**Symposium: Review Article**

**Medical treatment of peripheral arterial disease in the elderly**

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**Abstract** Smoking should be stopped and hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism be treated in elderly patients with peripheral arterial disease (PAD). Statins reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolemia. Antiplatelet drugs such as aspirin or clopidogrel, especially clopidogrel, angiotensin-converting enzyme inhibitors, and statins should be given to all persons with PAD. Beta blockers should be given if coronary artery disease is present. Exercise rehabilitation programs and cilostazol lengthen exercise time until intermittent claudication develops. Chelation therapy should be avoided. ([J Geriatr Cardiol 2007;4:93-100](https://www.jgeriatriccardiology.org).)

**Key Words** peripheral arterial disease; intermittent claudication; cilostazol; antiplatelet drugs; statins; angiotensin-converting enzyme inhibitors; beta-blockers; exercise rehabilitation

Peripheral arterial disease (PAD) is a chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PAD may cause intermittent claudication, which is pain or weakness with walking that is relieved with rest. The muscle pain or weakness after exercise occurs distal to the arterial obstruction. Since the superficial femoral and popliteal arteries are most commonly affected by atherosclerosis, the pain of intermittent claudication is most commonly localized to the calf. Atherosclerotic obstruction of the distal aorta and its bifurcation into the two iliac arteries may cause pain in the buttocks, hips, thighs, or the inferior back muscles as well as the legs.

Only one-half of elderly persons with documented PAD are symptomatic. Persons with PAD may not walk far or fast enough to induce muscle ischemic symptoms because of comorbidities such as pulmonary disease or arthritis, may have atypical symptoms unrecognized as intermittent claudication, may fail to mention their symptoms to their physician, or may have sufficient collateral arterial channels to tolerate their arterial obstruction. If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischemia occurs with pain at rest or tissue loss. The diagnosis of PAD is discussed elsewhere.

The prevalence of PAD increases with age. In one study of 1,160 men, mean age 80 years, and 2,464 women, mean age 81 years, PAD was present in 32% of men and in 26% of women. PAD coexists with other atherosclerotic disorders. Persons with PAD are also at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events. This article will discuss the medical treatment of PAD in the elderly. Indications for lower extremity angioplasty with stenting and bypass surgery, and indications for amputation are discussed elsewhere.

Correct implementation of medical therapy is primarily of importance to significantly reduce cardiovascular events and mortality associated with PAD. In addition, medical therapy may result in significant improvements in walking ability that may obviate the need for lower extremity angioplasty with stenting and bypass surgery. Treatment of PAD is efficacious in older men and in older women.

**Smoking cessation**

Current smoking significantly increased the risk for PAD 2.6 times in elderly men, mean age 80 years, and 4.6 times in elderly women, mean age 81 years. Smoking increases the risk of amputation in persons with intermittent claudication. Patency in lower extremity bypass grafts is also worse in smokers than in nonsmokers. Smoking cessation reduces the progression of PAD to critical leg ischemia and reduces the risk of myocardial infarction (MI) and death from vascular causes. Smoking cessation programs should be strongly encouraged in elderly persons with PAD. Smoking cessation is by far the most clinically and cost effective intervention for the treatment of PAD (Table 1).

Approaches to smoking cessation include use of nicotine patches or nicotine polacrilex gum, which are available over the counter. If this therapy is unsuccessful, nicotine nasal spray or treatment with the antidepressant bupropion should be considered. A nicotine inhaler may also be
used. The dosage and duration of treatment of each of these pharmacotherapies are discussed in detail elsewhere. Concomitant behavioral therapy may also be needed. Repeated physician advice is very important in the treatment of smoking addiction.

Treatment of hypertension

Hypertension significantly increased the risk for PAD 2.2 times in elderly men and 2.8 times in elderly women. Hypertension should be adequately treated to reduce cardiovascular morbidity and mortality in persons with PAD. Much of the evidence for treating hypertension in persons with PAD is extrapolated from data of persons with coronary artery disease (CAD). In the Heart Outcomes Prevention Evaluation (HOPE) Study of older persons, mean age 67 years, 1,715 persons had symptomatic PAD, and 2,118 persons had asymptomatic PAD with an ankle-brachial index (ABI) less than 0.9. In the HOPE Study, compared with placebo, ramipril 10 mg daily significantly reduced cardiovascular events by 25% in persons with symptomatic PAD. In this study, ramipril reduced the absolute incidence of cardiovascular events by 5.9% in persons with asymptomatic PAD and by 2.3% in persons with a normal ABI. In the HOPE Study, the antihypertensive properties of ramipril did not completely account for the observed risk reduction. Ramipril was also reported to improve walking ability in persons with PAD.

Among persons, mean age 60 years, with PAD in the Appropriate Blood Pressure Control in Diabetes trial, the incidence of cardiovascular events in persons treated with antihypertensive drug therapy with enalapril or nisoldipine was 13.6% if the mean blood pressure was reduced to 128/75 mm Hg versus 38.7% if the mean blood pressure was reduced to 137/81 mm Hg.

The blood pressure in elderly persons with PAD should be reduced to <140/90 mm Hg and to <130/80 mm Hg in persons with diabetes mellitus or chronic renal disease (Table 1). An angiotensin-converting enzyme (ACE) inhibitor should be included in the antihypertensive regimen.

Treatment of diabetes mellitus

Diabetes mellitus significantly increased the risk for PAD 6.1 times in elderly men and 3.6 times in elderly women. Elderly persons with diabetes mellitus and PAD and without CAD have a higher incidence of new coronary events than elderly nondiabetics with PAD and prior MI.Diabetes mellitus should be treated with the hemoglobin A1c level decreased to less than 7% to reduce the incidence of myocardial infarction (Table 1). The blood pressure should be lowered to <130/80 mm Hg in elderly persons with PAD and diabetes mellitus.

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Treatment of dyslipidemia

Dyslipidemia is a risk factor for PAD in elderly persons. Hypercholesterolemia significantly increased the risk of PAD 1.67 times. Treatment of dyslipidemia with statins has been demonstrated to reduce the incidence of mortality, cardiovascular events, and stroke in elderly persons with PAD and without CAD. At 5-year follow-up of 4,444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly reduced the incidence of intermittent claudication by 38%. Three studies have also demonstrated that statins improve walking performance in persons with PAD.

In a study of 264 men and 396 women, mean age 80 years (range 60-99 years), with symptomatic PAD and a serum LDL cholesterol of 125 mg/dl or higher, 318 of 660 persons (48%) were treated with a statin and 342 of 660 persons (52%) with no lipid-lowering drug. At 39-month fol-

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low-up, treatment with statins caused a significant independent reduction in the incidence of new coronary events of 58%, of 52% in persons with prior MI, and of 59% in persons with no prior MI. Persons older than 80 years of age had a similar reduction in the incidence of new coronary events as those younger than 80 years of age.

In the Heart Protection Study, 6,748 of the 20,536 persons (33%) had PAD. At 5-year follow-up, treatment with simvastatin 40 mg daily caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipids levels. These data favor administration of statins to elderly persons with PAD regardless of serum lipids levels.

On the basis of the available data, elderly persons with PAD and hypercholesterolemia should be treated with statins to reduce cardiovascular mortality and morbidity, to delay progression of PAD, and to improve exercise time. Since lipid-lowering therapy is underutilized in persons with PAD, intensive educational programs are needed to educate physicians to use lipid-lowering therapy in elderly persons with cardiovascular disease and dyslipidemia. On the basis of data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels. The serum LDL cholesterol should be reduced to <70 mg/dl (Table 1).

**Treatment of increased plasma homocysteine**

Increased plasma homocysteine level is a risk factor for PAD. Lowering of increased plasma homocysteine levels can be achieved by administering a combination of folic acid, vitamin B₆, and vitamin B₁₂. However, we do not have double-blind, randomized, placebo-controlled data showing that reduction of increased plasma homocysteine levels will reduce coronary events and slow progression of PAD in elderly persons with PAD.

**Treatment of hypothyroidism**

Hypothyroidism is a risk factor for PAD. Elderly persons with clinical or subclinical hypothyroidism should be treated with l-thyroxine to reduce the development of CAD and possibly of PAD (Table 1). There is no evidence showing that treatment with l-thyroxine will reduce the development of PAD or improve symptoms.

**Antiplatelet drugs**

Antiplatelet drugs that have been demonstrated to decrease the incidence of vascular death, nonfatal MI, and nonfatal stroke in persons with PAD are aspirin, ticlidipine, and clopidogrel. Aspirin inhibits platelet aggregation by inhibiting the cyclo-oxygenase enzyme reaction within the platelet, blocking the conversion of arachidonic acid to thromboxane A₂. Clopidogrel and ticloidipine are thienopyridine derivatives that inhibit platelet aggregation by inhibiting the binding of adenosine 5'-diphosphate to the platelet receptor.

The Antithrombotic Trialists’ Collaboration Group reported a meta-analysis of 26 randomized studies of 6,263 persons with intermittent claudication due to PAD. At follow-up, the incidence of vascular death, nonfatal MI, and nonfatal stroke was 6.4% in patients randomized to antiplatelet drugs versus 7.9% in the control group, a significant reduction of 23% caused by antiplatelet therapy.

The Antithrombotic Trialists’ Collaboration Group reported a meta-analysis of 12 randomized studies of 2,497 persons with PAD undergoing peripheral arterial grafting. At follow-up, the incidence of vascular death, nonfatal MI, and nonfatal stroke was 5.4% in persons randomized to antiplatelet drugs versus 6.5% in the control group, a significant reduction of 22% caused by antiplatelet therapy.

The Antithrombotic Trialists’ Collaboration Group reported a meta-analysis of 4 randomized studies of 946 persons with PAD undergoing peripheral angioplasty. At follow-up, the incidence of vascular death, nonfatal MI, and nonfatal stroke was 2.5% in patients randomized to antiplatelet drugs versus 3.6% in the control group, a significant reduction of 29% caused by antiplatelet therapy.

If one combines the 42 randomized studies of 9,706 persons with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular death, nonfatal MI, and nonfatal stroke at follow-up was 5.8% for persons randomized to antiplatelet drugs versus 7.1% for the control group, a significant reduction of 23% for antiplatelet therapy, with similar benefits among persons with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty.

Another meta-analysis of 24 studies of patients with PAD showed that compared to placebo, antiplatelet drug therapy significantly reduced nonfatal MI, nonfatal stroke, or vascular death by 22%.

**Aspirin**

Aspirin has been shown in patients with PAD to reduce the incidence of vascular death, nonfatal MI, and nonfatal stroke. Long-term treatment with aspirin has also been shown to improve the ABI and slow the progression of PAD as assessed by serial angiography and to reduce the need for arterial reconstruction when used for primary prevention of cardiovascular events in men.

Table 2 shows the efficacy of different doses of aspirin in reducing in high-risk persons the incidence of vascular death, nonfatal MI, and nonfatal stroke. Since aspirin doses greater than 150 mg daily do not reduce vascular death, nonfatal MI, and nonfatal stroke more than does a dose of 75 to 150 mg daily and cause more gastrointestinal bleeding than the lower doses, this author prefers a dose of 80 mg daily in treating elderly persons with atherosclerotic vascular disease.
recommend the use of clopidogrel 75 mg daily as an efficacy (ACC)/American Heart Association (AHA) guidelines more expensive than is aspirin. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines also state that oral anticoagulant therapy with warfarin should not be given to reduce the risk of adverse cardiovascular ischemic events in persons with atherosclerotic lower extremity PAD.

Angiotensin-converting enzyme inhibitors

Data from the HOPE Study showed that ramipril 10 mg daily significantly reduced cardiovascular events in persons with symptomatic PAD and in persons with asymptomatic PAD. ACE inhibitors as well as statins have many pleotropic effects to account for their vascular protective properties beyond their primary mode of action including inhibition of cellular proliferation, restoration of endothelial activity, inhibition of platelet reactivity, and an antioxidant potential. The ACC/AHA guidelines recommend treating persons with PAD with ACE inhibitors unless there are contraindications to the use of these drugs to reduce cardiovascular mortality and morbidity.

Beta blockers

Elderly persons with PAD are at increased risk for developing cardiovascular events. Many physicians have been reluctant to use beta blockers in persons with PAD because of concerns that beta blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies showed that beta blockers do not adversely effect walking capacity or the symptoms of intermittent claudication in persons with mild-to-moderate PAD.

An observational study was performed in 575 men and women, mean age 80 years, with symptomatic PAD and prior MI. Of the 575 persons, 85 persons (15%) had contraindications to the use of beta blockers. Of the 490 persons without contraindications to the use of beta blockers, 257 persons (52%) were treated with beta blockers. Adverse effects causing cessation of beta blockers occurred in 31 of the 257 persons (12%). At 32-month follow-up, use of beta blockers caused a 53% significant independent reduction in the incidence of new coronary events in elderly persons with PAD and prior MI. In a vascular surgery clinic, 301 of 364 persons (83%) with PAD and CAD were treated with beta blockers. Elderly persons with PAD and CAD should be treated with beta blockers unless there are contraindications to the use of these drugs (Table 1).

Statins

Elderly persons with PAD and hypercholesterolemia should be treated with statins to reduce cardiovascular mortality and morbidity and progression of PAD. Three double-blind, randomized, placebo-controlled studies have

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**Table 2. Efficacy of aspirin doses in decreasing vascular death, nonfatal myocardial infarction, and nonfatal stroke in high-risk patients**

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<th>Aspirin dose</th>
<th>Decrease in cardiovascular event</th>
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<td>500-1500 mg (34 trials)</td>
<td>19%</td>
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<tr>
<td>160-325 mg (19 trials)</td>
<td>26%</td>
</tr>
<tr>
<td>75-150 mg (12 trials)</td>
<td>32%</td>
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<tr>
<td>&lt;75 mg (3 trials)</td>
<td>13%</td>
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Adapted from reference 47
also demonstrated that statins improve walking performance in persons with PAD.64-66

In a study of 69 persons, mean age 75 years, with intermittent claudication, a mean ABI of 0.63, and a serum LDL of 125 mg/dl or higher, 3 of 34 persons (9%) treated with simvastatin and 6 of 35 persons (17%) treated with placebo died before the 1-year study was completed.68 Compared with placebo, simvastatin significantly increased the treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy.66

In a study of 354 persons, mean age 68 years, with intermittent claudication and hypercholesterolemia, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and significantly improved community-based physical activity.37 In a study of 86 persons, mean age 67 years, with intermittent claudication and hypercholesterolemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ABI at rest and after exercise, and significantly improved symptoms of claudication.38 Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders.69 The data suggest that non-cholesterol-lowering properties of statins favorably influence functioning in persons with and without PAD.66 Elderly persons with intermittent claudication should be treated with statins to improve walking performance as well as to reduce cardiovascular events and mortality (Table 1).

**Drugs to increase walking distance**

Numerous drugs have been shown to be ineffective in improving walking distance in persons with intermittent claudication.64,65 Two drugs, pentoxifylline and cilostazol, have been approved by the United States Food and Drug Administration for symptomatic treatment of intermittent claudication. In a vascular surgery clinic, 294 of 301 persons (98%) with intermittent claudication were treated with cilostazol and 301 of 301 persons (100%) with cilostazol or pentoxifylline.62

**Cilostazol**

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been shown in numerous trials to improve exercise capacity in persons with intermittent claudication,66-69 and in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline.68 Cilostazol has also been shown to cause a small increase in the ABI.69

However, cilostazol should not be administered to elderly persons with PAD who also have heart failure. Other contraindications to the use of cilostazol include a creatinine clearance <25 ml/min, a known predisposition for bleeding, or coadministration of CYP3A4 or CYP2C19 inhibitors such as cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, and HIV-1 protease inhibitors.

**Pentoxifylline**

Pentoxifylline is a methylxanthine derivative that improves the deformability of red cells and white cells. Many studies have found no consistent improvement with pentoxifylline in persons with intermittent claudication in comparison with placebo.70-72 The author’s experience is that pentoxifylline causes a small effect on walking ability in elderly persons with intermittent claudication, and, therefore, prefers to use cilostazol in treating these persons (Table 1).

**Other drugs**

Chelation therapy has been demonstrated to be ineffective in the therapy of PAD.73 Vasodilator drugs such as papaverine are ineffective in the treatment of intermittent claudication.74 In fact, vasodilator therapy may lead to a steal of blood away from the underperfused muscle. Beraprost sodium, an orally active prostaglandin I2, analogue, was demonstrated to be no more effective than placebo in persons with intermittent claudication.75 Naftidrofuryl76 and propionyl levocarnitine77 have been reported to improve exercise walking distance in persons with intermittent claudication but have not been approved for use in the United States.

**Exercise rehabilitation**

Exercise rehabilitation programs have been found to increase walking distance in persons with intermittent claudication through improvements in peripheral circulation, walking economy, and cardiopulmonary function.78 The optimal exercise program for improving claudication pain distance in persons with PAD uses intermittent walking to near-maximal pain during a program of at least 6 months.79 Strength training is less effective than treadmill walking, and does not augment the response to a walking exercise program whether used sequentially or concomitantly.80 The ACC/AHA guidelines recommend a program of supervised exercise training for patients with intermittent claudication (Table 1).77

**Foot care**

Persons with PAD must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily and the skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal infection of the feet must be treated. Socks should be wool or
other thick fabrics, and padding or shoe inserts may be used to prevent pressure sores. When a wound of the foot develops, specialized foot gear, including casts, boots, and ankle foot arthoses may be helpful in unweighting the affected area.11

In conclusion, correct implementation of medical therapy is primarily to significantly reduce cardiovascular events and mortality associated with PAD. In addition, medical therapy may result in significant improvements in walking ability that may obviate the need for lower extremity angioplasty with stenting and bypass surgery. Treatment of PAD is efficacious in older men and in older women.

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