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A High Ankle-Brachial Index Is Associated With Increased Cardiovascular Disease Morbidity and Lower Quality of Life

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Objectives The purpose of this study is to determine if an ankle-brachial index (ABI) ≥1.40 is associated with reduced quality of life (QoL).

Background Ankle-brachial index values ≥1.40 have been associated with some cardiovascular disease (CVD) risk factors and increased mortality, but the relationship to other disease morbidity such as reduced QoL has not been previously evaluated.

Methods The PARTNERS (PAD Awareness, Risk and Treatment: New Resources for Survival) program was a national cross-sectional study of 7,155 patients age >50 years recruited from 350 primary care sites. All sites performed the ABI using a Doppler device and a standardized technique.

Results A total of 296 subjects had an ABI ≥1.40 in at least 1 leg, and 4,420 had an ABI between 0.90 and 1.40. Diabetes, male gender, and waist circumference were positively associated with a high ABI, and smoking and dyslipidemia were inversely associated with a high ABI. After adjustment for age, gender, and the traditional CVD risk factors, and accounting for multiple comparisons, the high ABI group had significantly higher odds for foot ulcers ($p < 0.005$) and borderline associations with heart failure, stroke, and neuropathy. After the same adjustments and adjusting for patients with other CVD, the high ABI group scored 2.0 points lower on the physical component scale on the Medical Outcomes Study Standard Form–36 and 5.5 points lower on the Walking Impairment Questionnaire walking distance domain ($p < 0.05$ for both).

Conclusion Individuals with a high ABI have higher odds for foot ulcers and neuropathy, as well as lower scores on some physical functioning QoL domains. (J Am Coll Cardiol 2008;51:1292–8) © 2008 by the American College of Cardiology Foundation

The ankle-brachial index (ABI) provides information on the presence of systemic atherosclerosis and associated cardiovascular risk. For example, individuals with an ABI <0.90 have an elevated risk for incident cardiovascular disease (CVD) morbidity (1,2) and mortality events (3–5). Recent studies indicate, however, that dichotomizing the ABI using the 0.90 cut point may lead to underdiagnosis, because cohorts with an ABI >1.30 have been associated with higher levels of many CVD risk factors (6) as well as coronary artery calcium (7). This suggests that this upper cut point may also be associated with higher CVD morbidity. Recent studies have also documented more leg pain (8) and higher levels of CVD morbidity and mortality among those with an ABI above 1.40 (9,10). Accordingly, using data collected from a community-based clinic population in the PARTNERS (PAD Awareness, Risk and Treatment: New Resources for Survival) program, the aim of this study was to determine the risk factors, comorbid CVD conditions, and quality of life (QoL) associated with an ABI ≥1.40.

Methods

A detailed description of the methods used in the PARTNERS program has been published previously (11). In brief, PARTNERS was a cross-sectional survey of

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peripheral arterial disease (PAD) and other CVD prevalence and treatment that was performed at 27 regional coordinating centers selected for their expertise in PAD care. These regional centers identified 350 local primary care sites for patient evaluation. The local study physician and coordinator identified patients who met the eligibility criteria for the study. Sequential patients seen in these primary care practices underwent administration of standardized questionnaires, a review of their medical history, height, weight, blood pressure, and waist circumference, and each subject underwent an ABI measurement. The protocol was reviewed and approved by the institutional review boards at all study sites, and all patients provided written informed consent prior to participation.

Study population. Enrollment was based on predefined criteria based on the known epidemiology of PAD (12–17). Specifically, patients were enrolled if they were 70 years or older or if they were age 50 to 69 years and had a history of at least 10 pack-years of cigarette smoking or diabetes or both. Data were collected between June and October 1999.

At the study visit, subjects were classified for the presence of existing CVD or PAD, as well as new versus prior PAD based on the results of their ABI and medical history. Subjects were considered to have prior PAD if they had undergone prior lower extremity arterial revascularization regardless of their ABI value at the evaluation office visit, if the chart review revealed earlier abnormal vascular laboratory studies, or if their ABI was <1.00 at the evaluation visit. Patients with no previous history of PAD were considered to have new PAD if their ABI was ≤0.90 during the study office visit. A diagnosis of existing CVD required a documented history of coronary artery disease, cerebrovascular disease, or abdominal aortic aneurysm repair. A diagnosis of coronary artery disease was based on a history of angina (stable or unstable), myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery. Patients were considered to have cerebrovascular disease if they had a history of transient ischemic attack, stroke (ischemic or hemorrhagic), or carotid endarterectomy.

ABI technique. Prior to study initiation, all local sites received instruction and training on the accurate use of the Doppler technique and calculation of the ABI. A 5-mHz Doppler device (Elite-100R, Nicolet Vascular Inc., Golden, Colorado) was used at each site to measure the ABI. With the subject in the supine position, systolic blood pressures were measured in the brachial arteries and in both the dorsalis pedis and posterior tibial arteries of the lower extremities. The ABI was calculated separately for each leg by dividing the higher of the 2 ankle systolic pressures by the higher of the 2 brachial systolic pressures. The sensitivity and specificity of an ABI <0.90 are both >90% for an angiographically defined stenosis of 50% or more in a major leg artery (18). The reproducibility of the ABI is good (19,20).

Clinical subgroups. The normal ABI group was defined as patients having an ABI >0.90 and ABI <1.40 in both legs. The definition of the high ABI group required that patients have an ABI ≥1.40 in both legs or an ABI >1.40 in 1 leg and a normal ABI in the contralateral leg. Individuals with an ABI <0.90 in either leg or a history of lower extremity revascularization were classified as having PAD and were excluded from this analysis.

Atherosclerosis risk factors. *Smoking* was defined as 1 pack-year or more of tobacco use based on patient interview or chart review. *Diabetes* was determined from the medical record, regardless of whether it was type 1 or type 2. The diagnosis of diabetes included treatment for this condition defined as current use of dietary interventions or use of diabetes medications. Laboratory screening for prevalent diabetes was not performed. *Dyslipidemia* was defined from the medical record as past or present use of lipid-lowering agents or: 1) a total cholesterol concentration ≥240 mg/dl; 2) low-density lipoprotein cholesterol concentration ≥160 mg/dl; 3) high-density lipoprotein (HDL) cholesterol concentration of ≤35 mg/dl; 4) triglyceride concentration ≥200 mg/dl; or 5) a total cholesterol/HDL ratio of ≥5.0 (21). Lipid-lowering therapy was defined as the prescription of agents used to treat lipid abnormalities (e.g., statins, niacin, fibrates, and bile acid binding resin agents). A fasting lipid profile was not obtained as part of this program. *Hypertension* was defined as the self-reported use of calcium channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers, or diuretics for the indication of treatment of hypertension as well as either a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg.

Questionnaire data. Subjects were surveyed on their QoL by completing the Medical Outcomes Study Standard Form-36 (SF-36) and the Walking Impairment Questionnaire (WIQ). The SF-36 is composed of 2 summary measures (physical health and mental health) (22–24). Each of these is composed of 5 scales that attempt to capture relevant QoL information by asking questions from 1 of 36 different items. For instance, the role physical scale consists of 4 items that obtain information on problems with work as a result of physical health. The individual SF-36 scales have been shown to have good validity among patients with intermittent claudication (25). The WIQ is a valid measure of community walking ability in patients with and without PAD (26). The WIQ yields 3 summary scores: walking distance, walking speed, and stair climb.

Abbreviations and Acronyms

ABI = ankle-brachial index
BMI = body mass index
CHF = congestive heart failure
CVD = cardiovascular disease
HDL = high-density lipoprotein
OR = odds ratio
PAD = peripheral arterial disease
QoL = quality of life
SF-36 = Medical Outcomes Study Standard Form-36
WIQ = Walking Impairment Questionnaire

Statistical analyses. Demographic characteristics and risk factors were summarized as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Differences in demographics and risk factors between the normal and high ABI groups were tested with a 2-sided 2-sample *t* test for continuous variables and with a chi-square test (or Fisher exact test) for categorical outcomes (Table 1). A multiple logistic regression with stepwise selection was used to determine the set of demographic and risk factors that are independently associated with a high ABI. The prevalence of comorbid conditions was compared between the normal and high ABI groups using a chi-square (or Fisher exact test) and are reported in Table 2. Logistic regression was employed to adjust the prevalence of comorbid conditions for age, gender, race, diabetes, smoking (current, former, never), hypertension, dyslipidemia, and body mass index (BMI). Multiple linear regression models were used to compare the demographic and risk-adjusted means of the SF-36 and WIQ outcomes between the normal and high ABI groups. Adjustments were made for age, gender, race, diabetes, smoking (current, former, never), hypertension, dyslipidemia, BMI, and history of other CVD. Least-squares means by ABI group are reported in Table 3.

Because the inclusion criteria were different based on age at enrollment (i.e., 50 to 69 years vs. ≥70 years), we included interactions between age and both smoking and diabetes in the multivariable models. Inclusion of these interaction terms (i.e., smoking × age and diabetes × age) did not change the magnitude or significance of the associations between the high ABI and the outcomes for this study. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). A Bonferroni correction was used to adjust the critical region for statistical significance due to the number of statistical tests performed. Ten SF-36 items, 10 WIQ items, and 13 comorbidities were tested. Statistical significance is defined as $p < 0.005$ (5% type I error rate divided by 10 comparisons per QoL instrument).

Results

Subjects. Figure 1 shows a diagram of the number of subjects available for analysis after the following exclusions: 1) those with PAD defined as an ABI <0.90; 2) those with missing ABIs; and 3) those with missing demographic or risk factor covariates. There were 4,716 subjects in the analysis population. Also, not all subjects completed the QoL questionnaires. Therefore, only 3,215 subjects were included in the SF-36 analyses and 3,114 in the WIQ analyses.

Table 1 Demographic and Risk Factors by ABI Group

Risk Factor	ABI Group		p Value
	Normal (n = 4,420)	High (n = 296)	
Age, yrs (mean, SD)	70.1 (9.7)	71.1 (9.9)	0.09
Male, n (%)	2,024 (45.8)	200 (67.6)	<0.001
Race/ethnicity, n (%)			0.24
Non-Hispanic white	3,672 (83.1)	251 (84.8)	
Black	403 (9.1)	16 (5.4)	
Hispanic	184 (4.2)	15 (5.1)	
Native American	33 (0.7)	4 (1.3)	
Asian/Pacific Islander	80 (1.8)	7 (2.4)	
Other	48 (1.1)	3 (1.0)	
Smoking status, n (%)			<0.001
Current	658 (14.9)	19 (6.4)	
Former	1,831 (41.4)	127 (42.9)	
Never	1,931 (43.7)	150 (50.7)	
Diabetes mellitus, n (%)	1,538 (34.8)	131 (44.3)	0.001
Dyslipidemia, n (%)	2,842 (64.3)	172 (58.1)	0.03
Hypertension, n (%)	3,562 (80.6)	241 (81.4)	0.73
Other CVD, n (%)	1,544 (34.9)	124 (41.9)	0.02
BMI (kg/mm^2), mean (SD)	28.9 (6.2)	29.6 (7.0)	0.08
Waist circumference, mean (SD)	38.1 (6.0)	39.6 (5.9)	<0.001
SBP (mm Hg), mean (SD)	137.7 (19.5)	133.5 (18.3)	<0.001*
DBP (mm Hg), mean (SD)	77.8 (10.4)	76.0 (10.5)	<0.001
Left dorsalis pedis blood SBP (mm Hg), mean (SD)	150.0 (28.9)	173.8 (46.7)	<0.001*
Right dorsalis pedis blood SBP (mm Hg), mean (SD)	150.4 (29.2)	175.9 (45.6)	<0.001*
Left posterior tibial blood SBP (mm Hg), mean (SD)	155.6 (27.3)	185.2 (41.2)	<0.001*
Right posterior tibial SBP (mm Hg), mean (SD)	156.3 (27.5)	191.8 (43.1)	<0.001*

*The p values are biased as these measures are used in the ABI group definition.
ABI = ankle brachial index; BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 2 Comorbidities by ABI Group

Characteristic Comorbidities	ABI Group: Normal (n = 4,420)	ABI Group: High (n = 296)	p Value
Angina	760 (17.5)	58 (20.0)	0.28
Myocardial infarction	596 (13.7)	45 (15.5)	0.40
CHF	344 (7.9)	38 (13.1)	0.002
Angioplasty	363 (8.4)	34 (11.7)	0.05
Coronary artery bypass	449 (10.3)	43 (14.7)	0.02
Transient ischemic attack	221 (5.1)	21 (7.2)	0.11
Stroke	236 (5.4)	26 (8.9)	0.01
Carotid endarterectomy	84 (1.9)	6 (2.1)	0.86
Aneurysm	39 (0.9)	2 (0.7)	>0.99
Foot ulcer	64 (1.5)	13 (4.5)	<0.001
Neuropathy	565 (13.2)	58 (20.2)	<0.001
Venous thrombosis	177 (4.1)	17 (5.9)	0.14
Joint disease/rheumatoid arthritis	1,671 (38.6)	92 (32.1)	0.03

Values are expressed as n (%).
CHF = congestive heart failure; other abbreviations as in Table 1.

Among the 4,716 subjects with an ABI >0.90, the mean ABI was 1.09 ± 0.13. Of these subjects, 296 had an ABI ≥1.40 in either leg, and 4,420 had an ABI between 0.90 and 1.40. The mean (SD) age was 70.2 (9.7) and 52.8% were female. The majority were non-Hispanic white; of the rest, 8.9% were African American, 4.2% Hispanic, 1.8% Asian or Pacific Islander, and 0.8% Native American. Over 80% were hypertensive, 64% had high cholesterol, 56% were either current or former cigarette smokers, and 35% were diagnosed with diabetes mellitus.

Risk factors for an ABI ≥1.40. A comparison of the demographic and CVD risk factors by ABI group is provided in Table 1. Compared with those with a normal ABI, subjects with a high ABI had significantly lower levels of brachial artery systolic and diastolic blood pressure, a lower prevalence of dyslipidemia, and smoked less. Conversely, the high ABI group had significantly higher mea-

Table 3 HRQoL Adjusted for Demographic and Risk Factors by ABI Group

Characteristic	ABI Group: Normal (n = 4,420)	ABI Group: High (n = 296)	p Value
SF-36 scores			
Body pain	60.0	58.5	0.42
General health	59.1	56.0	0.04
Mental health	71.8	70.8	0.40
Physical functioning	59.0	55.4	0.05
Role, emotional	65.4	63.9	0.59
Role, physical	52.5	45.3	0.01
Social functioning	75.7	74.4	0.44
Vitality	54.1	51.4	0.08
Mental composite score	49.9	49.9	>0.99
Physical composite score	39.9	37.8	0.01
WIQ scores			
Calf pain	68.2	66.9	0.55
Chest pain	85.7	87.9	0.15
Dyspnea	74.0	76.0	0.32
Heart palpitations	84.2	85.7	0.36
Joint pain	59.6	57.1	0.27
Other problems	81.3	78.6	0.19
Stair climbing	58.2	55.4	0.19
Walking distance	65.6	60.1	0.04
Walking speed	52.6	48.3	0.03
Weakness	68.3	65.5	0.20

Means are adjusted for age, gender, race, smoking, diabetes, hypertension, dyslipidemia, BMI, and history of other CVD.
HRQoL = health-related quality of life; SF-36 = Medical Outcomes Study Standard Form–36; WIQ = Walking Impairment Questionnaire; other abbreviations as in Table 1.

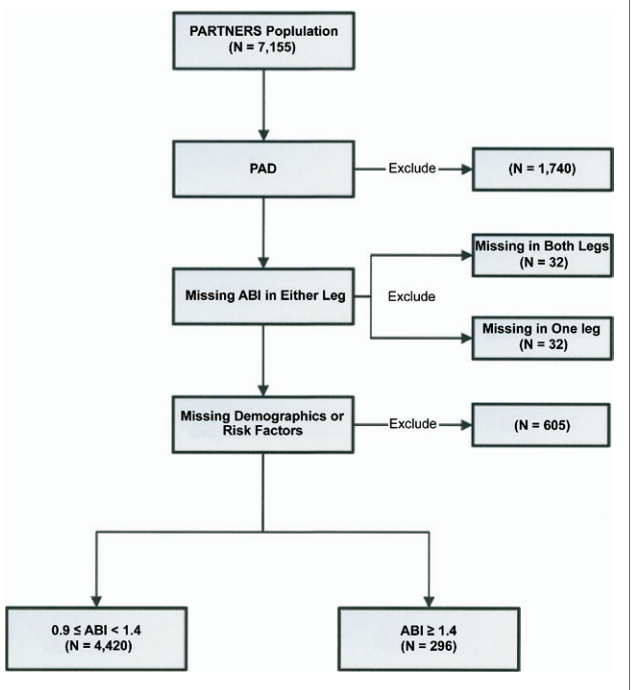

Figure 1 Flow Diagram of Subjects Available for Analysis

ABI = ankle-brachial index; PAD = peripheral arterial disease.

sured levels of each ankle systolic pressure, as well as a higher prevalence of diabetes mellitus and other CVD. The high ABI group had significantly more males and a larger waist circumference.

A multiple stepwise logistic regression model identified a positive association of male gender (odds ratio [OR] 2.45, 95% confidence interval [CI] 1.90 to 3.26), diabetes (OR 1.30, 95% CI 1.01 to 1.68), and waist circumference (OR 1.27, 95% CI 1.02 to 1.59 per 10-inch increase) with a high ABI and a negative association with dyslipidemia (OR 0.72, 95% CI 0.57 to 0.93), current smoking (OR 0.33, 95% CI 0.20 to 0.55), and former smoking (OR 0.69, 95% CI 0.57 to 0.93).

Cardiovascular and other comorbid diseases. Table 2 provides the prevalences by ABI group and unadjusted p values for the CVD comorbidities. After adjustment for age, gender, race, smoking, diabetes, hypertension, dyslipidemia, and BMI, those with a high ABI had a significantly higher prevalence of foot ulcers (OR 2.67, 95% CI 1.42 to 5.02, $p < 0.005$). The adjusted odds ratios with 95% confidence limits for ABI group in predicting the comorbidity are displayed in Figure 2. As shown, marginally significant associations ($p < 0.05$) of high ABI were found for congestive heart failure (CHF) (OR 1.58, 95% CI 1.09 to 2.30), stroke (OR 1.66, 95% CI 1.07 to 2.56), and neuropathy (OR 1.51, 95% CI 1.09 to 2.08).

Quality of life. Demographic and risk factor–adjusted means for the SF-36 and WIQ are presented in Table 3. Adjustment for age, gender, race, BMI, diabetes, dyslipidemia, hypertension, cigarette smoking, and history of other CVD revealed marginally significant reductions ($p < 0.05$) in QoL in the high ABI group for the general health (3.1 points), physical functioning (3.5 points), role physical (7.2 points), and physical component summary scales (2.0 points). Similarly, after adjusting for demographic and risk factors, the mean score for WIQ walking distance was marginally lower in the high ABI group by 5.5 points ($p = 0.04$) and was marginally lower for the walking speed score by 4.3 points ($p = 0.03$) compared with the normal ABI group.

Discussion

In this large national study of a primary care–derived population and among those with an ABI ≥1.40, 6.3% had an ABI ≥1.40 in at least 1 leg. Persons with a high ABI were more likely to be male and have diabetes and less likely to report current or former smoking and dyslipidemia. This is not the typical atherosclerosis risk profile as previously described for patients with coronary artery disease or PAD. Specifically, diabetes remained associated with a high ABI, as has been previously reported, but the reduced prevalence of smoking in this cohort has been observed in at least 1 other large prospective study (27) and remains difficult to explain.

An ABI ≥1.40 was associated with foot ulcers, and there were marginal associations for CHF, stroke, and neuropathy. Although these findings were adjusted for diabetes,

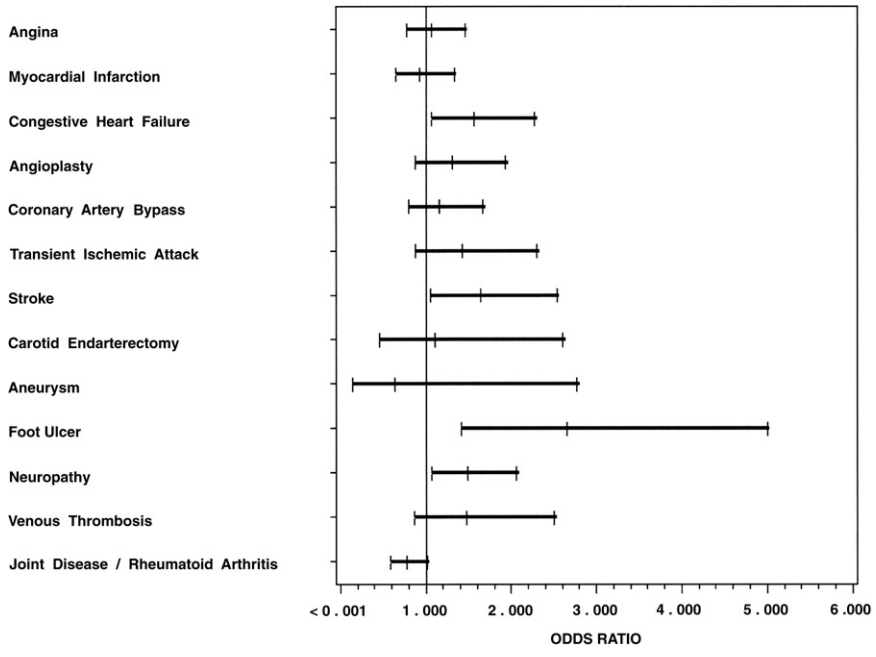

Figure 2 Odds Ratios for CVD Comorbidities in Those With an ABI ≥1.40 Compared With an ABI Between 0.90 and 1.40

Compared with those with a normal ABI, individuals with a high ABI have significantly higher odds for congestive heart failure, stroke, foot ulcers, and neuropathy. Odds ratios are adjusted for age, gender, race, smoking, diabetes, hypertension, dyslipidemia, and body mass index. ABI = ankle-brachial index; CVD = cardiovascular disease.

some residual confounding is a possibility. None of the SF-36 or WIQ adjusted means were statistically different between the normal and high ABI groups (when using a $p < 0.005$ to account for multiple tests). However, after accounting for multiple comparisons, several marginal QoL differences were found in measures of physical, but not mental, health as has been previously noted in patients with PAD (28).

The physiological mechanism resulting in an ABI above the normal range is usually assumed to be mechanical rigidity of the arteries in the lower extremities (29). Whether this is true for only modest ABI elevations is uncertain. For example, compared with those with an ABI in the normal range, individuals with a high ABI had much higher levels of systolic blood pressure in the ankles and modestly lower brachial artery systolic blood pressures compared with those with a normal ABI. Because the ABI is a ratio of systolic blood pressures, a high ABI could result from low brachial or high ankle pressures or both. Although the results here support the "both" hypothesis, compared with the normal ABI groups, the absolute differences for the ankle pressures were much greater than for the brachial pressures. If generalized reduced arterial compliance were the major mechanism leading to a modest ABI elevation, one would anticipate higher brachial pressures and a higher rate of hypertension in the high ABI cohort. This was not demonstrated in our study, and results from the ARIC (Atherosclerosis Risk in Communities) study (27) cohort showed a lower prevalence of hypertension in those with a high ABI. These results indicate that the factors that lead to a modestly high ABI are likely due to a complex vascular pathophysiology.

In the current study, diabetes was a significant risk factor for a high ABI. In many studies, diabetes has also been shown to be a risk factor for an ABI <0.90 (13,30–32). Notably, the effects of diabetes are complex, as this condition is associated with both atherosclerosis (i.e., the accumulation of atherosclerotic plaques resulting in flow limiting stenosis) (33–36) and medial calcification of the peripheral arteries (37–39). Unfortunately, there is a paucity of research on diabetes and upper extremity atherosclerosis (i.e., subclavian stenosis). In a study by Shadman et al. (40), diabetes was associated with a 10% higher risk for subclavian stenosis, but this difference was not statistically significant. It is unlikely that upper extremity subclavian atherosclerosis contributes to the high ABI values, as both brachial pressures were low and bilateral high-grade upper extremity atherosclerotic occlusive has not been observed in these relatively healthy populations.

From a community-based study of non-Hispanic whites and African Americans, the Cardiovascular Health Study (10) has previously reported a nearly 60% higher risk for all-cause mortality among those with an ABI >1.40. Similarly, the Strong Heart Study (9) reported relative risks of 1.77 and 2.09 for all-cause and CVD mortality, respectively, for those with an ABI above this same level. This result has been confirmed in a recent meta-analysis (41) of 16 studies internationally, although 1 exception (27) has been reported. Although the PARTNERS participants were not followed for incident CVD events, these data demonstrate that an ABI ≥1.40 was associated with significantly higher odds for foot ulcers and possibly several other CVD morbidities.

There is a gap in the literature on the relationship between a high ABI and measures that describe the health impact of vascular disease beyond vital status. One such domain is QoL. Accordingly, a primary focus of this study was to determine the relationship of high versus normal ABI values to several QoL domains. A suggestive association was found between an ABI ≥1.40 and walking distance, although this was nonsignificant after correction for multiple comparisons. It is well-known that there is a significant (albeit weak) correlation between low ABI values and functional limitations associated with walking (e.g., intermittent claudication) (42,43). These data provide preliminary evidence that a high ABI is also associated with walking impairment, although the mechanism underlying this observation remains obscure. Of note, the measurement of the ABI was conducted at 27 regional centers and 350 clinical sites across the U.S. and with minimal training. Therefore, there is a possibility of misclassification and the results presented likely represent conservative estimates of the associations.

Conclusions

The implications of this study are 3-fold. First, clinicians should consider the potential clinical significance of the entire range of ABI values when evaluating a patient for lower extremity arterial disease (e.g., high ABI values are not "normal"). Second, diabetic patients are at higher risk for either a high or low ABI (44). Third, a high ABI is now shown to be associated with decrements in some QoL measures, as well as CVD morbidity. Accordingly, future investigation may be warranted to evaluate the mechanism that underlies the derivation of the high ABI value and perhaps the effect of aggressive risk factor management of these patients in an effort to improve QoL while decreasing the risk for untoward CVD events.

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