From the Society for Vascular Surgery

Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication

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Peripheral arterial disease (PAD) continues to grow in global prevalence and consumes an increasing amount of resources in the United States health care system. Overall rates of intervention for PAD have been rising steadily in recent years. Changing demographics, evolution of technologies, and an expanding database of outcomes studies are primary forces influencing clinical decision making in PAD. The management of PAD is multidisciplinary, involving primary care physicians and vascular specialists with varying expertise in diagnostic and treatment modalities. PAD represents a broad spectrum of disease from asymptomatic through severe limb ischemia. The Society for Vascular Surgery Lower Extremity Practice Guidelines committee reviewed the evidence supporting clinical care in the treatment of asymptomatic PAD and intermittent claudication (IC). The committee made specific practice recommendations using the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system. There are limited Level I data available for many of the critical questions in the field, demonstrating the urgent need for comparative effectiveness research in PAD. Emphasis is placed on risk factor modification, medical therapies, and broader use of exercise programs to improve cardiovascular health and functional performance. Screening for PAD appears of unproven benefit at present. Revascularization for IC is an appropriate therapy for selected patients with disabling symptoms, after a careful risk-benefit analysis. Treatment should be individualized based on comorbid conditions, degree of functional impairment, and anatomic factors. Invasive treatments for IC should provide predictable functional improvements with reasonable durability. A minimum threshold of a >50% likelihood of sustained efficacy for at least 2 years is suggested as a benchmark. Anatomic patency (freedom from restenosis) is considered a prerequisite for sustained efficacy of revascularization in IC. Endovascular approaches are favored for most candidates with aortoiliac disease and for selected patients with femoropopliteal disease in whom anatomic durability is expected to meet this minimum threshold. Conversely, caution is warranted in the use of interventions for IC in anatomic settings where durability is limited (extensive calcification, small-caliber arteries, diffuse infrainguinal disease, poor runoff). Surgical bypass may be a preferred strategy in good-risk patients with these disease patterns or in those with prior endovascular failures. Common femoral artery disease should be treated surgically, and saphenous vein is the preferred conduit for infrainguinal bypass grafting. Patients who undergo invasive treatments for IC should be monitored regularly in a surveillance program to record subjective improvements, assess risk factors, optimize compliance with cardioprotective medications, and monitor hemodynamic and patency status. (J Vasc Surg 2015;61:2S-41S.)

DEVELOPMENT OF THE GUIDELINES DOCUMENT

The Society for Vascular Surgery (SVS) Lower Extremity Guidelines Committee began the process by developing a detailed outline of the diagnostic and management choices for peripheral arterial disease (PAD) by stage of disease. Given the broad scope of the field, the committee determined that this document should focus on the evaluation and management of

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Author conflict of interest: This information is available in the Appendix.

Independent peer-review and oversight has been provided by members of the SVS Document Oversight Committee: Peter Gloviczki, MD (Chair), Mark Eskandari, MD, Thomas Forbes, MD, Glenn LaMuraglia, MD, Michel Makaroun, MD, Russell Samson, MD, Timur Sarac, MD, Piergiorgio Settembrini, MD.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2014.12.009

asymptomatic disease and intermittent claudication (IC). Separate practice guidelines for critical limb ischemia (CLI) will be established in a future document. The committee developed sets of key questions and, with the input of a methodologist, condensed these into topics that framed systematic evidence reviews. The quantity and quality of evidence available was also an important factor in determining the rationale for the systematic review topics. De novo evidence reviews were undertaken to examine the rationale for screening in asymptomatic PAD and the comparative effectiveness of current treatments for IC. These systematic reviews are published jointly with this guideline document.[1,2]

The committee developed the practice guideline by assigning two or three members to create primary drafts of each section of the document, highlighting specific questions where recommendations were needed and appropriate. Each section was then reviewed and revised by the remainder of the writing group and the two co-chairs. All guideline recommendations were reviewed by the full committee and finalized via an iterative, consensus process. In considering available treatment modalities, we focused on options currently available to patients and physicians in the United States (U.S.).

The Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework was used for determining the strength of recommendation and the quality of evidence, as previously reported.[3] The quality of evidence is rated as high (A), moderate (B), or low (C). This rating is based on the risk of bias, precision, directness, consistency, and the size of the effect. The strength of recommendation is graded based on the quality of evidence, balance between benefits and harms, patients' values, preferences, and clinical context. Recommendations are graded as strong (1) or weak/conditional (2). The term "we recommend" is used with strong recommendations, and the term "we suggest" is used with conditional recommendations.

The methodologist assisted the committee in incorporating the evidence into the recommendations and helped in rating the quality of evidence and the strength of recommendations. Finally, this guideline was reviewed by the SVS Documents Oversight Committee that peer reviewed the document and provided content and methodology expertise.

CONFLICT OF INTEREST

All members of the committee provided updated disclosures on potential conflicts of interest (COI), in accordance with SVS policies.[4] The final roster of the Lower Extremity Guidelines Committee is in accordance with the current SVS COI policy, which is summarized elsewhere (http://www.vascularweb.org/about/policies/Pages/Conflict-of-Interest-Policy.aspx). COI disclosures for each of the writing group authors are listed at the end of the document in the Appendix.

1. EPIDEMIOLOGY AND RISK FACTORS

Although the worldwide prevalence of lower extremity PAD is uncertain,[5] an estimated 8 to 12 million Americans are affected by PAD.[6,7] A clear association between the prevalence of PAD and increased age has been established.[8,9] In an analysis of 2381 patients participating in the U.S. National Health and Nutrition Examination Survey, the prevalence of PAD was 4.3% overall, with a prevalence of 0.9% in patients aged between 40 and 49 years, 2.5% in patients aged between 50 and 59 years, 4.7% in patients aged between 60 and 69 years, and 14.5% in patients aged >69 years.[8] The prevalence of PAD is expected to increase in the United States and worldwide as the population ages, cigarette smoking persists, and the epidemics of diabetes mellitus, hypertension, and obesity grow.[7]

A recent meta-analysis of 34 studies that examined the prevalence and risk factors of PAD worldwide shattered some preconceived notions related to this disease.[5] With a conservative estimate of >202 million afflicted with this disease globally, this analysis showed a relative increase in PAD prevalence of 23.5% during the first decade of the new millennium. The most striking increases in prevalence were seen in low-income and middle-income countries (28.7%), although significant growth was also evident in high-income countries (13.1%). In high-income countries, PAD prevalence is equal between women and men, whereas in low-income and middle-income countries, PAD prevalence is higher in women, especially at younger ages. Increased longevity (age), smoking, and diabetes are the most strongly associated risk factors across all nations.

The economic effect of this growing burden of PAD is being experienced acutely in the United States and in many other industrialized nations. In 2001, the U.S. Medicare program spent an estimated >$4.3 billion on PAD-related treatment.[7] PAD-related treatment accounted for ~13% of all Medicare Part A and B expenditures for patients undergoing treatment for PAD and for 2.3% of total Medicare Part A and B expenditures during that year. These Medicare costs have continued to increase markedly. Analysis of data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry estimated total costs of vascular-related hospitalizations was $21 billion in the United States in 2004, with most costs associated with revascularization procedures.[10] Given the ongoing dramatic increases in the use of invasive treatments, these figures are likely underestimates of the current costs for PAD care in the United States.

Evidence of underlying PAD may be present in the absence of symptoms. For the purpose of this document, this is referred to as *asymptomatic disease*. Symptomatic PAD may present as IC, or with signs or symptoms consistent with limb-threatening ischemia, often referred to as *critical limb ischemia (CLI)*. In this guidelines document, we will only consider IC within the spectrum of symptomatic PAD.

IC is defined as a reproducible discomfort in a specific muscle group that is induced by exercise and then relieved with rest. Although the calf muscles are most often affected, any leg muscle group, such as those in the thigh or buttock, may be affected. This condition is caused by arterial obstruction proximal to the affected muscle bed, thereby attenuating exercise-induced augmentation of blood flow leading to transient muscle ischemia. IC is often the first clinical symptom associated with PAD and the most common. It is also well documented that many PAD patients experience

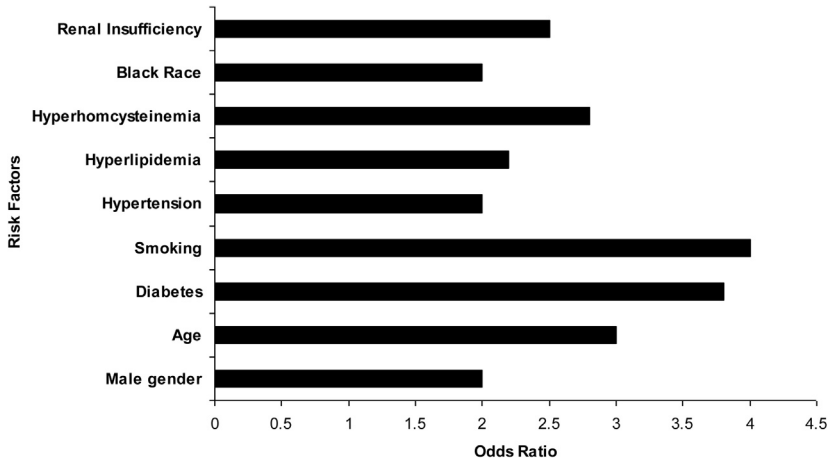

Fig 1. The approximate odds ratios (ORs) for risk factors associated with the development of peripheral arterial disease (PAD). Adapted from Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).[9]

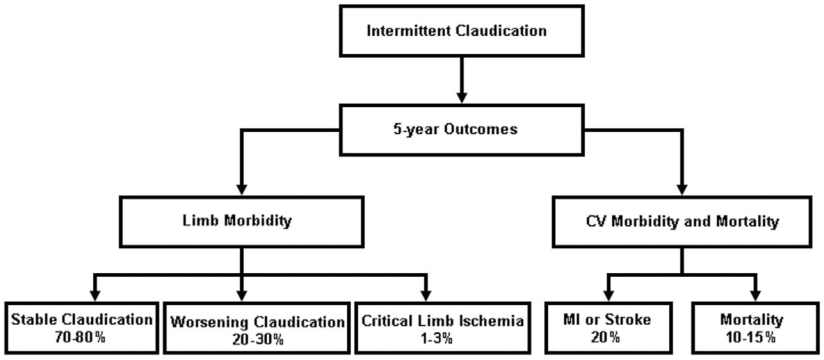

Fig 2. The natural history of patients with intermittent claudication (IC) treated with non-invasive management. *CV,* Cardiovascular; *MI,* myocardial infarction. Adapted from American College of Cardiology/Americal Heart Association guidelines.[43]

"atypical" leg symptoms that may reflect other pathophysiologic mechanisms (eg, myopathy) or the overlay of concomitant conditions, such as neuropathy, arthritis, and lumbar spine disease, that influence lower extremity function. Numerous population-based studies have attempted to ascertain the relative proportion of symptomatic patients amongst all those with PAD; taken in aggregate, these studies indicate that the ratio of symptomatic to asymptomatic PAD is on the order of 1:3.[9,11,12]

The risk factors associated with PAD are similar to those classically identified in the context of coronary artery disease, although the relative importance of these factors appears different (Fig 1).[8,11,13-18] Investigators from the Framingham Heart Study analyzing "factors of risk" for coronary artery disease were the first to identify demographic and comorbid factors independently associated with systemic atherosclerosis.[13,15] Numerous reports since have confirmed that advanced age, tobacco use, diabetes, hypertension, and hypercholesterolemia are the primary risk factors associated with PAD. More recent studies have identified non-Hispanic black race,[8,19] chronic renal insufficiency,[8,20] and elevated homocysteine levels[21,22] as additional factors associated with the onset of PAD. Elevated markers of inflammation, including high-sensitivity C-reactive protein, interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1, asymmetric dimethylarginine, β-2 macroglobulin, and cystatin C are novel risk factors whose clinical utility for predicting PAD onset or progression is not yet clear.[23-32]

2. DIAGNOSIS

Measurement of the ankle-brachial index (ABI) is the primary method for establishing the diagnosis of PAD. An ABI of ≤0.90 has been demonstrated to have high sensitivity and specificity for the identification of PAD compared with the gold standard of invasive arteriography.[9] Additional tests, such as carotid intima-media thickness[33,34] and brachial artery flow-mediated dilation,[35-37] have shown promise but have not been broadly applied because they require more specialized equipment and technical expertise.

Table I. The differential diagnosis for intermittent claudication (*IC*) (adapted from Inter-Society Consensus for the Management of Peripheral Arterial Disease [TASC II])[9]

Condition	*Location*	*Prevalence*	*Characteristic*	*Effect of exercise*	*Effect of rest*	*Effect of position*	*Other characteristic*
Calf IC	Calf muscles	3% of adult population	Cramping, aching discomfort	Reproducible onset	Quickly relieved	None	May have atypical limb symptoms on exercise
Thigh and buttock IC	Buttocks, hip, thigh	Rare	Cramping, aching, discomfort	Reproducible onset	Quickly relieved	None	Impotence. May have normal pedal pulses with isolated iliac artery disease
Foot IC	Foot arch	Rare	Severe pain on exercise	Reproducible onset	Quickly relieved	None	Also may present as numbness
Chronic compartment syndrome	Calf muscles	Rare	Tight, bursting pain	After much exercise (jogging)	Subsides very slowly	Relief with elevation	Typically heavy muscled athletes
Venous claudication	Entire leg, worse in calf	Rare	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep vein thrombosis, signs of venous congestion, edema
Nerve root compression	Radiates down leg	Common	Sharp lancinating pain	Induced by sitting, standing, or walking	Often present at rest	Improved by change in position	History of back problems. Worse with sitting. Relief when supine or sitting. Not intermittent
Symptomatic Baker cyst	Behind knee, down calf	Rare	Swelling, tenderness	With exercise	Present at rest	None	Not intermittent
Hip arthritis	Lateral hip, thigh	Common	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improved when not weight bearing	Symptoms variable. History of degenerative arthritis
Spinal stenosis	Often bilateral buttocks, posterior leg	Common	Pain and weakness	May mimic IC	Variable relief but can take a long time to recover	Relief by lumbar spine flexion	Worse with standing and extending spine
Foot/ankle arthritis	Ankle, foot, arch	Common	Aching pain	After variable degree of exercise	Not quickly relieved	May be relieved by not bearing weight	Variable, may relate to activity level and present at rest

The incremental value of ABI beyond standard risk scores (eg, Framingham) in predicting future death and cardiovascular events has been established by epidemiologic studies.[38] An ABI <0.9 or >1.4 portends an increased risk of major cardiovascular events.

The question of whether screening for PAD by ABI would yield public health benefit has been examined by several groups and remains an area of controversy. A recent review by the U.S. Preventive Services Task Force gave ABI screening an indeterminate rating, stating that there was insufficient evidence to assess the balance of benefits and harms.[39] The SVS-commissioned meta-analysis[1] demonstrates that ABI testing may incrementally improve cardiovascular risk prediction, but existing evidence does not support broad population screening of asymptomatic patients for PAD. However, future studies may identify targeted subgroups of patients, particularly those not yet on cardioprotective treatment regimens (eg, patients with diabetes alone, hypertension alone, or advanced age without clinically evident cardiovascular disease) that may benefit from PAD screening to trigger more aggressive medical management. To date, inadequate data exist to define these specific subgroups, and broad population screening appears unwarranted.

After a patient is identified with symptoms consistent with IC and an abnormal ABI, it is important to rule out other potential etiologies that can mimic PAD symptoms. The differential diagnosis for IC is extensive and is

summarized in Table I. By studying the characteristics associated with each condition listed in Table I, it is clear that most alternative diagnoses can be confirmed or excluded by a thorough history and physical examination. Careful characterization of the specific pattern of symptoms, with special attention to the factors that provoke, exacerbate, and relieve the symptoms, can almost always result in an accurate diagnosis.

Perhaps worthy of special mention is the differentiation of neurogenic claudication from vasculogenic claudication, because this is the most common clinical diagnostic challenge. In contrast to vasculogenic claudication, neurogenic claudication most often occurs secondary to nerve root compression on exit from the spinal canal. These symptoms may often include lower extremity pain that is radiating in nature, starting at the hips or buttocks and extending down the affected leg. In addition, radicular pain is frequently brought on by simple weight bearing or changes in posture (eg, rising after prolonged sitting) and relieved by a change in position to relieve the load on the spine (eg, lumbar flexion, sitting down). These features are in distinct contrast to vasculogenic claudication, which is induced by leg exercise and quickly relieved by rest (resulting in a decrease in muscular metabolic requirement), without a need to change position.

As mentioned, the cornerstone of the patient assessment for IC consists of a complete history and physical examination. Qualitative assessment of the extremity for signs of PAD includes the presence of weak or absent distal pulses, the absence of distal hair growth, evidence of dry skin secondary to apocrine gland dysfunction, and in the case of advanced PAD, nonhealing areas of skin breakdown. Quantitative assessment includes noninvasive vascular testing, of which the cornerstone is the measurement of the ABI. If the ABI is ≥1.4 secondary to noncompressibility of the arteries from calcification, a toe-brachial index is a useful alternative because the digital arteries are frequently not calcified. A toe-brachial index value of ≤0.7 is indicative of hemodynamically significant arterial insufficiency.[38] Although not necessary in all patients, further noninvasive testing with segmental pressures and pulse volume recordings can be helpful in objectively quantifying the magnitude of the deficit in perfusion and aiding in localizing the level of arterial obstruction.

In the setting of compelling symptoms and normal results on noninvasive vascular testing at rest, obtaining an ABI with exercise can be helpful. A challenge for establishing diagnostic criteria for the exercise ABI is the heterogeneity of the protocols used in vascular laboratories.[40-42] In general, this test is performed using a standardized treadmill protocol that asks patients to walk at a predetermined speed for a maximum of 5 minutes.[38] During the test, patients are asked to tell the personnel when they start to feel pain in the legs. Patients are encouraged to finish the entire test. Immediately after getting off of the treadmill, the exercise ABI is calculated. A drop in the ABI to a value ≤0.9 is indicative of a hemodynamically significant arterial obstruction.[38] Other more specific criteria include a drop of 30 mm Hg or 20% of the baseline ABI with exercise, and a delayed (>3 minutes) recovery.

Additional imaging modalities that can more precisely localize arterial lesions—arterial duplex, computed tomography angiography (CTA), magnetic resonance (MR) angiography (MRA), and contrast arteriography—should be reserved for patients in whom revascularization treatment is being considered. For those patients with asymptomatic PAD or IC who are not appropriate candidates for revascularization, the costs and potential risks associated with anatomic studies are not warranted.

Recommendations: Diagnosis of peripheral arterial disease (*PAD*)

		Grade	*Level of evidence*
2.1.	We recommend using the ABI as the first-line noninvasive test to establish a diagnosis of PAD in individuals with symptoms or signs suggestive of disease. When the ABI is borderline or normal (>0.9) and symptoms of claudication are suggestive, we recommend an exercise ABI.	1	A
2.2.	We suggest against routine screening for lower extremity PAD in the absence of risk factors, history, signs, or symptoms of PAD.	2	C
2.3.	For asymptomatic individuals who are at elevated risk, such as those aged >70, smokers, diabetic patients, those with an abnormal pulse examination, or other established cardiovascular disease, screening for lower extremity PAD is reasonable if used to improve risk stratification, preventive care, and medical management.	2	C
2.4.	In symptomatic patients who are being considered for revascularization, we suggest using physiologic noninvasive studies, such as segmental pressures and pulse volume recordings, to aid in the quantification of arterial insufficiency and help localize the level of obstruction.	2	C
2.5.	In symptomatic patients in whom revascularization treatment is being considered, we recommend anatomic imaging studies, such as arterial duplex ultrasound, CTA, MRA, and contrast arteriography.	1	B

ABI, Ankle-brachial index; *CTA,* computed tomography angiography; *MRA,* magnetic resonance angiography.

Summary of evidence: Diagnosis of peripheral arterial disease (*PAD*)

Clinical question	*Data source*	*Finding*	*Quality of evidence*
Accuracy of ABI in patients suspected to have PAD	Multiple nonrandomized diagnostic studies with comparison with the gold standard	ABI <0.9 has a sensitivity ranging from 79% to 95% with a specificity of >95%[43]	A-B
Accuracy of anatomic imaging studies and physiologic noninvasive studies in patients suspected to have PAD	Nonrandomized diagnostic studies with comparison with the gold standard	The combination of segmental limb pressures and pulse volume recordings had a diagnostic accuracy of 97%.[44] Duplex ultrasound imaging to detect a stenosis ≥50% in the aortoiliac tract: sensitivity, 86%; specificity, 97%; for the femoropopliteal tract: sensitivity, 80%; specificity, 96%; for the infragenicular arteries: sensitivity, 83%; specificity, 84%.[45] Accuracy of CT and MR imaging were >90%[46,47]	B-C
Benefits and harms of screening asymptomatic individuals with ABI	No data	No data on benefit or harm in patient-important outcomes[48]	C
Incremental value of adding ABI to traditional risk assessment tools (Framingham risk assessment)	Meta-analysis of cohort studies. Evidence is considered indirect because risk score is a surrogate outcome	Reclassification of risk and change in treatment recommendations in ~19% of men and 36% of women[49]	C

ABI, Ankle-brachial index; *CT*, computed tomography; *MR*, magnetic resonance.

3. MANAGEMENT OF ASYMPTOMATIC PATIENTS WITH PAD

The incidence of asymptomatic PAD in the U.S. population is substantial, extends across gender and race divisions, and may be readily confirmed by use of the ABI.[11,50] An important question is whether identification and treatment of the asymptomatic PAD population provides incremental health benefits beyond that derived from routine cardiovascular risk factor assessment and treatment. In addition to diagnosing PAD in patients with exertional leg symptoms or nonhealing wounds, the 2011 American College of Cardiology Foundation/American Heart Association PAD Guidelines recommend screening for PAD in all patients aged >65 years and in all patients aged >50 years with a history of diabetes or smoking.[51] As noted above, these recommendations run counter to the findings of the SVS-commissioned systematic review,[1] which suggests that no clear benefit is derived from screening for PAD in asymptomatic patients.

The recommendations of the U.S. Preventative Services Task Force in 2005 concluded that the harms of screening asymptomatic adults for PAD would outweigh any benefits.[52] The U.S. Preventative Services Task Force again addressed the issue of ABI screening in its 2013 publication[39] and concluded that "there is insufficient evidence to determine the balance of benefits and harms of screening for PAD with the ABI to prevent future cardiovascular disease outcomes." The conflicting recommendations and ongoing controversy demonstrate that although asymptomatic PAD is a sentinel indicator of cardiovascular morbidity and mortality, specific treatment pathways for this large PAD subpopulation remain poorly defined.

PAD primarily results from atherosclerotic occlusion of the arteries supplying the lower extremity. Consequently, management of asymptomatic PAD should be directed at accepted risk factor modification for patients with atherosclerosis. Pharmacologic strategies with proven benefit for symptomatic PAD have been empirically applied to the treatment of the asymptomatic PAD population. However, as noted below, certain pharmacologic interventions have failed to show benefit in the asymptomatic population, and others await verification. Nonetheless, accepted preventive strategies for atherosclerosis are appropriate for asymptomatic disease and for IC.

Smoking cessation. PAD severity has been shown to correlate to the extent of cigarette smoking.[53] In a broad sample of PAD patients, including ~27% who were asymptomatic, a community-based intervention ("stop smoking, keep walking") increased maximal walking distance and frequency of recreational ambulation.[54]

Antiplatelet therapy. The Aspirin for Asymptomatic Atherosclerosis Trial[55] randomized 3350 patients with asymptomatic PAD to treatment with enteric-coated aspirin (100 mg) or placebo. During 8 years of follow-up, no difference in vascular event rates was noted. However, this trial used an epidemiologic method of ABI determination in which the lower of the ankle pressures was used to calculate the ABI. Thus, the individuals in this study might not be fully representative of the universe of PAD patients with a greater burden of disease. At present, the benefit of antiplatelet therapy for patients with asymptomatic PAD and no other clinical cardiovascular disease is unknown.

Statin therapy. The Heart Protection Study established the protective effects of statin therapy in reducing mortality and cardiovascular events among individuals with PAD.[56] However, asymptomatic PAD patients were not specifically included unless they met other criteria, such as diabetes, hypertension, or other history of clinical cardiovascular or cerebrovascular disease. In addition to reducing cardiovascular event rates, statin use has been associated with improved lower extremity functioning.[57] This improvement was not related to improved lipid control or other confounding factors, and the association was noted in patients with and without PAD. At present, the benefit of lipid-lowering therapy in patients with asymptomatic PAD who lack other evidence of clinical cardiovascular disease (coronary, cerebral) or risk factors (diabetes, hypertension) remains unclear. Recently published treatment guidelines for lipid-lowering therapy suggest the use of statins should be considered in all individuals with an estimated 10-year risk of major cardiovascular events >7.5%.[58] This would seem to include any individual with established PAD.[6,50] Notably, the recommended risk estimation algorithm does not include evidence of PAD or the ABI value.[58]

Exercise and limb function. Although asymptomatic PAD patients do not report exertional leg discomfort by definition, careful assessment reveals impaired lower extremity function. An observational study of asymptomatic PAD patients demonstrated slower walking velocity, poorer standing balance, and other negative functional associations, despite correction for age, gender, smoking, and other comorbidities.[59] Whether targeted physical therapy interventions can reverse decline or improve functional performance and quality of life (QoL) in this population remains unclear.

Surveillance of asymptomatic patients for disease progression. In a small study of asymptomatic PAD patients, 35% of legs had developed new lower extremity arterial lesions on duplex scanning, and 26% of patients had developed new IC ≤1 year after diagnosis.[60] It is also important to note that some asymptomatic PAD patients, particularly those with diabetes, may develop CLI without an antecedent history of claudication. The incremental value and frequency of repeat ABI testing in asymptomatic PAD is not established but may be useful in higher-risk patients (eg, diabetic patients) or those with a lower baseline ABI. Regardless of hemodynamic or imaging findings, invasive treatments for PAD are only indicated for those with symptoms, with few exceptions noted below (eg, intervention for failing bypass graft or to support delivery of an indicated cardiovascular implant).

Recommendations: Management of asymptomatic disease

	Grade	*Level of evidence*
3.1. We recommend multidisciplinary comprehensive smoking cessation interventions for patients with asymptomatic PAD who use tobacco (repeatedly until tobacco use has stopped).	1	A
3.2. We recommend providing education about the signs and symptoms of PAD progression to asymptomatic patients with PAD.	1	Ungraded
3.3. We recommend against invasive treatments for PAD in the absence of symptoms, regardless of hemodynamic measures or imaging findings demonstrating PAD.	1	B

PAD, Peripheral arterial disease.

Summary of evidence: Management of asymptomatic disease

Clinical question	*Data source*	*Finding*	*Quality of evidence*
The effect of smoking cessation in patients with asymptomatic PAD	Observational studies in various settings applicable to patients with asymptomatic PAD	Smoking cessation reduces overall mortality and morbidity in smokers in general	A
Benefit for serial ABI testing (surveillance) in patients with asymptomatic PAD	Sparse data	No data on benefits and harms of surveillance	C

PAD, Peripheral arterial disease.

4. NONINTERVENTIONAL MANAGEMENT OF THE PATIENT WITH IC

As noted, IC is the most common clinical manifestation of PAD. Patients with IC may exhibit a wide range of symptom severity and associated effect on daily function. Moreover, concomitant conditions, such as cardiopulmonary disease, arthritis, spine disease, and obesity, can markedly limit exercise capacity in a synergistic fashion. Therefore, the treatment of IC must be individualized and based on a careful assessment of risk factors, compliance, and the subjective values of the patient. Of paramount importance at the time of the initial diagnosis is patient education, both regarding the long-term implications of PAD on cardiovascular health and to allay fears of amputation (Fig 2). Multiple studies have established that patients with IC are at increased risk for cardiovascular events, whereas the risk of major amputation is exceedingly low (<1% per year).[6,61] Establishing an appropriate therapeutic framework of risk reduction, lifestyle modification, and antiatherosclerotic medical therapies should always precede consideration of invasive procedures for IC.

Claudication significantly affects QoL, and this effect is often underestimated by treating physicians. IC is associated with severe functional impairment that can be significantly improved by intervention in properly selected patients. Multiple studies by McDermott et al[59,62,63] have objectively documented the adverse effect of PAD and claudication on patients' functional status. Even in patients with mild PAD, results of multiple tests of functional impairment, such as the 6-minute walk test, are significantly worse in PAD patients compared with those without PAD.[64] In addition to reduced functioning, severe PAD is associated with reduced survival.[63] Patients in the lowest quartile of an office-administered 6-minute walk performance test exhibited significantly increased mortality (odds ratio [OR], 2.36).

4A. Pharmacotherapy for patients with claudication: Risk reduction

Patients with IC carry a significant systemic burden of atherosclerosis and are at risk for its associated complications. These patients should have lifelong treatment designed to eliminate or modify known risk factors for atherosclerosis to reduce the risk of cardiovascular complications or death. In addition, treatment of risk factors can reduce the risk of periprocedural complications or death after any invasive treatments undertaken for PAD and may improve the patency of interventions. Many of the recommendations for risk-factor modification in PAD have been extrapolated from the literature on secondary prevention in coronary artery disease. This represents a notable gap in evidence specific to PAD and is particularly relevant in terms of setting defined treatment targets that are population-specific and disease-specific.

Smoking cessation. In observational studies, continued smoking is associated with higher rates of amputation, death, and myocardial infarction in patients with PAD compared with those who have quit.[65] Continued smoking has been associated with a twofold to threefold increase in the rate of lower extremity bypass graft failure compared with nonsmokers.[66,67]

Dyslipidemia. Treatment of dyslipidemia with statins reduces the likelihood of adverse cardiovascular events in patients with atherosclerosis.[56,68-70] Patients with PAD were designated as high or very high risk for adverse cardiovascular events by the National Cholesterol Educational Program Adult Treatment Panel #3 and are advised to undergo treatment to lower low-density lipoprotein cholesterol to <100 mg/dL or to <70 mg/dL in very high-risk individuals.[71] As noted above, the most recent guidelines on lipid therapy focus on the estimation of 10-year cardiovascular risk rather than specific lipid levels.

Although PAD per se is not included in the suggested risk estimation algorithm, historical data suggest that all PAD patients would meet the suggested threshold of a 7.5% 10-year risk. It is noteworthy that specific low-density lipoprotein targets have never been validated in the PAD population, who commonly demonstrate a phenotype of dyslipidemia (low high-density lipoprotein, elevated triglycerides), which contrasts with typical patients with isolated coronary artery disease. Statin therapy has also improved pain-free walking time in small studies of patients with IC.[72,73] The mechanism of this action is unknown. However, in the Claudication: Exercise vs Endoluminal Revascularization (CLEVER) trial,[74] conventional medical therapy, including statins for atherosclerosis, did not significantly improve walking ability or symptoms in patients with IC compared with supervised exercise or stenting (Section 5C).

Diabetes mellitus. The prevalence of PAD in patients with diabetes mellitus is estimated to be 29%.[75] Although it is unknown whether aggressive treatment to optimize serum glucose levels decreases the likelihood of adverse cardiovascular events in these patients, atherosclerosis tends to be more aggressive, and amputation rates in diabetic patients with atherosclerosis of the lower extremity are five to 10 times higher than in nondiabetic counterparts. Sensory neuropathy and increased susceptibility to infection contribute to the elevated rate of amputation.[9]

Hypertension. There is a strong association between hypertension and cardiovascular disease, including PAD; however, the relative risk is less for hypertension than for smoking or diabetes. Treatment of hypertension is indicated to reduce cardiovascular events, including congestive heart failure, stroke, and death.[76] There is no evidence that β-adrenergic blockers worsen the symptoms of IC.[77] Angiotensin-converting enzyme inhibitors (ACEIs) reduce the risk of death and nonfatal cardiac events in patients with left ventricular dysfunction.[78,79] In the Heart Outcomes Prevention Evaluation study, 4051 patients with PAD treated with ramipril had a 25% reduction of cardiac events.[80] This is notable, particularly in the context of a recent trial examining the effects of ramipril on walking performance (Section 4B).

Antiplatelet and antithrombotic agents. Numerous studies have demonstrated the benefit of antiplatelet therapy, especially aspirin, in doses of 75 to 325 mg/d in reducing rates of myocardial infarction, stroke, and vascular-related deaths in individuals with symptomatic lower extremity atherosclerosis.[81] The American Heart Association practice guidelines for lower extremity ischemia rated this treatment

recommendation class I-A.[43] In the 6452 patients with PAD in the Clopidogrel vs Aspirin In Patients At Risk of Ischaemic Events trial, clopidogrel reduced the myocardial infarction, stroke, or vascular death rate by 23.8% more than aspirin alone.[82] Although a single study demonstrated that combination aspirin and clopidogrel therapy was associated with a 20% relative risk reduction for myocardial infarction, cardiovascular death, or stroke,[83] there is no evidence to date that combination therapy is a more effective treatment for PAD than a single agent, and bleeding risks are increased.[84]

Warfarin has been demonstrated to reduce myocardial infarction or stroke in patients with coronary artery disease, although at the cost of a 4.5-fold increase in major bleeding.[85,86] There is no evidence that warfarin decreases the likelihood of adverse events related to PAD alone. Only one prospective trial exists comparing the effect of warfarin vs aspirin on graft patency. A similar number of graft occlusions occurred in both study cohorts, with a twofold increased risk of major bleeding in the warfarin cohort.[85]

Homocysteine-lowering drugs. Approximately 30% of patients with known PAD have elevated serum levels of homocysteine compared with 1% in the general population.[9] Folic acid and cobalamin (vitamin B_{12}) have been found to reduce serum homocysteine levels by 25% and 7%, respectively, in clinical trials. However, there are no data demonstrating that reducing homocysteine serum levels decreases the likelihood of adverse cardiovascular events in patients with PAD,[87] although clinical trials are ongoing.[87-89] Pending the outcomes of prospective trials, treating hyperhomocysteinemia with folic acid to reduce serum levels to <10 μmol/L is generally safe and well tolerated but is of no proven benefit.

4B. Pharmacotherapy for patients with IC to improve leg function

Medical management of IC is aimed at symptom relief (Table II) and slowing the progression of atherosclerotic disease. A number of drugs have been evaluated for use in patients with IC, but in the United States, there are currently only two Food and Drug Administration (FDA)-approved medications—cilostazol and pentoxifylline.[90-92] Of note, a recent review by the Royal College of Physicians in the United Kingdom identifies naftidrofuryl—widely available in Europe but not FDA-approved in the United States—as the drug of choice over both cilostazol and pentoxifylline in the medical management of symptomatic PAD.[93,94]

Pentoxifylline was the first drug approved by the FDA for IC in 1984. By reducing blood viscosity and retarding platelet aggregation, pentoxifylline use results in improved blood flow and enhanced tissue oxygenation in affected areas. Porter et al[91] revealed its effectiveness compared with placebo in a double-blind, placebo-controlled trial conducted at seven centers with use in outpatients. Pentoxifylline increased pain-free and maximal walking distance compared with placebo. Despite its significant findings in the Porter trial, clinical use of the drug has been limited due to the difficulty in identifying the IC patient who will predictably benefit.[95] Significant positive effects on the ABI at rest or after exercise have not been appreciated in multiple trials.[90,95,96] Although it has modest effect, pentoxifylline is well tolerated, safe, and relatively inexpensive. Dosing begins at 400-mg tablets three times per day and can be titrated up to 1800 mg/d. Side effects of nausea, headache, drowsiness, and anorexia have precluded long-term use in some patients. Hypertension can be exacerbated with use.

Cilostazol is a phosphodiesterase inhibitor that suppresses platelet aggregation and is also a direct vasodilator. Patients can notice improvement in maximal and pain-free walking distance in as short as 4 weeks.[92] Other phosphodiesterase inhibitors have been noted to increase mortality in patients with advanced heart failure; thus, cilostazol is contraindicated in patients with any level of heart failure. In addition to improving blood flow to the limb, there is evidence that cilostazol and pentoxifylline prevent lipid accumulation, oxidation, and coagulation (ie, preventing further progression of atherosclerosis). However, epidemiologic evidence suggests that many patients do not receive meaningful symptom relief with medical therapy alone. This is likely a result of the limited ability of drugs to enhance muscle function or limb blood flow to the levels observed with therapies such as exercise training or invasive revascularization.

The benefits of cilostazol in the treatment of IC were compared with those of pentoxifylline in a randomized controlled trial (RCT) performed by Dawson et al.[96] They found that cilostazol therapy significantly increased maximal walking distance by 107 m (54% increase) compared with a 64-m improvement in the pentoxifylline group (30% increase). There was no difference in maximal walking distance improvement between the pentoxifylline and placebo groups. Regarding the durability of the effect, a recent pooled analysis of seven RCTs demonstrated a significant benefit in maximal walking distance compared with placebo at 6 months.[92]

The ACEI ramipril is used in the treatment of hypertension and may also have beneficial effects in patients with PAD and IC. In the Heart Outcomes Protection Evaluation study,[97] treatment with ramipril reduced cardiovascular events and mortality even in patients without hypertension. Therefore, ramipril should be considered as a first-line choice for hypertension treatment in PAD patients, although it should be used with caution in the presence of renal artery stenosis. In a recent double-blind, placebo-controlled RCT, ramipril (10 mg/d for 24 weeks) was associated with significant improvements in pain-free and maximal treadmill walking times and in measures of physical function.[98] Given the modest size of this trial (212 patients) in three hospitals in Australia, further multicenter studies with longer follow-up are needed to support the routine use of ramipril for IC. This recommendation was stricken post-publication by the guidelines committee based on further review of the evidence and is no longer valid (see Supplementary Material on page 41S.e1, online only).

The vasoactive drug naftidrofuryl oxalate works by enhancing aerobic glycolysis and oxygen consumption in ischemic tissues, is commonly used in Europe, but is not currently approved in the United States. It has been shown to increase pain-free walking distance.[93,94]

Levocarnitine increases energy substrate for skeletal muscle metabolism. In clinical trials, a modest improvement

Recommendations: Medical treatment for intermittent claudication (*IC*)

		Grade	*Level of evidence*
4.1.	We recommend multidisciplinary comprehensive smoking cessation interventions for patients with IC (repeatedly until tobacco use has stopped).	1	A
4.2.	We recommend statin therapy in patients with symptomatic PAD.	1	A
4.3.	We recommend optimizing diabetes control (hemoglobin A_{1c} goal of <7.0%) in patients with IC if this goal can be achieved without hypoglycemia.	1	B
4.4.	We recommend the use of indicated β-blockers (eg, for hypertension, cardiac indications) in patients with IC. There is no evidence supporting concerns about worsening claudication symptoms.	1	B
4.5.	In patients with IC due to atherosclerosis, we recommend antiplatelet therapy with aspirin (75-325 mg daily).	1	A
4.6.	We recommend clopidogrel in doses of 75 mg daily as an effective alternative to aspirin for antiplatelet therapy in patients with IC.	1	B
4.7.	In patients with IC due to atherosclerosis, we suggest against using warfarin for the sole indication of reducing the risk of adverse cardiovascular events or vascular occlusions.	1	C
4.8.	We suggest against using folic acid and vitamin B_{12} supplements as a treatment of IC.	2	C
4.9.	In patients with IC who do not have congestive heart failure, we suggest a 3-month trial of cilostazol (100 mg twice daily) to improve pain-free walking.	2	A
4.10.	In patients with IC who cannot tolerate or have contraindications for cilostazol, we suggest a trial of pentoxifylline (400 mg thrice daily) to improve pain-free walking.	2	B

ACEI, Angiotensin-converting enzyme inhibitor; *PAD,* peripheral arterial disease.
A recommendation (4.11) for using ramipril in IC was originally made but subsequently deleted (see Supplementary Material on page 41S.e1, online only).

in maximal and pain-free walking distance has been seen compared with placebo; however, no benefit has been noted over exercise alone.[99,100] It is available in the United States over-the-counter as a dietary supplement.

4C. Exercise therapy for claudication

Exercise therapy has been a cornerstone in the management of IC for >40 years and has been the subject of case series, randomized trials, and meta-analyses (Table II). Exercise programs for patients with IC have been found to increase the distance to onset of claudication and increase the distance to maximum claudication pain. A meta-analysis of 1200 patients determined exercise therapy, compared with placebo or usual care, provides an overall improvement in walking ability of 50% to 200%, with improvements maintained for up to 2 years.[101] The American Heart Association for many years has considered the quality of the evidence supporting exercise therapy in the treatment of IC to be sufficiently robust to merit a Level I recommendation.[43]

Mechanism of benefit of exercise therapy. Exercise therapy is in essence athletic training, albeit on a much more limited scale than that generally associated with competitive athletes. Exercise therapy alone has been associated with improvement in walking biomechanics but not an improvement in resting ABI.[102] An underlying biochemical mechanism of benefit is therefore highly likely, but the precise mechanisms are unknown. Among the potential biomechanical or biochemical mechanisms of benefit of exercise therapy include are enlargement of existing collateral vessels, exercise induced angiogenesis, enhanced nitric oxide (NO) endothelium-dependent vasodilatation of the microcirculation, improved bioenergetics of skeletal muscle, and improved hemorrheology.

Requirements for exercise therapy. Participation in an exercise program for IC first requires an objective diagnosis, with vascular laboratory testing confirming the presence of PAD. Such testing may include measurement of the ABI, exercise treadmill testing or peripheral arterial duplex scanning, or both. Initiation of risk factor modification for atherosclerotic risk factors is a component of any exercise program. At a minimum, therapy with aspirin and statin medications should also be considered as pharmacologic adjuncts to any exercise program for IC (see above). Patients must be screened for sufficient cardiopulmonary reserve to tolerate an exercise program.[103]

Barriers to exercise therapy. There are both patient-specific and system-specific barriers to participation in exercise programs for IC. The exact magnitude of effect of these barriers is unknown, but in patients screened for participation in exercise research studies, far less than one-half are ever enrolled in the study. Perhaps the most important patient-specific limitations are compliance with an exercise program and that many patients with IC have medical comorbidities (angina, congestive heart failure, chronic

Summary of evidence: Medical treatment for intermittent claudication (*IC*)

Clinical question	*Data source*	*Finding*	*Quality of evidence*
The effect of smoking cessation in patients with IC	Observational studies in various settings applicable to patients with IC	Smoking cessation reduces overall mortality and morbidity in smokers in general	A
The effect of lipid lowering therapy on mortality and morbidity of patients with IC	Meta-analysis of 18 RCTs of lipid-lowering therapy in patients with PAD of the lower limb. Additional indirect evidence about benefit of statin therapy in secondary cardiovascular disease prevention is also relevant	Lipid-lowering therapy had no statistically significant effect on mortality (OR, 0.86; 95% CI, 0.49-1.50) or total cardiovascular events (OR, 0.8; 95% CI, 0.59-1.09) but improved total walking distance (152 m; 95% CI, 32.11-271.88 m) and pain-free walking distance (89.76 m; 95% CI, 30.05-149.47 m), with no significant effect on ABI[104]	A-B
The effect of diabetes control on mortality and morbidity of patients with IC	No direct trials in PAD; indirect evidence considered	Tight glycemic control in patients with type 2 diabetes reduced amputation (RR, 0.65; 95% CI, 0.45-0.94)[105]	B
The effect of antiplatelet therapy on mortality and morbidity of patients with IC	Meta-analysis[106] of 12 trials in patients with IC	Antiplatelet agents reduced all cause (RR, 0.76; 95% CI, 0.60-0.98), cardiovascular mortality (RR, 0.54; 95% CI, 0.32-0.93), and the risk of needing revascularization (RR, 0.65; 95% CI, 0.43-0.97). Major bleeding estimate was imprecise (RR, 1.73; 95% CI, 0.51-5.83). In one trial, clopidogrel had a modest advantage over aspirin	A
The effect of cilostazol and pentoxifylline on walking performance in patients with IC	Meta-analysis[107] of 26 trials in patients with IC	Compared with placebo, maximal walking distance for cilostazol and pentoxifylline increased by 25% (11 to 40 m) and 11% (−1 to 24 m), respectively. Pain-free walking distance increased by 13% and 9%, respectively	A for cilostazol and B for pentoxifylline (imprecision)

ABI, Ankle-brachial index; *CI,* confidence interval; *OR,* odds ratio; *PAD,* peripheral arterial disease; *RCT,* randomized controlled trial; *RR,* risk ratio.
The effect of ramipril on walking performance in patients with IC was originally included but has subsequently been deleted (see Supplementary Material on page 41S.e1, online only).

obstructive pulmonary disease, or arthritis) that may preclude them from participating. Patients should therefore be evaluated to ensure their medical comorbidities are sufficiently well controlled to allow safe participation in such a program. Many of the same factors that may render a patient a poor candidate for exercise therapy should be considered as relative contraindications to invasive treatments for IC because they negatively affect the risk-to-benefit analysis. Thus, an initial attempt at exercise therapy is an appropriate consideration for most patients with IC before revascularization. Although patients with severe hemodynamic compromise may improve with an exercise program, there are clearly patients with such advanced disease and disability that meaningful participation in an exercise program is not realistic. In addition, although supervised exercise programs are the most effective and well-studied form of exercise therapy, many U.S. insurance carriers do not currently provide benefits for participation in such programs. At present, this represents a major obstacle to the use of exercise therapy for IC in clinical practice.

Components of an exercise program for IC. Exercise programs for IC potentially consist of various forms of lower extremity exercise alone or in combination (walking, running, cycling, etc) or upper extremity exercise, or both, and vary with respect to intervals of training, duration of training, intensity of training, and claudication end points. Programs may be self-directed, supervised, of varying intensity, institution based or home based, and

may be combined with medical or interventional therapies, or both. A classic meta-analysis of the potential components of an exercise program for IC determined the greatest effects were achieved with a >6 month walking program that had at least three sessions per week of durations >30 minutes per session that used nearly maximal claudication pain as the claudication pain end point. Claudication pain end point, mode of exercise (walking), and duration of the exercise program were all independent predictors of increased walking distance with an exercise program.[108]

Type, duration, and intensity of exercise. The superiority of walking over other forms of lower extremity exercise, including cycling, stair climbing, tiptoe raises, dancing, and static and dynamic leg exercises, has been demonstrated.[111] Moreover, neither lower extremity strength training nor upper extremity aerobic exercise appear to augment responses to a walking exercise program.[109] Low-intensity exercise appears as equally effective as high-intensity exercise in improving claudication parameters, provided the duration of exercise is extended in the low-intensity group to achieve similar levels of exercise exposure.[110] However, use claudication end points of nearly maximal pain vs onset of pain does appear to produce greater changes in distance to onset and maximal pain.[108] Data supporting nearly maximal pain during exercise are derived from time to maximal claudication pain achieved with treadmill testing and may actually underestimate benefits under the submaximal conditions more characteristic of everyday community walking.[111]

The time length of exercise training sessions as well as its frequency and duration are important in achieving maximal benefit with training sessions: >30 minutes per session provides greater benefit than sessions for <30 minutes, scheduling more than three sessions per week is more effective than <3 sessions per week, and program lengths of >26 weeks are more effective than programs <26 weeks.[108]

Exercise programs can vary from completely unstructured programs based on patient instruction done on their own accord to programs that are supervised and institutionally based. All exercise programs depend on patient compliance, so it is not surprising that structured, supervised exercise programs demonstrate superior outcomes to unsupervised programs (home exercise programs) and are therefore the preferred strategy for exercise therapy when possible.

As previously stated, reimbursement for structured exercise programs in the United States is currently lacking, making self-directed home programs an important alternative for many patients. Home exercise programs may be able to be modified or supplemented to improve their effectiveness. Patterson et al[112] determined a 12-week home-based exercise program supplemented with a lecture program and weekly exercise instruction resulted in improvement at 6 months in initial claudication time and in maximal walking time. The improvements were statistically significant compared with baseline values, although not as great as those achieved with supervised exercise. Mouser et al[113] found that patients completing a home-based exercise program demonstrated improvement in the initial claudication distance and absolute claudication distances, although less than what would be expected in a supervised program. Unfortunately, 47% of those not completing the program dropped out by not returning for their follow-up appointment.

Providing patients with regular feedback on their progress and results may improve compliance with home-based programs. In one study, providing patients engaged in a home-based 12-week exercise program of intermittent walking to nearly maximal claudication pain with a step monitor to quantify their progress and results achieved the same level of patient adherence and increased claudication time and peak walking time to a similar degree as a supervised exercise program.[114]

Supplements to an exercise program. All exercise programs for treatment of IC, as noted above, should include atherosclerotic risk factor modification and best medical management. Interventional therapies, percutaneous or open, can also be viewed as a supplement to an exercise program. Conversely, exercise therapy can be used as a supplement to interventional procedures.

Angioplasty and stenting has been studied as an alternative to exercise therapy for IC and as a supplement to exercise therapy for IC. A systematic review examined the efficacy of catheter-based techniques as an alternative or as an adjunct to exercise therapy for treatment of IC.[115] The end points evaluated in the trials reviewed were mostly walking distances and QoL parameters. The authors concluded that the effectiveness of percutaneous transluminal angioplasty (PTA) and supervised exercise training were generally equivalent; however, despite similar end points in the trials, pooling of data was impossible due to marked heterogeneity of the data and only one of the nine randomized trials was of high quality.

The 6-month results of the CLEVER trial were reported in 2012.[74] The CLEVER trial randomized 111 patients with IC due to aortoiliac occlusive disease (AIOD) to one of three treatments: optimal medical care, optimal medical care plus supervised exercise, or optimal medical care plus stent revascularization. The primary end point was peak walking time on a graded treadmill test at 6 months. Secondary end points included assessment of QoL and free-living step activity.

At 6 months, changes in peak walking time were greatest with supervised exercise therapy combined with optimal medical care compared with both optimal medical care alone and stenting therapy combined with optimal medical care. Stenting provided greater improvement in peak walking time than optimal medical care alone. Measures of improvement in QoL were both greater for supervised exercise and stenting therapy compared with optimal medical care alone, but improvement in QoL parameters was greater for stent revascularization than supervised exercise. A conceptually similar

trial, Supervised Exercise Therapy or Immediate PTA for Intermittent Claudication in patients with an Iliac Artery Obstruction (SUPER Study), is planned for 15 Dutch centers with enrollment of 400 patients (ClinicalTrials.gov NCT01385774). Primary end points at 1 year are maximal walking distance and measures of health-related QoL.[116]

The costs of interventional treatment appear to be higher than those for supervised exercise therapy.[117] Overall, at this point, there are no compelling data to favor endovascular interventions over supervised exercise for treatment of IC in patients who are candidates for both forms of therapy.

Given its efficacy as primary therapy, it is not surprising that a number of small trials have suggested the benefit of exercise as an adjunct to percutaneous or open interventions performed for treatment of IC. A randomized trial of 70 patients treated with a percutaneous intervention primarily but not exclusively for AIOD demonstrated the addition of supervised exercise therapy to a percutaneous intervention improved absolute claudication distance at 6 months compared with percutaneous intervention alone.[118] Exercise therapy may also be beneficial after bypass surgery. In a small randomized study of 14 patients with IC comparing infrainguinal lower extremity bypass alone vs bypass with the addition of supervised exercise, the investigators found a significant increase in maximal walking distance with the addition of exercise to bypass.[119] In an older study, 75 patients with IC were randomly allocated treatment to surgical reconstruction alone, surgical reconstruction with the addition of supervised training, and supervised exercise alone. The surgical reconstructions were relatively evenly split between aortoiliac reconstructions and infrainguinal reconstructions, with three multilevel reconstructions and 23 bilateral reconstructions. Symptom-free and maximal walking distance were improved in all three groups, with the greatest improvement in the patients treated with the combination of open surgical reconstruction and supervised exercise therapy.[120]

Recommendations: Exercise therapy

		Grade	*Level of evidence*
4.12.	We recommend as first-line therapy a supervised exercise program consisting of walking a minimum of three times per week (30-60 min/session) for at least 12 weeks to all suitable patients with IC.	1	A
4.13.	We recommend home-based exercise, with a goal of at least 30 minutes of walking three to five times per week when a supervised exercise program is unavailable or for long-term benefit after a supervised exercise program is completed.	1	B
4.14.	In patients who have undergone revascularization therapy for IC, we recommend exercise (either supervised or home based) for adjunctive functional benefits.	1	B
4.15.	We recommend that patients with IC be followed up annually to assess compliance with lifestyle measures (smoking cessation, exercise) and medical therapies as well as to determine if there is evidence of progression in symptoms or signs of PAD. Yearly ABI testing may be of value to provide objective evidence of disease progression.	1	C

ABI, Ankle-brachial index; *IC,* intermittent claudication; *PAD,* peripheral arterial disease.

Summary of evidence: Exercise therapy

Clinical question	*Data source*	*Finding*	*Quality of evidence*
The effect of exercise on walking performance and morbidity in patients with IC	Meta-analysis of 22 RCTs at low risk of bias[101]	Compared with usual care or placebo, exercise significantly improved maximal walking time: 5.12 minutes (95% CI, 4.51-5.72 minutes), walking ability (50% to 200%), pain-free walking distance and maximal walking distance, but not the ABI, mortality, or amputation	A
The effect of supervised vs nonsupervised exercise on walking performance and morbidity in patients with IC	Meta-analysis of 14 RCTs[121]	Supervised exercise therapy showed statistically significant improvement in maximal treadmill walking distance compared with nonsupervised exercise therapy regimens (an increase in walking distance of ~180 m)	A

ABI, Ankle-brachial index; *CI,* confidence interval; *IC,* intermittent claudication; *RCT,* randomized controlled trial.

Table II. Summary of noninterventional treatments for intermittent claudication (IC)

References (first author)	*Modality*	*Treatment duration, months*	*Outcome measures (functional, hemodynamic, QoL)*	*FU duration, months*
Leng[126]	Exercise	3-15	Maximal walking time, pain-free walking distance	3-15
Gardner[108]		1-4	Maximal walking time, pain-free walking distance	3-15
Stewart[266]		1-15	Maximal walking time, pain-free walking distance	3-15
Porter,[91] Salhiyyah[95]	Pentoxifylline	6	Pain-free walking distance, maximal walking distance	6
Dawson,[96] Regensteiner[127]	Cilostazol	6	Maximal walking distance, QoL	6
Mondillo[73]	Statins	6	Pain-free walking time, maximal walking time	6

FU, Follow-up; *QoL,* quality of life.
The effect of ramipril on walking performance in patients with IC was originally included but has subsequently been deleted (see Supplementary Material on page 41S.e1, online only).

5. THE ROLE OF REVASCULARIZATION FOR IC

Patient selection for intervention

The natural history of IC is usually one of a slowly progressive decline in the ability to walk a distance before the onset of pain. With intensive medical management, <5% of patients will develop symptoms of advanced ischemia, such as ischemic rest pain and tissue loss, or will ultimately require amputation.[9,122] The relatively benign natural history of claudication must be weighed against the effect of the loss of ambulatory function on activities of daily living, occupation, and QoL. Consequently, the decision to intervene should be individualized, taking into consideration these factors as well as the clinical response to noninterventional therapies, and weighing the potential risks against the expected functional benefits for the patient. This initial consideration of candidacy is largely independent of technical factors, such as the anatomy of the occlusive lesions or the type of procedure, either endovascular or surgical, that would be required. Although most patients with IC who adhere to risk factor modification and conservative management decline slowly or generally maintain their current level of function, a significant minority (20%-30%) will develop increased disability over time that warrants intervention. Interventions for claudication are done to improve function in the setting of significant ongoing disability in an active person. In this context, it is important to recognize that some patients seek treatment based solely on the fear that IC will inexorably lead to amputation. Reassurance about the expected natural history of claudication to alleviate their anxiety may be all that is required in such patients and should always predate a discussion of invasive treatment. Performing prophylactic interventions in patients with IC that is minimally symptomatic or well tolerated has no benefit, may cause harm, and is never indicated.

It is also important to recognize that the degree of disability in claudication correlates relatively poorly with both physiologic testing and anatomic findings. It has been well established that the resting ABI, for example, is a modest predictor of the degree of walking impairment by self-reported symptoms or objective testing.[123,124] Similarly the burden of disease by anatomic imaging correlates poorly with function in everyday life. This may relate to nonvascular causes of walking impairment, the adaptation of each individual to the disability, and the variable contributions of collaterals. Justification for interventions for IC is not based primarily on physiologic (eg, ABI) measures or on anatomic findings but rather on the severity of functional impairment specific to arterial insufficiency and its perceived effect on QoL, supported by objective evidence of significant disease. Promoting intervention in an individual with mild disability based on physiologic or imaging studies is strongly discouraged.

Determining the degree of functional impairment from IC is not straightforward and varies from patient to patient.[125] This should be assessed from the patient's perspective and not based on the biases or value judgments of the physician. A patient's perception of the degree of impairment may vary according to his or her baseline level of physical activity; that is, moderate claudication may be perceived as severely disabling in a very active patient, whereas more severe claudication may be well tolerated in a more sedentary individual. IC causing loss of the ability to perform an occupation or that impairs basic activities of daily living and/or mobility often justifies invasive treatment. Equally important are QoL issues such as the need to provide care to a spouse or family member or loss of the ability to engage in recreational or social activities.

On the other hand, loss of ambulatory function may be multifactorial when arthritis of weight-bearing joints or the lumbar spine is also present. Treatment of PAD alone may not result in improved ambulatory function in patients so afflicted. Similarly, the treatment of IC may provide no benefit to patients with significant ischemic or structural heart disease, chronic obstructive pulmonary disease, morbid obesity, stroke, etc. In addition, such patients present a greater risk of complications or death, potentially outweighing the benefit of treatment, especially when surgery is required.

Numerous studies have demonstrated the efficacy of both endovascular and surgical therapy for the relief of symptoms of claudication by reducing pain and improving walking distance as well as gains in QoL and ambulatory function. Both forms of revascularization appear superior to medical therapy for limb-related outcomes, although not necessarily to supervised exercise training.[74,108,126] Pharmacologic treatment with cilostazol is a modestly effective and less expensive alternative to invasive treatment[127] and may be appropriate in some patients. In

most claudicant patients being evaluated initially, a 6-month trial of smoking cessation, risk factor modification, exercise, or cilostazol, or a combination, should be initiated before any invasive therapy.

Surgical and endovascular therapy (EVT) are likely to be similar in efficacy overall, although the quality of supporting evidence comparing the two is poor and the likelihood of durable clinical success different, especially for extensive disease, more distal disease, and disease involving the common or deep femoral arteries where surgery is usually preferred. Specific factors predicting treatment success should be carefully considered in each individual before determining the optimal strategy.

Anatomic patency and hemodynamic improvement are considered necessary (although not sufficient) for clinical success of revascularization in IC. In the setting of IC, where the limb is not threatened and the natural history is generally benign, durable benefit at low risk is required to justify invasive vascular treatment. The anatomic spectrum of disease in IC is broad, and has a major impact on both technical success and durability of vascular interventions. In selecting a revascularization strategy for patients with IC, the expected durability in the circumstance at hand should be carefully considered. We suggest that a minimal effectiveness threshold for invasive therapy in IC be a >50% likelihood of sustained clinical improvement for at least 2 years. Freedom from hemodynamically significant restenosis in the treated limb is considered a prerequisite for this goal.

Because anatomic durability is generally inferior for infrainguinal vs aortoiliac procedures and for bilateral vs unilateral infrainguinal interventions, most experienced clinicians have a higher treatment threshold for IC in these settings. In bilateral disease, treating physicians should consider the probability of overall efficacy as the product of expected outcomes in each limb, because functional gains are unlikely if success is achieved and maintained in one limb only. Similarly, as new data are published demonstrating the expected patency outcomes of evolving technologies in various anatomic and clinical settings, this suggested benchmark should be carefully considered before applying such strategies to everyday practice in claudicant patients. Patient-centered outcomes data are sorely needed to better define functional gains, symptom relief, and patient perceptions on the relative trade-offs (eg, durability of improvement vs need for repeat interventions) to better enable shared decision making in the invasive treatment of IC. The concept of a minimal clinically important difference has been developed for other chronic diseases to increase the relevance of study end points to patients and is needed in this field.[128]

Anatomic selection factors: Imaging

Once the decision has been made to consider invasive treatment, patients should undergo imaging studies to determine the arterial anatomy, the extent of disease, and whether they are best treated with EVT or open surgical therapy. This enables a more comprehensive discussion about risks, benefits, and durability trade-offs for various treatment options. Currently used imaging modalities include CTA,[129,130] MRA,[131] duplex ultrasound imaging,[132] and catheter angiography. Although all modalities may provide excellent imaging of the arterial circulation, each has its own unique set of advantages and disadvantages and may vary in quality and availability from institution to institution. Consequently, the modality of choice varies widely depending on clinical practice. There is insufficient evidence at present to define the most efficient, cost-effective strategy for arterial imaging in this population.

Catheter arteriography represents the gold standard due to superior image resolution and the unique ability of being able to perform a diagnostic study and EVT at the same time. However, catheter arteriography is invasive and may be complicated by contrast nephropathy, allergic reactions, and access-site events.

Modern, multislice spiral CT scans are noninvasive and provide image resolution of nearly the same quality as conventional arteriography. Moreover, the imaging data set can be reconfigured into different formats, including axial, coronal, sagittal, and three-dimensional images. However, CTA requires a large dose of intravenous contrast and is subject to artifact degradation due to calcification.

MRA has poorer resolution than angiography or CTA, but its images are not degraded by calcium, and like CTA, is noninvasive. Image quality is enhanced by the use of gadolinium; however, its use is contraindicated in patients with significant renal impairment due to the potential risk of causing nephrogenic systemic fibrosis. In addition, MRA cannot be used in patients with pacemakers and a variety of other implanted medical devices.

Duplex ultrasound arterial examination is most commonly used as a screening modality to confirm the diagnosis and to determine the severity of disease both before and after treatment. It is occasionally used as a primary imaging modality during EVT, principally in the setting of isolated focal disease in the superficial femoral artery (SFA).[133]

For patients with severe infrainguinal disease, assessment of available vein conduit is another important element in the decision process, given the superiority of good-quality saphenous vein for femoropopliteal (FP) bypass. Ultrasound vein mapping is therefore recommended as part of the preoperative evaluation of patients who are being considered as potential open bypass candidates (see below).

Aortoiliac occlusive disease

AIOD, or inflow disease, most commonly leads to buttock and thigh claudication. In men, bilateral iliac artery involvement or occlusion of the internal iliac arteries may be a cause of vasculogenic erectile dysfunction. With continued walking, it is not uncommon for patients with AIOD to also develop claudication in the calf muscles. With bilateral disease, symptoms can be quite severe and disabling due to the large number of muscle groups being affected.

Invasive treatments for AIOD are performed to provide symptom relief and functional improvements. The one scenario where treatment of asymptomatic AIOD

Recommendations: General considerations on invasive treatment for intermittent claudication (*IC*)

	Grade	*Level of evidence*
5.1. We recommend EVT or surgical treatment of IC for patients with significant functional or lifestyle-limiting disability when there is a reasonable likelihood of symptomatic improvement with treatment, when pharmacologic or exercise therapy, or both, have failed, and when the benefits of treatment outweigh the potential risks.	1	B
5.2. We recommend an individualized approach to select an invasive treatment for IC. The modality offered should provide a reasonable likelihood of sustained benefit to the patient (>50% likelihood of clinical efficacy for at least 2 years). For revascularization, anatomic patency (freedom from hemodynamically significant restenosis) is considered a prerequisite for sustained efficacy.	1	C

EVT, Endovascular therapy.

may be justified is to provide vascular access for another indicated cardiovascular implant (eg, thoracic endovascular aortic repair, endovascular aneurysm repair, transcatheter aortic valve replacement, mechanical circulatory support).

Surgical options for AIOD include direct aortic reconstructions (aortofemoral bypass [AFB], aortoiliac bypass, aortoiliac endarterectomy), which have proven to be most durable but also have significant morbidity and mortality. In patients with suitable anatomy or those deemed to be at high risk for aortic surgery, or both, extra-anatomic bypasses (axillary-femoral [AxFB], iliac-femoral [IFB], femoral-femoral bypass [FFB]) are less morbid alternatives but are also less durable.

A tremendous paradigm shift has occurred in the last two decades in the treatment of AIOD.[134] Although intersocietal guidelines previously recommended endovascular procedures as primary treatment for more focal disease and traditional surgery for more diffuse disease,[9,135] improvements in technology and endovascular techniques have resulted in EVT replacing open surgical bypass as a primary treatment for both focal and advanced AIOD in many cases. For iliac angioplasty using stents, long-term results compare favorably with open surgery.[135-139] Other techniques, including devices for crossing long-segment total occlusions,[140] stent grafts,[141,142] and hybrid procedures[143,144] combining iliac stenting with femoral endarterectomy or with FFB are alternatives to aortofemoral surgical reconstructions in appropriate patients with suitable anatomy. Open surgery is generally now reserved for patients with such extensive disease that EVT is impossible or ill advised, in patients with severe disease and associated aortic aneurysms, and in those with failed endovascular interventions (Table III).

5A. Aortoiliac revascularization: Catheter-based interventions

Aortic disease. Although open surgical reconstruction for aortic occlusive disease is considered the gold standard,[145,146] there is no question the incidence of aortic and iliac interventions is increasing, and interventional therapies have become more commonly used in treating this condition.[134] There are limited data providing information regarding the use of interventional therapy for treatment of aortic occlusive disease. Although initial information reported the use of angioplasty as a method of dealing with aortic occlusive disease,[147] stenting is the most commonly used approach in this vascular bed. Primary technical success rates for intervention vary from 90% to 100%, with 1-year primary patency rates from 75% to 100% and 4-year primary patency rates of 60% to 80%. Secondary patency can usually be maintained with repeat percutaneous interventional therapy, with 1-year and 5-year secondary patency noted to be 90% to 100% and 60% to 100%, respectively.[148-150]

Percutaneous approaches can be achieved through a femoral or brachial approach or combinations of the two approaches. Stent types used include balloon-expandable and self-expanding stents,[151] with or without covering. The choice of stent used relates to the type of disease and size of stent available. More calcific disease will usually require greater resistance to crush, which is achieved with balloon-expandable stents, whereas self-expanding stents are more readily available in slightly larger diameters. Few comparative data are available for assessing outcomes of these varied stent types. Covered stent placement in the aorta has few data on which to base any specific recommendations regarding use.[152]

Stents should be sized appropriately to the native aorta, with consideration given for the tissue displaced (especially calcific disease). This may necessitate undersizing the stent relative to the diameter of the native normal-caliber aorta to reduce the risk of rupture, which has been reported with this approach.

In general, care should be taken not to preclude possible AFB grafting in the future in surgical candidates, such as by extending stents into the perirenal aorta. Stents should not be placed across the orifice of the renal arteries, and disease abutting the renal ostia poses increased risk for obstruction or embolization of the renal arteries. The aortic bifurcation is best currently treated with "kissing stents" at the origin of the iliac arteries or with a combination of aortic stent placement down to the bifurcation and then kissing stents placed at the iliac vessel origins.[153,154] The use of aortic stent grafts for occlusive disease[142] has been described in only limited situations, and the routine use of this approach awaits further data acquisition.

Table III. Outcomes of revascularization for aortoiliac occlusive disease (AIOD) in patients with intermittent claudication (IC)

References (first author)	*Modality*	*FU duration, years*	*Patency (PAP), %*
Yilmaz,[154] Soga,[161] Ichihashi,[160] Indes[139]	PTA + stent	5	63-79
deVries,[157] Rutherford,[146] Reed,[180] Brewster,[182] Chiu[166]	AFB	5	81-93
Cham,[176] Melliere,[177] Van der Vliet,[178] Chiu,[166] Ricco[175]	IFB	5	73-88
Criado,[267] Ricco,[175] Mii[268]	FFB	5	60-83

AFB, Aortofemoral bypass; *FFB,* femorofemoral bypass; *FU,* follow-up; *IFB,* iliofemoral bypass; *PAP,* primary assistant patency; *PTA,* percutaneous transluminal angioplasty.

Caution should be exercised in the treatment of AIOD where concomitant aneurysm disease is also present. If an aneurysm is of sufficient size to meet treatment guidelines, therapy should be primarily guided by appropriate aneurysm exclusion with concomitant restoration of unimpeded blood flow to the lower extremities. In the case of small aneurysms, any treatment considered for symptomatic AIOD should achieve simultaneous aneurysm exclusion or not impede any future open or endovascular aneurysm repair options.

Mortality for endovascular interventions in the aorta can range from 1% to 3%, and morbidity ranges from 5% to 20%, with aortic rupture a possibility.[148-150] Importantly, one should be prepared for potential aortic rupture when embarking on treatment for an aortic lesion with interventional therapy. Renal dysfunction has been reported in 2% to 10% of patients. Intensive care unit stay, blood transfusion requirements, and infection rates are generally lower with EVT than with open aortic reconstructions.[155-157]

Iliac interventions. Angioplasty remains a therapy for treatment of iliac artery disease but has largely been supplanted by a primary stenting approach for this disease. In general, the more extensive and complex the occlusive disease, the more likely a primary stent approach will improve patency. For this reason, except for very focal disease, primary stenting of iliac occlusive disease offers the best approach for long-term patency.[137] The use of balloon-expandable vs self-expanding stents has been inadequately studied to claim an advantage of one device over another; however, certain characteristics and locations may favor one stent design over another. As in other beds, lesions with more calcium or especially ostial lesions favor the use of balloon-expandable stents, which have greater radial strength and resistance to crush. This allows for improved expansion and retention of vessel diameter after stent placement.

The percutaneous approach to iliac disease can vary from ipsilateral to contralateral groin to brachial, but one should be certain that devices with an appropriate length are available before initiating a procedure. If there is an expectation of the brachial approach being used, longer delivery systems should be available. When treating from the ipsilateral femoral approach, one should be certain that placement of the most distal stent will not be so close to the sheath access to prohibit accurate delivery. Here a contralateral or brachial approach is favored to allow placement of stents to the end of the diseased segment, which may be to the inguinal ligament.

Treatment of bilateral iliac occlusive disease is indicated in individuals with appropriate bilateral lesions and symptoms. Outcomes with bilateral interventions appear to be similar to those noted in individuals where a single side is treated; however, it is likely that patency is modestly reduced compared with unilateral interventions. Treatment in the common and external iliac arteries appears also to have similar outcomes. Use of uncovered stents across the orifice of the internal iliac artery will maintain adequate hypogastric artery perfusion in most instances, and it remains more important to treat the full extent of the disease than to limit coverage because of concern regarding stenting across the internal iliac artery origin. In situations where there is concern for flow preservation through a hypogastric artery, a kissing stent technique can be used at this bifurcation to maintain patency of both vessels; however, this is rarely necessary.

A key consideration in the treatment of iliac occlusive disease is the extension of the disease into the femoral artery. Use of stents in the common femoral artery (CFA) is not recommended because they are more likely to fracture or fail due to flexion of the artery that occurs with hip flexion. If disease extends into the CFA, the use of a hybrid approach combining femoral endarterectomy with iliac stenting is a better alternative in most patients.

Covered stents have been used in the treatment of iliac occlusive disease. Covered balloon-expandable stents had better primary patency rates when used in more complex lesions in the iliac artery.[141] In the prospective, randomized Covered vs Balloon Expandable Stent Trial,[141] covered balloon-expandable stents demonstrated better primary patency rates than bare-metal stents (BMSs) in AIOD, particularly in the more advanced lesions. However, in a more recent single-center, retrospective study, BMSs had superior patency to covered stents at 1 year.[158] Regardless of any potential patency advantages, covered stents may provide a safety margin in the treatment of calcified common iliac lesions or ectatic vessels where rupture is a distinct possibility. For the external iliac artery, flexible, self-expanding stents are recommended because of the motion these vessels undergo and the potential for kinking and crimping of balloon-expandable stents placed in this location. Similarly, covered versions of these stents have also been used in the external iliac artery, although specific indications favoring one vs the other are not clear.

Initial technical success for iliac stenting varies from 90% to 100% and depends on the extent of the disease, with more complex lesions having lower initial technical success rates. Long-segment occlusion of the external iliac artery, particularly in women or patients with smaller vessels or circumferential calcification, or both, remains an important

limitation for durable patency.[135] The 1-year primary and secondary patency rates range from 70% to 100% and 90% to 100%, respectively.[159] The 5-year primary and secondary patency rates are noted to be 60% to 85% and 80% to 95%, respectively.[139,159-161] Perioperative mortality can be expected to be approximately ≤1%,[139,161] and morbidity can range from 5% to 20%.[139,159] Long-term outcomes may be inferior in younger (<50 years) patients, particularly women.[162]

CFA interventions. Limited data are available to support the use of interventional therapy in occlusive disease of the CFAs, but several single-center experiences have been published,[163-165] presenting a technical success rate of nearly 90% and 1-year primary patency rate of 75%. Information on longer-term patency is limited, and no information is available regarding stent stability in this area over even this short period of time. Given the limited morbidity and risk entailed with femoral endarterectomy, the use of interventions in this vessel for the present time should be limited to those with a prohibitive risk for open surgical therapy related to local or systemic risk factors.

Hybrid interventions. The use of interventional therapies for iliac disease allows treatment of occlusive disease in patients with limited morbidity; however, when the disease extends into the CFAs, an approach using open surgical techniques to treat the CFA and stents to treat the iliac or inflow vessels offers an alternative to traditional aortofemoral grafting.[142,144,156] In these instances, the endarterectomy is extended proximally into the external iliac artery, and stenting is done into the upper area of the endarterectomy to limit progression of disease in an intervening segment. Surgical angioplasty of the femoral artery can be performed with an eversion or standard patch technique. Stenting of the iliac artery can usually be done from an ipsilateral approach, with the sheath entry site well below the upper extent of the endarterectomy to allow stents to be placed through the full length of the diseased segment.

Initial technical success with this approach is reported at 99% to 100% with 3-year to 5-year primary patency rates reported at 90% and secondary patency rates of 98% to 100%.[144] When compared with open aortofemoral reconstruction,[166] this approach appears to have similar low mortality, with associated reductions in systemic morbidity, infection risks, and a number of postsurgical complications while providing similar patency rates, especially when comparing secondary patency rates.

5B. Aortoiliac revascularization: Surgery

General considerations. Although endovascular intervention has become dominant in this vascular territory, surgery continues to have an important role in the current treatment of patients with disabling claudication secondary to AIOD. Relative indications for surgical vs endovascular approaches will be discussed below but primarily relate to disease distribution, prior interventions performed, and overall patient risk. A range of surgical options is available, depending on these and other technical considerations.

There are a number of key anatomic considerations that directly influence the choice of an optimal surgical strategy in AIOD. The nature and extent of aortic disease is preeminent. Axial imaging studies, typically CTA, are important in the revascularization planning. The location and severity of the occlusive lesions, as well as the presence of any aneurysmal changes, have direct implications. Noncontrast scans are particularly helpful in preoperative planning to assess calcification, which can severely complicate clamping and suturing. Total occlusions, most commonly up to the subrenal aorta, are best approached by direct reconstruction with thromboendarterectomy of the aortic cuff and an end-to-end bypass graft in suitable candidates. Combined occlusive and aneurysmal disease should be treated by complete exclusion of the aneurysmal segment rather than simple bypass. When choosing between end-to-end and end-to-side aortic graft configuration, the extent of disease in the subrenal aorta and the status of the pelvic circulation are major issues.[167,168] There are no clear differences in long-term outcomes for end-to-end vs end-to-side aortofemoral grafts[169,170]; however, the end-to-end technique requires less disease-free aorta and the graft is somewhat easier to cover with retroperitoneal tissue. In general, proximal anastomoses should be performed to the immediate subrenal segment (ie, the zone between the renal and inferior mesenteric arteries) because progression of atherosclerosis is highly likely in the more distal abdominal aorta and may limit durability.

The pattern of iliac disease encountered may be highly variable. Unilateral disease, with complete occlusion of both common and external iliac arteries, or occlusion of the external iliac artery alone, may be approached surgically with either in-line (unilateral AFB or IFB) or extra-anatomic (FFB or AxFB) strategies. The choice between these depends on patient risk, status of the contralateral iliofemoral system and contralateral groin, and suitability of the proximal common iliac or aorta for inflow anastomosis. The presence of pre-existing stents or stent grafts in any of these segments will also influence the choice and conduct of the procedure.

As noted above, the presence and severity of CFA disease is a critical point that often dictates whether a purely endovascular vs an open surgical or hybrid approach is undertaken. Long-term outcomes and limb status after reconstructions for AIOD are highly dependent on continued patency of the CFAs and deep femoral arteries (DFAs).[171,172] The presence of FP and distal occlusive disease is also common, particularly in smokers. For patients with disabling claudication and rest pain (Rutherford 2-4), inflow reconstruction of significant AIOD is frequently all that is required to improve symptoms. A staged approach is therefore recommended in such patients with multilevel disease, with re-evaluation of symptom status after inflow correction.

Direct (in-line) aortofemoral and iliofemoral reconstruction. Direct surgical revascularization for AIOD is often considered the gold standard for durable vascular interventions, with patency rates >80% at 10 years for AFB or aortoiliac endarterectomy.[145,173,174] Patency rates for unilateral IFB are also typically in the range of 90% at 3 to 5 years.[166,175-178] The disease pattern most amenable to endarterectomy (ie, localized lesions in the terminal aorta and common iliacs) is readily treated by

endovascular means; hence, this operation has become extremely uncommon in current practice.

Transperitoneal or retroperitoneal approaches may be used without significant differences in outcomes. Unilateral operations are readily performed via retroperitoneal approaches. In addition to considerations regarding the nature of the proximal anastomosis discussed above, a critical point is treatment of the CFAs and DFAs at the distal anastomosis. Ensuring an adequate caliber profunda outflow is essential and mandates careful preoperative and intraoperative evaluation. In circumstances of truly isolated AIOD and no or minimal disease in the common femoral/bifurcation, the anastomosis may be performed to the mid-CFA level. In all other circumstances, the arteriotomy in the CFA should allow direct interrogation of the DFA and SFA orifices, with use of adjunctive endarterectomy and patch angioplasty as needed based on burden and location of disease. Failure to address this critical point may significantly limit the durability of the bypass graft, because the presence or progression of outflow disease, or both, is the most common reason for midterm and late-term graft occlusions. Very rarely, disease spares the external iliac arteries and the femoral arteries, and in these circumstances, an aortoiliac bypass may be performed to the distal external iliac arteries via a transabdominal approach.[179] One must be cautious to ensure the absence of any significant femoral disease by imaging studies in such cases.

Prosthetic grafts (Dacron, expanded polytetrafluoroethylene [ePTFE]) are typically used for AFB and IFB and have excellent durability. Small graft sizes (eg, 12 × 6 mm) have been associated with decreased patency and should be avoided.[180] In the special circumstance of infected or contaminated fields, or removal of a previous infected graft, autogenous and cryopreserved conduits (artery or vein) have been used with good success.

Perioperative mortality for these procedures is generally <3%,[181] although morbidity may include cardiac, pulmonary, infectious, wound, and gastrointestinal complications in 10% to 15%. Patency rates for AFB, aortoiliac endarterectomy, and IFB, as noted, have ranged from 80% to 90% at 5-year and 10-year intervals.[156,157,166,173,174,180,182] Functional outcomes for claudicant patients, although less frequently reported, are generally quite good but depend on the presence of infrainguinal disease and modification of lifestyle and risk factors. Long-term complications include limb occlusions, pseudoaneurysm, graft infection, and graft-enteric fistula. Although the overall results are excellent, caution is warranted in certain subgroups of patients who have demonstrated inferior outcomes, particularly younger patients (age <50 years), hypercoagulable patients, and those with very small-caliber outflow vessels.[180] Younger patients with premature AIOD are a high-risk group reflecting poorly controlled risk factors, underlying genetic or biochemical predispositions, and a more aggressive vascular phenotype.[183] Conservative management of younger patients with AIOD is advocated because the initiation of surgical or endovascular interventions at a premature age can lead to accelerated progression toward a more critical stage of disease. Furthermore, recent data from clinical trials[74] support the role of exercise therapy as an initial strategy for claudicant patients with inflow disease, and this should be advocated as a primary treatment strategy, particularly in the younger patient.

Extra-anatomic reconstruction for AIOD. For patients with extensive patterns of AIOD who are deemed to be at high risk or technical complexity for direct surgical reconstructions, particularly those with advanced ischemic symptoms, extra-anatomic bypass grafts offer a suitable alternative. In general, extra-anatomic bypass grafts are not considered as a first-line approach for patients with IC because their long-term durability and hemodynamic effect are inferior to in-line reconstructions. Their use in patients with claudication should be limited to special circumstances such as graft or stent complications, hostile abdomen, or other factors precluding an endovascular or in-line surgical approach.

Key considerations in selecting an extra-anatomic strategy include whether the AIOD is unilateral or bilateral (and if bilateral, can unilateral inflow be corrected by suitable endovascular means), nature of prior interventions, and the status of the contralateral groin. FFB grafting can be readily done under regional or even local anesthesia with sedation, offering an important potential advantage. AxFB is challenging to perform under anything but a general anesthetic.

Angiographic imaging (CTA or catheter based) is recommended before performing extra-anatomic bypass grafting to fully evaluate the inflow and outflow anatomy. Direct angiography is mandatory for FFB if there is any suggestion of disease in the donor iliofemoral system by pulse examination, hemodynamic assessments, or axial imaging. Formal evaluation of the aortic arch vessels is not generally required for AxFB unless there is a discrepancy in brachial pressures or another reason to suspect brachiocephalic disease.

For FFB, the donor iliac system must be free of hemodynamically significant disease, or such disease—if present and of a localized nature—corrected by endovascular means with confirmed elimination of any translesional pressure gradients (<5 mm Hg mean pressure resting) before performing the bypass.[184] Interrogation and treatment of both donor and recipient CFAs, as noted above, is imperative to optimize long-term outcomes. The graft is placed in a deep subcutaneous, extrafascial tunnel across the suprapubic region of the lower abdomen. Dacron and ePTFE conduits have equal and acceptable results. Autogenous and cryopreserved grafts may be used for FFB in settings of infection. Care must be taken in regard to the lie of the graft in relation to the lower abdomen, particularly where there is a significant pannus. A gentle upside down "U" configuration is used, placing the heel of the anastomosis at the mid to distal CFA level to avoid kinking when standing upright. Mortality (<2%) and morbidity (10%) after FFB are generally low. Long-term outcomes are quite acceptable, with patency rates in the 55% to 80% range out to 5 years,[175] although significantly inferior to in-line reconstructions. Primary factors affecting patency are the status of the outflow vessels (ie, presence of severe disease in the SFA or DFA on the recipient side) and progression or recurrence of disease in the donor iliac system.[176,185]

AxFB is uncommonly used in the setting of claudication. It may be performed to one or both lower limbs, depending

on the clinical circumstances. Because flow rates through the long prosthetic axillofemoral graft limb are higher with bilateral grafts, the bifemoral configuration is generally preferred. The proximal anastomosis should be made to the second portion of the axillary artery, exposed by division or retraction of the pectoralis major muscle. Externally supported prosthetic conduits (Dacron or ePTFE) are used to resist compression along the chest wall. The tunnel should be placed anterior to the anterior-superior iliac spine and below the pectoralis major muscle, along the anterior axillary line. A variety of configurations have been used for the crossfemoral limb and distal anastomoses, without apparent influence on the outcome. The inverted "U" configuration, as used in FFB, is most commonly used.

As in all reconstructions for AIOD, careful attention is paid to the status of the CFA/DFA, and adjunctive endarterectomy or patch angioplasty are performed as needed. Operative mortality and morbidity for AxFB are low and similar to FFB.[186] Reported outcomes are inferior to AFB, IFB, and many series of FFB, with 5-year patency rates in the 50% to 75% range, although the reported results are variable and also dependent on the severity of outflow disease.[187] As a result of these limitations, AxFB is rarely advised for patients with claudication. When used in circumstances such as aortic graft infection or mycotic aneurysm, patients will often report some degree of functional limitation with aggressive exercise due to the inherent hemodynamic limitations of the long axillofemoral conduit.

Recommendations: Interventions for aortoiliac occlusive disease (*AIOD*) in intermittent claudication (*IC*)

		Grade	*Level of evidence*
5.3.	We recommend endovascular procedures over open surgery for focal AIOD causing IC.	1	B
5.4.	We recommend endovascular interventions as first-line revascularization therapy for most patients with common iliac artery or external iliac artery occlusive disease causing IC.	1	B
5.5.	We recommend the selective use of BMS or covered stents for aortoiliac angioplasty for common iliac artery or external iliac artery occlusive disease, or both, due to improved technical success and patency.	1	B
5.6.	We recommend the use of covered stents for treatment of AIOD in the presence of severe calcification or aneurysmal changes where the risk of rupture may be increased after unprotected dilation.	1	C
5.7.	For patients with diffuse AIOD (eg, extensive aortic disease, disease involving both common and external iliac arteries) undergoing revascularization, we suggest either endovascular or surgical intervention as first-line approaches. Endovascular interventions that may impair the potential for subsequent AFB in surgical candidates should be avoided.	2	B
5.8.	EVT of AIOD in the presence of aneurysmal disease should be undertaken cautiously. We recommend that the modality used should either achieve concomitant aneurysm exclusion or should not jeopardize the conduct of any future open or endovascular aneurysm repair.	1	C
5.9.	In all patients undergoing revascularization for AIOD, we recommend assessing the CFA. If hemodynamically significant CFA disease is present, we recommend surgical therapy (endarterectomy) as first-line treatment.	1	B
5.10.	In patients with iliac artery disease and involvement of the CFA, we recommend hybrid procedures combining femoral endarterectomy with iliac inflow correction.	1	B
5.11.	We recommend direct surgical reconstruction (bypass, endarterectomy) in patients with reasonable surgical risk and diffuse AIOD not amenable to an endovascular approach, after one or more failed attempts at EVT, or in patients with combined occlusive and aneurysmal disease.	1	B
5.12.	In younger patients (age <50 years) with IC, we recommend a shared decision-making approach to engage patients and inform them of the possibility of inferior outcomes with either endovascular or surgical interventions.	2	C
5.13.	We recommend either axial imaging (eg, CT, MR) or catheter-based angiography for evaluation and planning of surgical revascularization for AIOD.	1	Ungraded
5.14.	When performing surgical bypass for aortoiliac disease, concomitant aneurysmal disease of the aorta or iliac arteries should be treated as appropriate (exclusion) and is a contraindication to end-to-side proximal anastomoses.	1	Ungraded
5.15.	For any bypass graft originating from the CFA, the donor iliac artery must be free of hemodynamically significant disease or any pre-existing disease should be corrected before performing the bypass graft.	1	Ungraded

BMS, Bare-metal stent; *CFA,* common femoral artery; *CT,* computed tomography; *EVT,* endovascular therapy.

Summary of evidence: Interventions for aortoiliac occlusive disease (*AIOD*)

Clinical question	*Data source*	*Finding*	*Quality of evidence*
The effect of endovascular vs open surgery for AIOD on the outcomes of mortality, complications, and patency	Meta-analyses of mostly nonrandomized series (AIOD, not all IC)[139]	The open bypass group experienced more complications and greater 30-day mortality. At 1, 3, and 5 years, primary patency rates were greater in the open bypass group	B-C
The effect of PTA vs stent placement for AIOD on the outcomes of mortality, complications, and patency	Meta-analyses of mostly nonrandomized series (AIOD, data provided for IC).[137] Meta-analyses of mostly nonrandomized series (class C and D aortoiliac lesions)[138]	Complication and mortality rates were similar. Immediate technical success rate (PTA group, 91%; stent group, 96%); 4-year primary patency rates for PTA (65% for stenosis, 54% for occlusions) and for stents (77% for stenoses, 61% for occlusions)	B-C
The effect of endovascular vs open surgery for extensive AIOD on the outcomes of mortality, complications, and patency	Meta-analyses of nonrandomized series of EVT for extensive AIOD[188]	With endovascular approach, mortality ranged 1.2%-6.7% and complications ranged 3%-45%. Clinical symptoms improved in 83% to 100%. Technical success was achieved in 86% to 100% of the patients. The 4-year or 5-year primary and secondary patency rates were 60% to 86% and 80% to 98%, respectively	B-C

EVT, Endovascular therapy; *IC,* intermittent claudication; *PTA,* percutaneous transluminal angioplasty.

5C. Infrainguinal disease

Occlusive lesions of the FP segment most commonly present with IC involving the calf. Isolated lesions of the crural or foot arteries usually do not cause claudication, although disease involving both segments may cause severe calf claudication and symptoms can involve the foot. In many patients, unilateral calf claudication is well tolerated and may be managed conservatively, as previously described. For patients with more severe symptoms requiring treatment, a trial of exercise therapy, preferably supervised training[108,126] or approved pharmacologic treatment (cilostazol),[127] or both, should be undertaken before invasive therapy. If these measures are unsuccessful, invasive therapy may be appropriate after a detailed discussion with the patient. As previously noted, this discussion should cover the natural history of IC, the risks and benefits of open surgery and endovascular interventions, an estimate of long-term patency, likelihood of symptom relief, and the implications of failed therapy.

In the last decade, vascular specialists have readily adopted EVT as an attractive alternative to open bypass surgery for infrainguinal occlusive disease. PTA and stenting are the most commonly used EVTs for focal and intermediate-length stenosis.[9,189] However, the development of other techniques and technologies, such as subintimal angioplasty, devices for crossing and re-entering long-segment total occlusions, stent grafts, and mechanical and laser atherectomy, have made it possible to successfully treat even advanced disease,[190] leading some vascular specialists to advocate an endovascular-first approach for patients undergoing lower extremity revascularization.[191] In most cases, endovascular procedures are well tolerated with minimal complications, require short hospital stays, and result in rapid recovery.

However, endovascular procedures are less durable than surgical bypass and have a greater need for reintervention, especially in cases of diffuse stenosis or long-segment total occlusion of the superficial femoral or popliteal arteries, or both (Table IV). Although the frequency with which failed open or EVTs lead directly to clinical worsening is unclear, it undoubtedly occurs with either modality. This possibility must be carefully considered during discussions with patients, particularly those with bilateral disease and more challenging anatomy. In average-risk claudicant patients with advanced FP occlusive disease (FPOD), surgical bypass provides better durability, a decreased need for reintervention, and is usually well tolerated, with a low rate of complications. In bypasses crossing the knee joint, good-quality saphenous vein is the preferred conduit when available. EVT is a reasonable alternative in settings of favorable anatomy and in those with inadequate venous conduit.

For patients with IC, the reduced risk of complications, short recovery time, and rapid return to normal functioning

Table IV. Outcomes of intervention for femoropopliteal occlusive disease (FPOD) in patients with intermittent claudication (IC)

References (first author)	*Modality*	*FU duration, years*	*Patency (PAP), %*
Hunink,[193] Muradin,[269] Schillinger[270]	PTA	2	26-68
Schillinger,[270] Laird,[210] Matsumura[211]	PTA + stent	2	51-68
Kedora,[271] Shackles,[272] Geraghty[196]	Covered stent	1	53-77
Pereira,[273] Klinkert[274]	FP vein	5	70-75
Robinson,[275] Klinkert,[274] Pereira[273]	FP prosthetic	5	40-60

FP, Femoropopliteal; *FU,* follow-up; *PAP,* primary patency; *PTA,* percutaneous transluminal angioplasty.

with EVT has lowered the threshold for invasive treatment to include patients who were previously managed without invasive treatment when the only option was conventional surgery. However, there is no conclusive evidence supporting this more aggressive approach,[192] especially compared with supervised exercise.[76] Treatment guidelines from the American Heart Association[43] and the revised TransAtlantic Intersociety Consensus document[9] recommend the use of EVT as a first-line treatment for those patients requiring invasive therapy for focal and moderate disease, with open bypass recommended for diffuse disease or long-segment total occlusions, or both. However, the quality of evidence of the long-term efficacy of EVT compared with open surgical bypass for the treatment of IC is low. Consequently, the decision of which modality to use must be individualized and should take into account other clinical factors beyond arterial anatomy, including periprocedural risks, availability of conduit, and anticipated risk of wound complications. Patient preference, after full consideration of the trade-offs, plays an important role as well.

FP revascularization: Catheter-based intervention. IC can be caused by occlusive lesions in the aortoiliac segment (see previous section), as well as the CFA, SFA, profunda femoral, and popliteal arteries. How often occlusive lesions confined to the infrapopliteal arteries result in claudication remains unclear. Treatment of isolated infrapopliteal disease for relief of claudication is not advised. In patients with multisegment disease, the more proximal disease should be treated first and usually results in improvement in symptoms without extending treatment to the more distal arteries. Endovascular interventions are generally safe, with infrequent complications and lower levels of morbidity, mortality, and an earlier return to normal function than surgical bypass.

EVT options for FPOD include PTA alone, especially for short focal lesions <4 cm,[193] angioplasty with self-expanding stents,[194] angioplasty with balloon-expandable stents,[195] angioplasty with covered stent grafts,[196,197] atherectomy,[198-200] antimyoproliferative drug-coated balloons,[201-203] and drug-eluting stents (DESs).[204] Combination EVT involving atherectomy and DESs has been reported in European trials.[205]

Significant occlusive lesions of the CFA are generally treated with surgical endarterectomy and patch angioplasty, except in patients with significant comorbidities or hostile groins precluding surgical treatment. Combined open and endovascular hybrid procedures involving CFA endarterectomy and then angioplasty of either proximal iliac artery lesions (see above) or distal SFA lesions been shown to be effective for the management of claudication.[206,207] EVT of the CFA for claudication is an alternative treatment to open surgery for selected patients with hostile groins or multiple previous vascular procedures.[164,208] Primary intervention using balloon angioplasty and self-expanding stent placement has been reported; however, placement of stents within the CFA may be complicated by plaque shifting into the origin of the profunda femoral artery. Moreover, late failure resulting in CFA occlusion makes subsequent open or endovascular interventions more complicated. Stent fracture or vessel injury due to groin flexion point is an additional concern. Atherectomy has been reported as an alternative treatment option that obviates some of these problems.[209] In general, endovascular approaches to the CFA artery are not well proven, and disease in this artery is preferably treated surgically.

IC rarely results from isolated profunda femoral disease unless there is associated CFA or SFA disease. Endovascular intervention on the profunda femoral artery for claudication symptoms is of unproven value and may carry substantial risk to this most important source of collateral flow in the limb. The multiple branch points within the profunda femoral artery make angioplasty and stenting complicated. Similar to the common femoral bifurcation, atherosclerotic plaque near the branch points can shift plaque during angioplasty and occlude one of the branch vessels if not adequately protected.

The SFA is the most common site of atherosclerotic occlusive disease resulting in claudication. The severity of symptoms from occlusive disease in the SFA varies considerably, based on the extent of collateralization from the profunda femoral artery to the geniculate collateral arteries at the popliteal artery. After failure of an exercise program and optimization of medical therapy, endovascular intervention can be considered. Open surgical bypass success is dependent on arterial inflow, outflow, and the quality of the bypass conduit. Primary predictors of endovascular success and long-term patency differ significantly and include the length of the lesion, degree of stenosis, size of the artery, and degree of calcification.

PTA alone has been shown to be most effective for short focal lesions in the SFA (<4 cm). However, all angioplasties can be complicated by flow-limiting dissection, embolization, and acute arterial recoil with the associated risk of abrupt closure. The adjunct use of a self-expanding covered or BMS has been shown to be effective in improving patency of longer lesions in the SFA and to treat PTA-related complications of dissection and acute recoil. Several trials have demonstrated the efficacy and possible superiority of self-expanding stents in the treatment of longer SFA lesions. In the Randomized Study Comparing the Edwards Self-Expanding LifeStent vs Angioplasty-alone In Lesions Involving The SFA and/or Proximal Popliteal Artery (RESILIENT) study, nitinol BMSs were compared with angioplasty. Treatment of multiple lesions was permitted provided they were treated with one stent. The mean lesion treated was 7.1 cm in stent cohort and 6.4 cm in the angioplasty cohort. The reported observed patency at 1 year was 81.3% and 36.7%, respectively, for the stent and angioplasty groups.[194] In a 3-year follow-up of the RESILIENT study, freedom from target lesion revascularization and clinical success was significantly higher in the primary stent cohort, but no data were available on patency.[210]

The Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal By Using the Protege EverfLex Nitinol Stent System II (DURABILITY II) trial was a single-arm trial investigating the efficacy of a single self-expanding nitinol stent in the treatment of occlusive lesions in the SFA >4 and < 20 cm. Duplex-derived primary patency at 1 year was 77.2% for lesions with a mean length of 8.9 cm.[211] The Zilver PTX trial randomly assigned 471 patients with SFA lesions averaging 6.5 cm to treatment with a paclitaxel DES or PTA as a primary procedure and to BMS in a subset of 110 study patients who required further treatment for immediate failure of PTA alone. Patency at 1 year was 83.1% for DES and 32.8% for PTA. In the 110 patients undergoing salvage stenting for failed PTA, 1-year patency was significantly better for DES compared with BMS (89.9% vs 73%).[204] The patency superiority of paclitaxel DES over PTA (74.8% vs 26.5%) and BMS (83.4% vs 64.1%) was sustained in a 2-year follow-up report of the same study.[212]

PTFE-covered self-expanding stents have been used to treat long-segment lesions within the SFA for patients with claudication, although their superiority to BMSs is as yet unproven. The Viabahn Endoprosthesis with PROPATEN Bioactive Surface (VIA) vs Bare Nitinol Stent in the Treatment of Long Lesions in Superficial Femoral Artery Occlusive Disease (VIASTAR) prospective multicenter trial[213] compared BMSs with heparin-bonded PTFE covered stents in the treatment of long-segment SFA stenosis and found no statistically significant difference in 1-year primary patency by intention-to-treat analysis, although in the treatment per protocol cohort and in those with lesions >20 cm, patency was superior in the PTFE group. This study was flawed by protocol violations in >8% of cases.

The Viabahn vs Bare Nitinol Stent in the Treatment of Long Lesion Superficial Femoral Artery Occlusive Disease (VIBRANT) trial randomized 148 patients to PTFE covered or nitinol BMSs for lesions averaging 18 cm in length. At 3 years, primary patency was nearly identical (24.2% vs 25.9%).[196] Some authors have raised caution about the failure mode of covered stents in FPOD, with a higher proportion of acute limb ischemia events compared with BMS, particularly when distal collateral vessels are covered.[214] Covered stents may have a role in the treatment of diffuse in-stent restenosis in the SFA.[215] At the present time, given the increased cost and lack of clinical superiority over BMSs, a primary role for covered stents in the treatment of IC due to FPOD remains unclear. Balloon-expandable or self-expanding covered stents may have a role in the treatment of highly calcified focal SFA lesions, but this has not been prospectively evaluated.

Plaque excision by mechanical atherectomy using cutting blades, laser ablation, or "sanding" with a diamond-encrusted burr has been proposed as an alternative to angioplasty and stenting for symptomatic PAD. In a recent meta-analysis of four randomized studies including only 220 patients comparing atherectomy with other established treatments, including angioplasty, stenting, lower extremity bypass, and exercise therapy, the authors concluded there was no evidence to support the superiority of atherectomy over angioplasty for any outcome. They also observed that the quality of existing evidence is poor and recommended further study with properly powered trials.[199]

Antimyoproliferative drug-coated balloons have been evaluated for the treatment of SFA disease in patients with claudication. The Taxan with Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER),[202] Femoral Paclitaxel (FemPac),[203] and Moxy Drug Coated Balloon vs Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries (LEVANT 1)[201] studies demonstrated improved patency relative to PTA without drug coating but were limited by small sample sizes, heterogeneous patient populations, and incomplete follow-up. Two larger regulatory trials (LEVANT 2, IN.PACT SFA[216]) have recently reported improved patency for drug-coated versus uncoated balloon angioplasty in femoropopliteal disease. As a result, the FDA has recently approved two drug-coated balloon devices for the treatment of occlusive lesions in the SFA and popliteal artery. It remains unclear how drug coated balloon angioplasty will compare in durability to other approaches such as stents referenced above. Bioabsorbable DESs are currently being evaluated in Europe but are not available within the United States.

The efficacy of EVT must also be weighed against the potential for acute and long-term complications. Common endovascular complications include arterial dissection at the area of treatment site, arterial perforation, pseudoaneurysm creation, acute recoil associated with abrupt closure or restenosis, embolization distal to the site of intervention, and arteriovenous fistula creation. Implantation of a stent also carries specific, stent-related risk factors, including stent fracture, chronic arterial erosion, and perforation.

Long-term complications include restenosis with potential occlusion, loss of collateral branches at the site of the endovascular procedure, and late pseudoaneurysm formation. One additional consideration with EVT is its effect on subsequent open surgical bypass, which has been reported to be required in 10% to 25% of patients for failed interventions. In one study by Joels et al,[217] EVT altered the level of the expected outflow target to amore distal level in 30% of patients. Previous EVT, with or without stents, may adversely affect graft patency, limb salvage, and amputation-free survival compared with bypasses done as initial therapy for CLI.[218] Failure of stented endovascular interventions done for claudication has resulted in acute limb ischemia, especially when covered stents grafts have been used.[219] In addition to these observations, microembolization into the outflow bed and loss of potential outflow targets have been postulated as causes for the inferior results of secondary surgical bypass in these patients.

Catheter-based treatment of occlusive disease involving popliteal or more distal arteries, or both, has not been specifically evaluated for the treatment of IC and presents additional problems and the risk of significant complications. Popliteal occlusive disease may result in IC, especially when there are poorly developed collaterals from the profunda femoral artery through the geniculate arteries. EVT of popliteal artery occlusive disease is technically feasible; however, its long-term durability is not known, and failure in this location may result in limb-threatening ischemic symptoms or the need for a distal tibial bypass, or both. Flow-limiting dissection, occlusion, or perforation may result in the undesirable need to place a stent across the knee joint. Newer, more flexible stent designs may ultimately improve outcomes in the popliteal artery,[220] but comparative studies with adequate follow-up are not available at present. Consequently, it should be undertaken both with caution and some trepidation for claudication.

In most circumstances, isolated tibial disease does not present with symptoms of claudication and should not be undertaken for relief of claudication symptoms. Adding tibial angioplasty to a more proximal intervention to improve runoff in the hope of improving patency has not been studied. The durability of tibial angioplasty is worse than SFA angioplasty, averaging <40% at 3 years[221] in patients undergoing treatment for limb salvage, where it is most commonly performed. The need for reintervention at this level is high, and persistent failure after repeated attempts of reintervention with repeated failure may result in CLI requiring a distal bypass for salvage or major limb amputation. Isolated infrapopliteal interventions are not recommended for patients with IC.

FP revascularization: Surgery. The guidelines for conservative management of IC have been previously discussed. However, it is important to recognize that the benefits of medical therapy and exercise are actually quite modest. In a recent prospective study, absolute walking distance improvement with a home-based exercise program, the only type available to most patients, was <90 feet.[222] The effect of such a modest improvement on functional ability and QoL may be inadequate for many patients.

Bypass surgery has been a mainstay in the invasive treatment of IC for 5 decades, although much less frequently used in the last 10 to 15 years with the evolution and rapid expansion of catheter-based therapies (see above). The efficacy of surgical bypass for the relief of claudication symptoms is well established. A seminal report documented long-term functional outcomes in 14 patients who underwent vein bypass surgery for IC, demonstrating relief of symptoms and improved exercise performance and self-reported community-based walking abilities.[223] ABI improved in surgical patients by nearly 0.4, peak treadmill walking time by 9 minutes, and pain-free walking time by >6 minutes. Questionnaire scores for walking distance improved by 203% and walking speed by 130%. These improvements were not predicted from routine noninvasive testing alone. The authors were among the first to suggest that such functional status outcomes should be measured directly.[223]

The perceived morbidity associated with open surgical therapy for IC is an important factor in clinical decision making. As with any surgical procedure, the key to a successful outcome is appropriate patient selection. Ideal candidates for surgical bypass for claudication should have minimal comorbidities, good life expectancy, be significantly disabled specifically by claudication symptoms, and have reasonable runoff and good conduit available for bypass.

One of the major advantages of bypass compared with angioplasty is durability as measured by patency of the intervention. Van der Zaag et al[224] reported the results of a randomized trial of angioplasty vs surgical bypass in 56 patients with claudication and 5- to 15-cm-long lesions of the SFA. The primary end point was reocclusion. No 30-day deaths occurred in either group, confirming the observations of many others in nonprospective studies that surgical bypass for claudication is safe in appropriately selected patients. More than half of the angioplasty patients experienced a reocclusion. Surgical bypass was associated with a significant 31% absolute risk reduction for the end point of subsequent reocclusion. Clinical improvement in symptoms was also significantly better for patients who underwent bypass (absolute difference 20%). Only one patient among the 56 enrolled subsequently required amputation; that individual had been initially treated by angioplasty. No amputations were required in the bypass surgery patients.

Bypass surgery has also been shown to be associated with superior functional improvement compared with other treatment modalities by numerous investigators. Wolf et al[225] compared surgery and balloon angioplasty for peripheral vascular disease in a randomized fashion. Bypass and angioplasty both showed sustained improvements in hemodynamics and QoL. Primary success was more often achieved with bypass, but the differences were not significant. Lundgren et al[120] compared claudication patients who underwent surgical reconstruction vs physical training alone. Surgery was more effective, but the addition of physical training to surgery improved symptom-free walking distance even further. Surgery was significantly better than exercise therapy with regard to maximal walking time, ABI improvement, and peak exercise calf blood flow. A subgroup

of patients whose activity was also limited by cardiopulmonary disease in addition to claudication failed to demonstrate significant walking improvement despite improvements in ABI and calf flow, emphasizing the importance of careful patient selection when recommending any intervention, especially surgery, for claudication.

In a systematic review of the efficacy of bypass for chronic limb ischemia, the probability of an achieving an unlimited maximal walking performance, defined as at least 1000 meters, was 75% to 95% in patients who underwent bypass for claudication compared with only 10% to 20% in those treated solely by exercise training.[226] In another study where patients were randomized to surgical bypass, supervised exercise training, or observation alone, surgically treated patients showed a significant improvement in maximal walking power, stopping distance, postischemic blood flow, and great toe pressure at 1 year.[227] Patients randomized to physical exercise training did not demonstrate improvements in any outcome measure. Mortality and amputation rates were identical in both groups.

In a retrospective review, Koivunen and Lukkarinen[228] demonstrated that surgically treated patients had superior clinical outcomes and health-related QoL compared with EVT and conservative management. Specific improvements in surgically treated patients at 1 year included improvement in pain, mobility, sleep, and emotional reactions.

Additional factors determining the success of surgical bypass for claudication include technical and anatomic factors such as conduit, target vessel, and runoff. Available prospective, randomized data regarding choice of conduit for FP bypass demonstrate superior patency for vein grafts, even to an above-knee popliteal target, compared with PTFE bypass, after 2 to 3 years of follow-up.[229] In most patients, sustained walking improvement and improved QoL depend on maintenance of patency of the surgical reconstruction. This is particularly important when treating IC given the better functional ability and longer life expectancy compared with patients with limb-threatening ischemia.

However, when suitable autologous vein is unavailable, prosthetic bypass for claudication may be reasonable. AbuRahma et al[230] reported no difference in primary patency rates between saphenous vein and PTFE bypass in patients with IC and at least two-vessel to three-vessel runoff. Assisted primary patency rates were still statistically higher for vein grafts. The quality of the runoff circulation may also affect the results of surgical treatment for claudication. Zannetti et al[231] determined that absence of diabetes, minimal cardiac comorbidities, and angiograms predicting near normalization of the postoperative ABI resulted in excellent late outcomes and patient satisfaction in 82% of patients meeting these criteria.

The popliteal artery is the most common outflow vessel when an infrainguinal bypass is performed for claudication, usually above the knee. However, properly selected patients without a suitable popliteal artery target may also benefit from bypass. In a retrospective study of 57 femoral-tibial bypasses performed during a 16-year period for IC, graft patency rates were better than tibial bypass for limb salvage and equivalent to those achieved with FP bypass graft for claudication.[232] Vein conduit, 70% of which were saphenous vein, was used in all cases. Interviewed patients reported improved walking distance, reduced claudication, and a high degree of satisfaction.

Recommendations: Intervention for femoropopliteal occlusive disease (FPOD) in intermittent claudication (*IC*)

	Grade	*Level of evidence*
5.16. We recommend endovascular procedures over open surgery for focal occlusive disease of the SFA artery not involving the origin at the femoral bifurcation.	1	C
5.17. For focal lesions (<5 cm) in the SFA that have unsatisfactory technical results with balloon angioplasty, we suggest selective stenting.	2	C
5.18. For intermediate-length lesions (5-15 cm) in the SFA, we recommend the adjunctive use of self-expanding nitinol stents (with or without paclitaxel) to improve the midterm patency of angioplasty.	1	B
5.19. We suggest the use of preoperative ultrasound vein mapping to establish the availability and quality of autogenous vein conduit in patients being considered for infrainguinal bypass for the treatment of IC.	2	C
5.20. We recommend against EVT of isolated infrapopliteal disease for IC because this treatment is of unproven benefit and possibly harmful.	1	C
5.21. We recommend surgical bypass as an initial revascularization strategy for patients with diffuse FP disease, small caliber (<5 mm), or extensive calcification of the SFA, if they have favorable anatomy for bypass (popliteal artery target, good runoff) and have average or low operative risk.	1	B
5.22. We recommend using the saphenous vein as the preferred conduit for infrainguinal bypass grafts.	1	A
5.23. In the absence of suitable vein, we suggest using prosthetic conduit for FP bypass in claudicant patients, if the above-knee popliteal artery is the target vessel and good runoff is present.	2	C

EVT, Endovascular therapy; *SFA,* superficial femoral artery.

Summary of evidence: Intervention for femoropopliteal occlusive disease (FPOD) in intermittent claudication (*IC*)

Clinical question	*Data source*	*Funding*	*Quality of evidence*
Endovascular vs surgical reconstruction	Four RCTs and six observational studies reporting on 2817 patients with FP arterial disease[233]	EVT was associated with lower 30-day morbidity (OR, 2.93; 95% CI, 1.34-6.41) and higher technical failure (OR, 0.10; 95% CI, 0.05-0.22) than bypass surgery. No difference in 30-day mortality (OR, 0.92; 95% CI, 0.55-1.51). Higher primary patency in the surgical treatment arm was found at 1 (OR, 2.42; 95% CI, 1.37-4.28), 2 (OR, 2.03; 95% CI, 1.20-3.45), and 3 (OR, 1.48; 95% CI, 1.12-1.97) years after intervention. Progression to amputation occurred more commonly in the endovascular group at the end of the second (OR, 0.60; 95% CI, 0.42-0.86) and third (OR, 0.55; 95% CI, 0.39-0.77) year of intervention. The bypass group had higher amputation-free (OR, 1.31; 95% CI, 1.07-1.61) and overall survival (OR, 1.29; 95% CI, 1.04-1.61) rates at 4 years	C (risk of bias, indirectness because most trials enrolled CLI patients)
The effect of stenting vs no stenting in patients with IC on morbidity, mortality and patency	Meta-analysis of 8 RCTs (968 patients with IC or CLI and SFA disease)[189]	Primary patency better with stenting at 6 months but not 12 months	C (indirectness due to CLI patients included and imprecision of long-term outcome)
Balloon angioplasty with optional stenting vs routine stenting with nitinol stents	Meta-analysis of 4 RCTs (627 patients with IC or CLI and SFA disease)[234]	Mortality was similar in both groups (OR, 0.83; 95% CI, 0.39-1.77). Technical success was significantly higher in the stenting group (96% vs 64%; OR, 0.31; 95% CI, 0.09-0.92). The 12-month binary restenosis rate was significantly lower in the primary stenting group (OR, 3.02; 95% CI, 1.3-6.71)[7]	C (indirectness due to CLI patients included and imprecision)
Comparison of various stents	Network meta-analysis of 16 RCTs (2532 patients with IC or CLI and FP arterial disease)[235]	Technical success was highest with covered stents. Vascular restenosis was lowest with paclitaxel DES and with paclitaxel-coated balloons. Major amputations were rare in all treatment and control groups (pooled amputation rate of 0.7 events/100 person-years)	C (indirect comparisons, CLI patients included, imprecision)
Vein grafts vs PTFE	1 RCT in 43 claudicant patients (86 limbs)[230]	Complication rates were 5% for PTFE and 12% for saphenous vein graft, no operative deaths or perioperative amputations for either procedure. Primary, assisted primary, and secondary patency rates at 72 months: 68%, 68%, and 77% for PTFE and 76%, 83%, and 85% for saphenous vein graft	B (imprecision, small number of events)

CI, Confidence interval; *CLI,* critical limb ischemia; *DES,* drug-eluting stent; *OR,* odds ratio; *PAD,* peripheral arterial disease; *PTFE,* polytetrafluoroethylene; *RCT,* randomized controlled trial; *SFA,* superficial femoral artery.

Assessing the efficacy of revascularization for IC

Patients undergoing revascularization for claudication desire durable improvement in pain-free walking and functional independence. Claudication rarely progresses to limb loss, and as such, treatment with endovascular or open surgery should never result in major or minor amputation. Consequently, limb salvage is not considered proof of efficacy of any procedure undertaken to treat IC, and in fact, loss of the limb should be considered a catastrophic failure of therapy. The usual efficacy end points in clinical trials include standardized measures of walking ability such as the initial time to onset of claudication, maximal walking distance, and the 6-minute walk test; however, these end points are rarely used in clinical practice. Patients undergoing lower extremity revascularization for claudication should have documented improvement in symptoms as well as hemodynamic evidence of improvement in lower extremity perfusion. As stated above, anatomic patency is considered a prerequisite for sustained hemodynamic improvement and clinical benefit in IC.

Postintervention medical treatment

After intervention for lower extremity vascular disease, aggressive medical therapy is indicated not only to prevent future cardiovascular events but also to improve patency of the revascularization. Patients should be counseled on risk factor modification, as previously described, and have accepted pharmacologic treatment for system atherosclerosis, especially statins and antiplatelet therapy. In some patients, systemic anticoagulation may also be required.

Antiplatelet agents

Antiplatelet agents are generally used to treat patients after lower extremity bypass. Although, antiplatelet therapy has not been conclusively proven to improve bypass graft patency, its benefit in decreasing long-term postprocedural adverse cardiovascular events is sufficient indication for the use of these agents in most patients, who are considered to be at high risk for cardiovascular complications and stroke.

In a systematic review[236] of the effect of antiplatelet treatment compared with placebo on bypass graft patency, patients receiving antiplatelet therapy had improved patency at 1 year (OR, 0.62; 95% CI, 0.43-0.86). When venous and prosthetic bypasses were analyzed separately, there was no improvement in 12-month patency in patients undergoing venous bypass who received acetylsalicylic acid (ASA) or dipyridamole compared with placebo. Conversely, 12-month primary patency was markedly improved in patients undergoing prosthetic bypass who received ASA compared with placebo (OR, 0.22; 95%, CI, 0.12-0.38). Major bleeding events were more frequent in patients receiving ASA therapy but did not reach statistical significance.

The effect of adding clopidogrel to ASA was studied in 851 patients in the Clopidogrel and Acetylsalicylic Acid In Bypass Surgery for Peripheral Arterial Disease Trial (CASPAR).[237] This placebo-controlled RCT found no difference in outcome between patients receiving ASA vs ASA plus clopidogrel undergoing lower extremity bypass. However, the subset of patients undergoing prosthetic bypass (30%), demonstrated improved patency and limb salvage when receiving ASA combined with clopidogrel compared with ASA alone.

Anticoagulation

Several trials have studied the effect of ASA compared with warfarin on patency in lower extremity bypass. The prospective randomized Dutch Bypass Oral Anticoagulants or ASA (BOA) trial[85] randomized 2690 patients undergoing lower extremity bypass to coumarin (target international normalized ratio of 3-4.5) vs ASA (81 mg/d). Overall, there was no difference in patency at 12 months in the two cohorts; however, a subgroup analysis demonstrated superior patency for patients undergoing vein bypass receiving coumarin compared with those receiving ASA alone at 12 and 24 months (OR, 0.59; 95% CI, 0.46-0.76). This effect was not seen in those patients undergoing prosthetic bypass grafts, where patency was identical in those receiving ASA and coumarin. Twice as many bleeding complications were observed in patients receiving coumarin as in those receiving ASA.

Despite the findings of the BOA trial, most vascular surgeons in the United States choose not to routinely anticoagulate patients undergoing lower extremity vein bypass. However, anticoagulant therapy may be beneficial in specific circumstances where conditions are less than optimal. In a small trial by Sarac et al,[238] 56 patients undergoing high-risk vein bypass (defined as poor-quality conduit or runoff) were randomized to ASA plus warfarin vs ASA alone. The patients receiving ASA plus warfarin had a significantly improved patency and limb salvage at 3 years.

The ischemic consequences of graft thrombosis may be ameliorated by the use of anticoagulants after bypass surgery, especially when using prosthetic grafts. A multicenter prospective, randomized trial of 402 patients undergoing FP bypass with PTFE or saphenous vein and treated with ASA plus warfarin or ASA alone found graft thrombosis more commonly resulted in limb-threatening ischemia in prosthetic grafts than in vein grafts. However, patients with prosthetic graft thrombosis were less likely to present with acute limb ischemia if they were receiving warfarin.[239]

In summary, available clinical evidence does not conclusively support the use of antiplatelet agents to improve lower extremity vein bypass graft patency, although their use is still warranted to reduce future cardiovascular ischemic events and stroke. Patency may be improved with antiplatelet therapy in patients undergoing prosthetic bypass. The use of warfarin anticoagulation after lower extremity bypass remains controversial, and significant differences exist in its use between North American and European vascular surgeons. In the United States, anticoagulation is used selectively in vein bypass procedures with either suboptimal conduit or compromised runoff. Warfarin in addition to ASA is used in many patients receiving prosthetic grafts to reduce the ischemic consequences of bypass graft thrombosis. However, caution is warranted given the incremental bleeding risks associated with combination therapy, and existing evidence is inadequate to support a definitive recommendation at this time.

Recommendations: Postinterventional medical therapy in intermittent claudication (IC)

		Grade	*Level of evidence*
5.24.	In all patients after endovascular or open surgical intervention for claudication, we recommend optimal medical therapy (antiplatelets agents, statins, antihypertensives, control of glycemia, smoking cessation).	1	A
5.25.	In patients undergoing lower extremity bypass (venous or prosthetic), we suggest treatment with antiplatelet therapy (aspirin, clopidogrel, or aspirin plus clopidogrel).	2	B
5.26.	In patients undergoing infrainguinal endovascular intervention for claudication, we suggest treatment with aspirin and clopidogrel for at least 30 days.	2	B

Endovascular intervention

Limited data are available regarding therapies targeted at preventing restenosis or occlusion after endovascular procedures in patients with IC. A recent systematic review of four prospective randomized trials did not demonstrate any improvement in patency at 12 months with ASA compared with placebo.[240] Nonetheless, antiplatelet therapy may be warranted in patients undergoing EVT for claudication as part of an aggressive medical treatment program to prevent long-term cardiovascular complications such as stroke and myocardial infarction. In addition, the same review evaluated the potential effect of using higher-dose ASA (300-1000 mg) compared with lower-dose ASA (50-300 mg). No beneficial effect was observed with higher doses.[240]

Two RCTs investigated the effect of anticoagulation and cilostazol on patency. Koppensteiner et al[241] compared the use of low-molecular-weight heparin (LMWH) and ASA vs ASA alone in patients undergoing popliteal angioplasty. Improved patency was observed in patients treated with LMWH for with CLI, but this effect was not observed in patients treated for claudication.[241] Iida et al[242] observed a decrease in restenosis and reocclusion at 6, 12, and 24 months in patients treated with cilostazol compared with ticlopidine, similar to the beneficial effect observed with cilostazol in improving patency of coronary interventions and FP angioplasty in patients with end-stage renal failure.[243]

6. SURVEILLANCE AFTER REVASCULARIZATION FOR IC

Arterial reconstructions performed for IC may be unilateral, bilateral, suprainguinal, infrainguinal, or on occasion, unilateral or bilateral combinations of suprainguinal and infrainguinal reconstructions. Depending on the site and extent of the arterial occlusive process, reconstructions can be bypass operations with autogenous or prosthetic arterial substitutes, open endarterectomy, or various combinations of catheter-based techniques. Whatever method is selected for reconstruction, the goal is to improve patient QoL by improving pain-free walking distance and maximal walking distance while minimizing the need for additional arterial reconstructive procedures.

Surveillance of vein grafts performed for IC. Autogenous vein is the preferred conduit for open infrainguinal arterial reconstructions for treatment of claudication. Approximately one-third of lower extremity vein grafts will ultimately develop stenotic lesions that may threaten patency. The large majority of such lesions develop within the first year of graft implantation; however, vein grafts are never entirely free of the risk of developing stenosis. The risk of developing vein graft stenosis appears greater in operations performed for CLI, in operations performed with smaller-caliber venous conduits, procedures using nonsaphenous vein conduits, and in vein grafts with anastomosis to more distal (tibial or pedal) arteries. Surveillance protocols for lower extremity autogenous vein graft reconstructions were developed to detect graft stenosis before graft thrombosis and were based on this natural history and the assumption that a patent, hemodynamically uncompromised, lower extremity arterial reconstruction is optimal for maintaining ambulatory function and QoL. Failure of an arterial reconstruction performed for claudication will, at the very least, return the patient to his or her previous level of preoperative disability but may occasionally result in more severe symptoms, including limb-threatening ischemia. In addition, performing a secondary bypass for a thrombosed lower extremity vein graft is technically more difficult and complex than treatment of a failing but still patent graft.

Surveillance programs of lower extremity vein grafts may be solely clinical or both clinical and vascular laboratory based. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) working group recommended patients treated with lower extremity vein grafts be monitored for at least 2 years with a clinical surveillance program that consists of an interval history to detect new symptoms, pulse examination, and measurement of resting and, if possible, postexercise ABIs.[9] However, most vein graft arterial reconstructions are thought to fail through the development of intrinsic stenotic lesions within the venous conduit, at anastomotic sites, or in the outflow artery distal to the distal anastomosis. Most of these lesions occur within the first 12 to 18 months after surgery but can continue to develop or progress years later. Relying on clinical assessment alone may miss critical vein graft stenoses that threaten graft thrombosis, especially in patients treated for CLI (see below). Vascular laboratory-based surveillance programs of lower extremity vein grafts focus on detection using duplex ultrasound surveillance (DUS), grading, and monitoring of stenotic lesions

Summary of evidence: Postinterventional medical therapy

Clinical question	*Data source*	*Finding*	*Quality of evidence*
The effect of antiplatelet therapy on patency, limb salvage and survival in patients with IC who underwent endovascular or open surgical interventions	Systematic review[244] of 15 RCTs in patients with symptomatic PAD (including CLI) undergoing infrainguinal bypass surgery: ASA or ASA + dipyridamole vs placebo (6); ASA or ASA and dipyridamol vs pentoxifylline (2); ASA vs indobufen (1); ASA vs vitamin K antagonists (2); ASA + dipyridamole vs LMWH (1); ticlopidine vs placebo (1); ASA vs prostaglandin E1 (1); ASA vs naftidrofuryl (1)	Antiplatelet therapy improved venous and artificial graft patency compared with no treatment. More benefit in synthetic grafts	B
The effect of anticoagulants agents on patency, limb salvage and survival in patients with IC who underwent open surgical interventions	Systematic review[245] of 14 RCTs in patients undergoing infrainguinal arterial bypass surgery (including CLI)	Anticoagulants reduced the risk of limb loss at the longest follow-up (OR, 0.36; 95% CI, 0.19-0.69) and increased primary patency when venous grafts were analyzed separately (OR, 0.44; 95% CI, 0.14-1.42). Bleeding risk doubled compared with antiplatelets	B-C (rated down due to imprecision and indirectness)
The effect of antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion after peripheral EVT	Systematic review[240] of 22 RCTs with various comparisons. Secondary indirect evidence on benefits of antiplatelet agents in reducing cardiovascular morbidity and mortality	At 6 months postintervention, reocclusion was lower with high-dose ASA + dipyridamole (OR, 0.40; 95% CI, 0.19-0.84), but not for low-dose ASA + dipyridamole. No significant difference in reocclusion or restenosis was detected for high-dose ASA vs low-dose ASA, ASA/dipyridamole vs vitamin K antagonists, clopidogrel + aspirin vs LMWH + warfarin, or ticlopidine vs vitamin K antagonists. Clopidogrel and aspirin resulted in fewer major bleeding episodes compared with LMWH + warfarin	B-C (rated down due to imprecision and indirectness)

ASA, Acetylsalicylic acid; *CI,* confidence interval; *CLI,* critical limb ischemia; *EVT,* endovascular therapy; *IC,* intermittent claudication; *LMWH,* low-molecular-weight heparin; *OR,* odds ratio; *PAD,* peripheral arterial disease; *RCT,* randomized controlled trial.

within the graft or at the anastomoses thought to threaten graft patency, regardless of clinical presentation.

There is an extensive body of literature on the use DUS of lower extremity vein grafts performed for CLI. Most studies are retrospective analyses of single-institution case series. Prospective studies have also focused on patients with CLI and not claudication. Patients undergoing surgical bypass for claudication are generally healthier and more active than those treated for CLI and are theoretically more ambulatory and more apt to report recurrence of symptoms earlier than a minimally ambulatory, debilitated patient treated for CLI. Grafts placed for claudication usually extend to the popliteal artery, rarely more distally, and have superior patency compared with vein grafts placed for CLI. It is therefore not clear whether data derived for vascular laboratory-based DUS programs in patients treated for CLI are applicable or even necessary for patients treated for claudication.

The Vein Graft Surveillance Randomized Trial (VGST) was a prospective study in the United Kingdom that randomized 594 patients with patent vein grafts 30 days after surgery[246] to clinical surveillance or DUS in addition to clinical surveillance. Most the operations were from the CFA to the above-knee or below-knee popliteal artery, and the conduits were ipsilateral reversed saphenous vein in >90% of the procedures. Anastomotic sites and conduits largely mimicked those most used in vein grafts performed for claudication, even though two-thirds of the procedures in VGST were for CLI. A comparison of the two surveillance strategies at 18 months found no differences in primary, primary assisted, or secondary patency.

A smaller study from Sweden randomized 156 patients with lower extremity arterial reconstructions to intensive surveillance to include DUS (n = 79) vs routine clinical surveillance (n = 77).[247] Forty grafts, equally distributed between the two groups, were PTFE grafts. Only two grafts in each group were performed for claudication, and two-thirds of the grafts were performed to the popliteal artery. Among the vein grafts in the study there was improved assisted primary and secondary patency in the intensive surveillance group that included DUS.

Many single-institution series and one large prospective multi-institution series demonstrated improved vein graft patency for patients treated for CLI with a surveillance program using duplex ultrasound detection of graft stenoses.[248-252] In addition to a significant improvement in primary and assisted primary patency of vein grafts monitored with a DUS-based program, these studies and others have demonstrated revised grafts have excellent long-term patency comparable to grafts never undergoing revision.[253,254] None of the studies included patients treated for claudication. Whether the magnitude of the benefit of improved graft patency achieved in CLI patients, followed with duplex-based surveillance, would be comparable in patients undergoing vein bypass for claudication remains unknown. Nevertheless, the significance and consistency of evidence demonstrating benefit for a DUS-based program for lower extremity vein grafts done for CLI infers some benefit would be derived for grafts performed for claudication, especially during the first year after the bypass, although the strength of the evidence is weak. Optimal intervals for DUS are also not well defined. Current practice of many vascular surgeons in the United States is to obtain a postoperative duplex ultrasound assessment of vein grafts within the first month, at 3, 6, and 12 months, and every 6 to 12 months thereafter.

Surveillance of catheter-based interventions performed for IC. Residual and early recurrent stenoses commonly occur after endovascular procedures, particularly when performed for more complex disease.[255] The role of DUS after EVT is unclear. To date, no randomized trials of DUS after endovascular intervention have been performed, but many have extrapolated DUS protocols and criteria for peak systolic velocity (PSV) and velocity ratio (Vr) developed for infrainguinal vein grafts and applied them to follow-up after EVT. Duplex ultrasound can localize and grade the presence and degree of stenosis in the FP segment after angioplasty alone as well as after stent placement, particularly in the SFA, where authors have correlated duplex findings with angiography. Baril et al[256] reported that a PSV >275 cm/s and a Vr >3.5 were specific and predictive cutoff values for duplex determination of >80% in-stent restenosis after angioplasty and stent placement in the SFA.

Clinical follow-up alone, combined with ABI determination or toe pressure measurements, or both, in limb salvage patients, and with DUS have all been proposed methods of surveillance for catheter-based interventions. Available reports to date regarding the accuracy, predictive value, and benefits of DUS after EVT are conflicting. Mewissen et al[257] reported one of the earliest experiences with DUS after balloon angioplasty of the FP artery. They demonstrated the importance of hemodynamic assessments (ABI measurements and toe pressure measurements) in determining the degree of perfusion improvement, but these techniques could not discriminate between restenosis or occlusion of the angioplasty site and progression of disease proximal and distal to the treated segment. Early duplex scanning was performed at 1 month after successful FP angioplasty in 59 patients. Duplex imaging identified <50% diameter-reducing stenosis at 63% of angioplasty sites and >50% restenosis (Vr >2) in 27% of treated segments. They further observed that the presence of >50% stenosis at 30 days postintervention was predictive of clinical failure at 1 year ($P < .001$). Although this study has been used to justify surveillance and prophylactic intervention after angiography, this conclusion is questionable because DUS was not routinely performed in all patients. Sacks et al[258] found no difference in 3-year patency between patients with a normal duplex examination at 48 hours after angioplasty compared with those with an abnormal study (Vr >2.0), arguing against using DUS findings as a guide for prophylactic intervention. Spijkerboer et al[259] also reported that early DUS (1 day) findings did not correlate with clinical or hemodynamic success 1 year after SFA-popliteal angioplasty. In a more recent study, Humphries et al[260] reported that an abnormal duplex examination within the first 30 days of treatment in patients undergoing infrainguinal EVT for CLI, was associated with an increased subsequent risk of amputation.

Other investigators have reported that despite intense surveillance, outcomes after long-segment percutaneous treatment of SFA lesions are suboptimal. Gray et al[261] reported that even with close surveillance and prophylactic reintervention, anatomic patency after intervention with selective stenting for long-segment SFA lesions (mean length, 16.5 cm) at 1 year was poor, although clinical outcomes were favorable. After tibial interventions, Schmidt et al[262] reported an angiographic >50% restenosis rate of 31.2% and a treated segment occlusion rate of 37.6% at 3 months after treatment of long-segment (>8 cm) tibial lesions, despite high rates of clinical success and limb salvage in most patients with Rutherford 4 and 5 ischemia. These and other studies suggest that unlike vein graft surveillance, duplex-derived patency is poorly correlated with the clinical success of catheter-based interventions, making prophylactic interventions on the basis of duplex data highly questionable.

Clinical follow-up and hemodynamic assessment alone after infrainguinal EVT has been proposed. Tielbeek et al[263] reported a prospective assessment of 124 patients during a 5-year period who underwent EVT for femoropopliteal disease. Although a duplex-detected Vr >2.5 at the intervention site predicted subsequent occlusion of the treated arterial segment, they observed that only one patient with failure would have received a redo endovascular procedure at the time he had restenosis, supporting their bias that clinical and hemodynamic assessments were more useful than DUS for follow-up. Spijkerboer et al[264] monitored patients with serial DUS after iliac interventions and found that the clinical outcomes of patients with residual stenosis did not differ from patients with normal DUS studies. They also observed regression of some stenoses over time, without reintervention, an observation that has been confirmed by others after infrainguinal EVT.[265]

Bui et al[265] analyzed a consecutive series of 94 interventions in 85 patients for SFA-popliteal artery occlusive disease. Prophylactic interventions were rarely performed, and reinterventions were reserved almost exclusively for clinical indications such as recurrent symptoms or failure of wounds to heal. Patients were stratified by whether the initial scan performed in the first 30 days after the intervention was normal. Initial scans were normal in 61 limbs (65%) and remained normal during follow-up in 62% of these patients. In 17 limbs (28%), progressive stenoses were detected during DUS. The rate of spontaneous thrombosis without prophylactic reintervention in this group was only 10%. In this study, DUS was initially normal after about two-thirds of interventions, a rate quite similar to that reported for infrainguinal vein grafts.[249] However, only 62% of those patients with initially normal DUS studies remained normal during follow-up, in contrast to the 90% to 95% rate observed after vein graft placement; a de novo stenosis rate after EVT is ~28%, compared with 5% after vein grafting.[249] The authors also observed stabilization or resolution of stenosis after EVT occurred quite commonly despite early abnormal findings. One important difference observed compared with FP vein grafts is the poor correlation between the degree of stenosis and the likelihood of occlusion with EVT. Of the occlusions after EVT, 82% occurred when minimal or moderate stenosis (PSV, 200-300 cm/s; Vr, 2-3) had been detected before the intervention.[249,250] Moreover, had duplex findings been used as the sole indication for prophylactic reintervention, ~30 patients would have undergone a clinically unnecessary intervention.

Unlike vein graft stenosis, the natural history of stenosis after EVT remains uncertain, making the prediction of which lesion will progress to failure difficult to determine. As previously stated, the lack of reliable data documenting the natural history of the DUS-detected stenosis after EVT makes the practice of prophylactic intervention on the basis of stenosis highly questionable and possibly harmful. Moreover, there may be differences with respect to the behavior of restenoses after angioplasty alone compared with restenoses that develop after stent placement. There are data suggesting that durable salvage of thrombosed superficial FP stents is poor and that occlusion of such stents compromises runoff. Ihnat et al,[219] analyzing a series of 109 consecutive SFA stents, reported that stent occlusion was associated with a significant worsening of the SVS runoff score from 4.1 to 6.4, amounting to the loss of one runoff vessel for each episode of stent occlusion. If these finding are confirmed in future studies and accurate cutoff criteria predicting progression to

Recommendations: Surveillance after interventions for intermittent claudication (*IC*)

		Grade	*Level of evidence*
6.1.	We suggest that patients treated with open or endovascular interventions for IC be monitored with a clinical surveillance program that consists of an interval history to detect new symptoms, ensure compliance with medical therapies, record subjective functional improvements, pulse examination, and measurement of resting and, if possible, postexercise ABIs.	2	C
6.2.	We suggest that patients treated with lower extremity vein grafts for IC be monitored with a surveillance program that consists of clinical follow-up and duplex scanning.	2	C
6.3.	We suggest that patients who have previously undergone vein bypass surgery for IC and have developed a significant graft stenosis on DUS be considered for prophylactic reintervention (open or endovascular) to promote long-term bypass graft patency.	1	C

ABI, Ankle-brachial index; *DUS,* duplex ultrasound.

Summary of evidence: Surveillance after interventions for intermittent claudication (IC)

Clinical question	*Data source*	*Finding*	*Quality of evidence*
The effect of surveillance after revascularization for IC on patency (surveillance vs no surveillance, clinical follow-up vs duplex scanning, shorter interval of surveillance vs longer interval)	Data derived from CLI patients, uncontrolled and mostly in vein grafts. Two RCTs comparing clinical examination vs DUS	Improved vein graft patency with DUS (CLI patients). Two RCTs showed no difference between clinical examination and DUS	C (quality of evidence rated down due to indirectness, methodological limitation, and imprecision)

CLI, Critical limb ischemia; *DUS,* duplex ultrasound; *RCT,* randomized controlled trial.

clinical failure after SFA stenting can be determined, selective prophylactic reintervention after SFA stenting might be reasonable. At this time, however, no such data exist.

In summary, the natural history of stenotic lesions from EVT remains uncertain, and the benefits of intervention based on duplex findings alone not yet established. Until such criteria are available, patients undergoing EVT should have serial clinical follow-up, including simple hemodynamic measurements, at clinical intervals appropriate for the indication for intervention and the extent of disease treated. In general, those treated for CLI, and with long-segment occlusions should be monitored more closely than those treated for claudication.[219,261,265] The role of duplex imaging in these patients is currently unclear although useful in determining whether recurrent symptoms are due to stenosis or occlusion and to localize lesions, which might alter the treatment plan. Continued use of duplex may also help to clarify its role further, especially when correlated with clinical presentation, angiographic findings, and ultimate outcome.

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APPENDIX

Conflict of interest disclosure table for the SVS Lower Extremity Guidelines Committee

Writing group member				*Company relationships*					
First name	*Last name*	*Affiliation*	*Degree*	*Response*	*Officer, board member, trustee, owner or employee of a company*	*Direct owner of stock, stock options, or bonds of a company, excluding diversified mutual funds*	*Consultancy, scientific advisory committee membership, or lecturer for a company*	*Investigator for a company, including holding research grants from the company*	*Personal income from patents*
Michael	Conte (Chair)	University of California, San Francisco	MD	Yes	No	No	Cook Medical-Scientific Advisory Board Medtronic Inc-Scientific Advisory Board-Lecturer for Pfizer, Cook Medical, Medtronic Anges-Consultant	No	No
Frank	Pomposelli (Co-chair)	St. Elizabeth's Medical Center	MD	No	Member of the Board of Directors of TRACO LLC, a malpractice insurance company.	No	No	No	No
Daniel	Clair	Cleveland Clinic Foundation	MD	Yes	Yes	No	Boston Scientific, Cordis, Covidien, Endologix, Medtronic, W. L. Gore	Yes	No
Patrick	Geraghty	Washington University Medical School	MD	No	No	Yes	Cook Medical inc, money is paid to clinic.	Yes	No
James	McKinsey	Columbia University	MD	Yes	No	No	Covidien, Cook Medical, Spectranetics Lecturer; Aptus, Spectranetics—Scientific Advisory Committee; Cook Medical, Aptus DSMB (now dissolved)—consultant	No	No
Joseph	Mills	University of Arizona Health Science Center	MD	Yes	Yes	No	Novadaq- Lecturer; Anges—Scientific Advisory Committee	Novadaq	No
Gregory	Moneta	Oregon Health & Science University	MD	No	No	No	No	Participate in industry sponsored clinical trials as local investigator. No personal income. (Gore, Bolton, Harvest technologies)	No
Richard	Powell	Dartmouth-Hitchcock Medical Center	MD	Yes	No	No	Anges- Lecturer & Scientific Advisory Committee	No	No
Amy	Reed	Penn State Hershey College of Medicine	MD	No	No	No	No	No	No
Andres	Schanzer	University of Massachusetts Medical School	MD	Yes	No	No	Cook Medical—I have a consultant agreement in order to proctor fenestrated EVAR cases.	Cook Medical, Bolton Medical, Abbott, Proteon—I am our site PI on industry-sponsored trials but I receive no compensation.	No
Anton	Sidawy	George Washington University, Washington, D.C.	MD, MPH	No	No	No	No	No	No
Hassan	Murad	Mayo Clinic, Rochester, Minn	MD	No	No	No	No	No	No

SUPPLEMENTARY MATERIAL (online only).

A revised recommendation: Society for Vascular Surgery practice guidelines for the management of asymptomatic disease and claudication

The Society for Vascular Surgery has an established methodology[1] for the development of clinical practice guidelines that considers future emerging evidence. Changes in the evidence base necessitate subsequent updated recommendations. Recently, a report of a randomized controlled trial[2] that compared ramipril to a matching placebo was retracted.[3] The trial had shown that 10 mg/d of ramipril given for 24 weeks to patients with intermittent claudication (IC) increased mean pain-free walking time, maximum walking time, Walking Impairment Questionnaire scores and the Physical Component Summary score. The Society guideline published earlier this year[4] had considered evidence from this trial and suggested the use of ramipril in patients with IC (Recommendation 4.11). The recommendation was a weak one (ie, suggestion) because the trial was small and the results had not been replicated in other trials with a longer follow up period.

The Society's committee charged with developing guidelines for atherosclerotic occlusive disease of the lower extremities has decided to strike recommendation 4.11 based on the current state of evidence after retraction of this trial.

The committee notes that many patients with IC may still benefit from angiotensin-converting enzyme inhibitors (ACEIs) for other conditions such as hypertension and congestive heart failure, which are common in patients with PAD. ACEIs remain contraindicated in individuals with known renal artery stenosis. Further research is needed to determine if ACEIs have a useful role in the treatment of walking impairment or leg symptoms associated with IC.

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Added October 2015