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Peripheral Arterial Disease Morbidity and Mortality Implications

Beatrice A. Golomb, MD, PhD; Tram T. Dang, BS; Michael H. Criqui, MD, MPH

Peripheral arterial disease (PAD) has been estimated to reduce quality of life in approximately 2 million symptomatic Americans,¹ and millions more Americans without claudication are likely to suffer PAD-associated impairment.² PAD is a strongly age-dependent condition that contributes significantly to morbidity and healthcare expenditures in the elderly: There are 413 000 discharges per year with chronic PAD, 88 000 hospitalizations involving lower-extremity arteriography, and 28 000 discharges citing embolectomy or thrombectomy of lower-limb arteries.³ Figures for prevalence of asymptomatic PAD are several-fold higher. These figures were based on National Hospital Discharge Survey and National Vital Statistics System 1985 to 1987 US data; numbers of procedures had increased in the prior decade³ and are likely to have increased in the intervening years as the population continues to age. Even though few deaths were directly attributed to PAD, PAD has potent mortality implications. Although symptomatic disease directly affects functional capacity and quality of life by restricting ambulation, asymptomatic disease is also important, not only because it may augur risk of future compromised ambulation, lower-extremity ulcers, or need for vascular surgery or amputation, but perhaps most importantly because asymptomatic and symptomatic PAD are consistent and powerful independent predictors of coronary artery disease (CAD) and cerebrovascular disease (CBVD) events and mortality. The evidence relating PAD to prevalent and incident cardiac and cerebrovascular disease (CCVD) forms the focus of the present report.

Methods

A PubMed search (updated June 2005) covering years 1966 to 2005 yielded all abstracts with title words "peripheral artery disease," "peripheral arterial disease," or "peripheral vascular disease." These were reviewed for content pertaining to co-occurrence with or prediction by PAD of atherosclerotic disease and total mortality. Additional citations were identified from bibliographies of culled articles and consultation with experts. Identified citations with original epidemiological data pertaining to the relation of lower-extremity PAD to cardiovascular and overall morbidity and mortality were reviewed. Data were stratified into cross-sectional or retrospective studies versus prospective studies, to distinguish the cross-sectional association of PAD with prevalent CCVD from the prognostic significance of PAD for incident CCVD and mortality.

All studies with defined populations, PAD assessment, and outcome assessment for CCVD morbidity and mortality (or total mortality) were considered. Population characteristics, criteria for PAD and for CCVD outcomes, coprevalence of CCVD with PAD (cross-sectional data), and risk ratios and confidence intervals relating PAD to incident CCVD and mortality outcomes (prospective data) were extracted. Covariates adjusted in the studies' multivariable models examining PAD as a risk marker for incident cardiovascular and mortality outcomes were annotated. Findings relating PAD to atherosclerosis-relevant outcomes were tabulated by vascular bed.

Results

Cross-Sectional Data: Coprevalence

CAD in PAD

The prevalence of CAD in PAD patients ranged from 14% to 90%, which clearly reflects differences in sensitivity of the detection technique for CAD.^{4,5} CAD was present in 19% to 47% of PAD patients in studies using clinical history plus ECG; in 62% to 63% using stress tests (modified stress ECG or dipyridamole-stress thallium); and in 90% of subjects when angiography was used. Data are shown in Figure 1.^{6–26}

CBVD in PAD

PAD may be a particularly potent predictor of comorbid CBVD, with evidence of significant concurrent CBVD defined by carotid stenosis on Doppler imaging or by cerebrovascular events (Figure 2).^{7,8,10,11,16,19,20,26–30} As in Figure 1 for CAD in PAD, the prevalence of CBVD in PAD is a direct function of the sensitivity of CBVD assessment. Thus, comorbid carotid stenosis >30% was cited in ≈51% to 72% of subjects and stenosis >70% in 25%, and a history of clinical disease generally was seen in fewer subjects (although 1 study cited clinical disease in 35%). Notably, in a study of Chinese subjects with PAD, CAD, abdominal aortic aneurysm, CBVD symptoms, or asymptomatic carotid bruits in whom routine screening carotid duplex scans were performed, PAD subjects had the highest prevalence of significant (>70%) carotid stenosis, at 25%.³⁰ This compared with lower rates of significant carotid stenosis in patients with CAD (11%), carotid bruits (10%), and abdominal aortic aneurysm (9%), each of whom, in turn, had rates of significant stenosis greater than those of normal controls (0%; $P<0.001$).³⁰ This suggests that PAD may be a stronger

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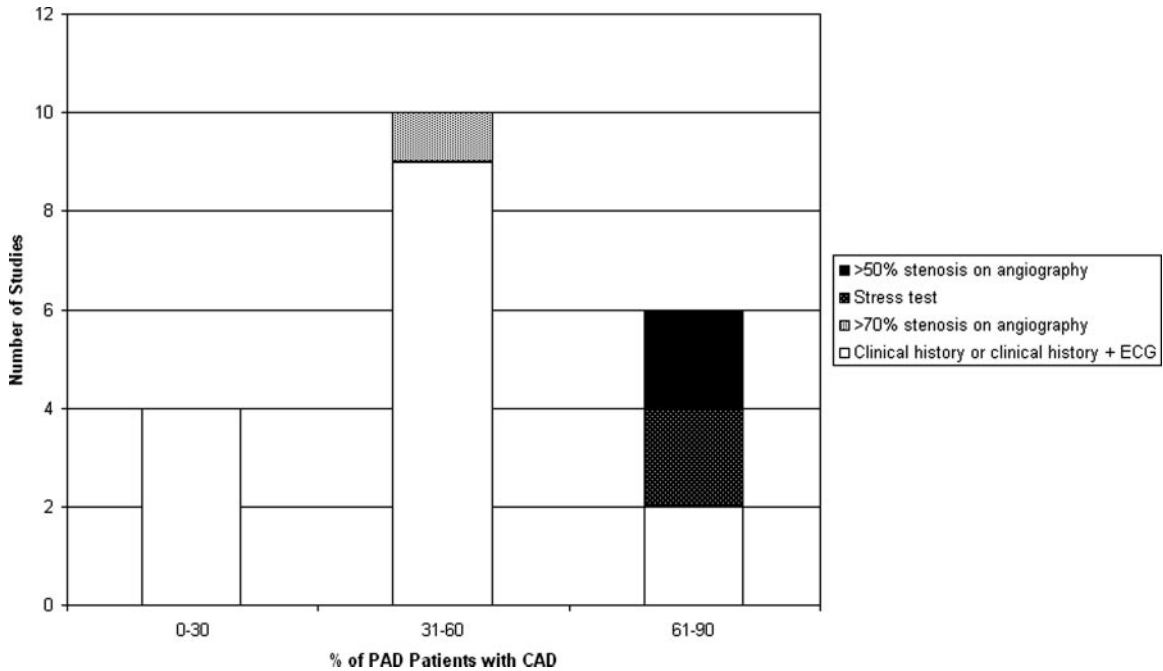


Figure 1. CAD prevalence in patients presenting with PAD. In 1 citation excluded from the Figure, upper- as well as lower-extremity PAD patients were included: 15% showed CAD defined by >50% stenosis on angiography.²⁵ In another, cross-sectional ORs were provided for prior MI (clinical history) in patients with PAD, defined by ABI <0.90 (OR: men 1.79, 95% CI 0.72 to 3.96; women 3.18, 95% CI 1.47 to 6.64), but information needed to calculate the percent with CAD was not provided.²⁶

predictor of concurrent CBVD risk than is CAD. In an evaluation of subjects aged 60 to 80 years from the Edinburgh Artery Study, carotid artery intimal-medial thickness by ultrasound, sometimes used as a gauge of subclinical CBVD, was significantly associated with PAD assessed by ankle-brachial index (ABI) <0.9 ($P<0.05$).³¹

CCVD in PAD

Perhaps more direct evidence of CCVD prevalence in PAD derives from comparisons of rates of CCVD in those with versus without PAD drawn from the same population. In a San Diego, Calif, population study of subjects aged 38 to 82 years, clinical CCVD was present in 29% of men with PAD

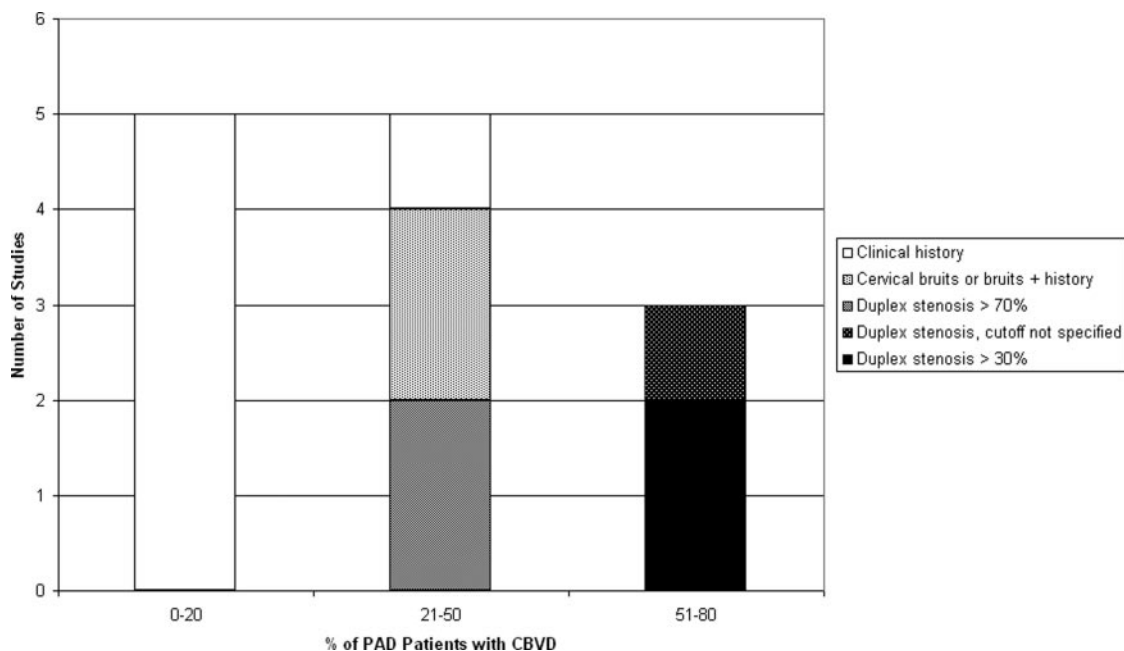


Figure 2. CBVD prevalence in patients presenting with PAD. An additional citation provides cross-sectional ORs for stroke (clinical history) in patients with PAD defined by ABI <0.90 (OR: men 1.02, 95% CI 0.28 to 3.94; women 2.94, 95% CI 1.09 to 7.42) but does not give information needed to calculate percent with CBVD.²⁶

(defined by noninvasive tests) versus 12% of men without PAD and 21% of women with and 9% of women without PAD.⁵ Thus, CCVD was 2 to 3 times more common in persons with than without PAD. Similarly, in a cross-sectional evaluation of a stratified sample of patients from 18 general practice clinics, in whom prevalence of PAD was 7% (95% confidence interval [CI] 5.2% to 7.9%), asymptomatic PAD (ABI <0.95) conferred a 3- to 4-fold excess risk of CAD and CBVD.³²

PAD in CCVD

Just as CCVD may be more common in those with PAD, so PAD may be more common in those with CCVD. In a San Diego cohort, PAD was present in 32% of men with clinical CCVD compared with 13% of men without and in 25% of women with CCVD versus 11% of women without.⁵ Thus, PAD was 2 to 3 times more common among those with than without CCVD. Hospital prevalence rates for Saudi Arabian patients aged 50 to 80 years (mean 59 years) for ABI <0.9 were 21% in those with CAD compared with 4% in controls without CAD, renal disease, or diabetes mellitus, which suggests a 5-fold increase in prevalence.³³

Prospective Data: PAD Prediction of Future CCVD Morbidity and Mortality and All-Cause Mortality

Because PAD shares many identified risk factors in common with CAD and CBVD, it is axiomatic that concomitant disease should be observed. Specifically, because traditional risk factors for CCVD are commonly present, those with PAD may be at heightened risk not only for coprevalent but also for future CAD and CBVD morbidity and mortality.

PAD Predicts CAD

Presence of PAD, by any of various criteria, is associated with increased risk of CAD and sequelae that may arise from CAD, including new angina, coronary artery bypass graft, nonfatal or total myocardial infarction (MI), congestive heart failure, and fatal MI and CAD death (Table 1).^{34–47} Comparison of findings according to PAD criteria suggests that symptomatic PAD (ie, intermittent claudication) is more strongly associated with subsequent symptomatic angina (risk ratio 2.3) than is asymptomatic PAD; indeed, major asymptomatic PAD was associated with no trend toward an increase in new angina, although minor asymptomatic disease showed a trend (41% increase).³⁵

PAD is associated with increases in risk for nonfatal MI across PAD categories (symptomatic, major asymptomatic, and minor asymptomatic), with risk ratios ranging from 1.2 to 1.4. (PAD in patients without prior CCVD is also associated with a significant 60% increase in progression to congestive heart failure after multivariate adjustment.³⁴) PAD by noninvasive criteria is more persuasively and significantly associated with fatal MI and CAD death, after univariate and multivariate adjustment; risk ratios range from a low of 1.9 in an Edinburgh, Scotland, medical population sample⁴³ to 3.2,³⁸ 5.0,⁴⁵ and 6.6⁴⁶ in other samples. A population-based study with 10-year follow-up and slightly more severe disease (ABI cutoff <0.8) showed the highest of these risks. Indeed, although this study entailed full multivariable adjustment,

data from the study suggest that limited adjustment (eg, for age and sex) yields risk ratios similar to those obtained with full adjustment.

PAD Predicts CBVD

Table 2 shows increased relative risks for CBVD outcomes in those with versus without PAD.^{35,37,39,40,43,48,49} ABI <0.9 was clearly and significantly associated with increased nonfatal (but not fatal) stroke in 1 study⁴³; in another analysis, severity of PAD was monotonically correlated with combined definite and possible stroke or transient ischemic attack.³⁵ A Spanish study found that PAD was associated with increased risk not only of ischemic stroke but also of hemorrhagic stroke (indeed, a somewhat higher risk ratio for hemorrhagic than ischemic stroke was observed).⁴⁸ Of note, PAD has also been associated with worse outcome in patients with stroke.⁵⁰

PAD Predicts CCVD Mortality

Because CAD and CBVD outcomes are increased in those with PAD, an increase in combined CCVD outcomes would be anticipated. Indeed, as Table 3 shows, both combined CCVD morbidity and mortality and CCVD mortality are increased in those with PAD, by all PAD definitions employed, with risk ratios ranging from approximately 2 to 6.^{34,35,37–39,43,45–47,51,52} Again, stringency of PAD criteria may influence the increase in risk for CCVD outcomes; thus, risk ratios for CCVD outcomes calculated from the San Diego population study, employing ABI <0.8 as a PAD criterion (more significant PAD),⁴⁶ are higher than those of studies using a threshold of ABI <0.9.

Another study, not represented in Table 3, is of interest with regard to the predictive power of PAD for CCVD outcomes. In a cohort of 1672 men and 2264 women aged 47 to 99 years participating in the Framingham Study, either absent pedal pulses (considered an indicator of PAD, although with imperfect sensitivity and specificity⁵³) or femoral and carotid bruits were associated with greater increased risk of CAD, congestive heart failure, and CBVD than was glucose intolerance (itself a powerful risk factor), and the combination was a still more potent predictor of CCVD-defining conditions.⁵⁴

PAD Predicts Overall Mortality

Some major risk factors predict CCVD mortality but not overall mortality in key target populations.⁵⁵ In contrast, PAD powerfully predicts overall mortality (Table 4).^{9,34,35,37–39,41,43,45,46,51,56–66} This is true in men and in women, in community cohorts, in medical-based cohorts, and in populations at heightened CCVD risk, such as elderly with systolic hypertension, with risk increases ranging from 50% to 400%. A mortality gradient with increased PAD severity has been shown. In a San Diego population-based study, 10-year mortality progressively increased from normal subjects to those with asymptomatic PAD, to those with severe symptomatic PAD.⁴⁶ The corresponding mortality figures were 15%, 45%, and 75%, respectively, even after adjustment for major CCVD risk factors and baseline CCVD. Similarly, in another study, a marked mortality gradient over 10 years was seen based on noninvasive testing, which progressed from ABI >0.85 (≈20% mortality), to ABI of 0.4 to 0.85 (≈50%), to ABI <0.4 (≈70%).⁶⁰ In a historical cohort study of persons over the

TABLE 1. Prediction of Coronary Disease by PAD

Population	PAD Definition	CAD Outcome	Characteristics	Risk Ratio	95% CI	Adjusted For
Cardiovascular Health Study: n=5714, M&F, age ≥ 65 y, 6-year F/U ³⁴	ABI <0.9	Angina	Medicare-eligible community cohort: (a) No prior CCVD (b) Prior CCVD	(a) 1.3 (b) 1.1	(a) 0.94–1.8 (b) 0.63–1.8	Age, sex, race, Cig, HTN, DM, SBP, DBP, TC, HDL-C, TG, fasting glucose, fasting insulin, creatinine
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ³⁵	(a) Minor asymp PAD (b) Major asymp PAD (c) IC	New angina	Medical based (general practice)	(a) 1.4 (b) 0.94 (c) 2.3*	(a) 0.87–2.3 (b) 0.38–2.3 (c) 1.04–5.1	Age
TACTICS-TIMI-18 Trial: n=2220, M&F, age 61 ± 12 y, F/U for duration of index hospitalization ³⁶	History of PAD (not further defined)	In-hospital CABG	Patients with unstable angina and NSTEMI	1.6*	1.1–2.6	History of prior CABG, elevated troponin, history of prior angina, ST-segment deviation, sex (other variables including age were also evaluated but not retained in final model)
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ³⁵	(a) IC (b) Major asymp PAD (c) Minor asymp PAD	Nonfatal MI§	Medical based (general practice)	(a) 1.2 (b) 1.4 (c) 1.3	(a) 0.52–2.8 (b) 0.77–2.7 (c) 0.80–2.0	Age
HOPE Study : n=8986, M&F, age ≥ 55 y, 4.5-year F/U ³⁷	(a) ABI 0.6–0.9 (without clinical PAD) (b) ABI <0.6 (without clinical PAD) (c) Clinical PAD	Nonfatal MI	CVD (CAD, stroke, PAD) or DM and an additional CAD risk factor¶ but no CHF or LV dysfunction	(a) 1.4 (b) 1.3 (c) 1.4	Test of trend $P < 0.004$ ††	Age, sex, smoking, HTN, history of MI, history of stroke, DM, heart rate, SBP, pulse pressure, creatinine
Cardiovascular Health Study: n=5714, M&F, age ≥ 65 y, 6-year F/U ³⁴	ABI <0.9	CHF	Medicare-eligible community cohort: (a) Prior CCVD (b) No prior CCVD	(a) 1.3 (b) 1.6†	(a) 0.9–1.8 (b) 1.1–2.3	Age, sex, race, Cig, HTN, DM, SBP, DBP, TC, HDL-C, TG, FG, FI, creatinine
HOPE Study : n=8986, M&F, age ≥ 55 y, 4.5-year F/U ³⁷	(a) ABI 0.6–0.9 (without clinical PAD) (b) ABI <0.6 (without clinical PAD) (c) Clinical PAD	CHF hospitalization	CVD (CAD, stroke, PAD) or DM and an additional CAD risk factor¶ but no CHF or LV dysfunction	(a) 1.3 (b) 2.0 (c) 2.2	Test of trend $P < 0.02$	Age, sex, smoking, HTN, history of MI, history of stroke, DM, heart rate, SBP, pulse pressure, creatinine
SHEP screenees: n=1537, M&F, age 75 ± 7 y, 1–2 years' F/U ³⁸	ABI <0.9	CAD M&M#	Hypertensive elderly	1.9	0.9–4.2	Age, sex
Malmö, Sweden patients: n=312, M&F, age 40–69 y, 10-year F/U ³⁹	Plethysmography meets 1 of 4 requirements**	Fatal & nonfatal MI	Referred for plethysmography; excludes DM or severe arterial insufficiency (a) Age 50–54 y: (b) Age 55–69 y:	(a) 1.2 (b) 4.7	(a) NS (b) $P < 0.005$	Age, sex
Prince of Songkla University Hospital (Thailand) patients: n=689, M&F, age 69 ± 8.4 y, F/U after CABG, "perioperative" not otherwise stated ⁴⁰	Presence of prior peripheral artery surgery, obvious aortoiliac stenosis, IC, and absence of pedal and posterior tibial artery pulses	Perioperative MI††	DM without CCVD	3.4†	1.3–8.6	Age, sex, DM, HTN, ejection fraction, preoperative stroke, chronic renal dysfunction
"Men Born in 1914" Study, Malmö, Sweden: n=474, males, age 68 y; 13-year mean F/U ⁴¹	ABI <0.9	Nonfatal MI and CAD death	Population-based cohort of 68-year-old men	1.8	1.1–3.0	Smoking, HTN, blood cholesterol, BMI
THROMBO substudy: n=1045, M&F, age ≥ 21 y, 26-month mean F/U ⁴²	Exertion-related calf, hip, or buttock discomfort when standing that was gone when sitting	CAD death, nonfatal reinfarction or unstable angina	Admitted to coronary care units with a documented MI	2.1‡	1.4–3.1	MI, angina pectoris
THROMBO substudy: n=1045, M&F, age ≥ 21 y, 26-month mean F/U ⁴²	Exertion-related calf, hip, or buttock discomfort when standing that was gone when sitting	CAD death or nonfatal reinfarction	Admitted to coronary care units with a documented MI	3.0‡	1.8–5.3	MI, DM, ejection fraction $\leq 30\%$
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ⁴³	ABI ≤ 0.9	CAD death (fatal MI)	Medical based (general practice)	1.9*	1.03–3.5	Age, sex, angina, MI, DM
Israeli patients excluded from Bezafibrate Infarction Prevention Study: n=14 697, M&F, age 45–78 y, 2.7 ± 1.7 -year F/U ⁴⁴	Clinical history	CAD death	Israeli CAD patients	1.6†	1.4–2.0	Age, sex, smoking, BMI, TC, HDL-C, TG, glucose, heart rate
SHEP screenees: n=1537, M&F, age 75 ± 7 y, 1- to 2-year F/U ³⁸	ABI <0.9	CAD death	Hypertensive elderly	3.2‡	1.4–7.5	Age, sex
Belgian men: n=2023, males, age 40–55 y, 10-year F/U ⁴⁵	ABI <0.9	CAD death	Working men, asymp at baseline	5.0†	1.8–11	Age
San Diego Population Study: n=624, M&F, age 38–82 y, 10-year F/U ⁴⁶	Multiple noninvasive tests	CAD death	Community and employed cohort: (a) No prior CCVD (b) All	(a) 4.3† (b) 6.6‡	(a) 1.4–2.8 (b) 2.9–15	Age, sex, Cig, SBP, HDL-C, LDL-C, log TG, FG, BMI, selection criteria (random vs hyperlipidemic)
THROMBO substudy: n=1045, M&F, age ≥ 21 y, 26-month mean F/U ⁴²	Exertion-related calf, hip, or buttock discomfort when standing that was gone when sitting	CAD death	Admitted to coronary care units with a documented MI	6.6‡	2.9–15	MI, stroke, ejection fraction $\leq 30\%$

TABLE 1. Continued

Asymp indicates asymptomatic; BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; Cig, cigarettes; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FG, fasting glucose; FI, fasting insulin; F/U, follow-up; HDL-C, HDL cholesterol; HOPE, Heart Outcomes Prevention Evaluation; HTN, hypertension; IC, intermittent claudication; LDL-C, LDL cholesterol; LV, left ventricular; M&F, male and female; M&M, morbidity and mortality; n, No. enrolled; NS, nonsignificant; NSTEMI, non-ST-segment elevation MI; SBP, systolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; TACTICS-TIMI-18, Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction-18; TC, total cholesterol; TG, triglycerides; THROMBO, Thrombogenic Factors and Recurrent Events study; and SBP, systolic blood pressure.

Two significant digits given for risk ratios/CIs except for values from 0.995 to 1.05. Here, additional digits are preserved to enable recognition of whether point estimate was less than or greater than 1.0.

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

§Definite and possible nonfatal MI.

||Risk ratios calculated from published table (unadjusted); P values for trend provided in published table (adjusted).

¶Risk factors include smoking, HTN, low HDL-C, hypercholesterolemia, and microalbuminuria.

#No clear definition for CCVD M&M was given in the paper itself or in the methods reference cited by the paper.⁴⁷ The methods reference paper does, however, define "cardiovascular disease" to include nonfatal or fatal MI, sudden and rapid cardiac death, CABG, angioplasty, nonfatal or fatal stroke, transient ischemic attack, aneurysm, and endarterectomy. This definition appears to exclude nonfatal or fatal LV failure, which were, however, tallied.

**Findings meet 1 of the following: (1) First flow < 14 mL/min $\times 100$ g; (2) amplitude of pulsation during maximal flow < 3 mm; (3) maximal flow < 17 mL/mm $\times 100$ g; and (4) delay time of maximal flow after release of arterial stasis ≥ 10 seconds.

††Apparently all were nonfatal; although deaths in this study were "mainly the result of cardiac problems," none were ascribed to MI.

‡‡Test of trend evaluates outcomes for ABI > 0.9 , ABI 0.6–0.9, ABI < 0.6 , and clinical PAD.

age of 40 years with PAD who had undergone previous ABI testing (PAD defined as ABI < 0.9) for whom data on mortality or occurrence of a vascular event were available (average 6 years of follow-up), the relative risk for mortality was 3.1 per 0.50 decrease of the ABI at rest.⁶⁷ Data from the Edinburgh Artery Study population also suggest a survival gradient with PAD severity, whether measured by ABI³⁵ or by "severity" gradient from minor asymptomatic disease through major asymptomatic disease to intermittent claudication.³⁵

As Table 4 also illustrates, PAD predicts increased mortality not only in general or medical populations but also in specialized populations defined by cardiovascular events or surgery,^{56,57,59,61,63,65} such as patients with acute MI^{56,59} or those undergoing coronary artery bypass grafting⁶⁵ (including both in-hospital mortality, after multivariate adjustment,⁶¹ and long-term mortality among that subset discharged alive⁶³). Associations of PAD with mortality and events have also been reported in subjects enrolled in randomized trials of drug treatment.⁶⁸ Notably, among PAD patients, lower ABI predicts greater mortality and cardiovascular morbidity.³⁷ Increased total mortality with PAD has been further shown in association with noncardiovascular events and surgery (not shown in Table 4). Thus, among patients undergoing renal transplant, low toe blood pressure or "toe brachial index," present in 32% of diabetics and 16% of nondiabetics, was associated with reduced survival.⁶⁹ In addition, peripheral atherosclerosis may be associated with increased complications and death in trauma patients. It has been theorized that even if the trauma does not directly affect diseased vessels, hypotension resulting from major trauma may lead to increased risk of thrombosis in vessels that have critical stenosis; moreover, if a diseased vessel is itself injured, bypass may be difficult, and amputation may be required.⁷⁰

Discussion

Data across many studies robustly support the finding that PAD cross-sectionally relates to CCVD morbidity and mortality, and more importantly, that PAD is a strong prospective predictor of CCVD morbidity and mortality and total mortality, independent of other adjusted risk factors. More stringent

criteria for PAD increase the strength of association, compatible with a biological gradient.

Additional observations substantiate the importance of these findings. PAD in the absence of known CAD predicted cardiovascular events more strongly than did CAD in the absence of PAD in the Heart Protection Study (30.5% versus 22.5% event rate, placebo group).⁷¹ Elsewhere, in CAD patients, PAD was found to be a stronger risk factor for CCVD death and total mortality than prior MI.⁵⁷

The basis of the "independent" association of PAD to CCVD remains incompletely characterized. PAD may be a proxy for generalized atherosclerotic disease burden and shared unmeasured risk factors, and/or it may itself causally induce increased risk. Because PAD shares with CAD and CBVD a number of CCVD risk factors, heightened risk of cardiovascular morbidity and mortality would be anticipated due to shared risk factors. The relation of PAD to future outcomes is preserved after adjustment for other recognized risk markers, which suggests that PAD confers independent risk for CAD and total mortality beyond that attributable to shared risk factors. Nonetheless, the prognostic significance of PAD could derive purely from its role as a proxy for generalized atherosclerotic disease burden and unmeasured common risk factors: Most studies do not adjust for all recognized risk factors, and even after adjustment, the possibility of residual confounding remains. Moreover, emerging risk factors for CCVD have been identified that are not adjusted in existing analyses, and new risk factors for CCVD continue to be defined. If PAD serves exclusively as a proxy for a cadre of potent and less potent CCVD risk factors and generalized atherosclerotic disease burden, its importance as a risk marker is not diminished; rather, the determination that increased risk is present dictates a need for more aggressive risk factor reduction.

Nonetheless, if PAD is in addition causally involved in promoting CCVD events or death, this may influence the approach to PAD and CCVD management. Two mechanisms were identified by which PAD may causally promote CCVD events and death. First and most obviously, clinical PAD reduces the ability to ambulate, and exercise is protective

TABLE 2. Prediction of CBVD by PAD

Population	PAD Definition	CBVD Outcome	Characteristics	Risk Ratio	95% CI	Adjusted For
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ⁴³	ABI ≤0.9	Nonfatal stroke	Medical based (general practice)	2.0*	1.05–3.8	Age, sex, angina, MI, DM
HOPE Study : n=8986, M&F, age ≥55 y, 4.5-year F/U ³⁷	(a) ABI 0.6–0.9 (without clinical PAD); (b) ABI <0.6 (without clinical PAD); (c) Clinical PAD	Nonfatal stroke	CVD (CAD, stroke, PAD) or DM and an additional CAD risk factor [¶] but no CHF or LV dysfunction	(a) 1.2 (b) 1.7 (c) 2.1	Test of trend <i>P</i> <0.0001 unadjusted; 0.24 adjusted	Age, sex, smoking, HTN, history of MI, history of stroke, DM, heart rate, SBP, pulse pressure, creatinine
Edinburgh artery study: n=1592 M&F, age 55–74 y, 5-year F/U ³⁵	(a) Minor asymp PAD (b) Major asymp PAD (c) IC	TIA or nonfatal stroke (definite and possible)	Medical based (general practice)	(a) 1.1 (b) 1.4 (c) 2.0	(a) 0.56–2.3 (b) 0.59–3.5 (c) 0.8–5.0	Age
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ⁴³	ABI ≤0.9	Fatal stroke	Medical based (general practice)	0.91	0.31–2.7	Age, sex, angina, MI, DM
Spain: n=928, M&F, age 40–85, 9-month F/U ⁴⁸	IC	(a) Stroke - cerebral infarct (b) Stroke - cortical infarct (c) Hemorrhagic stroke (d) Total stroke (fatal or nonfatal not stated)	Case-control and population-based study	(a) 3.2† (b) 3.1† (c) 5.0† (d) 3.4†	(a) 1.5–6.8 (b) 1.3–7.7 (c) 2.0–12 (d) 1.7–7.3	Age, sex, alcohol, smoking, HTN, hyperglycemia, and heart disease
Malmö, Sweden patients: n=312, M&F, age 40–69 y, 10 year F/U ³⁹	Plethysmography meets 1 of 4 requirements‡	Stroke - nonfatal and fatal	Referred for plethysmography; excludes DM or severe arterial insufficiency (a) Age 40–54 y (b) Age 55–69 y	(a) 4.9 (b) 3.6	NS	Age, sex
Prince of Songkla University Hospital (Thailand) patients: n=689, M&F, age 69±8.4 y, F/U after CABG, “postoperative not otherwise stated” [§] ⁴⁰	Prior peripheral artery surgery, obvious aortoiliac stenosis, IC, and absence of pedal and posterior tibial artery pulses	Stroke: “cerebral infarction”	Type II DM patients aged >20 y, no history of CVD, CAD, or stroke	0.71	0.17–3.0	Age, sex, DM, HTN, ejection fraction, preoperative stroke, chronic renal dysfunction
San Diego Population Study: n=624, M&F, age 38–82 y, 10-year F/U ⁴⁹	Multiple noninvasive tests	Cerebrovascular M&M#	Community and employed cohort (a) Male (b) Female	(a) 3.3* (b) 9.0†	(a) 1.1–9.3 (b) 2.3–36	Age, BMI, Cig, FG, log plasma TG, HDL-C, LDL-C, SBP

TIA indicates transient ischemic attack. Other abbreviations as in Table 1.

Two significant digits given for risk ratios/CIs except for values from 0.995 to 1.05. Here, additional digits are preserved to enable recognition of whether point estimate was less than or greater than 1.0.

**P*<0.05; †*P*<0.01.

‡(1) First flow <14 mL/min×100 g; (2) amplitude of pulsation during maximal flow <3 mm; (3) maximal flow <17 mL/mm×100 g; and (4) delay time of maximal flow after release of arterial stasis ≥10 sec.

§Follow-up not defined; cited as “postoperative” (stroke).

||Risk ratios calculated from published table (unadjusted); *P* values for trend provided in published table (adjusted).

¶Risk factors include smoking, HTN, low HDL-C, hypercholesterolemia, and microalbuminuria.

#Defined as fatal and nonfatal stroke.

against CAD and CBVD, in part through its beneficial effects on prominent risk factors, including insulin resistance, hypertension, and dyslipidemia. This consideration is not limited to patients with classic intermittent claudication. Many persons with PAD reported atypical, vague, or nonspecific symptoms, including fatigue and numbness. Although atypical, such symptoms also limit ambulation.

Second, PAD may directly promote myocardial and cerebral ischemia. PAD is linked to impaired peripheral endothelial function, with impaired vasodilation (or even vasoconstriction) in response to certain challenges such as stress. This appears responsible for the fall in left ventricular ejection fraction with stress seen in some CAD patients: Only those whose peripheral vascular resistance increased experienced

TABLE 3. Prediction of Cardiovascular Disease (Coronary and Cerebrovascular) by PAD

Population	PAD Definition	CCVD Outcome	Characteristics	Risk Ratio	95% CI	Adjusted For
HOPE Study [§] : n=8986, M&F, age ≥ 55 y, 4.5-year F/U ^{§7}	(a) ABI 0.6–0.9 (without clinical PAD); (b) ABI <0.6 (without clinical PAD); (c) Clinical PAD	CCVD M&M: (CVD mortality, MI, stroke)	CVD (CAD, stroke, PAD) or DM and an additional CAD risk factor but no CHF or LV dysfunction	(a) 1.4 (b) 1.4 (c) 1.7	Test of trend $P < 0.0003$	Age, sex, smoking, HTN, history of MI, history of stroke, DM, heart rate, SBP, pulse pressure, creatinine
SHEP screenees: n=1537, M&F, age 75 ± 7 y, 1- to 2-year F/U ^{§8}	ABI <0.9	CCVD: M&M¶	Hypertensive elderly	2.5†	1.5–4.3	Age, sex
Cardiovascular Health Study: n=5714, M&F, age ≥ 65 y, 6-year F/U ^{§4}	ABI <0.9	CCVD mortality	Medicare-eligible community cohort: Prior CCVD	1.5*	1.1–2.2	Age, sex, race, Cig, HTN, DM, SBP, DBP, TC, HDL-C, TG, FG, FI, creatinine
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ^{§5}	ABI <0.9	CCVD mortality	Medical (general practice) based	1.9†	1.2–3.0	Age, sex, angina, MI, DM
HOPE Study [§] : n=8986, M&F, age ≥ 55 y, 4.5-year F/U ^{§7}	(a) ABI 0.6–0.9 (without clinical PAD); (b) ABI <0.6 (without clinical PAD); (c) Clinical PAD	CCVD mortality	CVD (CAD, stroke, PAD) or DM and an additional CAD risk factor but no CHF or LV dysfunction	(a) 1.6 (b) 1.8 (c) 2.3	Test of trend $P < 0.0001$	Age, sex, smoking, HTN, history of MI, history of stroke, DM, heart rate, SBP, pulse pressure, creatinine
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ^{§5}	(a) Minor asymp PAD (b) Major asymp PAD (c) IC	CCVD mortality	Medical (general practice) based	(a) 1.7* (b) 2.1* (c) 2.7†	(a) 1.1–2.8 (b) 1.1–3.8 (c) 1.3–5.3	Age
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ^{§5}	ABI <0.9	CCVD mortality	Medical (general practice) based	1.9†	1.2–3.0	Age, sex, angina, MI, DM
Cardiovascular Health Study: n=5714, M&F, age ≥ 65 y, 6-year F/U ^{§4}	ABI <0.9	CCVD mortality	Medicare-eligible community cohort: (a) Prior CCVD (b) No prior CCVD	(a) 1.5* (b) 2.0†	(a) 1.1–2.2 (b) 1.2–3.4	Age, sex, race, Cig, HTN, DM, SBP, DBP, TC, HDL-C, TG, FG, FI, creatinine
getABI Study: n=6880, M&F, age 72.5 ± 5.3 y, 1-year F/U ^{§1}	ABI <0.9	CCVD: mortality	Elderly	(a) 2.0 (b) 2.9	(a) 1.1–3.8 (b) 1.6–5.2	(a) Age, sex, Cig, history of severe cardiac or cerebral event, DM, HTN, lipid disorders, homocysteine $>19.1 \mu\text{mol/L}$ (b) Age, sex
Italian patients: n=297, M&F, mean age 69 y (those with IC) and 84 y (those with critical ischemia), 4.0 \pm 3.0-year F/U ^{§2}	Symptomatic PAD (all had ABI <0.9)	CCVD mortality	White patients with symptomatic PAD at the University of Perugia, Italy	3.7	2.0–6.7	Age
SHEP screenees: n=1537, M&F, age 75 ± 7 y, 1- to 2-year F/U ^{§8}	ABI <0.9	CCVD mortality	Hypertensive elderly	3.7†	1.8–7.7	Age, sex
Belgian men: n=2023, age 40–55 y, 10-year F/U ^{§5}	ABI <0.9	CCVD mortality	Working men, asymp at baseline	4.2*	1.7–10	Age
San Diego population-based: n=474, M&F, age 38–82 y, 10-year F/U ^{§6}	Multiple objective	CCVD mortality	Community and employed cohort: (a) All (b) No CCVD, n=415	(a) 5.9‡ (b) 6.3‡	(a) 3.0–11 (b) 2.6–15	Age, sex, Cig, SBP, HDL-C, LDL-C, log TG, FG, BMI, selection criteria (random sample vs hyperlipidemia)
Malmö, Sweden patients: n=312, M&F, age 40–69 y, 10-year F/U ^{§9}	Plethysmography meets 1 of 4 requirements#	CCVD mortality	Referred for plethysmography; excludes DM or severe arterial insufficiency	4.4	$P < 0.001$ (calculated from data given)	None

Abbreviations as in Table 1.

Two significant digits given for risk ratios/confidence intervals except for values from 0.995 to 1.05. Here additional digits are preserved to enable recognition of whether point estimate was less than or greater than 1.0.

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

§Risk ratios calculated from published table (unadjusted), P values for trend provided in published table (adjusted).

||Risk factors include smoking, HTN, low HDL-C, hypercholesterolemia, and microalbuminuria.

¶No clear definition for CCVD M&M was given in the paper or in a reference cited by the paper.⁴⁷ The referenced paper does, however, define “cardiovascular disease” to include nonfatal or fatal MI, sudden and rapid cardiac death, CABG, angioplasty, nonfatal or fatal stroke, transient ischemic attack, aneurysm, and endarterectomy. This definition appears to exclude nonfatal or fatal LV failure, which were, however, tallied.

#(1) First flow $<14 \text{ mL/min} \times 100 \text{ g}$; (2) amplitude of pulsation during maximal flow $<3 \text{ mm}$; (3) maximal flow $<17 \text{ mL/mm} \times 100 \text{ g}$; and (4) delay time of maximal flow after release of arterial stasis ≥ 10 seconds.

this left ventricular ejection fraction reduction, which reduced stroke volume and cardiac output.⁷² CAD patients show abnormal coronary vasoconstriction (or loss of vasodilation) in response to endogenous stimuli such as acetylcholine, an effect that can be reproduced in animals by inducing coronary occlusion.⁷³ Analogously, peripheral ischemia—and PAD

patients—may show abnormal peripheral vasoconstriction in response to stress and other stimuli. The loss of normal vasodilation, or paradoxical vasoconstriction, may provoke a relative drop in ejection fraction and cardiac output, reducing oxygen delivery to vital organs during stress. PAD may thereby increase events in patients with otherwise comparable

TABLE 4. Prediction of Overall Mortality by PAD

Population	PAD Definition	Characteristics	Risk Ratio	95% CI	Adjusted For
Belgian consecutive admissions to CCU for AMI; n=1669, M&F, 5.5-year mean F/U ⁵⁶	Mixed: includes PAD and CBVD	CCU-based, post-MI (after MI recovery)	R=0.27	0.17–0.38; P<0.0001 for death§	Age, abnormal radiograph, Killip class, medications, weight, SBP, ventricular arrhythmias, DM, abnormal precordial pulsations
Coronary Artery Surgery Study: M&F, n=13 953 without PAD or CBVD; and n=1703 with PAD, age 54±9 y, 10-year mean F/U ⁵⁷	PAD if documented IC or absent pulses; or previous abdominal aortic or peripheral artery surgery	CAD patients	1.2†	P<0.003	LV systolic pressure, age, smoking, CHF, DM, LV EF, LV score, therapy, HTN, CAGE50, chronic lung disease, Canadian Heart Foundation class, prior MI
“Men Born in 1914” Study, Malmö, Sweden: n=474, males, age 68 y; 13-year mean F/U ⁴¹	ABI <0.9	Population-based cohort of 68-year-old men	2.0	1.4–2.9	Smoking, HTN, blood cholesterol, BMI
HOPE Study : n=8986 M&F, age ≥55 y, 4.5-year F/U ³⁷	(a) ABI 0.6–0.9 (without clinical PAD); (b) ABI <0.6 (without clinical PAD); (c) Clinical PAD	CVD (CAD, stroke, PAD) or DM and an additional CAD risk factor¶ but no CHF or LV dysfunction	(a) 1.5 (b) 1.7 (c) 2.1	Test of trend <0.0001	Age, gender, smoking, HTN, history of MI, history of stroke, DM, heart rate, SBP, pulse pressure, creatinine
Cardiovascular Health Study: n=5714, M&F, age ≥65 y, 6-year F/U ³⁴	ABI <0.9	Medicare-eligible community cohort: (a) Prior CVD (b) No prior CVD	(a) 1.5† (b) 2.4‡	(a) 1.2–1.9 (b) 1.9–3.1	Age, sex, race, Cig, HTN, DM, SBP, DBP, TC, HDL-C, TG, FG, FI, creatinine
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ⁴³	ABI ≤0.9	Medical (general practice) based	1.6†	1.1–2.1	Age, sex, angina, MI, DM
Edinburgh artery study: n=1592, M&F, age 55–74 y, 5-year F/U ³⁵	(a) Minor asymp PAD (b) Major asymp PAD (c) IC	Medical (general practice)-based	(a) 1.2 (b) 2.4‡ (c) 1.6	(a) 0.82–1.7 (b) 1.6–3.7 (c) 0.86–2.8	Age
Montefiore University Hospital peripheral vascular disease patients: n=1930, M&F, age >75 y, mean F/U men 3.9 y; women, 3.6 y ⁵⁸	Determined by Rose Questionnaire; ABI <0.9 (a) Mild PAD (ABI 0.90–0.71) (b) Moderate PAD (ABI 0.70–0.51) (c) Severe PAD (ABI ≤0.50)	Referred for arterial evaluation (a) Mild PAD (i) Male (ii) Female (b) Moderate PAD (i) Male (ii) Female (c) Severe PAD (i) Male (ii) Female	(a) (i) 1.2 (ii) 0.95 (b) (i) 1.6 (ii) 1.7 (c) (i) 2.0 (ii) 2.1	(a) (i) 0.77–1.7 (ii) 0.57–1.6 (b) (i) 1.2–2.2 (ii) 1.2–2.4 (c) (i) 1.4–2.7 (ii) 1.5–3.1	Age
Israeli CCU screened for SPRINT study: 5839, M&F, age 62±11 y, 5.5-year mean F/U ⁵⁹	IC or paresthesia at rest, confirmed with asymmetric, attenuated, or absent pulse on extremity	CCU-based, post-MI (a) (i) In-hospital (ii) 1-year (iii) 5-year (b) (i) In hospital (ii) 5-year	(a) (i) 1.8 (ii) 1.7 (iii) 1.5 (b) (i) 1.4 (ii) 1.02	(a) (i) P≤0.001 (ii) P≤0.005 (iii) P≤0.001 (b) 90% CI (i) 1.03–1.8 (ii) NS	(a) Unadjusted (b) Age, sex, HTN, angina, DM, stroke, site of infarction, CHF on admission
Patients referred by Mayo Clinic in Rochester, Minn: n=573, M&F, age 50–70 y, 4-year F/U ⁹	Clinical history and/or below 5th percentile of distribution of mean ABI values	DM, PAD, or both (a) With DM (b) Without DM	(a) 1.9† (b) 0.95	(a) 1.9–2.9 (b) 0.55–1.5	Age, sex, baseline ABI
Copenhagen consecutively referred IC patients: n=257, M&F, age 36–85 y, 6.5-year F/U ⁶⁰	IC	Referral patients: IC without rest pain, ulcers, or gangrene	2.2#	Significant	Age, sex

TABLE 4. Continued

Population	PAD Definition	Characteristics	Risk Ratio	95% CI	Adjusted For
Northern New England Cardiovascular Disease Study Group: regional cohort in hospital. n=3003, M&F, age mean 62, in-hospital F/U ⁶¹	PAD: IC, amputation, LE revascularization; absent pedal pulses	In-hospital, post-CABG, no concurrent CBVD (a) All (b) Clinical PAD (c) Subclinical PAD	(a) 2.0† (b) 1.9† (c) 2.2†	(a) 1.3–3.1 (b) 1.2–3.2 (c) 1.3–3.1	Age, EF, No. of vessels with >70% stenosis, modified Charlson comorbidity index, Cig, use of internal mammary artery graft
Strong Heart Study: n=4393, M&F, age 45–74 y, 8-year mean F/U ⁶²	(a) ABI <0.9 (vs 0.9–1.4) (b) ABI >1.4 (vs 0.9–1.4)	American Indians	(a) 2.1 (b) 2.2	(a) 1.9–3.0 (b) 1.8–2.7	None
Northern New England Cardiovascular Disease Study Group: consecutive patients discharged alive after CABG at 5 tertiary referral centers; n=2871, M&F, mean age 62 y, 4.4-year mean F/U ⁶³	PAD: IC, amputation, LE revascularization; absent pedal pulses	Discharged after successful CABG, no concurrent CBVD (a) All (b) Clinical PAD (c) Subclinical PAD	(a) 2.1† (b) 2.1† (c) 2.0†	(a) 1.4–2.9 (b) 1.3–3.3 (c) 1.2–3.4	Age, EF, No. of vessels with >70% stenosis, modified Charlson comorbidity index, Cig, use of internal mammary artery graft
University-affiliated community hospital; n=744; M&F, 10-year F/U ⁶⁴	ABI <0.85	Medical based	2.4	1.6–3.5	Age, SBP
Northern New England Cardiovascular Disease Study Group: post CABG, n=2817, M&F, age unstated, 5-year F/U ⁶⁵	IC, LE bypass, amputation, absent pedal pulse, AAA.	Post-CABG long-term outcomes	2.5 mortality ratio vs CAD alone	$P \leq 0.001$ ††	Age, sex (relative to Canada Population Table)
Malmö, Sweden patients: n=312, M&F, age 40–69 y, 10 year F/U ⁶⁹	Plethysmography meets 1 of 4 requirements**	Referred for plethysmography; excludes DM or severe arterial insufficiency	2.9	$P < 0.001$	None
getABI Study: n=6880, M&F, age 72.5±5.3 y, 1-year F/U ⁵¹	ABI <0.9	Elderly	(a) 2.7 (b) 2.0	(a) 1.7–4.2 (b) 1.3–3.3	(a) Age, sex (b) Age, sex, Cig, history of severe cardiac or cerebral event, DM, HTN, lipid disorders, homocysteine >19.1 μmol/L
Belgian men; n=2023, male, age 40–55 y (47±4 y), 10-year F/U ⁴⁵	ABI <0.9	Working men, asymp at baseline	2.8†	1.4–5.5	Age
San Diego population study; n=474, M&F, age 38–82 y, 10-year F/U ⁴⁶	By segmental BP and flow velocity by Doppler	Community and employed cohort: (a) All (b) No CVD (n=415)	(a) 3.1‡ (b) 3.1‡	(a) 1.9–4.9 (b) 1.8–5.3	Age, sex, Cig, SBP, HDL-C, LDL-C, log TG, FG, BMI, selection criteria (random sample vs hyperlipidemia)
Framingham cohort, n=5029, M&F, 10-year mortality F/U (after onset of IC) ⁶⁶	IC	Population cohort, total (a) Male (b) Female	(a) 2.2 (b) 4.1	(a) $P < 0.001$ (b) $P < 0.001$	Unadjusted
SHEP screenees: n=1537, M&F, age 75±7 y, 1- to 2-year F/U ⁶⁸	ABI <0.9	Hypertensive elderly	3.8‡	2.1–6.9	Age, sex

AAA indicates abdominal aortic aneurysm; AMI, acute MI; BP, blood pressure; CAGE50, number of coronary segments with stenosis $\geq 50\%$; CCU, coronary care unit; EF, ejection fraction; LE, lower extremity; and SPRINT, Secondary Prevention Reinfarction Israel Nifedipine Trial. Other abbreviations as in Table 1.

Two significant digits given for risk ratios/CIs except for values from 0.995 to 1.05. Here, additional digits are preserved to enable recognition of whether point estimate was less than or greater than 1.0.

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

§Peripheral vascular disease is 1 of the 3 most significant predictors of post-MI death, with age and abnormal chest radiograph; exceeds risk by prior MI or DM.

||Risk ratios calculated from published table (unadjusted); P values for trend provided in published table (adjusted).

¶Risk factors include smoking, HTN, low HDL-C, hypercholesterolemia, or microalbuminuria.

#Calculated from Figure 2 of reference. P value not calculable because the denominator was not given for the control group.

** (1) First flow <14 mL/min \times 100 g; (2) amplitude of pulsation during maximal flow <3 mm; (3) maximal flow <17 mL/mm \times 100 g; and (4) delay time of maximal flow after release of arterial stasis ≥ 10 seconds.

†† P value calculated from the death rates given.

CAD or CBVD. Consistent with this possibility, PAD patients with worse peripheral endothelial dysfunction experience more major cardiovascular events.⁷⁴

Although asymptomatic PAD strongly predicted most CCVD outcomes, major asymptomatic PAD was, strikingly, not associated with an increase in new angina, in contrast to findings for symptomatic PAD. This finding could have a foundation in pathways involved in pain perception. Patients who are free of pain despite major disease in 1 site (as with major asymptomatic PAD) may more likely be free of pain when disease arises in another vascular bed, as suggested by an increase in total MI but no trend toward increased angina. In contrast, symptomatic PAD (intermittent claudication) was associated with a strong and significant increase in symptomatic disease in the other site (angina). Individual differences in endogenous pain-signaling systems (including but not confined to opioid, substance P, serotonin, and nicotinic and muscarinic cholinergic signaling systems) and exogenous influences on pain (eg, caffeine, nicotine, antidepressants, corticosteroids, aspirin, and nonsteroidal antiinflammatory drugs) may modify perception of pain in both sites in parallel. Additionally, some factors, such as proinflammatory cytokines, conjointly dispose to cardiovascular disease and increased pain,^{75–77} whereas others, like hyperglycemia and glycation end products, dispose both to cardiovascular disease and impaired pain perception.⁷⁸ Thus, different profiles of cardiovascular disease–related mediators could typify persons who have and those who do not have pain, an avenue that can be explored in future research.

The data presented have several limitations. First, study populations and criteria for PAD and for CCVD outcomes varied across studies, which precludes pooled analysis; however, preservation of the qualitative finding despite this heterogeneity underscores the robustness of the association. Second, many studies did not control for all recognized and potential cardiovascular risk factors. The role of PAD as an independent predictor will merit ongoing reappraisal as CCVD risk factors emerge. Finally, the data are observational; however, randomized trial data would not strengthen the character of inference with regard to risk prediction by PAD, which is not predicated on causality. Moreover, interventions targeted to reduce PAD may reduce CCVD in parallel, rather than through their impact on PAD, so such data would do little to address the issue of a causal role for PAD in elevating CCVD risk.

The findings presented have important implications. Although PAD is linked strongly and apparently independently with CCVD morbidity and mortality, perhaps more strongly than prior MI, PAD is less emphasized and less systematically evaluated than other atherosclerotic conditions or risk factors such as hyperlipidemia and hypertension.² Moreover, once PAD is detected, treatment of atherosclerotic risk factors and prevention of atherothrombotic events is less reliably undertaken than in patients with CAD,^{2,79} although the future risk of atherosclerotic events and deaths is equivalent or greater. Although it has been known for many years that even mild, asymptomatic PAD increases the risk of cardiovascular disease events,⁴⁶ which impels (high) risk stratification based on the presence of PAD, recent clinical trial data showing the

benefits of both lipid therapy⁷¹ and antiplatelet therapy⁷¹ in PAD patients in preventing cardiovascular disease events provide a strong evidence base for aggressive medical therapy in these patients. Given the strong prognostic significance of PAD, ABI assessment may merit a more central role in CCVD risk assessment and in dictating receipt of cardiovascular protective treatments. Of note, in light of the escalating prevalence of PAD with advancing age, the role of PAD in adjudicating risk can be expected to assume mounting importance as the population ages.

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