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# Pathophysiology of peripheral arterial disease and risk factors for its development 


#### Abstract

Peripheral arterial disease (PAD) is a systemic atherosclerotic process for which the major risk factors are similar to those for atherosclerosis in the carotid, coronary, and other vascular beds. Among the traditional risk factors for PAD, those with the strongest associations are advanced age, smoking, and diabetes mellitus. M ore recently, a number of nontraditional risk factors for PAD have also been recognized. This article briefly reviews the pathophysiology of PAD and the evidence supporting established and emerging risk factors for its development.


Peripheral arterial disease (PAD) refers to atherosclerotic and thromboembolic processes that affect the aorta, its visceral arterial branches, and arteries of the lower extremities. ${ }^{1}$ PA D is a marker of systemic atherosclerosis and is found more frequently among persons with wellknown cardiovascular risk factors (Table 1), especially older age, smoking, or diabetes mellitus, or those with atherosclerosis in other vascular beds. M ore recently, a number of "nontraditional" risk factors for PAD have also been recognized, including race/ethnicity, elevations in inflammatory markers, chronic kidney disease, genetics, hypercoagulable states, and an abnormal waist-to-hip ratio (Table 1).

Risk-factor identification is highly important, as PAD is associated with reductions in functional capacity and quality of life as well as increased cardiovascular morbidity and mortality, mainly from myocardial infarction and stroke. This article briefly reviews the pathophysiology of PAD and examines current data on the contributions of traditional and emerging risk factors for PA D.

* Dr. Bartholomew reported that he has received honoraria from GlaxoSmithKline for teaching and speaking. Dr. Olin reported that he has received consulting fees from the Bristol-M yers Squibb/Sanofi Pharmaceuticals Partnership for serving on a medical advisory panel and has received research support and consulting fees from Genzyme.


## - PATHOPHYSIOLOGY OF PAD

A therosclerosis is a complex process that involves endothelial dysfunction, lipid disturbances, platelet activation, thrombosis, oxidative stress, vascular smooth muscle activation, altered matrix metabolism, remodeling, and genetic factors. ${ }^{2} \mathrm{M}$ ore recently, the role of inflammation in all stages of atherosclerosis development has been widely recognized. ${ }^{3}$

A therosclerosis frequently develops at arterial bifurcations and branches where endogenous atheroprotective mechanisms are impaired as a result of the effects of disturbed flow on endothelial cells. ${ }^{2}$ R isk factors such as increased age, diabetes mellitus, smoking, elevations in total and low-density lipoprotein (LDL) cholesterol, and hypertension play important roles in both the initiation and the acceleration of this process. ${ }^{2}$

## The stages of atherosclerosis

Pathologically, the stages of atherosclerosis are divided into lesion initiation, formation of the fatty streak, fibroproliferative atheroma development, and advanced lesion development. Lesion initiation results from endothelial dysfunction, while the fatty streak is an inflammatory lesion that develops first, affects the intima of the artery, and leads to formation of the foam cell. The fatty streak consists largely of smooth muscle cells, monocytes, macrophages, and T and B cells. ${ }^{4}$ The fibroproliferative atheroma originates from the fatty streak, containing larger numbers of smooth muscle cellsfilled with lipids. The advanced lesion results from continued accumulation of the cells that make up the fatty streak and fibroproliferative atheroma. The advanced lesion is highly cellular and contains intrinsic vascular wall cells (endothelial and smooth muscle) and inflammatory cells (monocytes, macrophages, and T lymphocytes) in addition to a lipid core covered by a fibrous cap. ${ }^{2-5}$

## Arteries compensate-up to a point

A rteries initially compensate for atherosclerosis by remodeling, which causes blood vessel sto increase in size. However, advanced lesions eventually intrude into the lumen, resulting in flow-limiting stenoses
and chronic ischemic syndromes. ${ }^{4,5}$
A cute arterial events occur if the fibrous cap is disrupted; the resulting exposure of the "prothrombotic" necrotic lipid core and subendothelial tissue leads to thrombus formation and flow occlusion. ${ }^{2}$

## TRADITIONAL RISK FACTORS

Traditional risk factors for PA D are similar to those that lead to atherosclerosis in the carotid, coronary, and other vascular beds. In the Framingham Heart Study, ${ }^{6}$ Cardiovascular Health Study, ${ }^{7}$ PA D Awareness, Risk and Treatment: N ew Resources for Survival (PA RTNERS) program, ${ }^{8}$ National Health and Nutrition Examination Survey ( NHANES ), ${ }^{9}$ and A therosclerosis Risk in C ommunities (A RIC) study, ${ }^{10}$ major risk factors for PA D included advanced age, cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension. A mong these, cigarette smoking and diabetes mellitus are the modifiable risk factors that place patients at the greatest risk for PA D (Figure 1). ${ }^{11,12}$

## Advanced age

The prevalence of PAD increases with age. In the Framingham Heart Study, subjects 65 years of age or older were at increased risk for development of PA D. ${ }^{6}$ A strong association between advanced age ( $\geq 70$ years) and PAD prevalence was also noted in the NHANES report: prevalence was $4.3 \%$ in subjects aged 40 years or older compared with $14.5 \%$ in those aged 70 years or older (Figure 2). ${ }^{9}$

Others have reported similar findings. Criqui et al reported the prevalence of PA D (defined by an abnormal ankle-brachial index [A BI]) to be $2 \%$ to $3 \%$ in individual saged 50 years or less compared with $20 \%$ in those aged greater than 75 years. ${ }^{13}$ Even higher PA D prevalence rates were observed in the C ardiovascular H ealth Study, which recruited older, M edicare-eligible adults ( $25 \%$ prevalence among subjects aged 80 to 84 years, and $30 \%$ among those 85 years or older), ${ }^{7}$ and in the PA RTNERS program (prevalence of $29 \%$ ), which included individuals aged 70 years or older or aged 50 to 69 years with a history of smoking or diabetes. ${ }^{8}$

A lthough PA D may be present in younger individuals ( $\leq 50$ years of age), such patients represent a very small percentage of cases. Younger patients with PA D tend to have poorer overall long-term outcomes, as well as a higher number of failed bypass surgeries leading to amputation, compared with their older counterparts. ${ }^{14-16}$

## Smoking

C igarette smoking is the single most important modifiable risk factor for the development of PA D and its

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TABLE 1
Risk factors for peripheral arterial disease
Traditional risk factors
Advanced age
Smoking
Diabetes mellitus
Hyperlipidemia
Hypertension
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## Nontraditional risk factors

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Race/ethnicity
Elevated levels of inflammatory markers
(C-reactive protein, fibrinogen, leukocytes, interleukin-6)
Chronic kidney disease
Genetics
Hypercoagulable states
(altered levels of D-dimer, homocysteine, lipoprotein[a])
Abnormal waist-to-hip ratio
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complications: intermittent claudication and critical limb ischemia. Smoking increases the risk of PAD approximately fourfold and accelerates the onset of PA D symptoms (intermittent claudication) by nearly a decade, with an apparent dose-response relationship between the pack-year history and PAD risk. ${ }^{717-19}$ Compared with their nonsmoking counterparts, smokers with PA D have poorer survival rates (death attributed to a major vascular event), are more likely to progress to critical limb ischemia, are twice as likely to progress to amputation, and have reduced arterial bypass graft patency rates. ${ }^{60,20-22}$

A Ithough both former smokers and current smokers are at increased risk of PA D, individuals who are able to stop smoking are less likely to develop rest pain and have improved survival ${ }^{20}$ (see also the article by G ornik and Creager beginning on page S30).

Notably, the association between smoking and PA D is about twice as strong as that between smoking and coronary artery disease (CA D)..$^{19,23}$ The reason for this disparity is not clear.

## Diabetes mellitus

Diabetes mellitus confers a 1.5 -fold to 4 -fold increase in the risk of developing symptomatic or asymptomatic PA D and is associated with an increased risk of cardiovascular events and early mortality among individuals with PA D..$^{24-26}$

In the Framingham H eart Study, 20\% of sympto-


FIGURE 1. Range of odds ratios for developing symptomatic peripheral arterial disease (PAD) (ie, intermittent claudication) according to various risk factors. Adapted, with permission, from reference 11.
matic patients with PAD were reported to have diabetes, although this might have been an underestimate because diagnoses were based on inquiries about symptoms of intermittent claudication rather than objective testing. ${ }^{6,24}$ In the NHANES report, which used the A BI to diagnose PA D, $26 \%$ of subjects with PA D were identified as having diabetes, ${ }^{9}$ while in the Edinburgh A rtery Study, which used a W orld H ealth $O$ rganization questionnaire or an A BI less than 0.90 , the prevalence of PA D was higher in individuals with diabetes or impaired glucose tolerance (20.6\%) than in those with normal glucose tolerance (12.5\%).. ${ }^{25}$ $M$ ore recently, the A RIC study found that a prior history of diabetes with insulin treatment was independently associated with a greater incidence of PAD, ${ }^{10}$ while the Multi-Ethnic Study of A therosclerosis (MESA) found that $26 \%$ of women and $27.5 \%$ of men with an A BI less than 0.90 had diabetes. ${ }^{26}$

In patients with diabetes, the prevalence and extent of PAD also appears to correlate with the age of the individual and the duration and severity of his or her diabetes. ${ }^{27}$ Diabetes is a stronger risk factor for PA D in women than in men, and the prevalence of PAD is higher in A frican A mericans and H ispanics with diabetes than in non-H ispanic whites with diabetes. ${ }^{12,24,27}$

The severity of diabetes also appears to play an
important role in the development of PA D. There is a $28 \%$ increase in the risk of PA D for every percentagepoint increase in hemoglobin ( Hb ) $\mathrm{A}_{1 c}$, and the seriousness of PA D appears to be related both to the duration of hyperglycemia and to glycemic control. ${ }^{24,27,28}$ PAD prevalence is also increased in individuals with impaired glucose tolerance, and the risk of PA D is significantly increased with higher $\mathrm{HbA}_{1 c}$ levels even among individuals with dysglycemia in the nondiabetic range ( $\mathrm{HbA}_{1 \mathrm{c}} \geq 5.3 \%$ ). ${ }^{27,29}$

Diabetes is most strongly associated with occlusive disease in the tibial arteries. ${ }^{27}$ Patients with PA D and diabetes are more likely to develop microangiopathy or neuropathy and to have impaired wound healing than those with PA D alone. ${ }^{27}$ Because diabetic neuropathy may often mask PA D symptoms, PA D is more commonly asymptomatic in diabetics; as a result, PA D tends to present later in life and in a more severe and rapidly progressive form in diabetics than in nondiabetics. ${ }^{27}$ PA D patients who have diabetes al so have a higher risk for ischemic ulceration and gangrene, which is one reason why diabetes is the most common cause for amputation in the $U$ nited States. ${ }^{27}$

Diabetes is believed to contribute to an increased risk of PA D for a number of reasons. Persons with diabetes are more likely than their nondiabetic counterparts to have additional risk factors for PA D, such as tobacco use, elevated blood pressure, and increased levels of triglycerides, cholesterol, and other blood lipids. ${ }^{25}$ They also appear to have more vascular inflammation, endothelial cell dysfunction, and abnormalities in vascular smooth muscle cells compared with nondiabetics. In addition, diabetes is associated with increases in platelet aggregation and impaired fibrinolytic function. ${ }^{27}$

## Hyperlipidemia

In the Framingham Heart Study, an elevated total cholesterol level was associated with a twofold increased risk for intermittent claudication. ${ }^{24}$ In the N H A N ES report, ${ }^{9}$ more than $60 \%$ of individuals with PA D had hypercholesterolemia, while in the PA RTNERS program, the prevalence of hyperlipidemia in patients with known PA D was $77 \%$. ${ }^{8}$

H yperlipidemia increases the adjusted likelihood of developing PA D by $10 \%$ for every $10-\mathrm{mg} / \mathrm{dL}$ rise in total cholesterol. ${ }^{30}$ It is now recognized that elevations in total cholesterol, LDL cholesterol, very lowdensity lipoprotein (VLDL) cholesterol, and triglycerides are all independent risk factors for PA D, whereas elevations in high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I appear to be protec-
tive. ${ }^{30}$ In 2001, the Third Report of the $N$ ational Cholesterol Education Program Adult Treatment Panel designated PAD as a CAD risk equivalent. ${ }^{31}$

The form of dyslipidemia seen most frequently in patients with PAD is the combination of a reduced HDL cholesterol level and an elevated triglyceride level, as commonly seen in patients with the metabolic syndrome and diabetes. ${ }^{23}$ In the C ardiovascular H ealth Study, both of these finding were reported in association with a decreased $A B I ;{ }^{7}$ however, in the A RIC study and the Edinburgh A rtery Study, both of which involved patients with diabetes, only elevated triglyceride levels were associated with PA D. ${ }^{10,25}$

## Hypertension

A lmost every epidemiologic study has shown a strong association between hypertension and PAD, with hypertension being reported in as many as $50 \%$ to $92 \%$ of patients with PA D. ${ }^{-9,2,24,32,33}$ In the NHANES report and the PA RTNERS program, PAD and hypertension were encountered together in $74 \%$ and $92 \%$ of enrolled subjects, respectively. 8.9 The Cardiovascular Health Study reported that $52 \%$ of patients with an A BI less than 0.90 had high blood pressure, ${ }^{7}$ and the Framingham Study demonstrated a 2.5 -fold to 4 -fold increase in the risk of developing intermittent claudication among both men and women with hypertension. ${ }^{24}$ In the Systolic Hypertension in the Elderly (SHEP) trial, $25.5 \%$ of participants had an A BI less than 0.90. ${ }^{33}$ Taken together, these studies underscore the high prevalence of PA D in patients with hypertension.

Recently, the Seventh Report of the Joint $N$ ational Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure acknowledged that PAD is equivalent in risk to ischemic heart disease. ${ }^{34}$

Patients with hypertension and PA D are at greatly increased risk of stroke and myocardial infarction independent of other risk factors. ${ }^{23,32}$ In the SHEP study of older adults with systolic hypertension, an A BI of 0.90 or less was associated with a twofold to threefold increase in total and cardiovascular mortality. ${ }^{33}$

## - NONTRADITIONAL RISK FACTORS

## Race/ethnicity

Several studies have shown PA D to be disproportionately prevalent in black and Hispanic populations, even after adjustment for traditional risk factors. ${ }^{7-9}$ A ge- and gender-adjusted analysis of the NHANES data showed that non-H ispanic blacks were approximately three times as likely to have PAD as nonH ispanic whites. ${ }^{9}$ In the C ardiovascular H ealth Study

## Advanced age as a risk factor for PAD



FIGURE 2. Prevalence of peripheral arterial disease (PAD) by age and gender, United States, 1999-2000 ( $\mathrm{N}=2,174$ ). Error bars are $95 \%$ confidence intervals (for age groups 40-49 and 50-59, estimates have a relative standard error > 30\% ). Reprinted, with permission, from: Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004; 110:738-743.
and the PARTNERS program, nonwhite subjects (predominantly black) were disproportionately affected by PA D. ${ }^{1,8}$ In the M ulti-Ethnic Study of A therosclerosis, which was designed to include an ethnically diverse population, PAD prevalence was highest among black men and women and lowest among H ispanic women and C hinese men. ${ }^{26}$

A recent population-based study by Criqui et al concluded that the excess risk of PA D in blacks was unexplained and was not related to diabetes, hypertension, or body mass index. ${ }^{35}$ In contrast to some other reports, these researchers also noted lower PA D rates among Hispanics, although the rates were not significantly different from those among nonHispanic whites. ${ }^{35}$

## Inflammation

Elevated levels of the inflammatory markers C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), and leukocytes have been observed in patients with atherosclerosis in other arterial beds; however, an association with PAD has not been established as clearly and only a few studies to date have looked at this relationship. ${ }^{7,936}$

Ridker and colleagues found in the Physicians' Health Study that elevated CRP levels predicted a future risk for development of PA D and greater extent of disease. ${ }^{36}$ The N H A N ES report showed that elevated fibrinogen and CRP levels were associated with PA D, ${ }^{9}$ and Wildman et al noted that elevated CRP or fibrinogen levels or an increased leukocyte count doubled the risk of developing PAD. ${ }^{37}$ In the InCHIANTI study (Invecchiare in Chianti, "aging in the Chianti population"), McDermott et al found increased levels of fibrinogen, CRP, and IL-6 in men and women with PA D (compared with persons without PAD) in a community population in Italy. ${ }^{38}$ In a separate study, M cDermott et al demonstrated that higher baseline levels of inflammatory markers were associated with greater lower extremity functional decline among a group of 337 men and women with PA D. ${ }^{39}$

## Chronic kidney disease

U ntil recently, very few epidemiologic studies recognized chronic kidney disease (reduced kidney function in a patient who is not receiving dialysis and is not a transplant recipient) as a risk factor for PA D. ${ }^{40,41}$

The overall prevalence of PAD in the $N$ ational Institutes of Health's United States Renal Data System in 1999 was 15\%, determined using the following clinical parameters: prior diagnosis of PAD, history of amputation, previous revascularization procedure, intermittent claudication, tissue gangrene, or a decrease in peripheral pulses on physical examination. ${ }^{41}$ Based on data from the N H A N ES report, 24\% of the population aged 40 years or older with renal insufficiency (estimated creatinine clearance $<60$ $\mathrm{mL} / \mathrm{min} / 1.73 \mathrm{~m}^{2}$ ) was estimated to have PA D (A BI < 0.90 ), compared with $3.7 \%$ of those whose creatinine clearance was greater than $60 \mathrm{~mL} / \mathrm{min} / 1.73 \mathrm{~m}^{2 .} .^{22} \mathrm{In}$ the Cardiovascular Health Study, 12\% of individuals with renal insufficiency (defined as serum creatinine $\geq 1.3 \mathrm{mg} / \mathrm{dL}$ in women and $\geq 1.5 \mathrm{mg} / \mathrm{dL}$ in men) had an ABI of less than 0.90 , compared with $7 \%$ of subjects with normal renal function. ${ }^{43}$ In the A RIC study, a low $\mathrm{ABI}(<0.90)$ was associated with an increase in serum creatinine levels over time. ${ }^{44}$

An association with PAD also appears to apply to more severe renal disease. The prevalence of an abnormal ABI $(<0.90)$ is much higher in patients with end-stage renal disease (ie, requiring hemodialysis) than in those with chronic kidney disease, ranging between $30 \%$ and $38 \% .{ }^{40}$ PAD patients with chronic kidney disease are at increased risk for critical limb ischemia, while those with end-stage renal disease are at increased risk for amputation. ${ }^{40}$ Several
studies have reported an increased risk of cardiovascular and all-cause mortal ity in hemodialysis patients, although this issue has not been examined as well among patients with milder chronic kidney disease.

The association between chronic kidney disease and PAD is independent of diabetes, hypertension, ethnicity, and age, and although the exact reason for this association is not known, it may relate to the increased vascular inflammation and markedly elevated plasma homocysteine levels seen in chronic kidney disease.

## Genetics

Genetic predisposition to PA D is supported by observations of increased rates of cardiovascular disease (including PAD) in "healthy" relatives of patients with intermittent claudication. A lthough the relative contributions of genes and environment to the pathogenesis of premature PA D are difficult to separate, one study found that one in four siblings of patients with premature PA D will have a vascular event before age 55 years, and up to half of asymptomatic siblings will develop occult disease at a young age ( $<50$ years). ${ }^{45}$

To date, no major gene for PA D has been detected, but an ongoing $N$ ational Institutes of H ealth-sponsored study in more than 2,000 subjects called "G enetic Determinants of Peripheral A rterial Disease" should help to clarify the role of genetics in PA D.

## Hypercoagulable states

H ypercoagulable states, or thrombophilia, represent an uncommon risk factor for PA D. H owever, in select patients-younger individuals who lack traditional risk factors, patients with a strong family history of premature atherosclerosis, and individuals in whom arterial revascularization fails for no apparent technical reason- evaluation for an underlying hypercoagulable condition should be considered.

Several recent studies have suggested an independent association between PAD and altered levels of hemostatic factors, including lipoprotein(a), homocysteine, antiphospholipid antibodies, and Ddimer. ${ }^{38,39,46,47}$ In particular, D-dimer levels appear to be inversely related to the A BI and have been associated with a greater decline in walking and poorer physical function scores. ${ }^{39}$

Evaluation for elevated homocysteine and lipoprotein(a) levels appears to be important in individuals with diffuse PAD who lack traditional risk factors. Hyperhomocysteinemia is associated with premature atherosclerosis and appears to be a stronger risk factor for PA D than for CA D. ${ }^{48,49}$ It has also been implicated in PAD progression and as a risk factor for failure of
peripheral interventions, although not all studies have shown such a relationship. ${ }^{49,50}$

Several studies have reported an increased prevaIence of elevated lipoprotein(a) in patients with PA D. A lthough there are conflicting data on the role of lipoprotein(a) as an independent risk factor for atherosclerosis, it may also be useful for screening individuals with premature PA D. ${ }^{10,46}$

## Abnormal waist-to-hip ratio

A lthough it is unclear whether any association exists between PA D and body mass index (BMI), an association between abdominal obesity and PAD has been reported. Planas et al demonstrated that an increased waist-to-hip ratio ( $>0.966$ ) was associated with a 1.7fold increase in the risk of PA D after adjustment for covariates. ${ }^{51}$

One explanation for the lack of association with BMI is the tendency of smokers (who are at increased risk for PAD) to have lower BM Is than nonsmokers.

## REFERENCES

1. Hirsch AT, H askal ZJ, H ertzer N R, et al. A C C/A HA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. J A m C oll C ardiol 2006; 47:1239-1312.
2. Faxon DP, Fuster V, Libby P, et al. A therosclerotic Vascular Disease Conference: Writing Group III: pathophysiology. Circulation 2004; 109:2617-2625.
3. Libby P, Ridker PM, M aseri A. Inflammation and atherosclerosis. Circulation 2002; 105:1135-1143.
4. R oss R. A therosclerosis- an inflammatory disease. N Engl J Med 1999; 340:115-126.
5. Kinlay S, Libby P, Ganz P. Endothelial function and coronary artery disease. Curr $O$ pin Lipidol 2001; 12:383-389.
6. Murabito JM, D'A gostino RB, Silbershatz H, Wilson W F. Intermittent claudication. A risk profile from The Framingham H eart Study. C irculation 1997; 96:44-49.
7. Newman A B, Siscovick D S, M anolio TA, et al. A nkle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. C ardiovascular H eart Study (CHS) C ollaborative Research G roup. Circulation 1993; 88:837-845.
8. H irsch AT, C riqui M H , Treat-J acobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JA M A 2001; 286:1317-1324.
9. Selvin E, Erlinger T P. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the $N$ ational H ealth and N utrition Examination Survey, 1999-2000. Circulation 2004; 110:738-743.
10. Wattanakit K, Folsom AR, Selvin E, et al. Risk factors for peripheral arterial disease incidence in persons with diabetes: the A therosclerosis Risk in Communities(A RIC) Study. A therosclerosis 2005; 180:389-397.
11. D ormandy JA, R utherford R B. M anagement of peripheral arterial disease (PA D). TA SC W orking G roup. TransA tlantic Inter-Society C onsensus (TA SC ). J V asc Surg 2000; 31(1 Pt 2):S1-S296.
12. Smith SC Jr, Milani RV, A rnett DK, et al. A therosclerosis Vascular Disease Conference: Writing Group II: risk factors. Circulation 2004; 109:2613-2616.
13. C riqui M H , Fronek A , K lauber M R , B arrett-C onnor E, G abriel 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; 71:516-522.

M oreover, many of the individuals at risk for PA D are elderly males, who typically have lower BM Is as well. ${ }^{52}$

## CONCLUSIONS

PA D is a systemic atherosclerotic process associated with high morbidity and mortality and significant impairment of quality of life, yet it remains underdiagnosed and undertreated. A dvanced age, smoking, and diabetes are clearly the most important risk factors for PAD. The association with diabetes is particularly concerning, given the exponential growth in diabetes prevalence in recent years. Recognizing these and other traditional risk factors for PA D (hyperlipidemia and hypertension), as well as the nontraditional factors reviewed above, is important to the management of PA D. N evertheless, even if clinicians focus largely on smoking and diabetes as risk factors, significant gains can be made in detecting PA D earlier and treating it more successfully.
14. Levy PJ, H ornung CA, H aynes JL, Rush DS. Lower extremity ischemia in adults younger than forty years of age: a community-wide survey of premature atherosclerotic arterial disease. J V asc Surg 1994; 19:873-881.
15. H arris LM, Peer R, C url G R , Pillai L, U pson J, Ricotta JJ. Longterm follow-up of patients with early atherosclerosis. J Vasc Surg 1996; 23:576-581.
16. V alentine RJ, M yers SI, Inman M H , R oberts JR , C lagett G P. Late outcome of amputees with premature atherosclerosis. Surgery 1996; 119:487-493.
17. Powell JT, Edwards RJ, W orrell PC , Franks PJ, G reenhalgh R M, Poulter NR. Risk factors associated with the development of peripheral arterial disease in smokers: a case-control study. A therosclerosis 1997; 129:41-48.
18. K annel W B, Shurtleff D. The Framingham Study. Cigarettes and the development of intermittent claudication. G eriatrics 1973; 28:61-68.
19. Price JF, M owbray PI, Lee AJ, R umley A , Lowe G D, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh A rtery Study. Eur H eart J 1999; 20:344-353.
20. Jonason T, Bergstrom R. C essation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. A cta M ed Scand 1987; 221:253-260.
21. Powell JT, G reenhalgh RM. Changing the smoking habit and its influence on the management of vascular disease. A cta C hir Scand Suppl 1990; 555:99-103.
22. Lassila R, Lepantalo M. Cigarette smoking and the outcome after lower limb arterial surgery. A cta C hir Scand 1988; 154:635-640.
23. Fowkes FG, H ousley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh A rtery Study. A m J Epidemiol 1992; 135:331-340.
24. K annel W B , M cG ee DL. U pdate on some epidemiologic features of intermittent claudication: the Framingham Study. J A m G eriatr Soc 1985; 33:13-18.
25. MacG regor A S, Price JF, H au C M, Lee AJ, C arson M N, Fowkes FG. Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease. The Edinburgh A rtery Study. Diabetes C are 1999; 22:453-458.
26. McDermott M M , Liu K, C riqui MH, et al. A nkle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. A m J Epidemiol 2005; 162:33-41.
27. A merican Diabetes A ssociation. Peripheral arterial disease in people with diabetes. Diabetes C are 2003; 26:3333-3341.
28. Selvin E, M arinopoulos S, Berkenblit G , et al. M eta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. A nn Intern M ed 2004; 141:421-431.
29. Muntner P, Wildman R P, Reynolds K, Desalvo KB, C hen J, Fonseca V. Relationship between H bA 1c level and peripheral arterial disease. Diabetes C are 2005; 28:1981-1987.
30. H iatt W R, H oag S, H amman R F. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. Circulation 1995; 91:1472-1479.
31. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of H igh Blood C holesterol in A dults (A dult Treatment Panel III). Third Report of the N ational Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of H igh Blood C holesterol in A dults (A dult Treatment Panel III) final report. Circulation 2002; 106:3143-3421.
32. Olin JW. H ypertension and peripheral arterial disease. Vasc M ed 2005; 10:241-246.
33. N ewman A B, Tyrrell KS, Kuller LH . M ortality over four years in SHEP participants with a low ankle-arm index. J A m Geriatr Soc 1997; 45:1472-1478
34. C hobanian AV, Bakris GL, Black H R, et al. The Seventh Report of the Joint $N$ ational Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JA M A 2003; 289:2560-2572.
35. C riqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. Circulation 2005; 112:2703-2707.
36. Ridker PM, C ushman M, Stampfer MJ, Tracy R P, H ennekens C H. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998; 97:425-428.
37. Wildman R P, M untner P, C hen J, Sutton-Tyrell K, He J. Relation of inflammation to peripheral arterial disease in the N ational H ealth and N utrition Examination Survey, 1999-2002. A m J C ardiol 2005; 96:1579-1583.
38. McDermott M M , G uralnik JM , C orsi A , et al. Patterns of inflammation associated with peripheral arterial disease: the InCHIANTI study. A m H eart J 2005; 150:276-281.
39. McD ermott M M, Ferrucci L, Liu K, et al. D-dimer and inflammatory markers as predictors of functional decline in men and women with and without peripheral arterial disease. J A m G eriatr Soc 2005; 53:1688-1696.
40. $\mathbf{O}^{\prime} \mathbf{H}$ are A M. M anagement of peripheral arterial disease in chronic
kidney disease. C ardiol Clin 2005; 23:225-236.
41. National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic and Hematologic Diseases. Patient characteristics. In: U nited States Renal Data System, U SRDS 2000 A nnual Data Report. Bethesda, M D: N ational Institutes of H ealth, N ational Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2000:339-348.
42. $\mathbf{O}^{\prime} \mathrm{H}$ are $\mathbf{A M}$, Glidden DV, Fox CS, et al. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the N ational H ealth and N utrition Examination Survey 1999-2000. Circulation 2004; 109:320-323.
43. Shlipak M G , Fried LF, C rump C , et al. C ardiovascular disease risk status in elderly persons with renal insufficiency. Kidney Int 2002; 62:997-1004.
44. O'H are AM, Rodriguez RA, Bacchetti P. Low ankle-brachial index associated with rise in creatinine level over time: results from the atherosclerosis risk in communities study. A rch Intern Med 2005; 165:1481-1485.
45. Valentine R J, V erstraete R, C lagett G P, C ohen JC. Premature cardiovascular disease is common in relatives of patients with premature peripheral atherosclerosis. A rch Intern M ed 2000; 160:1343-1348.
46. Sofi F, Lari B, R ogolino A , et al. Thrombophilic risk factors for symptomatic peripheral arterial disease. J Vasc Surg 2005; 41:255-260.
47. McDermott M M , G reen D, G reenland P, et al. Relation of levels of hemostatic factors and inflammatory markers to the ankle brachial index. A m J C ardiol 2003; 92:194-199.
48. Ridker PM, Stampfer MJ, R ifai N. N ovel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JA MA 2001; 285:2481-2485.
49. Welch G N, Loscalzo J. Homocysteine and atherothrombosis. N Engl J M ed 1998; 338:1042-1050.
50. Taylor LM Jr, DeFrang R D, H arris EJ Jr, Porter JM. The association of elevated plasma homocyst(e)ine with progression of symptomatic peripheral arterial disease. J V asc Surg 1991; 13:128-136.
51. Planas A, Clara A , Pou JM, et al. Relationship of obesity distribution and peripheral arterial occlusive disease in elderly men. Int J $O$ bes Relat M etab Disord 2001; 25:1068-1070.
52. Douketis JD, Sharma AM. Obesity and cardiovascular disease: pathogenic mechanisms and potential benefits of weight reduction. Semin Vasc M ed 2005; 5:25-33.

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