Pharmacotherapy and Behavioral Intervention for Peripheral Arterial Disease

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Lower-extremity peripheral arterial disease is a chronic disease process resulting from atherosclerotic obstruction of major vessels supplying the legs. A significant manifestation of systemic atherosclerosis, it is estimated to affect more than 10 million adults in the United States alone. The reported incidence is a conservative estimate, because many patients who suffer from symptoms of peripheral arterial disease attribute them to "normal aging" and may not report them to their physician. Additionally, physicians may miss the diagnosis if a comprehensive history and vascular examination are not a routine part of their assessment. The hallmark symptom of peripheral arterial disease is intermittent claudication, defined as reproducible muscular leg pain that is precipitated by exercise and relieved by rest. Intermittent claudication not only limits functional capacity and adversely affects quality of life but is also an ominous predictor of increased risk for myocardial infarction, stroke, and cardiovascular death. Due to the chronicity of atherosclerosis, medical intervention is most successful when a comprehensive team approach is utilized, involving the patient, family, and vascular health professionals. Treatment for peripheral arterial disease is aimed at first, minimizing symptoms and disease progression via smoking cessation, supervised exercise therapy, pharmacotherapy, and/or revascularization, and second, minimizing the risk of cardiovascular mortality via risk factor identification and reduction, and the use of antiplatelet therapy.
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Key words: Peripheral arterial disease • Atherosclerosis • Intermittent claudication • Limb ischemia • Antiplatelet therapy

Peripheral arterial disease (PAD), an important clinical manifestation of atherosclerosis, is very prevalent in Western populations. The prevalence increases with age, affecting 15%–29% of people over the age of 70 as assessed by an ankle-brachial index (ABI) below 0.9.[1–3] These numbers gain added significance because this segment of the population is growing rapidly.

Intermittent claudication, the first symptom of PAD, occurs in only 33%–50% of patients with known PAD documented by noninvasive assessment.[4] In those who are symptomatic, functional status is markedly impaired, with peak exercise performance reported to be only half that of healthy age-matched controls.[5,6] This impairment adversely affects quality of life because work and leisure activities are often severely limited.[7]

Pain at rest, typically described as worse at bedtime with horizontal positioning (and relieved by dependent positioning), or evidence of distal tissue necrosis (nonhealing ulcers, gangrene) indicate critical limb ischemia, a severe manifestation of PAD, which threatens the viability of the extremity because arterial perfusion is insufficient to meet even the basal metabolic demands of the tissue. The annual incidence of critical limb ischemia approximates 500 per million population.[4,8] Of patients with intermittent claudication, approximately 10% progress to limb-threatening ischemia in 5 years, and 25% of those with critical limb ischemia require amputation.[9] Amputation results in physical disability that is directly related to the level of limb loss, often resulting in loss of independence in the elderly.

The fact that as many as half of patients with an ABI below 0.9 have no lower-extremity symptoms at all has significant implications for the importance of a comprehensive vascular assessment in all patients over age 70, because the relative risk (RR) of fatal and nonfatal cardiovascular events in the presence of PAD is increased three- to fourfold, contributing to an annual mortality rate of 4.3%–4.9%.[10-12] The Cardiovascular Health Study reported a RR of myocardial infarction (MI) of 2.7% and a RR of stroke of 2.8% in patients with an ABI below 0.8.[13] Other studies also demonstrate a proportional relationship between prognosis and severity of disease.[4,12]

Treatment for Intermittent Claudication

Intermittent claudication may significantly interfere with the patient's quality of life. Although the limitations on walking distance remain stable in most patients, they also have marked impairment in overall functional capacity and exercise performance.[14,15] Treatment for intermittent claudication is aimed at improving mobility and quality of life and, in addition to risk factor modification (discussed at length subsequently), includes supervised exercise therapy. Controlling atherosclerotic disease progression and improving functional capacity require major changes in lifestyle and behavior that patients and families often find difficult to make on their own. Structured exercise programs can provide the necessary education, support, and encouragement patients need to incorporate these new behaviors successfully. Such programs, modeled after cardiac rehabilitation, have reported marked improvements in functional capacity and quality of life.[5,16–18]

Intermittent claudication may significantly interfere with the patient's quality of life and functional ability.

Controlled trials of exercise rehabilitation have demonstrated improvement in both initial and absolute claudication distance. A meta-analysis of 21 studies found those patients participating in a supervised, structured exercise program had a 180% increase in initial claudication distance, compared with a 40% increase in control groups.[19] Despite its demonstrated effectiveness, supervised exercise rehabilitation has several limitations, most notably the lack of available programs. Recently, the Centers for Medicare and Medicaid Services have established a current procedural terminology code for exercise rehabilitation in patients with PAD (code 93668).[20]

The two drugs currently approved by the U.S. Food and Drug Administration (FDA) to treat patients with symptoms of intermittent claudication are pentoxifylline (Trental®; Aventis Pharmaceuticals, Inc, Kansas City, MO) and cilostazol (Pletal®; Otsuka America Pharmaceutical, Inc, Rockville, MD). Pentoxifylline is a hemorheologic agent that decreases plasma viscosity, improves red and white blood cell flexibility, and exhibits antiplatelet effects.[21] Although initial anecdotal reports were encouraging, at least two meta-analyses of pentoxifylline trials concluded that the drug may have marginal benefit in improving walking distance, but the data do not support its widespread use.[22, 23]

Cilostazol, approved by the FDA in 1999 for the treatment of intermittent claudication, is a phosphodiesterase type 3 inhibitor known to inhibit platelet aggregation and vascular smooth muscle cell proliferation, and cause vasodilation. Several prospective randomized trials have reported that cilostazol improves walking distance in patients with intermittent claudication by 40%–50% compared to placebo after 12–24 weeks of treatment.[24–26] One of these placebo-controlled trials evaluated both pentoxifylline and cilostazol.[26] Pentoxifylline demonstrated no

benefit in either initial or absolute claudication distance as compared to placebo. Cilostazol, however, significantly improved both distances compared to placebo (Figure 1). Recommended dosing for cilostazol is 100 mg orally twice daily.

The predominant side effect of cilostazol is headache. Transient diarrhea, palpitations, and dizziness have also been described. Because of the potential risk of increased mortality in patients with congestive heart failure (CHF) treated with other phosphodiesterase type 3 inhibitors, the FDA has issued a warning regarding the use of cilostazol in patients with CHF.

Clinical trials are evaluating the effectiveness of compounds such as propionyl-L-carnitine, L-arginine, prostaglandins, and angiogenic growth factors in the treatment of PAD and intermittent claudication. Research related to angiogenic growth factors, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) is promising. One uncontrolled study suggested that intramuscular gene transfer therapy with phVEGF165 promotes healing of ischemic ulcers in patients with limb-threatening ischemia.[27] Recently, intra-femoral artery administration of recombinant bFGF was reported to increase treadmill exercise times compared to placebo.[28]

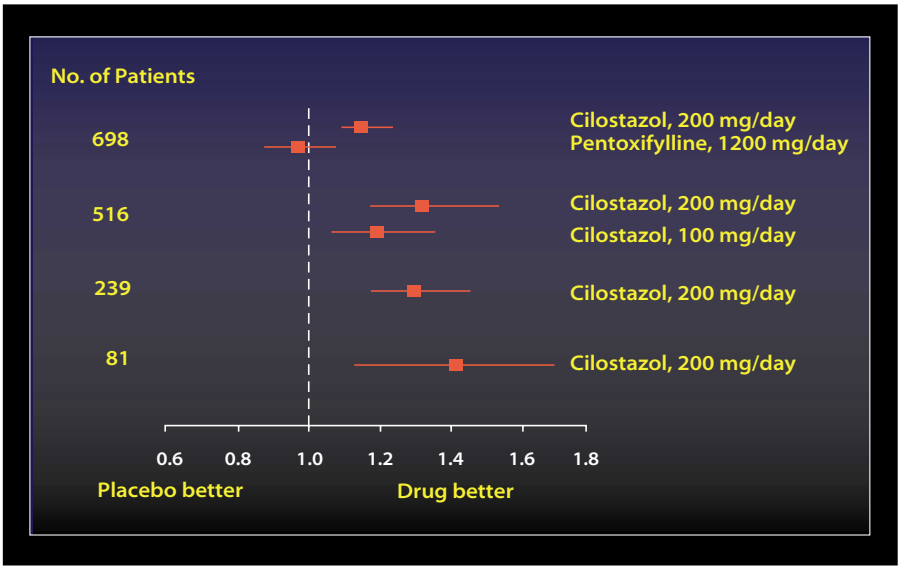

Figure 1. *Results of four randomized, placebo-controlled trials of cilostazol for the treatment of claudication: the data are shown as the geometric mean ratios of the maximal treadmill walking distance (on the horizontal axis) and 95% confidence intervals for cilostazol as compared with placebo. Reprinted with permission from Hiatt WR. Drug therapy: medical treatment of peripheral arterial disease and claudication.* N Engl J Med. *2001;344:1618.*

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Recognition and Modification of Significant Risk Factors for Peripheral Arterial Disease

The risk factors associated with atherosclerosis are common and are causally related to atherosclerosis regardless of its anatomic manifestations. Two of the risk factors most closely linked to PAD are cigarette smoking and diabetes mellitus.[29,30] Several large studies have reported a 1.7-fold to 5.6-fold increased risk of developing PAD in smokers and noted that the impact of smoking on the prevalence of PAD varies with the age of the study population and the number of cigarettes smoked daily.[2,31–33] Tobacco use is known to damage vascular endothelium, promote intravascular coagulation, and hasten the rate of disease progression. Additionally, cigarette smoking is associated with increased failure rates for percutaneous and surgical revascularization procedures and with an increased rate of amputations.[34–36]

Smoking cessation, albeit clinically challenging, has been demonstrated to slow disease progression and reduce the risks of MI and cardiovascular death.[34,37–39] Smoking cessation strategies should include structured cessation programs, ongoing education from and support by the health care team, nicotine replacement therapy, and bupropion therapy (Zyban®; GlaxoSmithKline, Philadelphia, PA). Hurt and colleagues demonstrated that bupropion therapy resulted in a 23.1% tobacco abstinence rate at 1 year in a placebo-controlled trial.[40]

Patients with diabetes mellitus have a RR for PAD of 3.0%–4.0%.[31,33] Additionally, diabetic neuropathy increases the risk for foot ulceration, and the symptom can mimic ischemic rest pain. Rigorous control of blood glucose prevents the small-vessel complications of diabetes, but similar benefit on the macrocirculation has not been ascertained.[41] Several large studies of intensive glucose control have evidenced a trend toward reduction in cardio-

vascular events, including MI, but have not demonstrated a reduction in the incidence of PAD or amputation. The Diabetes Control and Complications Trial compared intensive and conventional insulin therapy in 1441 Type 1 diabetics. Intensive therapy caused a trend toward reduction in cardiovascular events ($P = .08$) but had no effect on PAD risk.[42] The United Kingdom Prospective Diabetes Study evaluated 3867 patients with Type 2 diabetes, comparing intensive therapy with insulin or sulfonylurea to dietary therapy. Similarly, intensive therapy was associated with a trend toward reduction in MI ($P = .05$) but did not impact the risk of death or amputation due to PAD.[43] Nevertheless, the established benefits of intensive therapy on microcirculatory diabetic complications such as retinopathy, nephropathy, and neuropathy, along with the noted trends toward reduction in cardiovascular events, clearly warrant optimization of serum glucose in these patients.[44]

Additional atherosclerotic risk factors, including hypertension, hypercholesterolemia, and hyperhomocysteinemia, are associated with PAD.[28] Individuals with hypertension have nearly a twofold increased risk for developing intermittent claudication, and the risk of stroke, MI, and cardiovascular death is magnified in patients with PAD and hypertension.[45] Although it is recognized as a major risk factor by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[46] data are not available to demonstrate that treatment of hypertension alters the development of claudication or the progression of the disease in the peripheral circulation.

Alderman and colleagues reported an association between activation of the renin-angiotensin system and increased risk of adverse cardiovascular events in patients with hypertension.[47] The Heart Outcomes Prevention Evaluation (HOPE) Trial evaluated the impact of an angiotensin-converting enzyme (ACE) inhibitor, ramipril (Altace®; King Pharmaceuticals, Inc, Bristol, TN), on reduction of adverse cardiovascular events in patients with atherosclerosis.[48] In this study, more than 4000 (44%) patients had peripheral vascular diseases, defined as symptoms of intermittent claudication, a history of PAD, or an ABI below 0.9. In the entire study population, 17.7% of subjects in the placebo group experienced death, nonfatal MI, or stroke, compared with 14.1% of the ramipril-treated group, accounting for a 22% RR reduction. There was no significant difference in the protective effect of ramipril between subjects with PAD and those without it. This study emphasizes the importance of including patients with PAD in studies of secondary prevention of adverse cardiovascular events and suggests that ACE inhibitors reduce the risk of ischemic events in this population.

Several large clinical trials have established the benefits of lipid-lowering in patients with coronary artery disease, reducing the risk of nonfatal MI or cardiac death by 24%–34%.[49–51] Given the systemic nature of their disease and associated increased risk for adverse cardiovascular events, it is logical to presume a similar benefit for patients with PAD. Indeed, the recent Heart Protection Study prospectively randomized 20,536 patients with atherosclerosis or diabetes and a total cholesterol greater than 150 mg/dL to simvastatin and placebo.[52] Among the 6748 patients with PAD, there was an approximately 25% RR reduction in adverse cardiovascular events comprising death, MI, stroke, or revascularization over a 5-year period. Both the Cholesterol Lowering Atherosclerosis Study (CLAS)[53] and the Program on the Surgical Control of the Hyperlipidemias (POSCH)[54] demonstrated a beneficial yet small effect on the progression of femoral atherosclerosis, assessed angiographically. Prospective trials evaluating the impact of statins in patients with claudication are currently ongoing and should help to clarify further whether such a benefit exists for patients with PAD.[55] Until these results are available, it is advisable to follow current National Cholesterol Education Program (NCEP III) guidelines. Patients with objective evidence of PAD, irrespective of the presence of symptoms, should be treated with lipid-lowering therapy to reduce serum low-density lipoproteins (LDL) to below 100 mg/dL and serum triglycerides to below 150 mg/dL.[56]

Individuals with hypertension have nearly a twofold increased risk for developing intermittent claudication, and the risk of stroke, MI, and cardiovascular death is magnified in patients with PAD and hypertension.

Several studies have implicated elevated serum homocysteine levels as a strong, independent risk factor for atherosclerosis.[57–59] Additionally, an association between plasma homocysteine levels and progression of intermittent claudication has been reported.[59] There have been no published prospective studies linking effective treatment (eg, lowering homocysteine levels) to a decrease in ischemic events.

However, serum concentrations can be effectively lowered with B-complex vitamins, most notably folic acid.[60]

Antiplatelet Therapy

Another characteristic in the pathogenesis of atherosclerosis is a propensity for thrombosis. Several landmark studies have concluded that antiplatelet therapy reduces the risk of nonfatal MI, stroke, and death in patients with cardiovascular disease. The Antithrombotic Trialists' Collaboration conducted a meta-analysis of studies of antiplatelet drug therapy (primarily aspirin) which included more than 135,000 high-risk patients, and the main conclusion was that antiplatelet therapy reduced the risk of adverse cardiovascular events from 13.2% in the control group to 10.7% in the treatment group, an odds-reduction of 25%.[61] Thus antiplatelet therapy is recommended for secondary disease prevention in patients with known cardiovascular disease. This same group reviewed a subset of patients with symptomatic PAD and found that those who received antiplatelet therapy experienced a statistically significant reduction (23%) in serious cardiovascular events compared to the control group.

Aspirin has also been shown to alter the natural history of PAD progression. Results from the Physicians' Health Study evaluated the effects of low-dose aspirin (325 mg/day), compared to placebo, in more than 22,000 male physicians over an average treatment period of 5 years.[62] Those in the aspirin-treated group required 50% fewer surgical limb revascularizations than did those in the placebo group. However, the incidence of intermittent claudication was not statistically significantly different in the two groups.

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) Trial compared the efficacy of clopidogrel (Plavix®; Bristol-Myers Squibb Company, New York, NY), a ticlopidine-like antiplatelet agent, to aspirin in more than 19,000 patients with atherosclerosis manifested as ischemic stroke, MI, or PAD (defined by an ABI below 0.85, prior revascularization, or amputation secondary to ischemia).[63] The latter cohort included more than 6400 patients with PAD. Clopidogrel was associated with an overall RR reduction of 8.7% for adverse cardiovascular events. Patients with PAD seemed to receive the greatest benefit, with a RR reduction of 23.8% when compared to aspirin treatment alone (Figure 2).

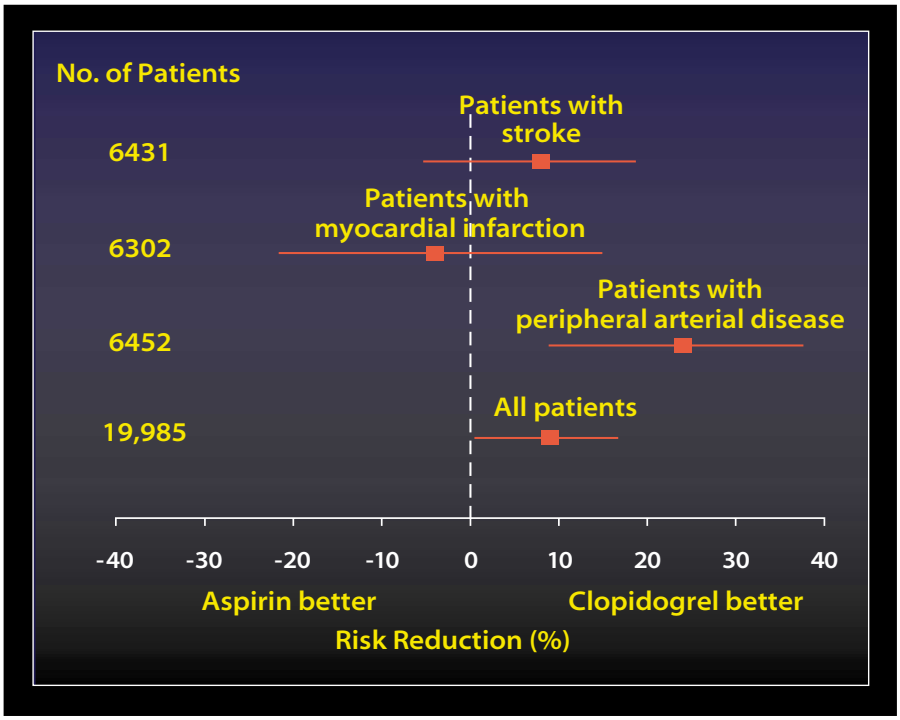

Figure 2. *Results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial: in the subgroup of patients with peripheral arterial disease, the primary end point of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or death from other vascular causes occurred at an annual rate of 4.9% in those taking aspirin and 3.7% in those taking clopidogrel, a reduction of 23.8%. Horizontal bars denote 95% confidence intervals. Reprinted with permission from Hiatt WR. Drug therapy: medical treatment of peripheral arterial disease and claudication.* N Engl J Med. *2001;344:1616.*

Although current data support the use of antiplatelet therapy in all patients with documented PAD unless contraindicated, this intervention remains widely underused. In the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study, 6979 patients aged 70 years or older, or aged 50–69 years with a history of cigarette smoking or diabetes, were evaluated by history and measurement of ankle-brachial indices. PAD was considered present if the ABI was under 0.9 or if there was a history of limb revascularization. One main outcome measure evaluated the treatment of PAD patients compared with that of other forms of cardiovascular disease. Although patients with PAD had similar risk profiles compared to patients with cardiovascular disease, antiplatelet therapies were prescribed less often

in patients with newly diagnosed PAD (33%) and known PAD only (54%), compared to 71% of patients with cardiovascular disease only ($P < .001$).[64] In the Minnesota Regional PAD Screening study, 40% of patients with PAD were receiving no antiplatelet therapy.[65] Physicians and nurses should strongly support the long-term use of antiplatelet medications for secondary prevention of adverse cardiovascular events.

Conclusion

Patients with PAD in the lower extremities may present with symptoms of intermittent claudication, which can adversely affect quality of life and impose severe limitations on overall functional capacity. More severe occlusive lesions may threaten the viability of the limb, resulting in critical ischemia necessitating emergent revascularization or amputation. Treatment of lower extremity PAD is aimed both at minimizing disease progression via modification of atherosclerotic risk factors and reducing symptoms with pharmacological intervention and structured exercise.

In addition to its direct impact on the legs, PAD is but one manifestation of a systemic disease process, atherosclerosis, and as such, is a predictor of increased risk of cardiovascular morbidity and mortality. Risk factor modification and antiplatelet therapy can dramatically reduce the risk of MI, stroke, and cardiovascular death in this patient population. ■

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Main Points

- Peripheral arterial disease (PAD), an important clinical manifestation of atherosclerosis, affects 15%–29% of people over the age of 70; intermittent claudication, the first symptom of PAD, occurs in 33%–50% of patients with known PAD.
- Of patients with intermittent claudication, approximately 10% progress to limb-threatening ischemia in 5 years, and 25% of those with critical limb ischemia require amputation.
- Controlling atherosclerotic disease progression and improving functional capacity require major changes in lifestyle and behavior that patients and families often find difficult to make; structured exercise programs can provide the necessary education, support, and encouragement.
- The two drugs currently approved by the U.S. Food and Drug Administration to treat patients with symptoms of intermittent claudication are pentoxifylline and cilostazol.
- Pentoxifylline may have marginal benefit in improving walking distance, but the data do not support its widespread use; cilostazol improves walking distance in patients with intermittent claudication by 40%–50% compared to placebo after 12–24 weeks of treatment.
- Two of the risk factors most closely linked to PAD are cigarette smoking and diabetes mellitus; smoking cessation has been demonstrated to slow disease progression and reduce the risks of myocardial infarction (MI) and cardiovascular death.
- Individuals with hypertension have nearly a twofold increased risk for developing intermittent claudication, and the risk of stroke, MI, and cardiovascular death is magnified in patients with PAD and hypertension.
- Patients with symptomatic PAD who received antiplatelet therapy experienced a statistically significant reduction (23%) in serious cardiovascular events compared to the control group.

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