Secondary Prevention and Mortality in Peripheral Artery Disease

National Health and Nutrition Examination Study, 1999 to 2004

Reena L. Pande, MD; Todd S. Perlstein, MD, MMSc;
Joshua A. Beckman, MD, MSc; Mark A. Creager, MD

Background—Whether individuals with peripheral artery disease (PAD) identified by screening ankle-brachial index benefit from preventive therapies to reduce cardiovascular risk is unknown. We aimed to determine the number of US adults with PAD who are not receiving preventive therapies and whether treatment is associated with reduced mortality in PAD subjects without known cardiovascular disease.

Methods and Results—We analyzed data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004 with mortality follow-up through December 31, 2006. We defined PAD as an ankle-brachial index ≤0.90. Of 7458 eligible participants ≥40 years, weighted PAD prevalence was 5.9±0.3% (mean±SE), corresponding to ≈7.1 million US adults with PAD. Statin use was reported in only 30.5±2.5%, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use in 24.9±1.9%, and aspirin use in 35.8±2.9%, corresponding to 5.0 million adults with PAD not taking statins, 5.4 million not taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 4.5 million not receiving aspirin. After adjustment for age, sex, and race/ethnicity, PAD was associated with all-cause mortality (hazard ratio, 2.4; 95% confidence interval, 1.9 to 2.9; $P<0.0001$). Even after exclusion of individuals with known cardiovascular disease, subjects with PAD had higher mortality rates (16.1±2.1%) than subjects without PAD or cardiovascular disease (4.1±0.3%), with an adjusted hazard ratio of 1.9 (95% confidence interval, 1.3 to 2.8; $P=0.001$). Among PAD subjects without cardiovascular disease, use of multiple preventive therapies was associated with 65% lower all-cause mortality (hazard ratio, 0.35; 95% confidence interval, 0.20 to 0.86; $P=0.02$).

Conclusions—Millions of US adults with PAD are not receiving secondary prevention therapies. Treatment with multiple therapies is associated with reduced all-cause mortality. (***Circulation*. 2011;124:17-23.**)

Key Words: cardiovascular diseases ■ mortality ■ peripheral arterial disease ■ peripheral vascular diseases ■ secondary prevention

Cardiovascular disease remains a major cause of morbidity and mortality in the United States. Individuals with peripheral artery disease (PAD), a manifestation of systemic atherosclerosis, are known to be at significantly increased risk of adverse cardiovascular events regardless of symptoms.[1,2] Despite multiple treatments known to decrease cardiovascular risk, several studies have shown that PAD remains underrecognized and undertreated.[3,4] However, the number of individuals in the United States with PAD who are not receiving preventive therapies that may reduce the risk of myocardial infarction, stroke, or death remains unknown.

Clinical Perspective on p 23

Current guidelines for the management of patients with PAD recommend lipid-lowering therapy with a statin to achieve a goal low-density lipoprotein (LDL) <100 mg/dL (or <70 mg/dL in high-risk patients)[5,6]; antihypertensive therapy to achieve a systolic blood pressure <140 mm Hg, recognizing that angiotensin-converting enzyme (ACE) inhibitors may have a unique role[7]; and antiplatelet therapy.[8] Most trials of secondary prevention have included PAD patients with previously recognized and symptomatic disease (such as intermittent claudication or prior peripheral revascularization), but whether these guidelines can be extended to patients with PAD identified by population screening, the majority of whom are likely to be asymptomatic, has not been well studied.

The ankle-brachial index (ABI) is a simple noninvasive test that can identify high-risk adults with PAD.[9–11] However, it is not known whether secondary prevention therapies can reduce mortality in patients identified solely by population-based ABI screening, especially in those without other manifestations of atherosclerotic vascular disease in whom these preventive therapies would already be indicated. Fur-

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From the Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA.
Guest editor for this article was William R. Hiatt, MD.
Correspondence to Reena L. Pande, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115.

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thermore, recent studies have called into question certain preventive therapies, aspirin therapy in particular, in patients with PAD.[12–14] This lack of evidence for screening-guided use of treatments for patients with unrecognized PAD has precluded the US Preventive Services Task Force from recommending screening for PAD with the ABI.[15]

We used the National Health and Nutrition Examination Survey (NHANES) to estimate the absolute number of US adults at high risk based on a low screening ABI who are not receiving preventive therapies recommended by established guidelines.[1,2] Furthermore, we aimed to determine whether treatment with multiple risk factor–modifying therapies was associated with reduced all-cause morality in adults identified with PAD who are otherwise free of established cardiovascular disease (CVD).

Methods

NHANES is an ongoing series of surveys that have been conducted by the National Center for Health Statistics since the early 1960s to assess the heath and nutritional status of the civilian US population using a complex, stratified, multistage survey design. NHANES has been reviewed and approved by the Institutional Review Board at the National Center for Health Statistics.

Ankle-Brachial Index

During the survey years of 1999 to 2004, ABI measurements were obtained as part of the NHANES lower-extremity examination in adults ≥40 years of age. With subjects in the supine position, systolic blood pressure was measured in the right arm and in the posterior tibial arteries at both ankles with an 8-MHz Doppler probe. We calculated the ABI for each leg by dividing the ankle pressure by the arm pressure. A diagnosis of PAD was assigned if either leg had an ABI ≤0.90.

Definitions of Variables of Interest

Age, sex, race/ethnicity, smoking status, and history of atherosclerotic CVD were based on self-report, as previously reported.[16,17] Diagnosis of CVD was based on an affirmative response to the question, "Has a doctor or other health professional ever told you that you had (coronary heart disease, angina [also called angina pectoris], heart attack [also called myocardial infarction], stroke)?" A diagnosis of hypertension was assigned if subjects reported a prior physician diagnosis of hypertension, if the measured SBP was ≥140 mmHg and/or diastolic blood pressure ≥90, or if subjects self-reported taking a prescription medication for hypertension. Hyperlipidemia was considered present if subjects reported a physician diagnosis of elevated cholesterol or had a total cholesterol level ≥240 mg/dL (6.21 mmol/L). The LDL levels were available in a subset of participants (n=3224) who had fasting blood samples drawn. Subjects were considered to have diabetes mellitus if they reported a physician diagnosis, were taking prescription medications for diabetes mellitus (either insulin or oral agents), or had blood nonfasting glucose values ≥200 mg/dL (11.1 mmol/L) or fasting glucose values ≥126 mg/dL (7 mmol/L). The Modification of Diet in Renal Disease study equation was used to estimate glomerular filtration rate, and estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot m^{-2}$ indicated chronic kidney disease.[18] Socioeconomic status was categorized on the basis of the poverty-income ratio, a ratio of self-reported income relative to the poverty threshold, with poverty-income ratio <1.0 indicating income below poverty level. Other self-reported socioeconomic variables included highest education level attained and health insurance status.

Definition of Preventive Treatments

Medication use was ascertained by self-report, and NHANES interviewers confirmed medication use by direct visualization of all prescription medication containers when available. Medication dose was not available. We specifically chose to evaluate guideline-recommended treatments: antiplatelet therapy (including aspirin, clopidogrel, dipyridamole, ticlopidine, or combinations), any statin therapy, and any ACE inhibitor or angiotensin receptor blocker (ARB).[1] We did not include treatments that would be indicated regardless of a diagnosis of PAD (such as smoking cessation aids or diabetes medications).

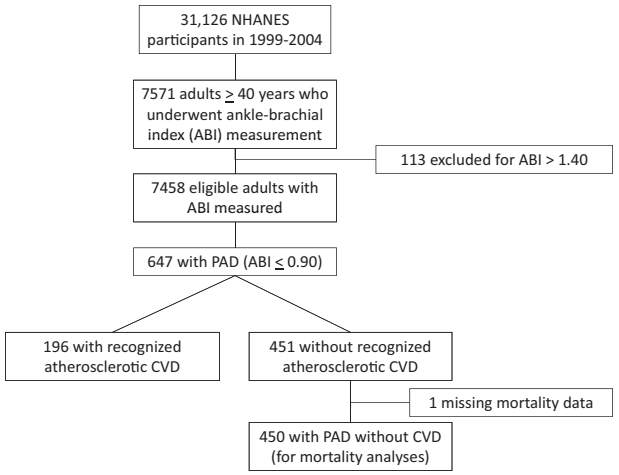

Figure. Flow diagram of derivation of sample population. NHANES indicates National Health and Nutrition Examination Survey; PAD, peripheral artery disease; and CVD, cardiovascular disease.

Primary Outcome

Mortality status was determined on the basis of a probabilistic record match with the National Death Index using demographic identifiers.[19,20] The primary outcome was all-cause mortality. For participants in NHANES 1999 to 2004, mortality follow-up data were available through December 31, 2006.

Statistical Methods

Analyses were performed with SAS version 9.1 (SAS Institute, Inc, Cary, NC) callable SUDAAN with use of appropriate sample weights, stratum, and primary sampling unit variables to account for the complex sample design of NHANES. Data are reported as weighted mean and SE or weighted percentile and SE. Comparisons of categorical variables were achieved with the χ^2 test. Population estimates were determined by multiplying the weighted prevalence estimates by the average population total of US adults ≥40 years of age provided in the Current Population Survey by the US Census Bureau for the years 1999 to 2004.

The primary mortality analysis estimated the association between mortality and the number of secondary prevention treatments used (0, 1, or multiple [≥2]) in PAD subjects without established CVD using univariate and multivariate Cox proportional hazards models. Multivariable analyses included demographics (age, sex, race/ethnicity), atherosclerotic risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, and chronic kidney disease), and socioeconomic factors (health insurance, education level, and income).

Relative risks are reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Time to event was calculated as the number of days from initial NHANES study visit to date of death. Subjects were censored if no death occurred by the end of the follow-up period, December 31, 2006. Time-varying covariates were included in the models to test the proportional hazards assumption, and no covariates were found to violate the proportional hazards assumption. A 2-sided value of $P<0.05$ was considered statistically significant for all analyses.

The first author (R.L.P.) had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1. Baseline Characteristics of All Peripheral Artery Disease Subjects (n=647)

Age, mean, y	67.8 (0.7)
Male sex, %	41.6 (2.5)
Race/ethnicity, % non-Hispanic white	78.1 (2.1)
Smoking status, % current or former	65.9 (2.0)
Diabetes mellitus, %	24.4 (2.6)
Hypertension, %	73.8 (2.4)
Hyperlipidemia, %	58.6 (2.3)
Chronic kidney disease (eGFR <60 $mL \cdot min^{-1} \cdot m^{-2}$), %	34.2 (2.5)
History of cardiovascular disease (including coronary and cerebrovascular disease), %	30.4 (2.4)
Ankle-brachial index, mean	0.77 (0.007)

Data are shown as either mean (SE) or % (SE).
eGFR indicates estimated glomerular filtration rate.

Results

During the years of 1999 to 2004, 7571 adults ≥40 years of age underwent measurement of ABI. Of those, we excluded 113 because their ABI was ≥1.40, indicating vascular calcification artifact. Among the remaining 7458 eligible subjects (Figure), PAD (ABI ≤0.90) was identified in 647 individuals. Baseline characteristics of all PAD subjects are shown in Table 1. The weighted prevalence of PAD was 5.9±0.3%, corresponding to nearly 7.1 million US adults (Table 2). Of these subjects, 196 had an established diagnosis of CVD (coronary heart disease, myocardial infarction, angina, or stroke), leaving 451 individuals with PAD but without recognized CVD. The prevalence of PAD was 4.7% among ABI-tested adults without established CVD, accounting for 4.9 million US adults (Table 2). Final mortality status was missing for 1 individual.

Secondary Prevention in Individuals With Peripheral Artery Disease With and Without Known Cardiovascular Disease

Among all 647 subjects with PAD, 69.5±2.5% were not taking a statin, 75.1±1.9% were not taking an ACE inhibitor or ARB, 64.2±2.9% were not taking aspirin, and 61±3.2% were taking no antiplatelet therapy (including aspirin, clopidogrel, dipyridamole, ticlopidine, or combination treatments; Table 3). Of PAD subjects, 68.4±3.8% had an LDL cholesterol level above the recommended goal of 100 mg/dL, and the vast majority had an LDL cholesterol level above the more aggressive target of 70 mg/dL (94.7±1.4%). Although 90.5±2.2% of PAD subjects with hypertension reported currently taking an antihypertensive medication, 45.7±2.3% of all PAD subjects still had a systolic blood pressure >140 mm Hg, and 63.9±2.4% had a systolic blood pressure >130 mm Hg.

Among the 451 PAD subjects without recognized atherosclerotic CVD, 81.7±2.7% were not taking a statin, 79.2±4.3% were not taking an ACEI or ARB, 73±3.1% were not taking aspirin, and no antiplatelet therapy was being used in 72.6±3.1% (Table 3). The LDL cholesterol level was >100 mg/dL in 70.7±4.3% of PAD subjects without CVD, and 96.7±1.4% had levels >70 mg/dL. Systolic blood pressure was >140 mm Hg in 44.4±3% of PAD subjects without CVD and >130 mm Hg in 64.9±3.2%.

Use of preventive therapies was significantly greater in the 196 PAD subjects with recognized CVD. Among PAD subjects with CVD, statin use was reported in 57.5% compared with only 18.3% in PAD subjects without CVD ($P<0.001$), ACEI/ARB therapy in 34.3% versus 20.8% ($P<0.001$), and antiplatelet therapy in 65.8% versus only 27.4% ($P<0.001$). Many more individuals with PAD who had recognized CVD were taking multiple (≥2) preventive therapies than individuals with PAD who did not have established CVD (55.1% versus 16.2%; $P<0.001$); conversely, significantly more subjects with PAD without CVD were taking no therapies at all (53.7% versus 14.9%; $P<0.001$). In the subset of PAD subjects without CVD, only a small fraction (4.3%) reported the use of all 3 types of medications.

Population Estimates of Nonuse of Recommended Therapies in Peripheral Artery Disease

Among the PAD subjects without established CVD, an estimated 4 million were not taking a statin, 3.6 million were not taking any antiplatelet therapy, and 4.2 million were not taking an ACEI or ARB. More than 3.3 million individuals with PAD had LDL cholesterol levels >100 mg/dL, and 4.6 million had LDL cholesterol levels >70 mg/dL. A large number of US adults with PAD had inadequately controlled systolic blood pressure, with 2.2 million having systolic blood pressure >140 mm Hg and 3.2 million having systolic blood pressure >130 mm Hg.

Peripheral Artery Disease and Mortality

Among all 647 PAD subjects, including those with CVD, 168 deaths were identified for a weighted mortality rate of 22.6% over a mean follow-up period of 4.4 years. In comparison, subjects without PAD (n=6811) had a weighted mortality

Table 2. Prevalence and Population Estimates of Peripheral Artery Disease in the United States

	All Subjects		Subjects With Recognized CVD		Subjects Without CVD	
	Weighted Percent	Population Estimate, n	Weighted Percent	Population Estimate, n	Weighted Percent	Population Estimate, n
Total US population estimate*		121 373 175	11.7 (0.6)	14 200 662 (740 376)	88.3 (0.6)	107 172 513 (728 239)
PAD prevalence	5.9 (0.3)	7 185 171 (384 267)	15.4 (1.6)	2 186 902 (227 211)	4.7 (0.3)	5 004 956 (265 788)

CVD indicates cardiovascular disease; PAD, peripheral artery disease. Values in parentheses are SE.
*US Census Bureau average estimates of US adults ≥40 years of age from 1999 to 2004.

Table 3. Population Estimates of Nonuse of Recommended Therapies in Peripheral Artery Disease

	All PAD Subjects (n=647)		PAD Subjects With Recognized CVD (n=196)		PAD Subjects Without CVD (n=451)	
	%	n	%	n	%	n
Statin nonuse	69.5 (2.5)	4 995 332 (179 414)	42.5 (4.2)	929 433 (91 850)	81.7 (2.7)	4 087 147 (135 444)
LDL >100 mg/dL	68.4 (3.8)	4 632 576 (256 021)	62.5 (5.7)	1 366 814 (124 653)	70.7 (4.3)	3 426 456 (209 269)
LDL >70 mg/dL	94.7 (1.4)	6 420 475 (94 200)	89.8 (2.8)	1 963 838 (61 233)	96.7 (1.4)	4 684 998 (65 760)
ACEI/ARB nonuse	75.1 (1.9)	5 395 919 (134 887)	65.6 (3.3)	1 434 608 (72 168)	79.2 (2.2)	3 964 926 (109 609)
SBP ≥140 mm Hg	45.7 (2.3)	3 246 751 (159 757)	48.9 (3.8)	1 069 395 (83 102)	44.4 (3.0)	2 186 748 (148 910)
Aspirin nonuse	64.2 (2.9)	4 535 159 (206 899)	44.1 (4.1)	964 424 (89 663)	73.0 (3.1)	3 654 114 (153 152)
Not taking any antiplatelet therapy	61.0 (3.2)	4 379 153 (228 488)	34.2 (4.6)	747 920 (100 597)	72.6 (3.1)	3 634 990 (156 014)

PAD indicates peripheral artery disease; CVD, cardiovascular disease (including myocardial infarction, angina, coronary heart disease, or stroke); LDL, low-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and SBP, systolic blood pressure. Values in parentheses are SE.

rate of 5.0%. After adjustment for age, sex, and race, PAD was significantly associated with all-cause mortality (HR, 2.4; 95% CI, 1.9 to 2.9; $P<0.0001$). This association persisted even after multivariable adjustment (HR, 1.78; 95% CI, 1.4 to 2.3; $P=0.0001$; Table 4).

There were 450 patients with PAD but without existing CVD in whom mortality data were available. Among these subjects, there were 89 deaths for a weighted death rate of 16.1%, significantly higher than the weighted death rate of 4.1% in non-PAD subjects without CVD ($P<0.0001$). Peripheral artery disease was strongly associated with all-cause mortality even after the exclusion of subjects with previously recognized CVD (adjusted HR, 1.9; 95% CI, 1.3 to 2.8; $P=0.001$; Table 4). All-cause mortality remained significantly higher in PAD subjects without CVD compared with non-PAD subjects after additional adjustment for traditional atherosclerotic risk factors (HR, 1.59; 95% CI, 1.1 to 2.4; $P=0.02$). This relationship did not persist after also accounting for socioeconomic variables, including education, insurance status, and income level (HR, 1.39; 95% CI, 0.9 to 2.2).

Secondary Prevention Therapies and Mortality in Individuals With Peripheral Artery Disease

Given the limited data on the role of preventive therapies on mortality in individuals with PAD but without previously recognized CVD, we focused on this subset for mortality analyses. Because treatment was not randomly assigned among participants in NHANES, we first explored differences in baseline characteristics based on number of treatments that might bias the association between treatment and mortality (Table 5). Subjects with PAD on multiple treatments were more likely to be older, men, and non-Hispanic whites, and to have a higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease. These individuals were also significantly more likely to have health insurance and to be in higher income categories. In subjects with PAD without known CVD, use of multiple preventive treatments (≥2) was associated with a 65% reduction in risk of all-cause mortality compared with PAD subjects receiving no treatments (HR, 0.35; 95% CI, 95% CI 0.2 to 0.86; $P=0.02$) after full multivariable adjustment including socioeconomic factors (Table 6).

Discussion

Using the nationally representative NHANES database, we estimate that millions of US adults with PAD do not receive secondary prevention treatments that may reduce the risk of adverse cardiovascular events. Peripheral artery disease subjects remain at significantly increased risk of all-cause death compared with those without PAD. Consistent with prior studies, we found a significantly increased risk of mortality in patients with PAD, with a 2-fold increased risk of all-cause mortality after multivariable adjustment even among individuals without recognized CVD at baseline, 16% of whom died during an average follow-up of 4.4 years. Thus, patients with PAD remain at high risk of all-cause mortality even in the absence of established CVD. These mortality rates in individuals with PAD may have important implications for the relative benefit that secondary prevention treatments can afford in this population.

Table 4. Risk of All-Cause Mortality Associated With Peripheral Artery Disease

	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Subjects without CVD (n=6385)	4.39 (3.1–6.2)	<0.0001	1.93 (1.3–2.8)	0.001	1.59 (1.1–2.4)	0.02	1.39 (0.9–2.2)	0.1
All subjects (n=7458)	5.28 (4.3–6.5)	<0.0001	2.36 (1.9–2.9)	<0.0001	1.9 (1.5–2.4)	<0.0001	1.78 (1.4–2.3)	0.0001

HR indicates hazard ratio; CI, confidence interval; and CVD, cardiovascular disease. Model 1: adjusted for age, sex, and race/ethnicity. Model 2: model 1 plus adjustment for atherosclerotic risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, and chronic kidney disease). Model 3: model 2 plus adjustment for health insurance status, education level, and socioeconomic status (based on poverty-income ratio).

Table 5. Baseline Characteristics of Peripheral Artery Disease Subjects According to Number of Secondary Prevention Treatments

Characteristic	No Treatment* (n=244)	1 Treatment (n=129)	Multiple Treatments (n=77)
Age (mean), y	63.7 (1.0)	69.8 (1.6)	70.4 (1.8)
Male sex, %	32.2 (3.8)	33.8 (5.5)	45.2 (6.6)
Race, non-Hispanic white, %	70.7 (3.6)	83.6 (2.4)	87.9 (3.8)
Diabetes mellitus, %	15.0 (2.1)	21.7 (4.3)	22.1 (5.6)
Hypertension, %	59.0 (4.4)	76.8 (5.8)	89.7 (3.9)
Hyperlipidemia, %	43.1 (3.7)	61.1 (5.9)	72.4 (6.3)
Smoking (current or former), %	59.2 (5.0)	62.8 (6.6)	68.4 (6.3)
Chronic kidney disease, %	19.8 (2.9)	32.2 (4.6)	45.3 (7.6)
Systolic blood pressure (mean), mm Hg	138.2 (1.4)	142.3 (3.7)	137.1 (2.3)
Body mass index (mean), kg/m^2	28.0 (0.6)	28.9 (0.6)	29.8 (1.3)
Ankle-brachial index (mean)	0.80 (0.01)	0.76 (0.01)	0.74 (0.02)
High school education, %	69.6 (3.5)	70.1 (4.8)	63.8 (6.6)
Socioeconomic status (based on poverty-income ratio), %			
Income below poverty level	21.1 (4.0)	11.4 (2.3)	5.3 (1.8)
Income 1–2 times poverty level	29.2 (3.3)	27.9 (5.1)	26.9 (6.7)
Income 2–3 times poverty level	17.4 (4.7)	28.2 (5.7)	23.4 (5.9)
Income 3–4 times poverty level	12.4 (3.1)	8.2 (3.5)	8.3 (4.3)
Income >5 times poverty level	19.9 (5.2)	24.2 (4.9)	36.1 (7.9)
Low socioeconomic status (income <2 times poverty level), %	50.3 (4.8)	39.4 (5.4)	32.2 (6.9)
Uninsured, %	13.9 (2.9)	2.6 (1.5)	0.8 (0.8)

*Includes antiplatelet therapy, statin use, and/or use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Our observational data found that treatment with ≥2 preventive therapies (including aspirin, statin, and/or ACEI/ARB) is associated with a 65% reduced risk of all-cause mortality in individuals with PAD who do not have previously established CVD. Yet, the role of ABI screening for the presence of PAD is controversial. The ABI is a simple, noninvasive test with high diagnostic accuracy for PAD,[9] and several studies have shown a strong association of lower ABI values and increased mortality.[10,11] Multiple therapies are known to reduce cardiovascular risk in individuals with established CVD. However, no studies have evaluated whether initiation of multiple secondary prevention therapies based on a low ABI in individuals without otherwise recognized CVD can indeed improve outcomes. The lack of existing data has been acknowledged by the US Preventive Services Task Force, which has assigned ABI screening an 'I' recommendation as a novel cardiovascular risk marker, indicating insufficient information to support its use in general clinical practice.[15]

Preventive Therapies in Peripheral Artery Disease

Although it is well recognized that individuals with PAD are inadequately treated with secondary prevention therapies,[3,4] no prior study has estimated the absolute number of individuals in the United States with PAD who are not receiving therapies that may reduce the risk of myocardial infarction, stroke, or death. The complex sampling methodology used in NHANES allows the calculation of nationally representative population estimates. From these NHANES data, we estimate that ≈5.0 million adults with PAD are not taking a statin, 5.4 million are not taking an ACEI/ARB, and 4.4 million are not receiving antiplatelet therapy. These estimations indicate that there are millions of adults in the United States with PAD with or without coexisting CVD who stand to benefit from secondary prevention treatments. Treatment use was significantly higher in PAD subjects with recognized CVD compared with those without previously established CVD. This finding supports the notion that identification of atherosclerotic vascular disease by ABI screening is likely to result in greater use of secondary prevention therapies.

Most prior studies of secondary prevention have included only individuals with recognized and/or symptomatic disease enrolled on the basis of symptoms of intermittent claudication or by a history of prior lower extremity revascularization.[5,7,8,21,22] For example, the Heart Protection Study, the Heart Outcomes Prevention Evaluation (HOPE) study, and the Antithrombotic Trialists' Collaboration meta-analysis, evaluating statins, ACEIs, and antiplatelet therapy, respectively, included predominantly symptomatic PAD subjects with either claudication or prior peripheral vascular intervention.[5,7,8] Whether the benefits of these agents would be applicable to individuals with asymptomatic PAD recognized solely on the basis of an abnormal ABI remains to be determined. Furthermore, the combined effect of multiple

Table 6. Cox Proportional Hazards Models of Mortality and Number of Preventive Therapies Used Among Peripheral Artery Disease Subjects Without Recognized Cardiovascular Disease

		Model 1		Model 2		Model 3	
	n	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
No preventive therapies*	244	Referent		Referent		Referent	
1 Preventive therapy	129	1.12 (0.6–2.1)	0.7	1.15 (0.6–2.2)	0.7	1.24 (0.6–2.5)	0.5
Multiple preventive therapies (≥2)	77	0.79 (0.4–1.7)	0.5	0.63 (0.2–1.7)	0.3	0.35 (0.2–0.86)	0.02

HR indicates hazard ratio; CI, confidence interval. Model 1: adjusted for age, sex, and race/ethnicity. Model 2: model 1 plus adjustment for atherosclerotic risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, and chronic kidney disease). Model 3: model 2 plus adjustment for health insurance status, education level, and socioeconomic status (based on poverty-income ratio).

*Therapies include statin, antiplatelet therapy, and/or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

preventive therapies to reduce mortality in PAD has not previously been studied.

The role of antiplatelet therapy, aspirin in particular, in reducing cardiovascular risk in individuals with newly detected PAD remains controversial. The Aspirin for Asymptomatic Atherosclerosis (AAA) trial evaluated asymptomatic, otherwise healthy individuals with previously unrecognized PAD and found that aspirin therapy alone did not reduce the risk of adverse cardiovascular events.[15] In addition, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) study found no benefit of aspirin in asymptomatic PAD subjects, all of whom had coexisting diabetes mellitus.[14] Several factors may have contributed to the apparent lack of benefit in these 2 studies, including the use of higher ABI thresholds (0.95 and 0.99, respectively), which may have reduced the specificity for detecting patients with PAD and lowered the overall mortality rate, thereby limiting the potential to see a therapeutic benefit. However, the findings are consistent with a recent meta-analysis by Berger and colleagues[12] that included both symptomatic and asymptomatic individuals with PAD. This meta-analysis also showed no significant benefit of aspirin in reducing all-cause or cardiovascular mortality, although the largest study included in the meta-analysis, the POPADAD study, enrolled exclusively individuals with diabetes mellitus, a population in which the role of aspirin therapy remains unclear.[12,14,23] These data stand in contrast to an earlier meta-analysis from the Antiplatelet Trialists' Collaboration that has supported a role of antiplatelet therapy in secondary prevention in all patients with atherosclerotic vascular disease.[8]

The use of statins for the prevention of cardiovascular events has been studied extensively in individuals with recognized and established vascular disease, including PAD.[5,6,24] Specifically, the Heart Protection Study demonstrated a 22% relative risk reduction with simvastatin compared with placebo of a first major vascular event.[5] However, the Heart Protection Study included only symptomatic PAD, and statin therapy has not specifically been evaluated in individuals with asymptomatic or previously unrecognized PAD. The HOPE study showed that ACE inhibitors reduce cardiovascular events by ≈25% in patients with symptomatic PAD.[7] Although ABI (determined by palpation of the foot pulse) was measured in HOPE, patients were not enrolled solely on the basis of a low ABI.[25]

Taken together, our data suggest that combination therapy with multiple risk-modifying therapies may be associated with clinical benefit in a population of individuals defined solely by an abnormal ABI. In the end, these data are hypothesis generating and underscore the need for a definitive clinical trial to determine whether cardiovascular risk–modifying therapies alone or in combination can in fact reduce mortality and cardiovascular events in subjects identified as being high risk by a screening ABI examination.

Limitations

The limitations of our study warrant consideration. First, despite the power of NHANES to allow population estimates for the United States, the mortality analyses included only the 450 individuals with PAD who did not have established CVD. This limited our power to observe effects of any individual treatments on outcomes in PAD, especially because only a small number of individuals were taking these therapies. Second, it is unknown whether a new diagnosis of PAD may have altered an individual's medical management; data in NHANES are collected at only a single time point, and no follow-up information is available regarding initiation of medications after the study visit. Third, the diagnosis of CVD was based on participant self-report and was not verified by medical record. However, we would expect any resulting misclassification to bias toward a null result. Finally, with respect to measurement of ABI, blood pressure was measured in only 1 arm and only in the posterior tibial artery, another factor that might raise the potential for misclassification.

Conclusion

In this nationally representative sample, population-based ABI measurement identified millions of high-risk US adults with PAD who were not receiving guideline-recommended secondary prevention therapies. Individuals with PAD, notably those without recognized CVD, were at a high risk of mortality. Treatment with multiple secondary prevention therapies was associated with reduced risk of all-cause mortality in this population. These observational findings highlight the critical need for a large-scale clinical trial to determine whether the implementation of secondary prevention therapies in high-risk individuals identified by ABI screening as having PAD can reduce mortality and cardiovascular events.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Cardiovascular disease remains a major cause of morbidity and mortality in the United States. Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis that confers a significantly increased risk of myocardial infarction, stroke, and death. Whether cardiovascular risk can be reduced by implementation of secondary prevention therapies (such as antiplatelet therapy, statins, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) in individuals with PAD identified by a screening ankle-brachial index measurement is unknown. Using data from the National Health and Nutrition Examination Survey (NHANES), we demonstrate that millions of high-risk US adults with PAD (ankle-brachial index $\leq$0.90) were not receiving guideline-recommended secondary prevention therapies. All-cause mortality was significantly higher in individuals with PAD, including those without previously recognized cardiovascular disease. Furthermore, treatment with multiple secondary prevention therapies was associated with significantly reduced risk of all-cause mortality in this population. Given the conflicting literature about the use of secondary prevention therapies, aspirin in particular, in patients with PAD, these observational findings underscore the importance of a large-scale clinical trial to determine whether implementation of multiple secondary prevention therapies specifically in high-risk individuals identified by ankle-brachial index screening as having PAD can indeed reduce cardiovascular morbidity and mortality.