

Critical Issues in Peripheral Arterial Disease Detection and Management

A Call to Action

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THIS CALL-TO-ACTION document is an initiative of the Prevention of Atherothrombotic Disease Network, an international, multidisciplinary network, adjoined by the mutual goal of increasing awareness, detection, and treatment rates of peripheral arterial disease (PAD) and increasing awareness of the interrelationship between PAD and the risk of ischemic events. Although the prevalence of PAD in Europe and North America is estimated at approximately 27 million people, PAD remains a largely underdiagnosed and

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undertreated disease. Several recent epidemiologic studies have revealed PAD detection rates of 20% to 30% when specific at-risk populations were screened. In an effort to guide diagnostic and treatment protocols, the Prevention of Atherothrombotic Disease Network has recommended 5 action items. These are to (1) increase awareness of PAD and its consequences; (2) improve the identification of patients with symptomatic PAD; (3) initiate a screening protocol for patients at high risk for PAD; (4) improve treatment rates among patients who have been di-

agnosed with symptomatic PAD; and (5) increase the rates of early detection among the asymptomatic population.

INTRODUCTION

Peripheral arterial disease is a distinct atherothrombotic syndrome that is associated with an elevated risk of cardiovascular and cerebrovascular events, including death, myocardial infarction (MI), and stroke. With the prevalence of PAD in Europe and North America estimated at approximately 27 million people, PAD is a critical public health issue.¹

The deleterious nature of PAD is compounded by its status as an underdiagnosed and undertreated disease. However, several recent developments suggest that this may be an opportune time to reexamine traditional assumptions regarding methods used to diagnose and manage PAD. These developments include (1) data from recent community surveys of PAD prevalence, treatment, and outcomes, which have shed new light on the magnitude of the burden of PAD and its undertreatment²⁻⁴; (2) a large body of epidemiologic evidence supporting the efficacy of the ankle-brachial index (ABI [also known as the ankle-brachial pulse index or the ankle/arm index]) as an effective diagnostic and risk-assessment tool⁵⁻⁸; (3) increasing awareness of the cost-effective benefit associated with the management of cardiovascular risk⁹; and (4) clinical study results showing that substantial risk reduction

can be achieved with pharmacologic intervention in PAD.¹⁰⁻¹²

This call-to-action document is an initiative of the Prevention of Atherothrombotic Disease Network, an international, independent group comprising specialists in the fields of vascular medicine, neurology, diabetology, nephrology, cardiology, and primary care. The mission of this network is to evaluate current data regarding the prevalence of PAD and thereby to (1) advocate for increased international awareness that PAD is a manifestation of disseminated atherothrombosis and (2) promote effective identification and treatment of patients with PAD to prevent ischemic events. The Prevention of Atherothrombotic Disease Network has achieved consensus that improvement in the detection of symptomatic PAD is of primary importance, since those with symptomatic PAD are at very high risk for an ischemic event and are likely to experience the greatest degree of risk reduction from pharmacologic therapy.

PAD EPIDEMIOLOGY, PREVALENCE, AND RISK FACTORS

Peripheral arterial disease is a progressive condition characterized by arterial stenosis and occlusions in the peripheral arterial bed; it can be symptomatic or asymptomatic. Symptomatic PAD ranges in severity from intermittent claudication to critical limb ischemia. Critical limb ischemia exists in part due to the late recognition of PAD, and if

From The Prevention of Atherothrombotic Disease Network. A complete list of the affiliations of the Prevention of Atherothrombotic Disease Network Executive Committee contributors is given at the end of this article.

untreated, can lead to nonhealing wounds, gangrene, and eventual amputation. In the population older than 55 years, PAD is an indicator of diffuse and significant arterial disease.¹

Intermittent claudication, a less severe but more common manifestation of symptomatic PAD, presents as reproducible limb discomfort during exercise, which is invariably relieved within minutes by rest. Patients with intermittent claudication often experience a diminishing quality of life due to a reduction in walking distance and speed, which translates into progressively limited mobility and independence; this loss of function may often exceed that observed in patients with other forms of cardiovascular disease (CVD).^{13,14} Unfortunately, many patients do not alert their physicians to the disease, since they attribute it to the nonspecific musculoskeletal symptoms of aging. Peripheral arterial disease is also associated, in all of its stages, with a profound impact on quality of life, affecting many domains not easily captured by current subjective tools.¹⁵

Most cases of PAD are asymptomatic.¹⁶ Asymptomatic PAD, similar to symptomatic PAD, is associated with an increased risk of atherothrombotic events, including MI and stroke,^{17,18} impaired lower extremity functioning,¹⁹ and internal carotid artery stenosis.^{20,21} The Limburg Peripheral Arterial Occlusive Disease (PAOD) study,¹⁷ a cross-sectional survey of 3650 patients aged 40 to 78 years, found that patients with asymptomatic PAD had a risk factor and comorbidity profile comparable with that of symptomatic patients.

PAD Prevalence

Based on current epidemiologic projections, 27 million people in Europe and North America (16% of the population 55 years and older) have PAD: an estimated 10.5 million people are symptomatic, and the majority, 16.5 million, are asymptomatic.¹ The prevalence of asymptomatic PAD was estimated in one study to be as high as 20% of the adult population.²²

Three recent programs—the Prevention of Progression of Arterial Disease and Diabetes (POPADAD),

the Minnesota Regional PAD Screening Program, and the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) program—have demonstrated high PAD detection rates of 20.1%, 26.5%, and 29%, respectively, when specific populations at risk for PAD were screened.

The ongoing POPADAD study evaluated 8000 patients 40 years and older who had type 1 or type 2 diabetes mellitus but no clinical symptoms of arterial disease. In the preliminary recruitment phase, patients were enrolled from 227 primary care facilities and 27 major hospitals throughout Scotland. Of these patients, 20.1% had an ABI value less than 0.95, which is clinically indicative of PAD.⁴

The Minnesota Regional PAD Screening Program, which evaluated 347 community-derived patients with leg pain or at high risk for PAD based on age and risk factor profile, detected PAD in 26.5% of the screened population.² The high PAD prevalence, low PAD awareness, and lower than anticipated treatment intensity served as the rationale for a larger subsequent survey in the United States.

The US PARTNERS program was a national survey designed to evaluate the prevalence of PAD and other cardiovascular diseases, assess the rate of physician and patient awareness of PAD diagnosis, and evaluate risk factor profiles and treatment with antiplatelet agents. The survey was performed in a primary care clinical setting. Patients were recruited from 320 primary care practices from across the country, and 6979 at-risk patients (patients older than 70 years or patients older than 50 years if they smoked or had diabetes) were assessed. The PARTNERS program found the prevalence of PAD in the population of patients older than 70 years and/or older than 50 years with comorbidities (eg, smoking and concomitant diabetes) to be 29%. Of the number of cases of PAD detected, as many as 44% were newly diagnosed with use of the ABI technique.³ These studies have illuminated the reality that within the high-risk population, a noteworthy amount of patients with PAD remain underdiagnosed.

Morbidity and Mortality

Peripheral arterial disease is a powerful indicator of systemic atherothrombotic disease. Regardless of whether symptoms are evident, patients with PAD have an increased risk of subsequent MI and stroke and are 6 times more likely to die within 10 years than patients without PAD.²³ In addition, the degree of symptom severity has been found to correlate with poor outcome. For example, a study that followed patients with PAD over 10 years found that survival rates decreased with increasing severity of PAD symptoms (**Figure 1**).²³ The association between symptomatic PAD and survival rate over a 15-year period is depicted in **Figure 2**. Patients with symptomatic PAD have a 15-year accrued survival rate of approximately 22%, compared with a survival rate of 78% in patients without PAD symptoms.^{24,25}

Patients presenting with symptomatic PAD are also at higher risk for developing chronic angina and are more likely to die from CVD.²⁶ Current US disease-based data sets have been used to compare 5-year mortality rates from common malignancies with the rate of PAD, thereby providing a “common sense” yardstick of relative risk. This analysis demonstrated that the patient survival rate for PAD is worse than the outcome for breast cancer and Hodgkin disease (**Figure 3**).^{27,28}

PAD DETECTION

Data from several surveys have been used to successfully identify and document a clinical profile of the population at risk for PAD, in whom directed screening is beneficial. In a recent study of patients at high risk for PAD,³ 44% were newly diagnosed with PAD, proving that there is a significant amount of PAD underdiagnosis within high-risk populations.

Advanced age, smoking, and diabetes are strongly associated with PAD.^{3,4,29} In one study, 50% of patients with diabetes were found to have PAD.⁴ Other PAD risk factors include hypertension, hyperlipidemia, male sex,³⁰ homocysteinemia,³¹ elevated plasma fibrinogen levels, el-

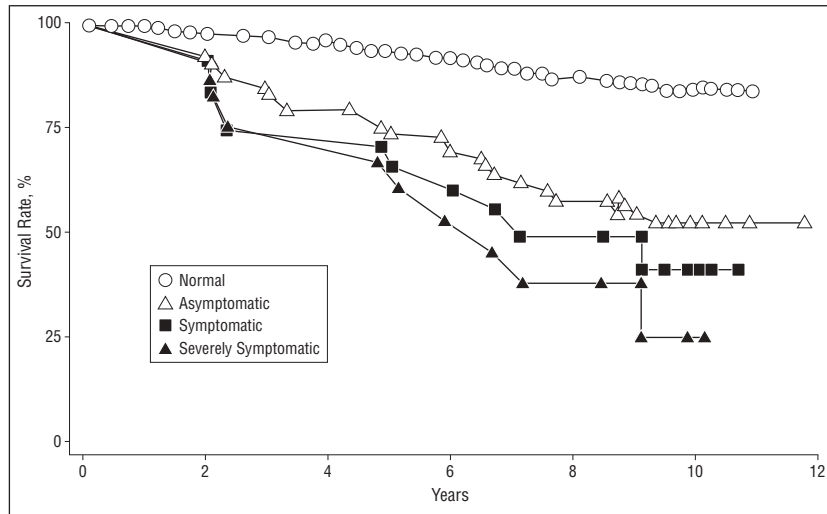


Figure 1. The 10-year survival rate for patients with and without peripheral arterial disease, as evidenced by the San Diego Artery Study.²³

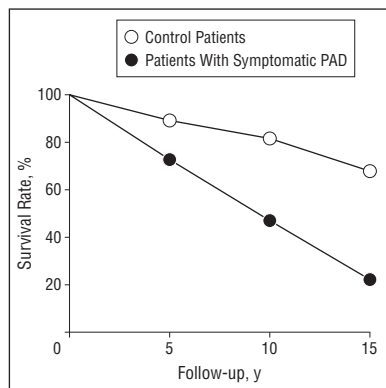


Figure 2. The survival rate over 15 years for patients with symptomatic peripheral arterial disease (PAD) vs control patients. Depicted is the relationship between the presence of symptomatic PAD and survival rate.^{24,25}

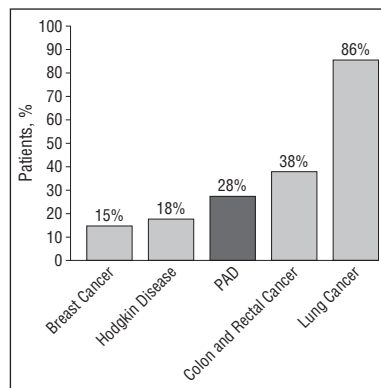


Figure 3. The 5-year mortality rates for common pathological conditions. The outcome from time of diagnosis of peripheral arterial disease (PAD) was found to be worse than the outcome for breast cancer and Hodgkin disease.^{27,28}

evated glucose level, prior MI,³² heart failure, history of stroke, and history of transient ischemic attack. **Figure 4** depicts the range of odds ratios for common symptomatic PAD risk factors.^{24,25}

A data-derived screening protocol for high-risk patients is critical, since most patients with PAD are asymptomatic and because it is estimated that approximately one third of symptomatic patients do not report their symptoms to a medical care provider.^{24,25} As demonstrated in PARTNERS, physicians who rely on a classic history of claudication alone to detect PAD will miss approximately 85% to 90% of patients with this high-risk atherothrombotic disease.³ Physicians who rely on the bedside pulse examination alone, valuable as this technique remains, will

also miss as many as half of PAD cases in practice.³³

Intermittent claudication is the primary, and often only, clear symptom in patients with PAD. Several epidemiologic questionnaires have been developed and widely used; however, they were designed to be used to diagnose symptomatic PAD only, and they are associated with varying levels of sensitivity.^{34,35} Although a clinical examination specifically targeted to PAD diagnosis and patient interview to assess walking difficulty yield low rates of detection individually, a thorough physical examination and verbal inquiry are recommended. Patient interviews may yield critical information instantly, and a thorough physical examination may detect commonly associated manifestations such as

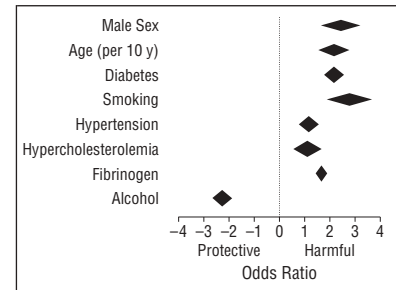


Figure 4. Common peripheral arterial disease (PAD) risk factors. Depicted is the range of odds ratios for developing symptomatic PAD. Excluding unmodifiable factors, the most important risk factors for developing intermittent claudication are diabetes and smoking.^{24,25}

coronary artery disease, aortic aneurysm, and increased creatinine from bilateral renal stenosis. As noted previously, other diagnostic tools typically used to detect PAD, such as peripheral pulse measurement, have not been found to provide a high degree of accuracy (peripheral pulse measurement has been found to have high false-positive and false-negative rates).^{24,25} Thus, an accurate, widely applicable, objective method to assess peripheral vascular function is clearly valuable.

Ankle-Brachial Index

The ABI is a noninvasive, simple, inexpensive measurement to assess the patency of the lower extremity arterial system.⁶ The ABI is measured by having the patient lie in the supine position, with subsequent performance of the ankle and brachial blood pressure measurements using a 5- to 7-MHz handheld Doppler device. Ideally, the posterior tibial and dorsalis pedis artery systolic pressures are both measured and compared with the arm pressure. The ABI value is calculated by dividing the higher of the ankle systolic pressures by the higher of 2 systolic brachial pressures. The ABI takes approximately 10 minutes to perform.

To date, the ABI is the most effective, accurate, and practical method of PAD detection. A diagnosis of PAD is based on the presence of limb symptoms or an ABI measurement less than 0.9. Whereas a resting ABI value of 1.0 is generally considered normal, a resting ABI value less than 0.9 approaches 95% sensitivity in detecting angiogram-positive disease, and it is associated

with the presence of 50% or greater stenosis in 1 or more major vessels. It is almost 100% specific in excluding healthy individuals. Furthermore, an ABI value less than 0.9 is highly predictive of morbidity and mortality from cardiovascular events linked with PAD.^{3,35,36} A comparison of detection rates reveals that the ABI is more sensitive and specific than several standard screening tests (**Table 1**). Major randomized clinical trials such as the POPADAD⁴ and Aspirin for Asymptomatic Atherosclerosis (AAA) studies are currently under way to evaluate the potential benefits of antiplatelet therapy in patients with a low ABI value.

The ABI allows for PAD detection at all stages of the disease process and can stratify the severity of both asymptomatic and symptomatic disease with a numerical value. In a study to determine the relationship between ABI and morbidity and mortality in patients with PAD, the 5-year cumulative survival rate was 63% for patients with a resting ABI value less than 0.50, 71% for patients with an ABI value between 0.50 and 0.69, and 91% for patients with an ABI value between 0.70 and 0.89.⁷ Individuals with an ABI value less than 0.90 are twice as likely to have coronary heart disease (CHD) than those with a normal ABI and have an increased risk of fatal and nonfatal MI, stroke, and death from cardiovascular causes, as well as all-cause death (**Table 2**).^{8,26} The ABI is a useful tool because it provides the clinician not only with a means of identification of PAD, but also with information regarding the severity of PAD that can assist in guiding a treatment approach (ie, >0.90, normal; 0.71-0.90, mild PAD; 0.41-0.70, moderate PAD; ≤0.40, severe PAD⁴⁰).

The initial responsibility for the detection of PAD should be with the primary care provider, supported by vascular specialty consultants and public health officials. Identifying the high-risk PAD population by developing and implementing a clinically effective and cost-effective screening protocol will contribute to the rate of disease detection and may have a significant beneficial impact. One of the most important initiatives of the Prevention of Atherothrombotic Disease Network is to

Table 1. Effectiveness of the ABI vs Other Common Screening Tests

Diagnostic Test	Sensitivity, %	Specificity, %
Pap smear ³⁷	30-87	86-100
Fecal occult blood test ³⁸	37-78	87-98
Mammography ³⁹	75-90	90-95
ABI ^{5,35,36}	95	100

Abbreviation: ABI, ankle-brachial index.

improve the diagnosis of PAD by screening high-risk individuals.

Limitations of the ABI

Although the ABI is an effective diagnostic tool, it does not measure the effectiveness of preventive treatment. Some elderly and diabetic patients have calcified arteries that prevent occlusion of blood flow by the blood pressure cuff, which may result in an unusually high ABI reading (>1.50). Patients with high-grade aortoiliac arterial stenoses or occlusions may also occasionally present with a normal ABI at rest due to the presence of a rich collateral arterial network. These patients must be referred for other tests, such as toe pressure measurement, Doppler waveform analysis, pulse volume recording, duplex arterial ultrasound study, or exercise Doppler stress testing.

PAD MANAGEMENT

Published PAD treatment guidelines from the United Kingdom recommend aggressive management of risk factors, which includes emphasizing the importance of lifestyle modifications.^{41,42} To date, no treatment guidelines have been published to guide treatment in the United States. However, it has been universally proposed that clinicians must treat PAD-specific symptoms to decrease functional impairment, improve quality of life, and decrease rates of amputation and underlying systemic atherothrombosis to reduce subsequent cardiovascular ischemic events, especially MI and stroke.^{2,3}

An estimated US \$151 billion in direct and indirect costs are attributable to CVD in the United States alone. Cost-effectiveness analysis reveals that the management of risk factors such as smoking, hypertension,

and hypercholesterolemia improves clinical outcomes at acceptable cost-effectiveness ratios, typically less than \$20 000 per year of life saved. From the patient, clinician, and societal perspectives, cost-effectiveness analysis supports the need for aggressive modification of cardiovascular risk factors and aggressive treatment in patients with PAD.⁹ An economic evaluation by the PAD TransAtlantic Inter-Society Consensus (TASC) Working Group determined that treatment with antiplatelet therapy (low-dose aspirin [acetylsalicylic acid] or another approved antiplatelet agent, unless contraindicated) was a cost-effective means of reducing cardiovascular and cerebrovascular event risk in patients with symptomatic PAD.^{24,25}

Treatment of Commonly Associated PAD Risk Factors

Smoking Cessation. Cigarette smoking is the most preventable cause of cardiovascular morbidity and mortality and is a primary PAD risk factor. Smoking is implicated in one third of all deaths from coronary artery disease, elevates the risk of sudden death, doubles the risk of stroke, and synergistically contributes to the deleterious nature of other risk factors.^{43,44} It is important to educate, encourage, and assist the PAD patient in quitting smoking. However, successful lifestyle modification among this population is notoriously difficult. A report from the American Lung Association revealed that although 70% of smokers surveyed would like to quit smoking, only 34% attempt to quit per year, and an average of only 2.5% succeed.⁴⁵ Treatment strategies include smoking cessation programs and nicotine replacement therapy. In the PARTNERS program, smoking cessation interventions were prescribed in only approximately half

Table 2. Risk of a Cardiovascular Event Over a 5-Year Period According to ABI Value at Study Entry*

5-y Incidence	ABI					P Value for Trend
	>1.1 (n = 538)	1.1-1.01 (n = 478)	1.0-0.91 (n = 278)	0.90-0.71 (n = 198)	≤0.70 (n = 90)	
Nonfatal MI	4	5	5	7	9	.06
Nonfatal stroke	1	2	3	3	3	.02
Fatal MI	2	3	4	6	10	≤.001
Fatal stroke	1	1	1	1	6	.14
Death						
Cardiovascular causes	4	4	6	8	21	≤.001
Noncardiovascular causes	7	7	5	9	13	.19
All causes	11	10	11	16	34	≤.001

Abbreviations: ABI, ankle-brachial index; MI, myocardial infarction.
*Data are percentage of patients unless otherwise specified.

of those with PAD.³ Thus, opportunities for prevention are commonly missed.

Hyperlipidemia. The association between the reduction of total cholesterol or low-density lipoprotein cholesterol and preventive benefit is well established.⁴⁶ Primary prevention trials have shown that lipid-lowering agents are effective in reducing cardiovascular events in older persons with hypercholesterolemia.^{47,48} Because of the high risk of cardiovascular events associated with hyperlipidemia, lipid levels should be lowered to recommended goals.^{48,49} Although there are currently no data documenting the relative efficacy of lipid-lowering therapy in patients with low ABI values and normal cholesterol levels, upcoming clinical trial data are expected to illuminate the potential benefits of lowering lipid levels in this population.

Hypertension and Diabetes. Anti-hypertensive therapy in patients with CVD has also been shown to provide protective benefits. For example, both diuretics and β -blockers have been proven to decrease rates of stroke, MI, heart failure, renal failure, and death.⁵⁰ Treating elderly patients with isolated systolic hypertension reduces the rate of a large number of cardiovascular end points.^{51,52} Furthermore, treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to decrease blood pressure, reduce mortality in patients with congestive heart failure, and prevent death and congestive heart failure when initiated early after the on-

set of acute MI. A major contributor to this new evidence is the large, placebo-controlled Heart Outcomes Prevention Evaluation (HOPE) trial, which found that the ACE inhibitor ramipril prevented death, MI, and other ischemic events in patients with a range of cardiovascular risks (including coronary artery disease, stroke, PAD, or diabetes plus 1 additional risk factor). Data from the HOPE trial suggest a greatly expanded role for ACE inhibition in the prevention and management of CVD.⁵³ However, careful follow-up of patients receiving an ACE inhibitor is critical owing to high concomitant rates of renal artery stenosis in patients with PAD. Despite the demonstrated benefits of antihypertensive therapies, few studies have evaluated the benefits of therapy in PAD-specific patient groups.

Two United Kingdom Prospective Diabetes Studies (UKPDS) demonstrated the benefits of blood pressure reduction on microvascular and macrovascular complications in patients with type 2 diabetes mellitus.^{54,55} The specific benefits of glycemic control have not yet been prospectively defined for the PAD population but have been extrapolated from studies such as UKPDS 38 and 39.

Managing PAD Symptoms

Patients with symptomatic PAD often have a decreased quality of life because of pain during walking and limitations of mobility. The primary symptom, intermittent claudication, results from inadequate blood flow to the musculature. In-

termittent claudication is most often characterized by a reproducible, painful aching or cramping in muscle groups of the leg that is caused by walking and relieved by rest.⁵⁶ Strategies for treating intermittent claudication are aimed at improving symptoms and reducing the progression of atherosclerosis. Positive outcomes have been shown with a treatment regimen that includes risk factor modification, particularly smoking cessation and control of diabetes, exercise, and pharmacotherapy.^{56,57}

Managing Critical and Acute Limb Ischemia

Critical limb ischemia in its most severe form is a threat to the limb and usually signals the need for intervention, such as revascularization or amputation. Hemodynamic parameters that indicate a diagnosis of critical limb ischemia include an ABI value less than 0.4, an ankle systolic pressure less than 50 mm Hg, or a toe systolic pressure less than 30 mm Hg. Patients without prohibitive operative risk should usually undergo an attempt at revascularization (either surgical or endovascular) rather than immediate amputation. Limb preservation by means of revascularization is cost-effective, provides a better quality of life, and is associated with lower preoperative morbidity and mortality than amputation.⁵⁸

Anticoagulants and antithrombotics have been recommended to treat acute limb ischemia, although revascularization is still considered the "gold standard."⁵⁹ In patients with acute embolic occlusion, ret-

rospective data have found that anticoagulant therapy with heparin or another anticoagulant reduces the frequency of recurrence.⁶⁰

Risk Reduction With Pharmacologic Intervention

Preventing the cardiovascular and cerebrovascular events associated with PAD is crucial to patient survival. Antiplatelet agents are widely recognized for their efficacy in reducing the occurrence of vascular events in patients with atherothrombotic disease.^{10-12,24,25}

Data suggest that aspirin therapy may modify the natural history of chronic lower extremity insufficiency and reduce the risk of associated cardiovascular events.⁶⁰ Aspirin therapy is currently recommended by the American Heart Association for use in patients with a wide range of manifestations of CVD.^{1,61,62} A meta-analysis of 145 randomized trials that included more than 100 000 patients (70 000 "high-risk" patients with vascular disease or another condition associated with occlusive vascular disease risk compared with 30 000 "low-risk" patients) found that long-term aspirin therapy significantly reduced overall vascular mortality as well as nonfatal stroke and MI. Among high-risk patients, aspirin therapy reduced the risk of nonfatal MI by one third, nonfatal stroke by one third, and death from all vascular causes by one sixth. These benefits were observed in patients of all ages and were unrelated to the presence of diabetes and hypertension.¹⁰ Despite compelling evidence that treatment with antiplatelet therapy attenuates risk, results from the PARTNERS study depicted the rate of antiplatelet therapy undertreatment in patients with PAD: within the total study population, fewer than half of participants received antiplatelet therapy.³

The adenosine diphosphate receptor antagonist clopidogrel also provides protection from the cardiovascular and cerebrovascular events associated with PAD. Clinical trial data show that clopidogrel is significantly more effective than aspirin therapy in preventing atherothrombotic vascular events.¹¹ In the Clopidogrel vs Aspirin in Patients at Risk

of Ischemic Events (CAPRIE) study, clopidogrel, 75 mg/d, provided a relative risk reduction in the composite end point of ischemic stroke, MI, or vascular death by 8.7% ($P = .04$) over aspirin, 325 mg/d, in patients with recent MI, recent stroke, or established PAD and by 23.8% in those enrolled based on PAD as the qualifying condition.¹¹ Based on a meta-analysis of data from the Antiplatelet Trialists' Collaboration¹⁰ and CAPRIE, in a population similar to that studied in CAPRIE, clopidogrel therapy can be expected to prevent 24 atherothrombotic events per 1000 patients per year, whereas aspirin therapy can be expected to prevent 19 atherothrombotic events per 1000 patients per year, a relative risk reduction of 26%. The potential role of other antithrombotic agents has not been prospectively evaluated in PAD populations.

The dosage of any agent used in the management of PAD should be determined by a patient's global atherothrombotic risk assessment. Clinical trial data have not yet clearly defined the optimal aspirin dosage for either primary or secondary prevention of atherothrombotic events. The Antiplatelet Trialists' Collaboration meta-analysis¹⁰ suggests that a dose response exists for safety; however, there is no evidence to support that a similar effect exists for efficacy. Thus, the current recommendation of the Antiplatelet Trialists' Collaboration is to use low-dose aspirin (75-150 mg/d).

A number of novel agents to treat the symptoms associated with PAD are in various stages of development. As our call to action is focused on increasing PAD awareness and detection, as well as mitigating the atherothrombotic risks associated with this disease, a discussion of symptomatic relief is beyond its scope. At least 1 novel class of agents, the factor Xa inhibitors, is being evaluated to determine effects on atherothrombotic risk reduction in PAD, and consequently deserves special mention. Inhibition of factor Xa, a serine protease directly responsible for thrombin generation, is an attractive antithrombotic approach. A number of oral and parenteral factor Xa inhibitors are in various stages of development for the treatment of

atherothrombotic disease. These agents may represent a new treatment approach, though additional information is required.

Role of Exercise Rehabilitation in the Treatment of PAD

Exercise rehabilitation has also been used as an alternative to pharmacologic therapies in the treatment of PAD and may serve as a primary symptom-relieving intervention. This treatment consists of an extended exercise-training program that relies on treadmill or track-based training performed 3 times per week for a minimum of 12 weeks. Programs with these characteristics have proven effective at increasing pain-free and maximal treadmill walking distance among patients who had experienced exercise-limiting claudication due to PAD. In a recent meta-analysis of randomized trials, it was found that exercise training increased maximal treadmill walking distance by 179 m. There are, however, limitations to exercise rehabilitation treatment. The best results require a motivated patient in a supervised setting. These supervised sessions are not typically covered by medical insurance. Despite the documented efficacy of structured exercise programs for claudication, few have historically been available because of limited reimbursement by health care payers.⁶³ The recent publication in the United States of an American Medical Association Current Procedural Terminology Code (93668) for PAD rehabilitation is expected to accelerate the availability of such programs in the future.⁶⁴

CALL TO ACTION

The presence of PAD significantly increases the risk for atherothrombotic ischemic events such as MI and stroke. This call to action by the Prevention of Atherothrombotic Disease Network was initiated to consolidate the current international data that documents that the presence of PAD is clear evidence of disseminated atherothrombotic disease and that the diagnosis and treatment of PAD are critical for patient survival. Despite the well-

documented clinical impact of PAD, a vast unmet need exists with respect to diagnosis and treatment. To that end, the Network recommends focusing on 5 action items, which are summarized below.

Item 1: Increase Awareness of PAD and Its Consequences

An educational initiative is necessary to inform both clinicians and patients regarding the ischemic burden associated with PAD. The clinical "definition" of PAD (ie, the presence of an ABI value <0.9, with or without classic leg symptoms) needs to be clearly disseminated. Peripheral arterial disease is not just a disease of the legs, but rather evidence of disseminated arterial disease that is highly predictive of cardiovascular and cerebrovascular morbidity and mortality. The emergence of new data underscoring the deleterious nature of PAD has led to the recent formation of vascular disease foundations and networks to promote educational programs that focus on improving disease awareness.

Item 2: Improve the Identification of Patients With Symptomatic PAD

A public awareness campaign to improve the rate of diagnosis of patients with PAD will be most efficient if initially directed at the identification of patients with symptomatic disease. Approximately one third of symptomatic patients do not report symptoms to their medical care providers, and, therefore, do not receive treatment (J.J.F.B., oral presentation, 2001). Patient and physician education is needed to address this problem.

Item 3: Initiate a Screening Protocol for Patients at High Risk for PAD

Identifying the high-risk PAD population with a clinically effective and cost-effective screening protocol will greatly contribute to the rate of disease detection. The existence of 1 or more traditional PAD risk factors (eg, diabetes, hypertension, and smoking) is a strong indication of possible arterial disease, warrant-

ing more comprehensive assessment, including performing an ABI assessment.

Item 4: Improve Treatment Rates Among Patients Who Have Been Diagnosed With Symptomatic PAD

While it is presumed that all patients with PAD merit intensive risk reduction interventions, a stepwise approach to such a large international population provides the greatest efficacy. Patients with leg symptoms are more likely to be identified and will benefit from greater risk reduction than those with asymptomatic disease. Despite the known protective benefits, a significant percentage (approximately 30%-40%) of patients with diagnosed, symptomatic PAD do not receive antiplatelet agents^{3,10} (J.J.F.B., oral presentation, 2001). It is essential to increase physician awareness, through a variety of pathways, of the risk reduction associated with antiplatelet agent therapy and global risk reduction therapies in patients with symptomatic PAD.

Item 5: Increase the Rates of Early Detection Among the Asymptomatic Population

The Prevention of Atherothrombotic Disease Network calls for an increase in detection rates among the asymptomatic population, which comprises most patients with PAD. Several clinical trials have found that the ischemic risk associated with asymptomatic PAD is comparable with that of symptomatic PAD.^{17,24-26} Owing to the limited amount of clinical evidence associated with pharmacologic therapy of asymptomatic PAD, the Network recommends waiting for further evidence before unequivocally recommending pharmacotherapy in this population. The Network recommends treating risk factors commonly associated with PAD, such as hyperlipidemia and hypertension.

SUMMARY

Peripheral arterial disease is a powerful indicator of systemic atherothrombotic disease and a critical

public health issue affecting an estimated 27 million people.¹ It is imperative to increase the awareness of PAD as a distinct atherothrombotic syndrome that predicts stroke, MI, and death, and to publicize the protective benefits of early diagnosis and treatment.

A diagnosis of PAD mandates aggressive risk factor management and pharmacologic therapy, including antiplatelet agents. Risk factor management is similar to that for other cardiovascular or cerebrovascular conditions, such as CHD, and includes addressing lifestyle factors, such as smoking cessation, treating associated conditions (eg, diabetes and hypertension), lowering lipids to an acceptable level, and preventing ischemic events with aggressive antiplatelet therapy.^{10,11,41-44}

Although the Prevention of Atherothrombotic Disease Network recommends improving diagnosis of PAD in the asymptomatic population, it advocates waiting for further evidence before unequivocally recommending treatment owing to limited clinical evidence in this population. The results of 2 upcoming trials will help elucidate the potential benefits of antiplatelet agents in the asymptomatic population. The POPADAD study, which has completed its initial recruitment and thus providing data on PAD diagnostic rates, includes patients with diabetes who have no clinical manifestation of vascular disease. The AAA trial includes high-risk patients with asymptomatic disease. The POPADAD study and AAA trial have enrolled patients based on the singular criterion of decreased ABI; results are expected in 3½ years and 4 years, respectively.³ In the interim, the Network recommends focusing on improving the treatment of patients with diagnosed, symptomatic PAD, since they have the highest clinical risk for ischemic events.

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REFERENCES

- Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation*. 1996;94:3026-3049.
- Hirsch AT, Halverson SL, Treat-Jacobson D, et al. The Minnesota Regional Peripheral Arterial Disease Screening Program: toward a definition of community standards of care. *Vasc Med*. 2001; 6:87-96.
- Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317-1324.
- Elhadd TA, Robb R, Jung RT, Stonebridge PA, Belch JFF. Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. *Practical Diabetes Int*. 1999;16:163-166.
- Newman AB, Shemanski L, Manolio TA, et al, for the Cardiovascular Health Study Collaborative Research Group. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. 1999;19:538-545.
- Papamichael CM, Lekakis JP, Stamatelopoulou KS, et al. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. *Am J Cardiol*. 2000;86:615-618.
- Sikkink CJ, van Asten WN, van't Hof MA, van Langen H, van der Vliet JA. Decreased ankle/brachial indices in relation to morbidity and mortality in patients with peripheral arterial disease. *Vasc Med*. 1997;2:169-173.
- 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.
- West JA. Cost-effective strategies for the management of vascular disease. *Vasc Med*. 1997;2: 25-29.
- Antiplatelet Trialists' Collaboration. 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.
- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
- Zusman RM, Chesebrough JH, Comerota A, et al. Antiplatelet therapy in the prevention of ischemic vascular events: literature review and evidence-based guidelines for drug selection. *Clin Cardiol*. 1999;22:559-573.
- Priollet P. Quality of life and peripheral arterial disease: perspectives for the future. *Drugs*. 1998;56 (suppl 3):49-58.
- Regensteiner JG, Treat-Jacobson D, Walsh ME, et al. PARTNERS: the impact of peripheral arterial disease (PAD) on health-related quality of life (HQL) [abstract]. *Circulation*. 2000;102(suppl 2): II-400.
- Treat-Jacobson DT, Halverson SL, Ratchford A, Regensteiner JG, Lindquist R, Hirsch AT. A patient-derived perspective of health-related quality of life with peripheral arterial disease. *J Nurs Schol*. 2002;34:55-60.
- 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.
- Hooi JD, Stoffers HE, Kester AD, et al. Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease: the Limburg Peripheral Arterial Occlusive Disease (PAOD) Study. *Scand J Prim Health Care*. 1998;16:177-182.
- Criqui MH, Denenberg JO. The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease. *Vasc Med*. 1998;3:241-245.
- McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the Women's Health and Aging Study. *Circulation*. 2000;101:1007-1012.
- Simons PC, Algra A, Eikelboom BC, Grobbee DE, van der Graaf Y, for the SMART Study Group. Carotid artery stenosis in patients with peripheral arterial disease: the SMART study. *J Vasc Surg*. 1999;30:519-525.
- House AK, Bell R, House J, Mastaglia F, Kumar A, D'Antuono M. Asymptomatic carotid artery stenosis associated with peripheral vascular disease: a prospective study. *Cardiovasc Surg*. 1999; 7:44-49.
- Dormandy JA. Epidemiology and natural history of arterial diseases of the lower limbs. *Rev Prat*. 1995;45:32-36.
- 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.
- Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group. Management of peripheral arterial disease (PAD). *J Vasc Surg*. 2000;31:S1-S296.
- Dormandy JA, Rutherford RB, for the TransAtlantic Inter-Society Consensus (TASC) Working Group. Management of peripheral arterial disease (PAD). *Int Angiol*. 2000;19(suppl 1):1-310.
- 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.
- American Cancer Society. Cancer Facts & Figures 2000. Available at: http://www.cancer.org/docroot/stt/content/stt_1x_2000_facts_and_figures.asp. Accessed 2000.
- Kempczinski RF, Bernhard VM. Introduction and general considerations [section VIII, management of chronic lower limb ischaemia]. In: Rutherford RB, ed. *Vascular Surgery*. 3rd ed. Philadelphia, Pa: WB Saunders; 1989:643-652.
- Murabito JM, D'Agostino RB, Silbershatz H, Wilson PWF. Intermittent claudication: a risk profile from the Framingham Heart Study. *Circulation*. 1997;96:44-49.

30. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985;71:510-515.
31. Hoogeveen EK, Kostense PJ, Beks PJ, et al. Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non-insulin-dependent diabetes mellitus: a population-based study. *Arterioscler Thromb Vasc Biol*. 1998;18:133-138.
32. Cupples LA, Gagnon DR, Wong ND, Ostfeld AM, Kannel WB. Preexisting cardiovascular conditions and long-term prognosis after initial myocardial infarction: the Framingham Study. *Am Heart J*. 1993;125:863-872.
33. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation*. 1985;71:516-521.
34. Leng GC, Fowkes FGR. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol*. 1992;45:1101-1109.
35. Dormandy J, Heeck L, Vig S. Intermittent claudication: a condition with underrated risks. *Semin Vasc Surg*. 1999;12:96-108.
36. Fowkes FGR, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol*. 1991;20:384-392.
37. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med*. 2000;132:810-819.
38. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med*. 1996;334:155-159.
39. Ferrini R, Mannino E, Ramsdell E, Hill L. Screening mammography for breast cancer: American College of Preventive Medicine practice policy statement. *Am J Prev Med*. 1996;12:340-341.
40. Society for Vascular Medicine and Biology (SVMB) and Society for Vascular Nursing (SVM). *Peripheral Arterial Disease: Marker of Cardiovascular Risk*. Manchester, Mass: SVMB/SVM; 1999.
41. Ramsay LE, Williams B, Johnston GD, et al, for the British Hypertension Society. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *J Hum Hypertens*. 1999;13:569-592.
42. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, and British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *BMJ*. 2000;320:705-708.
43. Tierney S, Fennessy F, Hayes DB. ABC of arterial and vascular disease: secondary prevention of peripheral vascular disease. *BMJ*. 2000;320:1262-1265.
44. Lakier JB. Smoking and cardiovascular disease. *Am J Med*. 1992;93(suppl 1A):8S-12S.
45. American Lung Association. *Trends in Tobacco Use*. New York, NY: American Lung Association, Epidemiology and Statistics Unit; 2001.
46. Gotto AM Jr. Statin therapy: where are we? where do we go next? *Am J Cardiol*. 2001;87(suppl):13B-18B.
47. Aronow WS. Treatment of older persons with hypercholesterolemia with and without cardiovascular disease. *J Gerontol A Biol Sci Med Sci*. 2001;56A:M138-M145.
48. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1308.
49. SIGN (Scottish Intercollegiate Guidelines Network). *Lipids and the Primary Prevention of Coronary Heart Disease: A National Clinical Guideline*. Edinburgh, Scotland: SIGN; 1999. Publication 40.
50. Cruickshank JM. The case for beta-blockers as first-line antihypertensive therapy. *J Hypertens Suppl*. 1992;10:S21-S27.
51. Systolic Hypertension in the Elderly Program Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255-3264.
52. Staessen JA, Fagard R, Thijs L, et al, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997;350:757-764.
53. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-153.
54. United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.
55. United Kingdom Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ*. 1998;317:713-720.
56. Beebe HG. Intermittent claudication: effective medical management of a common circulatory problem. *Am J Cardiol*. 2001;87:14D-18D.
57. Tjon JA, Riemann LE. Treatment of intermittent claudication with pentoxifylline and cilostazol. *Am J Health Syst Pharm*. 2001;58:485-496.
58. Santilli JD, Santilli SM. Chronic critical limb ischemia: diagnosis, treatment and prognosis. *Am Fam Physician*. 1999;59:1899-1908.
59. SIGN (Scottish Intercollegiate Guidelines Network). *Antithrombotic Therapy: A National Clinical Guideline*. Edinburgh, Scotland: SIGN; 1999. Publication 36.
60. Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. *Chest*. 2001;119(suppl):283S-299S.
61. Albers GW, Hart RG, Lutsep HL, Newell DW, Sacco RL. Supplement to the guidelines for the management of transient ischemic attacks: a statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. *Stroke*. 1999;30:2502-2511.
62. SIGN (Scottish Intercollegiate Guidelines Network). *Drug Therapy for Peripheral Vascular Disease: A National Clinical Guideline*. Edinburgh, Scotland: SIGN; 1998. Publication 27.
63. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA*. 1995;274:975-980.
64. *Current Procedural Terminology (CPT)*. Chicago, Ill: American Medical Association; 2001.