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PERIPHERAL ARTERIAL DISEASE:

RECOGNITION AND CONTEMPORARY MANAGEMENT

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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-

* Dr. McDermott reported that she has received honoraria for educational activities from the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership.

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-

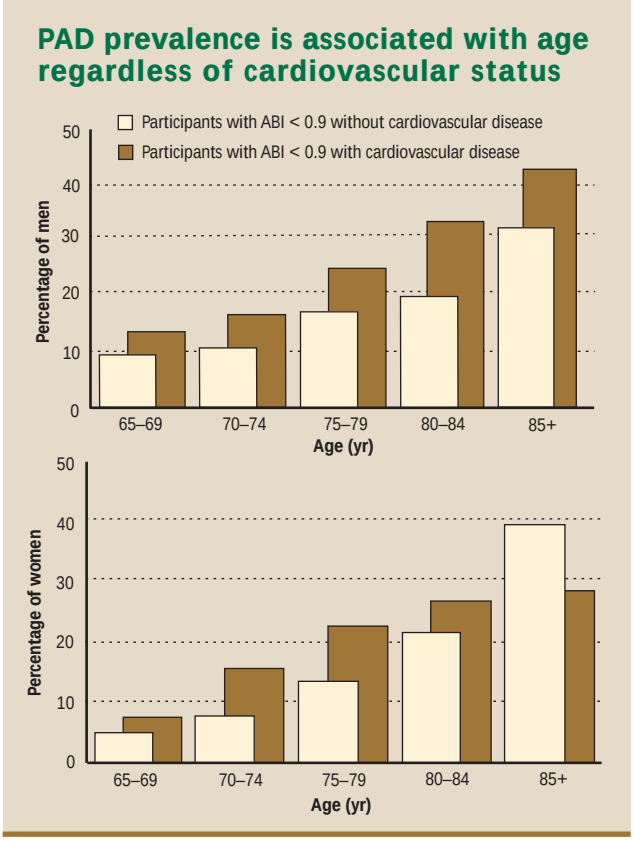

FIGURE 1. Prevalence of peripheral arterial disease (ankle-brachial index [ABI] < 0.9) by age group among community-dwelling men (top) and women (bottom) in the Cardiovascular Health Study (N = 5,084).[7] Reprinted, with permission, from reference 7.

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

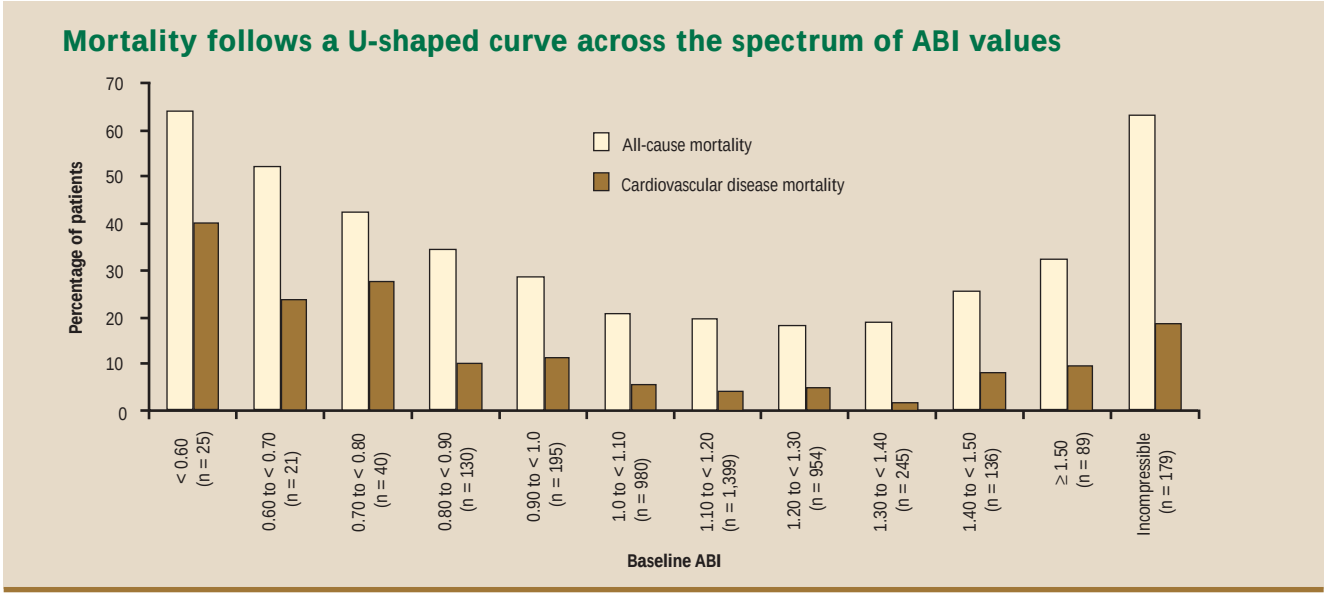

FIGURE 2. All-cause and cardiovascular mortality according to ankle-brachial index (ABI) group in the Strong Heart Study, 1988 to 1999 (N = 4,393).[15] Relative to subjects with normal ABIs (1.10 to < 1.20 and 1.20 to < 1.30), both all-cause and cardiovascular mortality are increased in subjects with 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.

REFERENCES

1. American Heart Association. Heart disease and stroke statistics—2006 update. Dallas, TX: American Heart Association; 2006. Available at: www.americanheart.org/presenter.jhtml?identifier=1928.
2. Rose GA. The diagnosis of ischemic heart pain and intermittent claudication in field surveys. Bull World Health Organ 1962; 27:645–658.
3. Reunanen A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. Acta Med Scand 1982; 211:249–256.
4. De Backer G, Kornitzer M, Sobolski J, Denolin H. Intermittent claudication: epidemiology and natural history. Acta Cardiol 1979; 34:115–124.
5. Smith WCS, Woodward M, Tunstall-Pedoe H. Intermittent claudication in Scotland. In: Fowkes FGR, ed. Epidemiology of Peripheral Vascular Disease. London, UK: Springer-Verlag; 1991:109–115.
6. Fowkes FG, Housley E, Cawood EH, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991; 20:384–392.
7. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Circulation 1993; 88:837–845.
8. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286:1317–1324.
9. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation 1985; 71:516–522.
10. McDermott MM, Mehta S, Greenland P, et al. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. Arch Intern Med 1999; 159:387–392.
11. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States. Results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004; 110:738–743.
12. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA 2001; 286:1599–1606.
13. English JA, Carrell ES, Guidera SA, Tripp HF. Angiographic prevalence and clinical predictors of left subclavian stenosis in patients undergoing diagnostic cardiac catheterization. Catheter Cardiovasc Interv 2001; 54:8–11.
14. McDermott MM, Criqui MH, Liu K, et al. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease. J Vasc Surg 2000; 32:1164–1171.
15. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality. The Strong Heart Study. Circulation 2004; 109:733–739.
16. Newman AB, Tyrrell KS, Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. J Am Geriatr Soc 1997; 45:1472–1478.
17. Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol 1996; 25:1172–1181.
18. McDermott MM, Feinglass J, Slavensky R, Pearce WH. The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. J Gen Intern Med 1994; 9:445–449.
19. McDermott MM, Liu K, Criqui MH, et al. Ankle-brachial index and subclinical cardiac and carotid disease: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2005; 162:33–41.
20. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006; 113:388–393.
21. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. Diabetologia 1988; 31:16–23.
22. Wang J, Criqui MH, Denenberg JO, McDermott MM, Golomb BA, Fronek A. Exertional leg pain in patients with and without peripheral arterial disease. Circulation 2005; 112:3501–3508.
23. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004; 292:453–461.
24. McDermott MM, Greenland P, Liu K, et al. The ankle-brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med 2002; 136:873–883.
25. Arseven A, Guralnik JM, O'Brien E, et al. Peripheral arterial disease and depressed mood in older men and women. Vasc Med 2001; 6:229–234.
26. McDermott MM, Criqui MH, Ferrucci L, et al. Obesity, weight change, and functional decline in peripheral arterial disease. J Vasc Surg 2006; 43:1198–1204.
27. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower decline in patients who walk more. Ann Intern Med 2006; 144:10–20.
28. McDermott MM, Ferrucci L, Liu K, et al. D-dimer and inflammatory markers as predictors of functional decline in men and women with and without peripheral arterial disease. J Am Geriatr Soc 2002; 53:1688–1696.

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Pathophysiology of peripheral arterial disease and risk factors for its development

ABSTRACT

Peripheral arterial disease (PAD) is a systemic atherosclerotic process for which the major risk factors are similar to those for atherosclerosis in the carotid, coronary, and other vascular beds. Among the traditional risk factors for PAD, those with the strongest associations are advanced age, smoking, and diabetes mellitus. More recently, a number of nontraditional risk factors for PAD have also been recognized. This article briefly reviews the pathophysiology of PAD and the evidence supporting established and emerging risk factors for its development.

Peripheral arterial disease (PAD) refers to atherosclerotic and thromboembolic processes that affect the aorta, its visceral arterial branches, and arteries of the lower extremities.[1] PAD is a marker of systemic atherosclerosis and is found more frequently among persons with well-known cardiovascular risk factors (Table 1), especially older age, smoking, or diabetes mellitus, or those with atherosclerosis in other vascular beds. More recently, a number of "nontraditional" risk factors for PAD have also been recognized, including race/ethnicity, elevations in inflammatory markers, chronic kidney disease, genetics, hypercoagulable states, and an abnormal waist-to-hip ratio (Table 1).

Risk-factor identification is highly important, as PAD is associated with reductions in functional capacity and quality of life as well as increased cardiovascular morbidity and mortality, mainly from myocardial infarction and stroke. This article briefly reviews the pathophysiology of PAD and examines current data on the contributions of traditional and emerging risk factors for PAD.

* Dr. Bartholomew reported that he has received honoraria from GlaxoSmithKline for teaching and speaking. Dr. Olin reported that he has received consulting fees from the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership for serving on a medical advisory panel and has received research support and consulting fees from Genzyme.

PATHOPHYSIOLOGY OF PAD

Atherosclerosis is a complex process that involves endothelial dysfunction, lipid disturbances, platelet activation, thrombosis, oxidative stress, vascular smooth muscle activation, altered matrix metabolism, remodeling, and genetic factors.[2] More recently, the role of inflammation in all stages of atherosclerosis development has been widely recognized.[3]

Atherosclerosis frequently develops at arterial bifurcations and branches where endogenous atheroprotective mechanisms are impaired as a result of the effects of disturbed flow on endothelial cells.[2] Risk factors such as increased age, diabetes mellitus, smoking, elevations in total and low-density lipoprotein (LDL) cholesterol, and hypertension play important roles in both the initiation and the acceleration of this process.[2]

The stages of atherosclerosis

Pathologically, the stages of atherosclerosis are divided into lesion initiation, formation of the fatty streak, fibroproliferative atheroma development, and advanced lesion development. Lesion initiation results from endothelial dysfunction, while the fatty streak is an inflammatory lesion that develops first, affects the intima of the artery, and leads to formation of the foam cell. The fatty streak consists largely of smooth muscle cells, monocytes, macrophages, and T and B cells.[4] The fibroproliferative atheroma originates from the fatty streak, containing larger numbers of smooth muscle cells filled with lipids. The advanced lesion results from continued accumulation of the cells that make up the fatty streak and fibroproliferative atheroma. The advanced lesion is highly cellular and contains intrinsic vascular wall cells (endothelial and smooth muscle) and inflammatory cells (monocytes, macrophages, and T lymphocytes) in addition to a lipid core covered by a fibrous cap.[2–5]

Arteries compensate—up to a point

Arteries initially compensate for atherosclerosis by remodeling, which causes blood vessels to increase in size. However, advanced lesions eventually intrude into the lumen, resulting in flow-limiting stenoses

and chronic ischemic syndromes.[4,5]

Acute arterial events occur if the fibrous cap is disrupted; the resulting exposure of the "prothrombotic" necrotic lipid core and subendothelial tissue leads to thrombus formation and flow occlusion.[2]

TRADITIONAL RISK FACTORS

Traditional risk factors for PAD are similar to those that lead to atherosclerosis in the carotid, coronary, and other vascular beds. In the Framingham Heart Study,[6] Cardiovascular Health Study,[7] PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) program,[8] National Health and Nutrition Examination Survey (NHANES),[9] and Atherosclerosis Risk in Communities (ARIC) study,[10] major risk factors for PAD included advanced age, cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension. Among these, cigarette smoking and diabetes mellitus are the modifiable risk factors that place patients at the greatest risk for PAD (Figure 1).[11,12]

Advanced age

The prevalence of PAD increases with age. In the Framingham Heart Study, subjects 65 years of age or older were at increased risk for development of PAD.[6] A strong association between advanced age (≥ 70 years) and PAD prevalence was also noted in the NHANES report: prevalence was 4.3% in subjects aged 40 years or older compared with 14.5% in those aged 70 years or older (Figure 2).[9]

Others have reported similar findings. Criqui et al reported the prevalence of PAD (defined by an abnormal ankle-brachial index [ABI]) to be 2% to 3% in individuals aged 50 years or less compared with 20% in those aged greater than 75 years.[13] Even higher PAD prevalence rates were observed in the Cardiovascular Health Study, which recruited older, Medicare-eligible adults (25% prevalence among subjects aged 80 to 84 years, and 30% among those 85 years or older),[7] and in the PARTNERS program (prevalence of 29%), which included individuals aged 70 years or older or aged 50 to 69 years with a history of smoking or diabetes.[8]

Although PAD may be present in younger individuals (≤ 50 years of age), such patients represent a very small percentage of cases. Younger patients with PAD tend to have poorer overall long-term outcomes, as well as a higher number of failed bypass surgeries leading to amputation, compared with their older counterparts.[14–16]

Smoking

Cigarette smoking is the single most important modifiable risk factor for the development of PAD and its complications: intermittent claudication and critical limb ischemia. Smoking increases the risk of PAD approximately fourfold and accelerates the onset of PAD symptoms (intermittent claudication) by nearly a decade, with an apparent dose-response relationship between the pack-year history and PAD risk.[7,17–19] Compared with their nonsmoking counterparts, smokers with PAD have poorer survival rates (death attributed to a major vascular event), are more likely to progress to critical limb ischemia, are twice as likely to progress to amputation, and have reduced arterial bypass graft patency rates.[6,20–22]

Although both former smokers and current smokers are at increased risk of PAD, individuals who are able to stop smoking are less likely to develop rest pain and have improved survival[20] (see also the article by Gornik and Creager beginning on page S30).

Notably, the association between smoking and PAD is about twice as strong as that between smoking and coronary artery disease (CAD).[19,23] The reason for this disparity is not clear.

Diabetes mellitus

Diabetes mellitus confers a 1.5-fold to 4-fold increase in the risk of developing symptomatic or asymptomatic PAD and is associated with an increased risk of cardiovascular events and early mortality among individuals with PAD.[24–26]

In the Framingham Heart Study, 20% of sympto-

TABLE 1
Risk factors for peripheral arterial disease

Traditional risk factors
Advanced age
Smoking
Diabetes mellitus
Hyperlipidemia
Hypertension
Nontraditional risk factors
Race/ethnicity
Elevated levels of inflammatory markers (C-reactive protein, fibrinogen, leukocytes, interleukin-6)
Chronic kidney disease
Genetics
Hypercoagulable states (altered levels of D-dimer, homocysteine, lipoprotein[a])
Abnormal waist-to-hip ratio

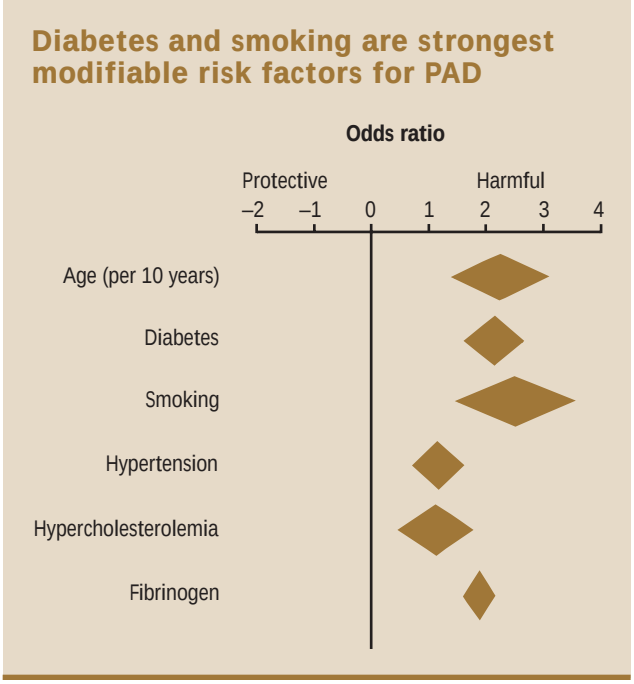

FIGURE 1. Range of odds ratios for developing symptomatic peripheral arterial disease (PAD) (ie, intermittent claudication) according to various risk factors. Adapted, with permission, from reference 11.

matic patients with PAD were reported to have diabetes, although this might have been an underestimate because diagnoses were based on inquiries about symptoms of intermittent claudication rather than objective testing.[6,24] In the NHANES report, which used the ABI to diagnose PAD, 26% of subjects with PAD were identified as having diabetes,[9] while in the Edinburgh Artery Study, which used a World Health Organization questionnaire or an ABI less than 0.90, the prevalence of PAD was higher in individuals with diabetes or impaired glucose tolerance (20.6%) than in those with normal glucose tolerance (12.5%).[25] More recently, the ARIC study found that a prior history of diabetes with insulin treatment was independently associated with a greater incidence of PAD,[10] while the Multi-Ethnic Study of Atherosclerosis (MESA) found that 26% of women and 27.5% of men with an ABI less than 0.90 had diabetes.[26]

In patients with diabetes, the prevalence and extent of PAD also appears to correlate with the age of the individual and the duration and severity of his or her diabetes.[27] Diabetes is a stronger risk factor for PAD in women than in men, and the prevalence of PAD is higher in African Americans and Hispanics with diabetes than in non-Hispanic whites with diabetes.[12,24,27]

The severity of diabetes also appears to play an important role in the development of PAD. There is a 28% increase in the risk of PAD for every percentage-point increase in hemoglobin (Hb) A_{1c}, and the seriousness of PAD appears to be related both to the duration of hyperglycemia and to glycemic control.[24,27,28] PAD prevalence is also increased in individuals with impaired glucose tolerance, and the risk of PAD is significantly increased with higher HbA_{1c} levels even among individuals with dysglycemia in the nondiabetic range ($HbA_{1c} \geq 5.3\%$).[27,29]

Diabetes is most strongly associated with occlusive disease in the tibial arteries.[27] Patients with PAD and diabetes are more likely to develop microangiopathy or neuropathy and to have impaired wound healing than those with PAD alone.[27] Because diabetic neuropathy may often mask PAD symptoms, PAD is more commonly asymptomatic in diabetics; as a result, PAD tends to present later in life and in a more severe and rapidly progressive form in diabetics than in nondiabetics.[27] PAD patients who have diabetes also have a higher risk for ischemic ulceration and gangrene, which is one reason why diabetes is the most common cause for amputation in the United States.[27]

Diabetes is believed to contribute to an increased risk of PAD for a number of reasons. Persons with diabetes are more likely than their nondiabetic counterparts to have additional risk factors for PAD, such as tobacco use, elevated blood pressure, and increased levels of triglycerides, cholesterol, and other blood lipids.[25] They also appear to have more vascular inflammation, endothelial cell dysfunction, and abnormalities in vascular smooth muscle cells compared with nondiabetics. In addition, diabetes is associated with increases in platelet aggregation and impaired fibrinolytic function.[27]

Hyperlipidemia

In the Framingham Heart Study, an elevated total cholesterol level was associated with a twofold increased risk for intermittent claudication.[24] In the NHANES report,[9] more than 60% of individuals with PAD had hypercholesterolemia, while in the PARTNERS program, the prevalence of hyperlipidemia in patients with known PAD was 77%.[8]

Hyperlipidemia increases the adjusted likelihood of developing PAD by 10% for every 10-mg/dL rise in total cholesterol.[30] It is now recognized that elevations in total cholesterol, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglycerides are all independent risk factors for PAD, whereas elevations in high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I appear to be protec-

tive.[30] In 2001, the Third Report of the National Cholesterol Education Program Adult Treatment Panel designated PAD as a CAD risk equivalent.[31]

The form of dyslipidemia seen most frequently in patients with PAD is the combination of a reduced HDL cholesterol level and an elevated triglyceride level, as commonly seen in patients with the metabolic syndrome and diabetes.[23] In the Cardiovascular Health Study, both of these finding were reported in association with a decreased ABI;[7] however, in the ARIC study and the Edinburgh Artery Study, both of which involved patients with diabetes, only elevated triglyceride levels were associated with PAD.[10,25]

Hypertension

Almost every epidemiologic study has shown a strong association between hypertension and PAD, with hypertension being reported in as many as 50% to 92% of patients with PAD.[7–9,24,32,33] In the NHANES report and the PARTNERS program, PAD and hypertension were encountered together in 74% and 92% of enrolled subjects, respectively.[8,9] The Cardiovascular Health Study reported that 52% of patients with an ABI less than 0.90 had high blood pressure,[7] and the Framingham Study demonstrated a 2.5-fold to 4-fold increase in the risk of developing intermittent claudication among both men and women with hypertension.[24] In the Systolic Hypertension in the Elderly (SHEP) trial, 25.5% of participants had an ABI less than 0.90.[33] Taken together, these studies underscore the high prevalence of PAD in patients with hypertension.

Recently, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure acknowledged that PAD is equivalent in risk to ischemic heart disease.[34]

Patients with hypertension and PAD are at greatly increased risk of stroke and myocardial infarction independent of other risk factors.[23,32] In the SHEP study of older adults with systolic hypertension, an ABI of 0.90 or less was associated with a twofold to threefold increase in total and cardiovascular mortality.[33]

NONTRADITIONAL RISK FACTORS

Race/ethnicity

Several studies have shown PAD to be disproportionately prevalent in black and Hispanic populations, even after adjustment for traditional risk factors.[7–9] Age- and gender-adjusted analysis of the NHANES data showed that non-Hispanic blacks were approximately three times as likely to have PAD as non-Hispanic whites.[9] In the Cardiovascular Health Study and the PARTNERS program, nonwhite subjects (predominantly black) were disproportionately affected by PAD.[7,8] In the Multi-Ethnic Study of Atherosclerosis, which was designed to include an ethnically diverse population, PAD prevalence was highest among black men and women and lowest among Hispanic women and Chinese men.[26]

A recent population-based study by Criqui et al concluded that the excess risk of PAD in blacks was unexplained and was not related to diabetes, hypertension, or body mass index.[35] In contrast to some other reports, these researchers also noted lower PAD rates among Hispanics, although the rates were not significantly different from those among non-Hispanic whites.[35]

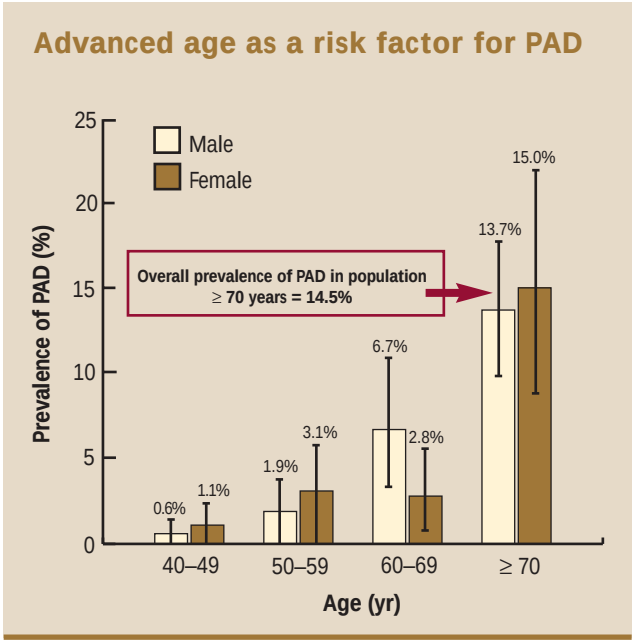

FIGURE 2. Prevalence of peripheral arterial disease (PAD) by age and gender, United States, 1999–2000 (N = 2,174). Error bars are 95% confidence intervals (for age groups 40–49 and 50–59, estimates have a relative standard error > 30%). Reprinted, with permission, from: Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004; 110:738–743.

Inflammation

Elevated levels of the inflammatory markers C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), and leukocytes have been observed in patients with atherosclerosis in other arterial beds; however, an association with PAD has not been established as clearly and only a few studies to date have looked at this relationship.[7,9,36]

Ridker and colleagues found in the Physicians' Health Study that elevated CRP levels predicted a future risk for development of PAD and greater extent of disease.[36] The NHANES report showed that elevated fibrinogen and CRP levels were associated with PAD,[9] and Wildman et al noted that elevated CRP or fibrinogen levels or an increased leukocyte count doubled the risk of developing PAD.[37] In the InCHIANTI study (*Invecchiare in Chianti*, "aging in the Chianti population"), McDermott et al found increased levels of fibrinogen, CRP, and IL-6 in men and women with PAD (compared with persons without PAD) in a community population in Italy.[38] In a separate study, McDermott et al demonstrated that higher baseline levels of inflammatory markers were associated with greater lower extremity functional decline among a group of 337 men and women with PAD.[39]

Chronic kidney disease

Until recently, very few epidemiologic studies recognized chronic kidney disease (reduced kidney function in a patient who is not receiving dialysis and is not a transplant recipient) as a risk factor for PAD.[40,41]

The overall prevalence of PAD in the National Institutes of Health's United States Renal Data System in 1999 was 15%, determined using the following clinical parameters: prior diagnosis of PAD, history of amputation, previous revascularization procedure, intermittent claudication, tissue gangrene, or a decrease in peripheral pulses on physical examination.[41] Based on data from the NHANES report, 24% of the population aged 40 years or older with renal insufficiency (estimated creatinine clearance < 60 mL/min/1.73 m^2) was estimated to have PAD (ABI < 0.90), compared with 3.7% of those whose creatinine clearance was greater than 60 mL/min/1.73 m^2.[42] In the Cardiovascular Health Study, 12% of individuals with renal insufficiency (defined as serum creatinine ≥ 1.3 mg/dL in women and ≥ 1.5 mg/dL in men) had an ABI of less than 0.90, compared with 7% of subjects with normal renal function.[43] In the ARIC study, a low ABI (< 0.90) was associated with an increase in serum creatinine levels over time.[44]

An association with PAD also appears to apply to more severe renal disease. The prevalence of an abnormal ABI (< 0.90) is much higher in patients with end-stage renal disease (ie, requiring hemodialysis) than in those with chronic kidney disease, ranging between 30% and 38%.[40] PAD patients with chronic kidney disease are at increased risk for critical limb ischemia, while those with end-stage renal disease are at increased risk for amputation.[40] Several studies have reported an increased risk of cardiovascular and all-cause mortality in hemodialysis patients, although this issue has not been examined as well among patients with milder chronic kidney disease.

The association between chronic kidney disease and PAD is independent of diabetes, hypertension, ethnicity, and age, and although the exact reason for this association is not known, it may relate to the increased vascular inflammation and markedly elevated plasma homocysteine levels seen in chronic kidney disease.

Genetics

Genetic predisposition to PAD is supported by observations of increased rates of cardiovascular disease (including PAD) in "healthy" relatives of patients with intermittent claudication. Although the relative contributions of genes and environment to the pathogenesis of premature PAD are difficult to separate, one study found that one in four siblings of patients with premature PAD will have a vascular event before age 55 years, and up to half of asymptomatic siblings will develop occult disease at a young age (< 50 years).[45]

To date, no major gene for PAD has been detected, but an ongoing National Institutes of Health–sponsored study in more than 2,000 subjects called "Genetic Determinants of Peripheral Arterial Disease" should help to clarify the role of genetics in PAD.

Hypercoagulable states

Hypercoagulable states, or thrombophilia, represent an uncommon risk factor for PAD. However, in select patients—younger individuals who lack traditional risk factors, patients with a strong family history of premature atherosclerosis, and individuals in whom arterial revascularization fails for no apparent technical reason—evaluation for an underlying hypercoagulable condition should be considered.

Several recent studies have suggested an independent association between PAD and altered levels of hemostatic factors, including lipoprotein(a), homocysteine, antiphospholipid antibodies, and D-dimer.[38,39,46,47] In particular, D-dimer levels appear to be inversely related to the ABI and have been associated with a greater decline in walking and poorer physical function scores.[39]

Evaluation for elevated homocysteine and lipoprotein(a) levels appears to be important in individuals with diffuse PAD who lack traditional risk factors. Hyperhomocysteinemia is associated with premature atherosclerosis and appears to be a stronger risk factor for PAD than for CAD.[48,49] It has also been implicated in PAD progression and as a risk factor for failure of

peripheral interventions, although not all studies have shown such a relationship.[49,50]

Several studies have reported an increased prevalence of elevated lipoprotein(a) in patients with PAD. Although there are conflicting data on the role of lipoprotein(a) as an independent risk factor for atherosclerosis, it may also be useful for screening individuals with premature PAD.[10,46]

Abnormal waist-to-hip ratio

Although it is unclear whether any association exists between PAD and body mass index (BMI), an association between abdominal obesity and PAD has been reported. Planas et al demonstrated that an increased waist-to-hip ratio (> 0.966) was associated with a 1.7-fold increase in the risk of PAD after adjustment for covariates.[51]

One explanation for the lack of association with BMI is the tendency of smokers (who are at increased risk for PAD) to have lower BMIs than nonsmokers. Moreover, many of the individuals at risk for PAD are elderly males, who typically have lower BMIs as well.[52]

CONCLUSIONS

PAD is a systemic atherosclerotic process associated with high morbidity and mortality and significant impairment of quality of life, yet it remains underdiagnosed and undertreated. Advanced age, smoking, and diabetes are clearly the most important risk factors for PAD. The association with diabetes is particularly concerning, given the exponential growth in diabetes prevalence in recent years. Recognizing these and other traditional risk factors for PAD (hyperlipidemia and hypertension), as well as the nontraditional factors reviewed above, is important to the management of PAD. Nevertheless, even if clinicians focus largely on smoking and diabetes as risk factors, significant gains can be made in detecting PAD earlier and treating it more successfully.

REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. J Am Coll Cardiol 2006; 47:1239–1312.
2. Faxon DP, Fuster V, Libby P, et al. Atherosclerotic Vascular Disease Conference: Writing Group III: pathophysiology. Circulation 2004; 109:2617–2625.
3. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105:1135–1143.
4. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999; 340:115–126.
5. Kinlay S, Libby P, Ganz P. Endothelial function and coronary artery disease. Curr Opin Lipidol 2001; 12:383–389.
6. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation 1997; 96:44–49.
7. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation 1993; 88:837–845.
8. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286:1317–1324.
9. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004; 110:738–743.
10. Wattanakit K, Folsom AR, Selvin E, et al. Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis 2005; 180:389–397.
11. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000; 31(1 Pt 2):S1–S296.
12. Smith SC Jr, Milani RV, Arnett DK, et al. Atherosclerosis Vascular Disease Conference: Writing Group II: risk factors. Circulation 2004; 109:2613–2616.
13. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation 1985; 71:516–522.
14. Levy PJ, Hornung CA, Haynes JL, Rush DS. Lower extremity ischemia in adults younger than forty years of age: a community-wide survey of premature atherosclerotic arterial disease. J Vasc Surg 1994; 19:873–881.
15. Harris LM, Peer R, Curl GR, Pillai L, Upson J, Ricotta JJ. Long-term follow-up of patients with early atherosclerosis. J Vasc Surg 1996; 23:576–581.
16. Valentine RJ, Myers SI, Inman MH, Roberts JR, Clagett GP. Late outcome of amputees with premature atherosclerosis. Surgery 1996; 119:487–493.
17. Powell JT, Edwards RJ, Worrell PC, Franks PJ, Greenhalgh RM, Poulter NR. Risk factors associated with the development of peripheral arterial disease in smokers: a case-control study. Atherosclerosis 1997; 129:41–48.
18. Kannel WB, Shurtleff D. The Framingham Study. Cigarettes and the development of intermittent claudication. Geriatrics 1973; 28:61–68.
19. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. Eur Heart J 1999; 20:344–353.
20. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand 1987; 221:253–260.
21. Powell JT, Greenhalgh RM. Changing the smoking habit and its influence on the management of vascular disease. Acta Chir Scand Suppl 1990; 555:99–103.
22. Lassila R, Lepantalo M. Cigarette smoking and the outcome after lower limb arterial surgery. Acta Chir Scand 1988; 154:635–640.
23. Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol 1992; 135:331–340.
24. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc 1985; 33:13–18.
25. MacGregor AS, Price JF, Hau CM, Lee AJ, Carson MN, Fowkes FG. Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease. The Edinburgh Artery Study. Diabetes Care 1999; 22:453–458.

26. McDermott MM, Liu K, Criqui MH, et al. Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. Am J Epidemiol 2005; 162:33–41.
27. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003; 26:3333–3341.
28. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004; 141:421–431.
29. Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. Diabetes Care 2005; 28:1981–1987.
30. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. Circulation 1995; 91:1472–1479.
31. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106:3143–3421.
32. Olin JW. Hypertension and peripheral arterial disease. Vasc Med 2005; 10:241–246.
33. Newman AB, Tyrrell KS, Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. J Am Geriatr Soc 1997; 45:1472–1478.
34. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289:2560–2572.
35. Criqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. Circulation 2005; 112:2703–2707.
36. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998; 97:425–428.
37. Wildman RP, Muntner P, Chen J, Sutton-Tyrell K, He J. Relation of inflammation to peripheral arterial disease in the National Health and Nutrition Examination Survey, 1999–2002. Am J Cardiol 2005; 96:1579–1583.
38. McDermott MM, Guralnik JM, Corsi A, et al. Patterns of inflammation associated with peripheral arterial disease: the InCHIANTI study. Am Heart J 2005; 150:276–281.
39. McDermott MM, Ferrucci L, Liu K, et al. D-dimer and inflammatory markers as predictors of functional decline in men and women with and without peripheral arterial disease. J Am Geriatr Soc 2005; 53:1688–1696.
40. O'Hare AM. Management of peripheral arterial disease in chronic kidney disease. Cardiol Clin 2005; 23:225–236.
41. National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic and Hematologic Diseases. Patient characteristics. In: United States Renal Data System, USRDS 2000 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2000:339–348.
42. O'Hare AM, Glidden DV, Fox CS, et al. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999–2000. Circulation 2004; 109:320–323.
43. Shlipak MG, Fried LF, Crump C, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. Kidney Int 2002; 62:997–1004.
44. O'Hare AM, Rodriguez RA, Bacchetti P. Low ankle-brachial index associated with rise in creatinine level over time: results from the atherosclerosis risk in communities study. Arch Intern Med 2005; 165:1481–1485.
45. Valentine RJ, Verstraete R, Clagett GP, Cohen JC. Premature cardiovascular disease is common in relatives of patients with premature peripheral atherosclerosis. Arch Intern Med 2000; 160:1343–1348.
46. Sofi F, Lari B, Rogolino A, et al. Thrombophilic risk factors for symptomatic peripheral arterial disease. J Vasc Surg 2005; 41:255–260.
47. McDermott MM, Green D, Greenland P, et al. Relation of levels of hemostatic factors and inflammatory markers to the ankle brachial index. Am J Cardiol 2003; 92:194–199.
48. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001; 285:2481–2485.
49. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998; 338:1042–1050.
50. Taylor LM Jr, DeFrang RD, Harris EJ Jr, Porter JM. The association of elevated plasma homocyst(e)ine with progression of symptomatic peripheral arterial disease. J Vasc Surg 1991; 13:128–136.
51. Planas A, Clara A, Pou JM, et al. Relationship of obesity distribution and peripheral arterial occlusive disease in elderly men. Int J Obes Relat Metab Disord 2001; 25:1068–1070.
52. Douketis JD, Sharma AM. Obesity and cardiovascular disease: pathogenic mechanisms and potential benefits of weight reduction. Semin Vasc Med 2005; 5:25–33.

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The clinical presentation of peripheral arterial disease and guidance for early recognition

ABSTRACT

Most patients with lower extremity peripheral arterial disease (PAD) are asymptomatic. Although intermittent claudication is the classic presenting symptom in those who are symptomatic, PAD often presents atypically as a result of associated comorbidities. The differential diagnosis involves consideration of many nonvascular and nonatherosclerotic causes of exercise-associated leg pain. Weak or absent pulses are the hallmark physical finding of PAD, and the ankle-brachial index is the most efficient objective test for documenting it. PAD may progress to acute limb ischemia (acute deterioration of limb flow) or critical limb ischemia (chronic compromise in limb perfusion resulting in rest pain and tissue loss), both of which can lead to limb loss without timely treatment.

Peripheral arterial disease (PAD) is common but grossly underrecognized and undertreated. Several factors contribute to its underrecognition. Notably, the majority of patients with lower extremity PAD are asymptomatic.[1,2] Other patients incorrectly attribute the symptoms of PAD to normal aging pains. Moreover, those who are symptomatic often do not present with the classic symptoms of intermittent claudication (IC) as defined in the Rose questionnaire of IC (ie, exertional leg pain) but instead report other exertional leg symptoms or present with progressive functional decline.[3]

Recognizing PAD is important because even its asymptomatic form is a strong marker for future cardiovascular events (stroke and myocardial infarction) and for functional impairment. Establishing the diagnosis identifies individuals who need more aggressive risk-factor modification and who may need other interventions targeted at improving their future cardiovascular outcomes and quality of life.[4–7] Such identification is particularly important in populations with a markedly elevated prevalence of PAD—the elderly, patients with diabetes, and current or past smokers.[1,8,9]

This article reviews the presentation of PAD and considerations in its evaluation and diagnosis, which Figure 1 summarizes in algorithmic form. Special attention is given to the differential diagnosis and signs of progression to acute limb ischemia and critical limb ischemia.

COURSE AND SEQUELAE OF PAD

The progression of PAD in an extremity usually is slow and follows a stepwise pattern. In cases in which rest pain or tissue loss (nonhealing ulcers or gangrene) is evident, the condition is termed *critical limb ischemia*. Sometimes an acute occlusive event in a vessel leads to rapid deterioration of a limb, termed *acute limb ischemia*, which requires emergent treatment.

Most patients with IC do not progress to critical limb ischemia but remain stable or suffer gradual worsening of symptoms over time. For instance, early findings from the Framingham Study showed that less than 2% of patients with PAD required major amputation.[3] A more recent study among a large series of men with IC found the cumulative 10-year rates of progression to ischemic ulceration and rest pain to be 23% and 30%, respectively.[10] A low ankle-brachial index (ABI) and diabetes were risk factors associated with development of ischemic ulcers and rest pain.[10] The cumulative 10-year rate of minor or major amputation in this population was less than 10%.[11]

In addition to the risk of these devastating limb outcomes, patients with IC have an annual mortality rate of approximately 12%, with death usually resulting from ischemic cardiovascular events.[11] Advanced age, a low ABI, diabetes requiring medication, and a history of stroke are independent predictors of death in patients with IC without rest pain or ischemic ulceration.[11]

EVALUATION FOR SUSPECTED PAD

History-taking

An accurate history is the key to the diagnosis of PAD. Eliciting atherosclerotic risk factors in the history may

*Both authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

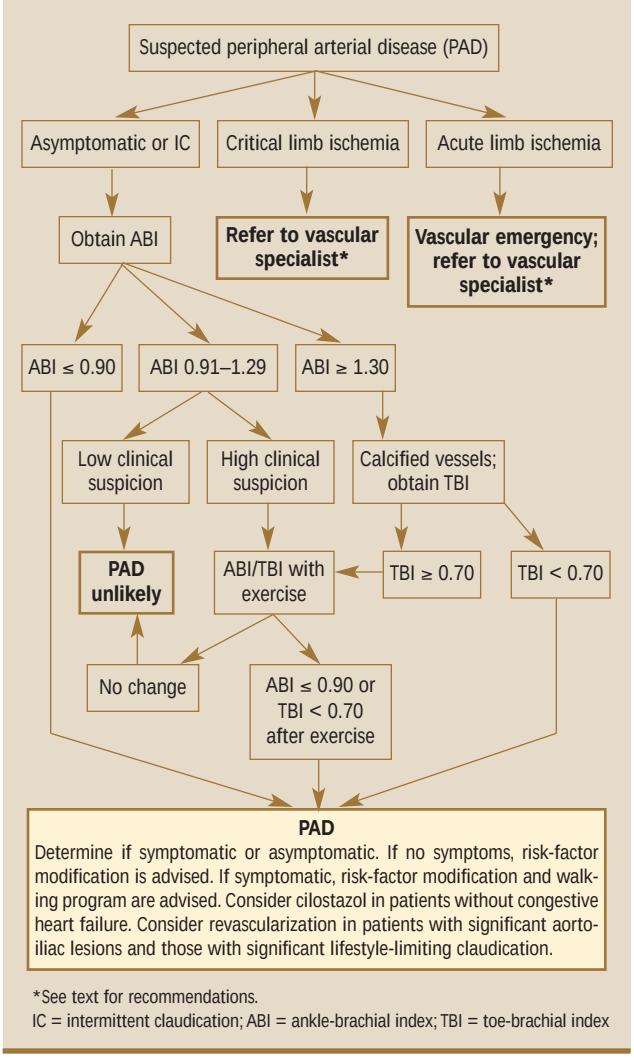


FIGURE 1. Algorithm for the evaluation and diagnosis of suspected peripheral arterial disease.

help to identify patients who, although asymptomatic, have evidence of PAD on physical examination or noninvasive testing. Risk factors for PAD include advanced age, current or past tobacco use, diabetes, hypertension, hyperlipidemia, and (less frequently) certain hypercoagulable states (see the preceding article in this supplement for a detailed discussion of risk factors for PAD).

Classic IC occurs after a defined amount of ambulation—ie, the distance required for symptoms to begin and to limit activity is reproducible. Symptom relief typically occurs within 10 minutes of rest or standing still and, notably, does not require sitting or lying down.

Symptoms correspond with diseased arterial level

Arterial disease in the lower extremity is generally broken down into three levels: aortoiliac disease, femoropopliteal disease, and tibial artery (crural, below-the-knee, or infrageniculate) disease. The location of symptoms can help pinpoint the anatomic area of disease. The diseased arterial segment is typically proximal to the affected muscle group, although multilevel PAD can cause symptoms throughout the leg. Thus, a patient with aortoiliac disease may experience pain in the hip, buttock, or thigh; femoropopliteal disease may result in calf pain; and tibial disease may result in foot claudication. Patients presenting with IC symptoms generally have single-level disease, whereas those presenting with rest pain or ulceration generally have multilevel disease.

Differential diagnosis

Although leg pain associated with exercise and relieved by rest is suggestive of IC, it is not sufficient for diagnosis. IC must be differentiated from lower extremity pain with nonvascular etiologies (Table 1).

Many concomitant disease processes can complicate the diagnosis of PAD. Both neurologic and musculoskeletal and venous pathology can cause leg pain or coexist with leg pain from PAD, confounding the diagnosis. False-positive diagnosis rates of up to 44% and false-negative rates of up to 19% have been reported after findings obtained by clinical evaluation were verified by noninvasive tests.[12] Calf claudication is commonly confused with pain from venous disease, nerve root compression, or spinal cord stenosis. Hip and buttock claudication is commonly confused with osteoarthritis of the hip or with spinal canal narrowing due to osteoarthritis. The nonatherosclerotic conditions that mimic IC and that should be considered in the differential diagnosis are discussed individually below.

Venous claudication occurs in patients with chronic venous insufficiency and those who develop post-thrombotic syndrome after deep venous thrombosis. The baseline venous hypertension in the obstructed veins worsens with exercise and produces a tight bursting pressure in the limb, usually worse in the thigh and uncommonly in the calf.[13] It usually is associated with evidence of venous edema in the leg. Venous claudication tends to improve with cessation of exercise, but total resolution takes much longer than resolution of IC and may require leg elevation.

Chronic compartment syndrome is an uncommon cause of exercise-induced leg pain. It tends to occur in young athletes, who develop increased pressure within a fixed compartment, compromising perfusion and function of the tissues within that space. It results from tight thickened fascia, from muscular hypertrophy, or

when external pressure is applied to the leg (as with casting or taping). The presentation is one of tight bursting pressure in the calf or foot following participation in endurance sports or other robust exercise. The pain subsides slowly with rest, but intracompartmental pressure testing before and after exercise is the diagnostic test of choice.

Peripheral nerve pain is usually attributable to nerve root compression by herniated disks or osteophytes and typically follows the dermatome of the affected root. Pain typically begins immediately upon walking and may be felt in the calf or lower leg. The pain is not quickly relieved by rest and may even be present at rest. There may be a sensation of pain running down the back of the leg as well as a history of back problems.

Spinal cord compression from narrowing secondary to lumbar spine osteoarthritis. In patients with cauda equina syndrome, upright positioning aggravates the narrowing of the spinal canal, thereby causing symptoms. Although symptoms may be associated with walking, upright standing also may produce pain, weakness, or discomfort in the hips, thighs, and buttocks, and even a sensation of numbness and paresthesias. Symptoms are alleviated by sitting or flexing the lumbar spine forward as opposed to standing, which alleviates pain in IC. Patients with spinal cord compression typically have pain on physical examination during a straight leg-raise test.

Hip and knee osteoarthritis. Osteoarthritis in joints is typically worse in the morning or at the initiation of movement. The degree of pain may vary from day to day, and the pain does not cease promptly upon stopping exercise or standing. The pain typically improves after sitting, lying down, or leaning against an object to alleviate weight-bearing on the joint. It may be affected by weather change and may be present at rest.

Nonatherosclerotic etiologies of arterial disease. Thromboangiitis obliterans, popliteal artery entrapment syndrome, cystic adventitial disease, fibromuscular dysplasia, and exercise-induced endofibrosis of the iliac arteries are other arterial causes of IC or critical limb ischemia. All of these conditions typically produce a decrease in the exercise or resting ABI; they are usually differentiated from atherosclerotic etiologies by the history and physical examination.

TABLE 1
Differential diagnosis of intermittent claudication

- Atherosclerotic intermittent claudication
- Venous claudication
- Chronic compartment syndrome
- Hip or knee osteoarthritis
- Peripheral nerve pain (diabetic neuropathy)
- Spinal cord compression or cauda equina syndrome
- Nonatherosclerotic etiologies with similar presentation
  - Thromboangiitis obliterans (Buerger disease)
  - Popliteal artery entrapment syndrome
  - Cystic adventitial disease
  - Fibromuscular dysplasia
  - Exercise-induced endofibrosis of the iliac arteries

Comorbidities complicate symptom detection

Because the prevalence of PAD increases with advancing age, the patients most likely to have PAD are likely to have other age-related conditions that may contribute to lower extremity symptoms or may make such symptoms harder to detect.[14] In many elderly patients, comorbidity-related limitations in physical activity can cause lower extremity symptoms to be overlooked or missed, delaying the diagnosis of PAD. For example, patients with severe coronary artery disease or chronic obstructive pulmonary disease may be unable to walk far enough to experience the typical symptoms of IC until the disease progresses to critical limb ischemia. PAD itself can cause patients to slowly and unwittingly adapt and limit their lifestyles to avoid symptoms.

Physical examination

Physical examination of a patient with exercise-associated leg pain should include palpation of the abdominal aortic and bilateral femoral, popliteal, dorsalis pedis, and posterior tibial pulses; documentation of any iliac, femoral, or popliteal bruits; and inspection of the peripheral skin.

Pulses should be noted on a scale from 0 to 2, for absent, diminished, or normal.[8] Weak or absent pulses are the hallmark physical finding of PAD. Absence of the dorsalis pedis pulse alone does not imply PAD since congenital absence of this artery occurs in up to 10% of the population.[15] Enlarged or widened arteries may signify aneurysmal disease, commonly found in the aorta and popliteal arteries, which can be sources of atheroemboli or thromboemboli occluding the distal arterial tree.

Khan et al recently conducted a systematic literature review to evaluate the accuracy of the physical examination in predicting the presence or absence of PAD.[16] They concluded that physical examination findings are not sufficient alone and must be considered in the con-

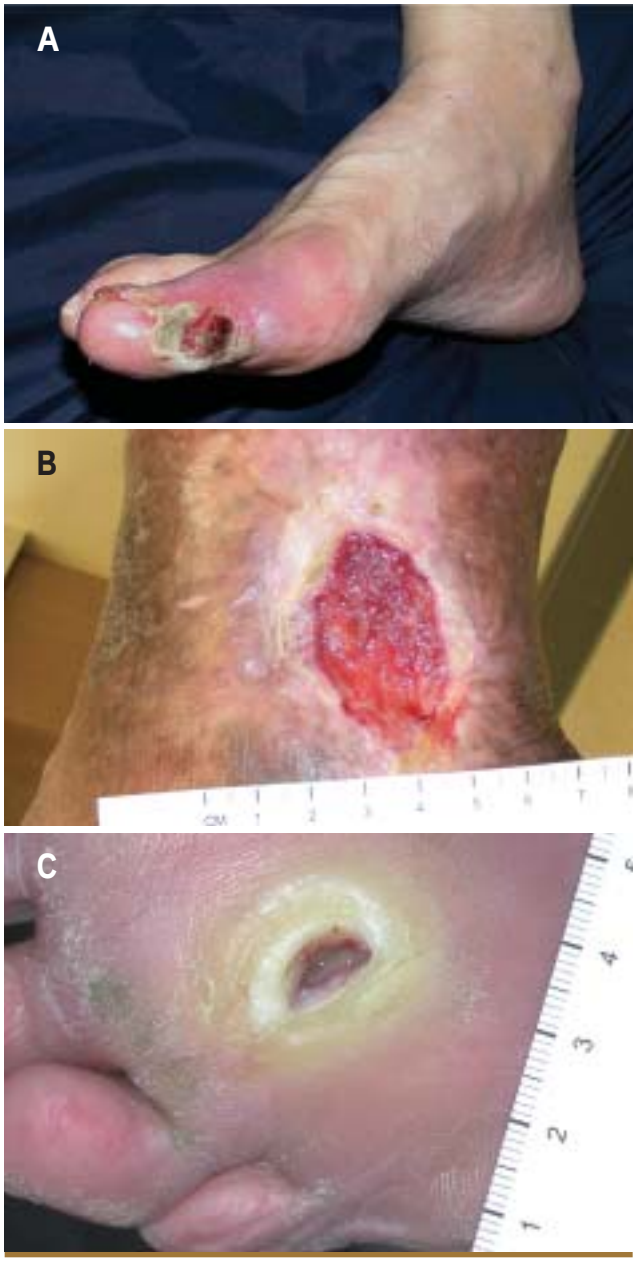
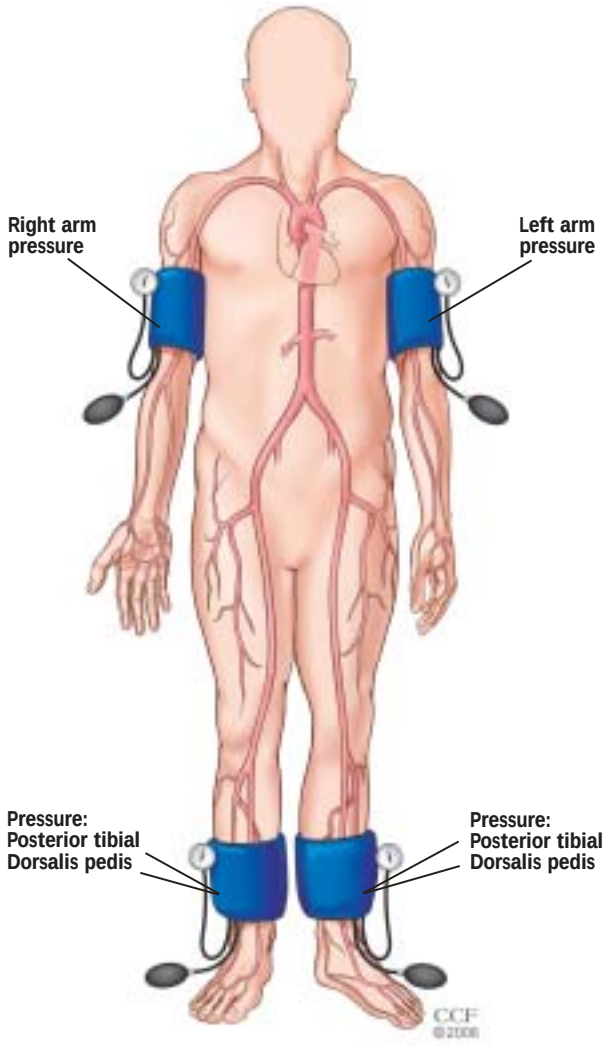


FIGURE 2. An ischemic ulcer in a patient with peripheral arterial disease that has progressed to critical limb ischemia (A), in contrast with a venous stasis ulcer (B) and a neurotrophic ulcer in a patient with diabetes (C).



$$\text{ABI} = \frac{\text{Lower extremity systolic pressure}}{\text{Brachial artery systolic pressure}}$$

FIGURE 3. The ankle-brachial index (ABI) is determined using a Doppler probe and blood pressure cuffs to measure the systolic pressure at both brachial arteries and at the dorsalis pedis and posterior tibial arteries of both legs. The highest pressure in each lower extremity is divided by the highest brachial pressure to establish the ABI.

text of risk factors for atherosclerosis to improve diagnostic accuracy. They noted that a PAD screening score derived from pulse readings using a handheld Doppler probe was particularly helpful for determining which patients should undergo further studies.[16]

Although not specific to PAD, thinning of the skin, atrophy or loss of the sweat glands, alopecia of the limb, and thickening of the nails are common findings. Besides short-distance IC and rest pain, signs of severe disease include dependent rubor, pallor on elevation, and ischemic ulceration over the affected segments. Dependent rubor often coincides with secondary edema due to maintaining the leg in a dependent position to alleviate symptoms of rest pain.

Arterial ulcers (Figure 2A) typically begin after trauma or injury to the limb and appear as pale-to-black, punctate, well-circumscribed lesions. They can be differentiated from venous stasis ulcers (Figure 2B), which

TABLE 2
Rutherford categories of acute limb ischemia

Category	Description/prognosis	Findings		Doppler signals	
		Sensory loss	Muscle weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	None to minimal (toes)	None	Inaudible	Audible
b. Immediately	Salvageable only with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound anesthesia	Profound paralysis	Inaudible	Inaudible

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typically are located in the medial lower calf ("gaiter distribution") and are characterized by thickened, brawny skin with hyperpigmentation from hemosiderin deposition. Diabetic ulcers (Figure 2C) are differentiated from arterial lesions in that they typically occur over weight-bearing areas, have hypertrophic callus formation around the edges, and commonly have associated infection.

Ankle-brachial index

The ABI is the most efficient objective test for documenting PAD in the lower extremity. It is performed using a handheld continuous-wave Doppler probe and blood pressure cuff to assess systolic pressures in both brachial arteries and in the dorsalis pedis and posterior tibial arteries of both legs (Figure 3). The highest ankle pressure in each leg is divided by the highest brachial pressure (for more detail on methods of calculating the ABI, see the article by McDermott at the beginning of this supplement).

In a well-rested supine patient, a normal ABI is 0.91 to 1.29, with values from 0.91 through 0.99 considered borderline normal.[17] An ABI of 0.90 or less is considered evidence of lower extremity PAD in epidemiologic studies. Patients with single-level PAD typically have an ABI from 0.50 to 0.90, whereas patients with severe multilevel disease typically have an ABI of less than 0.50.[18]

An ABI of 1.30 or greater suggests noncompressible or partially noncompressible vessels, which are the result of medial artery calcification (often associated with diabetes mellitus or chronic kidney disease). In such cases, a toe-brachial index should be obtained, since calcification rarely involves digital vessels. In an individual without PAD, the toe pressure is expected to be greater than 70% of the brachial pressure.[18]

A normal resting ABI does not exclude PAD. In patients with mild or very proximal occlusive lesions, pulses may be palpable at rest. Exercise testing increases the sensitivity of the ABI and is conventionally performed on a treadmill at a 12% incline at 2 mph for 5 minutes or until symptoms prohibit continuation of the test.

ACUTE LIMB ISCHEMIA

Acute limb ischemia is a clinical syndrome caused by an acute arterial occlusion, typically by a thrombus overlying a substantial plaque and less frequently by an atheroembolus or thromboembolus. Acute limb ischemia is classically described by the six "P's":

- Pulselessness
- Pain
- Pallor
- Poikilothermy (coldness)
- Paresthesia
- Paralysis.

Rutherford et al have defined three categories of acute limb ischemia to help clinicians risk-stratify these patients and determine the urgency of restoring flow to the affected limb (Table 2).[19]

Category I: Evaluate over ensuing days

A patient presenting with category I (viable) acute limb ischemia should be evaluated for possible thrombolysis, peripheral intervention, or bypass surgery over the ensuing several days. While the patient is evaluated, care must be taken to prevent further injury to an acutely threatened limb; this should include consideration of the use of heel protectors and methods to ensure limb warmth. Prompt initiation of platelet inhibition with aspirin, clopidogrel, or both is impor-

TABLE 3
Clinical criteria for categories of critical limb ischemia

Grade*	Category	Clinical description	Noninvasive laboratory description
0	0	Asymptomatic—no hemodynamically significant occlusive disease	Normal results of treadmill/stress test (5 min at 2 mph on 12% incline)
	1	Mild claudication	Treadmill exercise completed; postexercise ankle pressure > 50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Symptoms between those of categories 1 and 3
	3	Severe claudication	Treadmill exe rcise cannot be completed and postexercise ankle pressure < 50 mm Hg
II	4	Ischemic rest pain	Resting ankle pressure ≤ 40 mm Hg, flat or barely pulsatile ankle or metatarsal plethysmographic tracing, toe pressure < 30 mm Hg
III	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure ≤ 60 mm Hg, ankle or metatarsal plethysmographic tracing flat or barely pulsatile, toe pressure < 40 mm Hg
	6	Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	Same as for category 5

* Fontaine classification

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tant, along with consideration of systemic anticoagulation with heparin to prevent propagation of the thrombosis. The patient should be frequently evaluated for changes in the pulse examination or for new signs and symptoms that may place him or her in a more urgent category. In addition to conventional angiography, arterial duplex ultrasonography or magnetic resonance or computed tomographic angiography may help to further characterize the extent and level of disease and to plan for therapy.

Category II: Salvageable with prompt obstruction reversal

The second category of acute limb ischemia is threatened viability, in which the limb is salvageable without major amputation if the arterial obstruction is reversed quickly. Patients with this category of limb ischemia require emergent admission to the hospital with immediate consultation of a vascular specialist.

The category is subdivided into limbs under marginal (IIa) and immediate (IIb) threat. Differentiating between classes IIa and IIb is important because restoration of flow may be delayed without sequelae in some patients, whereas immediate flow restoration is required in other patients. Patients with class IIa acute limb ischemia generally have absent pedal Doppler signals with transient sensory loss limited to the toes and no loss of motor function. These patients typically are considered for intra-arterial thrombolysis, as they may tolerate the time required to perform this therapy. Thrombolysis usually takes more than 24 hours to dissolve an acute thrombus but allows identification of underlying lesions, permitting less invasive treatment.[20] In contrast, class IIb patients have more marked sensory deficits, commonly associated with motor weakness, and need immediate restoration of blood flow by endovascular or open surgical means to avoid major amputation and permanent nerve damage.

Category III: Irreversible ischemia requiring amputation

Category III denotes irreversible ischemia. These patients have absent Doppler signals with marked motor and sensory deficits and muscle rigor. They suffer permanent neuromuscular damage and require major amputation regardless of therapy.

CRITICAL LIMB ISCHEMIA

Critical limb ischemia is a clinical term to describe chronic and severe compromise in limb perfusion that results in failure to meet the basal metabolic needs. It is usually caused by atherosclerotic occlusive PAD and manifests as rest pain and/or tissue loss (ulcers or gangrene). Rutherford et al developed a detailed grading system for critical limb ischemia that is commonly used (Table 3).[19]

The first sign is rest pain

Rest pain is the earliest sign of critical limb ischemia and typically worsens with leg elevation at night, due

to loss of the supplemental effects of gravity on blood flow. Further progression of tissue hypoxia ultimately leads to tissue ulceration and gangrene. Differentiation from venous and diabetic ulcers is important (Figure 2), as previously described. In some PAD patients with venous disease or long-standing diabetes, ulcers can be attributed to two or three etiologies concomitantly.

In contrast to patients with IC, those with critical limb ischemia progress to limb loss in the absence of intervention to treat PAD and improve limb blood flow. In one study, 12.2% of patients with critical limb ischemia progressed to major amputation within 3 months and 20% died within 1 year.[21] A long-term study of 1,244 men with claudication found that diabetes mellitus and low ABI predicted the development of ischemic rest pain.[10] Patients with diabetes, neuropathy, infection, and chronic kidney disease are more likely to progress to limb loss.

Prompt referral indicated

Any patient with foot ulceration, rest pain, and an abnormal ABI or noncompressible vessels should be referred to a vascular specialist for evaluation of the level and extent of arterial blockages and to consider endovascular and open revascularization options.

REFERENCES

1. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004; 110:738–743.
2. Heidrich H, Wenk R, Hesse P. Frequency of asymptomatic peripheral arterial disease in patients entering the department of general and internal medicine of a general-care hospital. Vasa 2004; 33:63–67.
3. Kannel WB, Skinner JJ Jr, Schwartz MJ, Shurtleff D. Intermittent claudication. Incidence in the Framingham Study. Circulation 1970; 41:875–883.
4. Criqui MH, Denenberg JO, Langer RD, Fronek A. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. Vasc Med 1997; 2:221–226.
5. Feringa HH, Bax JJ, van Waning VH, et al. The long-term prognostic value of the resting and postexercise ankle-brachial index. Arch Intern Med 2006; 166:529–535.
6. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286:1317–1324.
7. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med 2003; 163:1939–1942.
8. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Concensus (TASC). J Vasc Surg 2000; 31(1 Pt 2):S1–S296.
9. Gofin R, Kark JD, Friedlander Y, et al. Peripheral vascular disease in a middle-aged population sample. The Jerusalem Lipid Research Clinic Prevalence Study. Isr J Med Sci 1987; 23:157–167.
10. Aquino R, Johnnides C, Makaroun M, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. J Vasc Surg 2001; 34:962–970.
11. Muluk SC, Muluk VS, Kelley ME, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. J Vasc Surg 2001; 33:251–257; discussion 257–258.
12. Marinelli MR, Beach KW, Glass MJ, Primozich JF, Strandness DE Jr. Noninvasive testing vs clinical evaluation of arterial disease. A prospective study. JAMA 1979; 241:2031–2034.
13. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Section B: intermittent claudication. Eur J Vasc Endovasc Surg 2000; 19(Suppl A):S47–S114.
14. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA 2000; 286:1599–1606.
15. Barnhorst DA, Barner HB. Prevalence of congenitally absent pedal pulses. N Engl J Med 1968; 278:264–265.
16. Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? JAMA 2006; 295:536–546.
17. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. A collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006; 47:1239–1312.
18. Strandness DE Jr. Duplex Scanning in Vascular Disorders. 2nd ed. New York, NY: Raven Press; 1993.
19. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997; 26:517–538.
20. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. N Engl J Med 1998; 338:1105–1111.
21. Long-term mortality and its predictors in patients with critical leg ischaemia. The I.C.A.I. Group (Gruppo di Studio dell'Ischemia Cronica Critica degli Arti Inferiori). The Study Group of Criticial Chronic Ischemia of the Lower Exremities. Eur J Vasc Endovasc Surg 1997; 14:91–95.

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Noninvasive diagnostic strategies for peripheral arterial disease

ABSTRACT

A variety of diagnostic methods for peripheral arterial disease (PAD) are available, each with strengths and limitations. The ankle-brachial index is a simple and useful screening tool for PAD that can be performed in the office setting. Segmental limb pressure examinations and pulse volume recordings aid in identifying the location of disease. Pulse volume recordings are especially useful, along with the ankle-brachial index, in assessing functional status during exercise. Duplex ultrasonography, magnetic resonance angiography, and computed tomographic angiography are helpful in providing anatomic detail and thus yield additional information for planning interventional therapy. Conventional angiography, the "gold standard" study for PAD diagnosis, is now usually pursued only once an intervention is planned.

Diagnostic testing for peripheral arterial disease (PAD) must be accurate, inexpensive, widely accessible, easy to perform, and preferably noninvasive.

A variety of noninvasive techniques are available to detect the presence of PAD as well as to localize areas of stenosis, assess severity of disease, and follow patients for disease progression or response to therapy. Several techniques can be performed in the outpatient office setting, facilitating rapid and accurate assessment of symptoms and offering an opportunity to screen asymptomatic individuals who are at risk for PAD. Once PAD has been diagnosed and there is interest in evaluating options for revascularization therapy, several imaging strategies exist. Recently, minimally invasive imaging techniques have offered excellent alternatives to contrast angiography, which is now reserved for patients in whom an intervention is planned.

This article reviews and assesses various noninvasive methods for diagnosing and evaluating PAD.

THE ANKLE-BRACHIAL INDEX

The ankle-brachial index (ABI) is a simple and inexpensive test that can identify patients with PAD by determining the ratio of systolic blood pressure at the ankle arteries relative to that at the brachial arteries. This test (also occasionally called the arm-ankle index) requires a blood pressure cuff and a handheld continuous-wave 5- to 10-mHz Doppler probe.

Measurements for the ABI should be obtained after the patient has been supine for 5 to 10 minutes. The test requires that the systolic blood pressure be recorded in both brachial arteries and in both dorsalis pedis and posterior tibial arteries. The ABI is calculated for each leg by dividing the highest ankle systolic pressure by the highest brachial systolic pressure, recording the value to two decimal places. In general, the ankle pressure will exceed the brachial pressure by 10 to 15 mmHg in healthy individuals as a result of higher peripheral resistance at the ankles.[1]

Interpreting the ABI

According to recently published practice guidelines for PAD management from the American College of Cardiology and the American Heart Association (ACC/AHA), ABI ratios are interpreted as follows[1]:

- ≥ 1.30: noncompressible vessel
- 1.00 to 1.29: normal
- 0.91 to 0.99: borderline (equivocal)
- 0.41 to 0.90: mild to moderate PAD
- 0.00 to 0.40: severe PAD.

An ABI of 0.90 or less has a sensitivity of 95% and a specificity of 100%, relative to contrast angiography, for detecting a stenotic lesion of at least 50% in the limb.[2]

Vessels are noncompressible when there is significant medial artery calcification. This finding is most commonly seen in some diabetic patients but may also be present in elderly individuals, patients with

* Dr. Begelman reported that she has no financial relationships that pose a potential conflict of interest with this article. Dr. Jaff reported that he has received honoraria for teaching and speaking from the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership.

† At the time this article was written, Dr. Begelman was employed in the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH.

chronic kidney disease who require dialysis, and patients receiving chronic steroid therapy.

An alternative: The toe-brachial index

The inability of the ABI to reliably detect PAD in the presence of noncompressible vessels is its primary limitation. A toe-brachial index may be a better test for assessing lower limb perfusion when the ABI is 1.30 or greater, because small arteries are less susceptible to calcification.[3] To obtain a toe-brachial index, the systolic pressure is measured from the great toe using a small cuff and a Doppler probe, similar to an ABI. Normal toe pressures run lower than brachial and ankle pressures. Therefore, a toe-brachial index less than 0.70 is considered diagnostic of PAD.

ABI correlates with outcomes

Epidemiologic studies have shown an association between the ABI and cardiovascular morbidity and mortality as well as between the ABI and reduced limb function.

In a cohort study of 154 patients with an ABI less than 0.90, Sikkink et al[4] reported the following 5-year cumulative survival rates, according to patients' resting ABIs:

- 63% for those with an ABI less than 0.50
- 71% for those with an ABI of 0.50 to 0.69
- 91% for those with an ABI of 0.70 to 0.89.

Resnick et al[5] expanded on this association in a study of all-cause and cardiovascular mortality in patients with either low ABIs (< 0.90) or high ABIs (> 1.40). Adjusted risk estimates for all-cause mortality, relative to patients with an ABI of 0.90 to 1.40, were 1.69 for patients with low ABIs and 1.77 for those with high ABIs; estimates for cardiovascular mortality were 2.52 and 2.09, respectively. The researchers concluded that there is a U-shaped association between ABI and mortality risk.

In fact, this and other studies are changing the definition of a "normal" ABI. Wang et al[6] showed that both low-normal ABIs (which they defined as 0.91 to 0.99) and high ABIs (≥ 1.40) were associated with higher rates of lower extremity symptoms than were normal ABIs (defined as 1.00 to 1.39 in this study). Similarly, McDermott et al[7] found that an ABI of 0.90 to 0.99 was associated with a significantly higher prevalence of subclinical atherosclerosis (increased carotid intima-media thickness and coronary artery calcium assessed by computed tomography) when compared with a normal ABI (defined as 1.10 to 1.29) in both men and women. Historically, individuals whose ABI fell within the range of 0.90 to 0.99 have been categorized as "normal" in population-based studies.

Who should be screened with the ABI?

The recent ACC/AHA practice guidelines for PAD management[1] recommend that a resting ABI be obtained for the following patient groups:

- Individuals with suspected PAD due to exertional leg symptoms or nonhealing wounds
- Individuals aged 70 years or older
- Individuals between 50 and 70 years of age who have a history of tobacco use or diabetes mellitus.

Additionally, the American Diabetes Association suggests that a screening ABI be performed in patients with diabetes who are younger than 50 years and have additional risk factors for PAD, such as smoking, hypertension, hyperlipidemia, or diabetes of long duration (> 10 years).[8]

Although clinicians now overwhelmingly recognize the benefits of measuring the ABI, use of this test has been limited as a result of a lack of reimbursement by most health care payers and time constraints.[9] A recent study suggests that automated oscillometry may be used for ABI measurements.[10] If its accuracy can be substantiated, automated oscillometry may help overcome the time-constraint barrier by facilitating more rapid measurement.

SEGMENTAL LIMB PRESSURE EXAMS AND PULSE VOLUME RECORDINGS

Segmental limb pressures. The location and extent of PAD can be further defined by segmental limb systolic pressure measurements, recorded with a Doppler instrument from plethysmographic cuffs placed over the brachial arteries and at various points on the lower limb, including the upper thigh, the lower thigh, the upper calf just below the knee, and the ankle (Figure 1). (Measurements at the lower thigh are omitted by vascular laboratories that use the three-cuff method.) Typically, a 20-mm Hg gradient between adjacent levels indicates underlying arterial stenosis. For example, segmental limb pressures of 120 mm Hg at the lower thigh and 100 mm Hg at the upper calf would suggest distal superficial femoral artery or popliteal artery disease.

Segmental limb pressure measurements have the same limitation as the ABI with regard to noncompressible vessels.

Although segmental limb pressures can be measured alone, they are more commonly obtained with pulse volume recordings; the combination of the two measures has a reported diagnostic accuracy of 97%.[11]

Pulse volume recordings, or arterial waveforms, are obtained with a cuff system that incorporates a pneumoplethysmograph to detect volume changes in

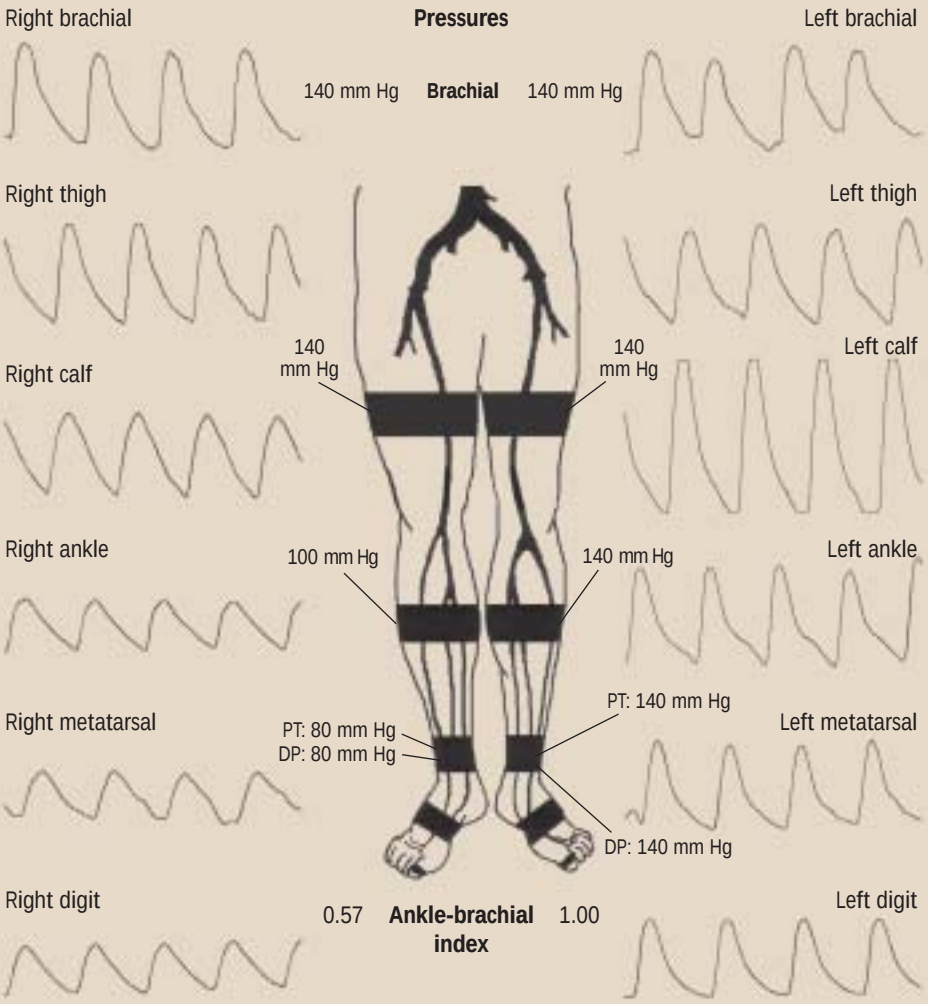

FIGURE 1. Segmental limb pressures, pulse volume recordings, and the ankle-brachial index (ABI) often are obtained in a single examination. All segmental limb pressures are systolic blood pressure measurements and recorded in millimeters of mercury (mm Hg). Cuffs at the brachial arteries (not shown in illustration) and ankles are used to record the systolic pressure for calculation of the ABI. Cuffs at these locations and the upper thigh, lower thigh (if using the four-cuff method not shown here), and upper calf are used to obtain pulse volume recordings and segmental limb pressures. Only pulse volume recordings are obtained from a cuff at the arch of the foot (transmetatarsal) and great toe. This patient has evidence of femoropopliteal and below-the-knee (tibial and/or peroneal) disease on the right. PT = posterior tibial; DP = dorsalis pedis.

the limb throughout the cardiac cycle. Changes in pulse contour and amplitude can be analyzed, providing additional information on the status of the underlying vessels.

A normal waveform has a steep upstroke, a sharp systolic peak, a narrow pulse width, a dicrotic notch, and a downslope bowing to the baseline[12] (Figure 2A). In the presence of arterial disease, the slope of the upstroke flattens, the peak becomes more rounded and has a wider pulse width, the dicrotic notch disappears, and the downslope bows away from the baseline (Figure 2B).

Valuable information about the status of small vessels can be obtained by wrapping a cuff around the arch of the foot or the first digit. Assessment of these vessels may help to further define the nature of the underlying disease (eg, differentiating an embolic event or small vessel vasculitis from large vessel atherosclerosis) and gauge the potential for digital wound healing. Although pulse volume recordings are a subjective tool for evaluation, waveforms that are dampened or flat at the transmetatarsal or first-digit levels relative to the ankle level suggest small vessel disease.

It should be recognized that pulse volume recordings constitute a qualitative, not quantitative, study and may be less accurate than duplex ultrasonography for localizing a lesion.

EXERCISE STRESS TESTING

Exercise treadmill testing, combined with pre- and postexercise ABI measurements, can be used to determine whether a patient's lower extremity symptoms are due to PAD (claudication) or an alternate cause (pseudoclaudication) and to assess the functional status of a patient with PAD. It also is a good method of noninvasively detecting PAD when the

resting ABI is normal but there is a high clinical suspicion for arterial disease.

Performing the test: Look for a drop in ABI

Once a baseline ABI is obtained, the patient is placed on a treadmill using a constant speed and grade (often 2 mph at a 10% or 12% incline); variable-grade testing also can be used. The patient's leg symptoms, their intensity, and their location should be recorded at symptom onset, with changes during the examination, and at the time of maximal discomfort when the patient must stop walking. Any associated symptoms, such as shortness of breath, limb fatigue, or chest pain, also should be recorded. When the patient has walked until reaching maximal discomfort or a predefined end point (eg, 5 minutes), the ABI is remeasured at 1-minute intervals until the pre-exercise baseline is reached.[1] Because of time constraints, some vascular laboratories record only the 1-minute postexercise measurement.

Exercise produces significant peripheral vasodilatation; in the presence of arterial stenosis, this results in a significant blood pressure gradient. A normal individual will have no change or a slight increase in the ABI, whereas the ABI will drop in a patient with PAD.

A change in pulse volume recording morphology during exercise may be used to detect PAD in patients whose ABI cannot be calculated due to low pressures or vessel calcification.

Exercise treadmill tests should not be performed in patients with critical limb ischemia (ischemic rest pain or nonhealing ulcers/gangrene), significant musculoskeletal problems, or cardiopulmonary symptoms (unstable angina or shortness of breath).

Plantarflexion for physically limited patients

An alternative form of exercise testing, active pedal plantarflexion, correlates well with the more traditional treadmill technique.[13] This may be the preferred method for patients with physical limitations that prevent them from walking on a treadmill or when access to a treadmill is limited. After an ABI is obtained, the patient stands flat-footed, often with his or her fingertips resting against a wall for balance. The patient is then encouraged to perform repeated ankle plantarflexions by raising the heels off the floor with knees fully extended. When the patient has completed the test, either by executing 50 repetitions or developing symptoms, the ABI is repeated.

DUPLEX ULTRASONOGRAPHY

Arterial duplex ultrasonographic examination of the lower extremities can also be used to diagnose PAD. It is especially helpful in determining the location of disease and in delineating between stenotic and occlusive lesions, an added benefit when preparing for an intervention. Duplex ultrasonography combines Doppler waveform analysis and Doppler velocities.

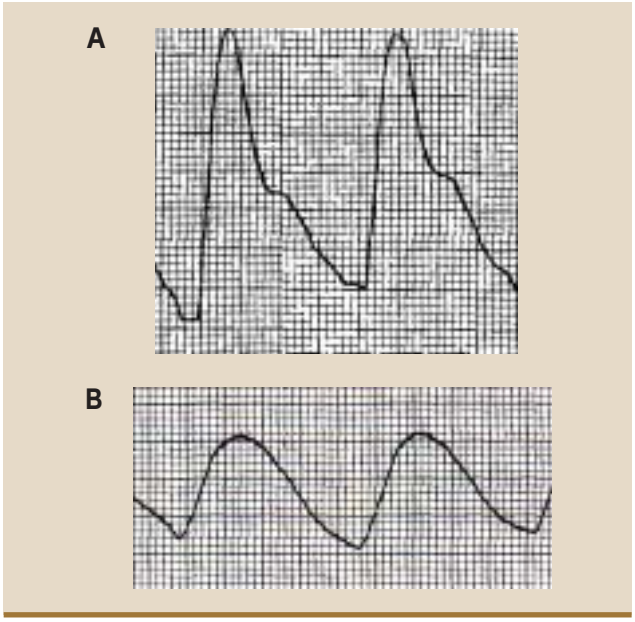

FIGURE 2. Pulse volume recordings showing a normal waveform in a healthy individual (A) and an abnormal waveform in a patient with peripheral arterial disease (B). In the presence of arterial disease, the slope flattens, the pulse width widens, and the dicrotic notch is lost.

A normal peripheral arterial Doppler waveform is triphasic (Figure 3A). Cardiac systole results in the initial forward flow, followed by a brief period of flow reversal in early diastole and subsequent forward flow in late diastole. The flow-reversal component, a result of high peripheral vascular resistance, is absent in the presence of hemodynamically significant stenosis (Figure 3B). Doppler waveform analysis can be used to identify other indicators of disease, including changes in pulsatility and the presence of turbulence.

Detecting and defining stenosis

The degree of stenosis is determined by a combination of waveform analysis and measurement of the peak systolic velocity. Five categories of stenosis have been described[14]:

- Normal (no stenosis)
- 1% to 19% stenosis, when flow disturbances result in changes in the waveform but not in the peak systolic velocity
- 20% to 49% stenosis, when the peak systolic velocity increases by 30% to 100% relative to

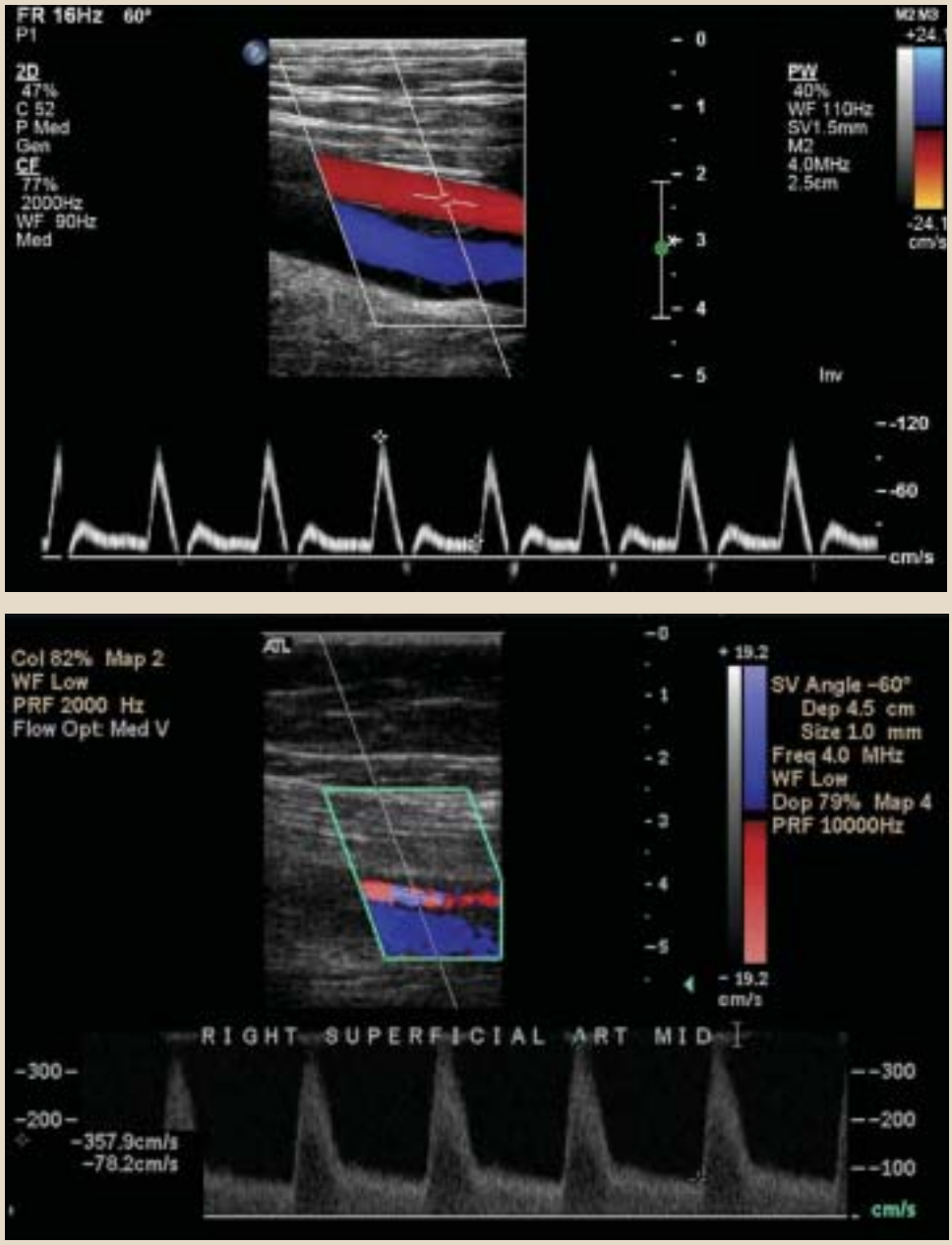

FIGURE 3. Doppler arterial waveforms from patients without (A) and with (B) peripheral arterial disease (PAD). In the setting of PAD, there is a loss of phasicity as well as a shift in the peak systolic velocity.

the proximal normal segment

- 50% to 99% stenosis, when the peak systolic velocity increases by greater than 100% relative to the proximal normal segment; typically there is a loss of flow reversal
- Occlusion, if no flow is identified in the artery.

Koelemay et al[15] performed a meta-analysis of studies on the utility of duplex ultrasonography for detecting occlusion or a stenosis of 50% or greater. They found sensitivity and specificity rates of 86% and 97%, respectively, for the aortoiliac arteries; 80% and 96% for the femoropopliteal arteries; and 83% and 84% for the infragenicular arteries (tibial and peroneal vessels).

Duplex ultrasonography is widely accepted and recommended for postrevascularization surveillance of vein grafts despite mixed results in published studies of its clinical utility.[1] Although surveillance scans of synthetic grafts or arteries after angioplasty are often performed, their value remains questionable.

Despite accuracy, some limitations

Although duplex ultrasonography is an accurate noninvasive test for PAD, it requires technical expertise that may be lacking in many centers. Other limitations are its diminished accuracy in assessing the aortoiliac vessels due to body habitus and bowel gas, signal "dropout" in heavily calcified vessels, and reduced sensitivity for significant stenosis in the presence of multiple lesions within close proximity (tandem lesions).

MAGNETIC RESONANCE ANGIOGRAPHY

Magnetic resonance angiography (MRA) is a particularly useful imaging tool in PAD. It does not expose patients to ionizing radiation, and the recent advent of non–iodine-based intravenous contrast agents (with minimal risk of nephropathy or hypersensitivity) offers advantages in evaluating revascularization options for patients.

Modern MR scanners make possible the prompt acquisition of images for analyzing the arterial tree from the suprarenal abdominal aorta to the distal calves (Figure 4). Impressive images of pedal arteries can also be obtained, although these often require separate "staging" to obtain maximal vessel resolution.

Documented utility in guiding revascularization

Early experience comparing contrast-enhanced MRA with duplex ultrasonography showed MRA to be impressively accurate in planning peripheral arterial revascularization. A retrospective series of 100 patients who underwent both imaging methods found that MRA was more effective than duplex ultrasonography in planning revascularization.[16] A recent prospective study compared pre-intervention duplex ultrasonography with contrast MRA in 295 patients, including 152 who also underwent contrast angiography as a reference standard.[17] Results for detecting significant stenosis were as follows:

- Sensitivity: 76% with ultrasonography vs 84% with MRA
- Specificity: 93% with ultrasonography vs 97% with MRA
- Accuracy: 89% with ultrasonography vs 94% with MRA.

The differences in sensitivity and specificity were statistically significant in favor of MRA.[17]

The ACC/AHA guidelines on PAD suggest that MRA may be useful in determining the location and severity of stenosis and may aid in decisions between endovascular and surgical revascularization.[1]

Patient-related and technological limitations

The limits of MRA center on patient factors and technology issues.

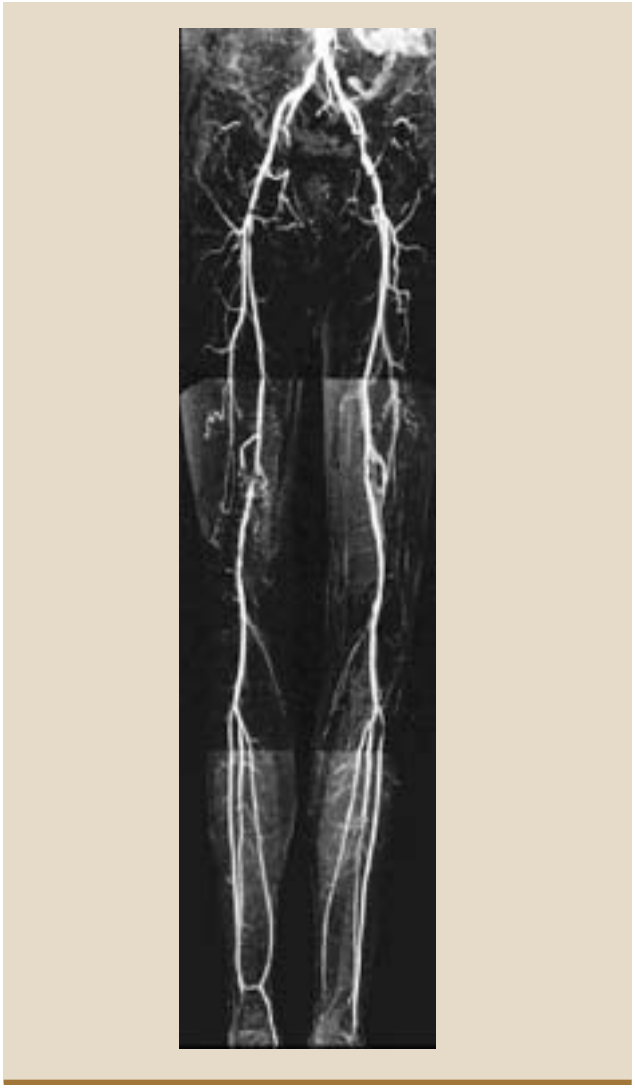

FIGURE 4. A gadolinium-enhanced magnetic resonance angiogram demonstrating excellent visualization from the suprarenal aorta to the ankles bilaterally. Note moderate bilateral external iliac artery disease.

Patients with implantable defibrillators and permanent pacemakers may not undergo MR studies, for fear of causing these devices to malfunction. Patients with intracranial aneurysm clips also are deemed to be at high risk if exposed to the magnetic environment. Claustrophobia also is a major issue, preventing approximately 10% of patients from completing MR studies.

From a technology standpoint, MR often has classified moderate stenoses as severe, and severe stenoses as occlusions. This tendency to overestimate the extent of stenosis may be avoided by close post-processing of images (using equipment enhancement techniques after the images have been obtained) and by improved

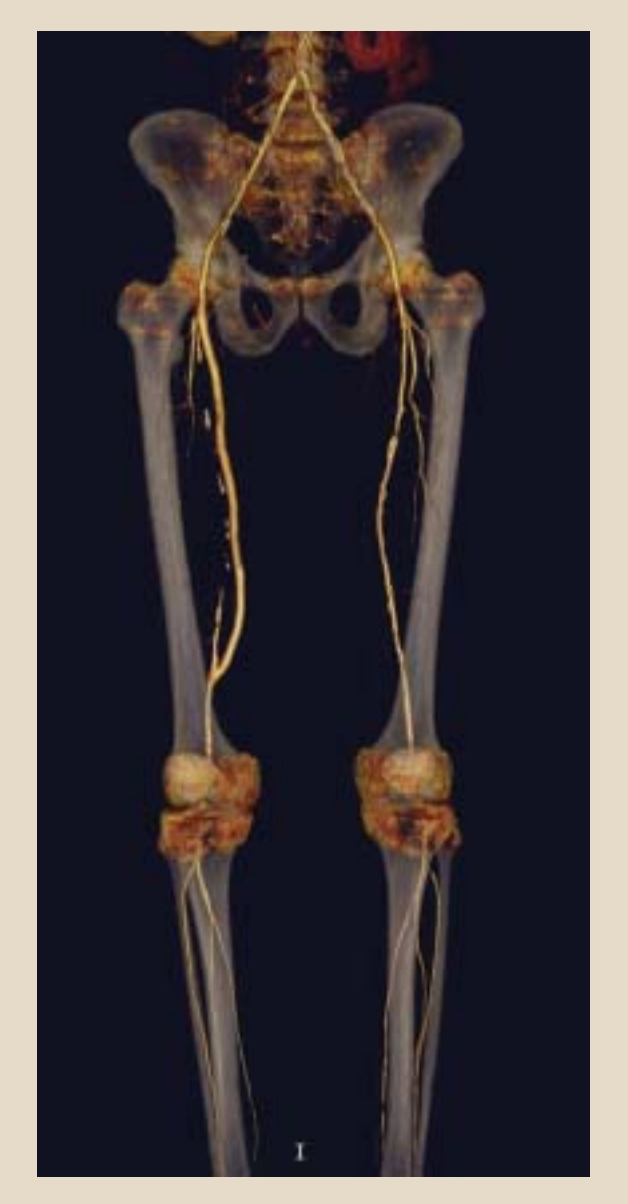

FIGURE 5. Computed tomographic angiogram showing a patent right femoropopliteal artery bypass graft and focal stenosis of the left superficial femoral artery.

timing of contrast agent administration. In addition, MRA cannot reliably detect arterial calcification, which is a potential limitation when revascularization options are being considered. Finally, the metal alloys used in current endovascular stents result in signal dropout, which precludes imaging of the in-stent segments, although MRA can reliably determine the presence of flow proximal and distal to the stent. With newer alloys, imaging within stents using MRA may become a reality.

COMPUTED TOMOGRAPHIC ANGIOGRAPHY

The use of computed tomographic angiography (CTA) as a diagnostic method in PAD is relatively recent, prompted by improvements in image resolution and scan times with the advent of 64-channel "multidetector" scanners. Rapid sequence acquisition provides detailed images from the suprarenal abdominal aorta to the ankles (Figure 5). In contrast to MRA, CTA visualizes calcification well, which is advantageous when considering revascularization strategies.

Promising data emerging

A recent comparative study of 25 patients who underwent CTA and contrast angiography of the lower extremity arteries found CTA to have the following detection rates for various degrees of stenosis:[18]

- 86% sensitivity and 90% specificity for stenosis of less than 50%
- 79% sensitivity and 89% specificity for 50% to 99% stenosis
- 85% sensitivity and 98% specificity for occlusion.

Early experience with multidetector CTA for evaluating peripheral arterial bypass grafts has been reported. Willmann et al[19] evaluated 85 bypass grafts in 65 patients by both duplex ultrasonography and four-channel CTA, finding each method to have excellent and comparable sensitivity and specificity for graft stenosis and other measures.

Evaluation of peripheral arterial stents can be performed with CTA, as there is no signal dropout during CTA scanning. However, the true degree of in-stent stenosis cannot be adequately quantified with current technology and scanning algorithms. The use of CTA has recently been evaluated in carotid artery stents,[20] suggesting utility in assessing post-carotid stent restenosis. However, no data are yet available on CTA for evaluating the patency of peripheral arterial stents.

The ACC/AHA guidelines on PAD suggest that CTA may be useful in planning revascularization strategies, offering faster image acquisition capabilities than MRA.[1]

Limitations from iodine-based contrast media

Because of the need for large volumes of iodinated contrast media administered via a peripheral intravenous cannula, CTA cannot be performed in patients with azotemia or in individuals at increased risk of contrast-induced acute tubular necrosis. In addition, repetitive CTA studies are not recommended, as they would result in patients receiving considerable doses of ionizing radiation.

CONTRAST ANGIOGRAPHY

Contrast angiography, the "gold standard" for the diagnosis of PAD,[1] is rarely required as a diagnostic tool. It is now reserved for patients with PAD who are being considered for endovascular or surgical revascularization, owing to the risks associated with an invasive procedure. Multiple studies suggest that contrast-enhanced MRA obviates the need for contrast angiography in most cases.[21] Similar data are emerging with CTA.[22]

GUIDANCE FOR CHOOSING AMONG DIAGNOSTIC OPTIONS

As detailed above, there are several options for the noninvasive detection and assessment of underlying PAD, each with its advantages and limitations. The preferred test depends on the indication for the study and, at least for imaging methods, the available technology and the available expertise in image acquisition and interpretation. For instance, duplex ultrasonography requires the skill of an experienced vascular technologist, specifically for assessment of aortoiliac segments.

Patient factors also play a significant role. For example, a patient with critical limb ischemia and azotemia is a suboptimal candidate for CTA because of the iodinated contrast media required. A similar patient with an implantable defibrillator is not a candidate for MRA.

The ACC/AHA practice guidelines on PAD[1] recommend the following options for the clinical indications outlined:

- Asymptomatic PAD—ABI
- Symptomatic PAD—ABI; pulse volume recordings and/or segmental limb pressure examination; duplex ultrasonography; or ABI with exercise stress testing to assess functional status
- Possible pseudoclaudication—ABI with exercise
- Candidate for revascularization—duplex ultrasonography, MRA, or CTA.

For most patients, conventional contrast angiography should be performed only if an intervention or surgery is planned.

REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. J Am Coll Cardiol 2006; 47:1239–1312.
2. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000; 31(Suppl):S5–S34.
3. Brooks B, Dean R, Patel S, Wu B, Molyneaux L, Yue DK. TBI or not TBI: that is the question. Is it better to measure toe pressure than ankle pressure in diabetic patients? Diabet Med 2001; 18:528–532.
4. Sikkink CJ, van Asten WN, van't Hof MA, van Langen H, van der Vliet JA. Decreased ankle/brachial indices in relation to morbidity and mortality in patients with peripheral arterial disease. Vasc Med 1997; 2:169–173.
5. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004; 109:733–739.
6. Wang JC, Criqui MH, Denenberg JO, McDermott MM, Golomb BA, Fronek A. Exertional leg pain in patients with and without peripheral arterial disease. Circulation 2005; 112:3501–3508.
7. McDermott MM, Liu K, Criqui MH, et al. Ankle-brachial index and subclinical cardiac and carotid disease: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2005; 162:33–41.
8. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003; 26:3333–3341.
9. Mohler ER 3rd, Treat-Jacobson D, Reilly MP, et al. Utility and barriers to performance of the ankle-brachial index in primary care practice. Vasc Med 2004; 9:253–260.
10. Beckman JA, Higgins CO, Gerhard-Herman M. Automated oscillometric determination of the ankle-brachial index provides accuracy necessary for office practice. Hypertension 2006; 47:35–38.
11. Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. Am J Surg 1979; 138:211–218.
12. Darling RC, Raines JK, Brener BJ, et al. Quantitative segmental pulse volume recorder: a clinical tool. Surgery 1972; 72:873–877.
13. McPhail IR, Spittell PC, Weston SA, Bailey KR. Intermittent claudication: an objective office-based assessment. J Am Coll Cardiol 2001; 37:1381–1385.
14. Strandness DE Jr. Peripheral arterial system. In: Strandness DE Jr, ed. Duplex Scanning in Vascular Disorders. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:118–143.
15. Koelemay MJ, den Hartog D, Prins MH, Kromhout JG, Legemate DA, Jacobs MJ. Diagnosis of arterial disease of the lower extremities with duplex ultrasonography. Br J Surg 1996; 83:404–409.
16. Leiner T, Tordoir JH, Kessels AG, et al. Comparison of treatment plans for peripheral arterial disease made with multi-station contrast medium-enhanced magnetic resonance angiography and duplex ultrasound scanning. J Vasc Surg 2003; 37:1255–1262.
17. Leiner T, Kessels AG, Nelemans PJ, et al. Peripheral arterial disease: comparison of color duplex US and contrast-enhanced MR angiography for diagnosis. Radiology 2005; 235:699–708.
18. Bui TD, Gelfand D, Whipple S, et al. Comparison of CT and catheter arteriography for evaluation of peripheral arterial disease. Vasc Endovascular Surg 2005; 39:481–490.
19. Willmann JK, Mayer D, Banyai M, et al. Evaluation of peripheral arterial bypass grafts with multi-detector row CT angiography: comparison with duplex US and digital subtraction angiography. Radiology 2003; 229:465–474.
20. Goldman CK, Morshedi-Meibodi A, White CJ, Jaff MR. Surveillance imaging for carotid in-stent restenosis. Catheter Cardiovasc Intervent 2006; 67:302–308.
21. Koelemay MJ, Lijmer JG, Stoker J, Legemate DA, Bossuyt PM. Magnetic resonance angiography for the evaluation of lower extremity arterial disease: a meta-analysis. JAMA 2001; 285:1338–1345.
22. Kock MC, Adriaensen ME, Pattynama PM, et al. DSA versus multi-detector row CT angiography in peripheral arterial disease: randomized controlled trial. Radiology 2005; 237:727–737.

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Contemporary management of peripheral arterial disease: I. Cardiovascular risk-factor modification

ABSTRACT

Patients with peripheral arterial disease (PAD) are at increased risk of myocardial infarction or stroke, since multiple vascular beds, beyond the extremities, are likely to be affected by atherosclerosis. In addition to management of leg symptoms in patients with PAD, aggressive modification of cardiovascular risk factors is essential. Smoking cessation, antiplatelet medications, statin drugs, and blood pressure control are proven therapies and strategies for prolonging the lives of patients with PAD. Intensive glycemic control in diabetic patients with PAD lowers the risk of microvascular complications, such as nephropathy, and may reduce the risk of major cardiovascular events and lower extremity amputation. Although aggressive cardiovascular risk-factor modification for patients with PAD may be intuitive, these lifesaving medical therapies for PAD are greatly underprescribed.

The greatest threat to the health of patients with peripheral arterial disease (PAD) is the high risk of a myocardial infarction (MI) or stroke rather than the possibility of a limb-related event. For internists or cardiovascular physicians who care for patients with PAD, the relationship between atherosclerosis of the lower extremities and major cardiovascular events offers a unique opportunity for lifesaving intervention through aggressive risk-factor modification.

This article reviews the evidence base for potentially lifesaving medical therapies for patients with PAD (Table 1) and presents key recommendations from comprehensive practice guidelines for the management of patients with PAD issued in late 2005 by the American College of Cardiology and the American Heart Association (ACC/AHA) and based on a broad consensus of vascular experts.[1]

* Dr. Gornik reported that she has received research grant support from Pfizer. Dr. Creager reported that he has received consulting fees from Genzyme, Sigma Tau, Vasogen, and Wyeth, and has received consulting fees as well as honoraria for teaching and speaking from the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership.

WHY IS RISK-FACTOR MODIFICATION CRITICAL?

As detailed earlier in this supplement, the diagnosis of PAD places a patient at high risk of major cardiovascular events, specifically MI, stroke, and death. An abnormal ankle-brachial index (ABI) is a marker of a high burden of atherosclerosis throughout the body, including the coronary and carotid circulations. Most patients with PAD who undergo coronary angiography have evidence of significant coronary artery disease, and many who undergo ultrasonography have carotid plaques.[2,3]

PAD as a coronary risk equivalent

PAD increases the risk of MI or stroke.[3–5] Patients with PAD have a twofold to fourfold increase in the risk of all-cause mortality and a threefold to sixfold increase in the risk of cardiovascular death relative to patients without PAD.[4,6–8] Indeed, patients with PAD have a higher risk of an MI or a stroke than of a limb-related event, such as a lower extremity ulcer, gangrene, or the need for amputation. This fact often comes as a surprise to patients with PAD, who may be more focused on leg symptoms and the risk of amputation.

The risk of a major cardiovascular event is elevated in patients with PAD regardless of whether they have classic intermittent claudication, atypical symptoms, or asymptomatic disease that is diagnosed solely on the basis of an abnormal ABI.[9] The risk of a major cardiovascular event is highest among patients with the most severe PAD, such as those with critical limb ischemia (ie, ischemic rest pain, ulcer, or gangrene), in whom 1-year event rates are as high as 20% to 25%.[10,11]

In light of these overwhelming data, all patients with PAD should be targeted with the same secondary prevention goals as patients with coronary artery disease. Peripheral arterial disease is a true coronary risk equivalent.[12]

Physician awareness of risk is low

Unfortunately, multiple studies have found that physician awareness of the link between PAD and cardiovascular events is poor, and patients with PAD are less likely to be prescribed risk-modifying treatments, such as antiplatelet medications or statins, than patients with coronary artery disease.[13–16] The remainder of this

article reviews the role that each of these treatments can play in the management of patients with PAD.

SMOKING CESSATION

Tobacco smoking is a potent risk factor for PAD. Among patients with PAD, ongoing tobacco smoking is associated with limb-related events and adverse cardiovascular outcomes. Patients with PAD who continue to smoke are at increased risk of developing critical limb ischemia and of requiring limb amputation.[17–19] Moreover, the risk of failure of lower extremity bypass grafts is increased at least threefold among patients who continue to smoke.[19]

One observational study demonstrated a dose-response relationship between the number of cigarettes smoked daily and the likelihood of amputation.[18] Patients with PAD who stop smoking have improved overall survival compared with those who continue to smoke.[17,20] In a prospective study of 133 patients with symptomatic PAD who underwent lower extremity revascularization or lumbar sympathectomy, the 5-year survival rate for those who stopped smoking was nearly double that for patients who continued to smoke.[20] A randomized clinical trial of smoking cessation would not be ethical, given the overwhelming evidence in favor of smoking cessation.

Counseling, formal programs indicated for all smokers

All patients with PAD who continue to smoke should receive aggressive smoking cessation counseling, and patients should be referred to a formal smoking cessation program, if available.

Several pharmacologic options available

Pharmacologic therapies for smoking cessation that have demonstrated efficacy, such as bupropion and nicotine replacement therapy, should be prescribed as appropriate.[21,22]

A new drug, varenicline, was recently approved by the US Food and Drug Administration for smoking cessation on the basis of six randomized clinical trials that demonstrated efficacy vs placebo or bupropion.[23] Varenicline is a partial nicotinic acetylcholine receptor agonist. Its most commonly reported adverse effects in clinical trials were nausea, headache, insomnia, and abnormal dreams.[23,24] Its typical starting dose is 0.5 mg once daily, which is titrated to a target dose of 1 mg twice daily over a 7-day period and continued for 12 weeks.[24]

Other pharmacologic therapies for smoking cessation are in development.

A cornerstone of PAD management

Aggressive smoking cessation efforts, including physician counseling, referral to a structured smoking cessation program, and pharmacotherapy, constitute one of the most important interventions a physician can make in caring for patients with PAD.

TABLE 1
Lifesaving therapies for all patients with peripheral arterial disease (PAD)

Smoking cessation
- In-office counseling
- Formal smoking cessation, behavior modification programs
- Pharmacotherapy (nicotine replacement, bupropion, varenicline)

Antiplatelet therapy
- Aspirin 75–325 mg daily or clopidogrel 75 mg daily
- Combination aspirin + clopidogrel for patients with recent acute coronary syndrome or with coronary or endovascular stent

Lipid-lowering therapy ("statins")
- Target low-density lipoprotein (LDL) cholesterol < 100 mg/dL
- Consider target LDL cholesterol < 70 mg/dL for patients at highest risk of a cardiovascular event, including diabetic patients, current smokers, those with a recent acute coronary syndrome (ie, myocardial infarction or unstable angina), and those with multiple components of metabolic syndrome

Blood pressure control
- Goal blood pressure < 140/90 mm Hg (< 130/80 mm Hg for patients with diabetes or chronic kidney disease)
- Consider ACE inhibitor or angiotension receptor blocker as agent of choice for hypertensive patients with PAD
- Consider low-dose ACE inhibitor for normotensive patients with PAD
- Beta-blockers are *not* contraindicated among patients with intermittent claudication

Adapted from reference 1.

ANTIPLATELET THERAPY

Multiple clinical trials have demonstrated that antiplatelet therapy, typically with aspirin, decreases mortality and cardiovascular events, particularly MI and ischemic stroke, among high-risk patients with PAD. A meta-analysis of 42 randomized trials that enrolled more than 9,700 patients with symptomatic PAD found that antiplatelet therapy was associated with a 23% reduction in the risk of MI, stroke, or cardiovascular death relative to placebo.[25]

Long-term antiplatelet therapy also improves patency rates among patients who have undergone peripheral arterial bypass grafting or angioplasty, and

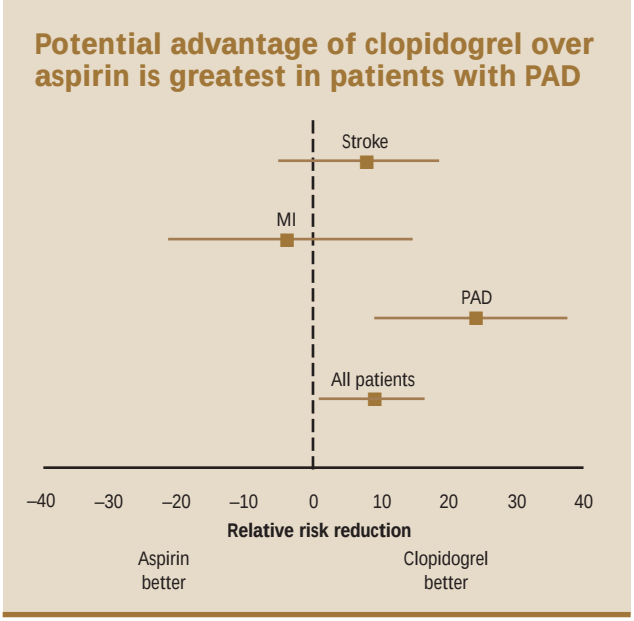

FIGURE 1. Mean percentage reductions (with 95% confidence intervals) in relative risk of a major cardiovascular event with clopidogrel vs aspirin among patients with atherosclerotic vascular disease in the CAPRIE study, according to disease subgroup at enrollment.[27] Major cardiovascular events were defined as myocardial infarction (MI), ischemic stroke, or vascular death. The risk reduction associated with clopidogrel was greatest among patients randomized on the basis of symptomatic peripheral arterial disease (PAD) (RR = 0.76, *P* = .0028). Reprinted from reference 27, copyright 1996, with permission from Elsevier.

has thus become the standard of care for patients undergoing arterial revascularization.[26]

Clopidogrel vs aspirin

The adenosine diphosphate receptor antagonist clopidogrel may be used as an alternative to aspirin. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, regimens of clopidogrel (75 mg daily) and aspirin (325 mg daily) were directly compared among 19,185 patients with atherosclerotic vascular disease, more than 6,400 of whom were enrolled on the basis of symptomatic PAD (intermittent claudication with abnormal ABI or prior revascularization or amputation).[27] After nearly 2 years of follow-up, there was a statistically significant 8.7% reduction in the relative risk of the primary end point of MI, ischemic stroke, or vascular death among patients randomized to clopidogrel compared with those randomized to aspirin (*P* = .043). In a post hoc analysis, the benefit of clopidogrel appeared to be greatest in the subset of patients enrolled on the basis of PAD, in whom the relative risk reduction was 23.8% (Figure 1).

Clopidogrel plus aspirin?

Most recently, the effects of clopidogrel in combination with aspirin have been studied in the Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial.[28] This study included patients with either established atherosclerotic vascular disease or multiple risk factors for atherothrombotic events. Among the 15,603 patients randomized, 2,838 had symptomatic PAD.

There was no overall benefit of clopidogrel in addition to low-dose aspirin (75 to 162 mg daily) compared with aspirin alone in terms of the primary end point of MI, stroke, or cardiovascular death among all patients enrolled. In subset analyses, there was a significant 12% relative reduction in the primary end point among patients enrolled with established cardiovascular disease, as opposed to high-risk asymptomatic patients (*P* = .046). Rates of bleeding events requiring blood transfusion were significantly higher among patients randomized to combination therapy.[28]

Published subset analyses of the CHARISMA study, particularly of the subpopulation with PAD, are anticipated.

Recommendations

On the basis of the above evidence, it is recommended that all patients with PAD, including asymptomatic patients with an abnormal ABI, receive antiplatelet therapy with either aspirin or clopidogrel.[1] Data are limited regarding the optimal aspirin dose for the prevention of cardiovascular and limb-related events among patients with PAD. A daily aspirin dose between 75 and 325 mg/day is generally recommended on the basis of meta-analyses and published clinical trials.[25–28] Although efficacy data, on the basis of the CAPRIE study, favor clopidogrel for patients with PAD, the choice of antiplatelet agent should be made on a patient-by-patient basis, taking into consideration comorbid conditions, tolerability, and cost.

Routine prescription of combination antiplatelet therapy with clopidogrel and aspirin is not recommended at this time unless it is warranted for another indication, such as recent acute coronary syndrome or coronary or endovascular stenting.

LIPID-LOWERING THERAPY

Hypercholesterolemia is a risk factor for development of PAD, as it is for atherosclerosis in all arterial beds, and treatment of hyperlipidemia is a vital component of risk-factor modification for patients with PAD. Among those with symptomatic PAD, aggressive cholesterol management, particularly with HMG-CoA

reductase inhibitors ("statins"), can prevent major cardiovascular events and may even improve symptoms of intermittent claudication.

Reductions in mortality and vascular events

Researchers with the Heart Protection Study randomized 20,536 patients with atherosclerotic vascular disease or diabetes mellitus to receive simvastatin (40 mg daily) or placebo, and then followed them for a mean of 5 years for incident cardiovascular events.[29] The study enrolled patients with a wide range of cholesterol values, including normocholesterolemia, so long as the total cholesterol concentration was at least 135 mg/dL. Among the entire study population, statin therapy was associated with a 13% reduction in all-cause mortality relative to placebo, a 17% reduction in cardiovascular mortality, and a 24% reduction in the incidence of a first major vascular event. The benefits of statin therapy among patients with PAD was similar to that among patients enrolled on the basis of symptomatic coronary artery disease.

Statin therapy has also been associated with reduced perioperative mortality among patients with PAD undergoing major vascular surgery.[30,31]

Improvements in intermittent claudication, better functional capacity

In addition to preventing cardiovascular events and prolonging the lives of patients with PAD, statins appear to exert a benefit in terms of intermittent claudication.

In the Scandinavian Simvastatin Survival Study, hypercholesterolemic patients with coronary artery disease were less likely to develop intermittent claudication if they were randomized to simvastatin rather than placebo.[32]

In a randomized trial of high-dose (80 mg/day) or low-dose (10 mg/day) atorvastatin vs placebo for the treatment of intermittent claudication, the time to onset of claudication was increased by 63% among patients receiving high-dose atorvastatin compared with 38% among placebo recipients (P = .025).[33] Patients were treated for 12 months. Despite an increase in pain-free walking time with high-dose atorvastatin, there was no significant difference in maximal walking time among the three groups.

A recent longitudinal cohort study evaluated whether statin use had an effect on functional capacity among patients with PAD followed for at least 1 year.[34] It found that patients who were taking statins had less functional decline over time, in terms of walking velocity, 6-minute walking distance, and a summary performance score of lower extremity function, compared with patients who were not taking statins. This study did not assess for any differences in effect based on the dose or duration of statin therapy or the type of statin used.

TABLE 2
Standard doses of statins required to achieve a 30% to 40% reduction in LDL cholesterol*

Drug	Dose (mg/d)	LDL reduction (%)
Atorvastatin	10	39
Lovastatin	40	31
Pravastatin	40	34
Simvastatin	20–40	35–41
Fluvastatin	40–80	25–35
Rosuvastatin	5–10	39–45

* Estimated reductions in LDL cholesterol obtained from US Food and Drug Administration package inserts for each drug. Every doubling of the dose above these standard doses is associated with an approximate 6% additional decrease in LDL level.

LDL = low-density lipoprotein

Adapted, with permission, from reference 35.

Recommendations

In light of this multitude of benefits, all patients with PAD should receive a statin in the absence of very low cholesterol or a contraindication. Available statins, along with the doses typically used in their clinical trials, are listed in Table 2.[35]

In published guidelines for the management of hypercholesterolemia, target low-density lipoprotein (LDL) cholesterol values for patients with PAD are identical to those for patients with coronary artery disease.[1,12,35] Patients with PAD should be treated with statins to a target LDL cholesterol level of less than 100 mg/dL, with a target of 70 mg/dL considered for patients at highest cardiovascular risk, including those with recent acute coronary syndrome, current smokers, patients with diabetes mellitus, and those with multiple components of the metabolic syndrome.

Though there is little clinical trial evidence to support the use of other agents for hypercholesterolemia (ie, ezetimibe, fibric acid derivatives, and niacin) in patients with PAD, these agents should be considered for patients in whom statin therapy fails to achieve the target LDL cholesterol level and for patients with hypertriglyceridemia or low levels of high-density lipoprotein cholesterol.

TREATMENT OF HYPERTENSION

Hypertension is a common comorbidity in patients with PAD, and aggressive blood pressure control is important

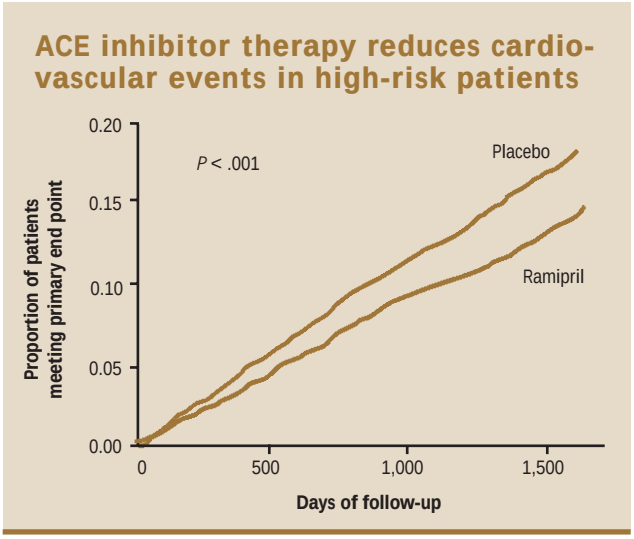

FIGURE 2. Kaplan-Meier estimates of the primary end point (stroke, myocardial infarction, or cardiovascular death) in the HOPE study of 9,297 high-risk patients with atherosclerotic vascular disease or diabetes mellitus.[37] The ACE inhibitor ramipril was associated with a significant 22% relative reduction in this end point compared with placebo. The study included 4,051 patients with symptomatic peripheral arterial disease. Reprinted, with permission, from reference 37.

for preventing stroke, MI, congestive heart failure, and death. Among patients with atherosclerotic vascular disease, diabetes mellitus, and chronic kidney disease, intensive blood pressure control is particularly important for preventing major cardiovascular events.

Treatment itself more important than choice of antihypertensive

Any class of antihypertensive drug may be used for patients with PAD, though clinical evidence is most supportive of the use of thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and beta-blockers in these patients.[36–38] The presence of PAD, with or without intermittent claudication, is not a contraindication to beta-blocker use. Indeed, beta-blockers are vital therapy for patients with PAD who have had a previous MI, have congestive heart failure, or are undergoing major vascular surgery.[39]

Treatment can benefit even normotensive patients

Among patients at highest risk of a cardiovascular event, including those with diabetes and those with PAD, aggressive blood pressure lowering reduces cardiovascular events, even in normotensive patients.

The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated a 22% relative reduction in the primary end point of stroke, MI, or cardiovascular death among patients with vascular disease or diabetes mellitus who received the ACE inhibitor ramipril compared with those who received placebo (Figure 2).[37] This randomized trial included 4,051 patients with symptomatic PAD. Of note, patients in this study had an average baseline blood pressure of 139/79 mm Hg and thus were not hypertensive by traditional criteria.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial randomized normotensive diabetic patients to receive intensive blood pressure lowering (with the ACE inhibitor enalapril or the calcium channel blocker nisoldipine) or placebo.[38] Among patients in the standard therapy (placebo) group, the odds of stroke, MI, or vascular death were inversely related to the ABI, and the 5-year event rate among these very high-risk patients was 38.7% (Figure 3). In the intensive therapy group, blood pressure was lowered from a mean of 135/84 mm Hg to a mean of 128/75 mm Hg, and the odds of a major cardiovascular event among these intensively treated patients was similar between those with a low ABI and those without PAD (Figure 3). These findings highlight the important protective effect of aggressive blood pressure control in diabetic patients with PAD.

Recommendations

A target blood pressure of less than 140/90 mm Hg for patients with PAD is generally recommended in published guidelines, with a more aggressive target of less than 130/80 mm Hg for patients with diabetes mellitus or chronic kidney disease.[1,40] Patients with both diabetes mellitus and PAD are perhaps the group at highest cardiovascular risk and warrant the most intensive blood pressure control. Among normotensive patients with PAD, addition of an ACE inhibitor should be considered for maximal secondary prevention, in light of the HOPE study.[37] An angiotensin receptor blocker is an alternative agent for patients allergic to, or intolerant of, ACE inhibitors.

Given the association of lower extremity PAD with atherosclerosis in all other arterial beds, the astute clinician should be mindful of the possibility of renovascular hypertension among patients with PAD who have multidrug-resistant hypertension (ie, not responsive to at least three medications at adequate doses). In such cases, a diagnostic work-up for renal artery stenosis should be considered, using duplex ultrasonography, magnetic resonance angiography, or computed tomography.

GLYCEMIC CONTROL FOR PATIENTS WITH DIABETES

The importance of intensive glycemic control to prevent microvascular events—retinopathy, nephropathy, and neuropathy—in patients with diabetes melli-

tus is well established.

Potential beneficial effects of intensive glycemic control on the prevention of macrovascular events, such as MI, stroke, and amputation, are less certain. Long-term data from the Diabetes Control and Complications Trial recently demonstrated a significant reduction in major cardiovascular events among patients with type 1 diabetes treated with intensive glycemic control.[41] However, the United Kingdom Diabetes Protection Study did not find a significant reduction in PAD-related events with intensive glucose control in patients with type 2 diabetes.[42]

Diabetic patients with PAD are at particularly high risk of developing a nonhealing ulceration and requiring amputation. In one study of patients with PAD who underwent lower extremity angiography, the presence of diabetes mellitus increased the odds of lower extremity amputation fivefold.[43] In the Strong Heart Study, conducted among American Indians, intensive glycemic control was associated with a decreased likelihood of lower extremity amputation.[44]

Recommendations

The American Diabetes Association has published guidelines specifically for the management of diabetic patients with PAD.[45] These guidelines recommend aggressive treatment with oral medications, insulin, or both in diabetic patients with PAD to achieve a goal hemoglobin A_{1c} of less than 7.0%. They also recommend that all diabetic patients older than 50 years undergo a screening ABI test.

Meticulous foot care also is critical for diabetic patients, and especially those with PAD. Diabetic patients with PAD should be advised to wear comfortable shoes at all times, should perform daily self-inspection of the feet, and should be evaluated regularly by a trained health care provider. Customized footware is recommended for select diabetic patients with PAD.

EXERCISE

Patients with PAD often are forced into a sedentary lifestyle because of the limiting effects of exertional leg symptoms and decreased functional abilities. A sedentary lifestyle is associated, in turn, with increased cardiovascular risk. Among sedentary patients, regular exercise can lead to substantial improvement in many cardiovascular risk factors, including blood pressure, body weight, serum lipid levels, and blood glucose. In addition to modifying the cardiovascular risk profile, exercise is one of the most effective treatments for intermittent claudication (see the next article in this supplement).

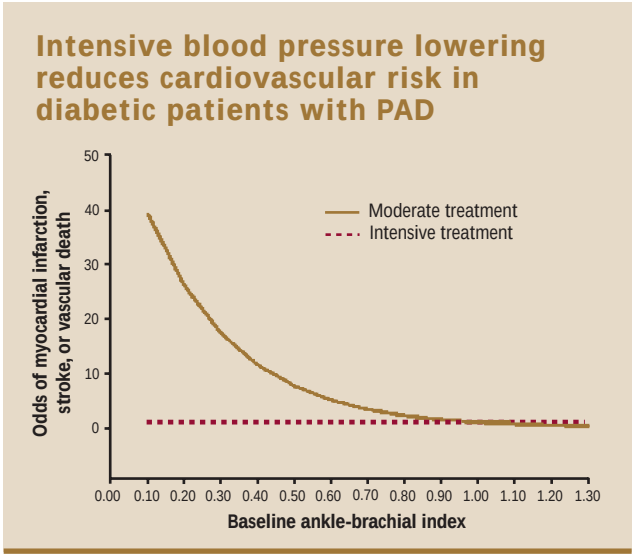

FIGURE 3. Relationship between ankle-brachial index (ABI) and cardiovascular events among normotensive diabetic patients randomized to intensive blood pressure treatment (with enalapril or nisoldipine) or moderate treatment (placebo) in the ABCD trial.[38] Whereas the ABI is inversely related to cardiovascular risk in the moderate treatment group, there is no relationship between the ABI and cardiovascular risk in the intensive treatment group, demonstrating the protective effects of blood pressure lowering in patients with a low ABI, indicative of peripheral arterial disease (PAD). Reprinted, with permission, from reference 38.

PAD exercise rehabilitation programs: Effective but not widely available

Supervised exercise rehabilitation programs improve pain-free walking distance by up to 180% of baseline values.[46] In addition to exercise training, PAD rehabilitation programs incorporate an educational component, focused on optimal nutrition, weight reduction, and smoking cessation, to maximize cardiovascular risk reduction. All patients with symptomatic PAD should be considered for referral to a supervised PAD exercise rehabilitation program.

Unfortunately, despite demonstrated efficacy and cost-effectiveness, such programs are not widely available, largely because of a lack of third-party payer reimbursement. In 2001, the American Medical Association established a Current Procedural Terminology (CPT) code for supervised exercise rehabilitation for PAD (CPT 93668). This development, together with ongoing intersocietal advocacy efforts to broaden reimbursement for PAD rehabilitation, provides hope that such programs may proliferate in the future.

In the absence of an available supervised exercise rehabilitation program, patients with PAD should be encouraged to begin a walking program. A recent study found that patients with PAD who engaged in self-directed walking exercise at least three times per

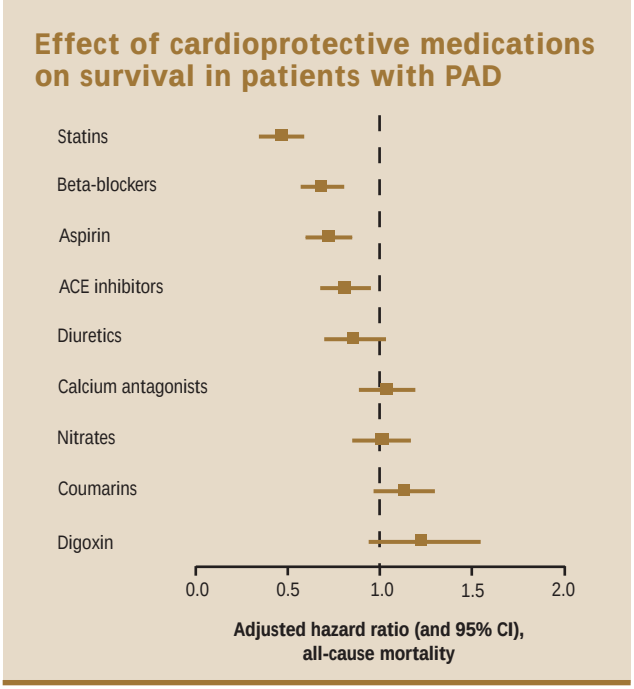

FIGURE 4. Hazard ratios (with 95% confidence intervals) for all-cause mortality associated with nine cardiovascular medications taken by 2,420 consecutive patients with peripheral arterial disease (PAD) in a prospective observational cohort study.[16] Ratios were adjusted for baseline cardiovascular risk factors and propensity scores. Statins, aspirin, beta-blockers, and ACE inhibitors were associated with improved survival. Adapted from data in reference 16.

week had less annual functional decline (in terms of 6-minute walk distance, walking velocity, and summary performance score) than patients with PAD who walked less frequently or not at all.[47]

OTHER THERAPIES

Oral anticoagulation is not routinely recommended for patients with PAD in the absence of another indication, such as atrial fibrillation, a mechanical prosthetic valve, or venous thromboembolism.[1] Oral anticoagulation may be recommended for a subset of patients with a high risk of bypass graft occlusion.

Although epidemiologic studies have established a link between hyperhomocysteinemia and PAD, randomized studies of patients with coronary artery disease and atherosclerotic vascular disease have not demonstrated a benefit of homocysteine-lowering therapy (with folic acid and vitamins B_6 and B_{12}) on cardiovascular outcomes.[48,49] Therefore, we do not recommend these B-complex vitamins for the treatment of hyperhomocysteinemia in patients with PAD.

THE CHALLENGE: WIDER USE OF SIMPLE BUT LIFESAVING TOOLS

Aggressive cardiovascular risk-factor modification prevents MI, stroke, and death in patients with PAD. The therapies to achieve it are well established in the preventive medicine toolbox of the general internist, family practitioner, and cardiologist. A recent 8-year cohort study of 2,420 patients with PAD found that aspirin, statins, beta-blockers, and ACE inhibitors were each independently associated with improved long-term survival (Figure 4).[16] These findings suggest that aggressive cardiovascular risk-factor modification with multimodal drug therapy, combined with smoking cessation and exercise, can further prevent cardiovascular events and reduce mortality among patients with PAD.

Despite the familiarity of these therapies, many clinicians do not adequately use them to prolong the lives of their patients with PAD. Multiple studies have demonstrated a lack of physician awareness of the high cardiovascular risk associated with PAD, along with alarming underutilization of aspirin, statins, and antihypertensive agents in these patients.[11,13–16] Cardiovascular risk assessment and aggressive risk-factor modification is the most important aspect of managing the patient with PAD—a patient in whom simple interventions can yield lifesaving results.

REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines. Circulation 2006; 113:e463–e654.
2. Valentine RJ, Grayburn PA, Eichhorn EJ, Myers SI, Clagett GP. Coronary artery disease is highly prevalent among patients with premature peripheral vascular disease. J Vasc Surg 1994; 19:668–674.
3. Zheng ZJ, Sharrett AR, Chambless LE, et al. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis 1997; 131:115–125.
4. Newman AB, Sutton-Tyrrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. JAMA 1993; 270:487–489.
5. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 2004; 110:3075–3080.
6. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992; 326:381–386.
7. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996; 313:1440–1444.
8. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Athero-

sclerosis 1991; 87:119–128.
9. Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol 1996; 25:1172–1181.
10. Dormandy J, Heeck L, Vig S. The fate of patients with critical leg ischemia. Semin Vasc Surg 1999; 12:142–147.
11. Conte MS, Bandyk DF, Clowes AW, et al. Risk factors, medical therapies and perioperative events in limb salvage surgery: observations from the PREVENT III multicenter trial. J Vasc Surg 2005; 42:456–464.
12. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285:2486–2497.
13. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286:1317–1324.
14. McDermott MM, Hahn EA, Greenland P, et al. Atherosclerotic risk factor reduction in peripheral arterial disease: results of a national physician survey. J Gen Intern Med 2002; 17:895–904.
15. Rehring TF, Sandhoff BG, Stolcpart RS, Merenich JA, Hollis HW Jr. Atherosclerotic risk factor control in patients with peripheral arterial disease. J Vasc Surg 2005; 41:816–822.
16. Feringa HH, van Waning VH, Bax JJ, et al. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. J Am Coll Cardiol 2006; 47:1182–1187.
17. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand 1987; 221:253–260.
18. Lassila R, Lepantalo M. Cigarette smoking and the outcome after lower limb arterial surgery. Acta Chir Scand 1988; 154:635–640.
19. Willigendael EM, Teijink JA, Bartelink ML, et al. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. J Vasc Surg 2005; 42:67–74.
20. Faulkner KW, House AK, Castleden WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. Med J Aust 1983; 1:217–219.
21. Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. N Engl J Med 2002; 346:506–512.
22. Anderson JE, Jorenby DE, Scott WJ, Fiore MC. Treating tobacco use and dependence: an evidence-based clinical practice guideline for tobacco cessation. Chest 2002; 121:932–941.
23. US Food and Drug Administration. FDA news release, May 11, 2006: FDA approves novel medication for smoking cessation. Available at: http://www.fda.gov.bbs/topics/NEWS/2006/NEW01370.html. Accessed July 5, 2006.
24. Chantix (varenicline) package insert. New York, NY: Pfizer Labs; May 2006.
25. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71–86.
26. Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. BMJ 1994; 308:159–168.
27. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996; 348:1329–1339.
28. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354:1706–1717.
29. Heart Protection Study Collaboration Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7–22.
30. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003; 107:1848–1851.
31. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004; 39:967–975; discussion 975–976.
32. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). Am J Cardiol 1998; 81:333–335.
33. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation 2003; 108:1481–1486.
34. Giri J, McDermott MM, Greenland P, et al. Statin use and functional decline in patients with and without peripheral arterial disease. J Am Coll Cardiol 2006; 47:998–1004.
35. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227–239.
36. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981–2997.
37. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342:145–153.
38. Mehler PS, Coll JR, Estacio R, et al. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. Circulation 2003; 107:753–756.
39. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–1794.
40. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289:2560–2572.
41. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643–2653.
42. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853.
43. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care 2001; 24:1433–1437.
44. Resnick HE, Carter EA, Sosenko JM, et al. Incidence of lower-extremity amputation in American Indians: the Strong Heart Study. Diabetes Care 2004; 27:1885–1891.
45. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003; 26:3333–3341.
46. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA 1995; 274:975–980.
47. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. Ann Intern Med 2006; 144:10–20.
48. Bonaa KH, Njolstad I, Ueland PM, et al; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006; 354:1578–1588.
49. Lonn E, Yusuf S, Arnold MJ, et al; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006; 354:1567–1577.

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Contemporary management of peripheral arterial disease: II. Improving walking distance and quality of life

ABSTRACT

Intermittent claudication (IC) is the classic complaint associated with peripheral arterial disease (PAD) and can significantly limit a patient's lifestyle and workplace abilities. IC is defined as reproducible pain affecting the muscles of the lower extremities that begins and increases with activity and resolves with rest. The clinical goals of management include increasing walking distance and improving quality of life. A dedicated, supervised walking program is the foundation of IC management. In addition, two drugs have been approved by the US Food and Drug Administration for the treatment of IC: cilostazol and pentoxifylline. Other agents and treatment strategies have been investigated, and some show clinical promise.

Intermittent claudication (IC) is the classic symptom associated with peripheral arterial disease (PAD). It is defined as activity-induced, reproducible symptoms of ischemia affecting the muscles of the calves, thighs, or buttocks. IC may be described as fatigue, aching, burning, numbness, weakness, or clumsiness of the limb that begins and increases with exertion. Upon rest, the symptoms of IC resolve within approximately 5 to 10 minutes.

Depending on its severity, IC may limit patients' lifestyles and vocational abilities. For this reason, patients with PAD deserve a comprehensive approach to IC management. Dedicated exercise as well as pharmacologic therapy may improve the symptoms of IC. This article reviews the roles of exercise programs and approved medications for the management of IC and surveys evidence on emerging treatment options.

PATHOGENESIS OF IC: AN ACCUMULATION OF ANAEROBIC BYPRODUCTS

With exertion, as the metabolic requirement of the muscle increases, the impaired lower extremity blood flow in a patient with PAD cannot supply sufficient oxygen and glucose to support aerobic metabolism. This allows anaerobic byproducts to accumulate and results in the IC symptoms of muscle pain and fatigue.

HOW IS IC THERAPY ASSESSED?

Measured variables such as pain-free walking distance and maximal walking distance can be assessed and may improve with medical therapy. In addition, subjective quality-of-life measures have been shown to improve in many clinical studies of IC-related treatment. However, clinically meaningful improvement in walking distance and physical functioning is highly subjective and patient-dependent. For this reason, goal-directed medical therapy cannot be overemphasized.

EXERCISE: THE FOUNDATION OF IC THERAPY

A dedicated and supervised exercise program is of paramount importance for improving walking distance in patients with IC. Although such programs are underutilized, they should serve as the foundation for the medical management of IC. Moreover, patients may derive additional benefits from exercise independent of any functional improvements, such as lipid-lowering, glucose-lowering, and blood pressure-lowering effects.

Benefit of exercise may involve a training effect

The mechanism by which exercise rehabilitation improves walking distance is not entirely clear but appears to be related to a training effect. It has been suggested that the periods of intermittent hypoxia induced by ischemia during exercise may initiate adaptive responses within muscle.[1] These responses may include loss of muscle mass and generalized muscle wasting as well as changes in muscle fiber type. Several metabolic adaptations related to oxidative metabolism, with increased aerobic capacity and diminished anaerobic glycolysis, have also been demonstrated.[1]

Regular exercise also may promote improvement in collateral flow to the ischemic muscles. This is demonstrated by collateral development in patients with chronic occlusions. These collaterals are generally believed to represent further development of preexisting vessels due to pressure gradients across areas of occlusion

* Dr. Carman reported that she has received honoraria for teaching and speaking from Bristol-Myers Squibb and Sanofi-Aventis. Dr. Fernandez reported that he has received honoraria for teaching and speaking from Otsuka America Pharmaceutical.

TABLE 1
Results and recommendations from two meta-analyses of exercise programs for patients with intermittent claudication (IC)

Authors	No. studies	Key findings on effects of exercise rehabilitation	Recommended characteristics of a program for maximal improvement
Gardner/ Poehlman[3]	21	Increased mean distance to onset of IC pain by 179%, from 125.9 ± 57.3 m at baseline to 351.2 ± 188.7 m* Increased mean distance to maximal IC pain by 122%, from 325.8 ± 148.1 m at baseline to 723.3 ± 591.5 m*	• Supervised • Duration of 6 months or more • Use of walking as sole mode of exercise • 3 or more sessions per week lasting > 30 min each • Walking to the point of near-maximal pain
Bulmer/ Coombes[4]	22	Produced median improvement of 119% in pain-free walking ability (range, 14% to 276%) Produced median improvement of 83% in absolute walking ability (range, 23% to 210%)	• Supervised • Duration of 20 weeks or more • Use of intermittent-intensity treadmill walking at a pain-free threshold • 3 sessions per week lasting 45 min each

* $P < .001$

promoting hypertrophy of existing vessels rather than the development of new arteries.[2] Exercise training has also been shown to increase the number of mitochondria and capillaries in trained muscles, which may allow for increased cellular oxygen extraction, increased aerobic metabolism, and a reduction in anaerobic glycolysis.[2] Nevertheless, although many patients may derive symptom improvement from an exercise program, changes in blood flow using the ankle-brachial index and other means of measurement rarely document improvement.

Supervised, frequent, and sustained walking programs improve functionality

Many different forms of exercise rehabilitation, such as walking, polestriding (a form of walking with poles similar to cross-country skiing without the skis), resistance training, exercise cycling, and stair-climbing, have been investigated. Moreover, studies have used many different protocols, which makes interpretation of this large body of data somewhat difficult. Nevertheless, two large meta-analyses of clinical trials that used exercise rehabilitation for the treatment of IC have found substantial mean and median improvements in walking ability across 21 and 22 studies, respectively, following exercise rehabilitation (Table 1).[3,4] The authors of each meta-analysis concluded by identifying the components of an exercise program that had the greatest impact on improving walking performance, as also outlined in Table 1. Consistent with these meta-analyses, a recent prospective study among patients with PAD showed that self-directed walking exercise was associated with significantly less functional decline when performed at least three times weekly compared with only one to two times a week.[5]

All patients with PAD should be encouraged to exercise. For PAD patients with IC, the above two meta-analyses specifically support the utility of a walking program consisting of at least 3 sessions per week that ideally last 45 minutes per session. Supervised walking programs have demonstrated superior performance over unsupervised programs. Referral to a supervised PAD rehabilitation program, when available, is preferred over a self-directed walking program, and supervised programs now have a specific Current Procedural Terminology code (CPT 93668) for reimbursement.

What is the best level of exercise intensity?

The required level of exercise intensity remains somewhat unclear. In our experience, asking patients to walk to near-maximal pain may hamper participation, since repeated pain and discomfort may limit patients' adherence. We find that asking patients to walk past the point of initial onset of claudication symptoms is a good alternative, as this still allows for hypoxic stimulation to the muscles without causing undue distress.

APPROVED PHARMACOLOGIC THERAPIES

Beyond the foundational role of exercise in the management of IC, two pharmacologic agents have received US Food and Drug Administration (FDA) approval for the treatment of IC: cilostazol and pentoxifylline. Each agent should be used in conjunction with a supervised exercise program as well as with cardiovascular risk-factor modification and antiplatelet therapy, as discussed in the preceding article in this supplement.

The recently published practice guidelines for PAD

management from the American College of Cardiology and American Heart Association recommend cilostazol as an effective therapy for improving symptoms and increasing walking distance in patients with PAD and IC, and they recommend pentoxifylline as a second-line alternative to cilostazol.[6]

Cilostazol: Effects and dosing considerations

Cilostazol is a reversible phosphodiesterase 3 inhibitor that increases available cyclic adenosine monophosphate (c-AMP). The agent's mechanism of action for increasing walking distance in patients with IC is poorly understood but appears to relate to its c-AMP–mediated vascular properties. Cilostazol has vasodilatory effects, antiplatelet properties, and vascular antiproliferative effects.[7] It also reduces serum triglycerides and increases high-density lipoprotein cholesterol while exerting no effects on low-density lipoprotein cholesterol or lipoprotein(a).[8,9]

The recommended dose of cilostazol is 100 mg orally twice daily, to be taken on an empty stomach. Common side effects include gastrointestinal complaints, including nausea or change in stool characteristics (incidence of approximately 15% for each), headache (approximately 30% incidence), and palpitations (9% incidence).[10] The impact of these side effects may be lessened by reducing the starting dose to 50 mg twice daily for several weeks before increasing to the full dose. This regimen may also prove useful in elderly patients, who seem particularly vulnerable to side effects. For many patients, side effects abate with continued use of the medication.

Patients should avoid grapefruit juice when taking cilostazol. Dose reduction should be considered in patients who are also taking drugs metabolized by the cytochrome P-450 isoenzymes (including omeprazole, erythromycin, ketoconazole, and diltiazem), as these may reduce cilostazol metabolism. Because several other phosphodiesterase inhibitors have been associated with decreased survival in patients with heart failure, cilostazol should not be used in patients with any severity of heart failure. No recommendations exist for patients known to have a decreased ejection fraction without evidence of heart failure. Whether these patients should be permitted to use the drug is unknown. To date no excess cardiovascular morbidity or mortality has been associated with cilostazol.[10] However, since other drugs are available and may be useful for IC, cilostazol may be best avoided in patients with a decreased ejection fraction.

Because of its antiplatelet properties, cilostazol has been demonstrated to prolong bleeding time.[11] In one small study, when cilostazol was combined with aspirin, clopidogrel, or both, the bleeding time was significantly prolonged.[11] While this effect has not been shown to have clinical significance in trials, discontinuing cilostazol prior to surgery or other procedures may be prudent. Cilostazol should also be withheld in patients at increased risk for bleeding or in those experiencing a bleeding event.

Pentoxifylline: Effects and dosing considerations

Pentoxifylline, a methylxanthine derivative, was approved by the FDA for the treatment of IC in 1984. Although its mechanism of action is poorly understood, it is thought to function via intracellular c-AMP phosphodiesterases. Pentoxifylline displays hemorrheologic effects including decreased blood viscosity, increased red blood cell and leukocyte deformability, reduced platelet adhesion, inhibition of neutrophil adhesion and activation, and possibly reduced fibrinogen concentrations.[6,7,12]

The recommended dose is 400 mg orally three times daily, to be taken with food. Gastrointestinal complaints are the most common side effects.[7,12] Pentoxifylline is metabolized in the liver, although the primary compound and metabolites are excreted in the urine.[12] Caution in dosing is indicated in patients with hepatic impairment or decreased renal excretion.[7,12]

Clinical trials

Cilostazol vs placebo. Several trials have compared cilostazol with placebo in patients with IC. All of them have demonstrated improvement in walking distance (both maximal walking distance and pain-free walking distance) with cilostazol. Many of the trials also have evaluated health-related quality-of-life measures using validated, self-reported questionnaires including the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Short Form-36 (SF-36).

The results of these studies are reflected in two recently published meta-analyses of randomized, placebo-controlled trials that used both treadmill walking protocols and quality-of-life questionnaires to assess cilostazol's effects.[9,13] Two dosages of cilostazol were examined—50 mg twice daily and 100 mg twice daily.

One meta-analysis included eight trials and demonstrated significantly greater increases from baseline in both maximal walking distance and pain-free walking distance with both cilostazol dose groups relative to placebo (Table 2).[9]

The other meta-analysis included six phase 3 trials and reported its results according to whether the studies used graded or constant-load treadmill protocols (graded protocols, in which the treadmill speed and/or

TABLE 2
Improvement in walking distance in a meta-analysis of eight placebo-controlled trials of cilostazol[9]

Treatment	Increase in MWD	Increase in PFWD
Placebo	21%	40%
Cilostazol 50 mg bid	44%*	60%*
Cilostazol 100 mg bid	50%*	67%*

MWD = maximal walking distance; PFWD = pain-free walking distance
* $P < .05$ vs placebo

incline are increased during the protocol, are more demanding and typically demonstrate smaller improvements than do constant-load protocols, which use a fixed incline and speed).[13] In studies using a graded protocol, patients taking cilostazol 100 mg twice daily had a 40% increase in maximal walking distance compared with a 20% increase for placebo recipients ($P < .0001$); results were similar for pain-free walking distance ($P < .0001$ for the difference vs placebo). In studies using a constant-load protocol, maximal walking distance increased 76% in patients taking cilostazol 100 mg twice daily compared with 20% in those taking placebo ($P < .0001$); again, results were similar for pain-free walking distance ($P < .0001$). Patients randomized to cilostazol 50 mg twice daily also demonstrated improvement relative to placebo in all the evaluated parameters, but improvement was less than with the 100-mg regimen.

Both meta-analyses showed statistically significant improvements with cilostazol relative to placebo on self-reported WIQ measures of walking distance, walking speed, stair-climbing ability, and pain severity.[9,13]

Pentoxifylline vs placebo. Although the tolerability of pentoxifylline is generally good, it has been suggested that its therapeutic benefit may not be considerably greater than that of placebo.[14,15] However, a meta-analysis of 11 randomized, placebo-controlled, double-blind trials in patients with IC found that pentoxifylline increased treadmill-measured pain-free walking distance by an average of 30 meters and increased absolute claudication distance by approximately 48 meters relative to placebo.[16] The authors cautiously pointed out that 30 meters of treadmill walking is equivalent to 90 meters of walking on flat ground, suggesting that pentoxifylline may play a role in increasing functional walking distance in patients with IC.[16]

TABLE 3
Results from a 24-week comparative trial of cilostazol and pentoxifylline in moderate to severe IC[15]

Treatment	Increase in MWD (m)	Pts with >50% increase in MWD	Increase in PFWD (m)	Pts with symptoms worsened/ unchanged
Placebo (n = 239)	65	27%	57	30%
Cilostazol 100 mg bid (n = 227)	107*	41%	94†	23%
Pentoxifylline 400 mg tid (n = 232)	64‡	27%	74‡	34%

IC = intermittent claudication; MWD = maximal walking distance; PFWD = pain-free walking distance
* $P < .001$ vs placebo and vs pentoxifylline
† $P < .001$ vs placebo and $P = .02$ vs pentoxifylline
‡ Not significantly different from placebo

Direct comparative trial. One randomized, double-blind, multicenter trial has directly compared cilostazol, pentoxifylline, and placebo in patients with moderate to severe IC.[15] As detailed in Table 3, cilostazol was associated with significantly greater increases in both maximal and pain-free walking distance at 24 weeks compared with both placebo and pentoxifylline, whereas the increases with pentoxifylline were not significantly different from those with placebo. Moreover, cilostazol recipients were more likely to have a greater than 50% improvement in walking distance and less likely to have their IC symptoms worsen or remain the same compared with both the placebo and pentoxifylline groups (Table 3). None of the treatments significantly affected patients' responses on the SF-36 or the WIQ instruments relative to baseline.[15]

Response may take several months

For both cilostazol and pentoxifylline, therapeutic benefit appears to have a relatively slow onset and improvement in function and walking distance increases over time. Most trials have evaluated improvement at 4, 12, 16, and 26 weeks of therapy. It is important to stress to patients that these medications take several months to yield improvement. Most clinicians favor a minimum of 12 weeks of therapy before declaring a patient unresponsive to one of these drugs.

As indicated above, not all patients will demonstrate

improvement. One small trial evaluated the effects of withdrawal of cilostazol or pentoxifylline in patients with IC.[17] In this study, the cilostazol (n = 16), pentoxifylline (n = 13), and placebo (n = 16) recipients all demonstrated increases from baseline in pain-free and maximal walking distance over a 24-week period; however, none of these increases was statistically significant, likely owing to the small numbers of patients enrolled. Following completion of the 24-week treatment period, the cilostazol and pentoxifylline groups were treated with placebo for 6 weeks. After withdrawal of therapy, the cilostazol group lost 49% of the improvement in walking distance that had been gained during therapy, whereas no change after crossover was seen in the pentoxifylline or placebo groups. The authors concluded that patients who respond to cilostazol will likely suffer decreased walking performance after withdrawal of the drug, returning to near-baseline walking distances, while patients whose symptoms have not improved with pentoxifylline should be withdrawn from therapy.[17] In addition, although subjective reporting of improvement is helpful, objectively documenting improvement using treadmill-based protocols may be beneficial.[17]

THERAPIES UNDER ONGOING INVESTIGATION FOR IC

In addition to the two FDA-approved therapies for IC, several other therapies and treatment strategies show promise for improving IC symptoms and walking performance in patients with PAD.

Statins

In addition to their role in reducing cardiovascular events in patients with PAD (see preceding article), the HMG-CoA reductase inhibitors ("statins") have demonstrated beneficial effects in terms of increasing walking distance and improving leg function in patients with PAD in a small number of trials.

In a study of 60 patients, simvastatin increased the time to onset of IC symptoms compared with placebo at both 6 and 12 months.[18] In another trial, conducted among 86 patients with IC, those randomized to simvastatin 40 mg/day had a statistically significant increase in pain-free and maximal walking distance at 6 months compared with those randomized to placebo.[19]

Another research team randomized 354 patients with IC to placebo or to atorvastatin 10 mg or 80 mg daily and found that pain-free walking time increased by 63% after 12 months in patients taking atorvastatin 80 mg/day compared with 38% in placebo recipients ($P = .025$).[20] Differences in the increase in maximal walking time did not reach statistical significance, however, and no significant differences were noted in the ankle-brachial index (ABI) or in SF-36 or WIQ scores.[20]

In a study of 641 men and women with and without PAD, those subjects who were taking statins had significantly better performance on tests of 6-minute walk distance and 4-meter walking velocity and a significantly better summary performance score than did the subjects who were not taking statins.[21] Among the 392 subjects with PAD (ABI < 0.90), statin use was associated with improvements in 4-meter walking velocity and in the summary performance score after adjusting for confounding variables.[21]

Although the precise mechanism by which statins may increase exercise tolerance and improve walking ability remains unknown, it likely relates to the statins' pleiotropic effects on vascular endothelium, which extend far beyond lipid reduction. It is likely that many of these effects may play a role in PAD.[22]

ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors also may benefit patients with PAD by improving endothelial function. Few studies have investigated ACE inhibitors for IC, however, and all have been small. In the most recent trial, a 24-week randomized study among 40 patients with symptomatic PAD, ramipril 10 mg/day was associated with significant increases in mean pain-free walking time and maximal walking time compared with placebo.[23]

Therapeutic angiogenesis

Therapeutic angiogenesis has been shown to promote collateral blood vessel formation and improve blood flow. Trials using vascular endothelial growth factor (VEGF) gene transfer began in 1994. Since then, a number of differently engineered and recombinant angiogenic growth factors, including VEGF, basic fibroblast growth factor, hepatocyte growth factor, and hypoxia-inducible factor-1, have been studied, both in critical limb ischemia and in IC. Unfortunately, clinical outcomes have not been overwhelmingly positive, and some trials have been confounded by significant side effects such as skin rash, edema, and proteinuria.[6,7,14,24]

The only study to date to demonstrate some positive results, the TRAFFIC trial,[25] investigated the use of recombinant fibroblast growth factor-2 (rFGF-2). The study randomized 190 patients to placebo or either single-dose or double-dose intra-arterial infusion of rFGF-2. The single-dose arm demonstrated a significant increase in peak walking time at 90 days relative to the placebo arm, but this difference was not maintained at 180 days. Moreover, the time to onset of IC symptoms was not different between the treat-

ment arms and no subjective differences were identified using the WIQ or SF-36 questionnaires.

Trials of therapeutic angiogenesis are continuing and are using a variety of vectors and transfer methods.

L-Carnitine and propionyl-L-carnitine

L-Carnitine and propionyl-L-carnitine have been investigated for IC in several studies and appear to enhance skeletal muscle metabolism. Both compounds have been shown to improve exercise performance, increase pain-free and maximal walking time, and increase muscle strength in patients with PAD.[26–28] No serious adverse events have been documented with either compound. In a 6-month randomized study comparing propionyl-L-carnitine (2 g/day orally) with placebo in 155 patients with IC, time to onset of claudication increased by 39% from baseline in the propionyl-L-carnitine group compared with 14% in the placebo group ($P < .001$).[27] Peak walking time also improved significantly more with propionyl-L-carnitine.[27] Treatment with propionyl-L-carnitine also significantly improved WIQ assessments of perceived walking distance and speed as well as SF-36 assessments of physical role functioning, bodily pain, and transition to a better health state.[27] Propionyl-L-carnitine therapy remains under investigation for IC and PAD.

L-Arginine

L-Arginine, a substrate for nitrous oxide synthase, is a precursor of endothelium-derived nitrous oxide, a potent endogenous vasodilator. It also appears to be a competitive inhibitor of asymmetric dimethylarginine, a nitric oxide synthase inhibitor.[29,30] Supplementation with L-arginine (by intravenous infusion and orally) has been investigated in patients with IC, but results have been inconsistent. A recent pilot study evaluated 3-g, 6-g, and 9-g L-arginine supplements along with placebo in patients with PAD and demonstrated improvement in both pain-free and maximal walking distance in all groups, including the placebo group. The 3-g dose group had the greatest improvement in maximal walking distance, and this dose is expected to serve as a foundation for future investigations.[29]

OTHER INVESTIGATED THERAPIES

Prostaglandin derivatives have undergone trials for IC and critical limb ischemia. Amendt recently published a meta-analysis of 13 prospective, randomized, controlled trials evaluating prostaglandins in patients with IC.[31] Nine of the studies employed intravenous or intra-arterial infusion of prostaglandin E_1 (PGE_1), and four studies used the oral agents beraprost, iloprost, or AS-013 (an oral PGE_1 prodrug). PGE_1 was more effective than the other prostaglandins and placebo in increasing pain-free walking distance and maximal walking distance. However, intravenous or intra-arterial infusion therapy is clinically impractical and further study may be warranted.

Two of the studies in this meta-analysis evaluated oral beraprost in comparison with placebo. In one trial, patients who were randomized to 6 months of beraprost therapy (n = 209) demonstrated statistically significantly greater increases in both pain-free and maximal walking distance compared with patients randomized to placebo (n = 213).[32] These results, however, were not confirmed by a larger subsequent placebo-controlled trial.[33] In addition, anticipated adverse events related to the prostanoid, such as headache, vasodilation, diarrhea, pain, and nausea, were statistically more frequent in the beraprost group than in the placebo group.[33]

Further investigation of prostaglandins for IC is required before their use can be endorsed.

Naftidrofuryl and buflomedil are approved for the treatment of IC in Europe but are not currently available in the United States. Naftidrofuryl (nafronyl oxalate) is a serotonin antagonist; buflomedil is an alpha$_1$/$_2$-adrenergic antagonist. In a meta-analysis of six randomized, blinded clinical trials, naftidrofuryl demonstrated a significant increase in pain-free and maximal walking distance relative to placebo.[34]

Immunomodulation therapy has been explored in light of findings that patients with PAD have elevated serum markers of inflammation including high-sensitivity C-reactive protein (hs-CRP), interleukin-6, monocyte chemoattractant protein-1, and soluble intercellular adhesion molecule type-1.[35,36] The SIMPADICO trial investigated a novel immunomodulation therapy for the treatment of IC. While hs-CRP levels were reduced in patients following therapy, there were no changes in pain-free or maximal treadmill walking distance or in quality-of-life measures.[37]

Other experimental therapies. Chelation therapy, anticoagulation, vitamin E, ginkgo biloba, ketanserin, glutathione, policosanol, ticlopidine, calcium channels blockers such as verapamil and nifedipine, and many other therapies have been investigated in patients with IC.[6,7,14,38] At this time, none of these agents is advocated for the treatment of IC.

SUMMARY

Exercise rehabilitation with a supervised treadmill walking program should serve as the foundation for the comprehensive medical management of IC. In addition, two drugs, cilostazol and pentoxifylline, have

been FDA-approved for the treatment of IC in conjunction with an exercise program. Favorable increases in walking distance and subjective improvement in quality-of-life measures have been demonstrated with cilostazol, whereas results with pentoxifylline are less convincing. Both drugs are fairly well tolerated, with minor side effects reported. Other pharmacologic agents and therapeutic angiogenesis are undergoing investigation for the treatment of IC, but their efficacy and potential role remain to be better defined.

REFERENCES

1. Clanton TL, Klawitter PF. Invited review: adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. J Appl Physiol 2001; 90:2476–2487.
2. McCombs PR, Subramanian S. The benefits of exercise in intermittent claudication: effects on collateral development, circulatory dynamics and metabolic adaptations. Ann Vasc Surg 2002; 16:791–796.
3. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. JAMA 1995; 274:975–980.
4. Bulmer AC, Coombes JS. Optimising exercise training in peripheral arterial disease. Sports Med 2004; 34:983–1003.
5. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. Ann Intern Med 2006; 144:10–20.
6. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). Circulation 2006; 113:e463–e654.
7. Jacoby D, Mohler III ER. Drug treatment in intermittent claudication. Drugs 2004; 64:1657–1670.
8. Elam MB, Heckman J, Crouse JR, et al. Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. Arterioscler Thromb Vasc Biol 1998; 18:1942–1947.
9. Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol 2002; 90:1314–1319.
10. Pratt CM. Analysis of the cilostazol safety database. Am J Cardiol 2001; 87(Suppl):28D–33D.
11. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. J Vasc Surg 2003; 38:710–713.
12. Windmeier C, Gressner AM. Pharmacologic aspects of pentoxifylline with emphasis on its inhibitory actions on hepatic fibrosis. Gen Pharmacol 1997; 29:181–196.
13. Regensteiner JG, Ware Jr JE, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc 2002; 50:1939–1946.
14. Dean SM. Pharmacologic treatment for intermittent claudication. Vasc Med 2002; 7:301–309.
15. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000; 109:523–530.
16. Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. CMAJ 1996; 155:1053–1059.
17. Dawson DL, DeMaioribus CA, Hagino RT, et al. The effect of withdrawal of drugs treating intermittent claudication. Am J Surg 1999; 178:141–146.
18. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. Am J Cardiol 2003; 92:711–712.
19. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med 2003; 114:359–364.
20. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation 2003; 108:1481–1486.
21. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003; 107:757–761.
22. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005; 96(Suppl):24F–33F.
23. Ahimastos AA, Lawler A, Reid CM, Blombery PA, Kingwell BA. Ramipril markedly improves walking ability in patients with peripheral arterial disease. Ann Intern Med 2006; 144:660–664.
24. Morishita R, Aoki M, Ogihara T. Does gene therapy become pharmacotherapy? Exp Physiol 2005; 90:307–313.
25. Lederman RJ, Mendelsohn FO, Anderson RD, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. Lancet 2002; 359:2053–2058.
26. Hiatt WR. Carnitine and peripheral arterial disease. Ann NY Acad Sci 2004; 1033:92–98.
27. Hiatt WR, Regensteiner JG, Creager MA, et al. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. Am J Med 2001; 110:616–622.
28. Barker GA, Green S, Askew CD, Green AA, Walker PJ. Effect of propionyl-L-carnitine on exercise performance in peripheral arterial disease. Med Sci Sports Exerc 2001; 33:1415–1422.
29. Oka RK, Szuba A, Giacomini JC, Cooke JP. A pilot study of L-arginine supplementation on functional capacity in peripheral arterial disease. Vasc Med 2005; 10:265–274.
30. Gornik HL, Creager MA. Arginine and endothelial and vascular health. J Nutr 2004; 134(10 Suppl):2880S–2887S.
31. Amendt K. PGE_1 and other prostaglandins in the treatment of intermittent claudication: a meta-analysis. Angiology 2005; 56:409–415.
32. Lièvre M, Morand S, Besse B, Fiessinger JN, Boissel JP. Oral beraprost sodium, a prostaglandin I2 analogue, for intermittent claudication. Circulation 2000; 102:426-431.
33. Mohler ER III, Hiatt WR, Olin JW, Wade M, Jeffs R, Hirsch AT. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I_2 analogue. J Am Coll Cardiol 2003; 41:1679–1686.
34. Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. Arch Intern Med 1999; 159:337–345.
35. Nylænde M, Kroese A, Stranden E, et al. Markers of vascular inflammation are associated with the extent of atherosclerosis assessed as angiographic score and treadmill walking distances in patients with peripheral arterial occlusive disease. Vasc Med 2006; 11:21–28.
36. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004; 29:439–493.
37. Olin JW, Hiatt WR, Mohler E, et al. A multicenter, randomized, double-blind, placebo-controlled study of immune modulation therapy in patients with symptomatic peripheral arterial disease: the SIMPADICO trial. Late-breaking oral presentation at the 55th Annual Scientific Session of the American College of Cardiology; March 13, 2006; Atlanta, GA.
38. Dawson DL. Comparative effects of cilostazol and other therapies for intermittent claudication. Am J Cardiol 2001; 87(Suppl):19D–27D.

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Contemporary management of peripheral arterial disease: III. Endovascular and surgical management

ABSTRACT

Traditional indications for invasive treatment in patients with peripheral arterial disease (PAD) have been salvage of a threatened limb or improvement of functional capacity in cases of disabling intermittent claudication, but advances in interventional therapy may be lowering the threshold for these therapies. Percutaneous transluminal angioplasty (PTA), with or without stent placement, is the most common endovascular intervention in patients with occlusive lower extremity PAD. In general, PTA is best suited to cases of short-segment stenosis or large-bore vessels, whereas surgery is best applied to multilevel occlusions involving smaller and more distant vessels. This article reviews endovascular therapy, catheter-based thrombolysis, and surgical revascularization procedures in patients with PAD, with special attention to recommendations from new American College of Cardiology/American Heart Association guidelines.

The classic indications for invasive (endovascular or surgical) treatment in patients with lower extremity peripheral arterial disease (PAD) are salvage of a threatened limb (usually presenting as rest pain, nonhealing ulceration, or gangrene) and improvement of functional capacity in patients with short-distance, lifestyle- or vocation-limiting intermittent claudication (IC). Several considerations must be taken into account before a patient with IC is offered the option of any invasive revascularization therapy (Tables 1 and 2).[1,2]

Recent advances in the management of vascular disease, combined with the evolution of experienced vascular interventionalists and the increasingly multidisciplinary approach to peripheral interventions, have improved the risk-benefit ratio of percutaneous revascularization procedures. This shift, along with current understanding of the elusive symptomatology of PAD and its alarming effects on functional status (beyond those of IC), may have lowered the threshold for invasive therapy of lower extremity arterial occlusive disease. This article reviews current understanding of when and how patients with lower extremity PAD are best managed with revascularization therapies, with the recognition that more clinical trials are needed to further examine these strategies and test newer devices.

ENDOVASCULAR INTERVENTIONS

Explosive—and continuing—growth

Since Dotter and Judkins first described percutaneous catheter-based angioplasty for the treatment of symptomatic PAD in 1964,[3] peripheral interventional procedures have proliferated. The use of angioplasty to treat lower extremity disease increased sevenfold in the United States between 1979 and 1996.[4] In some regions the growth has been even more explosive. For example, the annual rate of percutaneous transluminal angioplasty (PTA) for lower extremity PAD, adjusted for age and sex, rose 24-fold (from 1 to 24 per 100,000 residents) in Maryland from 1979 to 1989.[5] More recent estimates suggest that this proliferation continues, with the number of peripheral interventions increasing from 90,000 in 1994 to more than 200,000 in 1997, making endovascular intervention the fastest growing therapeutic area of vascular medicine.[6] While this growth rate already exceeds the growth rate of coronary interventional procedures, this growth is expected to continue as endovascular techniques become applicable to many peripheral arterial conditions that traditionally have been managed surgically.

The most commonly used percutaneous strategy for the treatment of infrainguinal occlusive disease is PTA with or without stent placement. Other strategies, such as subintimal angioplasty, cutting-balloon angioplasty, cryoplasty, and the use of atherectomy devices (eg, laser and thermal devices), are also employed and considered valuable in subgroups of patients. Newer techniques, such as the use of drug-

* Dr. AlMahameed reported that he has received honoraria for teaching and speaking from Sanofi-Aventis, GlaxoSmithKline, and Pfizer. Dr. Bhatt reported that he has received honoraria for teaching, speaking, and consulting from Sanofi-Aventis and from Bristol-Myers Squibb.

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TABLE 1
Indications for revascularization in patients with intermittent claudication (IC)

Before a patient with IC is offered the option of any invasive revascularization therapy, either endovascular or surgical, the following considerations must be taken into account:

- Whether patient has a predicted or observed lack of adequate response to exercise therapy and IC pharmacotherapies
- Whether patient has severe disability, ie, is unable to perform normal work or has very serious impairment of other activities important to him/her
- Whether patient has another disease that would limit exercise even if IC were improved (eg, angina or chronic respiratory disease)
- Whether patient's anticipated natural history and prognosis justify the intervention
- Whether morphology of the lesion is such that the appropriate intervention would have low risk and a high probability of initial and long-term success

Adapted from reference 1.

eluting or biodegradable stents, are considered investigational at present.

Generally, endovascular therapy of PAD is associated with a low rate of serious adverse outcomes in most patients. However, contrast-induced acute renal failure, contrast-related allergic reactions, atheromatous (renal and lower extremity) embolization, and access-related complications such as pseudoaneurysm, arteriovenous fistula, bleeding, and hematoma can all be seen.[2]

What determines indications and outcomes?

In light of differences in structural and anatomic characteristics, the lower extremity arterial system can be divided into three distinct anatomic territories:

- Aortoiliac
- Femoropopliteal
- Infrapopliteal (also referred to as crural, below-the-knee, infrageniculate, or tibioperoneal).

The indications and outcomes of endovascular procedures differ depending on the segment involved as well as other systemic factors (see discussion of these factors in following paragraph). In general, optimal PTA results are achieved when the procedure is offered for short-segment stenosis of large-bore vessels, whereas surgical methods are best applied to multilevel occlusions involving smaller and more distant vessels. Proposed patient-specific predictors of long-term patency following percutaneous therapy include the following:[7–9]

- Lesion severity at baseline (fewer, concentric, noncalcific, and stenotic lesions, as opposed to heavily calcific and occluded arterial segments)
- Anatomy of the affected limb (greater baseline inflow and presence of two- or three-vessel runoff)
- The limb's physiologic adaptation to ischemia, as manifested by clinical presentation (claudication as the presenting symptom rather than critical or acute limb ischemia)
- Angiographic response of the limb to intervention (absence of residual stenosis following angioplasty)
- Physiologic response of the lesion to intervention (normalization of the ankle-brachial index to > 0.90 at 24 hours after the procedure).

Systemic factors, such as ongoing smoking, the presence of diabetes mellitus,[9] and optimal control of other atherosclerotic risk factors such as hyperlipidemia, hypertension, obesity, and a sedentary lifestyle play a fundamental role in the long-term fate of the arterial segment that is the target of the intervention (Table 3).

Endovascular therapy of iliac artery disease

The iliac arteries are most amenable to endovascular therapy and, if disease is present, require intervention first. Successful iliac artery angioplasty improves the inflow and augments collateral blood flow, thus leading to more durable results even when other segments are affected in the same leg. Available PTA techniques have shown an impressive 88% success rate for recanalization of occluded common or external iliac arteries,[10,11] with a 5-year cumulative patency rate as high as 66%.[12] A meta-analysis of six PTA studies and eight stent studies showed a higher initial success rate and an overall 39% reduction in long-term failures (after 4 years) with iliac stents compared with PTA alone, regardless of the indication for the procedure (claudication vs critical limb ischemia) or the type of underlying lesion (stenotic vs occlusive).[13]

Despite the clinical benefits of iliac stent placement as demonstrated by this meta-analysis,[13] many endovascular specialists favor selective stent use for distinctly complex lesions, for those with flow-limiting dissections, or when PTA results are unsatisfactory. Recently published guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) for the management of PAD give a class IB recommendation for PTA as primary therapy for common and/or external iliac artery stenoses and occlusions and a class I recommendation for stenting as primary therapy for such lesions (evidence level B for common lesions and level C for external lesions) (Table 2).[2]

TABLE 2
Key ACC/AHA recommendations on revascularization therapy for lower extremity peripheral arterial disease*

Presentation/ indication	Class	Evidence level	Recommendations
Intermittent claudication (IC)	I	A	Endovascular procedures are indicated for patients with vocation- or lifestyle-limiting IC who have shown inadequate response to exercise or pharmacotherapy and have a favorable lesion profile (eg, focal aortoiliac occlusive disease)
		B	Endovascular procedures are the preferred therapy for TASC type A iliac and femoropopliteal lesions
		B	Primary stenting is the preferred therapy for common iliac artery stenoses and occlusions
		B	Provisional stenting is indicated as salvage therapy following a suboptimal result from iliac artery balloon dilation
		C	Stenting is effective as primary therapy for external iliac artery stenoses and occlusions
		C	Translesional pressure gradients should be obtained to evaluate borderline (50% to 75%) angiographic iliac arterial stenoses before intervention
	IIa	C	Stents, lasers, cutting balloons, atherectomy devices, and thermal devices can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation
	III	C	Primary stent placement is not recommended in the femoral, popliteal, or tibial arteries
			Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD
Critical limb ischemia (CLI)	I	B	Inflow lesions should be addressed first
		B	An outflow revascularization procedure should be performed only if symptoms of CLI or infection persist despite inflow revascularization
	III	C	Surgical and endovascular intervention is not indicated in patients with severe decrements in limb perfusion (eg, ankle-brachial index < 0.40) in the absence of clinical symptoms of CLI
Acute limb ischemia (ALI)	I	A	Catheter-based thrombolysis is recommended for patients with ALI (Rutherford categories I and IIa†) of less than 14 days' duration
		B	Patients with a salvageable extremity should undergo emergent anatomic evaluation for revascularization
	IIa	B	Mechanical thrombectomy devices can be used as adjunctive therapy for ALI due to peripheral arterial occlusion
	IIb	B	Catheter-based thrombolysis or thrombectomy may be considered for patients with ALI (Rutherford category IIb†) of more than 14 days' duration
	III	B	Patients with a nonviable extremity should not undergo evaluation or attempts at revascularization

* Adapted from reference 2. Strength of recommendations is greatest for class I, then class II, etc. Evidence base is strongest for level A, then level B, etc. See reference 2 for full details.

† See table on page S19 of this supplement for explanation of Rutherford categories.

ACC/AHA = American College of Cardiology/American Heart Association; TASC = TransAtlantic Inter-Society Consensus

Furthermore, iliac artery endovascular therapy serves as an excellent adjunctive procedure for preserving inflow to surgical bypass grafts in patients with coexistent infrainguinal disease. In a study of 70 consecutive patients undergoing femorofemoral bypass grafting, iliac PTA (with and without stenting) provided adequate inflow to the graft for more than 14 years after the procedure, providing an alternative to aortofemoral bypass surgery.[14]

Relative contraindications to endovascular therapy of occlusive iliac disease include long occlusions (> 5 cm), iliac artery aneurysmal disease, atheroembolic disease, and long-segment, severe diffuse bilateral aortoiliac disease.[15]

TABLE 3
Factors that increase risk of limb loss in patients with critical limb ischemia

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Endovascular therapy of femoropopliteal disease

Atherosclerotic involvement of the femoropopliteal segment is the most common cause of IC.[16] Whereas stenotic lesions are more common in the iliac arteries, occlusions (typically long segments) are far more prevalent in the femoropopliteal system (Figure 1). In addition to being smaller than the iliac arteries, the femoropopliteal arteries have higher resistance, are more susceptible to spasm, and have lower overall blood flow rates. These factors, combined with the numerous external forces exerted on this segment (extension/contraction, torsion, compression, and flexion) and the impact of inflow and outflow status on procedural outcome, explain the higher rate of restenosis (more than 50% to 80% in some reports) following femoropopliteal PTA.[16] Although primary stent placement in this territory does not seem to significantly improve late patency rates (likely due to a high incidence of in-stent restenosis), such a strategy actually appears costly, increasing initial treatment costs by as much as $3,000 relative to primary PTA.[17]

Given these findings, the recent ACC/AHA guidelines on PAD management recommend against primary stent placement in the femoral, popliteal, or tibial arteries (Table 2).[2] Provisional stent use (in which stent placement is limited to cases of suboptimal PTA results or cases of vessel recoil) remains an acceptable alternative.

Endovascular therapy of infrapopliteal disease

Although described in the early work of Dotter and Judkins,[3] use of infrapopliteal (tibioperoneal trunk, anterior tibial, posterior tibial, and peroneal arteries) endovascular therapy has been far more limited. Infrapopliteal PTA (with and without stenting) is primarily offered to patients who present with critical limb ischemia or debilitating short-distance IC (walking distance < 200 m) who are not candidates for surgical revascularization. Infrapopliteal PTA is also used to complement proximal revascularization procedures, such as femoropopliteal PTA or bypass surgery, particularly when poor outflow threatens the long-term patency of the proximal segment. Although balloon-expandable coronary stents are the only available option for use in the infrapopliteal vasculature, dedicated and vessel-specific drug-eluting and biodegradable stents are being tested for use in this territory.

While the decision to intervene is typically based on the specifics of the individual patient, the following principles are noteworthy to help guide the practice of infrapopliteal PTA:

- Proximal lesions (aortoiliac or femoropopliteal) should always be fixed first when possible
- Surgical bypass grafting is an excellent initial treatment for critical limb ischemia when severe multilevel (including crural) disease is present, and must be pursued whenever possible
- Despite the high incidence of restenosis, temporarily restoring flow to one infrapopliteal artery allows delivery of sufficient nutrients to heal ischemic ulcers and, occasionally, ease rest pain symptoms
- IC alone is rarely a qualifying indication for infrapopliteal PTA except in special situations.

CATHETER-BASED THROMBOLYSIS

Thrombolytic therapy may lead to total or partial resolution of arterial thrombus in patients presenting with acute limb ischemia. Such rapid restoration of flow to the ischemic limb enhances long-term patency and frequently uncovers underlying stenotic lesions that may be amenable to simultaneous revascularization using endovascular techniques.

Three randomized, controlled, multicenter trials that compared thrombolysis to open surgical revascularization supported a role for catheter-based thrombolysis and underscored the importance of careful patient selection as a critical step in avoiding hemorrhagic complications.[18–20] The incidence of such complications in one review ranged from 1% for hemorrhagic stroke to 5% for major hemorrhage and 15% for minor hemorrhage.[21]

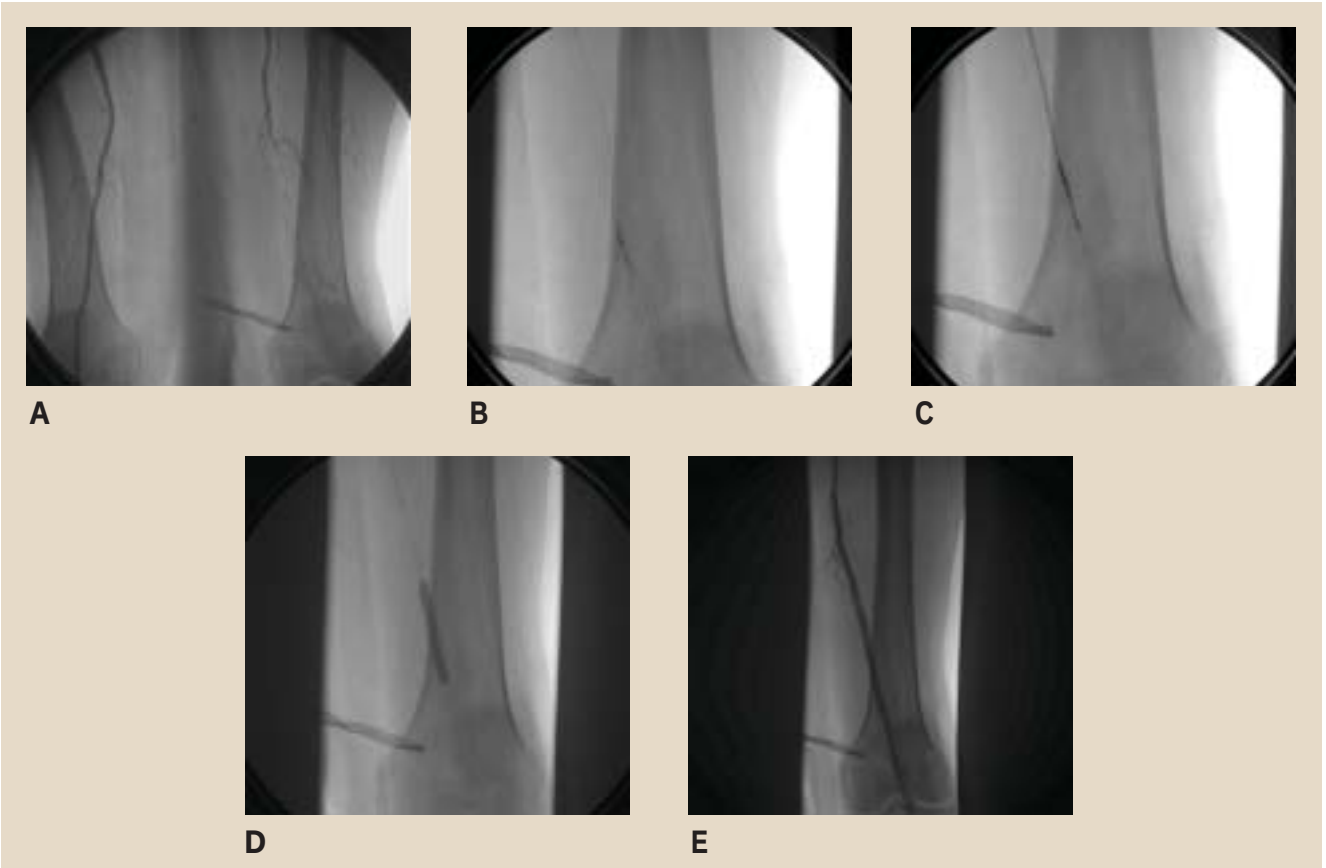

FIGURE 1. Percutaneous recanalization of an occluded left superficial femoral artery (SFA) in a patient with severe, lifestyle-limiting intermittent claudication. The resting ankle-brachial index on the left side was 0.64, which dropped to 0.43 with exercise. Angiography (A) showed a completely occluded long segment of the left SFA. The wire was purposefully passed into the subintimal part of the vessel (B). A Pioneer™ catheter (Medtronic, Minneapolis, MN) was placed in the subintimal space over the wire (C) and, with intravascular ultrasonographic guidance, the true lumen of the distal SFA was entered with a needle and a second wire was passed through that. Balloon angioplasty was performed with a 5 mm x 40 mm balloon (D), and overlapping 7 mm x 120 mm and 7 mm x 40 mm nitinol self-expanding stents were placed (E), producing an excellent angiographic result. Historically, this sort of lesion was treated conservatively or, if the symptoms were disabling, with open surgery. With current endovascular technology, percutaneous revascularization is often possible.

The ACC/AHA guidelines on PAD recommend catheter-based thrombolysis as an effective and beneficial initial treatment for acute limb ischemia[2] (Rutherford categories I and IIa, ie, patients in whom the limb is not immediately threatened or is salvageable if promptly treated; see previous article by Lyden and Joseph), and it is commonly used for treatment of bypass graft thrombosis.

SURGICAL REVASCULARIZATION PROCEDURES

Surgical revascularization of occlusive PAD has been the conventional strategy for lower extremity revascularization since placement of the first synthetic vascular bypass graft in 1952.[22] The two surgical techniques commonly offered are bypass grafting and endarterectomy. While bypass grafting is favored in cases of distal, multilevel, or diffuse occlusive disease, endarterectomy is an excellent option for lesions localized to the aortoiliac, common femoral, or profunda arteries. Dual procedures, using both endarterectomy (of diseased proximal segments) and bypass grafting (of occluded distal vessel), are occasionally offered to severely affected patients.

Autogenous vein grafts (using the patient's own veins) are preferred for infrainguinal bypass grafting, whereas synthetic grafts have shown excellent patency rates when used for aortofemoral bypass grafting.[23] The saphenous vein grafts are the most commonly used autologous grafts, but the cephalic and basilic veins can also be used if needed. Reversed vein grafts are created by disconnecting, reversing (so that forward blood flow is not obstructed by the vein valves), and reconnecting the autologous vein to bypass the dis-

eased arterial segment. In situ vein grafts are formed by leaving the native vein in place, disrupting the vein valves using a surgical instrument (to prevent blood flow impediment), and ligating the perforator veins to avert the formation of arteriovenous fistulas. An apparent mismatch in the size of the reversed vein graft and the native artery (usually at the distal anastomotic site) is not uncommon with in situ vein grafts. It can lead to increased Doppler velocities, which may be interpreted as graft anastomotic stenosis. This is an important distinction that all physicians caring for these patients need to be aware of to avoid misinterpretation of future graft duplex testing.

When distal bypass grafting is the procedure of choice, the surgeon should make every attempt to use a native vein, given the superior long-term patency of native veins (70% to 80% at 5 years) compared with prosthetic grafts of the infrapopliteal vessels.[24–27]

PERIOPERATIVE AND LONG-TERM CARE OF THE VASCULAR SURGERY PATIENT

Patients undergoing noncardiac vascular surgery are at high risk for serious perioperative complications such as cardiac death, nonfatal myocardial infarction, stroke, wound or graft infection, atheroembolization, and peripheral nerve injury.

Although preoperative cardiovascular risk stratification should be emphasized, recent data suggest that preoperative coronary revascularization in this population is not always justified. The Coronary Artery Revascularization Prophylaxis (CARP) trial explored this issue in 510 patients with known, stable coronary artery disease who were scheduled for elective peripheral vascular surgery (33% for abdominal aortic aneurysm repair and 67% for infrainguinal bypass).[28] The patients were randomized to coronary artery revascularization (coronary artery bypass grafting in 41% and percutaeous coronary intervention in 59%) or no revascularization before the planned surgery. Outcomes were similar between the groups in terms of postoperative mortality and acute myocardial infarction at 30 days, left ventricular ejection fraction at 3 months, and survival after a median follow-up of 2.7 years. Furthermore, undergoing coronary revascularization delayed vascular surgery significantly, with a median interval of 54 days between randomization and vascular surgery in the coronary revascularization group compared with 18 days in the control group.

The authors concluded that coronary revascularization before elective vascular surgery is not indicated for patients with stable cardiac symptoms.[28] Elective preoperative cardiac catheterization before elective vascular surgery, however, should be pursued when a preoperative evaluation suggests unstable cardiac symptoms or advanced cardiac disease (such as severe left main or three-vessel coronary artery disease [CAD], multivessel CAD with severe left ventricular dysfunction, or severe aortic stenosis).

Benefits from perioperative beta-blockers, statins

Perioperative use of beta-blockers significantly reduces the risk of cardiovascular events and mortality associated with noncardiac vascular surgery and improves the patency of autogenous infrainguinal bypass grafts.[29,30]

Benefits from perioperative statin therapy in patients undergoing vascular surgery have also been reported recently, including significant reductions in perioperative mortality and in adverse cardiovascular events.[31,32] Statins also appear to improve the patency rates of autogenous infrainguinal bypass grafts.[33]

Our practice is to start all patients on adequate beta-blockade (to a target heart rate of less than 60 beats per minute) and add a statin (for those not already receiving one) before the vascular surgical procedure, and to continue these agents postoperatively if tolerated. The preoperative clearance visit is a convenient opportunity to initiate such medications.

Close follow-up needed to ensure lasting benefit

Following invasive therapy, the vascular patient should receive ongoing care and close follow-up. Surveillance vascular studies (such as serial arterial/graft duplex scans and resting/exercise ankle-brachial index measurement) are necessary to evaluate the continued patency of the segment or segments that were intervened upon. These studies, together with the symptoms reported by the patient at rest and with exertion, are important tools to help the vascular specialist decide on the need, proper timing, and best strategy for future interventions.

Additionally, implementing strict global cardiovascular risk-reduction strategies—including stringent risk-factor modification, exercise, and a healthy diet—is key to ensuring a successful and lasting outcome from the interventional procedure. Lifelong antiplatelet therapy (aspirin 325 mg/day or clopidogrel 75 mg/day, or both for select individuals [see table on page S31 of this supplement]), a supervised exercise/walking program, blood pressure control to less than 140/90 mm Hg, and control of low-density lipoprotein cholesterol to less than 100 mg/dL (with statins and other lipid-lowering agents), together with adequate diabetes control and complete smoking cessation, are all critical lifesaving and limb-saving measures following peripheral revascularization.

REFERENCES

1. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000; 31(1 Pt 2):S1–S296.
2. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). Circulation 2006; 113:e463–e654.
3. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction. Description of a new technique and a preliminary report of its applicaton. Circulation 1964; 30:654–670.
4. Feinglass J, Brown JL, LoSasso A, et al. Rates of lower-extremity amputation and arterial reconstruction in the United States, 1979 to 1996. Am J Public Health 1999; 89:1222–1227.
5. Tunis SR, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease. N Engl J Med 1991; 325:556–562.
6. Krajcer Z, Howell MH. Update on endovascular treatment of peripheral vascular disease: new tools, techniques, and indications. Tex Heart Inst J 2000; 27:369–385.
7. Murray JG, Apthorp LA, Wilkins RA. Long-segment (≥ 10 cm) femoropopliteal angioplasty: improved technical success and long-term patency. Radiology 1995; 195:158–162.
8. Matsi PJ, Manninen HI, Vanninen RL, et al. Femoropopliteal angioplasty in ptients with claudication: primary and secondary patency in 140 limbs with 1-3–year follow-up. Radiology 1994; 191:727–733.
9. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty. Factors influencing long-term success. Circulation 1991; 83:I70–I80.
10. Ring EJ, Freiman DB, McLean GK, Schwarz W. Percutaneous recanalization of common iliac artery occlusions: an unacceptable complication rate? AJR Am J Roentgenol 1982; 139:587–589.
11. Colapinto RF, Stronell RD, Johnston WK. Transluminal angioplasty of complete iliac obstructions. AJR Am J Roentgenol 1986; 146:859–862.
12. Schurmann K, Mahnken A, Meyer J, et al. Long-term results 10 years after iliac arterial stent placement. Radiology 2002; 224:731–738.
13. Bosch JL, Hunink MG. Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. Radiology 1997; 204:87–96.
14. Perler BA, Williams GM. Does donor iliac artery percutaneous transluminal angioplasty or stent placement influence the results of femorofemoral bypass? Analysis of 70 consecutive cases with long-term follow-up. J Vasc Surg 1996; 24:363–369; discussion 369–370.
15. White CJ. Non-surgical treatment of patients with peripheral vascular disease. Br Med Bull 2001; 59:173–192.
16. Martin EC. Transcatheter therapies in peripheral and noncoronary vascular disease. Introduction. Circulation 1991; 83(2 Suppl):I1–I5.
17. Greenberg D, Rosenfield K, Garcia LA, et al. In-hospital costs of self-expanding nitinol stent implantation versus balloon angioplasty in the femoropopliteal artery (the VascuCoil Trial). J Vasc Interv Radiol 2004; 15:1065–1069.
18. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. J Vasc Surg 1994; 19:1021–1030.
19. The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. Ann Surg 1994; 220:251–266; discussion 266–268.
20. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. N Engl J Med 1998; 338:1105–1111.
21. Berridge DC, Makin GS, Hopkinson BR. Local low dose intra-arterial thrombolytic therapy: the risk of stroke or major haemorrhage. Br J Surg 1989; 76:1230–1233.
22. Voorhees AB Jr, Jaretzki A III, Blakemore AH. The use of tubes constructed from vinyon "N" cloth in bridging arterial defects. Ann Surg 1952; 135:332–336.
23. Veith FJ, Gupta SK, Ascer E, et al. Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. J Vasc Surg 1986; 3:104–114.
24. Taylor LM Jr, Edwards JM, Porter JM. Present status of reversed vein bypass grafting: five-year results of a modern series. J Vasc Surg 1990; 11:193–205; discussion 205–206.
25. Belkin M, Knox J, Donaldson MC, et al. Infrainguinal arterial reconstruction with nonreversed greater saphenous vein. J Vasc Surg 1996; 24:957–962.
26. Ouriel K. Peripheral arterial disease. Lancet 2001; 358:1257–1264.
27. Albers M, Romiti M, Brochado-Neto FC, Pereira CA. Meta-analysis of alternate autologous vein bypass grafts to infrapopliteal arteries. J Vasc Surg 2005; 42:449–455.
28. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004; 351:2795–2804.
29. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–1794.
30. Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005; 41:602–609.
31. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003; 107:1848–1851.
32. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004; 39:967–975; discussion 975–976.
33. Abbruzzese TA, Havens J, Belkin M, et al. Statin therapy is associated with improved patency of autogenous infrainguinal bypass grafts. J Vasc Surg 2004; 39:1178–1185.

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