HEATHER L. GORNIK, MD, MHS*
Sections of Vascular Medicine and Clinical Cardiology
Department of Cardiovascular Medicine
Cleveland Clinic, Cleveland, OH

MARK A. CREAGER, MD*
Department of Medicine, Cardiovascular Division
Brigham and Women's Hospital and Harvard Medical School
Boston, MA

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

ABSTRACT

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

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

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

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WHY IS RISK-FACTOR MODIFICATION CRITICAL?

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

PAD as a coronary risk equivalent

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

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

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

Physician awareness of risk is low

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

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

SMOKING CESSATION

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

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

Counseling, formal programs indicated for all smokers

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

Several pharmacologic options available

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

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

Other pharmacologic therapies for smoking cessation are in development.

A cornerstone of PAD management

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

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

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

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

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

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

Adapted from reference 1.

ANTIPLATELET THERAPY

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

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

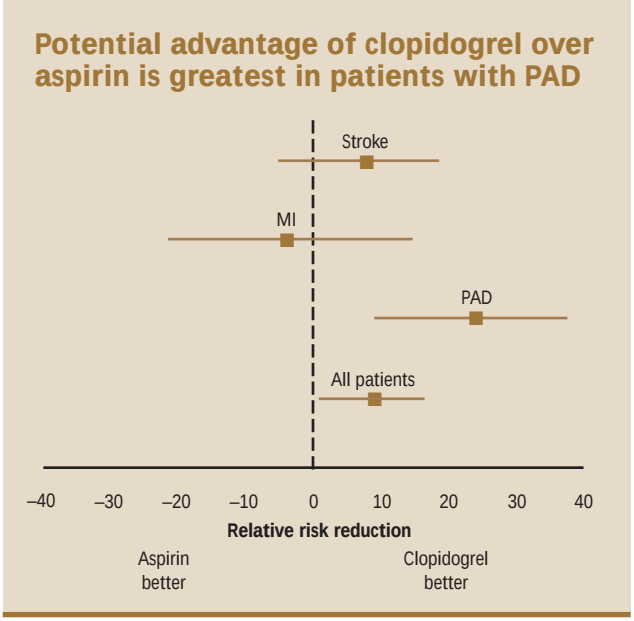

FIGURE 1. Mean percentage reductions (with 95% confidence intervals) in relative risk of a major cardiovascular event with clopidogrel vs aspirin among patients with atherosclerotic vascular disease in the CAPRIE study, according to disease subgroup at enrollment.[27] Major cardiovascular events were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

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

Clopidogrel vs aspirin

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

Clopidogrel plus aspirin?

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

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

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

Recommendations

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

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

LIPID-LOWERING THERAPY

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

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

Reductions in mortality and vascular events

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

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

Improvements in intermittent claudication, better functional capacity

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

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

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

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

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

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

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

LDL = low-density lipoprotein

Adapted, with permission, from reference 35.

Recommendations

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

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

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

TREATMENT OF HYPERTENSION

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

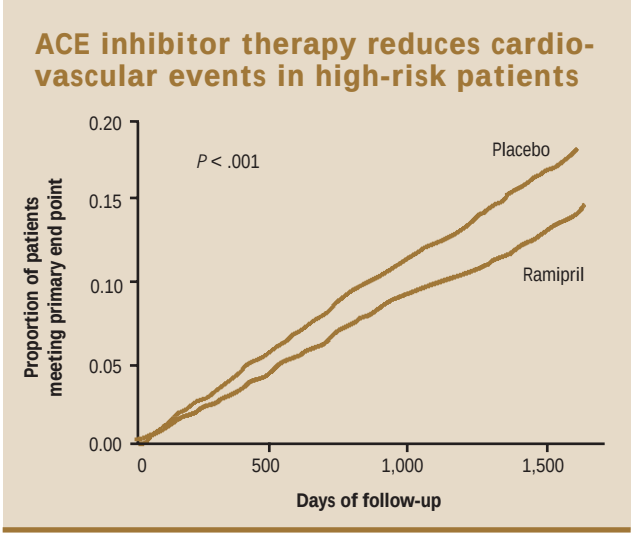

FIGURE 2. Kaplan-Meier estimates of the primary end point (stroke, myocardial infarction, or cardiovascular death) in the HOPE study of 9,297 high-risk patients with atherosclerotic vascular disease or diabetes mellitus.[37] The ACE inhibitor ramipril was associated with a significant 22% relative reduction in this end point compared with placebo. The study included 4,051 patients with symptomatic peripheral arterial disease. Reprinted, with permission, from reference 37. Copyright © 2000 Massachusetts Medical Society. All rights reserved.

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

Treatment itself more important than choice of antihypertensive

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

Treatment can benefit even normotensive patients

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

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

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

Recommendations

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

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

GLYCEMIC CONTROL FOR PATIENTS WITH DIABETES

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

tus is well established.

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

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

Recommendations

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

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

EXERCISE

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

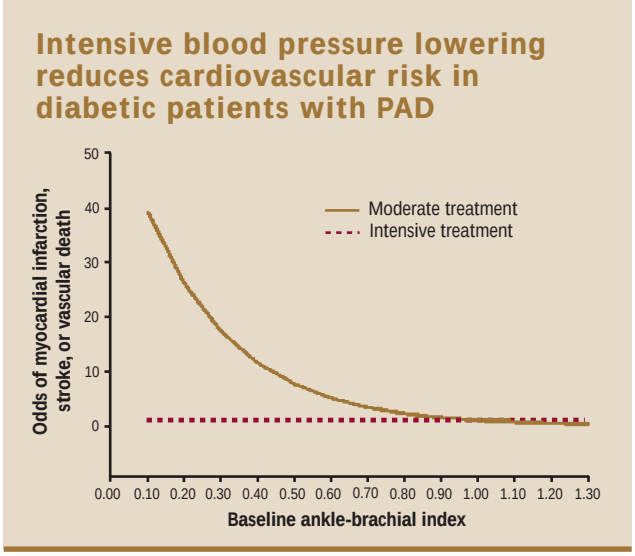

FIGURE 3. Relationship between ankle-brachial index (ABI) and cardiovascular events among normotensive diabetic patients randomized to intensive blood pressure treatment (with enalapril or nisoldipine) or moderate treatment (placebo) in the ABCD trial.[38] Whereas the ABI is inversely related to cardiovascular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

PAD exercise rehabilitation programs: Effective but not widely available

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

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

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

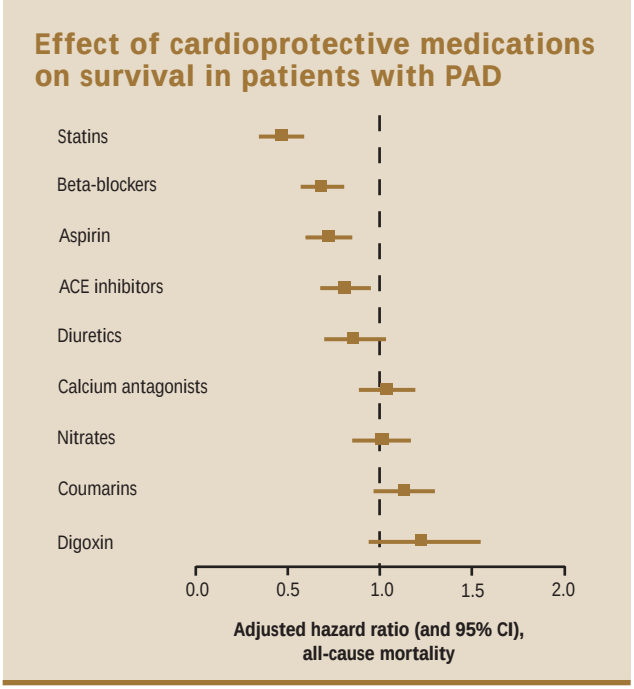

FIGURE 4. Hazard ratios (with 95% confidence intervals) for all-cause mortality associated with nine cardiovascular medications taken by 2,420 consecutive patients with peripheral arterial disease (PAD) in a prospective observational cohort study.[16] Ratios were adjusted for baseline cardiovascular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

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

OTHER THERAPIES

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

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

THE CHALLENGE: WIDER USE OF SIMPLE BUT LIFESAVING TOOLS

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

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

REFERENCES

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

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

Address: *Heather L. Gornik, MD, MHS, Sections of Vascular Medicine and Clinical Cardiology, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, S60, Cleveland, OH 44195; gornikh@ccf.org.*