In Brief

Peripheral arterial disease (PAD) is a common atherosclerotic disease affecting the quality of life of > 8 million Americans. PAD is characterized by atherosclerotic stenoses of arteries that supply the lower extremities and is associated with a marked increase in the short-term risk of heart attack, stroke, amputation, and death. Adherence to pharmacological therapies and modification of lifestyle factors, including increasing moderate physical activity along with supervised exercise, smoking cessation, and a healthy dietary intake, are central to the successful management of PAD. The improvement of an adverse cardiovascular risk profile is a proven and crucial strategy to lower the risk of major morbid and mortal events for individuals with PAD.

Management of Peripheral Arterial Disease

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Peripheral arterial disease (PAD) is a serious condition that increases individual and population-based risk of heart attack, stroke, death, and amputation and decreases quality of life and functional independence. It affects millions of Americans, especially those with diabetes. Furthermore, the economic burden of PAD is substantial.[1]

What Is Lower-Extremity PAD?

Lower-extremity PAD is most commonly caused by atherosclerosis, a blockage of the inner lining of an artery by fatty deposits that results in poor perfusion of the skin, muscles, and limb.[2] The diagnosis of lower-extremity PAD is commonly established by the resting ankle-brachial index (ABI; calculated as the systolic blood pressure in the right or left ankle divided by the higher of the two brachial artery pressures, with values < 0.90 diagnostic of PAD).

PAD most often affects the arteries that supply the legs, but it may also occur in any non-coronary circulation, including the arms, brain, stomach, kidney, or any vital organ. The blockage that occurs in the legs or feet may cause an intermittent fatigue, cramping sensation, or pain that is called intermittent claudication, which is the most recognized symptomatic subset of lower-extremity PAD.

Evidence-based guidelines for the diagnosis, treatment, and management of PAD have been developed and pub-

lished by vascular health physicians and unanimously approved by associated cardiovascular health professional organizations and the National Heart, Lung, and Blood Institute.[2] These guidelines are available online at www.acc.org and www.americanheart.org.

Prevalence of PAD

PAD affects 8–12 million adults ≥ 40 years of age in the United States and affects similar proportions of men and women.[2,3] About 20–30% of individuals with PAD have diabetes.[4–7] Compared to whites, the likelihood of PAD is 50% greater among African Americans [2,3,8] and 55% lower among Chinese.[8] The National Health and Nutrition Examination Survey (NHANES) for 1999–2000 showed that the age-adjusted prevalence of PAD was 11.7% in non-Hispanic whites, 19.5% in non-Hispanic blacks, and 15.6% in Hispanic men and women.[9] The risk of PAD increases substantially with age.[1–3] The prevalence of PAD is 4.8, 12.0, and 22.0% for men and women aged 60–69 years, 70–79 years, and ≥ 80 years, respectively.[9] The prevalence of claudication, as a less sensitive symptomatic marker of PAD, is 0, 2.4, and 2.7% for men and women aged < 60 years, 60–69 years, and ≥ 70 years or more, respectively.[10]

PAD is associated with significant morbidity and mortality. A low ABI (< 0.90) has been associated with an increased risk of all-cause mortality (relative risk [RR] 1.60; 95% confidence interval [CI] 1.32–1.95); cardiovascular mortality (RR 1.96; 95% CI 1.46–2.64); fatal and non-fatal coronary heart disease (RR 1.45; 95% CI 1.08–1.93); and fatal and non-fatal stroke (RR 1.35; 95% CI 1.10–1.65).[11] In a cross-sectional study that evaluated both walking impairment and quality of life among individuals with both PAD and other cardiovascular diseases, the impact of PAD on functional status was equal to or worse than that of individuals of comparable age with coronary and other cardiovascular diseases.[12]

Patients with diabetes are more likely to develop symptomatic PAD. In a cross-sectional study, lower-extremity function was assessed in 460 male and female patients with PAD, 147 of whom also had diabetes.[13] Individuals with PAD and diabetes had worse lower-extremity function with shorter distances walked and at a slower pace than those with PAD alone, which may be explained by diabetes-related neuropathy.[13] Patients with both PAD and diabetes are at higher risk than PAD patients without diabetes for the progression of their PAD, as well as developing manifestations of coronary heart disease.[7] Further, the presence of concomitant diabetes in individuals with PAD may result in more severe anatomic arterial disease, as well as a distribution of disease in more distal leg arterial segments, which is associated with higher rates of lower-extremity amputation.[14,15]

The prevalence of amputation in PAD varies regionally, but overall risk is < 3–4% of the total PAD population. It is important to note that rates of leg amputation in individuals with PAD and diabetes are associated with great regional variation. These disparate rates are likely the result of differing care pathways offered to individuals at risk, further amplifying the national PAD outcomes health disparity.[16]

Risk Factors for Development of PAD

The risk factors for PAD are similar to those for other atherosclerotic diseases, including age, smoking, diabetes, high blood pressure, and dyslipidemia. Recently low-grade inflammation was identified as an independent risk factor for development and progression of PAD. Specifically, elevated levels of C-reactive protein are associated with risk of developing PAD.[17] Smokers have 2.5 times the risk of developing PAD of nonsmokers, [2,13,18] and individuals with diabetes have 2–4 times the risk of developing PAD.[13,19] To prevent microvascular complications, the American Diabetes Association recommends for individuals with diabetes a target hemoglobin A_{1c} (A1C) level of < 7.0%.[19] However, data to support more aggressive control of glycemia to prevent macrovascular arterial endpoints, including amputation, are lacking.[13] In the Reduction of Atherothrombosis for Continued Health (REACH) study, an international registry of 69,055 atherothrombotic patients aged ≥ 45 years to monitor risk factor control and use of risk reduction strategies, 44.2% of 8,273 patients with PAD also had diabetes.[20] Cardiovascular ischemic event rates in individuals with PAD were higher than those with coronary disease alone.[21]

About 33% of U.S. adults (≥ 18 years of age) have high blood pressure; however, only 35% of hypertensive individuals have achieved target goals for the treatment of their blood pressure.[3] In the REACH registry, > 80% of PAD patients aged ≥ 45 years were hypertensive, and 92% were taking at least one antihypertensive medication.[20] The prevalence of high LDL cholesterol (≥ 160 mg/dl) among U.S. adults >18 years of age was 25.3% according to NHANES 1999-2004.[3] Among PAD patients in this registry, 66.7% had been diagnosed with hypercholesterolemia; of these, 70% were prescribed at least one lipid-lowering medication (64% were taking statins).[20] Beyond these international registry data, undertreatment of risk factors and lower use of risk reduction therapies have been demonstrated from the NHANES population-based data and other studies.[5,22]

Awareness of PAD as a prevalent cardiovascular disease, and its associated risk, is very low as demonstrated by a recent population-based national survey of > 2,500 white, Hispanic, and African-American adults with a mean age of 67 years.[23] Less than one in four Americans > 50 years of age—a group characterized by high rates of risk factors and leg pain—were at all aware of the existence of PAD. Fifty percent of individuals did not know that diabetes and smoking increased the risk for PAD, and less than one-fourth of the cohort that had heard of PAD was aware that PAD increased the risk of heart attack and stroke. Less than one in seven of the "PAD-aware" cohort was knowledgeable that PAD was the major cause of leg amputation. Awareness of PAD was lower among individuals with lower income and education levels.

In the PAD Awareness, Risk and Treatment: New Resources for Survival study of PAD treatment in a primary care setting, most patients with PAD were aware of their diagnosis; however, many of their primary care physicians were not.[5] As might be anticipated, atherosclerosis risk factors were treated less frequently in those whose PAD diagnosis was not previously established. However, treatment intensity was also less in those PAD patients who had a prior PAD diagnosis established compared to CAD patients in the same practice setting.

This undertreatment of PAD likely contributes to the high rates of heart attack, stroke, amputation, hospitalization, and death. Establishment of a prompt PAD diagnosis provides a compelling opportunity to provide cost-effective prevention of disability and death.

Diagnosis

PAD symptoms

About 50% of individuals with PAD are asymptomatic. Among individuals experiencing symptoms, the most common one is claudication, which is the fatigue, aching, cramping, or frank pain that is provoked in leg muscles during activity and that resolves with rest.[2,19] At least half of individuals with PAD experience leg discomfort both at rest and with exercise as a result of the presence of multiple illnesses that impair leg function. This clinical presentation is known as "atypical leg pain." Manifestations of severe PAD include ischemic leg pain that occurs at rest or the development of a nonhealing skin ulcer or gangrene. This constellation of severe ischemic symptoms is known as "critical limb ischemia" and is a medical emergency. More rarely, acute limb ischemia may occur when leg arterial blood flow is suddenly obstructed by an embolic or in situ thrombus.

Establishing the diagnosis

The resting ABI is used to establish the lower-extremity PAD diagnosis in patients suspected of PAD symptoms, defined as individuals with exertional leg symptoms, with nonhealing wounds, who are ≥ 70 years of age, or who are ≥ 50 years of age with a history of smoking or diabetes.[2,5] The ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower-extremity PAD and establish a baseline. The toe-brachial index should be used to establish a lower-extremity PAD diagnosis in patients in whom lower-extremity PAD is clinically suspected but in whom the ABI test is not reliable because of noncompressible vessels. Leg segmental pressure measurements are useful to establish a lower-extremity PAD diagnosis when anatomical localization of lower-extremity PAD is required to create a therapeutic plan.

Exercise treadmill tests are recommended to provide the most objective evidence of the magnitude of the functional limitation of claudication and to measure the response to therapy. A standardized exercise protocol (either fixed or graded) with a motorized treadmill should be used to ensure reproducibility of measurements of pain-free walking distance and maximal walking distance. Exercise treadmill tests with measurement of pre-exercise and post-exercise ABI values are recommended to provide diagnostic data useful in differentiating arterial claudication from non-arterial causes of leg pain. Duplex ultrasound of the extremities is useful to diagnose the anatomic location and degree of stenosis of PAD. More advanced imaging techniques, such as computed tomography or magnetic resonance angiography, may also be useful for individuals who require an arterial revascularization procedure to improve symptoms when medical therapies are ineffective or when limb survival is threatened. For these individuals, use of percutaneous transluminal angioplasty or open vascular surgical revascularization may be beneficial, and both noninvasive and invasive arterial imaging can effectively guide the revascularization approach.

Treatment

The goals of treatment in PAD are *1*) to improve leg ischemic symptoms and *2*) to reduce the risk of heart attack, stroke, amputation, and death.[2] Optimal PAD care is always best achieved by the combined use of pharmacological treatment and lifestyle changes,[24] with more limited use of revascularization procedures (e.g., angioplasty or surgery) when medical therapy alone is not effective in improving claudication symptoms or in preventing amputation.

Lifestyle intervention

PAD symptoms may be reduced and managed through lifestyle modification, including exercise and physical activity, smoking cessation, and a healthy diet.[1,24]

Exercise and physical activity. Physical activity is known to promote and maintain health, including lower blood pressure, inflammation markers, and lipids; reduced prevalence of overweight and depression; and improved exercise capacity and blood rheology.[2,25] For individuals with diabetes and PAD, physical activity is recommended because success in treatment of PAD may be measured in distance walked without pain.[17,25] In a systematic review of 10 randomized clinical trials of exercise programs in patients with symptomatic claudication, supervised exercise therapy was effective in increasing walking time compared to standard care.[26] Higher level or longer duration of physical activity is related to longer survival and lower risk of death from cardiovascular disease among PAD patients.[2,19,25–27] For more detailed information on recommendations for supervised exercise, please see the article by Stewart et al.[28]

Smoking cessation. Smoking cessation is a key modifiable risk factor for increasing survival and reducing the potential for disease progression. Smoking increases the risk of leg amputation, the risk of developing coronary heart disease or stroke, and mortality among PAD patients.[2,18,19]

Dietary intake. Few published studies have investigated the relation between dietary intake and risk of development of PAD. Cross-sectional studies of the relationship between nutrient intakes and PAD have shown a lower risk of PAD with a higher intake of vegetable fatty acids (i.e., olive oil and canola oil) ≥ 34.4 g/day (odds ratio [OR] 0.39; 95% CI 0.16, 0.97) and vitamin E intake ≥ 7.7 mg/day (OR 0.37; 95% CI 0.16, 0.84).[29] The main vegetable fat consumed in this study was olive oil, which is rich in both monounsaturated and polyunsaturated fatty acids, as well as flavonoids and terpenes. It is known that polyunsaturated fatty acids favorably influence serum cholesterol concentrations and endothelial function,[30] while flavonoids and terpenes function as antioxidants.[31]

Vitamin E, found mainly in cooking oils, also contains antioxidant and anti-inflammatory properties and inhibits platelet aggregation.[32] In a case-control study of antioxidant intake and PAD, lower vitamin C intake was reported in PAD cases compared to control subjects.[33] Lower levels of ascorbic acid and higher C-reactive protein levels were observed in PAD patients compared to hypertensive individuals or healthy control subjects.[34]

It is possible that intakes of vegetable oil (i.e., olive oil), vitamin E, and vitamin C are markers for the Mediterranean diet pattern, which has been associated with lower risk of chronic disease in numerous

studies.[35-37] We note that data that attempt to define atherosclerosis risk derived from both prospective and cross-sectional population surveys has unknown relevance to the treatment of established PAD. Given that dietary intervention trials have yet to be performed in a PAD population, the potential benefit and risk of altered dietary fat, vitamin C, or vitamin E consumption is not known.

Adverse levels of risk factors for PAD, including high blood pressure, diabetes, and dyslipidemia, however, all may be improved with dietary intake. Cardioprotective nutrition interventions, which include reduction in saturated fat, *trans* fats, and dietary cholesterol, and interventions to improve blood pressure should be a part of the treatment plan.[38] The cardioprotective dietary pattern should be individualized to provide a fat intake of 25–35% of total calories, < 7% of total calories from saturated fat and *trans* fatty acids, and < 200 mg of cholesterol per day. This pattern can lower LDL cholesterol up to 16% and decrease risk of cardiovascular disease. The Dietary Approaches to Stop Hypertension diet[39] demonstrated a reduction in blood pressure of 8–14 mmHg. It is rich in fruits and vegetables and includes low-fat dairy products, nuts, and whole grains and is low in sodium, total fat, and saturated fat. In observational studies of young and middle-aged adults, greater intakes of fruit, vegetables, and whole-grain products were associated with a lower risk of developing elevated blood pressure.[40,41]

In epidemiological studies, low to moderate alcohol intake has been protective for development of PAD, coronary heart disease, and type 2 diabetes.[42–44] Alcohol may promote its beneficial effect on cardiovascular disease and risk factors through beneficial modification of lipids, hemostatic factors and fibrinolysis, inflammatory markers, and glucose control parameters.[43,45]

Eating a healthy diet pattern based on the *Dietary Guidelines for Americans*[46] or following the American Diabetes Association[47] nutrition recommendations for individuals with diabetes is known to prevent or improve adverse cardiovascular disease risk factors and to promote vascular health. According to the *Dietary Guidelines for Americans*, adults should eat a sufficient number and variety of foods from the fruit, vegetables, dairy, grain, and meat groups each day while staying within individual energy needs.[46] In particular, selection of fruit and vegetables from all subgroups is recommended, including dark green, orange, legume, starchy, and other vegetables, as well citrus, berries, melons, and other fruit. In addition, intake of 1–2 servings of fish per week is associated with improved vascular health.[46,48] The *Dietary Guidelines for Americans*, first developed in 1980 and updated in 2005 by the U.S. Department of Agriculture (USDA) and the Department of Health and Human Services, provides science-based advice to promote health and reduce risk for major chronic disease through diet and physical activity. [46] In addition, the USDA developed a tool called the Food Guide Pyramid (found at www.mypyramid.gov), which translates the *Dietary Guidelines for Americans* into messages that may assist consumers in improving their eating habits.[49]

Medical therapies

To reduce adverse cardiovascular event rates associated with PAD, lifelong treatment should include modification or elimination of atherosclerotic risk factors, such as smoking, diabetes, dyslipidemia, and hypertension and promotion of daily exercise and adoption of a nonatherogenic diet.[2] Medical therapy (pharmacotherapy) is mandatory when target levels of blood pressure, LDL cholesterol, and plasma

Table 1. PAD Resources

	The P.A.D. Coalition and Vascular Disease Foundation	National Heart, Lung, and Blood Institute (NHLBI)
Web site address	www.padcoalition.org and www.vdf.org	www.aboutpad.org
Purpose	The **P.A.D. Coalition** is a nonprofit alliance of leading health organizations, vascular health professional societies, and government agencies that have united to raise public and health professional awareness about lower-extremity PAD Committed to improving PAD patient outcomes, the P.A.D. Coalition is coordinated by the Vascular Disease Foundation, a national, not-for-profit section 501(c)(3) organization.	NHLBI provides leadership that links basic and clinical research to public and professional health awareness programs regarding diseases of the heart, blood vessels, and lung. To raise national awareness about PAD, NHLBI, in cooperation with the P.A.D. Coalition, is sponsoring the "Stay in Circulation: Take Steps to Learn About P.A.D." campaign.
Key website components:	• The health professionals section includes PAD treatment guidelines, clinical practice tools, PAD guideline slide sets, and treatment information. • The public section includes information on risk factors, warning signs. and treatments for PAD. • The site provides access to the "PAD Education Network," a membership-driven program that provides clinical practices, hospitals, and health systems with access to news about PAD, public and professional PAD awareness resources, and an online directory of other members involved in PAD care.	• The health professionals section includes PAD care guidelines, pocket guides, multimedia learning presentations, patient education materials, and more. • To support PAD community awareness campaigns, the site provides free access to "Stay In Circulation" campaign materials, including resource flyers, PAD fact sheets, posters, wallet cards, radio ads, and an educational PAD video.

glucose cannot be achieved by lifestyle changes alone.

Antiplatelet therapy is indicated to reduce the risk of myocardial infarction (MI), stroke, or vascular death in individuals with PAD. Aspirin, in daily doses of 75–325 mg, is recommended as a safe and effective therapy to reduce this risk. Clopidogrel, 75 mg per day, is recommended as an effective alternative antiplatelet therapy.[50] Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in these patients.[51]

Statin therapy is indicated for all patients with PAD to achieve a target LDL cholesterol level of < 100 mg/dl. In very-high-risk PAD patients (those with any poorly controlled risk factor, such as diabetes), statin therapy is indicated to achieve a target LDL cholesterol of < 70 mg/dl. Treatment with a fibric acid derivative can be useful for PAD patients with low HDL cholesterol and elevated triglycerides.

Antihypertensive therapy should be administered to hypertensive patients with PAD to achieve a goal of < 140/90 mmHg (for individuals without diabetes) or < 130/80 mmHg (for individuals with diabetes or chronic renal disease) to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death.[52,53] Treatment of diabetes with medical nutrition therapy, exercise, and medications targeting glycemic control is essential to achieve an A1C of < 7%.

Claudication treatment

Pharmacotherapy to improve walking distance is proven to increase pain-free walking, and use of cilostazol is recommended as a first-line treatment for all individuals with PAD and claudication (though this medication is contraindicated for use in the rare individuals who have PAD and concomitant heart failure).[54] Endovascular procedures, including balloon angioplasty and stenting, are indicated for individuals with a vocational or lifestyle disability resulting from intermittent claudication; when clinical features suggest a likelihood of symptomatic improvement, there has been an inadequate response to exercise or pharmacological therapy, and there is a very favorable risk-benefit ratio. Surgical interventions are indicated in PAD patients in whom an endovascular procedure would be less suitable and successful.[2]

Summary and Conclusion

PAD is a major and common health problem affecting many individuals with or at risk for developing diabetes. Like diabetes and pre-diabetes, PAD often goes undiagnosed until the disease has progressed. It is important that diabetes health professionals understand the diagnosis and treatment of PAD, as defined by current treatment guidelines, so they can support individuals with diabetes who are affected by this disease. Diabetes professionals are in a key position to identify individuals at risk for developing PAD, provide education, and refer individuals for appropriate care.

Addressing health behaviors (i.e., tobacco use, diet, physical activity, and supervised exercise) and adherence to pharmacological therapies is crucial to the successful management of both diabetes and PAD. Table 1 provides information about two organizations that provide useful information for health care professionals and patients.

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