Peripheral arterial disease (PAD) defines a broad range of arterial pathologies affecting all but the coronary arteries and can include thromboembolism and aneurysm formation. PAD is estimated to affect about 5% of Americans aged 40 years and older, approximately two thirds of whom are asymptomatic. The prevalence increases significantly in those older than 70 years, with reported rates of 12% to 14.5%. These estimates account for nearly 8 million Americans, 6 million of whom are older than 70 years. There does not appear to be a gender difference among these rates, with a PAD of 3.7% reported for both men and women. However, a higher prevalence among black Americans compared with whites consistently has been shown, an effect that does not appear to be accounted for entirely by the increased prevalence of hypertension and diabetes.

Symptomatic PAD can manifest as pain in the lower extremities only with exertion (claudication) or at worst as pain at rest, ulceration, and/or gangrene. The latter case, critical limb ischemia, often necessitates invasive intervention with revascularization or amputation. However, the incidence of such severe complications is relatively low, with reported amputation rates of less than 10% and revascularization rates of 18% in 10 years. Only about 25% of those with symptoms deteriorate over the course of their disease.

PAD is associated with a significantly increased risk of cardiovascular disease (CVD). The prevalence of coronary artery disease among those with symptomatic PAD has been reported to be as high as 60%, based on only history, physical examination, and resting electrocardiogram, and as high as 90% among those who undergo coronary angiography. Mortality due to CVD events accounts for 75% of all deaths in PAD patients, with a 10-year risk of death from coronary heart disease more than 6 times greater in those with PAD than in those without the disease. There is also a high prevalence of cerebrovascular disease among those with PAD, with estimates of about 40% to 50%. Risk of mortality from any cause in patients with PAD is as much as 3 times higher over 10 years than in the absence of PAD.

These observations underscore the importance of recognizing that atherosclerosis is a diffuse process and that the presence of PAD often signifies concomitant disease in other arterial beds. Yet despite its high prevalence and associated risks, PAD remains under-recognized among primary care physicians, especially in relation to other cardiovascular diseases.

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This article focuses on the most common manifestations of lower extremity PAD, marked by progression of systemic atherosclerosis with plaque formation and eventual blood flow obstruction. These processes can lead directly to end-organ ischemia, which causes significant morbidity and functional impairment. Aspects regarding noninvasive medical management of PAD are also discussed.

**RISK FACTORS**

**Smoking**

Cigarette smoking has repeatedly been shown to be associated with PAD and is widely considered to be the most significant risk factor for PAD. Multiple prospective studies have not only confirmed this two- to tenfold increased relative risk (RR) but have also demonstrated a dose-response effect. For instance, among those smoking more than 20 cigarettes per day, the RR of developing claudication is 2.11, which decreases slightly to 1.75 for those smoking 11 to 20 cigarettes per day. Even patients with only environmental smoke exposure demonstrate vascular endothelial dysfunction, which is a predictor of clinical atherosclerosis and CVD. Smoking also accelerates progression of claudication symptoms and increases the need for revascularization and amputation among those with known PAD. Although no randomized controlled trials have been conducted to confirm whether smoking cessation improves claudication symptoms, several studies have demonstrated improvements in walking distance and pain among those who quit smoking versus those who continue to smoke. Additionally, a recent meta-analysis confirmed that smoking cessation improves bypass graft patency rates to those of never-smokers, even in those who stopped smoking after their lower extremity graft surgery. Overall, there appears to be an improvement in the risk for vascular events with smoking cessation, particularly with respect to improved coronary event risk.

**Diabetes Mellitus**

Diabetes mellitus, a known risk factor for coronary heart disease, also significantly increases the risk for PAD. The mechanism appears to be related to endothelial and vascular smooth muscle dysfunction that creates a prothrombotic milieu. PAD prevalence is 2 to 4 times higher among diabetic compared with nondiabetic patients. A high prevalence of PAD has also been found among newly diagnosed type 2 diabetic patients, as shown recently in the Screening for Arteriopathy (SCAR) study in which 21.1% of 2559 newly diagnosed diabetic patients had undiagnosed PAD (ankle-brachial index [ABI] < 0.9). Similarly, screening of American primary care patients with diabetes in the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study found that 33% had previously undiagnosed PAD. Among the Framingham cohort, diabetic men and women had a RR of 3.5 and 8.6, respectively, for developing claudication versus nondiabetic patients. Infrapopliteal arterial occlusive disease and medial artery calcification are more likely to occur among diabetic patients, and these abnormalities appear to correlate with duration and severity of poor glycemic control. Patients with diabetes account for 45% to 70% of nontraumatic lower extremity amputations in the United States; whether these amputations are due to PAD has not been specifically reported.

There have been no studies that definitively show that strict glycemic control reduces macrovascular diabetic complications, including incident PAD or progression. However, a trend in reducing macrovascular events, specifically myocardial infarction (MI), and a definite reduction in microvascular complications have been demonstrated; therefore, strict glycemic control is strongly recommended.

**Dyslipidemia**

Dyslipidemia has also been shown to be an important risk factor for PAD. Elevations in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels have all been found to be associated with PAD prevalence and incidence. In fact, for every 10-mg/dL increment in total cholesterol level, the risk for developing PAD increases by approximately 10%. Elevated lipoprotein (a) level has also been found to be associated with PAD. Similarly, elevated high-density lipoprotein (HDL) and apolipoprotein A-I levels have been found to be negatively associated with PAD and disease severity.

Medical treatment of dyslipidemia has been a mainstay of treatment for PAD, in part for its overall reduction in CVD risk. For example, in the Heart Protection Study, 2701 PAD patients were enrolled among a total of 20,536 subjects at high risk for CVD events. Among those with PAD but no previous coronary heart disease, a small but significant (5.8%; P < 0.0001) reduction in major vascular events was observed in those treated with simvastatin versus placebo, and an 18% reduction in CVD death was observed in those with an LDL cholesterol level less than 116 mg/dL. Reductions in disease progression have also been shown. In the Cholesterol Lowering Atherosclerosis Study, treatment of 188 men with coronary artery disease and PAD with colestipol and niacin showed significant stabilization or even regression of angiographic femoral
artery atherosclerosis. Among 255 men with coronary artery disease enrolled in the Regression Growth Evaluation Study (REGRESS), carotid and femoral artery intima-media thickness, which predict CVD events, were reduced with pravastatin treatment compared with placebo.

Lipid lowering is not only beneficial in terms of reducing overall CVD risk but also in improving claudication symptoms. For instance, a post-hoc subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) showed that treatment with simvastatin was associated with a significant 38% risk reduction in development or worsening of intermittent claudication. Several clinical trials specifically designed to study lipid-lowering effects on claudication using statins have also been performed and have demonstrated significant improvements in pain-free walking time after 3 to 12 months of treatment.

**Hypertension**

Hypertension is also a common finding in and risk factor for PAD. Few studies have evaluated blood pressure treatment in patients with PAD exclusively. However, multiple studies of blood pressure–lowering that have included PAD patients indicate that strict blood pressure control, particularly among those with diabetes, effectively reduces CVD events. Evidence from the Appropriate Blood Pressure Control in Diabetes trial showed that intensive blood pressure control (< 130/80 mm Hg) among diabetic patients with PAD significantly reduced the risk for MI, stroke, or other vascular events compared with normotensive patients ($P = 0.009$), even at the lowest ABI levels. Therefore, optimization of blood pressure is standard of care for PAD, as it is for other CVD disorders.

**Emerging Risk Factors**

Emerging risk factors that have been found to correlate with PAD include high-sensitivity C-reactive protein, fibrinogen, and homocysteine.

**CLINICAL PRESENTATION**

Claudication, characterized by the onset of pain, cramping, or discomfort in the lower extremities with exertion that is relieved with rest, is the classic symptom of PAD. Reproducibility of onset within a given walking distance or incline is also a characteristic of claudication, with discomfort typically resolving after 2 to 5 minutes of rest. Various questionnaires have been developed to standardize identification of claudication; the most commonly used is the Rose questionnaire (Table 1). Despite the common association of claudication and PAD, most PAD patients present with atypical, if any, leg symptoms, which are often attributed to arthritis, nonspecific muscular pain, or aging. For instance, the multicenter PARTNERS program demonstrated that only 8.7% of more than 1800 subjects with PAD had leg symptoms that fit the classic Rose criteria. Much more common (40%–60%) are atypical leg symptoms, such as vague muscle or joint aches and pains. Pain with both exertion and rest or the absence of pain due to inactivity were recently found to be associated with more functional impairment and higher comorbidities in PAD patients than classic claudication. The differential diagnoses that should be considered when a patient reports lower extremity discomfort are shown in Table 2.

Pain at rest associated with ischemic ulcerations and/or gangrene indicate severe occlusive PAD (critical limb ischemia), which warrants urgent surgical referral and potential revascularization or amputation. Vascular surgery referral before development of the critically ischemic limb is generally reserved for cases of disabling claudication or for patients who have failed conservative medical management.

Other historical elements that may be reported by PAD patients include hair loss or decreased distribution of hair in the lower extremities, unexplained ulcers or skin lesions of the lower extremities, problems with toenail growth, or change in skin coloration or temperature. Leriche syndrome, which includes claudication, impotence, global muscle atrophy, and poor wound healing of the lower extremities, may be present and indicates obstructive aorto-iliac disease.

Physical examination should incorporate inspection of the peripheral vasculature as well as cardiac

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**Table 1. Rose Questionnaire for Intermittent Claudication**

<table>
<thead>
<tr>
<th>Questions</th>
<th>Expected Answers for Positive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you get pain in either leg on walking?</td>
<td>Yes</td>
</tr>
<tr>
<td>Does pain begin when standing still or sitting?</td>
<td>No</td>
</tr>
<tr>
<td>Do you get this pain in your calf/calves?</td>
<td>Yes</td>
</tr>
<tr>
<td>Do you get it if you walk uphill or hurry?</td>
<td>Yes</td>
</tr>
<tr>
<td>Do you get it when you walk at an ordinary pace on the level?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Does it ever disappear while walking?</td>
<td>No</td>
</tr>
<tr>
<td>What do you do if you get it while walking?</td>
<td>Stop or slow down</td>
</tr>
<tr>
<td>What happens to the pain if you stand still?</td>
<td>Relieved in ≤ 10 min</td>
</tr>
</tbody>
</table>
examination (Table 3). Femoral, popliteal, posterior tibialis, and dorsalis pedis pulses should be palpated and auscultated, noting the character and symmetry of upstrokes and presence of femoral bruits. Palpation of the abdomen for an aneurysm and auscultation for bruits should be performed. Lower extremity venous filling time should also be assessed. This procedure involves raising the leg of the supine patient 45 degrees for 1 minute, then having the patient sit up with legs dangling to gravity, while noting the time it takes for the vein to refill above the skin surface. An abnormal filling time is more than 20 seconds.

Skin examination should be performed, with assessment of tone, texture, color, temperature, and hair pattern distribution as well as assessment for any ulcers or other nonhealing wounds, particularly those with a necrotic base involving the distal extremities that may suggest vascular insufficiency or thromboembolism. Of these physical findings, the most specific for the presence of PAD are bilaterally abnormal pedal pulses, cool extremity on one side, prolonged venous filling time, and presence of a femoral bruit. Although these tests are relatively specific (> 92%), they are not sensitive, and absence of these signs should not discourage additional diagnostic testing if clinical suspicion is elevated. Even in the absence of suggestive symptoms, presence of the risk factors discussed previously should prompt consideration of PAD.

### Table 3. Physical Examination and Findings in Lower Extremity Peripheral Arterial Disease

<table>
<thead>
<tr>
<th>Focus of Lower Extremity Examination</th>
<th>Potential Signs</th>
</tr>
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<tbody>
<tr>
<td>Pulses</td>
<td></td>
</tr>
<tr>
<td>Palpation</td>
<td>Diminished, absent, or asymmetric upstrokes; pulsatile mass (abdomen)</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Bruit</td>
</tr>
<tr>
<td>Skin</td>
<td>Ulcers or nonhealing wounds, edema, atrophic tone, hair loss, diminished nail thickness, cool temperature (particularly if asymmetric), dryness</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>&lt; 0.90 or &gt; 1.40</td>
</tr>
<tr>
<td>Venous filling time</td>
<td>&gt; 20 sec</td>
</tr>
</tbody>
</table>

### Diagnostic Studies

#### Ankle-Brachial Index

The ABI is a simple, noninvasive, and inexpensive diagnostic tool that correlates well with angiographically demonstrated PAD and can be used to follow disease progression. It is a well-validated predictor of CVD events and mortality, even among patients who are asymptomatic, and the degree of ABI reduction correlates with prognosis. In the normal circulation, systolic blood pressure at the ankle is slightly greater than or equal to that at the brachial artery, and the ratio of the ankle systolic blood pressure to the brachial systolic blood pressure is normally 1.00 to 1.30. In PAD, the systolic blood pressure of arteries distal to occlusive lesions is lowered, and the ABI may fall to less than 1.0. An ABI less than 0.90 is considered diagnostic of PAD. An ABI of 0.70 to 0.89 is generally considered to indicate mild PAD, ABIs of 0.40 to 0.69 correspond to moderate PAD, and severe disease is marked by an ABI less than 0.40. Recent evidence also indicates that an ABI greater than 1.40 is a risk factor for PAD and warrants further diagnostic confirmation. The resting ABI has a reported sensitivity of 97% and specificity of 100% for distinguishing between normal and angiographic PAD. Given its ease of use, relatively low expense, and diagnostic utility, the ABI should be performed routinely as part of the initial evaluation for lower extremity ischemic symptoms.
of the screening physical examination, particularly for those with risk factors for PAD.

The ABI is measured while the patient is in the supine position. A blood pressure cuff is placed on the upper arm and inflated to occlude brachial artery blood flow. A Doppler ultrasound velocity signal probe is placed over the brachial artery to detect return of blood flow as the cuff is slowly deflated. The procedure is then repeated in the other arm. The higher of the 2 systolic blood pressure measurements is taken as the brachial systolic blood pressure. The blood pressure cuff is then positioned around the ankle, and Doppler-detected systolic blood pressure values with cuff deflation are recorded over the posterior tibialis and dorsalis pedis arteries. The process is repeated for the other leg. Traditionally, the higher of the 2 lower extremity systolic blood pressure values is used on each side for ABI calculations, and the lowest ABI determined from measurements between both legs is then considered the patient’s ABI. However, this standard has recently been challenged by evidence showing that using the lower systolic blood pressure value from the lower extremities is more sensitive. Thus, current guidelines may change as more evidence emerges.

The ABI has limited ability to diagnose PAD in the setting of calcific tibial peroneal arteries with elevated ABI values greater than 1.30, especially in patients with diabetes. ABI values more than 1.30 are now considered abnormal and warrant additional diagnostic testing. These patients should be referred to an accredited vascular laboratory for measurement of a toe-brachial index or other noninvasive testing. Also, the ABI is dependent on the brachial artery systolic blood pressure truly reflecting central systolic blood pressure, which may not be the case in patients with advanced vascular disease (eg, patients with bilateral subclavian artery stenoses). Finally, the ABI can only indicate presence of disease. Its use in combination with the pulse examination, however, can be helpful in distinguishing the level of disease. For instance, an abnormal ABI in addition to normal femoral pulses would exclude significant aortoiliac occlusive disease or in the presence of normal popliteal pulses would indicate disease in the tibial artery. Nevertheless, additional testing must be performed to actually localize stenotic lesions.

**Exercise Testing**

Measurement of ABI in conjunction with exercise testing may provide additional diagnostic assistance, particularly in patients with claudication symptoms but with a normal resting ABI or pulses on examination. During exertion, relative reductions in blood flow and systolic blood pressure from normal are enhanced. Thus, in PAD patients, ankle systolic blood pressure may decrease to low or undetectable levels with low-level workloads and then return to baseline after a few minutes at rest. An ABI greater than 0.90 at rest, which then decreases by 20% after exercise, is diagnostic of PAD. This test can be performed on a treadmill by having the patient walk at a standard speed and grade for a predetermined distance or until claudication develops. Alternatively, the test can be performed using heel raises as exertion. The patient should be asked to stand facing a wall using their hands for balance. Maintaining the knees in straight position, the patient should alternately stand as high as possible on their toes and flattening their feet for 30 to 50 repetitions. Immediately after exercise testing, the patient should be positioned supine and another ankle systolic blood pressure measurement obtained for recalculation of the ABI. If the exercise produces pain or discomfort without a change in ABI, another diagnosis should be considered.

**Segmental Pressures and Pulse-Volume Recordings**

Measurement of segmental pressures and pulse-volume recordings can be used to help diagnose PAD when the ABI is nondiagnostic and can additionally localize potential arterial lesions. Differences in systolic blood pressure values and pulse waveform magnitudes and contours are compared between limb segments proximally and distally to site(s) of occlusion. When combined, these tests have 95% accuracy compared with angiography. Alternatively, Doppler velocity waveform analysis can be performed instead of pulse-volume recording by placing a continuous-wave Doppler probe over multiple arterial segments to assess blood flow velocity and velocity patterns. Within each pulse cycle, changes from the normal triphasic flow pattern (marked by forward, reverse, and late-forward flow) can be assessed to detect pressure- or flow-reducing lesions.

**MEDICAL MANAGEMENT**

**Risk Factor Modification**

Once identified, risk factors associated with PAD should be treated and managed using targeted and aggressive strategies (Table 4), as they are known to lead to other manifestations of atherothrombotic disease, including MI and stroke. The most recent American Heart Association and American College of Cardiology guidelines advocate the following recommendations to help reduce CVD risk:

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• Initiate or intensify lipid-lowering therapy, with a goal LDL cholesterol level of 100 mg/dL or less, or 70 mg/dL or less among patients at higher risk for CVD. These higher-risk characteristics include patients with multiple risk factors, especially diabetes, and/or poorly controlled risk factors; characteristics of the metabolic syndrome, including a triglyceride level of 200 mg/dL or greater, non-HDL cholesterol of 130 mg/dL or greater, or HDL cholesterol of 40 mg/dL or less in men or 50 mg/dL or less in women; or patients with acute coronary syndromes. Statin therapy is recommended for all PAD patients without contraindications.

• Initiate or intensify antihypertensive therapy, with goal blood pressure less than 140/90 mm Hg in nondiabetic patients and less than 130/80 mm Hg among diabetic patients. β-Blockers have not been found to impair walking capacity compared with placebo and therefore are not contraindicated for blood pressure-lowering among PAD patients. Among diabetic patients, proper foot care, hygiene, and immediate attention to any foot lesions or ulcerations should be incorporated as part of routine care. Additionally, glycemic control with a goal hemoglobin A1c of less than 7% is recommended.

• Smoking cessation should be recommended to current smokers, with active follow-up. Comprehen-

<table>
<thead>
<tr>
<th>Table 4. Medical Management of Peripheral Arterial Disease</th>
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<tbody>
<tr>
<td>General Strategy</td>
</tr>
<tr>
<td>Antplatelet therapy</td>
</tr>
<tr>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Lipid lowering</td>
</tr>
<tr>
<td>Blood pressure control</td>
</tr>
<tr>
<td>Diabetes control</td>
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</tbody>
</table>

Symptom Management

<table>
<thead>
<tr>
<th>General Strategy</th>
<th>Examples/Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Supervised exercise rehabilitation</td>
</tr>
<tr>
<td>Medications</td>
<td>Cilostazol, pentoxifylline</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein.

Exercise Therapy and Rehabilitation

Exercise rehabilitation therapy has been shown to improve claudication symptoms. Increases of 179% in walking distance before pain onset have been reported, and a 122% improvement in distances walked before attaining maximal pain has been observed. Additionally, benefits in overall functional status, quality of life, and total caloric expenditures are associated with increased exercise. Supervised walking sessions of at least 30 minutes each (≥ 3 times/wk) and achieving near-maximal claudication pain performed consistently for at least 6 months are recommended for symptomatic PAD patients.

Pharmacotherapy for Claudication

Cilostazol, a type 3 phosphodiesterase inhibitor, has been shown to improve maximal walking distance by as much as 40% to 60% over a 3- to 6-month treatment period. Benefits in functional status, quality of life, and ABI also have been demonstrated. Treatment with cilostazol 100 mg twice daily is currently recommended for patients with lifestyle-limiting claudication, and improvements in symptoms may be observed as early as 4 weeks of treatment. However, cilostazol should not be used in patients with heart failure, as detrimental effects have been observed in such patients treated with other drugs of this class.

Pentoxifylline, a methylxanthine derivative administered at 400 mg 3 times/day, may be used as a second-line agent to cilostazol, as it has been shown to marginally improve walking distances. However, the observed...
and expected improvements are modest at best, and, as with cilostazol, symptomatic improvement may not occur until after at least 4 weeks of treatment.

SUMMARY

PAD is a prevalent condition that confers significant morbidity and mortality. The most common etiology of PAD is atherosclerosis, and its presence is a marker of diffuse atherosclerotic disease in other vascular beds. Although PAD significantly increases risk of death from coronary heart disease, it remains clinically under-recognized and undertreated.

Although claudication is the most classic symptom, individuals with PAD more often present with atypical leg symptoms or no symptoms at all. However, identifying PAD risk factors, including smoking, diabetes, advanced age, hyperlipidemia, and hypertension, should prompt further work-up to determine whether PAD is present. Once diagnosed, aggressive risk factor modification should ensue as well as secondary prevention treatment with antiplatelet therapy. Symptomatic individuals may benefit from exercise and/or pharmacologic therapy. Identification and treatment of PAD is essential for effective CVD risk management, and routine screening with ABI in patients older than 70 years or in diabetic patients older than 50 years should be considered.

REFERENCES


47. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. Am J Cardiol 2003;92:711–2.
48. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol


