

Peripheral Arterial Disease

Identification and Implications

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Peripheral arterial disease (PAD) is most commonly a manifestation of systemic atherosclerosis in which the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque. Patients with PAD are at triple the risk of all-cause mortality and at more than 6 times the risk of death from coronary heart disease as those without the disease, yet PAD is probably the most underdiagnosed and least aggressively managed atherosclerotic disease. In the diagnosis of PAD, a detailed history and physical examination are extremely important, although limited by a lack of consistent sensitivity and specificity. Other office-based noninvasive tests, including the ankle-brachial index, can be easily performed to confirm the diagnosis and help stratify the risk. The ankle-brachial index correlates well with disease severity and functional symptoms and can also be used to assess disease progression and to predict cardiovascular and cerebrovascular mortality. Once diagnosed, risk factor modification, symptomatic relief, and secondary prevention strategies with antiplatelet agents form the core of medical management of PAD.

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Peripheral arterial disease (PAD) is most commonly a manifestation of systemic atherosclerosis in which the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque.¹ When the resulting obstruction impedes blood flow, symptoms may range from pain on exertion that is relieved by rest (claudication), the most classic manifestation of PAD,^{2,3} to pain at rest (critical limb ischemia).⁴ Epidemiologic studies have shown that approximately 2% to 3% of men and 1% to 2% of women 60 years and older have mild to moderate symptoms of claudication.⁵⁻⁸ The prevalence of PAD increases with advancing age, as approximately 20% of people older than 70 years have the disease.⁹ However, relatively few of these patients will develop severe complications in the peripheral vasculature.^{10,11} After 5 to 10 years, less than one third of patients with claudication report pain, less than 20% require vascular surgery, and less than 10% require amputation.^{10,12}

The most important implication of PAD in terms of morbidity and mortality

is that PAD serves as a strong surrogate marker for the severity of atherosclerotic disease in other vascular territories.¹³ The detection of coronary artery disease is directly related to the intensity of the evaluation for atherosclerotic disease. In patients with PAD, the prevalence of coronary artery disease ranges from 20% to 60% when based on medical history, physical examination, and electrocardiography and up to 90% in patients who have undergone coronary angiography.¹³⁻¹⁵ Likewise, cerebrovascular disease has been diagnosed in up to 40% to 50% of patients with PAD.^{13,14,16} Hence, the presence of atherosclerotic disease in 1 vascular bed should not be approached as a localized, isolated disease but as a marker for potentially insidious disease in other vascular regions.^{13,16,17} This concept becomes evident when the increased morbidity and mortality due to cardiovascular and cerebrovascular atherothrombotic events in patients with PAD is considered.

According to American Heart Association 2002 data, cardiovascular disease accounted for 60% of all deaths in the United States.¹⁸ Cardiovascular disease is the most common cause of death in patients with

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PAD, accounting for up to 75% of deaths.¹⁹ A 10-year mortality study showed that patients with large-vessel PAD have a 3.1-fold greater risk of all-cause mortality and a 6.6-fold greater risk of death from coronary heart disease than patients with no PAD.²⁰ Another 10-year study showed that patients with large-vessel PAD have a 3-fold excess cardiovascular morbidity at baseline compared with control subjects of the same sex.²¹ Recent publication of the Peripheral Arterial Disease Awareness, Risk and Treatment: New Resources for Survival study stresses the need for heightened awareness of PAD as a marker for atherosclerotic disease.²² In this multicenter, cross-sectional survey of 6979 patients, PAD was detected in 29% of the patient population.²² Among patients who had a diagnosis of PAD only, 55% were newly diagnosed, while among patients who had concurrent PAD and cardiovascular disease, 35% were newly diagnosed as having PAD.²² Eighty-three percent of the patients with a previous diagnosis of PAD were aware of the diagnosis, but only 49% of their physicians had recognized the PAD diagnosis at the time of screening ($P < .01$).²² Such discrepancy between patient and physician awareness of PAD was similar whether or not cardiovascular disease was present.²² The relative underdiagnosis of PAD in this study was accompanied by less intensive treatment of risk factors and thereby became a barrier to effective secondary prevention of atherosclerotic events.²²

DIAGNOSIS OF PAD

Despite the importance of early detection of atherosclerotic disease, the diagnosis of PAD is often overlooked during routine physical examinations.²³ Although cardiac histories are performed in most examinations (92%), routine histories concerning PAD are elicited by only 37% of internists.²⁴ Internists are also much more likely to routinely perform heart and lung examinations (95%) than to palpate the dorsalis pedis pulse (60%) or calculate an ankle-brachial index (ABI) (8%).²⁴ Even in the few patients who have symptoms of claudication, leg pain is often not mentioned because such complaints are attributed to growing old, arthritis, or muscular pain.^{25,26} Hence, physician and patient apathy, misconceptions, and lack of awareness concerning the serious morbidity and mortality associated with PAD are significant barriers to both PAD diagnosis and effective secondary prevention of vascular events.²² A detailed history and physical examination with special emphasis on the peripheral vasculature in addition to noninvasive (eg, ABI, exercise testing, segmental pulse pressures, ultrasonic duplex scanning) and, where necessary, invasive diagnostic testing are essential for the diagnosis of PAD.

HISTORY AND PHYSICAL EXAMINATION

History

A comprehensive patient history is a valuable first step in the examination of the patient with suspected PAD. Physical examination should include measurement of blood pressure, auscultation of pulses and bruits, palpation of pulses (bilateral), exploration of skin (tone,

texture, color, and temperature) and pattern of hair distribution, and presence of skin lesions or ulcers. Claudication, characterized by cramping, tightness, tiredness, or aching in the lower extremities, is brought on by exercise and relieved with rest.²⁶ Patients may describe Leriche syndrome, which includes claudication, impotency, and global atrophy of the lower extremities due to aortoiliac obstructive disease.²⁷ Other manifestations noted by patients may be hair loss on the feet and ankles as well as problems with toenail growth. The patient interview can provide important clues to the potential location of an arterial occlusion, since the discomfort occurs in the muscle group just distal to the obstruction.²⁶ For example, discomfort in the calf is characteristically due to superficial femoral artery atherosclerosis, whereas discomfort in the hip, thigh, or buttock is often due to aortoiliac occlusion.²⁶ The walking distance required to induce symptoms is reproducible because pain is consistently experienced at a certain distance, terrain, and grade.²⁶ Resolution of discomfort usually requires a 2- to 5-minute rest, although pain may be slower to resolve if the patient continues walking until severe pain develops.²⁶

Differential Diagnosis

A thorough history can help differentiate symptomatic PAD from symptoms of pseudoclaudication, which are due to lumbar canal stenosis or lumbar radiculopathy rather than PAD.²⁶ In pseudoclaudication, a variable level of exercise is required to produce symptoms; symptoms may occur with standing, and relief often requires taking weight off the extremity, a change in body position, or an extended rest period (10-20 minutes).²⁶ Other possible diagnoses that mimic claudication may include lower-pressure hydrocephalus, spinal cord arteriovenous fistula, and other primary vasculopathies. A patient's report of pain at rest or the presence of ischemic ulcerations or gangrene indicates severe arterial disease, referred to as *critical limb ischemia*.^{26,28}

Limitations of the Patient History

One important limitation of the medical history in patients with PAD is that many patients subsequently diagnosed as having PAD on the basis of noninvasive testing do not initially present with classic symptoms of claudication.^{3,22,29,30} One way the patient's history has been assessed has been with claudication questionnaires. This is exemplified by the Rose claudication questionnaire for detecting PAD.^{2,25} These questionnaires have been validated in clinical studies and at the present time are routinely used only for research purposes. In some patients who do report symptoms, the disease has already become severe, affecting multiple arterial segments, before the patient notices a problem.²⁶ Patients with claudication or even asymptomatic patients with reduced ABI (those not having classic claudication) are known to be at higher risk of cardiovascular events.¹⁰ If the physician is unsure whether the patient's history is consistent with claudication, further testing with ABI may be warranted because ABI is predictive of cardiovascular events.³¹

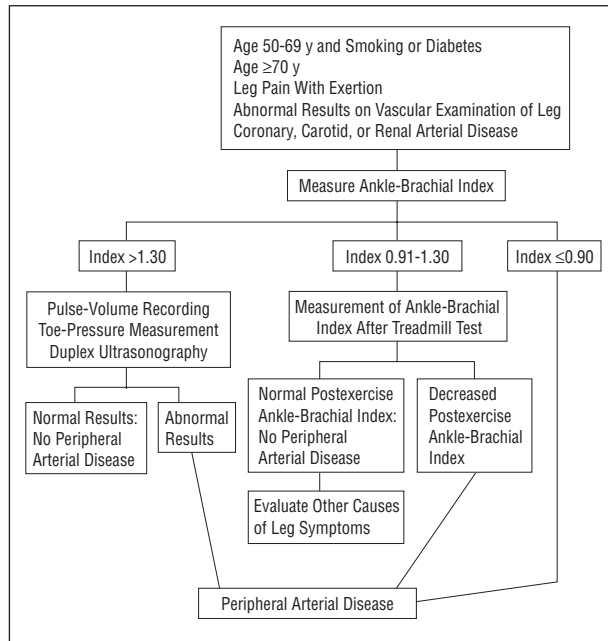


Figure 1. Examination of patients in whom peripheral arterial disease is suspected. Reprinted with permission from Hiatt.³³ Copyright 2001, Massachusetts Medical Society. All rights reserved.

Physical Examination

The lower extremities should be inspected for the obvious appearance of ulcers, gangrene, edema, and atrophy as well as for less obvious changes in nail thickness, absence of hair growth and perspiration, dry skin, and cool temperature.^{25,26} Careful palpation of pulses and auscultation of bruits can assist in determining the site(s) or severity of occlusive disease, particularly when this information is correlated with claudication distance and pain location.^{4,25} The femoral, popliteal, posterior tibial, and dorsalis pedis pulses should be palpated, comparing each pulse with the corresponding ipsilateral and radial pulses.^{25,26} Pulses should be graded consistently as absent, diminished, or normal (graded scale of 0-2).²⁵ Among the pulse irregularities seen in patients with PAD, dorsalis pedis abnormalities are the most prevalent; a portion of these, however, may be due to a fairly common congenital absence of the pedal pulse, the prevalence of which in the literature varies from 4.0% to 32.5%.³² However, the absence of a posterior tibial pulse is always abnormal.²⁶ Superficial femoral artery occlusion, the most common arterial lesion in claudication, is indicated by normal femoral and absent distal pulses.²⁵ Other combinations of pulse and bruit findings indicate disease in other areas. For example, a diminished femoral pulse coupled with a pronounced bruit over the iliac artery indicates significant iliac stenosis.²⁵ A normal popliteal pulse with no pedal pulses may be evident in patients with infrapopliteal occlusive disease.²⁵ In any case, the absence of pulses and presence of bruits may herald the presence of significant atherosclerotic disease.^{25,28}

Atherosclerosis is not a focal disease. For this reason, the physical examination should be conducted with attention to its multisystemic nature. Assessment of the circulatory and cardiovascular systems should begin with

blood pressure (BP) measurement in both arms.²⁶ If subclavian or brachiocephalic arterial disease is present, a discrepancy in BP may be detected and the higher of the 2 values should be used.²⁶ Further examination of the cardiovascular system may disclose signs of subclavian or cervical (both carotid and vertebral) bruits, abdominal aneurysm, cardiac murmurs, arrhythmia, or other conditions that may impact patient care.^{25,26}

Limitations of the Physical Examination

The sensitivity, specificity, and predictive values of traditional clinical evaluation methods, such as pulse palpation, for the detection of PAD were compared in the San Diego Lipid Research Clinics Program Prevalence Study population.³⁰ Overall, it was found that claudication and an abnormal femoral pulse were very specific for PAD diagnosis (95%-99%) but were not sensitive ($\leq 20\%$).³⁰ The absence of a dorsalis pedis pulse was fairly sensitive (50%) but less specific (73.1%) and had a very low positive predictive value (17.7%).³⁰ The optimal combination of sensitivity (71.2%) and specificity (91.3%) and moderate positive predictive value (48.7%) was found with an abnormal posterior tibial pulse.³⁰ However, according to these findings, use of the posterior tibial pulse alone would miss a diagnosis of PAD in about 30% of patients, and fewer than half of patients with the abnormal pulse would actually have PAD.³⁰ Although the physical examination provides important qualitative information and is critical to overall patient treatment, additional noninvasive testing ensures the diagnosis and aids in risk stratification of patients with suspected PAD⁴ (**Figure 1**³³).

ANKLE-BRACHIAL INDEX

The ABI is a simple, inexpensive, noninvasive tool that correlates well with angiographic disease severity and functional symptoms.^{26,34-36} In the normal circulation, systolic BP (SBP) is amplified down the lower limbs such that the ankle SBP is slightly greater than or equal to the brachial SBP.⁴ When the measured ankle SBP is divided by the brachial SBP, the resulting ABI is normally between 1.0 and 1.3.³³ However, in areas of arterial narrowing, SBPs distal to areas of impeded flow are reduced.⁴ In PAD, ankle SBPs fall below brachial SBPs and the ABI is reduced to less than 1.^{4,34} An ABI less than 0.90 is considered diagnostic of PAD.^{25,26,33} Mild disease correlates with an ABI ranging from 0.70 to less than 0.90, whereas moderate disease correlates with an ABI ranging from 0.40 to less than 0.70, and severe disease is associated with an ABI less than 0.40.²⁶ Studies evaluating the diagnostic accuracy of the ABI have demonstrated that it can differentiate between normal and angiographically diseased limbs with a sensitivity of 97% and a specificity of 100%³⁷ and that the resting ABI is a significant predictive variable for the severity of angiographic disease.³⁸

ABI Technique

The ABI can be measured in a primary care or hospital setting, since the equipment required is inexpensive and por-

table^{26,33,39} (**Figure 2**). An ordinary BP cuff is positioned over the upper arm and inflated above SBP. A Doppler ultrasonic velocity signal probe is then placed over the brachial artery to detect the resumption of blood flow with cuff deflation. Measurement of SBP is repeated on the other arm. If a discrepancy exists, the higher of the 2 SBP values is used. For measurement of ankle SBP, the BP cuff is moved to the ankle and blood flow resumption is detected with the Doppler probe over the posterior tibial artery and then over the dorsalis pedis artery. Again, if there is a discrepancy in SBP between the 2 arteries, the higher value is used. The process should be repeated for the other leg. The lowest ABI between both legs is the ABI that stratifies the patient's risk for a poor outcome.

Limitations of ABI

The major limitation of the ABI to establish the diagnosis of PAD is that calcific tibial peroneal arteries may be rendered noncompressible, especially in patients with diabetes, resulting in erroneously high ABI values.⁴ Because there is poor correlation between calcification and severity of atherosclerosis,⁴ the ABI is generally unreliable in this situation. Patients with incompressible arteries should be referred to an accredited vascular laboratory for measurement of a toe-brachial index or other noninvasive testing.^{25,26}

Furthermore, the ABI is dependent on the brachial pressure being a true measure of central systolic pressure. This may not be the case in patients with bilateral subclavian artery stenosis, occasionally seen in diabetic patients or those with advanced vascular disease.²⁵ Other limitations of the ABI that should be recognized when surgery is considered include its inability to localize arterial lesions accurately⁴⁰ and the lack of an association between ABI and the predicted potential for wound healing.⁴¹

ABI to Monitor Disease Progression

Changes in the ABI over time can also be used to monitor disease progression.⁴² In a series of 508 patients studied for the natural course of PAD, there was only modest categorical progression of disease; however, more quantitative progression occurred than was evident from categorical progression. During an average 4.6-year follow-up, quantitative progression of PAD was evidenced by a mean ABI change of -0.02 (95% confidence interval, -0.031 to -0.007).⁴² With regard to the use of the ABI as a monitoring tool for individual patients, changes in the ABI that exceed ± 0.15 are considered to be outside the range of experimental error and indicate disease progression.⁴ An improved ABI suggests enhanced perfusion via collateral vessels, whereas deterioration marks disease progression or decreased perfusion secondary to problems with a revascularization procedure.⁴

ABI to Assess Functional Capacity

Several studies have shown that the ABI is independently associated with impaired lower extremity functioning, even in asymptomatic patients. The Women's Health and Aging Study, an observational study of dis-

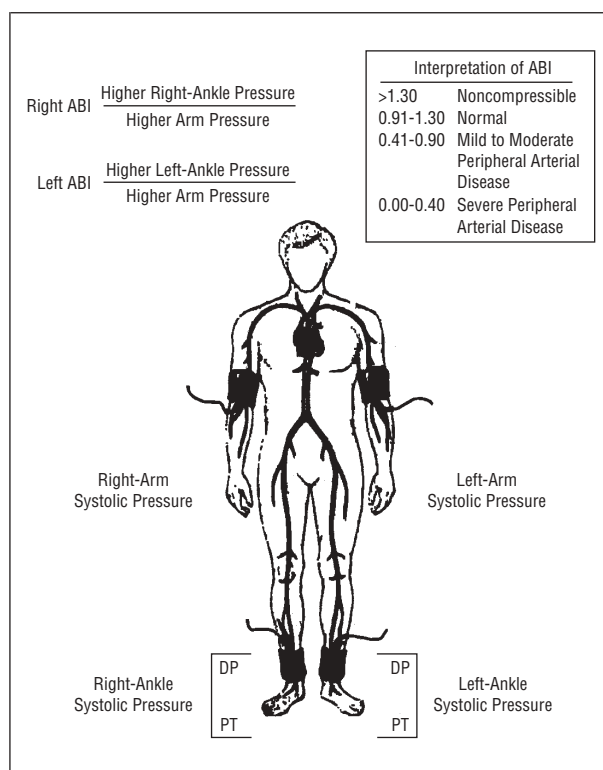


Figure 2. Measurement of the ankle-brachial index (ABI). DP indicates dorsalis pedis artery; PT, posterior tibial artery. Reprinted with permission from Hiatt.³³ Copyright 2001, Massachusetts Medical Society. All rights reserved.

abled women 65 years or older living in and around Baltimore, Md, used the ABI as a measure of lower extremity function.⁴³ Decreasing ABI values were associated with progressive worsening in functional scores, even after adjustment for age, sex, race, smoking status, and comorbidities.⁴³ In asymptomatic women, lower ABI scores correlated with slower walking velocity, poorer standing balance score, slower time to arise, and fewer blocks walked per week.⁴³ In the Study of Osteoporotic Fractures, the relationship between ABI (≤ 0.90) and lower extremity function was evaluated in 1492 women 65 years or older. Results showed that 82 patients (5.5%) had an ABI less than 0.90, consistent with PAD; of them, 67 (82%) did not manifest the typical symptoms of claudication.⁴⁴ Patients with an ABI less than 0.90 had significantly lower hip abduction force, knee extension force, walking velocity, and number of blocks walked than those with an ABI of 0.90 or greater.⁴⁴ Other studies have shown that progressive PAD is associated with muscle fiber loss, poorer leg strength, and slower walking velocity.³⁴ Patients with claudication and very low ABI are at increased risk of disease progression, leading to gangrene, ulcers, and amputation.^{8,34}

ABI as a Predictor of Cardiovascular Morbidity and/or Mortality

The ABI is well established as an independent predictor of cardiovascular morbidity and mortality. In the Cardiovascular Health Study, 5888 adults 65 years or older were monitored for cardiovascular events after establishing a baseline cardiovascular disease status and ABI mea-

Table 1. Adjusted Relative Risk for Mortality for Levels of Ankle-Brachial Index*

Categories of ABI	RR	95% CI	P Value
<0.4	3.35	2.16-5.20	<.001
0.4-0.85	2.02	1.34-3.02	<.001
>0.85	1.00	Reference	

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; RR, relative risk.

*Adjusted for all baseline variables. Reprinted from McKenna et al.⁴⁸ Copyright 1991, with permission from Elsevier.

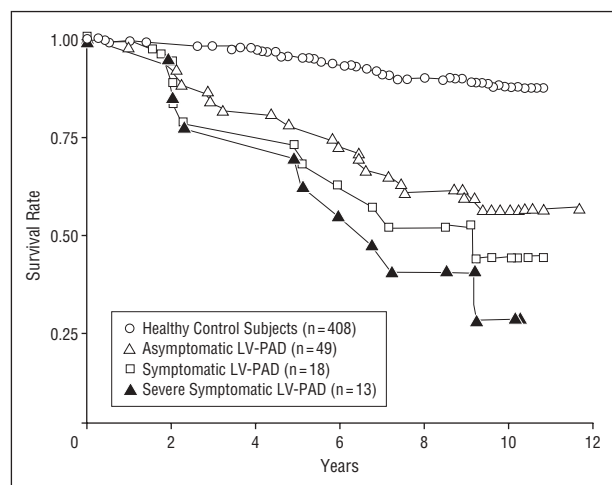


Figure 3. Kaplan-Meier survival curves based on mortality from all causes among healthy control subjects and subjects with symptomatic or asymptomatic large-vessel peripheral arterial disease (LV-PAD). Reprinted with permission from Criqui et al.²⁰ Copyright 1992, Massachusetts Medical Society. All rights reserved.

surement.⁴⁵ At 6-year follow-up, the age- and sex-adjusted relative risk (RR) of ischemic events, given a low ABI for patients with prevalent cardiovascular disease at baseline, were as follows: total mortality, 1.50; cardiovascular disease mortality, 2.04; total myocardial infarction (MI), 1.61; and PAD, 6.52 (all with $P < .01$).⁴⁵ For patients with no prevalent cardiovascular disease at baseline, the 6-year age- and sex-adjusted RR of events, given a low ABI, were as follows: total mortality, 2.44; cardiovascular disease mortality, 2.86; total MI, 2.02; angina, 1.64; congestive heart failure, 2.30; and PAD, 10.59 (all with $P < .01$).⁴⁵ Crude mortality rate at 6 years was highest in patients who had cardiovascular disease and a low ABI (<0.90) at baseline (32.3%; $P < .90$) and was lowest in patients with neither of these risk factors at baseline (8.7%; $P < .01$).⁴⁵ A significant progressive decline in survival was seen with each 0.1 decrement in ABI that was less than 1.0.⁴⁵

Data from the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial⁴⁶ confirm these findings in a cohort of 2180 patients with PAD and ABI data.⁴⁷ For each 0.1 decrement in ABI measurement, there was a corresponding 10.2% increase in RR for ischemic stroke, nonfatal MI, or vascular death ($P = .04$).⁴⁷ In addition, patients with an ABI less than or equal to 0.5 had a higher annual event rate than patients with an ABI greater than 0.5 (5.4% vs 4.1%).⁴⁷ Results from another study showed that mortality from cardiovascular dis-

ease was highest among patients with an ABI less than 0.40 and lowest among patients with an ABI of 0.85 to 1.50.⁴⁸ After adjusting for age, sex, race, risk factors, and history of coronary disease, an ABI of 0.40 to 0.85 was associated with a more than 2-fold increase in mortality, and an ABI less than 0.40 was associated with a more than 3-fold increase, compared with patients with an ABI greater than 0.85 (**Table 1**).⁴⁸

Similar findings concerning the relationship between ABI and morbidity and mortality were found in the Edinburgh Artery Study of 1592 men and women 55 years and older.³¹ An ABI less than 0.9 was associated with an increased risk of total mortality (RR, 1.79; $P \leq .001$), cardiovascular death (RR, 2.29; $P \leq .001$), fatal MI (RR, 2.21; $P \leq .01$), and nonfatal stroke (RR, 1.91; $P \leq .05$)³¹ during a period of 5 years.

ABI in Asymptomatic PAD

A subgroup of patients have been found to have a reduced ABI but no complaints of claudication pain. Results of several studies highlight the importance of the ABI as a predictor of cardiovascular or all-cause mortality in these asymptomatic patients.^{20,49,50} A 10-year follow-up of 67 patients with an established diagnosis of PAD, based on an ABI of 0.80 or less, showed a dramatic increase in rate of mortality of both men (61.8%) and women (33.3%) with PAD when compared with men (16.9%) and women (11.6%) without the disease.²⁰ After adjusting for age, sex, and other cardiovascular risk factors, the RR of all-cause death, death from cardiovascular disease, and death from coronary heart disease was 3.1, 5.9, and 6.6, respectively, when compared with those with no evidence of disease. After excluding subjects with a history of cardiovascular disease at baseline, the RR of death from coronary heart disease did fall from 6.6 to 4.3; however, this still represents a statistically significant elevation of risk. These findings confirm that PAD (as diagnosed by ABI) is a strong and independent predictor of subsequent mortality, especially deaths due to coronary heart disease. In terms of risk of mortality and degree of PAD symptoms, results showed that unilateral, moderately severe, asymptomatic disease and disease isolated to the posterior tibial artery increased the risk of death from coronary heart disease and cardiovascular disease from 3- to 6-fold when compared with patients without evidence of disease. This suggests that substantial risk exists for patients who would not usually demand clinical attention. Kaplan-Meier survival curves based on mortality from all causes among normal subjects and subjects with symptomatic and asymptomatic large-vessel PAD confirm the overall poor prognosis with advancing disease and the alarmingly high risk in asymptomatic patients whose disease would not be detected clinically (**Figure 3**).²⁰

The Systolic Hypertension in the Elderly Program study was originally designed to study the effect of treatment in patients with systolic hypertension, but it also provides mortality data for a subset of 1287 patients without evidence of cardiovascular disease or symptoms of PAD.⁴⁹ At 4 years of follow-up, the odds of cardiovascular and total mortality in patients with an ABI less than 0.90 were approximately 3 times the odds in patients with ABI of 0.90

Table 2. Relationship Between Peripheral Arterial Disease and Total Mortality*

Source	Duration of Study, y	Cohort Description	RR for Total Mortality for PAD vs Control Subjects (95% CI)	Adjusted RR or Relative Hazard for Mortality for PAD vs Control Subjects (95% CI)
Criqui et al, ²⁰ 1992	10	565 Community-dwelling men and women	Men, 3.3 (1.9-6.0); women, 2.2 (1.2-5.3)	All subjects, 3.1 (1.9-4.9)
Vogt et al, ⁵¹ 1993	13	1027 Women and 903 men identified in a blood flow laboratory	Men, 2.23 (1.99-2.49); women, 2.59 (2.29-2.92)	Men, 1.8 (1.5-1.9); women, 1.3 (1.2-2.0)
Ogren et al, ⁵² 1995	10	470 Men aged 68 y from Malmo, Sweden	2.4 (2.2-2.8)	2.0 (1.3-3.0)
Leng et al, ³¹ 1996	5	Men and women aged 55-74 y, randomly selected from 11 general medicine practices	1.79 (1.32-2.43)	1.58 (1.14-2.18)
Newman et al, ⁴⁹ 1997	4	1267 Community-dwelling men and women aged \geq 60 y without clinical cardiovascular disease at baseline	2.79 (1.88-4.13) (Age- and sex-adjusted)	2.76 (2.33-3.20)

Abbreviations: CI, confidence interval; PAD, peripheral arterial disease; RR, relative risk.

*PAD was measured with the ankle-brachial index in these studies. Reprinted from McDermott.³⁴ Copyright 1999, with permission from Elsevier.

or greater.⁴⁹ The significance of this increase in mortality is further illustrated by the fact that total mortality in the patients with subclinical PAD (ABI <0.90) approached that of patients with a history of cardiovascular disease (17% vs 20%).⁴⁹ In a separate study of 2023 middle-aged asymptomatic men without coronary heart disease, a reduced ABI was an independent predictor of coronary and cardiovascular mortality.⁵⁰ At 10 years, the RR for all-cause (2.77; $P = .01$), cardiovascular (4.16; $P = .01$), and coronary (4.97; $P = .006$) mortality were increased for subjects with an ABI less than 0.90 vs those with a normal ABI.⁵⁰ Hence, the evidence strongly suggests that the value of the ABI to predict cardiac events and mortality extends to the asymptomatic patient who would not normally present for medical attention.

Given these data and those from other studies in symptomatic and asymptomatic patients with PAD, strong evidence now argues for the more widespread use of the ABI in routine clinical practice^{20,31,34,49,51,52} (**Table 2**).

ABI and Stroke

At least 2 studies have specifically examined the ability of ABI measurement to predict ischemic stroke.^{53,54} In the Atherosclerosis Risk in Communities study, 14839 adults aged 45 to 64 years were followed up for more than 7 years for stroke incidence.⁵³ The incidence of ischemic stroke was inversely related to the ABI, with the rate of stroke in patients with ABI less than 0.80 (6.5 events per 1000 person-years) being approximately 5 times greater than the rate in patients with an ABI of at least 1.20 (1.2 events per 1000 person-years).⁵³ However, the significance of ABI as a predictor of ischemic stroke was reduced once the hazard rates were adjusted for other risk factors.⁵³ This is congruent with results from other studies that indicate the link between PAD and stroke to be weaker than the link between PAD and coronary artery disease.²⁵ In the Honolulu Heart Program, an age-adjusted 2-fold excess risk of stroke was noted in men with an ABI less than 0.90 compared with those having an ABI of 0.90 or greater ($P < .01$).⁵⁴ The relationship between ABI and stroke was similar and statistically significant with or without risk factors such as diabetes and hypertension ($P < .05$).

OTHER NONINVASIVE TECHNIQUES

Exercise Testing

Measurement of ABI coupled with exercise testing can provide additional information on the dynamics of claudication.⁴ Exercise testing may be especially useful in patients with claudication symptoms who have a normal ABI or normal pulse at rest.^{26,37} In healthy subjects, ankle SBP is maintained during moderate exercise.⁴ However, in patients with claudication, ankle SBP falls to low or undetectable levels with low-level workloads and returns to baseline after a few minutes of rest.⁴ A standard exercise treadmill can be used for this assessment by allowing the patient to walk at a standard speed and grade for a predetermined period (ie, 2 mph at 12% incline for 5 minutes) or until claudication develops.^{4,25} Immediately after exercise, the patient is asked to lie in a supine position and the ankle SBP is measured.⁴ In patients with PAD, the post exercise ABI will drop significantly.²⁶ If the exercise produces pain or discomfort while the ABI remains normal or unchanged, PAD is not the cause of the symptoms.^{25,26}

An alternative method of exercise testing that requires no special equipment is active pedal plantarflexion (heel raises).^{55,56} The patient stands facing a wall while using light fingertip support for balance. Keeping knees straight, the patient raises his or her heels as high as possible and then immediately lowers them; the cycle is repeated 30 to 50 times. As with treadmill testing, the ankle SBP is measured with the patient in a supine position immediately after completing the exercise sequence.^{55,56} Excellent correlation of ABI values obtained by either treadmill exercise testing or pedal plantarflexion has been demonstrated in 2 separate comparative evaluations.^{55,56} Pedal plantarflexion is an alternative to the treadmill exercise test.^{55,56}

Segmental Pressures and Pulse Volume Recordings

When further detection, localization, or characterization of potential arterial lesions is necessary, other noninvasive or invasive tests are required. The measurement of seg-

mental pressures and pulse volume recordings can localize occlusions of limb segments by comparing the differences in the SBPs and the magnitude and contour of pulse volumes to segments located most proximally and distally to the site of occlusion.^{4,25} When used in combination, segmental pressures and pulse volume recordings have demonstrated 95% accuracy as compared with angiography.²⁵ An alternative to pulse volume recording is Doppler velocity waveform analysis,^{4,25} in which a continuous-wave Doppler probe is used over multiple arterial segments to detect the blood flow velocity and the velocity patterns.²⁵ Within each pulse cycle, the probe can detect the quality and magnitude of the triphasic flow pattern (forward, reverse, and late forward flow) to detect any pressure- or flow-reducing lesions.⁴ Disadvantages of Doppler velocity waveform analysis include a high dependence on operator technique and the inability to pinpoint the artery being studied.^{4,25} However, both Doppler velocity waveform analysis and pulse volume recording are particularly useful in assessing diabetic patients with incompressible arteries, since false elevations in the ABI and segmental pressures are expected.^{4,25}

Ultrasonic Duplex Scanning

When it is necessary to localize occlusions more precisely than arterial segments or to more fully characterize the severity and morphologic features of occlusions, ultrasonic duplex scanning is a noninvasive preliminary alternative to angiography.²⁵ Duplex ultrasound can provide information concerning artery wall thickness, degree of flow turbulence, vessel morphologic characteristics, and changes in blood flow velocity in areas of stenosis.³⁵ The accuracy (specificity) of the duplex ultrasound is very high (92%-98%), although its sensitivity for assessing stenosis is variable.³⁵ Several investigators have noted that its sensitivity for detecting lesions in the iliac and superficial femoral arteries is higher than for detecting stenosis in the popliteal or common femoral arteries.³⁵ In contrast, duplex ultrasound may be more sensitive than invasive angiography for detecting patent distal vessels.³⁵ Because of the relative expense of duplex ultrasound compared with other noninvasive tests, its use should be reserved for patients for whom detailed knowledge of vessel morphologic and flow characteristics are required.³⁵ Appropriate applications for duplex ultrasound include preparation for planned angioplasty or surgical procedure, detection of restenosis after an endovascular procedure, or surveillance of femoropopliteal or distal saphenous vein grafts for detection of myointimal lesions before graft failure.^{4,26} Other noninvasive imaging techniques such as magnetic resonance angiography and spiral computed tomography may be used in addition to or instead of duplex scanning to assess certain lesions before surgical management.²⁵ Although noninvasive imaging studies are becoming more commonly used preoperatively, catheter-based angiography is still considered the gold standard.

RISK REDUCTION

Once patients with clinical or subclinical PAD are identified, the primary aim of medical management is to re-

duce morbidity and mortality through aggressive risk factor reduction, initiate antiplatelet therapy, and provide symptomatic relief where possible.^{25,57}

Risk Factor Modification

Risk factors for developing PAD include advanced age, cigarette smoking, diabetes mellitus, an elevated homocysteine level, hyperlipidemia, and hypertension. Risk factor reduction is of utmost importance in patients with PAD, as the risk factors for the development of PAD are common to the development of other manifestations of atherothrombotic disease, including MI and stroke.^{4,17,22,33} Hence, any modification of a risk factor for the purpose of attenuating PAD should also be beneficial in reducing the risk of coronary or cerebrovascular disease.¹⁷

Antiplatelet Therapy

Antiplatelet therapy for prevention of secondary vascular events is the cornerstone of pharmacologic intervention in PAD. Antiplatelet agents have reduced the risk of nonfatal MI, ischemic stroke, and vascular death in patients with atherosclerotic cardiovascular disease by approximately 25%.^{33,58} The Antiplatelet Trialists' Collaboration reported a 23% reduction in serious vascular events in patients diagnosed as having PAD and treated with antiplatelet therapy when compared with controls ($P = .004$).⁵⁸ Although many of the patients in the meta-analysis were receiving aspirin, the use of aspirin for the secondary prevention of ischemic events in patients with PAD has not received approval from the Food and Drug Administration because of a lack of sufficient evidence⁵⁹; however, its use in these patients recently received guideline recommendation.⁵ Although aspirin may reduce serious vascular events, most high-risk patients remain at risk of ischemic vascular events.⁵⁸ Evidence indicates that clopidogrel is slightly more effective than aspirin.^{46,58}

The CAPRIE trial randomized 19 185 patients with recent MI, recent stroke, or PAD (6452 patients) to receive clopidogrel, 75 mg once daily, or aspirin, 325 mg once daily, for 1 to 3 years.⁴⁶ Overall, there was an 8.7% risk reduction in favor of clopidogrel in the composite primary end point (ischemic stroke, MI, or vascular death) when compared with aspirin ($P = .04$).⁴⁶ Although CAPRIE was not powered to assess differences between subgroups, when patients with PAD were considered separately, the RR for the risk of a primary end point event was reduced by 23.8% (4.9% vs 3.7%) in favor of clopidogrel.⁴⁶

Combination antiplatelet therapy using 2 synergistic yet mechanistically different agents may further reduce platelet activity. Results of the recent Clopidogrel in Unstable Angina to Prevent Recurrent Events and Percutaneous Coronary Intervention—Clopidogrel in Unstable Angina to Prevent Recurrent Events trials have shown that combination antiplatelet therapy using clopidogrel and aspirin reduces the risk of ischemic events by 20% to 30%, depending on end points, in patients with acute coronary syndromes, including those undergoing percutaneous coronary interventions.^{60,61} The efficacy and safety of this combination in the PAD population will need to be clarified by future clinical research. Until that time, among the an-

tiplatelet agents, clopidogrel remains the only one to have a Food and Drug Administration–approved indication for use in reducing ischemic events (MI, stroke, and vascular death), in several vascular territories, in patients with established atherosclerotic disease including recent stroke, recent MI, or established PAD.

SYMPTOMATIC RELIEF

Exercise Rehabilitation Therapy

Exercise rehabilitation therapy has favorable effects on cardiovascular risk factors in addition to its known potential to improve symptoms of claudication. Cardiovascular benefits of regular exercise include improvement in glucose metabolism, reduction in levels of cholesterol and triglycerides, and enhancement of smoking cessation.²⁵ For patients with claudication symptoms, exercise rehabilitation therapy is one of the most effective medical therapies.⁴ Exercise has been associated with an average 179% increase in initial claudication distance (ie, the distance to onset of claudication pain), a 122% increase in maximal walking distance on the treadmill, and improvements in community-based walking ability, functional status, quality of life, total caloric expenditure, and physical functioning.²⁵ Patients should be counseled that exercise must be continued for its effects to be maintained.³³ Given that patient motivation may be a significant factor limiting success, the most successful programs stress regularity and consistency over intensity.⁴ Of note, a Current Procedural Terminology code (93668) is available for supervised exercise rehabilitation treatment for patients with claudication.⁶²

Pharmacologic Agents

Two pharmacologic agents, pentoxifylline and cilostazol, while not indicated for secondary prevention of atherosclerotic vascular events, may be useful for the management of disabling symptoms due to claudication.⁶³ Pentoxifylline, a methylxanthine derivative, has multiple pharmacologic properties, including rheologic activity and a weak antithrombotic effect.⁵ Some clinical trials have shown that pentoxifylline improves maximal treadmill walking distances.^{33,64} Unfortunately, this effect has generally been modest (a 12% increase) and has not differed statistically significantly from placebo in all trials.^{5,33,64,65} For these reasons, the American College of Chest Physicians currently recommends that pentoxifylline not be used routinely in patients with claudication.⁵

Cilostazol, a type 3 phosphodiesterase inhibitor, is the most recent addition to Food and Drug Administration–approved products for claudication.⁶³ Initial claudication distances and absolute claudication distances have been approximately doubled with cilostazol as compared with placebo in randomized, controlled clinical trials.⁶⁶ However, patients with arrhythmias or a recent history of MI, revascularization, or unstable angina were excluded from the claudication clinical trials.⁶⁶ Other beneficial effects include significant improvements in functional status, quality of life, and ABI.⁶⁶ Cilostazol has not been associated with severe hematologic adverse events

or with the increased cardiac mortality seen with other phosphodiesterase inhibitors.⁶⁶ Cilostazol is contraindicated for use in patients with heart failure, since the long-term effects of this agent in this population are unknown.⁶⁶ Thus, cilostazol may improve pain-free walking distance for patients in whom lifestyle modifications are insufficient to control symptoms and/or in whom revascularization is not an option.

CONCLUSIONS

Peripheral arterial disease, a manifestation of atherosclerotic disease, is often asymptomatic, yet its presence is an important marker for atherosclerotic disease in other vascular beds. Patients with PAD are at up to 6-fold greater risk of death from coronary heart disease and 3-fold greater risk of all-cause mortality than patients with no evidence of disease. Prospective studies evaluating mortality rates in PAD have also demonstrated that the risk of mortality increases with age^{10,12} and severity of PAD^{12,13,20} and is higher in men than in women.^{13,20} Overall, cumulative 5- and 10-year mortality rates for men with PAD were 42% and 65%, respectively, in a 15-year follow-up cohort¹²—a rate significantly greater than expected for an age-adjusted US population without PAD (10-year mortality, <30%).^{12,17} Despite these disturbing numbers, physician awareness of the diagnosis of PAD is relatively low. Patients with PAD are not always treated as aggressively with risk-factor modification and antiplatelet therapies as are patients with other manifestations of atherosclerotic disease.

Peripheral arterial disease can be easily and inexpensively diagnosed by measuring the ABI. A low ABI correlates with a greater risk of atherothrombotic events in other vascular beds. Even asymptomatic patients with reduced ABI values are at increased risk for cardiovascular morbidity and mortality. Treatment strategies for patients with diagnosed PAD include risk-factor modification, secondary prevention with an antiplatelet agent, and symptomatic relief. The measurement of the ABI in clinical practice may uncover lower extremity atherosclerotic disease, which portends an increased risk of cardiovascular events, and should be considered routine in selected populations such as those older than 70 years or older than 50 years with diabetes or a history of smoking.

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