Review Article

Medical Treatment of Peripheral Arterial Disease: A Comprehensive Review

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Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis that affects more than 10 million people in the United States. The risk factors associated with PAD are similar to those found in patients with coronary artery disease and cerebrovascular disease. Medical therapy of PAD must include modification of cardiovascular risk factors with application of strict secondary prevention guidelines. For improvement in quality of life, a structured exercise rehabilitation program remains the most effective noninterventional treatment strategy, but it is difficult to employ from economic and patient-compliance perspectives. Newer pharmacologic therapies have demonstrated efficacy in patients with intermittent claudication. Emerging strategies for management of these patients include revascularization and maximal medical therapy for improvement of physical function as well as reduction in risk for subsequent major cardiovascular events. This article will review the clinical data supporting aggressive medical interventions for patients with PAD.

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Abbreviations: ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, CAD = coronary artery disease, CLI = critical limb ischemia, FDA = Food and Drug Administration, LDL = low-density lipoprotein, PAD = peripheral arterial disease

PERIPHERAL arterial disease (PAD) is a common manifestation of systemic atherosclerosis that affects an increasing population in the United States. Physicians commonly mistake PAD for musculoskeletal or neurologic disorders because manifestations of PAD may mimic nonvascular etiologies. Patients with symptomatic PAD are functionally impaired, often unable to perform daily activities (1). Similarly, PAD represents a marker for premature cardiovascular events (eg, myocardial infarction, stroke) and vascular-related death. With the recent advances in endovascular therapy, awareness of this diagnosis among cardiovascular subspecialty physicians is increasing. Primary care physicians (eg, family practice, internal medicine, podiatric medicine) may not appreciate the prevalence of PAD, the magnitude of associated cardiovascular disease in patients with PAD, and the benefits of aggressive risk factor intervention in these patients.

DEFINITION OF PERIPHERAL ARTERIAL DISEASE

PAD is defined as obstructive arterial disease of the lower extremities that reduces arterial flow during exercise or, in advanced stages, at rest. The presentation of PAD is varied and may appear as asymptomatic arterial disease with abnormal noninvasive test results, symptomatic disease presenting as classic or atypical intermittent claudication, or critical limb ischemia (CLI). Classic (ie, Rose) intermittent claudication is characterized by exertional discomfort in a major muscle group of a lower limb that develops with exercise and is promptly relieved with rest. A significant proportion of patients with symptomatic PAD will not describe classic symptoms, making the diagnosis more difficult. CLI manifests as ischemic rest pain (nocturnal foot/toe discomfort that interferes with sleep), nonhealing ischemic ulcers (painful, dry skin ulcers commonly found over distal bony prominences or toes), or gangrene (skin/soft-tissue necrosis resulting from severe impairment in arterial circulation).

More than 50% of patients with PAD are asymptomatic or have atypical symptoms, one third have classic symptoms of intermittent claudication, and 10% of patients develop CLI (1). The spectrum of PAD is not a continuum. Patients commonly present with CLI without having experienced symptoms earlier—the classic example is the patient with diabetes mellitus who sustains minor trauma to a foot after wearing ill-fitting shoes and develops gangrene, never having experienced claudication in the past.

EPIDEMIOLOGY

The prevalence of PAD depends on how one defines the disease. Given the inaccuracy of physical examination,

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Table 1
Summary Statistics for Risk Factors by Intermittent Claudication Status

	Intermittent Claudication		
	With	Without	*P* Value
Male sex (%)	56	42	<.0001
Mean age (y)	64	60	.0001
High-normal blood pressure (%)	16	19	.1302
Stage 1 hypertension (%)	29	28	.4164*
Stage 2 hypertension (%)	36	22	.0001†
Diabetes (%)	20	6	.0001
Daily cigarette smoking rate	10	7	.0001
Mean cholesterol (mg/dL)	248	239	.0018
Preexisting CHD (%)	34	12	.0001

* Stage 1 hypertension: systolic blood pressure 140–159 mm Hg; diastolic blood pressure 90–99 mm Hg.
† Stage 2 hypertension: systolic blood pressure ≥160 mm Hg; diastolic blood pressure ≥100 mm Hg.
Note.—Reproduced with permission from reference 6. CHD = coronary heart disease.

use of pulse examination as the sole criterion will grossly overestimate the true prevalence (2). In contrast, a historical query for the presence of intermittent claudication underestimates the prevalence of PAD. Epidemiologic studies have wide-ranging prevalence rates from 1.6% to 12%, whereas other studies that use objective disease detection with noninvasive tests have reported prevalence rates from 3.8% to 33% (1).

Noninvasive methods for disease definition in epidemiologic surveys have usually included statistically validated claudication questionnaires. The Edinburgh Claudication Questionnaire (a modification of the World Health Organization/Rose claudication questionnaire), when compared with independent assessment by two physicians of 300 patients older than 55 years of age, demonstrated a sensitivity of 91% and a specificity of 99% for the diagnosis of intermittent claudication (3).

The ankle-brachial index (ABI), which is a comparison of systolic blood pressure in the dorsalis pedis and posterior tibial arteries of the lower limb to that in the brachial artery of the arm with use of a hand-held Doppler device, has been validated against angiographic confirmation of PAD and found to be 95% sensitive and almost 100% specific (4). In clinical practice, this is the most simple, inexpensive, reliable, and reproducible method of identifying patients with PAD.

The age-adjusted prevalence of PAD as defined by ABI no greater than 0.9 is 12% (1). PAD prevalence rates defined by noninvasive testing are reported to be 2.5% at 40–59 years of age, 8.3% at 60–69 years, and 18.8% at 70–79 years (5).

RISK FACTORS FOR THE DEVELOPMENT OF PAD

The risk of developing PAD can be predicted by age and well-defined atherosclerotic risk factors, including tobacco use, diabetes mellitus, hypercholesterolemia, and hypertension. Framingham Heart Study data have defined age, sex, serum cholesterol level, hypertension, tobacco use, diabetes mellitus, and coronary heart disease as factors associated with an increased risk for PAD and intermittent claudication (5) (**Table 1**). This risk factor profile is useful in determining populations and patients at risk.

Age

The prevalence of PAD increases sharply with age, from 3% in patients younger than 60 years of age to 20% in patients older than 75 years of age (5). Data from subjects in the Framingham study revealed that the prevalence of PAD increased 10-fold from men aged 30–44 to men aged 65–74 and almost 20-fold in women in the same age groups (6,7). In the two other epidemiologic studies (8,9), prevalence rates increased with advancing age for intermittent claudication and PAD defined with the use of objective tests.

Hypertension

The role of hypertension as a major risk factor for the development and progression of PAD is well-demonstrated in the Framingham Offspring Study and the German Epidemiological Trial in ABI (10,11). However, no studies are available to evaluate whether antihypertensive therapy directly alters the progression of symptomatic PAD. The Appropriate Blood Pressure Control in Diabetes study demonstrated a marked reduction in cardiovascular events in normotensive PAD patients with diabetes when treated with an intensive blood pressure–lowering strategy compared with standard antihypertensive therapy (12). In the most recent guidelines from the Joint National Committee on the Detection, Evaluation, and Treatment of Hypertension, PAD is considered equivalent in risk to ischemic heart disease, which supports the use of aggressive blood pressure control (13).

Tobacco Use

The single most important modifiable risk factor for the development of atherosclerotic disease is tobacco use. The amount and duration of tobacco use correlate directly with the development and progression of PAD (14). Multiple factors seem to be involved in the atherogenic effect of tobacco use: activation of the sympathetic system with resultant vasoconstriction, oxidation of low-density lipoprotein (LDL) cholesterol, inhibition of tissue plasminogen activator release from the endothelium, increased blood fibrinogen concentration, increased platelet activity, increased expression of plaque tissue factor, and endothelial dysfunction (15).

Smoking increased the risk of intermittent claudication by a factor of eight to 10 in the Reykjavik Study (16), and cessation of tobacco use resulted in a 50% reduction in rates of intermittent claudication over a 20-year period among Icelandic men. A cause-and-

effect relationship between the use of tobacco products and the development of PAD is best demonstrated by those patients who successfully discontinue tobacco use and have no further progression or regression of their PAD. Tobacco cessation results in improved ankle pressure and exercise tolerance in patients with intermittent claudication as early as 10 months after tobacco cessation (17). Tobacco cessation also has a major impact on the long-term risk of complications, including progression of PAD, myocardial infarction, and mortality. In a study by Jonason et al (18), the rates of development of rest pain in patients with intermittent claudication were 0 in nonsmokers and 16% in smokers, whereas 10-year rates of myocardial infarction were 11% and 53%, 10-year cumulative rates of cardiac death were 6% and 43%, and 10-year survival rates were 82% and 46% among nonsmokers and smokers, respectively. In addition, tobacco cessation is associated with improved postoperative arterial bypass graft patency rates (19).

Diabetes Mellitus

PAD is prevalent in patients with diabetes mellitus. Diabetes increases the risk for atherogenesis via deleterious effects on the vessel wall (eg, derangement of nitric oxide bioavailability in endothelial cells, stimulation of proatherogenic activity in vascular smooth muscle cells via reductions in phosphatidylinositol-3 kinase, and increases in oxidative stress and upregulation of protein kinase C receptor for advanced glycation end-products and nuclear factor–κB) as well as effects on blood cells (eg, enhanced platelet aggregation, hypercoagulable state) and rheology (eg, increased blood viscosity and fibrinogen levels) (20).

A survey of patients with diabetes 50 years of age or older demonstrated a prevalence of PAD of 29% (21). In the Rotterdam study (22), diabetes was present in 11.9% and 16% of male and female patients with abnormal ABI, versus 6.7% and 6.3% of those without PAD. In the Cardiovascular Health Study (23), diabetes was associated with a 3.8-fold increased prevalence of PAD in patients older than 65 years of age. In a Veterans Administration patient population with intermittent claudication, diabetes was the major independent predictor of death (24).

Hyperlipidemia

The Lipid Research Clinics Prevalence Study (25) confirmed the association of dyslipoproteinemia (specifically low levels of high-density lipoprotein cholesterol and elevated LDL cholesterol) with symptoms and signs of PAD. In the National Cholesterol Education Program Adult Treatment Panel III report on detection, evaluation, and treatment of high blood cholesterol in adults (26), PAD (regardless of diagnostic methods) was considered a coronary artery risk equivalent. Lipid-lowering agents, most commonly hydroxymethyl glutaryl coenzyme A reductase inhibitors (ie, statins), are thought to benefit patients with PAD by decreasing risk for coronary events and by potentially reversing atherosclerotic lesions. Data from the Scandinavian Simvastatin Survival Study of 4,444 patients with known cardiovascular disease revealed that use of simvastatin reduced episodes of new or worsening intermittent claudication by 38% (27). In patients with familial hypercholesterolemia treated with simvastatin for 2 years, the intima/media thickness in the femoral artery decreased by a mean of 0.283 mm. This suggests atherosclerotic disease reversal with statin treatment in patients at high risk with hypercholesterolemia (28).

Hyperhomocysteinemia

Multiple prospective and case-controlled studies have suggested that an increased plasma homocysteine concentration is an independent risk factor for atherothrombotic vascular disease in the coronary, cerebral, and peripheral vasculature. Homocysteine appears to promote atherogenesis by oxidative damage to vascular endothelial cells and increased proliferation of vascular smooth muscle cells. This is the result of direct oxidative metabolism of homocysteine to homocystine and homocysteine thiolactone and of oxidative modification of LDL, thereby promoting the formation of foam cells (29).

In a metaanalysis of 27 studies, a modest increase in homocysteine was independently associated with an increased risk of coronary artery disease (CAD), cerebrovascular disease, and PAD (30). In a prospective study of patients with symptomatic PAD, for each 1.0-μmol/L increase in plasma homocysteine level, there was a 3.6% increase in the risk of all-cause mortality at 3 years and a 5.6% increase in the risk of cardiovascular-related death (31).

C-Reactive Protein

C-reactive protein has emerged recently as a novel risk factor associated with risk of systemic atherosclerosis. C-reactive protein, together with the total cholesterol/high-density lipoprotein cholesterol ratio were the strongest independent predictors of development of symptomatic PAD in a study by Ridker et al (32). In the same study, C-reactive protein provided prognostic information in addition to standard lipid measures (32).

Chronic Renal Insufficiency

Chronic renal insufficiency has recently emerged as a risk factor strongly associated with PAD. In a cohort of 136 patients with varying degrees of chronic renal insufficiency, the prevalence rates of PAD were 22% in patients not yet undergoing dialysis, 30.6% in patients requiring dialysis, 4.6% in renal transplant recipients, and 1.7% in patients with normal renal function (33). The North Thames Dialysis study (34) of patients older than age 70 noted the prevalence of PAD to be 46% among patients undergoing chronic dialysis treatment.

In the National Health and Nutrition Examination Survey (35), the association of an ABI lower than 0.9 with renal insufficiency (defined as creatinine clearance less than 60 mL/min) was quite strong (odds ratio, 2.5) and was independent of age, diabetes, hypertension, CAD, stroke history, and hypercholesterolemia.

NATURAL HISTORY OF PAD

The impact of PAD on limb and life is quite different and has implications on management strategies. Weitz et al (1) defined the 5-year outcomes (on limb and life) of PAD on patients older than 55 years of age with intermittent claudication. The majority of patients

(>60%) have no progression of limb symptoms beyond the subsequent 5 years after initial presentation. Of the remaining patients, 27% demonstrate progression of symptoms, and the need for revascularization or limb loss occurs in a minority of patients (<10%).

Despite the relatively stable prognosis for the affected limb, there is a marked risk of cardiovascular morbidity and mortality during the 5 years after diagnosis of intermittent claudication. The rate of nonfatal cardiovascular events (myocardial infarction and stroke) is 20%, with a 5-year mortality rate of 30% (36). At the time of diagnosis of intermittent claudication, at least 10% of patients with PAD have concomitant cerebrovascular disease, and 28% have coronary heart disease. In the German Epidemiological Trial on ABI, the cerebrovascular event rate was 15% in the PAD group, versus 7.6% in the control group (odds ratio, 1.8), and the cardiovascular event rates were 28.9% and 17%, respectively (odds ratio, 1.5) (11).

The overall mortality rates in patients with intermittent claudication are 30% at 5 years, 50% at 10 years, and 70% at 15 years. The mortality rate of patients with intermittent claudication is approximately 2.5 times that in an age-matched general population (35). The majority of these deaths are caused by CAD, cerebrovascular disease, and other vascular diseases (ie, abdominal aortic aneurysm, mesenteric ischemia) (37). Subjects with asymptomatic PAD appear to have the same risk of cardiovascular events and death seen in patients with intermittent claudication (38).

For patients with CLI, the outcomes are significantly worse. In addition to the marked increase in rates of limb loss, 20% of these patients die within 6 months. The annual mortality rate in patients with CLI is 25%. Virtually all patients who present with gangrene and/or ischemic rest pain die within 10 years (35,39).

Severity of PAD can be defined based on ABI values (**Table 2**). An abnormal ABI is a potent predictor of cardiovascular events and premature mortality. In the Heart Outcomes Prevention Evaluation study (40), an abnormal ABI was a strong predictor of cardiovascular morbidity and mortality during 4.5 years of follow-up, even in patients without symptoms suggestive of PAD.

Table 2
Interpretation of ABI

ABI	Interpretation
>1.3	Noncompressible
0.91–1.3	Normal
0.41–0.9	Mild to moderate PAD
0–0.4	Severe PAD

Note.—Adapted with permission from Reference 1.

In the Cardiovascular Health Study (41), a statistically significant decrease in survival was observed for each decrement of 0.1 in ABI. The Strong Heart Study (42) demonstrated that an ABI greater than 1.4 (artifactually elevated as a result of arterial calcification, often seen in patients with diabetes mellitus, chronic renal insufficiency, and advanced age) is as strongly associated with cardiovascular mortality as an ABI less than 0.9. These findings have prompted the American Diabetes Association to recommend screening ABI in all diabetic patients older than age 50 and in diabetic patients younger than 50 years with other PAD risk factors (eg, smoking, hypertension, hyperlipidemia, or duration of diabetes greater than 10 years) (43).

MANAGEMENT OF PAD

The goals of therapy for patients with PAD are to prevent systemic atherosclerotic disease progression and clinical cardiovascular events, prevent limb loss, and improve functional status of patients with intermittent claudication.

Patients with PAD must be approached with the same intensity for secondary cardiovascular disease prevention and risk-factor modification as recommended for patients with CAD or carotid artery disease. In 2001, a multidisciplinary task force of the American College of Cardiology and American Heart Association published recommendations for risk factor modification in patients with atherosclerotic cardiovascular disease (44). In these guidelines, all patients diagnosed with PAD must receive aggressive therapy to prevent subsequent atherosclerotic disease and clinical events. Secondary prevention strategies include:

1. Tobacco cessation;
2. Physical activity;
3. Dietary modification;
4. Weight maintenance/reduction with target body mass index of 18.5–24.9 kg/m^2 and waist circumference less than 35 inches in women and less than 42 inches in men;
5. Blood pressure control;
6. Modification of elevated total and LDL cholesterol levels;
7. Antiplatelet therapy;
8. Angiotensin-converting enzyme (ACE) inhibitor therapy; and
9. Glycemic control in patients with diabetes mellitus.

Modification of risk factors requires knowledge, patience, and perseverance by the clinician, as most patients find this aspect of their care very challenging with limited short-term rewards.

Tobacco Cessation

The U.S. Public Health Service has recently published guidelines for treating tobacco use and dependence (45). These guidelines emphasize the importance of the systematic and consistent identification, documentation, and treatment of every tobacco user at every office visit. Treatment options consist of behavioral-modification counseling and short-term tobacco dependence pharmacotherapy. Effective first-line pharmacotherapies for tobacco dependence include sustained-release bupropion hydrochloride and nicotine supplements in varied delivery systems (eg, gum, respiratory inhalers, nasal spray, transdermal patches). At least one of these medications should be prescribed in the absence of contraindications.

Nicotine replacement appears to be a safe therapeutic intervention, even in outpatients with known cardiovascular disease. Concerns about excess cardiac toxicity associated with nicotine therapy and concurrent smoking, based on early case reports, appear to be unfounded (46).

Treatment with sustained-release bupropion alone or in combination with nicotine patches results in significantly higher long-term rates of smoking cessation than use of nicotine patches alone (47). The safety profile

of bupropion in patients with cardiovascular disease is similar to that observed in the general population (48). Unfortunately, the long-term abstinence rates remain poor. If standard methods of tobacco cessation fail, especially in patients with documented PAD, alternative methods (eg, hypnotherapy, acupuncture) should be considered, as the risk of continued smoking outweighs the risks of these nontraditional options.

Glycemic Control in Patients with Diabetes Mellitus

Patients with diabetes and PAD are more likely to present with CLI than patients without diabetes (20). As a result of the diffuse and distal nature of PAD in patients with diabetes mellitus and the associated diabetic sensory neuropathy, neuroischemic ulceration or infection is quite common after minor leg or foot trauma. These factors contribute to the increased incidence of CLI in this patient population. Outcomes of revascularization procedures for PAD are also less favorable in diabetic patients. In 2,653 patients followed for almost 25 years after lower-extremity revascularization, the presence of diabetes mellitus was the sole predictor of recurrent symptoms or progression of PAD (49).

The benefits of glycemic control on microvascular disease (diabetic proliferative retinopathy and nephropathy) in patients with type 1 and type 2 diabetes have been demonstrated in the Diabetes Control and Complications Trial (50) and the UK Prospective Diabetes Study (51). However, the effects on macrovascular disease (ie, PAD) have been less definitive. For instance, after 6.5 years of follow-up in the Diabetes Control and Complications Trial, there was a nonsignificant trend toward fewer cardiovascular events in the intensive insulin therapy group versus usual diabetes care (3.2% vs 5.4%; $P = .08$). The Diabetes Control and Complications Trial (50) was not designed to demonstrate reduction in large artery atherosclerotic events, and the small number of cardiovascular events precluded detection of any cardioprotective effect.

A surrogate marker of large artery atherosclerosis, carotid intima/media thickness, was used in longer-term follow-up in the Diabetes Control and Complications Trial. Aggressive glycemic control resulted in decreased progression of carotid intima/media thickness after 6 years of follow-up (52).

In a subgroup analysis of the UK Prospective Diabetes Study (51), reduction in the hemoglobin A_1c by 1% resulted in an 18% reduction in myocardial infarction, a 15% reduction in stroke, and a 42% reduction in episodes of PAD. We strongly recommend aggressive attempts at strict glycemic control with a target hemoglobin A_1c level less than 7.0 in all patients with PAD.

Reduction in High Blood Pressure

In the seventh report from the Joint National Committee on the Detection, Evaluation, and Treatment of hypertension (13), PAD is considered equivalent in risk to ischemic heart disease, therefore supporting aggressive blood pressure control. Guidelines for treatment of hypertension are beyond the scope of this article and may be found in the report (13). However, two classes of antihypertensive agents warrant specific comment.

In the past, β-blockers have been avoided in patients with intermittent claudication because of fears that β-blockade would lead to unopposed α-receptor vasoconstriction and deterioration in peripheral arterial circulation (ie, worsening intermittent claudication and development of CLI). A metaanalysis of published data suggests that β-blockers do not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild to moderate PAD (53). In patients with known CAD or medically treated aortic dissection in association with PAD, the benefits of β-blockers far outweigh any risk of deterioration in PAD status and should therefore be used.

Recent evidence suggests that the use of ACE inhibitors in patients with PAD may offer protection against major cardiovascular events beyond those expected from blood pressure lowering. The Heart Outcomes Prevention Evaluation study demonstrated that ramipril significantly reduced the rates of death, myocardial infarction, and stroke in patients who are at high risk for cardiovascular events, independent of antihypertensive impact (54). These same cardiovascular protective effects of ramipril were seen in patients with clinical or subclinical PAD (38).

Based on the available evidence, we recommend that patients with PAD be considered for treatment with ACE inhibitors if tolerated. ACE inhibitors may be first-line agents for hypertension in patients with PAD, Further data will be needed to provide a stronger recommendation regarding the use of ACE inhibitors in normotensive patients with PAD.

Reduction in Hypercholesterolemia

The Adult Treatment Panel of the National Cholesterol Education Program states that PAD represents equivalent risk to that of established CAD. Aggressive LDL cholesterol lowering must be offered to all patients with PAD to reduce subsequent risk of myocardial infarction, stroke, and vascular death (26). Moreover, recent data suggest that use of hydroxymethyl glutaryl coenzyme A reductase inhibitors may actually improve symptoms associated with PAD. Treatment with simvastatin in hypercholesterolemic patients with PAD resulted in an increase in pain-free and total walking distances, as well as improvement physical function (55,56). In another trial by Mohler et al (57), treatment with atorvastatin 80 mg/d for 12 months resulted in significant improvements in pain-free walking time and overall physical activity compared with placebo and atorvastatin 10 mg/d. A large-scale multicenter trial in patients with intermittent claudication in which several doses of nicotinic acid and lovastatin were compared with placebo is currently enrolling patients to determine if this pharmacologic strategy offers similar symptomatic benefit.

The Heart Protection Study (58) in the United Kingdom addressed the question of timing of statin therapy. This is the largest randomized trial (20,536 adults) of cardiovascular disease prevention to date among a broad population of patients at high risk. The addition of simvastatin to existing cardiovascular therapy safely produced substantial additional benefits regardless of patients' initial cholesterol concentrations. The decision to initiate statin therapy should be based on the 10-year risk of CAD. Given that PAD

confers a 10-year risk of death greater than 20%, all patients with PAD should be administered statin therapy independent of baseline LDL level. According to the guidelines set forth in the National Cholesterol Education Program, the target LDL level in patients with PAD should be less than 100 mg/dL (26). Recent data challenge this and suggest lower LDL cholesterol treatment goals (59). Further data specific to patients with PAD will be required before target LDL cholesterol levels less than 100 mg/dL are recommended. Statins are currently recognized as first-line agents to lower LDL levels in patients with PAD, and aggressive lipid lowering is mandatory in patients with PAD.

Hyperhomocystinemia

Despite the ease of therapy with vitamin supplements, before widespread screening of patients with PAD for hyperhomocystinemia is advocated, more evidence of the clinical efficacy of this therapy is needed. Recent randomized interventional trials failed to demonstrate any beneficial effect of folic acid administration on cardiovascular endpoints in patients with stable CAD and end-stage renal disease (60,61). In patients with ischemic stroke, the Vitamin Intervention for Stroke Prevention trial (62) failed to show any benefit of high-dose folic acid, pyridoxine, and cobalamin supplementation in stroke prevention.

Antiplatelet Therapy

Antiplatelet agents are recommended to prevent associated cardiovascular morbidity and mortality. Platelet activation is increased in patients with PAD, suggesting an underlying prothrombotic state (63) However, until recently, the use of aspirin in patients with PAD was not based on direct evidence, but only on analogous data in coronary and cerebral atherosclerosis, in which antiplatelet therapy has documented clear efficacy. In small studies (64,65), the routine use of low-dose aspirin by apparently healthy men reduced the need for peripheral artery surgery and delayed the onset and progression of PAD. A metaanalysis of antiplatelet treatment in patients after peripheral arterial bypass surgery demonstrated a nonsignificant effect on cardiovascular outcomes and survival but a mildly positive effect on the patency of peripheral arterial bypass grafts (66).

The Antithrombotic Trialists' Collaboration (67) summarized the results from 287 studies involving 135,000 patients randomized to receive antiplatelet therapy or placebo. This meta-analysis also evaluated 77,000 patients treated with different antiplatelet regimens. In the subset of patients treated with antiplatelet therapy for PAD (n = 9,214), antiplatelet therapy demonstrated a 23% reduction in serious vascular events, with similar benefits among patients with intermittent claudication and patients undergoing lower-extremity revascularization. Currently, there is no evidence supporting the additive effect of dipyridamole with aspirin in patients with PAD, as seen in patients with symptomatic cerebrovascular disease (64).

Ticlopidine, a thienopyridine derivative that blocks the activation of platelets by adenosine diphosphate, has demonstrated significant benefit in patients with PAD. However, enthusiasm for this drug has been tempered by the substantial risk of thrombocytopenia, neutropenia (which occurs in 2.3% of treated patients), and thrombotic thrombocytopenic purpura (which occurs in one in 2,000-4,000 patients) (68). We do not recommend the routine use of ticlopidine in patients with PAD.

Clopidogrel, a second thienopyridine derivative, has an action similar to ticlopidine without the serious hematologic side effects. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events study (69), a multicenter, multinational, prospective, randomized trial, evaluated aspirin versus clopidogrel in more than 19,000 patients with recent stroke or myocardial infarction or symptomatic PAD. Clopidogrel was associated with a modest yet significant reduction in the primary composite endpoint of myocardial infarction, ischemic stroke, and vascular death compared with aspirin. In a subgroup analysis of 6,452 patients enrolled in the trial with PAD, clopidogrel resulted in a relative risk reduction of 24% compared with aspirin (69). Clopidogrel is well-tolerated, with no increase in adverse events or discontinuation rates compared with aspirin. Clopidogrel has been associated with a low risk of adverse hematologic effects. The estimated risk of thrombotic thrombocytopenic purpura is four per 1 million patients, a level that does not warrant routine hematologic monitoring (70). Clopidogrel is the only antiplatelet agent approved by the United States Food and Drug Administration (FDA) specifically for the reduction of cardiovascular events in patients with PAD.

The combined effect of aspirin plus clopidogrel has been demonstrated in patients with acute coronary syndromes (71). Currently enrolling trials will address combination therapy in PAD; however, this recommendation cannot be made at present.

We recommend antiplatelet therapy in every eligible patient with PAD as primary prevention against major cardiovascular events and mortality. There are insufficient data supporting the use of a particular antiplatelet agent or combination antiplatelet therapy after endovascular therapy for PAD. If the economic issues of long-term clopidogrel are manageable, this agent is superior to aspirin in reducing the risk of major cardiovascular events and vascular death.

Exercise Therapy

Patients with intermittent claudication have marked impairment in exercise performance and overall functional capacity. Reduced walking capacity is associated with impairment in the performance of activities of daily living and in general quality of life. These patients' peak oxygen consumption measured during graded treadmill exercise is 50% of age-matched subjects with normal peripheral arterial circulation, indicating a level of impairment similar to patients with debilitating congestive heart failure (20).

Regular aerobic exercise reduces cardiovascular risk (by lowering cholesterol and blood pressure and improving glycemic control) and produces symptomatic improvement in patients with PAD. The beneficial effects of exercise may be explained by several mechanisms, including improvements in endothelial vasodilator function, skeletal muscle metabolism, blood viscosity, and inflammatory responses. Exercise training also improves oxygen extraction and walking

efficiency by decreasing oxygen consumption for the same workload (72).

In older patients with PAD, data have demonstrated that exercise rehabilitation lowered total and LDL cholesterol levels, was associated with a decrease in systolic blood pressure, and significantly increased pain-free and maximum walking distance (73). In a metaanalysis of randomized trials of exercise in patients with intermittent claudication, exercise therapy significantly improved pain-free walking time by 180% and maximal walking time by 150% at 6 months. Compared with percutaneous revascularization, supervised exercise produced significant improvements in walking time at 6 months and did not differ significantly from the results of surgical treatment (74).

We recommend a supervised exercise program that encompasses the following specific factors:

Duration greater than 30 minutes per session;

Frequency of at least three sessions per week;

Walking used as the mode of exercise;

Use of near-maximal pain during training as claudication pain endpoint;

Walking speed to achieve moderate claudication symptoms within the first 5 minutes; and

Program length of greater than 6 months.

Supervised exercise therapy is the most effective symptomatic therapy for patients with intermittent claudication. The main factors limiting success of exercise therapy include lack of patient motivation and compliance and the economic obstacles for reimbursement for supervised peripheral arterial rehabilitation programs in the United States. Unsupervised exercise rarely offers clinically meaningful benefit. Available data analyzing the implementation of supervised exercise in patients with PAD are not encouraging. In the United Kingdom, regular walking exercise programs were not followed by almost 50% of patients with intermittent claudication (75).

Pharmacologic Treatment of Peripheral Arterial Disease

Pentoxifylline (Trental; Aventis, Bridgewater, NJ), a methylxanthine derivative, improves red blood cell deformability, lowers fibrinogen levels, and retards platelet aggregation. It is the first medication approved by the FDA (in 1984) for the treatment of intermittent claudication (1).

A recent review of available trials concluded that the actual improvement in walking distance attributable to pentoxifylline is unpredictable, may not be clinically important compared with the effects of placebo, and does not justify the added expense for most patients (76). Based on current evidence, we do not recommend the routine use of pentoxifylline in patients with PAD.

Cilostazol, a phosphodiesterase III inhibitor, was the second oral agent approved for the treatment of mild to moderate intermittent claudication in 1999. In addition to its antiplatelet properties, cilostazol promotes vasodilation, increases plasma high-density lipoprotein, and decreases plasma triglyceride levels (1). However, the true mechanism whereby cilostazol improves pain-free walking distance is unknown. Cilostazol increases pain-free and maximum walking distances by 40%–70% and 65%–83%, respectively, after 12–24 weeks when used at the recommended oral dosage of 100 mg twice daily. Treatment with cilostazol is also associated with improvements in health-related quality of life (77).

In a pivotal prospective, multicenter, 24-week randomized trial comparing cilostazol to pentoxifylline and placebo in 698 patients with intermittent claudication, the improvement seen with cilostazol (a mean percent increase of 54% from baseline) was significantly greater than that seen with either pentoxifylline (a 30% mean percent increase) or placebo. Side effects such as headache, palpitations, and diarrhea were more common in the cilostazol group, but discontinuation rates were similar between cilostazol and pentoxifylline (16% vs 19%) (78).

Chronic use of phosphodiesterase III inhibitors in patients with congestive heart failure has been associated with an increase in mortality caused by a proarrhythmic effect. Therefore, cilostazol must not be prescribed to patients with intermittent claudication who have congestive heart failure (79).

The safety data from eight phase III clinical trials involving 2,702 patients and from postmarketing surveillance in the United States representing 70,430 patient-years of exposure did not reveal increased cardiovascular morbidity or mortality risk in patients receiving cilostazol (80).

Cilostazol should be taken 30 minutes before or 2 hours after eating because high-fat meals markedly increase its absorption. Diltiazem, grapefruit juice, or omeprazole can increase the serum concentration of cilostazol if they are taken concurrently. Cilostazol can be safely administered with aspirin or clopidogrel without any further increase in bleeding time (81). We recommend the use of cilostazol as initial therapy for patients with mild to moderate intermittent claudication.

Chelation Therapy

Chelation therapy has been promoted as a form of alternative medicine in the treatment of atherosclerotic cardiovascular disease for decades. A metaanalysis of available studies evaluating chelation therapy in patients with intermittent claudication demonstrated no measurable improvement in outcomes in patients with PAD (82). We do not recommend chelation therapy as a primary treatment modality of PAD.

POTENTIAL EMERGING THERAPIES

Vasodilator drugs such as papaverine were the first medications studied for the treatment of claudication. Several controlled trials have found no evidence of clinical efficacy of vasodilatory agents (1).

Over a period of many years, prostanoids have been evaluated as potential therapy in patients with intermittent claudication and CLI. Various studies have evaluated prostacyclin, prostacyclin analogues (iloprost and beraprost), and intravenous infusion of prostaglandin E_1. In a pooled analysis of five placebo-controlled trials including a total of 728 patients with CLI, intravenous infusion of iloprost demonstrated a 21% increase in ulcer healing rates compared with placebo, as well as a significantly lower rate of major limb amputation (83). Pooled data from 519 patients with intermit-

tent claudication randomized to receive oral prostanoids or placebo demonstrated improvement in mean maximum walking distance by 30% (84).

Naftidrofuryl is a 5-hydroxytryptamine-2 receptor antagonist with vasodilatory effects. A metaanalysis of four placebo-controlled trials of this agent revealed an improvement in maximum walking distance of 71 m, whereas pentoxifylline-treated patients had an improvement of 43.8 m (85). This agent is not approved by the FDA and is available only in Europe.

L-carnitine is an agent that facilitates the transfer of acylated fatty acids and acetate across mitochondrial membranes, thereby enhancing available energy stores and improving oxidative muscle metabolism. This agent has been tested in Europe to improve skeletal muscle abnormalities in PAD. In a small double-blind, placebo-controlled trial, patients treated with propionyl-L-carnitine noted an improvement of 73% in maximum walking distance compared with an improvement in placebo-treated patients of 46% (86). Propionyl-L-carnitine is not yet FDA-approved for treatment of intermittent claudication.

L-arginine induces nitric oxide formation and improves endothelial-dependent vasodilation in patients with PAD (87). In a very small ($n = 39$) prospective, randomized, placebo-controlled trial, L-arginine (given via intravenous infusion) demonstrated an impressive improvement in maximum walking distance of 155% in patients with claudication (88). This agent is currently available in nutritional supplements, but data supporting its' widespread use in PAD are lacking.

Angiogenic growth factors can stimulate the development of collateral arteries, an approach known as therapeutic angiogenesis. Many factors have been suggested for angiogenesis, including vascular endothelial growth factor, hepatocyte growth factor, fibroblast growth factor–4, and hypoxia-inducible factor–1.

Data supporting the use of angiogenesis in patients with intermittent claudication are emerging. The Regional Angiogenesis with Vascular Endothelial Growth Factor Trial (89) evaluated a single intramuscular injection of adenovirus-encoding vascular endothelial growth factor–121 to the lower extremities of patients with symptomatic PAD. The treatment was not associated with improved exercise performance or quality of life. The Therapeutic Angiogenesis with Recombinant Fibroblast Growth Factor–2 for Intermittent Claudication study (90) demonstrated moderate improvement in exercise capacity in patients with intermittent claudication after one dose of intraarterial recombinant fibroblast growth factor–2.

Other strategies include autologous implantation of bone marrow mononuclear cells, injection of granulocyte-macrophage colony-stimulating factor, and therapy based on transcription factors such as hypoxia-inducible factor–1α, which regulates the expression of multiple angiogenic genes. Many relevant trials are currently in progress (91).

Attempts at modification of the immune system as a therapy for PAD can be classified into immune modulation therapy and antibiotic therapy (92). One double blind, randomized, controlled trial used ex vivo stress of whole blood (including ultraviolet radiation, ozone exposure, and heat) to induce immune modulation followed by intramuscular injection of the treated blood. This process was repeated 12–24 times and did demonstrate a significant increase in initial claudication distance that was not sustained after therapy was discontinued (93). A larger-scale multicenter trial is currently enrolling.

Antichlamydial therapy has been tested in a randomized placebo-controlled trial that investigated the efficacy of roxithromycin (300 mg/d for 30 days) in 40 patients with PAD who were seropositive for *Chlamydia pneumoniae*. During the 2.7-year follow-up, 20% of the patients in the roxithromycin group versus 45% in the placebo group required revascularization. Progression of PAD was observed in 20% of the patients treated with roxithromycin, compared with 65% in the placebo group (94). This link between infection and atherosclerosis continues to be studied, and further data are forthcoming.

Intermittent pneumatic compression has been evaluated as possible treatment for patients with intermittent claudication and CLI. Possible mechanistic benefits include improved collateral circulation and antiplatelet activity related to changes in adenosine triphosphate thresholds for platelet aggregation (95). In a very small group of 25 patients with IC, intermittent pneumatic compression for 4.5 months resulted in improvement in maximum walking distance by 106% (96).

Gingko biloba is a non–FDA-approved dietary supplement with antiplatelet, vasodilatory, and antioxidant activity, which has been used in the treatment of intermittent claudication. As with other dietary supplements, the potency of gingko biloba preparations may vary and their purity is not assured. In a metaanalysis of several trials comparing gingko biloba preparations to placebo, there was a borderline-significant improvement in walking distance (97).

There has been no documented benefit of heparin, low–molecular-weight heparins, oral anticoagulants, and oral glycoprotein IIb/IIIa inhibitors as primary therapy for the symptoms of PAD (98).

CONCLUSIONS

Based on current evidence, noninterventional medical treatment of patients with PAD includes supervised exercise therapy, intensive risk factor interventions based on secondary prevention strategies, antiplatelet therapy, and cilostazol. Implementation of current secondary prevention guidelines in patients with PAD implies that all patients with an ABI of 0.9 or less will require aspirin with or without clopidogrel, an ACE inhibitor, and a statin (potentially independent of baseline blood pressure and cholesterol levels). A call to action has been raised, and efforts on a national level to improve the awareness of PAD among patients and caregivers alike are critical to prevent premature death and impaired quality of life among this expanding patient cohort.

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