aneurysm repair: influence of coronary artery disease. *J Vasc Surg* 1984;1:290-9.
1063. Reigel MM, Hollier LH, Kazmier FJ, et al. Late survival in abdominal aortic aneurysm patients: the role of selective myocardial revascularization on the basis of clinical symptoms. *J Vasc Surg* 1987;5:222-7.
1064. Glance LG. Selective preoperative cardiac screening improves five-year survival in patients undergoing major vascular surgery: a cost-effectiveness analysis. *J Cardiothorac Vasc Anesth* 1999;13:265-71.
1065. Golden MA, Whittemore AD, Donaldson MC, et al. Selective evaluation and management of coronary artery disease in patients undergoing repair of abdominal aortic aneurysms: a 16-year experience. *Ann Surg* 1990;212:415-20; discussion 420-3.
1066. Lachapelle K, Graham AM, Symes JF. Does the clinical evaluation of the cardiac status predict outcome in patients with abdominal aortic aneurysms? *J Vasc Surg* 1992;15:964-70; discussion 970-1.
1067. Suggs WD, Smith RB 3rd, Weintraub WS, et al. Selective screening for coronary artery disease in patients undergoing elective repair of abdominal aortic aneurysms. *J Vasc Surg* 1993;18:349-55; discussion 355-7.
1068. Hertzner NR, Mascha EJ, Karafa MT, et al. Open infrarenal abdominal aortic aneurysm repair: the Cleveland Clinic experience from 1989 to 1998. *J Vasc Surg* 2002;35:1145-54.
1069. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;351:2795-804. Erratum in: *N Engl J Med* 2005; 95:19.
1070. Darling RC 3rd, Cordero JA Jr, Chang BB, et al. Advances in the surgical repair of ruptured abdominal aortic aneurysms. *Cardiovasc Surg* 1996;4:720-3.
1071. Sicard GA, Reilly JM, Rubin BG, et al. Transabdominal versus retroperitoneal incision for abdominal aortic surgery: report of a prospective randomized trial. *J Vasc Surg* 1995;21:174-81; discussion 181-3.
1072. Cambria RP, Brewster DC, Abbott WM, et al. Transperitoneal versus retroperitoneal approach for aortic reconstruction: a randomized prospective study. *J Vasc Surg* 1990;11:314-24; discussion 324-5.
1073. Sieunarine K, Lawrence-Brown MM, Goodman MA. Comparison of transperitoneal and retroperitoneal approaches for infrarenal aortic surgery: early and late results. *Cardiovasc Surg* 1997;5:71-6.
1074. Blankensteijn JD, Lindenburg FP, Van der Graaf Y, et al. Influence of study design on reported mortality and morbidity rates after abdominal aortic aneurysm repair. *Br J Surg* 1998;85:1624-30.
1075. Lawrence PF, Gazak C, Bhirangi L, et al. The epidemiology of surgically repaired aneurysms in the United States. *J Vasc Surg* 1999;30:632-40.
1076. Heller JA, Weinberg A, Arons R, et al. Two decades of abdominal aortic aneurysm repair: have we made any progress? *J Vasc Surg* 2000;32:1091-100.
1077. Huber TS, Wang JG, Derrow AE, et al. Experience in the United States with intact abdominal aortic aneurysm repair. *J Vasc Surg* 2001;33:304-10; discussion 310-1.
1078. Dimick JB, Stanley JC, Axelrod DA, et al. Variation in death rate after abdominal aortic aneurysmectomy in the United States: impact of hospital volume, gender, and age. *Ann Surg* 2002; 235:579-85.
1079. Lloyd WE, Paty PS, Darling RC 3rd, et al. Results of 1000 consecutive elective abdominal aortic aneurysm repairs. *Cardiovasc Surg* 1996;4:724-6.
1080. Menard MT, Chew DK, Chan RK, et al. Outcome in patients at high risk after open surgical repair of abdominal aortic aneurysm. *J Vasc Surg* 2003;37:285-92.
1081. Ernst CB. Abdominal aortic aneurysm. *N Engl J Med* 1993; 328:1167-72.
1082. Johnston KW, Scobie TK. Multicenter prospective study of non-ruptured abdominal aortic aneurysms. I. Population and operative management. *J Vasc Surg* 1988;7:69-81.
1083. Richardson JD, Main KA. Repair of abdominal aortic aneurysms. A statewide experience. *Arch Surg* 1991;126:614-6.
1084. Hannan EL, Kilburn H Jr, O'Donnell JF, et al. A longitudinal analysis of the relationship between in-hospital mortality in New York State and the volume of abdominal aortic aneurysm surgeries performed. *Health Serv Res.* 1992;27:517-42.
1085. Johnston KW. Nonruptured abdominal aortic aneurysm: six-year follow-up results from the multicenter prospective Canadian aneurysm study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg* 1994;20:163-70.
1086. Katz DJ, Stanley JC, Zelenock GB. Operative mortality rates for intact and ruptured abdominal aortic aneurysms in Michigan: an eleven-year statewide experience. *J Vasc Surg* 1994;19:804-15; discussion 816-7.
1087. Kazmers A, Jacobs L, Perkins A, et al. Abdominal aortic aneurysm repair in Veterans Affairs medical centers. *J Vasc Surg* 1996;23:191-200.
1088. Wen SW, Simunovic M, Williams JI, et al. Hospital volume, calendar age, and short term outcomes in patients undergoing repair of abdominal aortic aneurysms: the Ontario experience, 1988-92. *J Epidemiol Community Health* 1996;50:207-13.
1089. Kantonen I, Lepantalo M, Salenius JP, et al. Mortality in abdominal aortic aneurysm surgery—the effect of hospital volume, patient mix and surgeon's case load. *Eur J Vasc Endovasc Surg* 1997;14:375-9.
1090. Bradbury AW, Adam DJ, Makhdooni KR, et al. A 21-year experience of abdominal aortic aneurysm operations in Edinburgh. *Br J Surg* 1998;85:645-7.
1091. Manheim LM, Sohn MW, Feinglass J, et al. Hospital vascular surgery volume and procedure mortality rates in California, 1982-1994. *J Vasc Surg* 1998;28:45-56; discussion 56-8.
1092. Dardik A, Lin JW, Gordon TA, et al. Results of elective abdominal aortic aneurysm repair in the 1990s: a population-based analysis of 2335 cases. *J Vasc Surg* 1999;30:985-95.
1093. Pearce WH, Parker MA, Feinglass J, et al. The importance of surgeon volume and training in outcomes for vascular surgical procedures. *J Vasc Surg* 1999;29:768-76; discussion 777-8.
1094. Sollano JA, Gelijns AC, Moskowitz AJ, et al. Volume-outcome relationships in cardiovascular operations: New York State, 1990-1995. *J Thorac Cardiovasc Surg* 1999;117:419-28; discussion 428-30.
1095. Kazmers A, Perkins AJ, Jacobs LA. Aneurysm rupture is independently associated with increased late mortality in those surviving abdominal aortic aneurysm repair. *J Surg Res* 2001;95:50-3.
1096. Huber TS, Seeger JM. Dartmouth Atlas of Vascular Health Care review: impact of hospital volume, surgeon volume, and training on outcome. *J Vasc Surg* 2001;34:751-6.
1097. Panneton JM, Lassonde J, Laurendeau F. Ruptured abdominal aortic aneurysm: impact of comorbidity and postoperative com-

- plications on outcome. *Ann Vasc Surg* 1995;9:535-41.
1098. Seiwert AJ, Elmore JR, Youkey JR, et al. Samuels Award. Ruptured abdominal aortic aneurysm repair: the financial analysis. *Surg Gynecol Obstet* 1995;170:91-6.
1099. Barry MC, Burke PE, Sheehan S, et al. An "all comers" policy for ruptured abdominal aortic aneurysms: how can results be improved? *Eur J Surg* 1998;164:263-70.
1100. Noel AA, Gloviczki P, Cherry KJ Jr, et al. Ruptured abdominal aortic aneurysms: the excessive mortality rate of conventional repair. *J Vasc Surg* 2001;34:41-6.
1101. Hertzner NR, Avellone JC, Farrell CJ, et al. The risk of vascular surgery in a metropolitan community: with observations on surgeon experience and hospital size. *J Vasc Surg* 1984;1:13-21.
1102. Johnston KW. Ruptured abdominal aortic aneurysm: six-year follow-up results of a multicenter prospective study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg* 1994;19:888-900.
1103. Amundsen S, Skjaerven R, Trippestad A, et al. Abdominal aortic aneurysms—a study of factors influencing postoperative mortality. Norwegian Aortic Aneurysm Trial. *Eur J Vasc Surg* 1989;3:405-9.
1104. Gloviczki P, Pairolero PC, Mucha P Jr, et al. Ruptured abdominal aortic aneurysms: repair should not be denied. *J Vasc Surg* 1992;15:851-7; discussion 857-9.
1105. Halpern VJ, Kline RG, D'Angelo AJ, et al. Factors that affect the survival rate of patients with ruptured abdominal aortic aneurysms. *J Vasc Surg* 1997;26:939-45; discussion 945-8.
1106. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, et al. Perioperative mortality of elective abdominal aortic aneurysm surgery: a clinical prediction rule based on literature and individual patient data. *Arch Intern Med* 1995;155:1998-2004.
1107. Brady AR, Fowkes FG, Greenhalgh RM, et al. Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial. On behalf of the UK Small Aneurysm Trial participants. *Br J Surg* 2000;87:742-9.
1108. Kazmers A, Perkins AJ, Jacobs LA. Outcomes after abdominal aortic aneurysm repair in those > or =80 years of age: recent Veterans Affairs experience. *Ann Vasc Surg* 1998;12:106-12.
1109. O'Hara PJ, Hertzner NR, Krajewski LP, et al. Ten-year experience with abdominal aortic aneurysm repair in octogenarians: early results and late outcome. *J Vasc Surg* 1995;21:830-7; discussion 837-8.
1110. Harris KA, Ameli FM, Lally M, et al. Abdominal aortic aneurysm resection in patients more than 80 years old. *Surg Gynecol Obstet* 1986;162:536-8.
1111. Collins TC, Johnson M, Daley J, et al. Preoperative risk factors for 30-day mortality after elective surgery for vascular disease in Department of Veterans Affairs hospitals: is race important? *J Vasc Surg* 2001;34:634-40.
1112. Shackley P, Slack R, Booth A, et al. Is there a positive volume-outcome relationship in peripheral vascular surgery? Results of a systematic Eur J Vasc Endovasc Surg 2000;20:326-35.
1113. Amundsen S, Skjaerven R, Trippestad A, et al. Abdominal aortic aneurysms: is there an association between surgical volume, surgical experience, hospital type and operative mortality? Members of the Norwegian Abdominal Aortic Aneurysm Trial. *Acta Chir Scand* 1990;156:323-7; discussion 327-8.
1114. Soisalon-Soininen S, Salo JA, Takkunen O, et al. Comparison of long-term survival after repair of ruptured and non-ruptured abdominal aortic aneurysm. *Vasa* 1995;24:42-8.
1115. Cho JS, Gloviczki P, Martelli E, et al. Long-term survival and late complications after repair of ruptured abdominal aortic aneurysms. *J Vasc Surg* 1998;27:813-9; discussion 819-20.
1116. Feinglass J, Cowper D, Dunlop D, et al. Late survival risk factors for abdominal aortic aneurysm repair: experience from fourteen Department of Veterans Affairs hospitals. *Surgery* 1995;118:16-24.
1117. Stonebridge PA, Callam MJ, Bradbury AW, et al. Comparison of long-term survival after successful repair of ruptured and non-ruptured abdominal aortic aneurysm. *Br J Surg* 1993;80:585-6.
1118. Norman PE, Semmens JB, Lawrence-Brown MM. Long-term relative survival following surgery for abdominal aortic aneurysm: a review. *Cardiovasc Surg* 2001;9:219-24.
1119. Evans SM, Adam DJ, Brittenden J, et al. Vascular Surgical Society of Great Britain and Ireland: long-term survival following repair of ruptured abdominal aortic aneurysm in patients over 75 years of age. *Br J Surg* 1999;86:696.
1120. Hallett JW Jr, Marshall DM, Petterson TM, et al. Graft-related complications after abdominal aortic aneurysm repair: reassurance from a 36-year population-based experience. *J Vasc Surg* 1997;25:277-84; discussion 285-6.
1121. Crawford ES, Beckett WC, Greer MS. Juxtarenal infrarenal abdominal aortic aneurysm: special diagnostic and therapeutic considerations. *Ann Surg* 1986;203:661-70.
1122. Ayari R, Paraskevas N, Rosset E, et al. Juxtarenal aneurysm: comparative study with infrarenal abdominal aortic aneurysm and proposition of a new classification. *Eur J Vasc Endovasc Surg* 2001;22:169-74.
1123. Faggioli G, Stella A, Freyrie A, et al. Early and long-term results in the surgical treatment of juxtarenal and pararenal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1998;15:205-11.
1124. Qvarfordt PG, Stoney RJ, Reilly LM, et al. Management of pararenal aneurysms of the abdominal aorta. *J Vasc Surg* 1986;3:84-93.
1125. Nypaver TJ, Shepard AD, Reddy DJ, et al. Repair of pararenal abdominal aortic aneurysms: an analysis of operative management. *Arch Surg* 1993;128:803-11; discussion 811-3.
1126. Jean-Claude JM, Reilly LM, Stoney RJ, et al. Pararenal aortic aneurysms: the future of open aortic aneurysm repair. *J Vasc Surg* 1999;29:902-12.
1127. Anagnostopoulos PV, Shepard AD, Pipinos II, et al. Factors affecting outcome in proximal abdominal aortic aneurysm repair. *Ann Vasc Surg* 2001;15:511-9.
1128. Cox GS, O'Hara PJ, Hertzner NR, et al. Thoracoabdominal aneurysm repair: a representative experience. *J Vasc Surg* 1992;15:780-7; discussion 787-8.
1129. Svensson LG, Crawford ES, Hess KR, et al. Experience with 1509 patients undergoing thoracoabdominal aortic operations. *J Vasc Surg* 1993;17:357-68; discussion 368-70.
1130. Coselli JS, LeMaire SA, Buket S, et al. Subsequent proximal aortic operations in 123 patients with previous infrarenal abdominal aortic aneurysm surgery. *J Vasc Surg* 1995;22:59-67.
1131. Schwartz LB, Belkin M, Donaldson MC, et al. Improvement in results of repair of type IV thoracoabdominal aortic aneurysms. *J Vasc Surg* 1996;24:74-81.
1132. Dunning PG, Duggill S, Brown AS, et al. Vascular Surgical Society of Great Britain and Ireland: total abdominal approach for repair of type IV thoracoabdominal aortic aneurysm. *Br J Surg* 1999;86:696.
1133. Martin GH, O'Hara PJ, Hertzner NR, et al. Surgical repair of aneurysms involving the suprarenal, visceral, and lower thoracic aortic segments: early results and late outcome. *J Vasc Surg* 2000;31:851-62.
1134. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc*

- Surg 1991;5:491-9.
1135. Anderson PL, Arons RR, Moskowitz AJ, et al. A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. *J Vasc Surg* 2004;39:10-9.
 1136. Jacobs TS, Won J, Gravereaux EC, et al. Mechanical failure of prosthetic human implants: a 10-year experience with aortic stent graft devices. *J Vasc Surg* 2003;37:16-26.
 1137. Zarins CK; AneuRx Clinical Investigators. The US AneuRx Clinical Trial: 6-year clinical update 2002. *J Vasc Surg* 2003;37:904-8.
 1138. Dillavou ED, Muluk SC, Rhee RY, et al. Does hostile neck anatomy preclude successful endovascular aortic aneurysm repair? *J Vasc Surg* 2003;38:657-63.
 1139. Arko FR, Filis KA, Seidel SA, et al. How many patients with infrarenal aneurysms are candidates for endovascular repair? The Northern California experience. *J Endovasc Ther* 2004;11:33-40.
 1140. Carpenter JP, Baum RA, Barker CF, et al. Impact of exclusion criteria on patient selection for endovascular abdominal aortic aneurysm repair. *J Vasc Surg* 2001;34:1050-4.
 1141. Becker GJ, Kovacs M, Mathison MN, et al. Risk stratification and outcomes of transluminal endografting for abdominal aortic aneurysm: 7-year experience and long-term follow-up. *J Vasc Interv Radiol* 2001;12:1033-46.
 1142. Mathison M, Becker GJ, Katzen BT, et al. The influence of female gender on the outcome of endovascular abdominal aortic aneurysm repair. *J Vasc Interv Radiol* 2001;12:1047-51.
 1143. Wolf YG, Arko FR, Hill BB, et al. Gender differences in endovascular abdominal aortic aneurysm repair with the AneuRx stent graft. *J Vasc Surg* 2002;35:882-6.
 1144. Veith FJ, Baum RA, Ohki T, et al. Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. *J Vasc Surg* 2002;35:1029-35.
 1145. White RA, Donayre C, Walot I, et al. Abdominal aortic aneurysm rupture following endoluminal graft deployment: report of a predictable event. *J Endovasc Ther* 2000;7:257-62.
 1146. Abraham CZ, Chuter TA, Reilly LM, et al. Abdominal aortic aneurysm repair with the Zenith stent graft: short to midterm results. *J Vasc Surg* 2002;36:217-24; discussion 224-5.
 1147. Zarins CK, Wolf YG, Lee WA, et al. Will endovascular repair replace open surgery for abdominal aortic aneurysm repair? *Ann Surg* 2000;232:501-7.
 1148. Zarins CK, White RA, Moll FL, et al. The AneuRx stent graft: four-year results and worldwide experience 2000. *J Vasc Surg* 2001;33(2 suppl):S135-45. Erratum in: *J Vasc Surg* 2001;33:1318.
 1149. Sapiirstein W, Chandeysson P, Wentz C. The Food and Drug Administration approval of endovascular grafts for abdominal aortic aneurysm: an 18-month retrospective. *J Vasc Surg* 2001;34:180-3.
 1150. Harris PL, Buth J. An update on the important findings from the EUROSTAR EVAR registry. *Vascular*. 2004;12:33-8.
 1151. Steinmetz E, Rubin BG, Sanchez LA, et al. Type II endoleak after endovascular abdominal aortic aneurysm repair: a conservative approach with selective intervention is safe and cost-effective. *J Vasc Surg* 2004;39:306-13.
 1152. Stelter W, Umscheid T, Ziegler P. Three-year experience with modular stent-graft devices for endovascular AAA treatment. *J Endovasc Surg* 1997;4:362-9.
 1153. Amesur NB, Zajko AB, Orons PD, et al. Endovascular treatment of iliac limb stenoses or occlusions in 31 patients treated with the Ancure endograft. *J Vasc Interv Radiol* 2000;11:421-8.
 1154. Baum RA, Shetty SK, Carpenter JP, et al. Limb kinking in supported and unsupported abdominal aortic stent-grafts. *J Vasc Interv Radiol* 2000;11:1165-71.
 1155. Fairman RM, Baum RA, Carpenter JP, et al. Limb interventions in patients undergoing treatment with an unsupported bifurcated aortic endograft system: a review of the Phase II EVT Trial. *J Vasc Surg* 2002;36:118-26.
 1156. Greenberg RK, Lawrence-Brown M, Bhandari G, et al. An update of the Zenith endovascular graft for abdominal aortic aneurysms: initial implantation and mid-term follow-up data. *J Vasc Surg* 2001;33(2 suppl):S157-64.
 1157. Conners MS 3rd, Sternbergh WC 3rd, Carter G, et al. Endograft migration one to four years after endovascular abdominal aortic aneurysm repair with the AneuRx device: a cautionary note. *J Vasc Surg* 2002;36:476-84.
 1158. Makaroun MS, Deaton DH. Is proximal aortic neck dilatation after endovascular aneurysm exclusion a cause for concern? *J Vasc Surg* 2001;33(2 suppl):S39-45.
 1159. Matsumura JS, Chaikof EL. Continued expansion of aortic necks after endovascular repair of abdominal aortic aneurysms. EVT Investigators. Endovascular Technologies, Inc. *J Vasc Surg* 1998;28:422-30; discussion 430-1.
 1160. de Virgilio C, Bui H, Donayre C, et al. Endovascular vs open abdominal aortic aneurysm repair: a comparison of cardiac morbidity and mortality. *Arch Surg* 1999;134:947-50; discussion 950-1.
 1161. Aziz IN, Lee JT, Kopchok GE, et al. Cardiac risk stratification in patients undergoing endoluminal graft repair of abdominal aortic aneurysm: a single-institution experience with 365 patients. *J Vasc Surg* 2003;38:56-60.
 1162. Cuypers PW, Gardien M, Buth J, et al. Cardiac response and complications during endovascular repair of abdominal aortic aneurysms: a concurrent comparison with open surgery. *J Vasc Surg* 2001;33:353-60.
 1163. Buth J, Laheij RJ. Early complications and endoleaks after endovascular abdominal aortic aneurysm repair: report of a multicenter study. *J Vasc Surg* 2000;31(1 pt 1):134-46.
 1164. Chuter TA, Reilly LM, Faruqi RM, et al. Endovascular aneurysm repair in high-risk patients. *J Vasc Surg* 2000;31(1 pt 1):122-33.
 1165. May J, White GH, Waugh R, et al. Improved survival after endoluminal repair with second-generation prostheses compared with open repair in the treatment of abdominal aortic aneurysms: a 5-year concurrent comparison using life table method. *J Vasc Surg* 2001;33(2 suppl):S21-6.
 1166. Buth J, van Marrewijk CJ, Harris PL, et al. Outcome of endovascular abdominal aortic aneurysm repair in patients with conditions considered unfit for an open procedure: a report on the EUROSTAR experience. *J Vasc Surg* 2002;35:211-21.
 1167. Blum U, Voshage G, Beyersdorf F, et al. Two-center German experience with aortic endografting. *J Endovasc Surg* 1997;4:137-46.
 1168. May J, White GH, Yu W, et al. Endovascular grafting for abdominal aortic aneurysms: changing incidence and indication for conversion to open operation. *Cardiovasc Surg* 1998;6:194-7.
 1169. Amesur NB, Zajko AB, Orons PD, et al. Embolotherapy of persistent endoleaks after endovascular repair of abdominal aortic aneurysm with the Ancure-endovascular technologies endograft system. *J Vasc Interv Radiol* 1999;10:1175-82.
 1170. Becquemin J, Bourriez A, D'Audiffret A, et al. Mid-term results of endovascular versus open repair for abdominal aortic aneurysm in patients anatomically suitable for endovascular

- repair. *Eur J Vasc Endovasc Surg* 2000;19:656-61.
1171. Zarins CK, White RA, Fogarty TJ. Aneurysm rupture after endovascular repair using the AneuRx stent graft. *J Vasc Surg* 2000;31:960-70.
1172. Blum U, Hauer M, Pfammatter T, et al. Percutaneous endoprostheses for treatment of aortic aneurysms. *World J Surg* 2001;25:347-52; discussion 353-4.
1173. Fairman RM, Velazquez O, Baum R, et al. Endovascular repair of aortic aneurysms: critical events and adjunctive procedures. *J Vasc Surg* 2001;33:1226-32.
1174. Holzenbein TJ, Kretschmer G, Thurnher S, et al. Midterm durability of abdominal aortic aneurysm endograft repair: a word of caution. *J Vasc Surg* 2001;33(2 suppl):S46-54.
1175. Howell MH, Strickman N, Mortazavi A, et al. Preliminary results of endovascular abdominal aortic aneurysm exclusion with the AneuRx stent-graft. *J Am Coll Cardiol* 2001;38:1040-6.
1176. Sicard GA, Rubin BG, Sanchez LA, et al. Endoluminal graft repair for abdominal aortic aneurysms in high-risk patients and octogenarians: is it better than open repair? *Ann Surg* 2001;234:427-35; discussion 435-7.
1177. Dattilo JB, Brewster DC, Fan CM, et al. Clinical failures of endovascular abdominal aortic aneurysm repair: incidence, causes, and management. *J Vasc Surg* 2002;35:1137-44.
1178. Sampram ES, Karafa MT, Mascha EJ, et al. Nature, frequency, and predictors of secondary procedures after endovascular repair of abdominal aortic aneurysm. *J Vasc Surg* 2003;37:930-7.
1179. Ouriel K, Greenberg RK, Clair DG, et al. Endovascular aneurysm repair: gender-specific results. *J Vasc Surg* 2003;38:93-8.
1180. Shames ML, Sanchez LA, Rubin BG, et al. Delayed complications after endovascular AAA repair in women. *J Endovasc Ther* 2003;10:10-5.
1181. Moore WS, Rutherford RB. Transfemoral endovascular repair of abdominal aortic aneurysm: results of the North American EVT phase I trial. *EVT Investigators. J Vasc Surg* 1996;23:543-53.
1182. Coppi G, Pacchioni R, Moratto R, et al. Experience with the Stentor endograft at four Italian centers. *J Endovasc Surg* 1998;5:206-15.
1183. Becquemin JP, Lapie V, Favre JP, et al. Mid-term results of a second generation bifurcated endovascular graft for abdominal aortic aneurysm repair: the French Vanguard trial. *J Vasc Surg* 1999;30:209-18.
1184. Zarins CK, White RA, Schwarten D, et al. AneuRx stent graft versus open surgical repair of abdominal aortic aneurysms: multicenter prospective clinical trial. *J Vasc Surg* 1999;29:292-305; discussion 306-8.
1185. Zarins CK, White RA, Hodgson KJ, et al. Endoleak as a predictor of outcome after endovascular aneurysm repair: AneuRx multicenter clinical trial. *J Vasc Surg* 2000;32:90-107.
1186. Beebe HG, Cronenwett JL, Katzen BT, et al. Results of an aortic endograft trial: impact of device failure beyond 12 months. *J Vasc Surg* 2001;33(2 suppl):S55-63.
1187. Faries PL, Brener BJ, Connelly TL, et al. A multicenter experience with the Talent endovascular graft for the treatment of abdominal aortic aneurysms. *J Vasc Surg* 2002;35:1123-8.
1188. Matsumura JS, Brewster DC, Makaroun MS, et al. A multicenter controlled clinical trial of open versus endovascular treatment of abdominal aortic aneurysm. *J Vasc Surg* 2003;37:262-71.
1189. Harris PL, Vallabhaneni SR, Desgranges P, et al. Incidence and risk factors of late rupture, conversion, and death after endovascular repair of infrarenal aortic aneurysms: the EUROSTAR experience. *European Collaborators on Stent/graft techniques for aortic aneurysm repair. J Vasc Surg* 2000;32:739-49.
1190. Vallabhaneni SR, Harris PL. Lessons learnt from the EUROSTAR registry on endovascular repair of abdominal aortic aneurysm repair. *Eur J Radiol* 2001;39:34-41.
1191. Peppelenbosch N, Buth J, Harris PL, et al. Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. *J Vasc Surg* 2004;39:288-97.
1192. Riambau V, Laheij RJ, Garcia-Madrid C, et al. The association between co-morbidity and mortality after abdominal aortic aneurysm endografting in patients ineligible for elective open surgery. *Eur J Vasc Endovasc Surg* 2001;22:265-70.
1193. Walker SR, Macierewicz J, MacSweeney ST, et al. Mortality rates following endovascular repair of abdominal aortic aneurysms. *J Endovasc Surg* 1999;6:233-8.
1194. Birch SE, Stary DR, Scott AR. Cost of endovascular versus open surgical repair of abdominal aortic aneurysms. *Aust N Z J Surg* 2000;70:660-6.
1195. Clair DG, Gray B, O'hara PJ, et al. An evaluation of the costs to health care institutions of endovascular aortic aneurysm repair. *J Vasc Surg* 2000;32:148-52.
1196. Bosch JL, Lester JS, McMahon PM, et al. Hospital costs for elective endovascular and surgical repairs of infrarenal abdominal aortic aneurysms. *Radiology* 2001;220:492-7.
1197. Sternbergh WC 3rd, Money SR. Hospital cost of endovascular versus open repair of abdominal aortic aneurysms: a multicenter study. *J Vasc Surg* 2000;31:237-44.
1198. Carpenter JP, Baum RA, Barker CF, et al. Durability of benefits of endovascular versus conventional abdominal aortic aneurysm repair. *J Vasc Surg* 2002;35:222-8.
1199. Bertges DJ, Zwolak RM, Deaton DH, et al. Current hospital costs and medicare reimbursement for endovascular abdominal aortic aneurysm repair. *J Vasc Surg* 2003;37:272-9.
1200. Arko FR, Hill BB, Reeves TR, et al. Early and late functional outcome assessments following endovascular and open aneurysm repair. *J Endovasc Ther* 2003;10:2-9.
1201. Schermerhorn ML, Finlayson SR, Fillinger MF, et al. Life expectancy after endovascular versus open abdominal aortic aneurysm repair: results of a decision analysis model on the basis of data from EUROSTAR. *J Vasc Surg* 2002;36:1112-20.
1202. Cuypers P, Buth J, Harris PL, et al. Realistic expectations for patients with stent-graft treatment of abdominal aortic aneurysms: results of a European multicentre registry. *Eur J Vasc Endovasc Surg* 1999;17:507-16.
1203. Ohki T, Veith FJ, Shaw P, et al. Increasing incidence of midterm and long-term complications after endovascular graft repair of abdominal aortic aneurysms: a note of caution based on a 9-year experience. *Ann Surg* 2001;234:323-34; discussion 334-5.
1204. Ouriel K, Clair DG, Greenberg RK, et al. Endovascular repair of abdominal aortic aneurysms: device-specific outcome. *J Vasc Surg* 2003;37:991-8.
1205. Cuypers PW, Laheij RJ, Buth J. Which factors increase the risk of conversion to open surgery following endovascular abdominal aortic aneurysm repair? The EUROSTAR collaborators. *Eur J Vasc Endovasc Surg* 2000;20:183-9.
1206. Laheij RJ, Buth J, Harris PL, et al. Need for secondary interventions after endovascular repair of abdominal aortic aneurysms: intermediate-term follow-up results of a European collaborative registry (EUROSTAR). *Br J Surg* 2000;87:1666-73.
1207. Conner MS 3rd, Sternbergh WC 3rd, Carter G, et al. Secondary procedures after endovascular aortic aneurysm repair. *J Vasc Surg* 2002;36:992-6.

1208. Ayerdi J, McLafferty RB, Markwell SJ, et al. Indications and outcomes of AneuRx Phase III trial versus use of commercial AneuRx stent graft. *J Vasc Surg* 2003;37:739-43.
1209. Sternbergh WC, Nordness PJ, York JW, et al. Endo-exuberance to endo-reality: trends in the management of 431 AAA repairs between 1996 and 2002. *J Endovasc Ther* 2003;10:418-23.
1210. Zarins CK, Bloch DA, Crabtree T, et al. Aneurysm enlargement following endovascular aneurysm repair: AneuRx clinical trial. *J Vasc Surg* 2004;39:109-17.
1211. Laheij RJ, van Marrewijk CJ, EUROSTAR Group. The evolving technique of endovascular stenting of abdominal aortic aneurysm; time for reappraisal. *Eur J Vasc Endovasc Surg* 2001; 22:436-42.
1212. Ouriel K, Srivastava SD, Sarac TP, et al. Disparate outcome after endovascular treatment of small versus large abdominal aortic aneurysm. *J Vasc Surg* 2003;37:1206-12.
1213. Scheinert D, Schroder M, Steinkamp H, et al. Treatment of iliac artery aneurysms by percutaneous implantation of stent grafts. *Circulation* 2000;102(19 suppl 3):III253-8.
1214. Hausegger KA, Mendel H, Tiessenhausen K, et al. Endoluminal treatment of infrarenal aortic aneurysms: clinical experience with the Talent stent-graft system. *J Vasc Interv Radiol* 1999; 10:267-74.
1215. Howell MH, Zaqq M, Villareal RP, et al. Endovascular exclusion of abdominal aortic aneurysms: initial experience with stent-grafts in cardiology practice. *Tex Heart Inst J* 2000; 27:136-45.
1216. Criado FJ, Wilson EP, Fairman RM, et al. Update on the Talent aortic stent-graft: a preliminary report from United States phase I and II trials. *J Vasc Surg* 2001;33(2 suppl):S146-9.
1217. Valentine RJ, Decaprio JD, Castillo JM, et al. Watchful waiting in cases of small abdominal aortic aneurysms: appropriate for all patients? *J Vasc Surg* 2000;32:441-8; discussion 448-50.
1218. Zarins CK, Shaver DM, Arko FR, et al. Introduction of endovascular aneurysm repair into community practice: initial results with a new Food and Drug Administration-approved device. *J Vasc Surg* 2002;36:226-32; discussion 232-3.
1219. Trastek VF, Pairolero PC, Joyce JW, et al. Splenic artery aneurysms. *Surgery* 1982;91:694-9.
1220. Cohen JR, Shamash FS. Ruptured renal artery aneurysms during pregnancy. *J Vasc Surg* 1987;6:51-9.
1221. Ohta M, Hashizume M, Tanoue K, et al. Splenic hyperkinetic state and splenic artery aneurysm in portal hypertension. *Hepatogastroenterology* 1992;39:529-32.
1222. Kobori L, van der Kolk MJ, de Jong KP, et al. Splenic artery aneurysms in liver transplant patients. *Liver Transplant Group. J Hepatol* 1997;27:890-3.
1223. Lee PC, Rhee RY, Gordon RY, et al. Management of splenic artery aneurysms: the significance of portal and essential hypertension. *J Am Coll Surg* 1999;189:483-90.
1224. Carmeci C, McClenathan J. Visceral artery aneurysms as seen in a community hospital. *Surg Gynecol Obstet* 2000;179:486-9.
1225. Carr SC, Mahvi DM, Hoch JR, et al. Visceral artery aneurysm rupture. *J Vasc Surg* 2001;33:806-11.
1226. Stone WM, Abbas M, Cherry KJ, et al. Superior mesenteric artery aneurysms: is presence an indication for intervention? *J Vasc Surg* 2002;36:234-7; discussion 237.
1227. Tham G, Ekelund L, Herrlin K, et al. Renal artery aneurysms: natural history and prognosis. *Ann Surg* 1983;197:348-52.
1228. Henriksson C, Björkerud S, Nilson AE, et al. Natural history of renal artery aneurysm elucidated by repeated angiography and pathoanatomical studies. *Eur Urol* 1985;11:244-8.
1229. Hallett JW Jr. Splenic artery aneurysms. *Semin Vasc Surg* 1995; 8:321-6.
1230. Kasirajan K, Greenberg RK, Clair D, et al. Endovascular management of visceral artery aneurysm. *J Endovasc Ther* 2001; 8:150-5.
1231. Angelakis EJ, Bair WE, Barone JE, et al. Splenic artery aneurysm rupture during pregnancy. *Obstet Gynecol Surv* 1993;48:145-8.
1232. Salam TA, Lumsden AB, Martin LG, et al. Nonoperative management of visceral aneurysms and pseudoaneurysms. *Surg Gynecol Obstet* 1992;164:215-9.
1233. Carr SC, Pearce WH, Vogelzang RL, et al. Current management of visceral artery aneurysms. *Surgery* 1996;120:627-33; discussion 633-4.
1234. Sandgren T, Sonesson B, Ahlgren R, et al. The diameter of the common femoral artery in healthy human: influence of sex, age, and body size. *J Vasc Surg* 1999;29:503-10.
1235. Graham LM, Zelenock GB, Whitehouse WM Jr, et al. Clinical significance of arteriosclerotic femoral artery aneurysms. *Arch Surg* 1980;115:502-7.
1236. Whitehouse WM Jr, Wakefield TW, Graham LM, et al. Limb-threatening potential of arteriosclerotic popliteal artery aneurysms. *Surgery* 1983;93:694-9.
1237. MacSweeney ST, Skidmore C, Turner RJ, et al. Unravelling the familial tendency to aneurysmal disease: popliteal aneurysm, hypertension and fibrillin genotype. *Eur J Vasc Endovasc Surg* 1996;12:162-6.
1238. Lawrence PF, Lorenzo-Rivero S, Lyon JL. The incidence of iliac, femoral, and popliteal artery aneurysms in hospitalized patients. *J Vasc Surg* 1995;22:409-15; discussion 415-6.
1239. van Keulen CJ, van de Akker E, Pals G, et al. The role of type III collagen in the development of familial abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1999;18:65-70.
1240. Lanne T, Hansen F, Mangell P, et al. Differences in mechanical properties of the common carotid artery and abdominal aorta in healthy males. *J Vasc Surg* 1994;20:218-25.
1241. Makita S, Ohira A, Tachieda R, et al. Dilation and reduced distensibility of carotid artery in patients with abdominal aortic aneurysms. *Am Heart J* 2000;140:297-302.
1242. Tilson MD, Dang C. Generalized arteriomegaly: a possible predisposition to the formation of abdominal aortic aneurysms. *Arch Surg* 1981;116:1030-2.
1243. Ward AS. Aortic aneurysmal disease: a generalized dilating diathesis. *Arch Surg* 1992;127:990-1.
1244. Callum KG, Lea Thomas M, Browse NL. A definition of arteriomegaly and the size of arteries supplying the lower limbs. *Br J Surg* 1983;70:524-9.
1245. Duffy ST, Colgan MP, Sultan S, et al. Popliteal aneurysms: a 10-year experience. *Eur J Vasc Endovasc Surg* 1998;16:218-22.
1246. Taurino M, Calisti A, Grossi R, et al. Outcome after early treatment of popliteal artery aneurysms. *Int Angiol* 1998;17:28-33.
1247. Baxter BT, McGee GS, Flinn WR, et al. Distal embolization as a presenting symptom of aortic aneurysms. *Surg Gynecol Obstet* 1990;160:197-201.
1248. Gifford RW Jr, Hines EA Jr, Janes JM. An analysis and follow-up study of one hundred popliteal aneurysms. *Surgery* 1953;33:284-93.
1249. Dawson I, Sie RB, van Bockel JH. Atherosclerotic popliteal aneurysm. *Br J Surg* 1997;84:293-9.
1250. Dawson I, van Bockel JH, Brand R, et al. Popliteal artery aneurysms. Long-term follow-up of aneurysmal disease and results of surgical treatment. *J Vasc Surg* 1991;13:398-407.

1251. Dawson I, Sie R, van Baalen JM, et al. Asymptomatic popliteal aneurysm: elective operation versus conservative follow-up. *Br J Surg* 1994;81:1504-7.
1252. Lowell RC, Gloviczki P, Hallett JW Jr, et al. Popliteal artery aneurysms: the risk of nonoperative management. *Ann Vasc Surg* 1994;8:14-23.
1253. Schroder A, Gohlke J, Gross-Fengels W, et al. [Popliteal aneurysms—surgical management versus conservative procedure] *Langenbecks Arch Chir Suppl Kongressbd* 1996;113:857-63.
1254. Roggo A, Brunner U, Ottinger LW, et al. The continuing challenge of aneurysms of the popliteal artery. *Surg Gynecol Obstet* 1993;177:565-72.
1255. Szilagyi DE, Schwartz RL, Reddy DJ. Popliteal arterial aneurysms: their natural history and management. *Arch Surg* 1981;116:724-8.
1256. Poirier NC, Verdant A, Page A. [Popliteal aneurysm: surgical treatment is mandatory before complications occur] *Ann Chir* 1996;50:613-8.
1257. Stiegler H, Mandler G, Baumann G. Prospective study of 36 patients with 46 popliteal artery aneurysms with non-surgical treatment. *Vasa* 2002;31:43-6.
1258. Jivegard L, Holm J, Bergqvist D, et al. Acute lower limb ischemia: failure of anticoagulant treatment to improve one-month results of arterial thromboembolectomy: a prospective randomized multi-center study. *Surgery* 1991;109:610-6.
1259. Jarrett F, Makaroun MS, Rhee RY, et al. Superficial femoral artery aneurysms: an unusual entity? *J Vasc Surg* 2002;36:571-4.
1260. Cutler BS, Darling RC. Surgical management of arteriosclerotic femoral aneurysms. *Surgery* 1973;74:764-73.
1261. Roseman JM, Wyche D. True aneurysm of the profunda femoris artery. Literature review, differential diagnosis, management. *J Cardiovasc Surg (Torino)* 1987;28:701-5.
1262. Levi N, Schroeder TV. Blood transfusion requirement in surgery for femoral artery aneurysms. *J Cardiovasc Surg (Torino)* 1997;38:661-3.
1263. Levi N, Schroeder TV. Arteriosclerotic femoral artery aneurysms: a short review. *J Cardiovasc Surg (Torino)* 1997;38:335-8.
1264. Defraigne JO, Limet R. [An unusual presentation of an aortic abdominal aneurysm, source of diagnostic errors: chronic rupture] *Rev Med Liege* 1997;52:535-40.
1265. Farina C, Cavallaro A, Schultz RD, et al. Popliteal aneurysms. *Surg Gynecol Obstet* 1989;169:7-13.
1266. Anton GE, Hertzner NR, Beven EG, et al. Surgical management of popliteal aneurysms. Trends in presentation, treatment, and results from 1952 to 1984. *J Vasc Surg* 1986;3:125-34.
1267. Cole CW, Thijssen AM, Barber GG, et al. Popliteal aneurysms: an index of generalized vascular disease. *Can J Surg* 1989;32:65-8.
1268. Inahara T, Toledo AC. Complications and treatment of popliteal aneurysms. *Surgery* 1978;84:775-83.
- 1268a. Lilly MP, Flinn WR, McCarthy WJ, III, et al. The effect of distal arterial anatomy on the success of popliteal aneurysm repair. *J Vasc Surg* 1988;7:653-60.
1269. Reilly MK, Abbott WM, Darling RC. Aggressive surgical management of popliteal artery aneurysms. *Surg Gynecol Obstet* 1983;145:498-502.
1270. Schellack J, Smith RB 3rd, Perdue GD. Nonoperative management of selected popliteal aneurysms. *Arch Surg* 1987;122:372-5.
1271. Towne JB, Thompson JE, Patman DD, et al. Progression of popliteal aneurysmal disease following popliteal aneurysm resection with graft: a twenty year experience. *Surgery* 1976;80:426-32.
1272. Graham L. Femoral and popliteal aneurysms. In: Rotherford RB, ed. *Vascular Surgery*. 5th ed. Philadelphia, Pa: WB Saunders; 2000:1345-56.
1273. Adiseshiah M, Bailey DA. Aneurysms of the femoral artery. *Br J Surg* 1977;64:174-6.
1274. Baird RJ, Gurry JF, Kellam J, et al. Arteriosclerotic femoral artery aneurysms. *Can Med Assoc J* 1977;117:1306-7.
1275. Sapienza P, Mingoli A, Feldhaus RJ, et al. Femoral artery aneurysms: long-term follow-up and results of surgical treatment. *Cardiovasc Surg* 1996;4:181-84.
1276. Feld R, Patton GM, Carabasi RA, et al. Treatment of iatrogenic femoral artery injuries with ultrasound-guided compression. *J Vasc Surg* 1992;16:832-40.
1277. Fellmeth BD, Roberts AC, Bookstein JJ, et al. Postangiographic femoral artery injuries: nonsurgical repair with US-guided compression. *Radiology* 1991;178:671-5.
1278. Johns JP, Pupa LE Jr, Bailey SR. Spontaneous thrombosis of iatrogenic femoral artery pseudoaneurysms: documentation with color Doppler and two-dimensional ultrasonography. *J Vasc Surg* 1991;14:24-9.
1279. Kazmers A, Meeker C, Nofz K, et al. Nonoperative therapy for postcatheterization femoral artery pseudoaneurysms. *Am Surg* 1997;63:199-204.
1280. Kresowik TF, Khoury MD, Miller BV, et al. A prospective study of the incidence and natural history of femoral vascular complications after percutaneous transluminal coronary angioplasty. *J Vasc Surg* 1991;13:328-33; discussion 333-5.
1281. Samuels D, Orron DE, Kessler A, et al. Femoral artery pseudoaneurysm: Doppler sonographic features predictive for spontaneous thrombosis. *J Clin Ultrasound* 1997;25:497-500.
1282. Schaub F, Theiss W, Busch R, et al. Management of 219 consecutive cases of postcatheterization pseudoaneurysm. *J Am Coll Cardiol* 1997;30:670-5.
1283. Toursarkissian B, Allen BT, Petrinc D, et al. Spontaneous closure of selected iatrogenic pseudoaneurysms and arteriovenous fistulae. *J Vasc Surg* 1997;25:803-8; discussion 808-9.
1284. Weatherford DA, Taylor SM, Langan EM, et al. Ultrasound-guided compression for the treatment of iatrogenic femoral pseudoaneurysms. *South Med J* 1997;90:223-6.
1285. Chatterjee T, Do DD, Mahler F, et al. A prospective, randomized evaluation of nonsurgical closure of femoral pseudoaneurysm by compression device with or without ultrasound guidance. *Catheter Cardiovasc Interv* 1999;47:304-9.
1286. Coghlan JG, Cowell R, Jepson N, et al. Simplified method for compression of femoral false aneurysms. *Eur Heart J* 1995;16:1589-92.
1287. Cox GS, Young JR, Gray BR, et al. Ultrasound-guided compression repair of postcatheterization pseudoaneurysms: results of treatment in one hundred cases. *J Vasc Surg* 1994;19:683-6.
1288. Dean SM, Olin JW, Piedmonte M, et al. Ultrasound-guided compression closure of postcatheterization pseudoaneurysms during concurrent anticoagulation: a review of seventy-seven patients. *J Vasc Surg* 1996;23:28-34, discussion 34-5.
1289. Hajarizadeh H, LaRosa CR, Cardullo P, et al. Ultrasound-guided compression of iatrogenic femoral pseudoaneurysm failure, recurrence, and long-term results. *J Vasc Surg* 1995;22:425-30; discussion 430-3.
1290. Hertz SM, Brenner BJ. Ultrasound-guided pseudoaneurysm compression: efficacy after coronary stenting and angioplasty. *J Vasc Surg* 1997;26:913-6; discussion 916-8.
1291. Kumins NH, Landau DS, Montalvo J, et al. Expanded indications for the treatment of postcatheterization femoral pseudoa-

- neurysms with ultrasound-guided compression. *Surg Gynecol Obstet* 1998;176:131-6.
1292. Langella RL, Schneider JR, Golan JF. Color duplex-guided compression therapy for postcatheterization pseudoaneurysms in a community hospital. *Ann Vasc Surg* 1996;10:27-35.
1293. Paulson EK, Kliewer MA, Hertzberg BS, et al. Ultrasonographically guided manual compression of femoral artery injuries. *J Ultrasound Med* 1995;14:653-9.
1294. Perkins JM, Gordon AC, Magee TR, et al. Duplex-guided compression of femoral artery false aneurysms reduces the need for surgery. *Ann R Coll Surg Engl* 1996;78:473-5.
1295. Sorrell KA, Feinberg RL, Wheeler JR, et al. Color-flow duplex-directed manual occlusion of femoral false aneurysms. *J Vasc Surg* 1993;17:571-7.
1296. Steinkamp HJ, Werk M, Felix R. Treatment of postinterventional pseudoaneurysms by ultrasound-guided compression. *Invest Radiol* 2000;35:186-92.
1297. Edgerton JR, Moore DO, Nichols D, et al. Obliteration of femoral artery pseudoaneurysm by thrombin injection. *Ann Thorac Surg* 2002;74:S1413-5.
1298. Olsen DM, Rodriguez JA, Vranic M, et al. A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 2002;36:779-82.
1299. La Perna L, Olin JW, Goines D, et al. Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. *Circulation* 2000;102:2391-5.
1300. Mohler ER III, Mitchell ME, Carpenter JP, et al. Therapeutic thrombin injection of pseudoaneurysms: a multicenter experience. *Vasc Med* 2001;6:241-4.
1301. Friedman SG, Pellerito JS, Scher L, et al. Ultrasound-guided thrombin injection is the treatment of choice for femoral pseudoaneurysms. *Arch Surg* 2002;137:462-4.
1302. Lonn L, Olmarker A, Geterud K, et al. Treatment of femoral pseudoaneurysms. Percutaneous US-guided thrombin injection versus US-guided compression. *Acta Radiol* 2002;43:396-400.
1303. Hughes MJ, McCall JM, Nott DM, et al. Treatment of iatrogenic femoral artery pseudoaneurysms using ultrasound-guided injection of thrombin. *Clin Radiol* 2000;55:749-51.
1304. Kang SS, Labropoulos N, Mansour MA, et al. Expanded indications for ultrasound-guided thrombin injection of pseudoaneurysms. *J Vasc Surg* 2000;31:289-98.
1305. Liao CS, Ho FM, Chen MF, et al. Treatment of iatrogenic femoral artery pseudoaneurysm with percutaneous thrombin injection. *J Vasc Surg* 1997;26:18-23.
1306. Reeder SB, Widlus DM, Lazinger M. Low-dose thrombin injection to treat iatrogenic femoral artery pseudoaneurysms. *AJR Am J Roentgenol* 2001;177:595-8.
1307. Sackett WR, Taylor SM, Coffey CB, et al. Ultrasound-guided thrombin injection of iatrogenic femoral pseudoaneurysms: a prospective analysis. *Am Surg* 2000;66:937-40; discussion 940-2.
1308. Taylor BS, Rhee RY, Muluk S, et al. Thrombin injection versus compression of femoral artery pseudoaneurysms. *J Vasc Surg* 1999;30:1052-9.

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