PREFACE

With an aging population owing to our longer life span, peripheral arterial disease will become more common than its already high prevalence. It has usually been assigned a less important role in the education of the lay public and physicians, in contrast to coronary artery and cerebrovascular disease. The importance of peripheral arterial disease, symptomatic and asymptomatic, to the practicing physician and cardiologist is that it predicts disease in other vascular beds—serving as a prognostic factor for myocardial infarction, stroke, and mortality. Furthermore, there is impaired functional capacity and severe disability, particularly in those with critical limb ischemia.

The diagnosis of peripheral arterial disease is often obvious from the history and physical examination, but with the development of noninvasive techniques, especially the Doppler flowmeter, the diagnosis can easily be documented in both symptomatic and asymptomatic patients by all physicians. There are exciting new therapeutic modalities including gene therapy, endovascular interventions, and new pharmaceutical agents.

In *Peripheral Arterial Disease: Diagnosis and Treatment,* we acquaint physicians with all aspects of peripheral arterial disease. Because of the limitations of medical therapy, there is now a special emphasis on prevention of peripheral arterial disease and a special emphasis on risk factors and their treatment. Risks factors are considered from the point of view of the pathophysiologist (Chapter 1), epidemiologist (Chapter 2), and vascular specialist (Chapter 9). The pathogenesis of arteriosclerosis is presented first, followed by a comprehensive treatise on the epidemiology and natural history of the disease. The chapter on the clinical evaluation of intermittent claudication contains the very important differential diagnosis section. A combined chapter on hemodynamics and vascular laboratory testing gives the reader insight into the physiological and pathophysiological basis of the available diagnostic tests. The role of angiography, including newer noninvasive modalities, is discussed.

Regarding treatment, a chapter on risk factors and antiplatelet therapy is especially timely, with a focus on the prevention of myocardial infarctions, strokes, and mortality in peripheral arterial disease patients. Exercise rehabilitation is covered in depth, for it is one of the most effective treatments for peripheral arterial disease. Pharmacotherapy, including new agents for intermittent claudication, and endovascular interventions are the subjects of separate chapters. The intriguing, emerging field of angiogenesis is introduced with appropriate caution. There is a detailed discussion of the time-honored surgical approach to revascularization. For the consultant, a chapter follows on the preoperative evaluation and perioperative management of the vascular disease patient.

There are separate chapters discussing such special problems as peripheral arterial disease in women, management of the diabetic foot, and large vessel vasculitis. Although the concentration is on arteriosclerosis obliterans, two less common causes of peripheral artery disease, arterial embolus and thromboangiitis obliterans, are worthy of separate chapters. Finally a common problem that is often encountered by clinicians involved with catheter-based interventions, atheroembolism, is discussed.

By providing a comprehensive overview and detailed accounting of all aspects of peripheral arterial obstructive disease, we hope to empower the clinician with the skills and knowledge to diagnose and treat this important and often overlooked disorder.

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2 The Epidemiology and Natural History of Peripheral Arterial Disease

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CONTENTS

INTRODUCTION

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis, and is defined by progressive stenosis or occlusion within the arteries of the lower extremities. Although PAD is the currently accepted international term for this clinical syndrome *(1)*, historically, other names have been used interchangeably, including peripheral arterial occlusive disease (PAOD), arteriosclerosis obliterans (ASO), lower extremity occlusive disease (LEAD), and peripheral vascular disease (PVD). Widely prevalent, it has been estimated that more than 8.4 million people are afflicted with this disease in the United States *(2,3)*. As with other clinical atherosclerotic syndromes, the etiology of PAD is due to both modifiable (diabetes, smoking, hypertension, and hypercholesterolemia) and nonmodifiable (e.g., age, gender, family history) risk factors.

The decreased blood flow to the legs caused by PAD may be mild or severe, resulting in a broad range of symptoms. Patients may not suffer recognizable limb symptoms, or they may experience intermittent claudication (IC), or manifest symptoms of severe limb ischemia. IC, the most common symptom of PAD, is defined as fatigue, cramping,

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or frank pain of the gluteal, thigh, or calf muscles that is consistently provoked by exercise and that is reproducibly relieved by rest. Patients with IC are often limited in their daily activities owing to this walking impairment and in turn experience a diminished quality of life. With continued exposure to atherosclerotic risk factors, PAD may progress to critical limb ischemia (CLI), which portends a severe diminution in quality of life, and is associated with a high rate of amputation and a marked increase in short-term mortality. Thus, PAD is a common manifestation of atherosclerosis that is associated with a range of symptoms, a variable impact on quality of life, and a heightened risk of cardiovascular ischemic events.

Whereas the clinical diagnosis of PAD is dependent on the vascular history, the physical examination, and selective use of noninvasive vascular laboratory and invasive angiographic criteria, the epidemiologic definition of PAD is based on measurement of the ankle–brachial index (ABI). The ABI serves as a simple and accurate noninvasive tool to objectively assess lower extremity blood flow, and any ABI value < 0.90 defines the presence of PAD. This dependence on the ABI is based on data demonstrating that an abnormal pulse examination alone underestimates the true prevalence of PAD, and may specifically underestimate small-vessel PAD *(4)*. These data from Criqui and colleagues demonstrated that the sensitivity and specificity of an abnormal pulse detecting PAD were 77% and 86%, respectively, while the positive and negative predictive values (PPV) were 40% and 97%, respectively. Other surveys have suggested that the sensitivity of an absent pulse to predict the presence of PAD may be only 5% and the positive predictive value as low as 20% *(5)*. In contrast, the ABI has high sensitivity and specificity for angiographically defined PAD *(6,7)*. It should be noted that an abnormal ABI is not only diagnostic of PAD, but is also a predictor of cardiovascular morbidity and mortality *(8)*.

CLASSICAL ATHEROSCLEROTIC RISK FACTORS AND THE DEVELOPMENT OF PAD

Specific risk factors have been associated with the development of peripheral arterial, coronary artery, and cerebrovascular disease. These traditional risk factors include smoking, diabetes, family history, hypertension, and hyperlipidemia *(9,10)*. The relative risk (RR) of developing PAD is most closely associated with diabetes (RR 4.05), current smoking (RR 2.55), increasing age (in 5-yr increments, RR 1.54), hypertension (RR 1.51), hyperhomocystinemia (RR 1.44), and elevated total cholesterol (RR 1.10 per 10 mg/dL increment) (Fig. 1). Compared to the impact of these risk factors on coronary artery disease (CAD) prevalence rates, smoking and diabetes are particularly prominent factors in the development of PAD.

Tobacco Smoking

Smoking is one of the primary risk factors for developing PAD, especially in young individuals. Smoking causes damage to the vascular endothelium, promotes coagulation, and accelerates the progression of atherosclerosis *(11)*. In the Cardiovascular Health Study, the relative risk of developing PAD was 2.5 for current smokers *(12)*. Another study found that the relative risk of developing PAD was increased as much as sevenfold in ex-smokers and as much as 16-fold in current smokers, as compared to those who had never smoked *(13)*. Just as PAD prevalence is known to be directly related

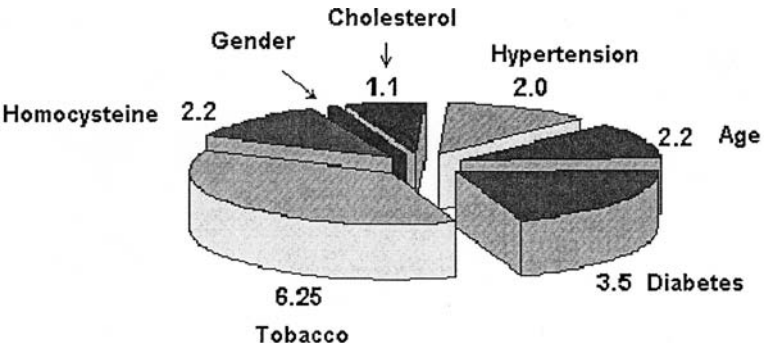

Fig. 1. The relative risk of developing PAD associated with each atherosclerosis risk factor. Tobacco use and diabetes confer the highest relative risk for PAD. PAD is a "gender neutral" atherosclerotic syndrome, although the onset of PAD is delayed in women until after menopause. (Modified from Newman AB, Siscovick DS, Manolio TA, et al. Ankle–arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. Circulation. 1993; 88:837–845.)

to population-based smoking rates, so too has the prevalence of PAD been shown to decrease with a decline in current smoking rates. The landmark Reykjavik Study *(14)* prospectively observed Icelandic males for 18 yr and identified smoking and serum cholesterol level as the only significant risk factors, other than age, that predicted the incidence of IC in this defined population. Smoking was shown to increase the risk of IC eight- to tenfold. More importantly, the prevalence and incidence of IC in the male Icelandic population fell sharply after 1970, as lifestyle-derived exposure to atherosclerotic risk factors improved in the population at risk. The relationship between tobacco use and claudication prevalence was also noted in the Framingham Study. In this American cohort of 5209 individuals, aged 30–62 yr at enrollment and followed for 34 yr, there was a direct correlation between the amount of cigarette smoking in the population and the incidence of IC. A similar relationship was noted between tobacco use and the incidence of stroke and transient ischemic attacks and the population-based burden of total cardiovascular disease *(15)*.

Smoking not only has been shown to cause a more rapid development of PAD with long-term use, but is also associated with the development of "premature atherosclerosis" and a particular syndrome of PAD in young women who are heavy smokers. These young women may develop an atherosclerotic "hypoplastic aortoiliac syndrome" in their third and fourth decades of life, causing both claudication and/or CLI *(16)*. The morbidity associated with this syndrome can be significant, because a high fraction may progress to severe limb ischemia that may require aorto-bifemoral bypass surgery *(16)*. The impact of continued tobacco use on PAD progression has also been demonstrated by the work of Jonason and colleagues, who demonstrated that patients with PAD who continue to smoke face a markedly increased risk of developing CLI, with as many as 18% of a PAD population developing CLI with continued tobacco use *(17)*. Furthermore, the mortality rate within a 5-yr period is approx 40–50% due to myocardial infarction (MI) or stroke *(18,19)*. Patients with PAD who undergo limb bypass who continue to smoke suffer lower patency rates and higher amputation rates than those who quit *(20,21)*.

Diabetes Mellitus

Another common risk factor, diabetes mellitus, promotes acceleration of the atherosclerotic process, resulting in a higher incidence of peripheral, coronary, and cerebrovascular disease. The exact pathophysiologic relationship of diabetes to development of PAD is unclear, as there are both direct effects of hyperglycemia as well as an increased frequency of hypertension and hyperlipidemia in patients with diabetes. Patients with the metabolic syndrome (defined by insulin resistance, increased triglycerides, decreased high-density lipoprotein [HDL], and small dense low-density lipoprotein [LDL] particles) seem to have an especially elevated risk for developing PAD *(9)*. In the Cardiovascular Health Study, the relative risk for developing PAD was increased more than fourfold for those with diabetes *(12)*. The high prevalence of PAD in individuals with diabetes has been demonstrated in the Hoorn Study, in which almost 21% of those elderly individuals with diabetes had an ABI < 0.9, and in which almost 42% had either an abnormal ABI, diminished ankle pulse, or history of prior limb bypass surgery *(22)*.

Diabetes serves as a powerful risk factor for development of atherosclerosis of the large- and medium-sized muscular conduit arteries that supply the lower extremity and it is this effect that leads to the greatest burden of PAD in diabetic patients. However, diabetes is also associated with multisegmental and more distal arterial stenoses, and may damage the microvascular circulation, which makes revascularization difficult. The diffuse anatomic arterial disease, magnitude of small vessel disease, associated neuropathy, propensity for infection, and impaired wound healing common in diabetics may together contribute to the higher incidence of amputation among them *(23)*. Whether this particularly adverse PAD natural history can be altered by aggressive glycemic control has not yet been demonstrated in prospective clinical trials *(24,25)*.

Hyperlipidemia

Hyperlipidemia alters the endothelial cells of the arterial wall, which leads to the formation of atherosclerotic lesions. Endothelial cells play a key role in preventing this process. They produce nitric oxide, which inhibits monocytes, leukocytes, and platelet adhesion to the arterial lining; decrease LDL permeability; and prevent smooth muscle cell proliferation *(26)*. LDL cholesterol is one of the major causes of endothelial dysfunction and smooth muscle injury. It is this initial alteration to the endothelium that allows lipoprotein to enter the arterial wall, become oxidized, and promote the development of the fatty streak, which is the earliest lesion in atherosclerosis. This in turn leads to a more complex lesion causing arterial stenosis or occlusion *(27)*. Elevated levels of LDL cholesterol pose an increased risk of developing cardiovascular disease and PAD *(28)*. In the Framingham Heart Study, individuals with total cholesterol levels > 270 mg/dL had twice the incidence of developing IC *(29)*. In addition, people with IC had a higher mean cholesterol level *(10)*.

Hypertension

Twenty-four percent of the U.S. population has hypertension, and thus the impact of this common vascular risk factor on PAD prevalence rates is high *(30)*. Hypertension causes complex alterations in the structure of the arterial wall. Endothelial function is impaired, collagen may replace elastin in arterial walls, and there is medial hypertrophy (31). All these factors contribute to decreasing vascular compliance *(31)*. Hypertension

leads to more aggressive atherosclerosis in all circulations, and is a recognized risk factor for cerebrovascular and coronary disease. Hypertension is now also recognized as a major risk factor for developing PAD *(32)*.

One clinical investigation that evaluated the association between hypertension, cardiovascular event rates, and PAD, the Systolic Hypertension in the Elderly Program (SHEP), demonstrated a 27% reduction in coronary ischemic events in patients actively treated for their systolic hypertension *(33)*. A subgroup of the SHEP cohort with peripheral atherosclerotic disease was shown to experience significantly fewer cardiovascular ischemic events and less mortality when systolic hypertension was actively treated vs placebo (the relative risk of a cardiac event in the placebo group vs active treatment was 2.2) *(33)*. This supports the need for aggressive hypertensive management in patients with PAD to decrease rates of mortality and ischemic events. Although the treatment of hypertension would be expected to impact beneficially the prognosis of PAD symptoms or limb outcomes, there have been no investigations to address this hypothesis.

Newer Risk Factors for the Development of PAD

There is increasing interest in the association between the development of PAD and selected newer risk factors, such as hyperhomocystinemia *(34,35)*. Recent studies have also shown that markers of vascular inflammation, such as an elevated C-reactive protein (CRP) value, may predict the future risk of developing PAD *(36)*.

Hyperhomocystinemia

Elevated homocysteine has been shown to be an independent risk factor associated with development of premature atherosclerosis or atherothrombosis *(37)*. A genetic mutation of the enzyme involved with homocysteine metabolism or a deficiency of essential B vitamins leads to elevated homocysteine levels. Homocysteine is a highly reactive amino acid that is known to cause endothelial cell dysfunction and injury resulting in platelet activation, thrombosis, and increased vascular smooth muscle proliferation leading to more aggressive atherogenesis *(38)*.

Inflammation and Infection

The formation and progression of atherosclerosis are presumed to be due to the complex interplay of classical risk factors, in association with an intravascular inflammatory process *(39)*. A fatty streak, which is the earliest lesion of atherosclerosis, is a pure inflammatory lesion consisting of monocyte-derived macrophages and T lymphocytes *(40)*. One marker that may prove useful to detect this inflammatory process is the CRP. In the Physicians' Health Study and the Women's Health Study, individuals with the highest CRP levels at baseline showed a two- to sevenfold higher risk of stroke, three- to sevenfold higher risk of MI, and four- to fivefold higher risk of severe PAD or vascular events compared to the control group *(41,42)* (Fig. 2). In addition, the Monitoring Trends and Determinants in Cardiovascular Disease Augsburg Cohort (MONICA) also showed that CRP is a predictor of cardiovascular disease *(43)*.

The possibility that chronic infection and inflammation due to atypical organisms may contribute to the pathogenesis of atherosclerosis in coronary, cerebral, and peripheral vessels has recently been a subject of investigation. The infectious microorganisms that have been linked to atherosclerotic plaque formation include cytomegalovirus (CMV), the herpes viruses, *Chlamydia pneumoniae*, and *Helicobacter pylori (44)*.

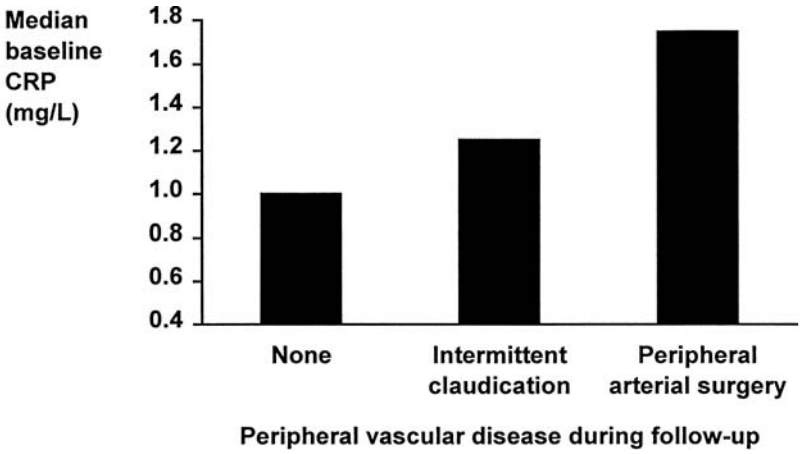

Fig. 2. C-reactive protein (CRP) is an inflammatory marker of atherosclerosis and is elevated in patients with PAD. High-sensitivity CRP levels are elevated in individuals with claudication, and are highest in those patients with PAD who required vascular surgical intervention, as compared to individuals with no PAD. (Modified from: Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens, CH. Plasma concentration of C-reative protein and risk of developing peripheral arterial disease. Circulation 1998;97: 425-428.)

These microorganisms have been found in high serum concentrations and/or within the arterial wall plaque of individuals with atherosclerosis. It has been hypothesized that such infectious agents could enter vascular endothelial cells and promote plaque formation or rupture. In addition, the leukocytes, macrophages, and lymphocytes within the evolving atheroma may also be infected by these organisms, and this may further promote lesion progression. Although this infection-mediated hypothesis is under active investigation as a cause of coronary artery disease, it is not yet known whether these putative infectious causes of atherosclerosis are important risk factors for PAD.

THE HIGH PREVALENCE OF PAD

PAD is a common syndrome that affects a large proportion of most adult populations worldwide. Claudication is the symptomatic expression of PAD and therefore defines a subset of the total population with PAD. The landmark Framingham Heart Study initially described the high prevalence of PAD. This large cohort study has followed 2336 men and 2873 women between the ages of 28 and 62 at standardized examinations every 2 yr since 1948 *(29)*. The Rose claudication questionnaire was utilized to define the prevalence of IC as a marker of PAD. This study demonstrated that the annual incidence of PAD increased with age and in relation to the previously described risk factors *(29)*. The age-specific annual incidence of IC for ages 30–44 was 6 per 10,000 men and 3 per 10,000 women, and this incidence increased to 61 per 10,000 men and 54 per 10,000 women within the ages of 65–74. In this initial Framingham cohort, the investigators noted that IC was twice as prevalent among men as compared to women *(45)*. A risk profile of age, sex, serum cholesterol, hypertension, cigarette smoking, diabetes, and CAD were all associated with an increased risk of developing claudication. Male sex,

increasing age, and smoking conferred a 1.5-fold increased risk for developing IC. Diabetes and stage 2 (or greater) hypertension were associated with a more than twofold increase in IC, while clinical evidence of CAD almost tripled the risk *(10)*.

In another population study, Criqui and colleagues evaluated the prevalence of PAD among an older defined population of 613 men and women in Southern California, utilizing a battery of four noninvasive tests—the Rose questionnaire, the pulse examination, the ABI, and the pulse wave velocity (PWV)—to assess the prevalence of PAD *(46)*. Use of the Rose questionnaire severely underestimated the prevalence of PAD demonstrating the insensitivity of this tool to assess true population rates for PAD. Basing the diagnosis solely on history and physical examination also showed low sensitivity for detecting PAD *(9)*. PAD detection increased two to seven times over the detection rate of the Rose questionnaire when the ABI and pulse wave velocity techniques were applied. On the other hand, an abnormal limb pulse examination overestimated the prevalence by twofold. Using the objective noninvasive ABI and PWV techniques, the prevalence of PAD in this population was 2.5% among individuals $<$ 60 yr of age, 8.3% among those between 60 and 69 yr, and 18.8% among those older than 70 yr *(9)* (Fig. 3).

The San Luis Valley Diabetes Study evaluated the prevalence of PAD among diabetics in a Hispanic and a white population *(5)*. The diagnostic tool used in this study was an ABI of 0.94 at rest, 0.73 post-exercise, and 0.78 after reactive hyperemia. The prevalence of PAD was 13.7% using this diagnostic criteria. Notably, a history of IC or an absent pulse exam were uncommon findings within this population (5).

The Edinburgh Artery Study in 1988 randomly selected 1592 individuals ages 55–74 with IC determined by the World Health Organization questionnaire, the ABI, and the hyperemia test. These participants were followed prospectively for 5 yr for subsequent cardiovascular events and death *(47)*. The prevalence of IC was 4.5% and the incidence was 15.5 per 1000 person-years *(47,48)*. In individuals who were symptomatic initially, 28.8% continued to have pain after 5 yr, 8.2% underwent revascularization or amputation, and 1.4% developed ischemic ulcers *(47)*. Of those individuals who were asymptomatic, 8.0% had advanced PAD with significant blood flow impairment *(48)*.

The relevance of these epidemiologic data to current medical practice has been assessed most recently in the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) program *(49)*. This was a large prospective survey designed to determine the prevalence of PAD in American primary care practices by applying the ABI to a targeted cohort of 6979 patients evaluated in 350 large volume primary care practices in 25 American cities. In this study, patients older than 70 yr of age or between 50 and 69 yr old with a history of cigarette smoking or diabetes were evaluated prospectively during the course of routine office practice. The diagnosis of PAD was established by either a prior chart diagnosis or by demonstration of an ABI of $\leq$ 0.90 during the study screening. Using this technique, PAD was detected in a high fraction (29%) of the study population. Within this population, 13% of these patients had PAD only, and 16% had both PAD and another form of atherosclerotic cardiovascular disease (a clinical manifestation of CAD, cerebrovascular disease, or aortic aneurysmal disease). Although PAD was obviously prevalent in this targeted population, the diagnosis was new in 55% of those patients with “PAD only” and in 35% of patients who had both PAD and CVD. As anticipated, the prevalence of tobacco use (23% current, 37%

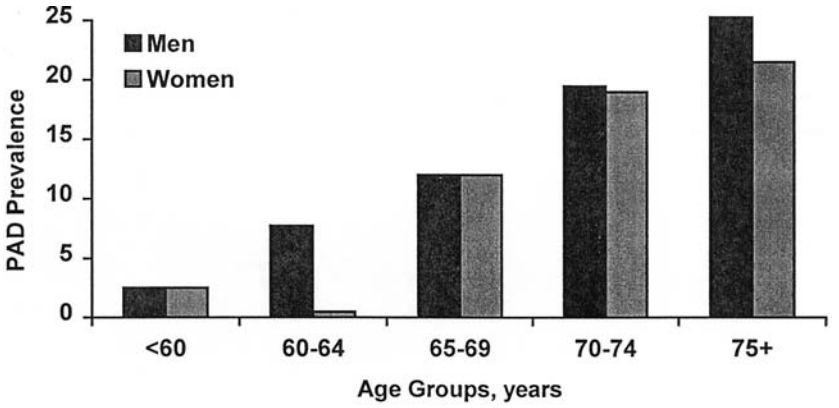

Fig. 3. The increased prevalence of PAD in men and women with advancing age. (Modified from: Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985;71:510-515.)

former), hypertension (69%), hyperlipidemia (47%), and diabetes (38%) was elevated in the PAD-only cohort.

Thus, current epidemiologic and community survey data demonstrate a high prevalence of PAD in individuals in the United States and Europe that increases with advancing age and with increasing exposure to atherosclerosis risk factors.

RELATIONSHIP OF PAD TO OTHER ATHEROSCLEROTIC SYNDROMES

Atherosclerosis is a systemic disease that may affect multiple arteries throughout the body. The diagnosis of PAD should be considered a marker for increased risk of coexistent atherosclerosis involving other vascular territories regardless of whether the patient is asymptomatic or suffers claudication symptoms. It has been shown that individuals diagnosed with PAD have a higher coprevalence of CAD and cerebrovascular disease *(29,32,49)*. Patients found to have lower extremity arterial occlusive disease should undergo a focused physical examination to ascertain if there is coexistent coronary or carotid disease, or an aortic aneurysm.

In a large study by Hertzer and colleagues, severe CAD was found angiographically in 36% of patients with an abdominal aortic aneurysm and in 28% of patients with lower extremity occlusive disease *(50)*. In a separate report, carotid bruits were noted in 11% of patients with abdominal aortic aneurysm and 25% of patients with PAD, while a significant number of patients (44%) proved to have high-grade ($>$ 75%) carotid stenoses or occlusions *(51)*.

In a study of coprevalence of atherosclerotic syndromes by Aronow and Ahn in a long-term care facility, 25% of patients over 62 yr of age had at least two manifestations of atherosclerosis *(52)*. Of patients with CAD, 33% also had PAD and 32% had experienced an ischemic stroke. Of patients with a history of ischemic stroke, 53% also had CAD and 33% also had PAD. Conversely, of those patients with PAD, 58% had CAD and 34% had suffered an ischemic stroke *(52)*.

The clinical overlap of PAD with other atherosclerotic vascular disease was also well defined in the recent Minnesota Regional PAD Screening Program *(53)*. This population, defined by age and presence of exertional limb pain, segregated an elderly (mean age 73 yr) community population into PAD and non-PAD subjects. Of the subjects with PAD, a history of cerebrovascular disease was present in 14% and a history of CAD was present in 56.5%. Non-PAD subjects had much less disease burden—only 2% had cerebrovascular disease and only 26% had CAD.

PAD AS A MARKER OF INCREASED RISK FOR VASCULAR ISCHEMIC EVENTS

Individuals with PAD suffer an increased risk of developing angina, congestive heart failure, fatal and nonfatal MI, fatal and nonfatal stroke, and death. Individuals with PAD suffer a 20–40% increased risk of nonfatal MI *(47)*, 60% risk of developing congestive heart failure *(8)*, and a two- to sevenfold increased risk of death *(2,47)*. The 5-yr longitudinal survey performed in the Edinburgh Artery Study demonstrated an equivalent increased risk for coronary ischemic events and death in both symptomatic and asymptomatic patients with PAD *(47)*. The ABI was shown to be a predictor of cardiovascular events among patients with PAD in the Edinburgh Artery Study, as well as an independent risk factor in the Cardiovascular Health Study *(8)*. The lower the ABI, the greater the occurrence of a fatal or nonfatal MI *(54)*. McKenna and colleagues have documented a 5-yr mortality of approx 30% and 50% in patients with an ABI of 0.70 and 0.40, respectively *(55)*. Even minimal decrements in ABI portend a heightened mortality *(56)*. As noted above, most data suggest that this increased risk of cardiovascular ischemic events and increased mortality is comparable, whether the PAD itself is associated with limb symptoms or not. However, those patients with the most severe limb symptoms or CLI do suffer a magnified short-term risk of ischemic events and death *(2)* (Fig. 4).

The clinical overlap between PAD and cerebrovascular disease also underlies the increased risk of brain ischemic events in those with PAD of any severity. It has also been shown that there is a correlation between symptomatic and asymptomatic PAD and increased intima–media thickness within the carotid arteries *(57)*. The ABI has been shown to be a potent predictor for cerebrovascular events *(54)* and an independent risk factor in the Cardiovascular Health Study *(8)*. Individuals with an ABI < 0.9 had a relative risk of 1.05–3.77 for subsequent stroke *(54)*. In the Edinburgh Artery Study, asymptomatic PAD patients were found to have an increased risk of a nonfatal stroke, although this was not demonstrated for fatal strokes *(47)*. In the study of Ness and colleagues, 42% of elderly patients with PAD (mean age 80) had a coexistent stroke *(58)*.

THE NATURAL HISTORY OF PAD

PAD causes significant morbidity and mortality because of its systemic manifestations. The epidemiology of PAD has been assessed in a number of international investigations that are reviewed in this chapter. However, whereas most clinicians consider patients with claudication to represent the primary clinical presentation, the Rotterdam Study of 7715 patients demonstrated that the vast majority of patients with PAD reported no symptoms of claudication *(59)*.

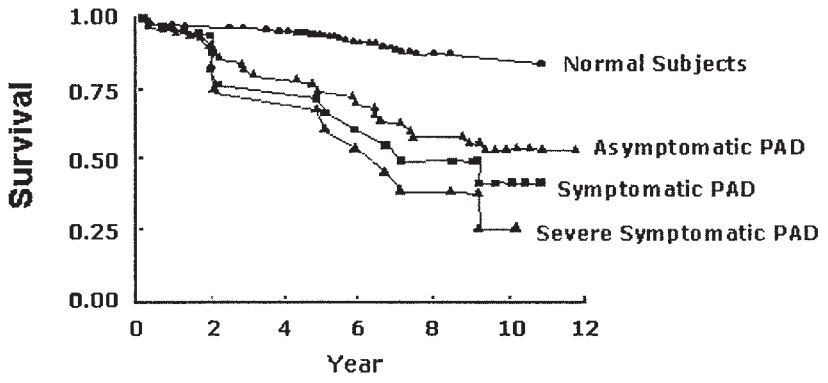

Fig. 4. The survival of all patients with PAD is significantly decreased compared to normal subjects. For patients with severe PAD, 5-yr survival is approx 30%, compared with an approx 80% survival in normal subjects. For patients with asymptomatic or symptomatic PAD, 5-yr survival is only slightly better than for those with severe PAD. (Modified from Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. New Engl J Med 1992;326:381-386. With permission ©1999 Massachusetts Medical Society.)

CLI occurs when PAD progresses to critical impairment of blood flow to the limb due to arterial stenosis or occlusion and may be considered the end stage of the disease. Individuals afflicted by CLI develop rest pain in the affected limb that worsens with elevation and improves with dependency. Dormandy and colleagues reviewed the data from 10 trials that followed patients with IC for 5–18 yr and who did not undergo surgical treatment *(60)*. The general consensus from these studies was that most patients with IC (75%) experience stabilization of their symptoms. Overall, in a population of patients with claudication, only 15–20% ever develop CLI and only 10% require amputation *(61)* (Fig. 5). But as iterated earlier in this chapter, this prognosis is not entirely favorable because the risk of ischemic events and death due to systemic atherosclerotic disease remains formidable, and, unlike that for some patients with PAD, does not improve over time.

THE MODERN ERA: MEDICAL TREATMENT OF PAD MODIFIES THE NATURAL HISTORY

In past decades, the natural history of PAD was defined by the inexorable anatomic progression of arterial stenoses, both within limb arteries and other systemic arteries, with adverse clinical consequences. Past paradigms recounted this natural history with a fatalism that was based on the reality that atherosclerotic risk factors would cause damage that was unlikely to be affected by medical therapies or by vascular surgical interventions. This paradigm no longer applies to the natural history of PAD in modern health care systems, and it is likely that prevalence rates and cardiovascular ischemic event rates are now, more than ever, within the control of the patient and his or her clinician. "Modifiable" risk factors, when modified successfully during long-term care, lead to a more benign natural history and improved clinical outcomes. A comprehensive approach to the medical treatment of PAD is beyond the scope of this chapter; however, risk factor modification and antiplatelet therapies that may alter the natural history of PAD merit careful review (*see* Chapter 9).

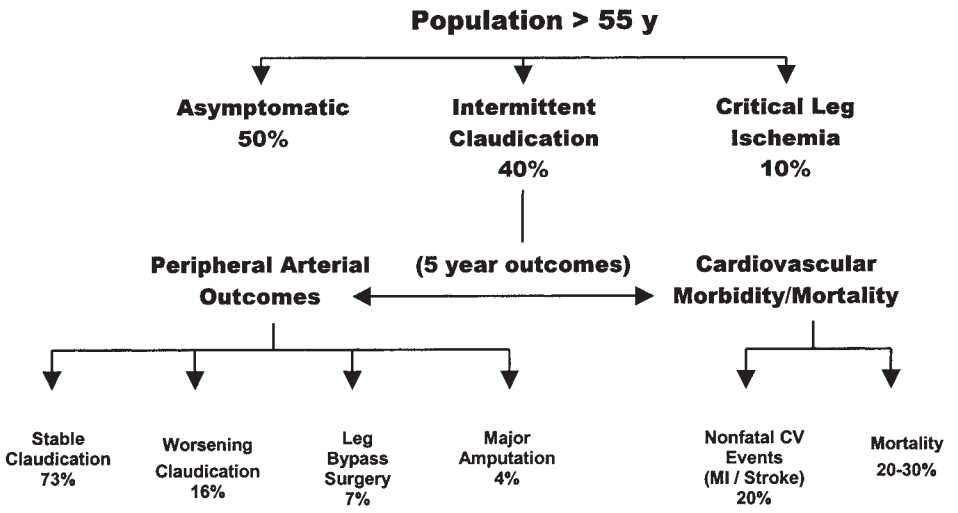

Fig. 5. The natural history of patients with PAD, demonstrating the relative frequency of limb and systemic cardiovascular ischemic events during 5 yr of follow-up. The rates of fatal and nonfatal cardiovascular ischemic events and death are higher than rates of severe limb ischemia. (Modified from Weitz JI, Byrne J, Clagett P, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation. 1996; 94:3026-3049.)

SUMMARY

PAD is a manifestation of systemic atherosclerosis that is defined by progressive stenosis or occlusion of the arteries of the lower extremities. PAD affects approx 8.4 million Americans and both PAD prevalence and rates of progression increase in association with exposure to atherosclerosis risk factors. The relative risk of developing PAD is most closely associated with diabetes (RR 4.05), current smoking (RR 2.55), increasing age (in 5-yr increments, RR 1.54), hypertension (RR 1.51), hyperhomocystinemia (RR 1.44), and elevated total cholesterol (RR 1.10 per 10 mg/dL increment). Although diabetes and a history of tobacco use are most predictive of PAD risk, hypertension and hypercholesterolemia are highly prevalent in individuals with PAD and serve as potent therapeutic targets that can modify the systemic risk of PAD. PAD severity is also associated with increased levels of high-sensitivity C-reactive protein.

The clinical presentation of PAD includes a spectrum that spans individuals with no apparent lower extremity ischemic symptoms, those who experience IC (discomfort in the limb muscles with exertion), and those with symptoms of severe limb ischemia (pain at rest, nonhealing wounds, or gangrene). Patients with IC are often limited in their daily activities as a result of this walking impairment and in turn experience a diminished quality of life. In a population of patients with claudication, only 15–20% ever develop CLI and only 10% require amputation, yet all face a high risk of systemic cardiovascular ischemic events. With continued exposure to atherosclerotic risk factors, the progression of PAD to critical limb ischemia portends a severe diminution in quality of life, and is associated with a high rate of amputation and a marked short-term increase in mortality.

The diagnosis of PAD should be considered a marker for increased risk of coexistent atherosclerosis regardless of whether the patient is asymptomatic or symptomatic and is most closely predicted by diminution of the ABI. The lower the ABI, the greater the

occurrence of a fatal or nonfatal myocardial infarction and death. Individuals with PAD have a higher coprevalence of CAD and cerebrovascular disease. In elderly patients with PAD, as many as 58% may have coexistent CAD and 34% may have a past history of ischemic stroke. This coprevalence of atherosclerotic syndromes in patients with PAD underpins a markedly increased rate of cardiovascular ischemic events in this population. Individuals with PAD suffer a 20–40% increased risk of nonfatal MI, 60% risk of developing congestive heart failure, and a two- to sevenfold increased risk of death.

Thus, PAD is a common manifestation of atherosclerosis that is associated with a range of symptoms, a variable impact on quality of life, and a heightened risk of cardiovascular ischemic events. Poor control of atherosclerosis risk factors is associated with more rapid progression of the PAD natural history, more severe limb symptoms, increased rates of limb loss, and increased mortality. Despite limitations in the treatment database, medical therapies are known to improve the natural history of PAD.

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