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The magnitude of the problem of peripheral arterial disease: Epidemiology and clinical significance

ABSTRACT

The prevalence of lower extremity peripheral arterial disease (PAD) varies across populations, based on the groups studied and the detection methods used. The ankle-brachial index (ABI) is a more sensitive tool for PAD detection than is screening for intermittent claudication (IC); only about 10% to 30% of patients diagnosed with PAD based on the ABI have classic symptoms of IC. The prevalence of PAD increases markedly with older age and in persons with diabetes or a history of smoking; prevalence also is elevated in persons with hyperlipidemia, hypertension, or chronic kidney disease. PAD is more prevalent in primary care medical practices than in community-dwelling populations. PAD (defined as an ABI < 0.90) is associated with a twofold to threefold increased risk of cardiovascular mortality. Borderline and low-normal ABI values, as well as elevated ABI values (> 1.30 or > 1.40), are increasingly recognized as being associated with elevated cardiovascular mortality. Persons with PAD have significantly increased functional impairment and elevated rates of functional decline relative to those without PAD.

Lower extremity peripheral arterial disease (PAD) affects 8 million men and women in the United States,[1] and PAD is likely to become increasingly prevalent as Americans survive longer with chronic diseases.

PAD is associated with an increased risk for cardiovascular morbidity and mortality, independent of risk factors for atherosclerosis. Moreover, PAD is debilitating: persons with PAD have substantial functional impairment and increased rates of functional decline compared with their counterparts without PAD. Diagnosing PAD is important in order to implement appropriate therapies for preventing cardiovascular morbidity and mortality, improving functional impairment, and preventing further functional decline.

This article sets the stage for the remainder of this supplement by reviewing the prevalence of PAD in defined populations and outlining the clinical significance of this widespread but underdiagnosed disease.

PREVALENCE OF INTERMITTENT CLAUDICATION

The prevalence of PAD varies across populations, based in part on the methods used to define its presence. More sensitive measures for PAD yield a higher prevalence.

Intermittent claudication (IC) is considered the most classic symptom of PAD. Early epidemiologic studies of PAD relied on the Rose questionnaire of IC[2] to assess the incidence, prevalence, and significance of PAD.

The classic symptom of Rose IC is exertional calf pain that causes the patient to stop walking, resolves within 10 minutes of rest, does not resolve while the patient is walking, and does not begin at rest.

The prevalence of IC varies from 1% to 5% across epidemiologic studies,[3–7] with higher prevalences observed in older patient populations.

THE ANKLE-BRACHIAL INDEX: A MORE SENSITIVE MEASURE OF PAD

The ankle-brachial index (ABI) is a much more sensitive measure of PAD than the Rose questionnaire of IC. The ABI is a ratio of Doppler-recorded systolic blood pressures in the lower and upper extremities. Systolic pressures are normally 8% to 15% higher at the ankle than at the arm, as systolic pressures increase with increasing distance from the heart to approximately the third generation of arterial branches.

The ABI declines with lower extremity arterial obstruction, and greater obstruction is associated with progressively lower ABI levels. Epidemiologic studies have used an ABI of less than 0.90 as a threshold for the presence of PAD.

Most patients with PAD do not have classic IC

Studies using the ABI to screen patients for PAD have documented a much higher prevalence of PAD than older studies that used the Rose questionnaire of IC.[7–9]

Among participants in the Cardiovascular Health Study,[7] an epidemiologic evaluation of community-

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TABLE 1
Prevalence of lower extremity PAD and IC in select epidemiologic studies and primary care medical practices

Study (year)	Characteristics of population screened	Prevalence of PAD*	Prevalence of IC	Comments
Lipid Research Clinics[9] (1985)	624 participants in the Lipid Research Clinics population; mean age, 66 yr	11.3%	9.2% among subjects with PAD	Ankle-brachial index and lower extremity flow velocity were used to assess PAD prevalence
Cardiovascular Health Study[7] (1993)	5,084 community-dwelling men and women aged ≥ 65 yr	12%	2% of entire population	PAD prevalence increased dramatically with older age
McDermott et al[10] (1999)	137 subjects with PAD from a noninvasive vascular laboratory (Group 1); 27 subjects with previously undiagnosed PAD from a general medicine practice (Group 2); and 105 subjects without PAD (Group 3)	Not applicable	Group 1: 29% Group 2: 3.8% Group 3: 3.8%	Low prevalence of IC in Group 2 (general medicine practice) is likely due to exclusion of patients with previously diagnosed PAD from this group
PARTNERS study[8] (2001)	6,979 men and women identified from primary care medical practices who were either aged ≥ 70 yr *or* aged 50–69 yr with history of diabetes mellitus or cigarette smoking.	29%	11% among subjects with PAD	Higher prevalence of PAD in this study may be due to inclusion of older age or history of PAD risk factors among inclusion criteria. Findings suggest a high prevalence of PAD in primary care settings.
National Health and Nutrition Examination Survey (NHANES)[11] (2004)	2,174 men and women aged ≥ 40 yr	4.3%	Not provided	Prevalence of PAD may have been underestimated because brachial systolic pressure was measured in only one arm and lower extremity arterial pressures were measured only in posterior tibial arteries
Multi-Ethnic Study of Atherosclerosis (MESA)[19] (2005)	3,458 women (mean age, 62.6 yr) and 3,112 men (mean age, 62.8 yr), all with no history of clinically evident coronary or cerebrovascular atherosclerotic disease	3.7% in both men and women	Not provided	Lower prevalence of PAD in this study is likely due to exclusion of patients with history of clinically evident heart disease or stroke

* Unless otherwise noted in "Comments," prevalence of PAD was based on noninvasive testing with the ankle-brachial index.
PAD = peripheral arterial disease; IC = intermittent claudication

dwelling men and women aged 65 years or older, the prevalence of PAD as defined by an ABI less than 0.90 was 12%, whereas only 2% of participants had a positive Rose questionnaire for IC (Table 1).

The PARTNERS study (PAD Awareness, Risk, and Treatment: New Resources for Survival),[8] which used the ABI to screen for PAD among individuals from primary care clinics, found the prevalence of PAD to be 29%, whereas only 11% of these patients with PAD had IC (Table 1).

Most men and women diagnosed with PAD based on the ABI do not have classic symptoms of IC. As shown in Table 1, the prevalence of classic symptoms of IC varies from approximately 10% to 30% in patients diagnosed with PAD based on the ABI.[7–10]

VARIATIONS IN PAD PREVALENCE ACROSS EPIDEMIOLOGIC STUDIES

The prevalence of PAD has varied across defined populations (Table 1), typically owing to differences in characteristics of the population screened and, as mentioned above, the method of measuring PAD.

Prevalence of PAD in defined populations

Prevalence rises substantially with age. The Cardiovascular Health Study of 5,084 community-dwelling men and women aged 65 years or older found the prevalence of PAD to increase dramatically with increasing age.[7] Among men with a history of heart disease or stroke, the prevalence of PAD exceeded 30% in those aged 80 to 84 years and exceeded 40% in those aged 85 or older (Figure 1). Associations between older age and higher prevalence of PAD also were observed in both men and women without a history of heart disease or stroke (Figure 1).[7]

Prevalence linked to atherosclerotic risk factors. Traditional atherosclerotic risk factors are associated with an increased prevalence of PAD. Thus, PAD prevalence is higher in populations that include current or former cigarette smokers and patients with a history of diabetes mellitus, hyperlipidemia, or hyper-

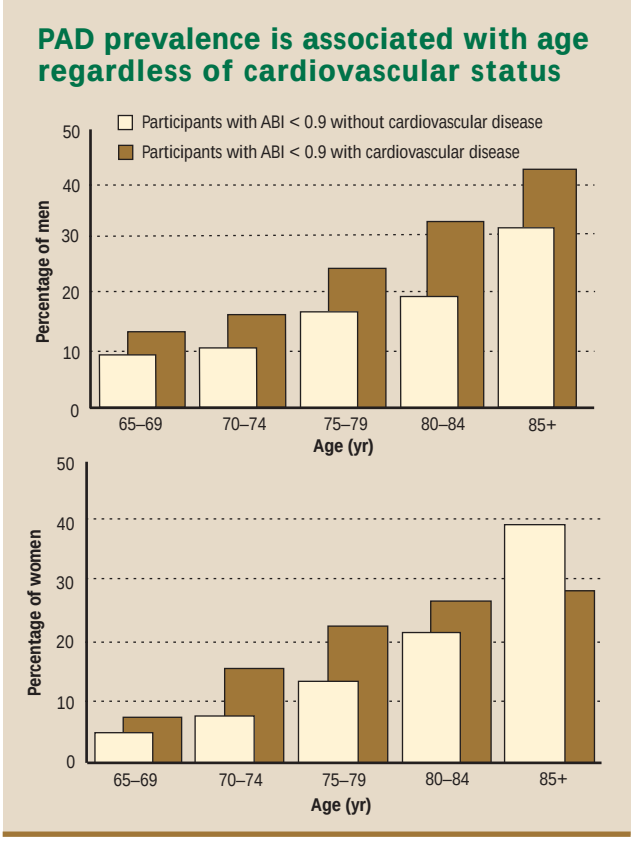

FIGURE 1. Prevalence of peripheral arterial disease (ankle-brachial index [ABI] < 0.9) by age group among community-dwelling men (top) and women (bottom) in the Cardiovascular Health Study (N = 5,084).[7] Reprinted, with permission, from reference 7.

tension. Among traditional risk factors for cardiovascular disease, cigarette smoking and diabetes mellitus have a particularly strong association with PAD.

Other populations with an elevated prevalence of PAD include persons with chronic kidney disease, African Americans, and organ transplant recipients.[11]

High prevalence in primary care practices. The prevalence of PAD is higher in primary care medical practices than in populations of community-dwelling men and women.[7–9,11,12] The PARTNERS study,[8] the largest study of PAD prevalence in primary care practice settings to date, used ABI screening in 6,979 men and women from 350 primary care medical practices across the United States. Participants were either 70 years of age or older or 50 to 69 years of age with a history of diabetes mellitus or cigarette smoking. The prevalence of PAD was 29% overall. Thirteen percent of participants had a low ABI without other clinically evident atherosclerotic disease. Nearly 45% of participants with an ABI less than 0.90 had not previously been known to have PAD, suggesting that the presence of PAD is commonly missed in primary care practices. Participants with previously unrecognized PAD were less likely to have leg symptoms typical of IC and were more likely to be asymptomatic than participants with previously recognized PAD. These findings underscore the importance of not limiting evaluation for PAD to patients who have classic symptoms of IC.

How ABI is measured affects PAD detection

The method of ABI measurement also can influence PAD detection and, in turn, its reported prevalence. An ABI can be calculated for the posterior tibial and dorsalis pedis arteries in each leg. Epidemiologic studies that measure pressure only in the posterior tibial artery, but not the dorsalis pedis artery, may miss some patients who have isolated PAD in the dorsalis pedis arteries. Similarly, measuring the brachial systolic pressure in only one arm for the ABI calculation can result in underdiagnosis of PAD.

Patients with PAD have an increased prevalence of subclavian stenosis. For example, in a study of 492 patients undergoing coronary catheterization,[13] the prevalence of left-sided subclavian stenosis was 11.5% in patients with PAD compared with 1.5% in patients without PAD and with no risk factors for atherosclerotic disease. In patients with subclavian stenosis, measuring the brachial artery pressure in the arm with lower blood pressure will result in overestimation of the ABI.

ABI sensitivity is maximized by optimal calculation method

Maximizing the sensitivity of the ABI for PAD requires measurement of both brachial artery pressures and both the dorsalis pedis and posterior tibial artery pressures. The ABI can be calculated in one of several ways:

- A separate ABI may be calculated for each lower extremity artery, and the lowest ABI calculated may be considered the ABI.
- The posterior tibial and dorsalis pedis artery pressures for each leg can be averaged to determine the ABI for each leg.
- The highest of the posterior tibial and dorsalis pedis artery pressures in each leg can be used to calculate the ABI.

Of these methods, the first is the most sensitive for diagnosing PAD and the third is least sensitive.[14]

See the articles by Lyden and Joseph, starting on page S15, and by Begelman and Jaff, starting on page S22, for further discussion of ABI measurement.

PAD IS ASSOCIATED WITH CARDIOVASCULAR MORTALITY ACROSS MULTIPLE POPULATIONS

PAD confers a twofold to threefold increase in the risk

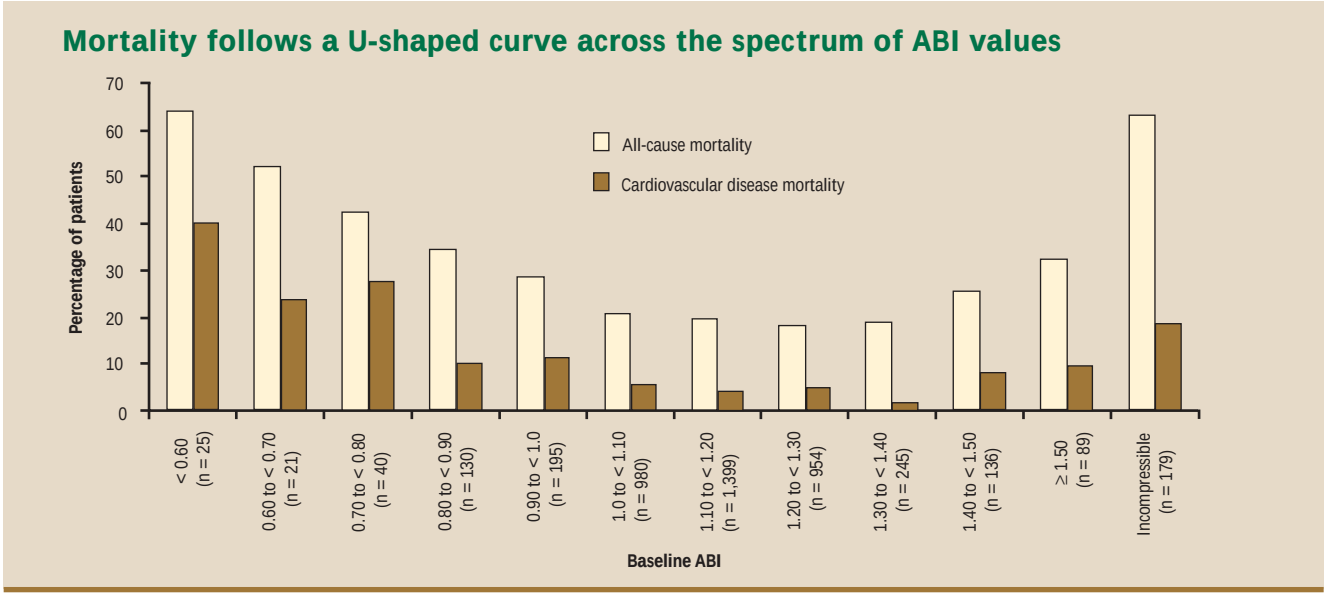

FIGURE 2. All-cause and cardiovascular mortality according to ankle-brachial index (ABI) group in the Strong Heart Study, 1988 to 1999 (N = 4,393).[15] Relative to subjects with normal ABIs (1.10 to < 1.20 and 1.20 to < 1.30), both all-cause and cardiovascular mortality are increased in subjects with borderline (0.90 to < 1.0) and low-normal (1.0 to < 1.10) ABIs as well as in subjects with ABIs of 140 or greater, creating a U-shaped curve. Reprinted, with permission, from reference 15.

of total mortality and mortality from cardiovascular disease.[15,16] Associations between PAD and cardiovascular mortality are independent of age, body mass index, cigarette smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure, fasting glucose levels, and history of angina, myocardial infarction, stroke, or other heart problems.[15,16] The association between a low ABI and increased cardiovascular mortality has been observed in multiple populations, including those with and without classic IC symptoms[17] and in both clinical and community settings. Associations between PAD and cardiovascular mortality have been reported over relatively short-term (3 to 4 years) and long-term (10 years) follow-up.

Among patients with PAD, more severe disease, as measured by the ABI, is associated with increased mortality. For example, mortality is higher in patients with an ABI less than 0.50 than in those with an ABI between 0.50 and 0.90.[18]

Based on the well-established association between PAD and increased risk of cardiovascular mortality, clinicians should apply global cardiovascular risk reduction strategies to all patients with PAD to reduce their risk of cardiovascular death and other ischemic events.

SIGNIFICANCE OF BORDERLINE ABI VALUES

Although the ABI threshold for defining the presence of PAD is typically 0.90, patients with ABI values between 0.90 and 1.10 may have early or mild lower extremity atherosclerosis. Because systolic pressures are normally 8% to 15% higher at the ankle than at the arm, persons with no lower extremity atherosclerosis have an ABI greater than 1.00. Thus, an ABI of 0.90 to 0.99 can be defined as "borderline" and an ABI of 1.00 to 1.09 can be defined as "low normal."

In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort of ethnically diverse community-dwelling men and women without clinically evident cardiovascular disease,[19] participants with borderline and low-normal ABI values (defined as above) had an increased burden of subclinical atherosclerosis compared with participants with normal ABI values (defined as 1.10 to 1.29). In this cohort of patients aged 45 to 84 years without clinically evident coronary or cerebrovascular disease, 3.7% of both men and women had an ABI less than 0.90, consistent with PAD. A borderline ABI (ie, 0.90 to 0.99) was present in 10% of women and 4% of men, and a low-normal ABI (ie, 1.00 to 1.09) was present in 36% of women and 21% of men. Compared with women with a normal ABI (1.10 to 1.29), women with a borderline ABI had significantly higher carotid artery atherosclerosis as measured by carotid intima-media thickness (IMT). Compared with men with a normal ABI, men with a borderline or low-normal ABI had significantly increased carotid artery atherosclerosis as measured by carotid IMT. Among men, those with a borderline ABI had significantly higher coronary artery calcium than those with a normal ABI.[19]

Consistent with these associations, earlier data from the Strong Heart Study[15] suggest that borderline and low-normal ABI values are associated with increased total mortality and cardiovascular mortality relative to normal ABI values (Figure 2).

In a separate analysis of participants in the Cardiovascular Health Study,[20] subjects with an ABI

of 0.91 to 1.00 had increased total mortality and increased cardiovascular mortality at 11-year follow-up compared with subjects with an ABI of 1.11 to 1.20, even after adjusting for age, sex, race, diabetes, serum creatinine, body mass index, cholesterol levels, smoking, systolic and diastolic blood pressures, C-reactive protein, antihypertensive medications, and prevalent coronary heart disease, stroke, and heart failure. Participants with an ABI of 1.01 to 1.10 also had higher rates of mortality than the reference ABI group (1.11 to 1.20), but the differences were not statistically significant after adjusting for the confounders listed above.[20]

ASSOCIATIONS BETWEEN ELEVATED ABI VALUES AND INCREASED MORTALITY

Traditionally, elevated ABI values (ie, > 1.30 or > 1.40) have been considered of little diagnostic worth since they indicate the presence of noncompressible lower extremity arteries that preclude accurate measurement of ankle systolic pressure. However, noncompressible arteries may indicate the presence of medial artery calcification, a condition common in patients with diabetes and chronic kidney disease that is associated with increased mortality.[21] In addition, individuals with ABI values greater than 1.40 have a higher prevalence of classic IC symptoms and atypical exertional leg symptoms relative to individuals with ABIs of 1.10 to 1.40, suggesting the possibility of an increased prevalence of PAD among individuals with elevated ABI values.[22]

Consistent with these findings, the Strong Heart Study[15] recently demonstrated a significant association between elevated ABI values (ie, > 1.40) and mortality. In this study of 4,393 American Indians followed prospectively for 8.3 years, a baseline ABI greater than 1.40 was associated with a 1.8-fold increase in total mortality and a twofold increase in cardiovascular mortality compared with a normal ABI, defined as 0.90 to 1.40 (Figure 2). These findings were observed in both diabetic and nondiabetic participants and were independent of atherosclerotic risk factors for cardiovascular disease. The magnitude of increased mortality risk with an ABI greater than 1.40 was similar to that with an ABI less than 0.90.[10]

Similar associations between ABIs greater than 1.40 and both total and cardiovascular mortality were observed in the Cardiovascular Health Study.[20] Thus, across the spectrum of ABI values, the association between the ABI and mortality appears to be U-shaped: patients with an ABI that is either less than 1.10 or greater than 1.40 have increased total and cardiovascular mortality (Figure 2).

PAD AND FUNCTIONAL IMPAIRMENT AND DECLINE

Persons with PAD have increased functional impairment and increased rates of functional decline compared with persons without PAD;[23,24] specifically, they have lower physical activity levels, slower walking speed, poorer balance, and poorer walking endurance.[24] This functional impairment affects quality of life and may lead to the increased prevalence of depressive symptoms that has been observed in patients with PAD.[25] Even patients with PAD who are asymptomatic have significantly impaired lower extremity function compared with those who do not have PAD.[12]

Variability in leg symptoms and impairment

Among PAD patients without classic symptoms of IC, some are asymptomatic, having no exertional leg symptoms, while others have exertional leg symptoms other than IC.[12] Reasons for this variability in leg symptoms are unclear. However, associated lower extremity diseases such as knee or hip arthritis, spinal disk disease, and spinal stenosis are more common in PAD patients with atypical leg symptoms than in those with classic IC, suggesting that comorbidities contribute to the spectrum of atypical exertional leg symptoms seen in patients with PAD.[11,12] In addition, some patients with PAD are asymptomatic because they have severely limited their walking activity to avoid exertional leg symptoms.[12]

Magnitude of functional decline associated with PAD

In a cohort study of 676 men and women with and without PAD who were followed prospectively for 2 years,[23] average annual declines in 6-minute walk performance were as follows:

- –73.0 feet for participants with a baseline ABI less than 0.50
- –58.8 feet for participants with a baseline ABI of 0.50 to less than 0.90
- –12.6 feet for participants with a baseline ABI of 0.90 to 1.50.

The between-group differences were statistically significant ($P = .019$). Among 470 men and women who were able to walk continuously for 6 minutes at baseline, those with a baseline ABI less than 0.50 were more than 12 times more likely than those with a normal baseline ABI (defined as 1.10 to 1.50) to lose the ability, at 2-year follow-up, to complete the 6-minute walk test without stopping.[23]

PAD patients with no symptoms or atypical symptoms are also at risk of decline

Perhaps because they have restricted their activity to avoid exertional leg symptoms, patients with asympto-

matic PAD are at particularly increased risk of functional decline relative to persons who do not have PAD. Compared with participants without PAD in the above prospective cohort study,[23] subjects with asymptomatic PAD had a greater mean decline in 6-minute walk performance at 2 years (–76.8 vs –8.67 feet per year, $P = .04$) and an increased odds ratio for becoming unable to walk for 6 minutes continuously (3.63; 95% confidence interval = 1.58 to 8.36, $P = .002$). Among PAD participants with atypical exertional leg symptoms in this cohort, those with exertional leg symptoms that sometimes began at rest had a greater mean decline in 6-minute walk performance compared with participants without PAD (–111 vs –8.67 feet per year, $P = .004$).

In addition, patients with PAD who are obese,[26] do not engage in self-directed exercise,[27] and have elevated levels of several inflammatory markers (high-sensitivity C-reactive protein, fibrinogen, serum amyloid A, and D-dimer)[28] are at increased risk for decline in physical function.

CONCLUSIONS

PAD is common and is expected to be increasingly prevalent as the US population lives longer with chronic disease. PAD is underdiagnosed by clinicians. Identifying PAD is important because of its association with increased cardiovascular mortality, functional impairment, and functional decline. Once identified, patients with PAD should be targeted for medical interventions to prevent cardiovascular events and functional decline, as detailed later in this supplement.

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