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Authors

Hyun, Suzanne
Forbang, Nketi I
Allison, Matthew A
et al.

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Ankle Brachial Index, Toe Brachial Index, and Cardiovascular Mortality in Participants With and Without Diabetes Mellitus

Suzanne Hyun, MD[a], **Nketi I. Forbang, MD**[b], **Matt A. Allison, MD, MPH**[b,c], **Julie O. Denenberg, MAS**[b], **Michael H. Criqui, MD, MPH**[b], and **Joachim H. Ix, MD, MAS**[b,c]

[a]Loma Linda University Medical Center, Loma Linda, CA

[b]School of Medicine, University of California San Diego, San Diego, CA

[c]Veterans Affairs San Diego Healthcare System, San Diego, CA

Abstract

Background—The prognostic utility of ankle brachial index (ABI) may be hampered in persons with diabetes due to peripheral arterial stiffening in the ankles. Stiffening of toe arteries occurs infrequently in diabetes.

Objectives—We aim to determine the nature of the relationship of the toe brachial index (TBI) and ABI with cardiovascular (CVD) mortality, and to determine whether the associations are modified in individuals with diabetes.

Methods—Individuals with clinically suspected atherosclerotic PAD who underwent ABI and TBI measurements in a vascular laboratory were followed longitudinally for CVD mortality.

Results—Among 469 (89% men) participants, the mean age was 68 ± 9 years and 36% had diabetes. The mean ABI was 0.83 ± 0.28 and the mean TBI was 0.60 ± 0.24. During 7.0 years (median) follow-up, there were 158 CVD deaths. Association of the ABI categories with CVD events differed in diabetic vs. non-diabetic participants (P-interaction = .002). In contrast, association of the TBI categories with CVD events were similar irrespective of diabetes status (P-interaction = .17). Among diabetic patients, a U-shaped relationship was observed between ABI categories and CVD death; both those with low (< 0.90) and high (> 1.30) ABI were at higher risk than those with normal (0.90–1.30) ABI. In non-diabetic patients, association of ABI categories with CVD death was linear, such that those with ABI > 1.30 were at the lowest risk, whereas those with ABI < 0.90 were at higher risk. In contrast, the association of TBI categories with CVD death was linear irrespective of diabetes status. High TBI categories consistently predicted low risk, whereas risk was higher with progressively lower TBI categories.

Conclusions—Among diabetic individuals with clinically suspected PAD, both those with low and high ABI are at higher risk of CVD death. In contrast, a linear relationship was observed

Corresponding Author: Joachim H. Ix, MD, Division of Nephrology, University of California San Diego, 3350 La Jolla Village Drive, Mail Code 9111H, San Diego, CA 92161, Phone: (858) 552-8585, ext. 1657, joeix@ucsd.edu.

between TBI categories and CVD death irrespective of diabetes status. These findings suggest that stiffened ankle arteries may limit the predictive value of the ABI in individuals with diabetes; a limitation that may be overcome by measurement of the TBI.

INTRODUCTION

The ankle brachial index (ABI) is the principal diagnostic tool for PAD screening, and reflects the ratio of systolic blood pressure at the ankle relative to the arm. [1] However, its use is complicated in individuals with diabetes, who frequently have calcium deposition in the arterial media; a condition known as medial arterial calcification (MAC). The most common anatomic location for MAC is in the ankle arteries.[2] MAC contributes to arterial stiffening, which results in vessels that are more difficult to occlude in the ankle, artificially elevating the measured ankle systolic blood pressure which leads to falsely elevated ABIs. This may render the ABI less sensitive to detection of flow limiting atherosclerotic PAD in individuals with diabetes.

While MAC is common in the ankle arteries[2] the toe arteries are usually spared.[3] The toe brachial index (TBI) uses similar principles to the ABI, but reflects the systolic pressures in the great toe to that in the arm. Because MAC commonly spares the toes, the TBI may be useful to detect atherosclerotic PAD in individuals with MAC. Given concerns that the ABI may miss PAD in individuals with diabetes, both the American Diabetes Association[4] and the American Heart Association[5] and have recommended using TBI measurements to evaluate atherosclerotic PAD in individuals with incompressible ankle arteries, or when the ABI is high (> 1.30). While low ABI measurements are known to predict CVD events in individuals with and without diabetes[6], it is uncertain whether the associations of high ABI and CVD events differs by diabetes status, and whether or not the TBI measurement may provide useful information about CVD risk when MAC is present.

Given that MAC and atherosclerotic PAD may be co-existent in individuals with diabetes, MAC may render the ABI less sensitive for detection of atherosclerotic PAD in individuals with diabetes, and may therefore bias the relationship of ABI measurements with risk of CVD death towards the null. Since MAC is more common in diabetes, we hypothesized that low TBI measurements would be more strongly associated with CVD death than low ABI measurement, and that such differences would be more evident in patients with diabetes.

METHODS

Study Participants

Between 1990 and 1994, patients who were seen in the previous 10 years for noninvasive lower extremity arterial testing at the San Diego Veterans Administration Medical Center (VAMC) or the University of California, San Diego Medical Center (UCSDMC) vascular laboratory were invited to participate in this study. Of the 2,265 candidates, 481 had died, and among the remainder, 508 agreed to participate and returned for a repeat study evaluation. Among these, we excluded those with missing ABI measurements (n= 2, 0.4%), TBI measurements (n= 9, 1.8%), and CVD risk factor data (n=28, 6%), resulting in final analytic sample of 469 participants for this analysis.[7,8]

All participants gave written informed consent. The study protocol and consent forms were approved by the University of California, San Diego Investigational Review Board.

Vascular Assessment

The ABI and TBI protocol have been described in detail previously.[7,8] Briefly, brachial, ankle, and toe pressures were measured bilaterally. Blood pressure cuffs were placed on the arms, ankles, and the bases of the big toes and measurements were taken in a temperature-controlled environment, in the supine position, and after ten minutes of rest. Photoplethysmography was used to detect blood flow at the third finger for arm measurements and the great toe for ABI and TBI measurements. The ABI and TBI were computed using the arm with the higher systolic pressure due to the strong correlation between PAD and subclavian stenosis.[9]

The reproducibility of the ABI and TBI have been evaluated in prior studies. For the ABI, the 95% confidence intervals for reproducibility are between 0.10 and 0.15.[10–12] Variability of the TBI is greater, reported anywhere from the same as the ABI[13] to about twice that of the ABI[11]. The higher variability of the TBI may be due to higher susceptibility of toe arteries to vasoreactivity.[14]

Cardiovascular Disease Mortality

All participants were followed through December 31, 2001. Mortality was identified using the Social Security Death Index, and death certificates were obtained and coded by a certified nosologist using ICD-9 codes. When cause of death was coded 401 to 437.9, excluding 412, participants were classified as having died from CVD.

Other Measurements

Age, sex, ethnicity, and smoking history were self-reported. Participants were categorized as current, former, or never smokers. Diabetes was defined as a fasting plasma glucose ≥126 mg/dl, use of insulin, or oral hypoglycemic medications. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic pressure ≥ 90 mm Hg or use of antihypertensive medications. Body mass index (BMI) was calculated from values for weight and height as kg/m2. Dyslipidemia was categorized as use of lipid-lowering drugs or total cholesterol to high-density cholesterol ratio ≥ 5. Serum creatinine was measured by the rate Jaffe method, and combined with age, sex, and ethnicity in the 4-variable Modification and Diet in Renal Disease equation to estimate glomerular filtration rate (eGFR).[15]

Statistical Analysis

We began by categorizing participants into 4 groups based on clinical ABI cut-points (< 0.60, 0.60–0.89, 0.90–1.30, and >1.30). We compared differences in demographics and traditional CVD risk factors across ABI categories using Analysis of Variance (ANOVA) for continuous variables, and the chi square test or Fisher's exact test for categorical variables. Next, we categorized participants into 4 categories based on TBI scores, such that the percentage of participants in each TBI category was similar to those in the corresponding ABI categories (TBI < 0.40, 0.40–0.61, 0.62–1.08 and >1.08). We used Cox proportional hazards models to evaluate the associations of the ABI and TBI categories with time to CVD

death. The ABI category 0.90–1.30 and TBI category of 0.62–1.08 served as the reference category. The initial model was unadjusted. A final model adjusted for demographics and traditional CVD risk factors (age, sex, ethnicity, diabetes, smoking [current, former, never], systolic blood pressure, blood pressure medication use, total cholesterol, HDL cholesterol, cholesterol medication use, eGFR, and BMI). Finally, we tested multiplicative interaction terms (ABI*diabetes and TBI*diabetes) in the fully adjusted models. When statistically significant interactions were detected, we evaluated the association of ABI and TBI categories in diabetic and non-diabetic participants separately. Analyses were conducted using Stata SE version 11.0 (STATA corporation, College Station, TX). $P < .05$ was considered statistically significant for all analyses including interaction terms.

RESULTS

The mean age of the 469 study participants was 68 ± 9 (range 39–100) years. Four hundred and seventeen (89%) were men, reflecting heavy sampling from the Veterans Affairs medical center, and 168 (36%) had diabetes. The mean ABI was 0.83 ± 0.28 and the mean TBI was 0.60 ± 0.24. One hundred thirty-nine individuals (30%) had classic claudication symptoms, and 15 (3%) had at least one leg with an ABI < 0.40, suggesting critical limb ischemia, and CVD mortality risk did not differ significantly across these groups. Baseline characteristics by ABI categories are shown in Table 1. Compared to participants with normal ABI (0.90–1.30), those in lower ABI categories were older, more likely to have diabetes, hypertension, lower kidney function, and lower TBI measurements.

Figure 1 depicts the distribution of TBI measurements as a function of ABI measurements. While lower ABI scores were generally associated with lower TBI scores, the distribution of TBI scores was much more variable at higher ABI levels resulting in a non-linear relationship at higher levels.

During 7.0 years median follow-up, there were 158 CVD deaths. Seventy-five (47%) occurred in patients with diabetes. We created TBI categories so as to assign similar numbers of participants to each TBI group as were assigned to the corresponding ABI categories. Table 2 shows the number of CVD deaths by TBI and ABI categories overall and also stratified by diabetes.

We observed that the association of ABI categories with CVD death differed by diabetes status (P-interaction =.002). Figure 2 shows Kaplan Meier survival curves of ABI (2a) and TBI (2b) groups with CVD death, stratified by diabetes. Among non-diabetics, lower ABI levels were associated with a step-wise increase in CVD event risk. In non-diabetic participants, no CVD death events were observed in the group with ABI > 1.30, so the hazard ratios (HR) was not calculable in this group. In contrast, among participants with diabetes, the group with ABI levels between 0.90–1.30 had the lowest risk, whereas those with either lower or higher ABI had comparatively higher risk of CVD death. The nature of these relationships remained similar in Cox models adjusted for age and sex, and in fully adjusted models (Table 3).

We also observed that among persons with ABI scores < 0.60, the hazard ratio for CVD death was stronger in those without diabetes compared to those with diabetes (HR 3.81 vs. 2.83 respectively). To determine whether this part of the distribution of ABI categories contributed to the statistical effect modification by diabetes status, we conducted a sensitivity analysis excluding subjects with ABI > 1.30. In the remaining participants, the association of ABI with CVD death remained statistically significantly different by diabetes status (p interaction = 0.03).

In contrast to the distinct nature of the relationship of ABI categories with CVD death by diabetes status, the association of TBI categories with CVD death was similar irrespective of diabetes status (P-interaction = .17; Figure 2b). In both diabetic and non-diabetic participants, stepwise lower TBI scores were associated with progressively higher risk of CVD death. Participants in the highest TBI score category (> 1.08) were at the lowest risk of CVD death irrespective of diabetes status. The nature of these associations was similar in age and sex adjusted, and fully adjusted models (Table 3).

We also examined deaths from non–CVD causes. Neither the ABI nor the TBI was associated with non-CVD death in this cohort, and associations were similar irrespective of diabetes status (p interactions both > 0.35).

DISCUSSION

Among individuals referred to a vascular laboratory for suspected atherosclerotic PAD, we demonstrate that the association of ABI measurements with CVD mortality differs among persons with or without diabetes. Patients with lower ABI measurements were at a step-wise increased risk for CVD death in non-diabetics, but a U-shaped relationship was observed between the ABI and CVD death in diabetic patients. In contrast, the association of TBI categories with CVD death risk was linear irrespective of diabetes status. These findings may have important implications for screening PAD among individuals with diabetes.

Diabetes is a well-established risk factor for MAC[16], and MAC may falsely elevate the ABI.[17] Prior studies by our group in cohorts where both ABI measurements and lower limb x-rays were available simultaneously have demonstrated that nearly all diabetics with ABI measurements > 1.30 have arterial calcification on x-ray consistent with MAC.[18] In the current study, we found that individuals with diabetes and high ABI levels were at higher risk for CVD death than those with “normal” ABI levels (0.90–1.30). Similar findings were not observed using the TBI, and MAC is known to spare the toe arteries. We conclude that, when present, MAC may decrease the sensitivity of the ABI for detection of PAD, and may also diminish the strength of the association of the ABI with CVD death; a finding that may be overcome using the TBI.

Even when we excluded participants with ABI scores > 1.30, we observed that the association of low ABI scores with CVD death was stronger in non-diabetics than in diabetics. This finding suggests that MAC may be co-present and may increasing ABI scores among diabetics even when their ABI scores are in the normal or low range, thus biasing the ABI-CVD death association towards the null in diabetics. Our findings support

current recommendations by the ADA[4] and AHA[5], suggesting that diabetic patients with elevated or incompressible ankle arteries be referred for additional vascular testing, including the TBI. In such individuals, finding a normal or high ABI may not exclude atherosclerotic PAD. Instead, many such individuals will have MAC, which may preclude detection of atherosclerotic PAD using the ABI. However, because we also observed that the association of low ABI scores with CVD death was weaker in diabetics compared to non-diabetic patients, our findings suggest that even diabetic patients with normal or low ABI scores may benefit from additional vascular testing with the TBI. Such individuals may have more severe PAD and higher risk for CVD death than would be recognized by relying solely on the ABI, likely because concomitant MAC is leading to higher ABI values than would have otherwise been detected.

While the association of the TBI with CVD death was linear irrespective of diabetes status, the hazard ratios linking low TBI categories with CVD death were weaker compared to hazard ratios linking low ABI categories with CVD death. This may reflect differences in the reproducibility of the ABI and TBI. In prior studies, the reproducibility of the ABI has been reported between 0.10–0.15.[19,12] In contrast, the TBI evaluates systolic blood pressure in the great toe and digital arteries may be more susceptible to vasoconstriction and increased resistance in response to colder ambient temperature. [19] While the test-retest correlation of the TBI is less well studied[20] if vasospasm and greater susceptibility to temperature fluctuations lowers its reproducibility, this may have biased the association of the TBI with CVD mortality towards the null, and may have led to weaker associations of the TBI with CVD mortality relative to the ABI with the same outcome.[19,13,14] Another plausible explanation for weaker hazard ratios for the TBI may be because we set the intermediate TBI category (0.62–1.08) as our reference group. This was done to provide a subgroup with comparable prevalence to those with “normal” ABIs, to allow comparisons across the two diagnostic tests. However, our results disclosed a linear relationship of the TBI with CVD events. Had we set the highest TBI category as our reference group, then the lowest TBI group would have had stronger hazard ratios for CVD mortality than the lowest ABI category.

Strengths of this study include its relatively large sample size and long-term follow-up, concurrent availability of the ABI and TBI measurements both made in a vascular laboratory setting and a large number of participants with diabetes. The study also has important limitations. As we studied participants that had been referred to our vascular laboratory, the generalizability of the results to the general population is uncertain. We recruited heavily from our Veterans Affairs medical center, and most of the subjects were male. While we have demonstrated that high ABI has high specificity for MAC in diabetic subjects in prior studies[18], lower limb imaging confirming the presence of MAC was not available in this cohort.

In conclusion, among individuals with clinically suspected atherosclerotic PAD, the association of ABI measurements with CVD mortality is U-shaped in diabetic patients and linear in non-diabetic patients. In contrast, lower TBI scores were linearly associated with CVD mortality irrespective of diabetes status. Peripheral arterial stiffness in individuals with diabetes may limit the prognostic information obtained from ABI measurements. Diabetic

individuals with clinically suspected PAD might benefit from additional confirmatory tests for PAD irrespective of whether the ABI measurements are low, normal, or elevated.

Acknowledgments

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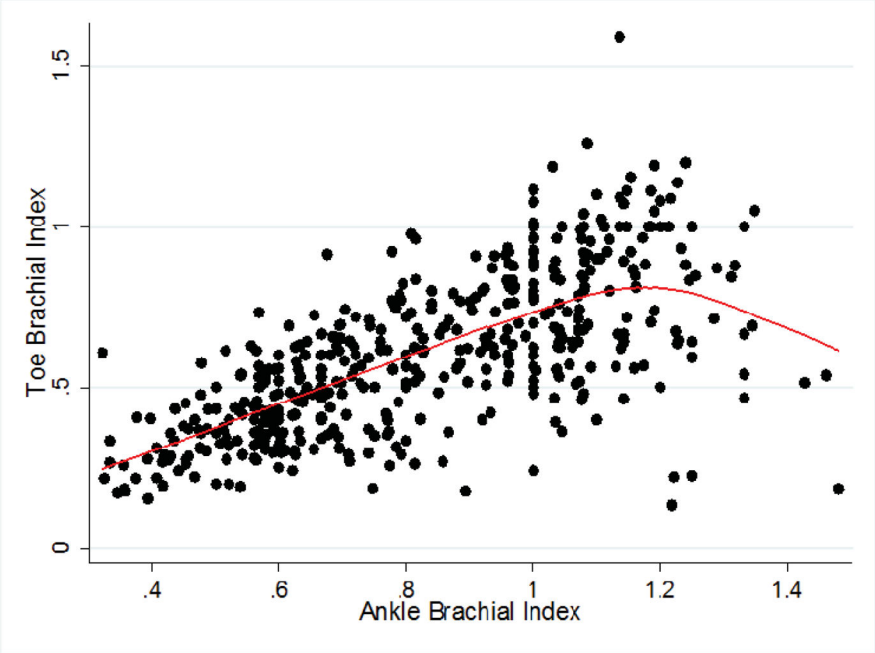

Figure 1.
Distribution of Toe Brachial Index Measurements by Ankle Brachial Index Measurements

Figure 2a.

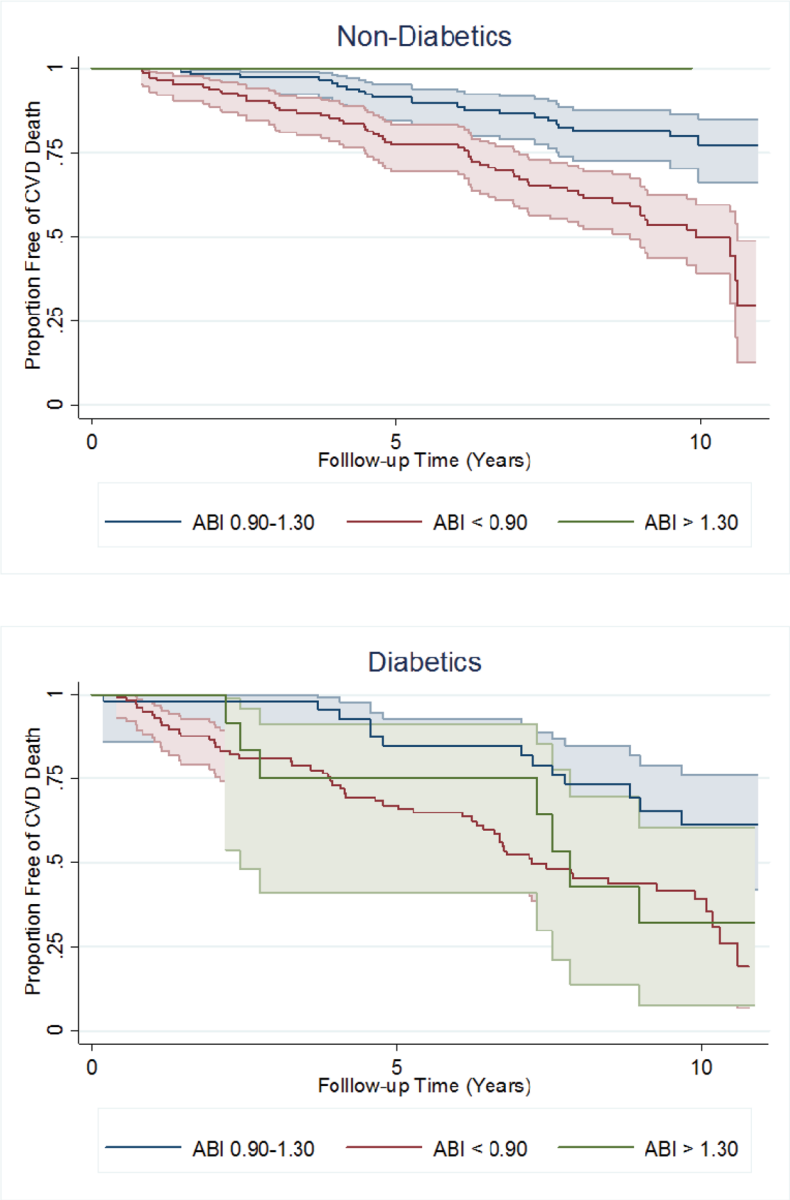

Figure 2b.

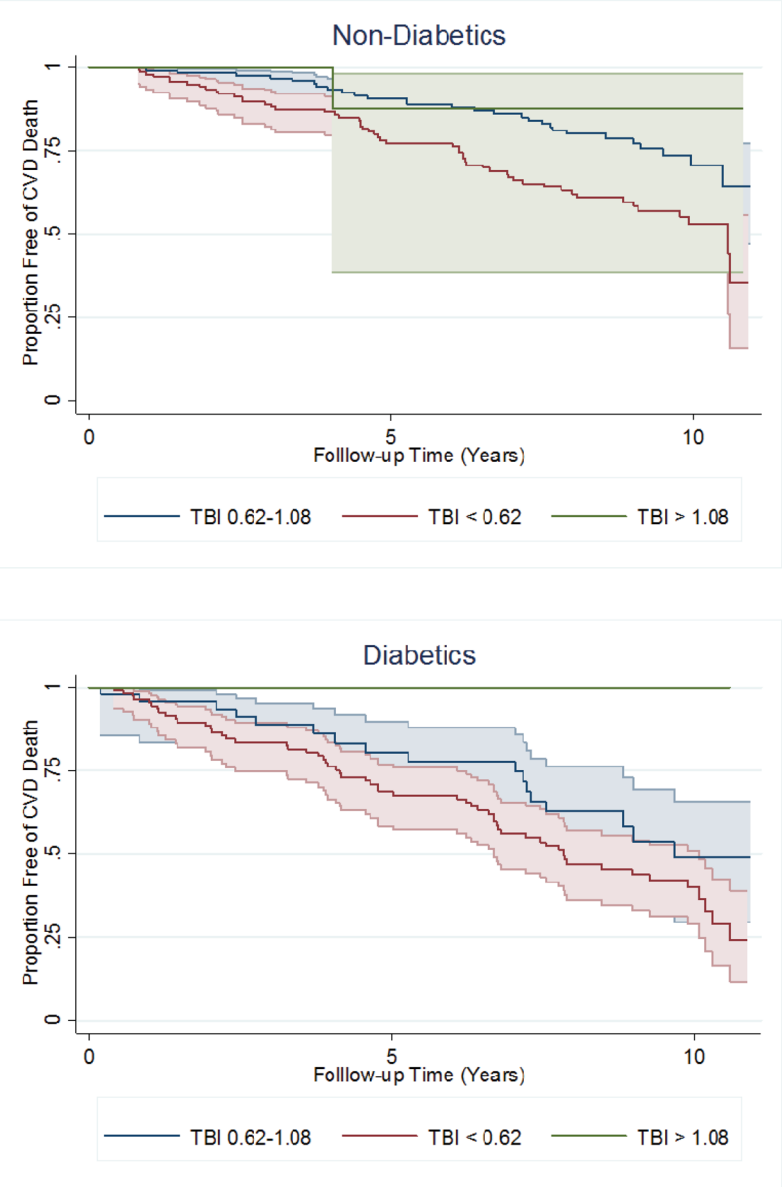

Figure 2.

Figure 2a. Kaplan Meier Curves of ABI Categories with Cardiovascular Disease Mortality in Individuals With and Without Diabetes

Figure 2b. Kaplan Meier Curves of TBI Categories with Cardiovascular Disease Mortality in Individuals With and Without Diabetes

Table 1

Baseline Characteristics by Ankle Brachial Index Categories

	ABI Categories				P value
N (%), Mean ± SD	**< 0.60 106 (22%)**	**0.60–0.89 160 (34%)**	**0.90–1.30 189 (40%)**	**> 1.30 14 (3%)**	
Age, years	70 ± 8	70 ± 8	66 ± 10	65 ± 9	< 0.01
Female	9 (8%)	17 (11%)	26 (14%)	0 (0%)	0.28
African American	5 (5%)	8 (5%)	5 (3%)	0 (0%)	0.55
Diabetes	49 (46%)	55 (34%)	52 (27%)	12 (86%)	< 0.01
Hypertension	90 (85%)	131 (81%)	128 (68%)	13 (92%)	< 0.05
Smoking					< 0.05
Current	36 (25%)	55 (38%)	52 (36%)	0 (0%)	
Former	58 (22%)	86 (33%)	108 (41%)	8 (3%)	
Never	12 (18%)	19 (28%)	29 (44%)	6 (9%)	
Body mass index, kg/m^2	27 ± 4	28 ± 12	27 ± 5	29 ± 6	0.67
Total cholesterol, mg/dL	214 ± 44	212 ± 41	204 ± 37	199 ± 47	0.10
HDL cholesterol, mg/dL	45 ± 12	46 ± 13	47 ± 15	43 ± 11	0.72
eGFR, ml/min/1.73m^2	54 ± 15	55 ± 14	59 ± 14	58 ± 17	< 0.05
Toe brachial index	0.38 ± 0.12	0.54 ± 0.16	0.78 ± 0.22	0.69 ± 0.24	< 0.01

ABI = ankle brachial index, HDL = high density lipoprotein, eGFR = estimated glomerular filtration rate

Table 2

Number of Deaths by Ankle Brachial Index and Toe Brachial Index Category Stratified by Diabetes

	All Participants		Diabetes		No Diabetes	
N (%)	**Total**	**CVD mort**	**Total**	**CVD mort**	**Total**	**CVD mort**
ABI Categories						
> 1.30	14 (3%)	7 (50%)	12 (7%)	7 (58%)	2 (1%)	0 (0%)
0.90–1.30	189 (40%)	37 (20%)	52 (31%)	14 (27%)	137 (46%)	23 (17%)
0.60–0.89	160 (34%)	55 (34%)	55 (32%)	25 (45%)	105 (35%)	30 (29%)
< 0.60	106 (23%)	59 (56%)	49 (29%)	29 (59%)	57 (19%)	30 (53%)
TBI Categories						
> 1.08	14 (3%)	2 (14%)	5 (3%)	1 (20%)	9 (3%)	1 (11%)
0.62–1.08	196 (42%)	45 (23%)	51 (30%)	17 (33%)	145 (48%)	28 (19%)
0.40–0.61	157 (33%)	59 (38%)	70 (42%)	34 (49%)	87 (29%)	25 (29%)
< 0.40	102 (22%)	52 (51%)	42 (25%)	23 (55%)	60 (20%)	29 (48%)

ABI = ankle brachial index, TBI = toe brachial index, CVD mort = cardiovascular disease mortality

Table 3

Associations of Ankle Brachial Index and Toe Brachial Index Categories with Cardiovascular Mortality Overall and Stratified by Diabetes

	All Participants		Diabetes		No Diabetes	
HR (95% CI)	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**
ABI Categories[c]						
> 1.30	2.99 (1.33, 6.74)	1.81 (0.77, 4.24)	2.47 (0.99, 6.14)	1.80 (0.68, 4.71)	--	--
0.90–1.30	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.60–0.89	1.99 (1.31, 3.03)	1.92 (1.24, 2.94)	2.21 (1.14, 4.26)	2.03 (1.01, 4.04)	1.72 (0.99, 2.97)	1.66 (0.94, 2.92)
< 0.60	3.87 (2.56, 5.85)	3.39 (2.18, 5.27)	3.06 (1.61, 5.81)	2.83 (1.42, 5.61)	3.90 (2.25, 6.74)	3.81 (2.13, 6.81)
TBI Categories[d]						
> 1.08	0.49 (0.11, 2.03)	0.47 (0.11, 2.00)	0.39 (0.05, 2.91)	0.39 (0.05, 3.14)	0.54 (0.07, 3.91)	0.44 (0.06, 3.35)
0.62–1.08	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.40–0.61	1.62 (1.09, 2.40)	1.36 (0.91, 2.05)	1.53 (0.84, 2.76)	1.44 (0.79, 2.62)	1.24 (0.71, 2.14)	1.14 (0.65, 2.02)
< 0.40	2.65 (1.77, 3.96)	2.25 (1.47, 3.43)	1.99 (1.06, 3.74)	2.28 (1.15, 4.55)	2.68 (1.58, 4.52)	2.19 (1.26, 3.80)

[a] Adjusted for age and sex

[b] Adjusted for age, sex, ethnicity, diabetes, smoking (current, former, never), systolic blood pressure, blood pressure medication use, total cholesterol, high density lipoprotein cholesterol, lipid medication use, estimated glomerular filtration rate, and body mass index.

[c] P-interaction by diabetes status in the fully adjusted model = .002

[d] P-interaction by diabetes status in the fully adjusted model = .17