Peripheral Artery Disease: Current Insight Into the Disease and Its Diagnosis and Management

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On completion of this article, you should be able to (1) identify the signs and symptoms of peripheral artery disease (PAD) and distinguish them for other diseases that can mimic PAD; (2) diagnose PAD using the history, findings on physical examination, and ankle brachial index; and (3) formulate an integrated treatment program to improve the symptoms and quality of life and decrease the high cardiovascular event rate.

Peripheral artery disease (PAD), which comprises atherosclerosis of the abdominal aorta, iliac, and lower-extremity arteries, is underdiagnosed, undertreated, and poorly understood by the medical community. Patients with PAD may experience a multitude of problems, such as claudication, ischemic rest pain, ischemic ulcerations, repeated hospitalizations, revascularizations, and limb loss. This may lead to a poor quality of life and a high rate of depression. From the standpoint of the limb, the prognosis of patients with PAD is favorable in that the claudication remains stable in 70% to 80% of patients over a 10-year period. However, the rate of myocardial infarction, stroke, and cardiovascular death in patients with both symptomatic and asymptomatic PAD is markedly increased. The ankle brachial index is an excellent screening test for the presence of PAD. Imaging studies (duplex ultrasonography, computed tomographic angiography, magnetic resonance angiography, catheter-based angiography) may provide additional anatomic information if revascularization is planned. The goals of therapy are to improve symptoms and thus quality of life and to decrease the cardiovascular event rate (myocardial infarction, stroke, cardiovascular death). The former is accomplished by establishing a supervised exercise program and administering cilostazol or performing a revascularization procedure if medical therapy is ineffective. A comprehensive program of cardiovascular risk modification (discontinuation of tobacco use and control of lipids, blood pressure, and diabetes) will help to prevent the latter.

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ABI = ankle brachial index; ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CI = confidence interval; CTA = computed tomographic angiography; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; MRA = magnetic resonance angiography; NHANES = National Health and Nutrition Examination Survey; PAD = peripheral artery disease

Peripheral artery disease (PAD) is underdiagnosed, undertreated, poorly understood, and much more common than previously thought.[1,2] In the current article, the term *peripheral artery disease* will be used to denote vascular diseases caused by atherosclerosis of the abdominal aorta, iliac, and lower-extremity arteries leading to stenosis or occlusion.

In primary care practices across the United States, 29% of patients who are older than 70 years or who are older than 50 years with a history of smoking or diabetes have been reported to have PAD.[1,3-5] Not only was the diagnosis of PAD frequently overlooked, but the cardiovascular risk factors were not treated as appropriately as in patients with CAD.

The diagnosis of PAD should not be overlooked for 2 important reasons. First, patients with PAD may experience many problems, such as claudication, ischemic rest pain, ischemic ulcerations, repeated hospitalizations, revascularizations, and limb loss.[4] These lead to a poor quality of life and a high rate of depression.[6,7] Even patients who have no leg symptoms have a poorer functional performance, poorer quality of life, smaller calf muscle area, and greater calf muscle fat than an age-matched group of patients without PAD.[8] Second, patients with PAD have a greater likelihood of experiencing a myocardial infarction (MI), stroke, and cardiovascular death and have a higher rate of all-cause mortality compared with patients without PAD.[9-11]

EPIDEMIOLOGY

Approximately 12% of the adult population has PAD, and the prevalence is equal in men and women.[12] A strong association exists between advancing age and the prevalence of PAD. Almost 20% of adults older than 70 years have PAD.[13] In an elderly hypertensive population from the Systolic Hypertension in the Elderly Program, the prevalence of PAD was 38% in black men, 25% in white men, 41% in black women, and 23% in white women.[14]

Claudication is the symptomatic expression of PAD; however, it occurs less frequently than has been reported previously. Patients may experience classic claudication,

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atypical leg pain, rest pain, ischemic ulcers, gangrene, or no symptoms at all (Table 1). In fact, asymptomatic disease may be present in up to 50% of patients with PAD.[4] Of the 460 patients in the Walking and Leg Circulation Study, 19.8% had no exertional leg pain, 28.5% had atypical leg pain, 32.6% had classic intermittent claudication, and 19.1% had pain at rest.[15] The Rotterdam Study identified a 19.1% prevalence of PAD in their cohort population; however, claudication was reported in only 6.3% in the PAD group.[16] In the Edinburgh Artery Study, the prevalence of claudication among 1592 participants aged 55 to 74 years was 4.5%, whereas asymptomatic PAD occurred in 8.0% of enrollees.[17]

RISK FACTORS

The most common risk factors associated with PAD are increasing age, diabetes, and smoking.[18]

Age

Persons aged 65 years or older in the Framingham Heart Study and persons aged 70 years or older in the National Health and Nutrition Examination Survey (NHANES) were at increased risk for the development of PAD.[4] The prevalence was 4.3% in participants older than 40 years compared with 14.5% in those older than 70 years.[19]

Smoking

Smoking is the single most important modifiable risk factor for the development of PAD. It is unknown why the association between PAD and smoking is about twice as strong as that between PAD and coronary artery disease (CAD).[20] Smokers have a risk of PAD that is 4 times that of nonsmokers and experience onset of symptoms almost a decade earlier. A dose-response relationship exists between pack-year history and PAD risk.[20-22] Furthermore, smokers have poorer survival rates, a greater likelihood of progression to critical limb ischemia and amputation, and decreased artery bypass graft patency rates when compared with nonsmokers. Both former and current smokers are at increased risk of PAD. However, patients who are able to stop smoking are less likely to develop critical limb ischemia and have improved survival.[23]

Diabetes Mellitus

Diabetes increases the risk of developing symptomatic and asymptomatic PAD by 1.5- to 4-fold and leads to an increased risk of cardiovascular events and early mortality.[24-26] In NHANES,[22] 26% of participants with PAD were identified as having diabetes, whereas in the Edinburgh Artery Study, the prevalence of PAD was greater in participants with diabetes or impaired glucose tolerance (20.6%) than in those with normal glucose tolerance (12.5%).[27] Diabetes mellitus is a stronger risk factor for PAD in women than men, and the prevalence of PAD is higher in African American and Hispanic diabetic populations.[26,28-30] Diabetes (and poor foot care) is the most common cause for amputation in the United States.[26]

Hyperlipidemia

In the Framingham Study, an elevated cholesterol level was associated with a 2-fold increased risk of claudication.[28] In NHANES, more than 60% of patients with PAD had hypercholesterolemia, whereas in the PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) program, the prevalence of hyperlipidemia in patients with known PAD was 77%.[1,22] Hyperlipidemia increases the adjusted likelihood of developing PAD by 10% for every 10 mg/dL rise in total cholesterol (to convert to mmol/L, multiply by 0.0259).[31] The 2001 National Cholesterol Education Program Adult Treatment Panel III considered PAD a CAD risk equivalent.[32]

Hypertension

Almost every study has shown a strong association between hypertension and PAD, and as many as 50% to 92% of patients with PAD have hypertension.[33] The risk of developing claudication is increased 2.5- to 4-fold in both men and women with hypertension.[28] In the Systolic Hypertension in the Elderly Program, 5.5% of the participants had an ankle brachial index (ABI) under 0.90.[34] Cumulatively, these studies underscore the high prevalence of PAD in patients with hypertension.

Nontraditional Risk Factors

Other risk factors that are associated with an increased prevalence of PAD include race and ethnicity (African Americans and those of Hispanic origin are at higher risk), chronic kidney disease, the metabolic syndrome, and levels of C-reactive protein, β_2-microglobulin, cystatin C, lipoprotein(a), and homocysteine.[29,34-41] A full discussion of these nontraditional risk factors is beyond the scope of this review.

CLINICAL PRESENTATION

The clinical presentation, natural history, and outcomes in patients with PAD are summarized in Figure 1.[4]

Symptoms

Peripheral artery disease has several distinct modes of presentation (Table 1). Because it is not uncommon for patients to deny that they have pain, it is helpful to reword the question to ask if they feel discomfort when walking. Patients with aortoiliac disease may experience exercise-

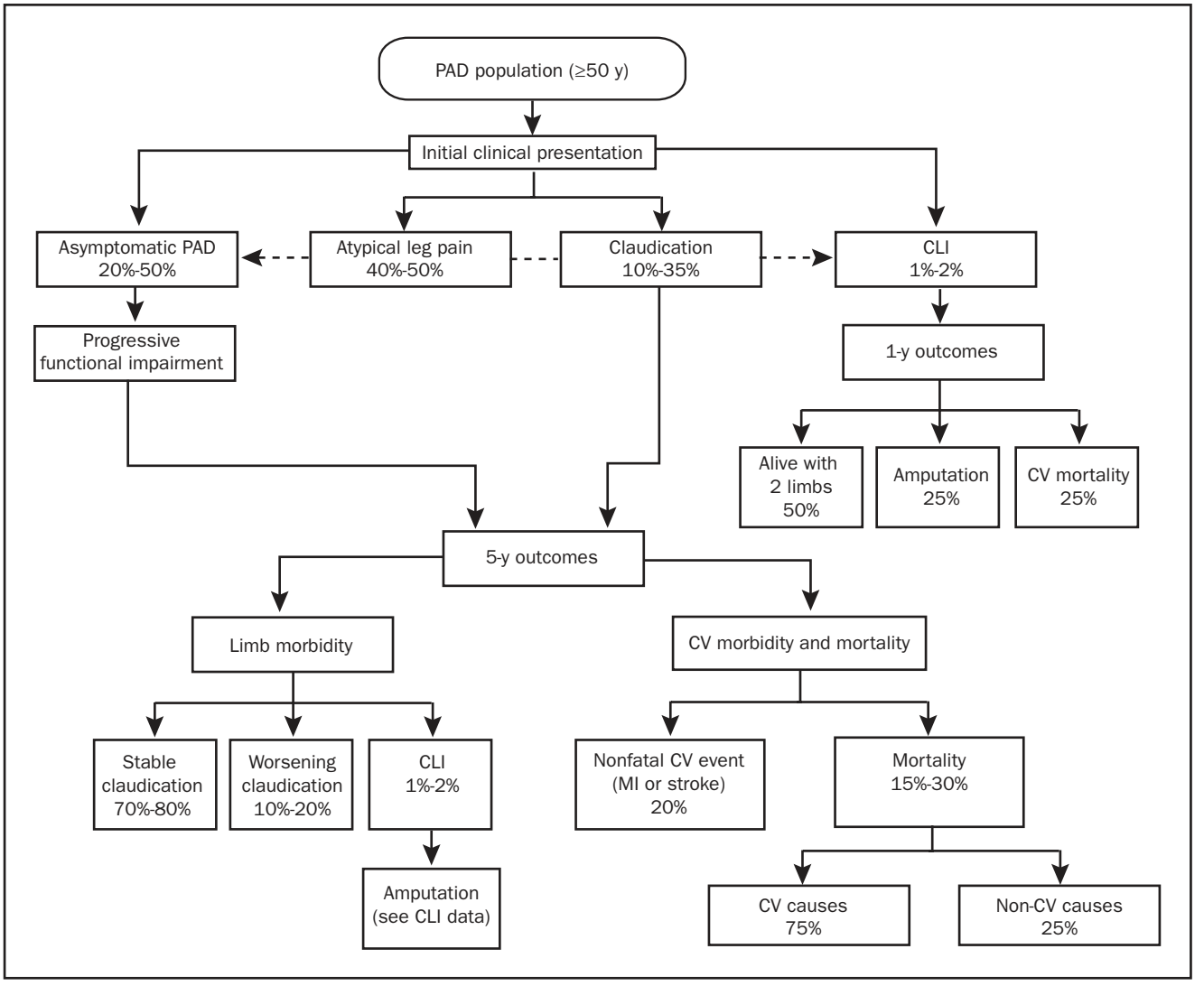

FIGURE 1. Natural history of peripheral artery disease (PAD). CLI = critical limb ischemia; CV = cardiovascular; MI = myocardial infarction. From *Circulation*,[4] with permission of the American Heart Association.

induced hip, buttock, or thigh discomfort or simply a sense of power failure. If patients walk until the symptoms become so severe that they can no longer walk, they may not receive relief for 15 or 20 minutes (because of lactic acid accumulation in the muscles) and may need to sit down. The discomfort of claudication is usually experienced one level distal to the level of obstruction (ie, superficial femoral or popliteal obstruction causes calf claudication; aortoiliac disease causes thigh, hip, or buttock claudication).

From the standpoint of the limb, the prognosis of patients with PAD is favorable in that the claudication remains stable in 70% to 80% of patients over a 10-year period (Figure 1).[4] In the remainder of patients, it may progress to disabling claudication, critical limb ischemia requiring revascularization, or (less commonly) amputation.[4,42]

The most common clinical manifestations of critical limb ischemia include pain at rest, ischemic ulcerations, and gangrene. Prognosis is particularly poor in patients in whom PAD progresses to critical limb ischemia, as demonstrated in Figure 1.[4,42]

Ischemic rest pain usually begins distally in the toes and foot, is worse with the leg elevated (eg, at night when the patient is in bed), and is relieved with dependency (hanging the leg over the side of the bed, standing or sitting in a chair). As the degree of ischemia worsens, patients may experience paresthesias, coldness of the extremity, muscular weakness, and stiffness of the foot and ankle joints.

The most common conditions associated with symptoms that may be confused with claudication are spinal stenosis or lumbar radiculopathy. Furthermore, elderly

TABLE 1. **Distinct Modes of Presentation in Patients With Peripheral Artery Disease**

Classic claudication
Pain, discomfort, aching, heaviness, tiredness, tightness, cramping, or burning in the calf, thigh, hip, and buttocks that (1) is reproducible with a similar level of walking from day to day, (2) disappears after several minutes of standing, and (3) occurs at the same distance once walking has resumed
Atypical leg pain
Lower-extremity discomfort that is exertional but does not consistently occur at the same distance walked and may require a longer period of time to resolve or require the patient to sit down or change body position
Asymptomatic
Without obvious symptoms, but usually associated with functional impairment on formal testing

patients may have both PAD from atherosclerosis and spinal stenosis (pseudoclaudication). It is only by a detailed history that one can distinguish which of these 2 common conditions is causing the symptoms in an individual patient (Table 2).[43]

Physical Examination

Much information can be gained from a carefully performed cardiovascular physical examination. In patients with PAD, the blood pressure should be obtained from each arm because associated subclavian artery disease is frequently present in these patients. A blood pressure difference exceeding 20 mm Hg indicates innominate, subclavian, or axillary disease. In addition, one should listen for bruits over the carotid and subclavian arteries; if present, they should be described as systolic, diastolic, or both.[44] Not only are bruits a clue to a potentially severe stenosis, but it has been shown in a recent meta-analysis involving 17,295 patients with 62,313 patient-years that the yearly MI rate and yearly cardiovascular death rate were 2 times greater in patients with than in those without carotid bruits.[45] The abdominal aorta should be palpated in all patients; if enlarged, the patient should undergo abdominal ultrasonography. The femoral, popliteal, dorsalis pedis, and posterior tibial arteries should be palpated and described as normal [2+], diminished [1+], or absent [0].[4] The presence of aneurysms in the femoral or popliteal artery should also be noted on the physical examination. The dorsalis pedis pulse may be absent in up to 12% of patients and thus is not considered an abnormal finding. However, it is never normal to have an absent posterior tibial pulse. Careful inspection of the feet should be undertaken to look for ulcerations, calluses, and tinea infection. Nail and foot care are important to help to prevent infection and amputation.

Physiology of Claudication

Claudication is a word derived from the Latin word *claudicato*, meaning to limp. The discomfort it causes results from reversible muscle ischemia. Blood flow is determined by the systemic blood pressure and the resistance to flow as represented by the formula (Flow = Pressure/Resistance). In healthy people, exercise causes vasodilatation, thereby decreasing peripheral vascular resistance and maintaining pressure distally. In patients with PAD, exercise causes increased demand for oxygen, yet only a fixed amount of blood can be delivered distally because of an obstruction to blood flow and vasodilatation that decreases outflow resistance. Thus, a fixed amount of blood is delivered to dilated capacitance vessels, causing a decrease in ankle pressure with exercise.[46]

Patients with PAD may experience not only hemodynamic abnormalities but also abnormalities of muscle structure and function. Muscle biopsy specimens from patients with PAD may show a decrease in the type II fast twitch fiber area. These findings have been associated with muscle weakness.[47] Furthermore, patients with claudication may develop progressive denervation over time.[48] These abnormalities have important clinical im-

TABLE 2. **Differentiating Intermittent Claudication From Pseudoclaudication**

Description of symptom	Intermittent claudication	Pseudoclaudication
Character of discomfort	Pain, tightness, cramping, heaviness, tiredness, and burning	Same plus tingling, weakness, and clumsiness
Location of discomfort	Buttock, hip, thigh, calf, and foot	Same
Exercise-induced?	Yes	Yes or no
Distance to claudication	Same each time	Usually variable
Occurs with standing	No	Yes
Relief	Stop walking and stand	Often must sit down or change body position

Adapted from *Peripheral Vascular Diseases*, 2nd ed.[43]

plications because patients with claudication have a slow walking speed, decreased step length and cadence, and impaired gait stability.[46] Hiatt and Brass[46] point out that reduced exercise capacity in patients with PAD cannot be explained by alterations in limb blood flow alone because of the presence of so many other abnormalities in muscle and nerve structure, function, and metabolism.

Differential Diagnosis of Claudication

A large number of conditions should be considered in patients who present with exercise-induced leg discomfort (Table 2). Several vascular conditions other than atherosclerotic PAD can cause claudication, including popliteal artery entrapment syndrome, cystic adventitial disease, fibromuscular dysplasia of the iliac or lower-extremity arteries, endofibrosis of the iliac artery associated with cycling, atheromatous embolization and vasculitis such as thromboangiitis obliterans (Buerger disease), Takayasu arteritis, or giant cell arteritis. Rarely, arthritis, myositis, and compartment syndrome may be mistaken for vascular claudication. Patients with iliac vein obstruction may develop venous claudication. Patients have described this as a burning pain when walking that feels like the leg is going to "burst." The patient must sit or lie down to obtain relief.

Clinical Outcomes

The ABI is the ratio of the ankle systolic pressure to the arm systolic pressure; an ABI of less than 0.90 indicates that the patient has PAD. A low ABI has been shown to be an independent predictor of increased mortality.[9,34,49-52] The 5-year mortality rate of patients with an ABI of less than 0.90 is approximately 25%.[51] Patients with an ABI of less than 0.90 are twice as likely to have a history of MI, angina, and heart failure than patients with an ABI of 1.0 to 1.5.[53,54] In a 10-year prospective study by Criqui et al,[10] PAD patients with and without a history of cardiovascular disease had a significantly increased risk of dying of any cause or as a result of cardiovascular disease or CAD than age-matched controls.[10] All-cause mortality was 3.1 times greater and cardiovascular disease mortality was 5.9 times greater in patients with than in those without PAD. The BARI (Bypass Angioplasty Revascularization Investigation) trial demonstrated that patients with multivessel CAD and PAD had a 4.9 times greater relative risk of death than those without PAD.[55] In a pooled analysis of mortality in 8 large randomized trials involving 19,867 patients who underwent percutaneous coronary intervention, Saw et al[56] demonstrated that the rates of death at 7 days, 30 days, 6 months, and 1 year and rates of MI were more than 2 times higher in patients with than in those without PAD.

DIAGNOSTIC EVALUATION

Exercise Treadmill Testing and ABI

Of all of the noninvasive methods for the diagnosis of PAD (Table 3),[4,57] the ABI, segmental blood pressure, and pulse volume waveform analysis are the only techniques that provide physiologic information about perfusion in the limb. Using a hand-held continuous wave Doppler ultrasound device, the higher systolic pressure measured from either the posterior tibial or dorsalis pedis (in each leg) is compared with the highest brachial pressure taken from either arm (Figure 2).[4] A normal ABI is 0.90 to 1.40. A reduction in the ABI indicates reduced blood flow to the lower extremity.[58,59] Measurement of the ABI does not define the level of obstructive disease, but it is accurate, simple to obtain, and correlates with the severity of the perfusion abnormality but not with the functional impairment that the patient may experience.

The diagnostic value of the ABI is limited in disease states that lead to noncompressibility of blood vessels (eg, patients with diabetes or renal failure). In these circumstances, the increase in ABI (>1.40) may be an artifact. In the Strong Heart Study, an ABI of greater than 1.40 was associated with increased all-cause and cardiovascular mortality.[9] In cases of noncompressibility at the ankle level, the toe brachial index (the ratio of the systolic pressure of the toe to that of the arm) may be used. Further details regarding segmental blood pressures, pulse volume recordings, and exercise ABIs are provided in Table 3.[4]

Duplex Ultrasonography

Duplex ultrasonography is a safe (no radiation or contrast agent) and cost-effective method of accurately determining the severity and location of stenosis and differentiating stenosis from occlusion. B-mode or gray-scale imaging displays a 2-dimensional image of the artery wall and lumen, permitting a rough evaluation of the lesion and atheroma characteristics. Color flow Doppler and pulsed wave Doppler allow an estimation of the stenosis severity on the basis of Doppler-derived velocity criteria.[60] Duplex ultrasonography is an accurate method for determining the degree of stenosis or length of occlusion of the arteries supplying the lower extremity.[61-63]

Furthermore, duplex ultrasonography may be useful in the follow-up of patients who have undergone endovascular (percutaneous transluminal angioplasty/stent) or surgical revascularization. Some clinicians routinely place their patients into an ultrasound surveillance program after angioplasty or stent implantation, and most surgeons do so after lower-extremity bypass surgery. The goal of such a program is to identify a problem (and thus prevent occlusion) should it occur.[64]

TABLE 3. **Noninvasive and Invasive Vascular Diagnostic Tools: Benefits and Limitations**[a]

Diagnostic tool[b]	Benefits	Limitations
ABIs	A quick, cost-effective way to establish or refute the diagnosis of PAD (see text) Useful to monitor the efficacy of therapeutic interventions	May not be accurate when systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff (noncompressible vessels at the level of the ankle), as occurs in some elderly patients and some patients with diabetes or renal failure
Toe-brachial indices	A quick, cost-effective way to establish or refute the diagnosis of PAD (see text) Can measure digital perfusion when small-vessel arterial disease is present Useful in patients with noncompressible vessels at the level of the ankle	Requires small cuffs and careful technique to preserve accuracy
Segmental pressure examination	Useful to establish or refute the diagnosis of PAD (see text) Useful to provide anatomic localization of lower-extremity disease Can provide data to predict limb survival and wound healing Useful to monitor the efficacy of therapeutic interventions	May not be accurate when systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff (noncompressible vessels at the level of the ankle), as occurs in some elderly patients and some patients with diabetes or renal failure
Pulse volume recording	Useful to establish the diagnosis of PAD Helpful in predicting outcome in CLI and risk of amputation Can be used to monitor limb perfusion after revascularization Usefulness maintained in patients with noncompressible vessels (ABI >1.3-1.4) undergoing revascularization procedures	Provides qualitative (rather than quantitative) measure of perfusion May not be accurate in more distal segments Less accurate than other noninvasive tests in providing arterial anatomic localization of PAD May be abnormal in patients with low cardiac output
Duplex ultrasonography	Can establish the diagnosis of PAD, provide anatomic localization, and define severity of lower-extremity arterial stenosis Can be useful to select candidates for endovascular or surgical revascularization Can be useful in following up patients after endovascular or surgical revascularization for restenosis	Accuracy is diminished in aortoiliac disease in some patients (who are obese or have bowel gas) Dense arterial calcification may limit diagnostic accuracy Sensitivity is diminished for detection of stenosis downstream from a proximal stenosis
Toe-up exercise testing with ABIs before and after exercise	Useful to diagnose PAD when resting ABI values are normal Can be performed in the absence of a treadmill with increased convenience and low cost	Provides qualitative (rather than quantitative) exercise diagnostic results Lower workload may not elicit symptoms in all patients with claudication
Treadmill exercise testing with ABIs before and after exercise	Helps to differentiate claudication from pseudoclaudication in patients with exertional leg symptoms Useful to diagnose PAD when resting ABI values are normal Objectively documents the magnitude of the symptom limitation in patients with claudication, especially when used with a standardized treadmill protocol Demonstrates the safety of exercise and provides data to individualize exercise prescriptions in patients with claudication before initiation of a formal program of therapeutic exercise training Useful to measure the objective functional response to claudication therapeutic interventions	Requires the use of a motorized treadmill, with or without continuous electrocardiographic monitoring, as well as staff familiar with exercise testing protocols
MRA	Useful to assess PAD anatomy and presence of significant stenosis Useful to help select patients who are candidates for endovascular or surgical revascularization Helpful to provide associated soft tissue diagnostic information that may be associated with PAD (eg, aneurysms, popliteal entrapment, and cystic adventitial disease)	May overestimate the degree of stenosis Not useful in patients who have metallic stents in place Cannot be used in patients with contraindications to magnetic resonance techniques (eg, pacemakers, defibrillators, intracranial metallic stents, clips, and coils) Gadolinium needs to be avoided in patients with an eGFR <30 mL/min/1.73[2]
Multidetector CTA	Useful to assess PAD anatomy and presence of significant stenosis Useful to help to select patients who are candidates for endovascular or surgical revascularization Helpful to provide associated soft tissue diagnostic information that may be associated with PAD (eg, aneurysms, popliteal entrapment, and cystic adventitial disease) Metal clips, stents, and metallic prostheses do not cause significant CTA artifacts Scan times are faster than for MRA	Requires iodinated contrast agent and ionizing radiation Use may be limited in patients with serious renal insufficiency
Catheter-based angiography	Pressure gradients and intravascular ultrasonography may be performed to determine the hemodynamic significance of a lesion Contrast angiography is used during the performance of endovascular procedures	Invasive evaluation is associated with a small risk of bleeding, infection, vascular access complications (eg, dissection, pseudoaneurysm, AV fistula, closure device injury, and hematoma), atheroembolism, contrast allergy, and contrast nephropathy

[a] ABI = ankle brachial index; AV = atrioventricular; CLI = critical limb ischemia; CTA = computed tomographic angiography; eGFR = estimated glomerular filtration rate; MRA = magnetic resonance angiography; PAD = peripheral artery disease.
[b] Tools are listed in order from the least to the most invasive and from the least to the most costly.
From *Circulation*,[4] with permission of the American Heart Association.

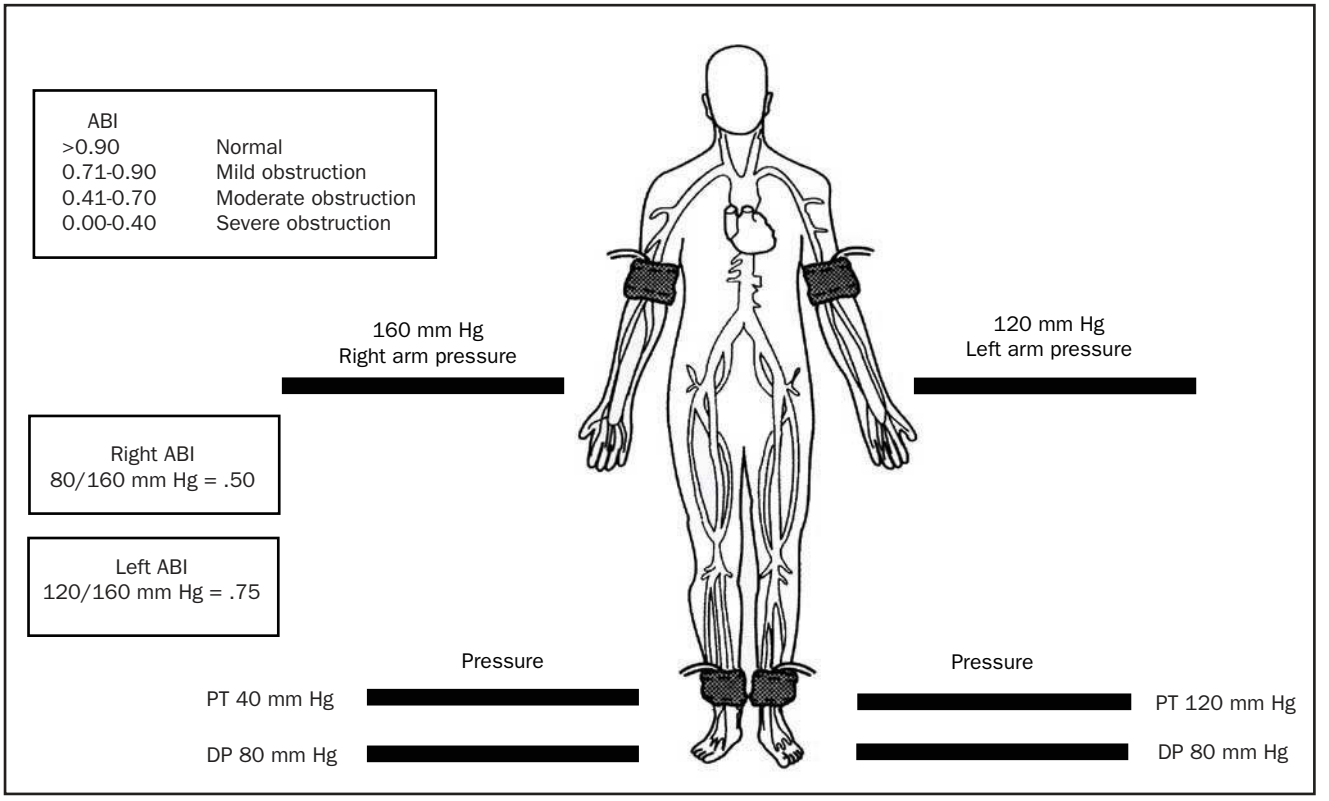

FIGURE 2. Calculation of the ankle brachial index (ABI). DP = dorsalis pedis; PT = posterior tibial artery.
Adapted from *N Engl J Med*,[12] with permission. ©2001 Massachusetts Medical Society. All rights reserved.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) of the aorta and peripheral vasculature can be performed rapidly with excellent image quality. Most vascular studies are performed with gadolinium-enhanced 3-dimensional MRA, which acquires angiographic-like images.[65-68] The quality of MRA is so good that it (or computed tomographic angiography [CTA]) has virtually replaced diagnostic angiography in determining what type of intervention is feasible. The success of MRA in identifying small runoff vessels meets or exceeds that of traditional catheter-based angiography.[69] With current technology, contrast-enhanced 3-dimensional MRA has a sensitivity of approximately 90% and a specificity of approximately 97% in the detection of hemodynamically significant stenoses in any of the lower-extremity arteries as compared with digital subtraction angiography.[64]

Computed Tomographic Angiography

Multidetector CTA provides high-resolution image quality quickly.[70] Current multidetector-row scanners acquire up to 250 simultaneous interweaving helices. Computed tomographic angiography has several advantages over conventional angiography, including volumetric acquisition, which permits visualization of the anatomy from multiple angles and in multiple planes after a single acquisition; improved visualization of soft tissues and other adjacent anatomic structures; and less invasiveness and thus fewer complications.[64,71,72] It also has several advantages over MRA, including higher spatial resolution, absence of flow-related phenomena that may distort MRA images, and the capacity to visualize calcification and metallic implants such as endovascular stents or stent grafts. The sensitivities and specificities are greater than 95% for identifying stenosis of greater than 50% and for correctly identifying occlusions.[73]

The main disadvantages of CTA compared with MRA are exposure to ionizing radiation and the need to use an iodinated contrast agent.

Digital Subtraction Angiography

Vascular imaging with ultrasonography, CTA, and MRA has replaced catheter-based techniques in the initial diagnostic evaluation of patients in most circumstances. Despite a paradigm shift away from catheter-based angiography as a purely diagnostic technique, its importance in intervention has increased dramatically.

The major advantage of digital subtraction angiography is the ability to selectively evaluate individual vessels, ob-

tain physiologic information such as pressure gradients, and image the layers of the blood vessel wall with intravascular ultrasonography and as a platform for percutaneous intervention. Exposure to ionizing radiation, use of iodinated contrast agents, and risks related to vascular access and catheterization are limitations of this technique.

Table 3[4] summarizes the benefits, limitations, and differences of the various tests used to diagnose and follow up patients with PAD.

TREATMENT

The 2 primary treatment goals in patients with PAD are to decrease cardiovascular morbidity and mortality and to improve limb-related symptoms (ie, claudication) and quality of life (Table 4).

TABLE 4. **Therapy for Peripheral Artery Disease**[a,b]

Decrease cardiovascular events	Improve symptoms
Smoking cessation	Smoking cessation[c]
Statin: goal LDL-C ≤70 mg/dL	Supervised exercise program
ACE inhibitor: goal BP <130/80 mm Hg	Cilostazol
	Percutaneous endovascular therapy
Antiplatelet therapy	Surgical revascularization
Diabetes treatment[d]	

[a] ACE = angiotensin-converting enzyme; LDL-C = low-density lipoprotein cholesterol.
[b] SI conversion factor: to convert LDL-C value to mmol/L, multiply by 0.0259.
[c] Although the improvement in symptoms is minimal, smoking cessation is effective in preventing progression of disease and is associated with a lower rate of critical limb ischemia and peripheral artery disease–related amputations.
[d] Optimal diabetes control has not been associated definitively with lower cardiovascular event rates, but it has shown a decrease in microvascular disease (eg, retinopathy, neuropathy, and nephropathy).

Lowering Cardiovascular Morbidity and Mortality

Aggressively managing risk factors such as tobacco use, high lipid levels, and hypertension is an essential component in lowering cardiovascular risk.

Smoking Cessation. It has been clearly shown that patients who successfully quit smoking have decreased rates of PAD progression, critical limb ischemia, amputation, MI, and stroke, as well as increased long-term survival.[23] Although the details of an effective smoking cessation program are beyond the scope of this article, it is important to convey to the patient that discontinuation of smoking is extremely important to overall well-being, preservation of the limb, and survival.[74,75] Because discontinuation of smoking or use of tobacco in any form is so important, it is the first item to be discussed with the patient during each office visit. In a nonjudgmental way, the clinician should convey to the patient how important discontinuing tobacco use is for cardiovascular health in general and for PAD in particular.

Lipid-Lowering Therapy. According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), PAD is a CAD risk equivalent, and thus the goal low-density lipoprotein cholesterol (LDL-C) level is less than 100 mg/dL (to convert to mmol/L, multiply by 0.0259).[32] Although many large-scale prospective clinical trials on the efficacy of LDL-C reduction in patients with CAD and stroke have been conducted, no prospective randomized trials have been conducted in patients with PAD.[76-78] Furthermore, intensive cholesterol lowering in patients with LDL-C levels at a baseline of less than 130 mg/dL (median value, 108 mg/dL) and increased C-reactive protein levels of greater than 2.0 mg/L (median value, 4.2 mg/L) (to convert to nmol/L, multiply by 9.524) significantly reduced the incidence of MI, stroke, revascularization, hospitalization for unstable angina, or death from cardiovascular causes in patients without clinical evidence of cardiovascular disease (hazard ratio, 0.56; $P<.001$).[79]

In the Heart Protection Study, which randomized 20,536 high-risk participants to 40 mg/d of simvastatin or placebo, a 24% relative risk reduction was observed in first-time cardiovascular events in patients who received simvastatin.[76] The subgroup of patients with PAD had similar cardiovascular benefits regardless of history of MI or CAD. Even the subgroup population who had LDL-C levels less than 100 mg/dL at baseline benefited from statin therapy.[76]

Independent of cholesterol-lowering effects, statin use improved walking distance and speed in patients with PAD[80]; indeed, patients with PAD who take statins have been shown to have less annual decline in lower-extremity performance than those who do not.[81] Several studies have evaluated the role of statins on claudication symptoms and walking duration and have shown that these agents may have a modest effect at best.[82,83]

The current recommendations advocate a goal LDL-C level of less than 100 mg/dL for patients with PAD; for very high-risk patients, the goal is an LDL-C level of less than 70 mg/dL.[4] Because all patients with PAD are at very high risk, lowering the LDL-C level to less than 70 mg/dL in all patients with PAD is reasonable.

Hypertension Management. Antihypertensive therapy should be administered to hypertensive patients with PAD to achieve a goal of less than 140/90 mm Hg for nondiabetic patients or of less than 130/80 mm Hg for patients with diabetes or chronic renal disease to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death.[4]

Although angiotensin-converting enzyme (ACE) inhibitors are considered the initial drug class of choice by some investigators, it is probably more important to treat

to achieve goal blood pressure levels than to insist on a specific antihypertensive agent.[33,84] With that caveat, and unless there are reasons to prefer another blood pressure–lowering agent, ACE inhibitors are an attractive first-line agent. They have favorable effects on the cardiovascular system well beyond their blood pressure–lowering capabilities.[85,86] In the HOPE (Heart Outcomes Prevention Evaluation) trial, patients with known vascular disease or diabetes and 1 other cardiovascular risk factor were randomized to ramipril or placebo. Patients treated with ramipril experienced a 22% reduction in the primary composite end point of MI, stroke, or cardiovascular death despite little blood pressure lowering.[87] Similar cardiovascular event reductions were observed with perindopril (20% relative risk reduction) in 12,218 patients with stable CAD, 883 of whom had PAD.[88]

Although there continues to be the opinion that β-blockers worsen claudication symptoms in patients with PAD, a meta-analysis of 11 randomized controlled trials by Radack and Deck[89] clearly showed that β-blockers do not worsen claudication in patients with PAD and may be used if clearly indicated.[33]

The role of diabetes management in patients with PAD is discussed in detail elsewhere.[26]

Antithrombotic Therapy. ***Aspirin.*** Antiplatelet agents such as aspirin are indicated for secondary prevention in high-risk cardiovascular patients. Although the benefits of aspirin in patients with CAD and carotid artery disease have been demonstrated by large-scale clinical trials,[90,91] several recent studies have questioned the efficacy of aspirin in patients with PAD.[92,93] Yet, the American College of Cardiology/American Heart Association Guidelines for the Management of Patients With Peripheral Arterial Disease (class I, level of evidence A) and the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) (grade A [symptomatic patients] and C [asymptomatic patients without CAD or carotid artery disease]) support aspirin use in patients with PAD.[4,94]

The Antithrombotic Trialists' Collaboration analyzed 287 randomized trials including more than 135,000 patients and reported that the odds of a vascular event (vascular death, nonfatal MI, or nonfatal stroke) were reduced by 22% in high-risk patients receiving antiplatelet therapy.[90] In the 9214 patients with PAD, antiplatelet medications reduced serious vascular events by 23%. A similar reduction was seen in patients with intermittent claudication and in patients undergoing peripheral bypass graft procedures or angioplasty.[90]

In a recent meta-analysis by Berger et al[92] evaluating 18 trials and 5269 participants, cardiovascular events were experienced by 251 (8.9%) of 2823 patients taking aspirin (alone or with dipyridamole) and by 269 (11.0%) of 2446 participants in the control group (pooled relative risk, 0.88; 95% confidence interval [CI], 0.76-1.04). It should be noted that the study was designed to detect a difference of 25% and was not powered to detect a smaller difference. Although not statistically significant, the point estimate (a relative risk reduction of 12.0%) showed a favorable trend.

Moreover, it must be acknowledged that aspirin therapy was associated with a reduction in the secondary outcome of nonfatal stroke (52 [1.8%] of 2823 vs 76 [3.1%] of 2446; relative risk, 0.66; 95% CI, 0.47-0.94; *P*=.02). This meta-analysis has a number of limitations, the most important of which is that the study that contributed the largest number of patients to the meta-analysis (24%) used an ABI of 0.91 to 0.99 to denote PAD, a range much higher than used in any other clinical trial.[95]

The AAA (Aspirin for Asymptomatic Atherosclerosis) trial screened 28,980 people; of these, 3350 had an ABI of less than 0.95 and were eligible for entry into the trial.[93] Participants were randomly assigned to receive 100 mg/d of aspirin or placebo and were followed up for a mean of 8.2 years. The primary end point was the composite of an initial fatal or nonfatal coronary event, stroke, revascularization, angina, claudication, transient ischemic attack, and all-cause mortality. No difference was noted in the event rate between the group receiving aspirin and the group receiving placebo. The aspirin group had more adverse events compared with the placebo group (hemorrhage, 2.0% vs 1.2%; gastrointestinal ulcer, 0.8% vs 0.5%; hazard ratio, 1.71; 95% CI, 0.99-2.97). However, this study has several important methodological problems, the most important of which is that 40% of the patients were nonadherent and did not take the aspirin as prescribed for the duration of the trial. Therefore, on the basis of class I, level A evidence, aspirin is still recommended as an antiplatelet agent for patients with PAD.[4,18]

Thienopyridines. Thienopyridine medications, such as ticlopidine and clopidogrel, inhibit the activation of platelets by adenosine diphosphate. Clopidogrel has been used as an alternative medication to aspirin in patients with PAD.[90,96,97]

The efficacy of clopidogrel has been directly compared with that of aspirin in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial.[98] Of the 19,185 high-risk cardiovascular patients (recent MI, recent ischemic stroke, PAD) recruited for the study, 6452 had PAD. The patients were randomized to either clopidogrel (75 mg/d) or aspirin (325 mg/d). After 3 years, an 8.7% relative risk reduction in MI, stroke, or cardiovascular death was observed in the group assigned to clopidogrel (*P*=.043). The PAD subgroup had the greatest benefit in favor of clopidogrel, with a 23.8% relative risk reduction over aspirin (95% CI, 8.9-36.2; *P*=.003).[98]

Although the combination of aspirin and clopidogrel was effective in decreasing cardiovascular events in patients with unstable angina,[99] the combination of clopidogrel and aspirin vs aspirin alone in a high-risk group of patients including those with PAD (CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance] trial) demonstrated no benefit of combination therapy.[100] The combination of clopidogrel and aspirin is commonly used in patients undergoing infrainguinal angioplasty and stenting; however, no clear evidence exists to support such a practice.

Newer Antiplatelet Agents. Several new agents have either been recently approved (prasugrel, a thienopyridine)[97,101] or are undergoing clinical investigation (SCH 530348, a thrombin receptor antagonist).[102,103] Their usefulness as antiplatelet agents in treating patients with PAD remains to be determined.

Warfarin. In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial, 2161 patients with PAD were randomly assigned to combination therapy with an antiplatelet agent and warfarin (goal international normalized ratio, 2-3) or an antiplatelet agent alone.[104] The combination therapy was no more effective than antiplatelet therapy alone and was associated with an increase in life-threatening bleeding (4.0% with combination vs 1.2% with antiplatelet therapy alone [relative risk, 3.41; $P<.001$]).

TABLE 5. **Approach to the Management of Claudication**[a,b]

Iliac disease	Infrainguinal disease
Clinical diagnosis	Clinical diagnosis
Hip, thigh, or buttock claudication	Calf claudication
Reduced or absent femoral pulse	Normal femoral pulses, reduced or absent popliteal, posterior tibial, and dorsalis pedis pulses
Therapy	Therapy
Iliac stent	Trial (4-6 mo) of exercise and cilostazol
Maximal medical therapy to reduce CV events	If benefit from trial is unsatisfactory, imaging with duplex ultrasonography, CTA, or MRA to define anatomy
	If anatomy suitable, consider percutaneous endovascular therapy
	If anatomy is unsuitable, discuss bypass surgery
	Maximal medical therapy to reduce CV events
Follow-up	Follow-up
ABI and duplex ultrasonography at first office visit and then every 6-12 mo thereafter or whenever symptoms recur	If treated medically, follow up clinically every 6 mo
	If patient underwent angioplasty, stent placement, or surgical bypass, obtain ABI and perform duplex ultrasonography at first office visit, then every 6 mo for 24 mo and then yearly

[a] ABI = ankle brachial index; CTA = computed tomographic angiography; CV = cardiovascular; MRA = magnetic resonance angiography.
[b] Assuming that the claudication interferes with the patient's lifestyle.

Medical Treatment of Claudication

An approach to the treatment of patients with claudication is shown in Table 5. Unfortunately, few randomized trials have been conducted to help guide therapy. Because the results of iliac stenting are good and the restenosis rate is low, stenting may be offered as first-line therapy in patients with iliac disease–related claudication that interferes with lifestyle (Table 5).[105,106] The CLEVER (Claudication: Exercise Vs. Endoluminal Revascularization) study, which was funded by the Heart, Lung, and Blood Institute of the National Institutes of Health, is a prospective, multicenter, randomized, controlled clinical trial evaluating the relative efficacy, safety, and health economic impact of 3 treatment strategies for people with aortoiliac disease and claudication. The treatment arms are: optimal medical care (claudication pharmacotherapy)[2]; optimal medical care and supervised exercise[3]; and optimal medical care and stent.[107-109] It is hoped that the CLEVER study will definitively establish the most appropriate and effective therapy for patients with aortoiliac disease.

Exercise Therapy. Several randomized prospective trials have demonstrated that supervised exercise is an effective method of treating patients with claudication.[110-113] The magnitude of effect from a supervised exercise program exceeds that achieved with any of the pharmacologic agents available.

A meta-analysis of 21 studies by Gardner and Poehlman,[110] which included both nonrandomized and randomized trials, showed that pain-free walking time improved by an average of 180% and maximal walking time by 120% in patients with claudication who underwent exercise training. Furthermore, a meta-analysis from the Cochrane Collaboration that included only randomized, controlled trials showed that exercise improved maximal walking ability by an average of 150% (range, 74%-230%).[114]

The PAD guidelines state that a program of supervised exercise training is recommended as an initial treatment modality for patients with claudication (class I, level of evidence A) and that supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least 3 times per week for a minimum of 12 weeks (class I, level of evidence A).[4]

Although exercise has many positive effects, the exact mechanism by which exercise therapy improves walking distance is unknown.[112] No convincing evidence supports the often stated claim that exercise promotes the growth of collateral vessels. Several comprehensive sources discuss the potential mechanisms of improvement.[46,112] Fur-

thermore, McDermott et al[115] have shown that patients who walk more (3 times weekly) experience a slower rate of functional decline within the next year.

An exercise program has several important limitations.[115] First, patients must be motivated, a difficult task because they experience discomfort every time they walk. Second, the best results occur when patients go to a center for supervised exercise, as with cardiac rehabilitation; however, lack of reimbursement for supervised training prevents its widespread use. Finally, patients who are told to "go home and walk" do not achieve the same improvement as patients in a supervised program.[116]

Pharmacologic Treatments. Two drugs have been approved by the Food and Drug Administration for the treatment of intermittent claudication: pentoxifylline and cilostazol. No randomized trial has compared the combination of exercise therapy with pharmacotherapy vs either one alone.[117] However, our approach is to use exercise and cilostazol at the outset for patients with infrainguinal disease and claudication (Table 5).

Pentoxifylline. Pentoxifylline is a methylxanthine derivative with hemorheological properties. It is thought to act by improving red blood cell and leukocyte flexibility, inhibiting neutrophil adhesion and activation, decreasing fibrinogen concentrations, and reducing blood viscosity.[118-120] However, a recent study failed to support this hypothesis in blood samples taken from patients with moderate to severe claudication.[121]

The beneficial response to pentoxifylline is small in most patients, and the overall data are insufficient to support its widespread use in patients with claudication.[12] Pentoxifylline should be reserved for patients who cannot take cilostazol, have not responded adequately to an exercise program, and/or are not candidates for revascularization procedures or clinical trials.[117,122-125]

Cilostazol. The mechanism by which cilostazol, a phosphodiesterase type 3 inhibitor, improves claudication is unknown, but the medication has the following properties: antiplatelet activity, vasodilatory properties, and in vitro inhibition of vascular smooth muscle cells. It may also cause an increase in high-density lipoprotein cholesterol levels and a decrease in triglyceride levels.[126]

Because cilostazol is a phosphodiesterase inhibitor similar to milrinone, it is contraindicated (black box warning) in patients with a history of congestive heart failure or in patients with an ejection fraction of less than 40%.[4] Long-term use of oral milrinone in cardiomyopathic patients was associated with increased mortality.[127] Cilostazol was administered at a dose of 100 mg twice daily. Total patient-years of exposure during treatment were 1046 for cilostazol and 1090 for placebo. During treatment, 18 deaths occurred among those taking cilostazol vs 19 deaths among those receiving placebo, for a hazard ratio of 0.99 (95% CI, 0.52-1.88). Cardiovascular deaths during treatment occurred in 14 patients who were taking cilostazol and 14 who were receiving placebo. Little difference was noted in the incidence of serious bleeding events in the 2 groups (affecting 18 patients taking cilostazol and 22 taking placebo). The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel, or anticoagulants at any time during the course of the study.

In a meta-analysis of 8 randomized, double-blinded, placebo-controlled trials, cilostazol increased maximal and pain-free walking distances by 50% and 67%, respectively.[126] Cilostazol was superior to placebo in most studies performed to date. Dawson et al[128] compared the efficacy and safety of cilostazol (100 mg twice daily) to pentoxifylline (400 mg 3 times daily) in patients with intermittent claudication. After 24 weeks, cilostazol significantly increased walking distance compared with pentoxifylline and placebo.[128] It should be noted that walking distance progressively increased during the 24 weeks of the study. Therefore, patients should be given an adequate trial of at least 4 months before a decision is made about whether the medication is working.

The most common adverse effects with cilostazol are headache, palpitations, and diarrhea. The CASTLE study[129] was a randomized, double-blinded, placebo-controlled safety study of cilostazol. A total of 717 patients received cilostazol, and 718 received placebo. This study demonstrated no safety signal for cilostazol on all-cause mortality or cardiovascular mortality. No increased bleeding was observed in those randomized to cilostazol. However, adherence to cilostazol therapy was poor. More than 60% of participants discontinued cilostazol by 36 months of treatment.[130]

The optimal dose of cilostazol is 100 mg twice daily; it should be given on an empty stomach (a half hour before or 2 hours after breakfast and dinner). Because of the inhibitory effects of cilostazol on metabolism, the dose should be halved in patients who are taking medications (eg, erythromycin, diltiazem, and omeprazole) that inhibit the cytochrome P450 isoenzymes CYP3A4 and CYP2C19.[131]

Other Agents. A whole host of therapies have been used in the treatment of claudication. Naftidrofuryl, a 5-hydroxytryptamine serotonin receptor inhibitor, has been available in Europe for a number of years and has shown some efficacy in improving claudication symptoms.[132,133] This benefit has not been confirmed by other reports using a 5-hydroxytryptamine antagonist.[134] Numerous therapies have been tested and found to be ineffective, including propionyl-L-carnitine, gingko biloba extract, L-arginine,

TABLE 6. **Guiding Principles for Revascularization in Patients With PAD**

Consider proceeding directly to CTA, MRA, or catheter-based angiography for patients with iliac disease–related claudication that interferes with lifestyle; proceed to stenting if iliac disease is confirmed. Unless the CLEVER trial suggests otherwise, the patency of stents in the iliac system is good, and stenting remains reasonable initial therapy for patients with aortoiliac disease and claudication (Table 5)[105,107,136]
Implement a 4- to 6-mo trial of medical therapy (exercise [supervised, if available, or home-based if not]) and cilostazol (if no contraindications) for patients with infrainguinal disease and claudication
Patients should have no other conditions that will limit their ability to walk after revascularization (eg, spinal stenosis, heart failure, chronic lung disease)
Inflow and outflow should always be assessed when considering revascularization; inflow problems should be revascularized first
If the goal is to heal ischemic ulcers, an attempt should be made to provide straight line flow to the foot
All patients should receive maximal medical management to lower the cardiovascular event rate and all-cause mortality
Patients with PAD should have their feet inspected during every office visit, as good foot care is essential to avoid amputations[137]
Patients should be directed to sources of education about PAD such as the PAD Coalition (www.padcoalition.org) or the NHLBI Stay in Circulation Web site (www.about pad.org)

CLEVER = Claudication: Exercise Vs. Endoluminal Revascularization; CTA = computed tomographic angiography; MRA = magnetic resonance angiography; NHLBI = National Heart, Lung, and Blood Institute; PAD = peripheral artery disease.

oral vasodilators, prostaglandins, avasimibe, and chelation therapy. A number of trials have used gene or cell-based therapy to treat patients with claudication, and their findings have been nicely summarized by Sneider et al.[135]

Revascularization

The 3 clear indications for revascularization in patients with PAD are ischemic rest pain, ischemic ulcers or gangrene, and claudication that interferes with the patient's lifestyle. Although the specific methods of endovascular (angioplasty, stent, atherectomy) or surgical therapy are beyond the scope of this article, certain principles should be adhered to when caring for patients with claudication.[105,106,136] These are summarized in Table 6.

CONCLUSION

Patients with PAD may experience claudication or critical limb ischemia or may have no symptoms at all. Both symptomatic and asymptomatic patients with PAD have a markedly increased rate of MI, stroke, and cardiovascular events. The 2 major strategies for treatment are: (1) to improve symptoms and quality of life with medical therapy alone (exercise, cilostazol) or percutaneous or surgical revascularization and (2) to prevent cardiovascular events with a comprehensive program that includes smoking cessation, an exercise program, control of blood pressure, achievement of goal LDL-C, antiplatelet therapy, and control of diabetes.

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