Chapter 7
Peripheral Artery Disease: An Overview

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Lower extremity peripheral artery disease (PAD), defined as atherosclerotic obstruction of the lower extremity arteries, now affects 8.5 million men and women in the United States and more than 200 million people worldwide [1, 2]. Atherosclerotic obstruction in the lower extremity arteries limits oxygen delivery to lower extremity skeletal muscle during walking activity, and in cases of extremely severe PAD, oxygen delivery can be limited at rest. Thus, people with PAD have difficulty walking long distances, due to inadequate oxygenation of lower extremity muscle during exercise, and patients with extremely severe PAD can develop critical limb ischemia including gangrene. Most patients with PAD will not develop critical limb ischemia, but have difficulty walking more than short distances due to ischemia of their limbs with walking. Consistent with this phenomenon, people with PAD have significantly greater functional impairment and higher rates of mobility loss, compared to people without PAD [3–5]. In addition, people with PAD typically have atherosclerotic blockages in the coronary and cerebrovascular arteries [6]. Therefore, people with PAD also have an increased risk of coronary ischemic events, stroke, and mortality, compared to people without PAD [7, 8]. Major therapeutic goals for people with PAD consist of improving walking ability and preventing cardiovascular events. This chapter describes the epidemiology of PAD, diagnosis of PAD, and clinical consequences of PAD. Therapeutic approaches to PAD are briefly summarized. The Table 7.1 provides a brief summary of risk factors, diagnosis, prognosis, and treatment for PAD.

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Table 7.1 Overview of peripheral artery disease

Characteristic	Evidence
Risk factors	Older age, diabetes, and cigarette smoking are the strongest risk factors for PAD. Hypertension, hyperlipidemia, and inflammation are also risk factors for PAD
Diagnosis	Ankle brachial index <0.90 is a widely accepted and noninvasive method for diagnosing PAD
Symptoms	Intermittent claudication is considered the most classical symptom of PAD. However, most people with PAD are either asymptomatic or report exertional leg symptoms other than claudication
Treatment	Treatment should focus on preventing cardiovascular events by prescribing antiplatelet therapy and a potent statin and by treating hypertension. Walking exercise improves mobility and prevents functional decline in PAD
Prognosis	People with PAD are at increased risk of cardiovascular events and all-cause mortality, compared to those without PAD. Most patients with PAD experience decline in walking endurance over time, although only a relatively small minority will ever develop critical limb ischemia

Epidemiology and Risk Factors for PAD

Older age is a major risk factor for PAD and the prevalence of PAD increases markedly with increasing age. PAD is uncommon in people younger than age 50 but affects as many as 20% of people age 80 and older [6, 8, 9]. PAD will be increasingly common as the population survives to older ages with chronic diseases. In addition to older age, traditional atherosclerotic disease risk factors, such as diabetes mellitus, cigarette smoking, hypertension, dyslipidemia, and increased inflammation are risk factors for PAD. Cigarette smoking and diabetes mellitus are particularly important risk factors for PAD [8, 10, 11]. For example, cigarette smoking and diabetes are stronger risk factors for PAD than for coronary artery disease [8, 9].

People who currently smoke have a 2.0- to 3.4-fold higher risk of PAD compared to people who never smoked [8]. Furthermore, there is a dose-dependent association between cigarette smoking and risk of PAD. Among male participants in the Health Professionals Follow-Up Study, men who smoked the most cigarettes had a 12.9-fold higher risk of developing PAD compared to men who had never smoked [12]. Smoking cessation reduces the risk of PAD, but smokers remain at increased risk for PAD for up to 20 years after quitting smoking, compared to individuals who never smoked cigarettes [8, 12]. Epidemiologic evidence shows that diabetes mellitus is associated with a 1.9–4.0-fold increased risk of PAD, even after adjustment for other potential confounders [8]. Some evidence suggests that more severe diabetes is associated with higher risk of PAD [8]. In addition, people with PAD who have diabetes are at higher risk of amputation and mortality compared to people with PAD who do not have diabetes. One report described that among people with PAD, those with diabetes had a fivefold higher risk of an amputation, compared to

those without diabetes [13]. Among people with PAD, those who have diabetes also tend to have more distal lower extremity atherosclerosis compared to those without diabetes [13, 14]. Hypertension, hyperlipidemia, and inflammation are also significant and independent risk factors for PAD [8, 12].

The prevalence of PAD is similar between men and women over age 65 [6, 15], but African-Americans have a higher prevalence of PAD compared to Caucasians, independent of differences in cardiovascular risk factors between African-Americans and Caucasians [6, 7]. For example, the Cardiovascular Health Study of 5084 community-dwelling men and women age 65 and older in the United States reported that nonwhite race (primarily African-American race) was associated with a 2.1-fold higher prevalence of PAD compared to Caucasians [15]. In the Women's Health and Aging Study, 328 of 933 community-dwelling women age 65 and older with mobility impairment had PAD. Those with PAD had a significantly higher prevalence of African-American participants, compared to those without PAD (36.3% vs. 24.8%) [16]. In summary, there are not significant differences in the prevalence of PAD between older men and women, but African-Americans have a higher prevalence, compared to Caucasians.

Symptoms and Diagnosis of Peripheral Artery Disease

The most classical symptom of PAD is intermittent claudication, defined as exertional calf pain that begins with walking activity, resolves within 10 minutes of rest, and does not begin while at rest [17, 18]. In people with PAD, exertional calf pain due to ischemia is caused by insufficient oxygen supply during walking activity. Symptoms resolve with rest, when the flow of oxygen-rich arterial blood is sufficient to meet oxygen requirements. Although intermittent claudication is considered the most classical symptom of PAD, most people with PAD have atypical leg symptoms other than classical intermittent claudication, and many people with PAD are asymptomatic – i.e., they have no exertional leg symptoms [3–5, 15, 16]. In patients identified from a community-dwelling setting with objectively documented PAD, approximately 60% report no exertional leg symptoms, and approximately 10% report classical exertional leg symptoms, with the remainder reporting exertional leg symptoms other than classical intermittent claudication [15]. In patients identified in a clinical practice setting, approximately 30% to 50% are asymptomatic and approximately 25 to 30% have classical symptoms of intermittent claudication [3–5]. Reasons for the range of leg symptoms and high prevalence of asymptomatic disease among people with PAD remain unclear. However, nearly 60% of people with asymptomatic PAD developed exertional leg symptoms during a 6-minute walk test [19], suggesting that many people with PAD restrict activity to avoid leg symptoms and subsequently become asymptomatic. People with PAD who report exertional leg symptoms other than intermittent claudication have a higher prevalence of diabetes, peripheral neuropathy, and spinal stenosis [3], suggesting that comorbid diseases may influence symptoms experienced during walking activity by people with PAD.

Only a small proportion of patients with PAD develop critical limb ischemia, the manifestation of end-stage PAD that may lead to amputation if not reversed. In one study, approximately 2.5% of patients with PAD developed rest pain or gangrene per year [8]. However, rates of progression to critical limb ischemia may be highest during the year after PAD is diagnosed [8], perhaps because severe PAD is more likely to be diagnosed than mild PAD.

Diagnosing PAD

Although symptoms of PAD are myriad and many people with PAD report no leg symptoms, PAD can be noninvasively diagnosed with the ankle brachial index (ABI), a ratio of Doppler-recorded systolic pressures in the lower and upper extremities. A normal ABI is 1.10–1.40 [20]. An ABI < 0.90 is reasonably sensitive and highly specific for a diagnosis of PAD [20, 21].

The ABI can be performed in the outpatient setting by measuring Doppler-recorded systolic pressures in the right and left brachial arteries and in the dorsalis pedis and posterior tibial arteries in each lower extremity. In healthy people without PAD, arterial pressures increase with greater distance away from the heart. This phenomenon results in higher systolic pressures at the ankle compared to the brachial arteries in people without lower extremity arterial obstruction. Therefore, people without lower extremity atherosclerosis typically have an ABI value ≥1.10 and <1.40, and an ABI < 0.90 is consistent with significant lower extremity atherosclerosis [20–24]. Lijmer et al. reported that an ABI < 0.91 had a sensitivity of 79% and a specificity of 96% for PAD in approximately 100 limbs, based on a comparison of the ABI value with angiographic study of the lower extremities [21]. The relatively low sensitivity of ABI < 0.90 occurs because some patients with PAD have medial calcinosis of their distal lower extremity arteries, resulting in ABI values above 1.10 even in the presence of significant lower extremity arterial obstruction [20]. Lower ABI values are indicative of more severe PAD. An ABI value <0.50 indicates severe PAD, while a value of 0.50–0.90 indicates mild to moderate PAD. People with an ABI value of 0.91–1.09 typically have mild PAD, and ABI values in this range are associated with higher rates of mobility loss and increased cardiovascular mortality rates, compared to people with ABI values of 1.10–1.40.

The ABI should be performed with the patient lying supine, after at least a 5-minute rest period. Appropriately sized blood pressure cuffs are placed over each brachial artery and at each ankle. At the ankle, the blood pressure cuff bladder should be positioned so that the artery marker is directly over the posterior tibial artery. Patients should be instructed not to talk during the examination, since talking can alter the systolic pressures during the test. A handheld Doppler is used to locate each artery before each arterial pressure measurement. Blood pressures are typically measured sequentially starting with the right upper extremity and them moving to the right lower extremity, left lower extremity, and the left upper extremity. In the lower extremities, the dorsalis pedis and the posterior tibial pressure are each mea-

sured. The probe should be positioned so that it detects the strongest signal from the artery prior to cuff inflation. Accurate ABI measurement consists of inflating the cuff sphygmomanometer to at least 20 mm above the systolic pressure and deflating the pressure no faster than 2 mm/second. The systolic pressure at which the pulse reappears is measured and recorded for each artery and used to calculate the ABI.

Calculating the ABI

An ABI may be calculated for each lower extremity artery, by dividing the lower extremity artery's pressure by the highest of the brachial artery pressures. The ABI is typically calculated for each leg, by dividing the highest of the two pressures in each leg by the highest of the left vs. right brachial artery pressures. The highest pressure in each leg is traditionally used to calculate the ABI for each leg, because the highest pressure represents the greatest arterial pressure reaching the foot. This information is useful when estimating the degree to which overall perfusion is compromised for each leg. However, it has been demonstrated that the ABI calculation using the average of the dorsalis pedis and posterior tibial artery pressures correlates most closely with functional impairment in people with PAD [24]. Using the lowest of the dorsalis pedis and posterior tibial pressures to calculate the ABI in each leg maximizes sensitivity of the ABI for the diagnosis of PAD [25] but is associated with lower specificity.

Association of PAD with Increased Risk of Mortality and Cardiovascular Events

It is well established that people with PAD have higher rates of all-cause mortality and cardiovascular events, compared to people without PAD [2, 26]. This association has been demonstrated in multiple observational studies both from community-dwelling settings and from medical center settings. To illustrate the association of the ABI with all-cause and cardiovascular mortality, the ABI Collaboration team of investigators combined data from 16 population-based observational studies that collected data on ABI and subsequent occurrence of cardiovascular events and mortality [26]. The meta-analysis included 24,955 men and 23,339 women with ABI values and 480,325 person years of follow-up [26]. Among men, cardiovascular mortality rates at 10-year follow-up were 18.7% for men with ABI < 0.90 vs. 4.4% for men with a normal ABI value (hazard ratio (HR) = 4.2, 95% confidence interval (CI) = 3.3–5.4) [26]. For women, cardiovascular mortality rates at 10-year follow-up were 12.6% among women with ABI < 0.90 and 4.1% in women with a normal ABI (HR = 3.5, 95% CI = 2.4–5.1) [26]. When men and women were stratified by Framingham Risk Score (FRS), an ABI < 0.90 was associated with an approximately twofold increased risk of 10-year all-cause mortality, cardiovascular

mortality, and coronary event rate, compared to normal ABI values. These and other data demonstrate that the ABI is both an important diagnostic tool for detecting PAD and also an important prognostic tool with regard to future cardiovascular risk. An advantage of the ABI compared to other measures of PAD is that it is a simple, noninvasive, and relatively inexpensive test. However, the ABI may be insensitive to detecting PAD when lower extremity arteries are affected by medial calcinosis, which is common in older people and in people with diabetes.

PAD and Lower Extremity Functional Impairment

Because PAD blocks oxygenated blood perfusion of lower extremity skeletal muscle during walking activity, oxygen requirements during activity exceed oxygen supply to lower extremity muscle, resulting in ischemic leg symptoms and/or weakness of the lower extremities on exertion. Consistent with this phenomenon, people with PAD have greater functional impairment, poorer physical activity levels, and higher rates of mobility loss than people without PAD [3–5, 16, 27–29]. These associations were demonstrated in the Walking and Leg Circulation Study (WALCS), in which 726 men and women age 55 and older with and without PAD underwent functional testing at baseline and were followed longitudinally with annual study visits, to document changes in mobility and walking performance over time [3, 27]. At baseline, compared to individuals with a normal ABI value, those with ABI < 0.50 were 11.7 times more likely to be unable to walk for 6 minutes without stopping, and those with an ABI of 0.70–0.90 were 2.7 times more likely to be unable to walk for 6 minutes without stopping [16]. At 5-year follow-up, participants with severe PAD in the WALCS cohort were 4.2 times more likely, and those with mild PAD were 3.2 times more likely to develop mobility loss, defined as the inability to walk ¼ mile or walk up 1 flight of stairs without assistance, compared to people without PAD [28]. These associations were independent of age, comorbidities, and other confounders. Furthermore, functional impairment and functional decline occurs even among people with PAD who report no exertional leg symptoms [3–5, 29]. The fact that many patients with PAD restrict their physical activity or slow their walking speed to avoid exertional ischemic leg symptoms is likely to further contribute to functional impairment and decline in people with PAD.

Therapeutic Interventions for People with PAD

Therapeutic strategies for people with PAD should focus on preventing cardiovascular events and improving functional impairment and preventing functional decline. Over the past 25 years, greater progress has been made in preventing cardiovascular events than in improving walking impairment or preventing mobility loss in people with PAD. Quitting smoking is associated with lower rates of critical

limb ischemia and cardiovascular event rates. Therefore, all patients with PAD who continue to smoke cigarettes should be helped to quit smoking. Clinical practice guidelines for people with PAD recommend antiplatelet therapy and treatment with a potent statin to prevent cardiovascular events [30]. Some evidence suggests that clopidogrel is more efficacious than aspirin for preventing cardiovascular events in people with PAD [31]. Recent evidence supports prescription of low-dose rivaroxaban (2.5 mg twice daily) in combination with low-dose aspirin in patients who have PAD and concomitant coronary artery disease and are high risk for cardiac and ischemic limb events [31]. Recent evidence suggests that adding vorapaxar to aspirin or clopidogrel can prevent progression to ischemic limb events including critical limb ischemia or acute limb ischemia [31].

Therapeutic Interventions for Improving Functional Performance and Preventing Functional Decline

Few medical therapies have been identified that improve walking performance in people PAD. In 2019, only two medications, cilostazol and pentoxifylline, have been FDA approved for treating PAD-associated ischemic symptoms. However, benefits from cilostazol are modest, improving treadmill walking performance by only approximately 25–40% [32, 33]. Side effects are common and include palpitations, dizziness, headaches, and diarrhea [32, 33]. In one study, 20% of patients discontinued cilostazol within 3 months [30]. Pentoxifylline does not improve walking performance meaningfully more than placebo, and the most recent clinical practice guidelines recommend against using pentoxifylline, due to lack of efficacy [30].

Supervised treadmill exercise is currently considered the most effective medical therapy for improving walking performance in people with PAD [34]. Based on consistent clinical trial evidence, demonstrating improved treadmill walking performance in response to supervised treadmill exercise interventions, in 2017, the Centers for Medicare and Medicaid Services (CMS) published a decision memorandum describing their intent to cover supervised exercise therapy for symptomatic peripheral artery disease. CMS now pays for up to three exercise sessions per week lasting 30–60 minutes per session for a duration of 12 weeks [34]. The exercise must take place in a hospital or outpatient hospital setting and must be delivered by qualified personnel trained with training in exercise therapy for patients with PAD. While the CMS decision to cover supervised exercise should increase access to this effective intervention, many patients with PAD find it burdensome to travel for supervised exercise three times weekly [35]. Furthermore, gains from supervised exercise may be lost, 6 months after completion of a supervised exercise program [36]. Alternative approaches to help patients with PAD adhere to walking exercise regimens are needed.

Home-based walking exercise avoids the time, effort, and cost associated with travel to a medical center for supervised exercise. For these reasons, home-based walking exercise has the potential to be more accessible and acceptable to patients

with PAD than supervised exercise programs. However, not all home-based exercise interventions have been effective [37, 38]. Recent evidence suggests that effective home-based exercise interventions require incorporation of behavioral methods and occasional medical center visits, to encourage adherence to the walking exercise program at home.

Conclusion

PAD is common, affecting approximately 10–15% of men and women age 65 and older. PAD will be increasingly common as the population lives longer with chronic disease. PAD is frequently underdiagnosed, in part because patients with PAD often report no exertional leg symptoms or have leg symptoms that are not consistent with classical intermittent claudication. The therapeutic approach to PAD consists of medical therapies to prevent cardiovascular events and exercise interventions to improve walking ability and prevent mobility loss. While the recent CMS determination to cover supervised exercise for people with PAD should increase access to this therapy, effective home-based exercise strategies that do not require frequent travel to a hospital-based exercise center are needed to maximize uptake of exercise activity by people with PAD.

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