Medical Treatment of Peripheral Arterial Disease

Graeme J. Hankey, MD

Paul E. Norman, DS

John W. Eikelboom, MBBS, MSc

PERIPHERAL ARTERIAL DISEASE (PAD) refers to any pathologic process causing obstruction to blood flow in the arteries exclusive of the coronary and cerebral vessels. In this article we focus on lower extremity PAD, which is a chronic obstructive disease of the aortic, iliac, and lower limb arteries usually caused by atherosclerosis.[1,2]

The most widely accepted, objective definition of PAD is a resting ankle-brachial index (ABI) of less than 0.90 (ie, the ratio of the ankle systolic blood pressure [as measured by Doppler ultrasound] and the higher of the 2 brachial systolic pressures is less than 0.90).[1,2] An ABI of less than 0.90 is up to 95% sensitive in detecting angiogram-positive disease.[1] A cutoff of less than 0.95 has been used in some epidemiologic studies[3] but may overestimate disease prevalence.

PAD affects approximately 20% (95% confidence interval [CI], 10%-30%) of adults older than 55 years and an estimated 27 million persons in North America and Europe.[2,4-12] About half of all people with PAD are asymptomatic.[3,13] The prevalence of PAD increases with age and prolonged exposure to smoking, hypertension, and diabetes.[2,4,5,14]

About one fifth of people with PAD have typical symptoms of intermittent

CME available online at www.jama.com

Context Peripheral arterial disease (PAD) affects approximately 20% of adults older than 55 years and is a powerful predictor of myocardial infarction, stroke, and death due to vascular causes. The goals of treatment are to prevent future major coronary and cerebrovascular events and improve leg symptoms.

Objective To review the best evidence for medical treatment of PAD.

Evidence Acquisition MEDLINE and the Cochrane database were searched from 1990 to November 2005 for randomized trials and meta-analyses of medical treatments for PAD. References from these articles were also searched. Search terms included, singly and in combination: *peripheral arterial disease*, *peripheral artery disease*, *PAD*, *randomized controlled trial*, *controlled trial*, *randomized*, and *meta-analysis*. Particular attention was directed toward randomized controlled trials and meta-analyses of clinically relevant medical treatments for PAD. Outcome measures included leg symptoms (intermittent claudication and walking distance), death, and major coronary and cerebrovascular events.

Evidence Synthesis Symptoms of leg claudication, walking distance, and quality of life can be improved by smoking cessation (physician advice, nicotine replacement therapy, and bupropion), a structured exercise program, statin drugs, cilostazol, and angiotensin-converting enzyme inhibitors. The risk of major coronary and cerebrovascular events can be reduced through lowering blood pressure with angiotensin-converting enzyme inhibitors and other antihypertensive drugs, use of statin drugs, antiplatelet therapy with aspirin or clopidogrel, and probably by stopping smoking.

Conclusion The substantial and increasing burden of PAD, and its local and systemic complications, can be reduced by lifestyle modification (smoking cessation, exercise) and medical therapies (nicotine replacement therapy, bupropion, antihypertensive drugs, statins, and antiplatelet drugs).

JAMA. 2006;295:547-553   www.jama.com

lower limb claudication, "rest pain," ulceration, or gangrene, and another third have atypical exertional leg symptoms.[13] The incidence of symptomatic PAD (intermittent claudication) in the general population in the Netherlands has been reported to be 1.0 (95% CI, 0.7-7.5) per 1000 population per year overall; 0.4 (95% CI, 0.3-10.0) for men, and 1.8 (95% CI, 1.0-10.3) for women.[3] The Framingham study reported higher incidence rates and a 2-fold male predominance (1.8% for women and 3.6% for men),[15] as did the Quebec Cardiovascular Study[16] and others.[17,18] The incidence of first-ever acute peripheral arterial events, defined as aortic events

(ruptured or acute symptomatic aortic or iliac aneurysm, or any thoracic aortic dissection), acute thromboembolic events (of the limbs or viscera), and critical limb ischemia (rest pain or ulcer-

Author Affiliations: Department of Neurology, Royal Perth Hospital and School of Medicine and Pharmacology, University of Western Australia, Perth (Dr Hankey); School of Surgery and Pathology, University of Western Australia (Dr Norman); and Department of Medicine, McMaster University, Hamilton, Ontario (Dr Eikelboom).
Corresponding Author: John Eikelboom, MBBS, MSc, Department of Medicine, McMaster University, Hamilton General Hospital McMaster Clinic, 237 Barton St E, Hamilton, Ontario, Canada L9K 1H8 (eikelbj @mcmaster.ca).
Clinical Review Section Editor: Michael S. Lauer, MD. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Michael S. Lauer, MD, at lauerm@ccf.org.

Table 1. Studies Reporting Risks of Death From All Causes and From Cardiovascular Disease in Patients With Peripheral Arterial Disease (PAD)

Study	No.	Age, y	Sex	PAD Symptoms	All-Cause Death				Cardiovascular Death, RR (95% CI)
					Controls, %	Patients, %	ARI, %	RR (95%CI)	
Criqui et al,[23] 1992	256	38-72	Men	. . .	1.7	6.2	4.5	3.3 (1.9-6.0)	5.1 (2.4-10.8)
	309		Women	. . .	1.2	3.3	2.1	2.5 (1.2-5.3)	4.8 (1.6-14.7)
Vogt et al,[24] 1993	1492	>65	Women	. . .	1.1	5.4	4.3	3.1 (1.7-5.5)	4.0 (1.3-8.5)
Kornitzer et al,[25] 1995	2023	40-55	Men	No	0.4	1.0	0.6	2.8 (1.4-5.5)	. . .
Leng et al,[18] 1996	1592	55-74	Men and women	Yes	2.0	3.8	1.8	1.6 (0.9-2.8)	2.7 (1.3-5.3)
				No	2.0	6.1	4.1	2.4 (1.6-3.9)	2.1 (1.1-3.8)
Newman et al,[26] 1997	669	≥60	Men	. . .	1.5	5.3	3.8	3.0 (2.8-5.3)	. . .
	868		Women	. . .	1.3	3.8	2.5	2.7 (1.6-4.6)	. . .
Newman et al,[27] 1999	5714	≥65	Men and women	. . .	4.5	7.8	3.3	1.5 (1.2-1.9)	2.0 (1.1-2.8)
Hooi et al,[28] 2004	3649	40-78	Men and women	All (n = 367)*	1.1	4.4	3.3	1.4 (1.1-1.7)	1.6 (1.2-2.1)
				Yes (n = 117)	1.1	. . .	. . .	1.4 (1.0-2.0)	1.6 (1.0-2.5)
				No (n = 245)	1.1	4.3	2.2	1.4 (1.1-1.8)	1.5 (1.1-2.2)

Abbreviations: ARI, absolute risk increase; CI, confidence interval; ellipses, not available; RR, relative risk.
*Includes 5 patients with PAD of unspecified type.

ation of sufficient severity to warrant hospital admission) in Oxfordshire in 2002-2005 has recently been estimated at 0.52 (95% CI, 0.43-0.61) per 1000 population per year.[19]

Among individuals with asymptomatic PAD, about 5% to 10% develop symptoms of PAD over 5 years.[20] A minority of patients with intermittent claudication develop symptoms of critical leg ischemia (rest pain and skin ulceration), with an incidence of 0.25 to 0.45 per 1000 people per year.[21,22] Critical leg ischemia is much more frequent in patients with diabetes.[14]

Although PAD is characterized by a slow and low rate of local symptoms and complications, it is also characterized by ongoing atherogenesis in other vascular beds and a very high rate of mortality (approximately 25%-30% within 5 years for patients with symptomatic PAD) due mainly to stroke and myocardial infarction (MI) (**TABLE 1**).[18,23-34]

Because of the aging of Western populations, the burden of PAD and its complications is likely to increase unless the incidence can be reduced and the complications prevented by effective, affordable, and widely available prophylactic therapies. This review summarizes the current evidence-based medical treatment of patients with atherosclerotic PAD. Invasive treatments such as angioplasty and arterial bypass surgery are not reviewed.

EVIDENCE ACQUISITION

We searched MEDLINE (January 1990 to November 2005) and the Cochrane electronic database (August 2005) for English-language articles that addressed the medical treatment of PAD. The search used the following terms, singly and in combination: *peripheral arterial disease*, *peripheral artery disease*, *PAD*, *randomized controlled trial*, *controlled trial*, *randomized*, and *meta-analysis*. We focused on randomized controlled trials (RCTs) or meta-analyses of RCTs because they provide the least biased and most robust evidence for the efficacy of treatments. We sought trials that studied the effect of medical treatments for PAD both on leg symptoms (intermittent claudication and walking distance) and on death and major coronary and cerebrovascular events.

EVIDENCE SYNTHESIS
Improving Leg Symptoms

Smoking Cessation. Smoking is the dominant modifiable risk factor for PAD; a dose-dependent relationship is present between smoking and severity of PAD.[10,35] Smoking cessation among patients with intermittent claudication does not significantly improve walking capacity but may reduce the severity of claudication[36] and the risk of developing rest pain.[37]

Smoking cessation can be facilitated to a modest extent in the general population by physician advice to quit smoking[37] and by use of nicotine replacement therapy[38] and bupropion[39] (**TABLE 2**). This likely also applies to patients with PAD,[40] although there have been no RCTs of methods of smoking cessation specifically in PAD.

Exercise. In patients with stable intermittent claudication, exercise significantly improves maximal walking time and overall walking ability.[41] Exercise is more effective than angioplasty for improving walking time and is also more effective than antiplatelet therapy, but it does not differ significantly from surgical treatment.[42] The optimal exercise program for improving distances walked without claudication pain in patients with PAD involves intermittent walking to near-maximal pain over a period of at least 6 months.[42] The mechanism by which exercise improves leg symptoms is uncertain, but it does not appear to operate through improvement of the ABI or growth of collateral vessels.[43]

Statin Drugs. In the randomized Scandinavian Simvastatin Survival Study (4S), simvastatin (20 to 40 mg/d) significantly reduced the incidence of new intermittent claudication from 3.6% (placebo) to 2.3% (simvastatin) over a median period of 5.4 years in 4444 patients with prior MI or angina pectoris (relative risk reduction [RRR], 0.62%; 95% CI, 0.44%-0.88%).[44] Both

simvastatin and atorvastatin also improve pain-free walking time.[45,46] Observational data suggest that it is the non–cholesterol-lowering properties of statins that favorably influence leg function in patients with PAD.[47,48]

Blood Pressure–Lowering Drugs. Contrary to prior belief, β-adrenergic antagonist drugs do not worsen intermittent claudication in patients with PAD but, if indicated, should be used with caution in severely affected patients.[49] The combination of atenolol and nifedipine marginally reduces maximal treadmill walking distance,[50] while angiotensin-converting enzyme inhibitors (captopril, perindopril) may improve walking distances.[51,52]

Cilostazol. Cilostazol is an inhibitor of phosphodiesterase type 3 and thereby inhibits platelet aggregation and causes vasodilation. A meta-analysis of 8 RCTs involving 2702 patients demonstrated that cilostazol improved maximum walking distance and pain-free walking distance.[53] Although cilostazol has not been associated with the increase in cardiac mortality seen with other phosphodiesterase inhibitors such as milrinone (which was developed for the treatment of heart failure), it remains contraindicated in patients with PAD who have coexistent cardiac failure.

Other Treatments. Ticlopidine[54] and ginkgo biloba special extract (Egb 761)[55,56] significantly increase pain-free walking distance. Numerous other therapies, such as naftidrofuryl, pentoxifylline, garlic, testosterone, levocarnitine, propionyl-L-carnitine, and chelation therapy have been evaluated in RCTs but have not been shown to be effective or are less effective than established treatments.[57-60] A variety of strategies to stimulate new collateral channels in peripheral ischemia, such as the use of growth factors and autologous bone marrow cells, are currently being evaluated.[61,62]

Preventing Systemic Complications of Coronary and Cerebral Atherosclerotic Arterial Disease

Smoking Cessation. Smoking cessation in the general population is associated with a rapid reduction in cardio-

Table 2. Medical Treatment of Peripheral Arterial Disease

Indication	Intervention	Method/Comment
Improving leg symptoms	Smoking cessation[36,37]	Physician advice Nicotine replacement therapy Bupropion
	Exercise[41,42]	Consider structured exercise program
	Statin drugs[44-46]	Benefit appears to be related to non–cholesterol-lowering properties of statins
	Blood pressure–lowering drugs[49-52]	Angiotensin-converting enzyme inhibitors
	Cilostazol[53]	Contraindicated in patients with heart failure
Preventing systemic complications	Smoking cessation[37]*	
	Weight loss[77,78]†	Consider in overweight patients with peripheral arterial disease
	Lowering blood pressure[66,67]	Effect determined by magnitude of blood pressure lowering
	Angiotensin-converting enzyme inhibitors[66,67]	Possible benefits beyond blood pressure–lowering effect
	Lowering blood cholesterol level[70]	
	Antiplatelet therapy[79-86]	Aspirin, with clopidogrel as suitable alternative

*No randomized evidence but based on convincing observational data.
†Efficacy unproven in randomized trials, but observational data are compelling.

vascular risk.[63] It is plausible to expect similar benefits of smoking cessation in patients with PAD, although the only RCT that examined the effect of smoking advice on mortality in such patients reported no statistically significant differences in death rates at 20 years.[36] However, observational data indicate that smoking cessation reduces MI and cardiac deaths and improves overall survival at 10 years among patients with intermittent claudication.[37]

Lowering Blood Pressure. The 5 main classes of antihypertensive drugs (diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists) are all effective for preventing cardiovascular events, and the magnitude of their effect is mainly determined by the magnitude of blood pressure lowering.[64,65]

Among 4051 patients with PAD (ABI <0.90) enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study, random assignment to ramipril (10 mg/d) (n=1966) was associated with an RRR of subsequent stroke, MI, and vascular death of approximately 25% (95% CI, 14%-37%), from 22% (placebo) to 17% (ramipril) after 5 years (mean) follow-up.[66] This result was

consistent with that observed in all 9297 patients at high vascular risk (RRR, 22%; 95% CI, 14%-30%).[66]

In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, more intensive blood pressure control was more effective than moderately intensive control for preventing cardiovascular events in 53 patients with PAD and type 2 diabetes.[67] The benefit of intensive blood pressure control was independent of drug class.

The results of the HOPE and ABCD trials in patients with PAD are consistent with those of a recent systematic review of RCTs assessing the effect of blood pressure lowering in all individuals, which showed that lowering blood pressure by about 10 to 12 mm Hg systolic and 5 to 6 mm Hg diastolic reduces the relative risk of stroke by about 38% and the risk of coronary events by about 16%, and that more intensive blood pressure lowering is more effective than less intensive lowering.[68]

There is some recent evidence suggesting that β-blockers are less effective than other antihypertensive drugs.[68] It remains uncertain whether angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists have significant additional prophylactic ef-

fects on coronary and cerebrovascular events that is independent of their effects on blood pressure.[66,67,69]

Lowering Blood Cholesterol Levels. Among 6748 patients with a history of PAD (with or without a history of coronary heart disease) and a plasma total cholesterol concentration of 3.5 mmol/L (135 mg/dL) or greater, random allocation to simvastatin (40 mg/d) (n=3384) was associated with an approximately 1.0-mmol/L (38.6-mg/dL) reduction in low-density lipoprotein cholesterol (LDL-C) concentration and an RRR of stroke, MI, vascular death, and revascularization procedures of approximately 20% (95% CI, 13%-27%), from 32.7% (placebo) to 26.4% (simvastatin) after 5 years of follow-up.[70] The results were similar among patients with a history of PAD only (from 30.5% [placebo] to 24.7% [simvastatin] after 5 years of treatment; RRR, 21%; 95% CI, 7%-33%) and in each subcategory based on sex, age, or baseline concentrations of total plasma cholesterol and LDL-C.[70]

These results are consistent with those of a recent meta-analysis of more than 90 000 individuals at high vascular risk, among whom statin therapy safely reduced the 5-year incidence of major vascular events by about one fifth (relative risk, 0.79; 95% CI, 0.77-0.81; $P<.001$) per 1.0-mmol/L reduction in LDL-C concentration, irrespective of the initial lipid profile and other presenting characteristics.[71]

Control of Blood Glucose Levels. It has been estimated that each 1% increase in glycosylated hemoglobin level is associated with a 28% increased risk of incident PAD[72] and with a 28% increased risk of death, independent of age, smoking status, blood pressure, or serum cholesterol concentration ($P<.002$).[73] Although randomized trials among patients with diabetes have shown that more intensive treatment of hyperglycemia results in fewer microvascular complications of diabetes (eg, retinopathy and renal damage) and decreased progression of carotid artery intima-media thickness, they have not shown significantly fewer macrovascular complications (ie, stroke, MI, death, or amputation due to PAD).[74-76]

Weight Loss. There are consistent observational data that increasing waist-to-hip ratio and body mass index are associated with increasing cholesterol, blood pressure, and blood glucose levels, as well as with increasing risk of cardiovascular disease and death.[77,78] There is, however, no evidence from RCTs that weight loss reduces vascular events.

Antiplatelet Therapy. The Antithrombotic Trialists' Collaboration meta-analysis of 195 trials of antiplatelet treatment vs control among a total of 135 640 patients at high risk of occlusive arterial disease demonstrated that antiplatelet therapy reduces the risk of MI, stroke, or cardiovascular death by about one quarter.[79] The size of the treatment effect in 9214 patients with PAD included in this analysis (5.8% vs 7.1%; 23% odds reduction; $P<.004$) was similar to that seen in other high-risk groups (acute or previous acute MI, previous stroke), and the benefits were evident in patients with PAD who experience intermittent claudication as well as those undergoing peripheral angioplasty or bypass surgery.[80,81]

Aspirin is the most widely evaluated antiplatelet agent for preventing cardiovascular events.[79,81] Individual trials in patients with PAD have not definitively established a benefit of aspirin for preventing MI, stroke, or cardiovascular death, but the results with aspirin are consistent with the overall effects of antiplatelet therapy in patients with PAD.[79,81,82] Likewise, the effectiveness of different doses of aspirin has not been definitively evaluated in PAD, but direct and indirect comparisons of different aspirin doses in the Antithrombotic Trialists' Collaboration meta-analysis suggest that 75 to 150 mg/d is at least as effective as higher doses (>150 mg/d) and is less likely to cause gastrointestinal and bleeding complications.[79,81]

Aspirin has not been shown to improve claudication, but it delays the rate of progression, reduces the need for intervention, and reduces graft failure in patients who have undergone revascularization procedures.[79,83,84]

Ticlopidine (250 mg twice daily) compared with placebo reduces the risk of MI, stroke, or death by about one third in patients with PAD.[82,85] However, it also causes thrombocytopenia (in approximately 2%-3% of patients), thrombotic thrombocytopenic purpura (in approximately 0.03% of patients), and potentially fatal neutropenia and has now largely been replaced by clopidogrel as the thienopyridine of choice.

The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that clopidogrel (75 mg/d) compared with aspirin (325 mg/d) reduced the risk of MI, stroke, or cardiovascular death by 8.7% (95% CI, 0.3%-16.5%; $P=.04$) in a broad range of high-risk patients.[86] The greatest benefit was evident in the subgroup of 6452 patients with PAD in whom there was a 23.8% (95% CI, 8.9%-36.2%) RRR for MI, stroke, or cardiovascular death in patients treated with clopidogrel compared with aspirin (4.9% per year vs 3.7% per year for aspirin vs clopidogrel, respectively).[86]

Several novel antiplatelet drugs, including picotamide (inhibits thromboxane A_2 synthase and blocks thromboxane A_2 receptors), triflusal (inhibits platelet aggregation and vascular inflammation), and ketanserin (S_2 serotonin receptor antagonist) have not been shown to be superior to aspirin for preventing systematic complications in patients with PAD.[79]

The combination of aspirin and clopidogrel is currently being compared with aspirin for preventing cardiovascular events in high-risk patients with PAD; results of the comparison are due to be presented in March 2006.[87]

Anticoagulant Therapy. No benefit of heparin, low-molecular-weight heparin, or oral anticoagulants has been established for intermittent claudication, but there is an increased risk of major bleeding, especially with oral anticoagulants.[88] Patients undergoing infrainguinal venous bypass may benefit from treatment with a vitamin K antagonist instead of, or in addition to, aspirin to maintain graft patency and improve survival, but the evidence is not conclusive.[89,90] The combination of

aspirin and warfarin compared with aspirin alone for the treatment of PAD, including among patients undergoing revascularization procedures, is currently being evaluated in the Warfarin and Vascular Evaluation (WAVE) trial.[91]

Summary of Treatment Evidence for PAD

Improving Leg Symptoms. Smoking cessation reduces the severity of claudication and may be enhanced by physician advice coupled with nicotine replacement therapy or bupropion.

Exercise at least 2 times per week, even in the presence of pain from intermittent claudication, increases walking time. For patients with claudication who consider their leg pain a barrier to exercise, structured exercise programs are appropriate. Walking through the claudication pain is not harmful and gradually increases walking distance.

Simvastatin reduces the incidence of new intermittent claudication, and simvastatin and atorvastatin both significantly increase pain-free walking time. Angiotensin-converting enzyme inhibitors appear to provide symptomatic relief of PAD, but the data are limited. Cilostazol improves maximal and pain-free walking distance and is a suitable treatment for disabling claudication, except in patients with symptoms of heart failure.

Preventing Systemic Complications of Coronary and Cerebral Atherosclerotic Arterial Disease. Although RCTs have not shown that smoking cessation saves lives, the evidence from observational studies for reduced mortality after smoking cessation is compelling. Smoking cessation is the main priority in risk factor management.

For patients with PAD, ramipril reduces the risk of serious vascular events by approximately one quarter and simvastatin by approximately one fifth. Because all patients with PAD are at increased risk of a vascular event, they should be considered for prolonged treatment with at least 1 blood pressure–lowering agent and a statin, irrespective of their baseline blood pressure and cholesterol level. Modest reductions in blood

---

Box. Management of Patients With Peripheral Arterial Disease Who Have Diabetes*

Target Levels of Risk Factors in Patients With Diabetes[14,92]

Blood pressure <130/80 mm Hg

Low-density lipoprotein cholesterol level <2.6 mmol/L (100 mg/dL)

Triglycerides level <1.7 mmol/L (150 mg/dL)

High-density lipoprotein cholesterol >1.1 mmol/L (40 mg/dL)†

Glycosylated hemoglobin level <7%

*To achieve targets, lifestyle interventions (diet and exercise) are recommended first, followed by pharmacological interventions, if necessary. Recommendations from the American Diabetes Association (2003).
†In women, a level above 1.3 mmol/L (50 mg/dL) may be appropriate.

---

pressure and cholesterol level achieve substantial and significant reductions in serious vascular events. The absolute benefit relates chiefly to an individual's absolute risk of such events and to the absolute reduction achieved in blood pressure and LDL-C level.

Early detection of diabetes and glucose intolerance, followed by careful control of glycemia and vascular risk factors to target levels (Box), is likely to improve long-term outcome.[14,92] According to current data, rigorous control of blood pressure and blood cholesterol level is more important than rigorous control of blood glucose level in preventing serious vascular events among individuals with diabetes.

Weight reduction should be a component of the management strategy of overweight patients with PAD.

Antiplatelet therapy should be used in all patients with PAD who do not have a specific contraindication. Aspirin is the preferred antiplatelet drug because it is effective and inexpensive. Clopidogrel is safer than ticlopidine and slightly more effective than aspirin, but it is much more expensive.

Anticoagulants are not indicated for the medical management of PAD but may have a role after infrainguinal bypass surgery.

Controversies and Uncertainties

Should ABI Be Used to Screen the General Population for PAD and Risk of Vascular Disease? The ABI is a simple, noninvasive, and reliable test that can be complementary to conventional vascular risk factor profiles to identify individuals from the general population who are at high risk of developing cardiovascular disease and could benefit from preventive measures.[93] After adjusting for conventional cardiovascular risk factors and prevalent cardiovascular disease, a low ABI (<0.90) is an independent predictor of cardiovascular risk.[94] A low ABI is also highly specific (88%-93%) for predicting future cardiovascular events (ie, a low ABI helps to "rule in" a high-risk patient), with likelihood ratios of about 2.5 (95% CI, 1.4-4.4) for coronary heart disease, 2.4 (95% CI, 1.8-3.4) for stroke, and 5.6 (95% CI, 3.4-9.1) for cardiovascular death.[94] However, because the sensitivity of a low ABI to predict future cardiovascular outcomes is low (ie, a normal ABI does not "rule out" a high-risk patient), the ABI lacks usefulness as a screening test for PAD in the general population.[94] Its optimal application may be as part of the vascular risk assessment among selected individuals without established vascular disease but older than 70 years or among those who are aged 50 to 69 years and have 1 or more cardiovascular risk factors (ie, elevated serum cholesterol level, hypertension, dysglycemia, tobacco exposure, or a family history of atherosclerotic disease).[94] Further clarification of the role of ABI awaits evaluation of its incremental predictive value over conventional methods of risk assessment in patients who may be at increased risk of cardiovascular disease.[94,95]

Is There a Role for Screening and Modifying Novel Risk Factors? Elevated blood levels of C-reactive protein predict the development of PAD in apparently healthy men, independently of elevated blood lipid levels,[96] and elevated blood levels of homocysteine, C-reactive protein, and fibrinogen have been reported in patients with PAD. However, it remains to be shown that these are both causal and modifiable risk factors for atherothrombosis. Traditional risk factors are still likely to account for most of the risk of cardiovascular disease worldwide.[97]

CONCLUSION

Peripheral arterial disease, particularly asymptomatic disease, is common and is likely to become more common as the population ages and as the diagnosis of hitherto unrecognized asymptomatic disease improves.

The importance of recognizing asymptomatic PAD is that it helps refine assessment of vascular risk and identify individuals at considerable risk for MI and stroke. This risk, along with severity of claudication in symptomatic patients, can be substantially reduced by modest reductions in the prevalence and level of causal risk factors by means of lifestyle modification and effective medical therapies. An enormous opportunity—and responsibility—exists to begin to translate the evidence into practice.[98]

REFERENCES

1. Dormandy JA, Rutherford RB; TASC Working Group. Management of peripheral arterial disease (PAD). *J Vasc Surg*. 2000;31:S1-S296.

2. Hirsch AT, Criqui MH, Treat-Jacobsen D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317-1324.
3. Hooi JD, Kester AD, Stoffers HE, Overdijk MM, van Ree JW, Knottnerus JA. Incidence and of risk factors for asymptomatic peripheral arterial disease: a longitudinal study. *Am J Epidemiol*. 2001;153:666-672.
4. Diehm C, Schuster A, Allemberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis*. 2004;172:95-105.
5. Faglia E, Caravaggi C, Marchetti R, et al. Screening for peripheral arterial disease by means of the ankle-brachial index in newly diagnosed type 2 diabetic patients. *Diabet Med*. 2005;22:1310-1314.
6. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RU. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol*. 1991;20:384-392.
7. Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH. Lower extremity arterial disease in elderly subjects with systolic hypertension. *J Clin Epidemiol*. 1991;44:15-20.
8. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam study. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
9. Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA. The prevalence of asymptomatic and unrecognised peripheral arterial occlusive disease. *Int J Epidemiol*. 1996;25:282-290.
10. Fowler B, Jamrozik K, Norman P, Allen Y. Prevalence of peripheral arterial disease: persistence of excess risk in former smokers. *Aust N Z J Public Health*. 2002;26:219-224.
11. getABI Study group. getABI: German epidemiological trial on ankle-brachial index for elderly patients in family practice to detect peripheral arterial disease, significant marker for high mortality. *Vasa*. 2002;31:241-248.
12. O'Hare AM, Glidden DV, Fox CS, Hsu C. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. *Circulation*. 2004;109:320-323.
13. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Arch Intern Med*. 1999;159:387-392.
14. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care*. 2003;26:3333-3341.
15. Kannel WB, McGee DL. Update on some epidemiological features of intermittent claudication. *J Am Geriatr Soc*. 1985;33:13-18.
16. Dagenais GR, Maurice S, Robitaille NM, et al. Intermittent claudication in Quebec men from 1974-1986: the Quebec Cardiovascular Study. *Clin Invest Med*. 1991;14:93-100.
17. Widmer LK, Biland L. Incidence and course of occlusive peripheral artery disease in geriatric patients. *Int Angiol*. 1985;4:289-294.
18. Leng GC, Lee AJ, Fowkes FGR, 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.
19. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet*. 2005;366:1773-1783.
20. Hooi JD, Stoffers HE, Knottnerus JA, van Ree JW. The prognosis of non-critical limb ischaemia: a systematic review of population-based epidemiological evidence. *Br J Gen Pract*. 1999;49:49-55.
21. Catalano M. Epidemiology of critical limb ischemia: northern Italian data. *Eur J Med*. 1993;2:11-14.
22. Ebskov L, Schroeder T, Holstein P. Epidemiology of leg amputation: the influence of vascular surgery. *Br J Surg*. 1994;81:1600-1603.

23. Criqui M, Langer R, 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.
24. Vogt MT, Cauley HA, Newman AB, Kuller LH, Hulley SB. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA*. 1993;270:465-469.
25. Kornitzer M, Dramiax M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology*. 1995;46:211-219.
26. Newman AB, Sutton-Tyrell K, Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. *J Am Geriatr Soc*. 1997;45:1472-1478.
27. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. 1999;19:538-545.
28. Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *J Clin Epidemiol*. 2004;57:294-300.
29. Newman AB, Sutton-Tyrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with low ankle-arm pressure index. *JAMA*. 1993;270:487-489.
30. Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ; The Coronary Artery Surgery Study (CASS) Investigators. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. *J Am Coll Cardiol*. 1994;23:1091-1095.
31. McDermott MM, Feinglass J, Slavensky R, Pearce WH. Tha ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. *J Gen Intern Med*. 1994;9:445-449.
32. Dormandy J, Heeck L, Vig S. The natural history of claudication: risk to life and limb. *Semin Vasc Surg*. 1999;12:123-137.
33. Aquino R, Johnnides C, Makaroun M, et al. Natural history of claudication: long-term serial follow-up of 1244 claudicants. *J Vasc Surg*. 2001;34:962-970.
34. Hooi JD, Stoffers HE, Kester AD, Knottnerus JA. Peripheral arterial occlusive disease: prognostic value of signs, symptoms, and the ankle-brachial pressure index. *Med Decis Making*. 2002;22:99-107.
35. Willigendael EM, Teijink JAW, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg*. 2004;40:1158-1165.
36. Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Arch Intern Med*. 1999;159:337-345.
37. Jonason T, Bergstron 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.
38. Lancaster T, Stead LF. Physician advice for smoking cessation. *Cochrane Database Syst Rev*. 2004;(4):CD000165 doi:10.1002/14651858.
39. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2004;(3):CD000146 doi:10.1002/14651858.
40. Hobbs SD, Bradbury AW. Smoking cessation strategies in patients with peripheral arterial disease: an evidence-based approach. *Eur J Vasc Endovasc Surg*. 2003;26:341-347.
41. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2000;(2):CD000990 doi:10.1002/14651858.
42. Gardner AW, Phoelman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA*. 1995;274:975-980.
43. Stewart KJ, Hiatt WR. Exercise training for claudication. *N Engl J Med*. 2002;347:1941-1951.
44. Pedersen TR, Kjekshus J, Pyörälä 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.

45. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol*. 2003;92:711-712.

46. Mohler ER, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation*. 2003;108:1481-1486.

47. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. *Circulation*. 2003;107:757-761.

48. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med*. 2003; 114:359-364.

49. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 1991;151:1769-1776.

50. Solomon SA, Ramsay LE, Yeo WW, Parnell L, Morris-Jones W. Beta blockade and intermittent claudication: placebo controlled trial of atenolol and nifedipine and their combination. *BMJ*. 1991;303:1100-1104.

51. Novo S, Abrignani MG, Pavone G, et al. Effects of captopril and ticlopidine, alone or in combination, in hypertensive patients with intermittent claudication. *Int Angiol*. 1996;15:169-174.

52. Lip GYH, Makin AJ. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Syst Rev*. 2003;(2):CD003075 doi:10.1002/14651858.

53. Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. *Am J Cardiol*. 2002;90:1314-1319.

54. Balsano F, Coccheri S, Libretti A, et al. Ticlopidine in the treatment of intermittent claudication: a 21-month double blind trial. *J Lab Clin Med*. 1989;114:84-91.

55. Horsch S, Walther C. Ginkgo biloba special extract Egb 761 in the treatment of peripheral arterial occlusive disease (PAOD)—a review based on randomized, controlled studies. *Int J Clin Pharmacol Ther*. 2004;42:63-72.

56. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med*. 2000;108:276-281.

57. Jepson RG, Kleijnen J, Leng GC. Garlic for peripheral arterial occlusive disease. *Cochrane Database Syst Rev*. 1997;(2):CD000095 doi:10.1002/14651858.

58. Price JF, Leng GC. Steroid sex hormones for lower limb atherosclerosis. *Cochrane Database Syst Rev*. 2001;(3):CD000188 doi:10.1002/14651858.

59. Brevetti G, Diehm C, Lambert D. European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol*. 1999;34:1618-1624.

60. Villaruz MV, Dans A, Tan F. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev*. 2002;(4):CD002785 doi:10.1002/14651858.

61. Lederman RJ, Mendelsohn FO, Anderson RD, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (TRAFFIC study): a randomised trial. *Lancet*. 2002;359:2053-2058.

62. Tateishi-Yuyama E, Mastubara T, Murohara T, et al. Therapeutic angiogenesis for patients with limb ischemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet*. 2002;360:427-435.

63. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004;328:1519.

64. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527-1535.

65. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke*. 2004;35:1024-1033.

66. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients [published corrections appear in *N Engl J Med*. 2000;342:748 and 2000;342:1376]. *N Engl J Med*. 2000;342:145-153.

67. Mehler PS, Coll JR, Estacia R, Esler A, Schrier RW, Hiatt WR. 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.

68. Lindholm LH, Carlberg B, Samuelsson O. Should β-blockers remain first choice in the treatment of primary hypertension? a meta-analysis. *Lancet*. 2005;366:1545-1553.

69. Hankey GJ. Angiotensin-converting enzyme inhibitors for stroke prevention: is there HOPE for PROGRESS after LIFE? *Stroke*. 2003;34:354-356.

70. Heart Protection Study Collaborative 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.

71. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.

72. UK Prospective Diabetes Study (UKPDS) 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) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837-853.

73. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in *Lancet*. 1998;352:1557]. *Lancet*. 1998;352:854-865.

74. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*. 2003;348:2294-2303.

75. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycaemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care*. 2002;25:894-899.

76. Khaw KT, Wareham N, Luben R, et al. Glycated hemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ*. 2001;322:15-22.

77. Harris T, Cook EF, Garrison R, Higgins M, Kannel W, Goldman L. Body mass index and mortality among nonsmoking older persons: the Framingham Heart Study. *JAMA*. 1988;259:1520-1524.

78. Yusuf S, Hawken S, Ôunpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005; 366:1640-1649.

79. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324:141]. *BMJ*. 2002;324:71-86.

80. Dörfer-Melly J, Büller HR, Koopman MM, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev*. 2003;(3):CD000535 doi:10.1002/14651858.

81. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med*. 2005;353:2373-2383.

82. Bergqvist D, Almgren B, Dickinson JP. Reduction of the requirement for leg vascular surgery during long-term treatment of claudicant patients with ticlopidine: results from the Swedish Ticlopidine Multicentre Study (STIMS). *Eur J Vasc Endovasc Surg*. 1995;10:69-76.

83. Hess H, Mietaschik A, Deichsel G. Drug-induced inhibition of platelet function delays progression of peripheral occlusive arterial disease: a prospective double-blind arteriographically controlled trial. *Lancet*. 1985;1:415-419.

84. Goldhaber SZ, Manson JE, Stampfer MJ, et al. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. *Lancet*. 1992;340:143-145.

85. Boissel JP, Peyrieux JC, Destors JM. Is it possible to reduce the risk of cardiovascular events in subjects suffering from intermittent claudication of the lower limbs? *Thromb Haemost*. 1989;62:681-685.

86. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.

87. Bhatt DL, Topol EJ; Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance Executive Committee. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J*. 2004; 148:263-268.

88. Cosmi B, Conti E, Coccheri S. Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev*. 2001;(2):CD001999 doi:10.1002/14651858.

89. Dörfer-Melly J, Büller HR, Koopman MM, Prins MH. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. *Cochrane Database Syst Rev*. 2003;(2):CD000536 doi:10.1002/14651858.

90. Collins TC, Souchek J, Beyth RJ. Benefits of anti-thrombotic therapy after infrainguinal bypass grafting: a meta-analysis. *Am J Med*. 2004;117:93-99.

91. WAVE Study Investigators. The effects of oral anticoagulants in patients with peripheral arterial disease: rationale, design and baseline characteristics of the WAVE trial including a meta-analysis of trials. *Am Heart J*. 2006; 151:1-9.

92. Solomon CG. Reducing cardiovascular risk in type 2 diabetes. *N Engl J Med*. 2003;348:457-458.

93. Caruana MF, Bradbury AW, Adam DJ. The validity, reliability, reproducibility and extended utility of ankle to brachial pressure index in current vascular surgical practice. *Eur J Vasc Endovasc Surg*. 2005;29:443-451.

94. Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol*. 2005;25:1463-1469.

95. Smith SC Jr, Greenland P, Grundy SM. Prevention Conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. *Circulation*. 2000;101:111-116.

96. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systematic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA*. 2001;285:2481-2485.

97. Yusuf S, Hawken S, Ounpuu S; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952.

98. Majumdar SR, McAlister FA, Furberg CD. From knowledge to practice in chronic cardiovascular disease: a long and winding road. *J Am Coll Cardiol*. 2004; 43:1738-1742.