

UC San Diego

Independent Study Projects

Title

The Relative Strength of Association of Ankle-Brachial vs. Toe-Brachial Index with Cardiovascular Mortality in Individuals With and Without Diabetes Mellitus.

Permalink

<https://escholarship.org/uc/item/024092jt>

Author

Hyun, Suzanne

Publication Date

2013

The Relative Strength of Association of Ankle-Brachial vs. Toe-Brachial Index with Cardiovascular Mortality in Individuals With and Without Diabetes Mellitus

Suzanne Hyun,¹ Matt Allison,^{1,2} Julie Denenberg,¹ Michael H. Criqui,^{1,2} Joachim H. Ix^{1,2,3,4}

- (1) School of Medicine, University of California San Diego, San Diego, CA.
- (2) Division of Preventive Medicine, Department of Family and Preventive Medicine, University of California San Diego, San Diego, CA.
- (3) Division of Nephrology and Hypertension, Department of Medicine, University of California San Diego, San Diego, CA.
- (4) Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, CA.

Key Words: Ankle Brachial Index, Toe Brachial Index, Diabetes, Guidelines

Corresponding Author:

Joachim H. Ix, MD, MAS
Division of Nephrology and Hypertension, Department of Medicine
University of California San Diego, and San Diego VA Healthcare System
3350 La Jolla Village Drive
Mail code 111-H
San Diego, CA 92161
Phone: (858) 552-8585, ext. 1657
Fax: (858) 552-7549
E-mail: joeix@ucsd.edu

Abstract

Background:

Individuals with diabetes frequently develop atherosclerotic peripheral arterial disease (PAD) and associated elevated risk of cardiovascular disease (CVD) death. However, the prognostic utility of ankle brachial index (ABI) may be hampered in diabetes due to peripheral arterial stiffening in the ankles. Stiffening of toe arteries occurs infrequently in diabetes.

Objective:

To determine the nature of the relationship of the toe brachial index (TBI) and ABI with CVD mortality, and to determine whether the nature of the associations are modified by diabetes.

Design and Setting:

Longitudinal study among individuals with clinically suspected atherosclerotic PAD who underwent ABI and TBI measurements in a vascular laboratory.

Main Outcome Measures:

CVD mortality

Results:

Among 469 participants, the mean age was 68 ± 9 years and 36% had diabetes. The mean ABI \pm SD was 0.83 ± 0.28 and the mean TBI \pm SD was 0.6 ± 0.24 . During 7.0 years (median) follow-up, there were 158 CVD deaths. The association of the ABI level with CVD events differed in diabetic vs. non-diabetic participants (p interaction 0.002). In contrast, the association of the TBI level with CVD events was similar irrespective of diabetes status (p interaction 0.17). Among diabetics, a U-shaped relationship was

observed between ABI scores and CVD death; both those with low (<0.90) and high (>1.30) ABI scores were at higher risk than those with intermediate risk. In non-diabetics, the relationship of ABI scores with CVD death was linear; 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 scores with CVD death was linear irrespective of diabetes status. High TBI scores consistently predicted low risk, whereas risk was higher with progressively lower TBI.

Conclusions:

Among diabetic individuals with clinically suspected PAD, both those with low and high ABI scores are at higher risk of CVD death. In contrast, a linear relationship was observed between TBI scores and CVD death irrespective of diabetes status. These findings suggest that stiffened ankle arteries may limit the predictive value of ABI scores in individuals with diabetes; a limitation that may be overcome by measurement of the TBI.

Introduction

Secular trends in diet and exercise have led to an epidemic of obesity and diabetes. (1) Diabetes commonly affects the systemic vasculature (2), and peripheral arterial disease (PAD) is the leading cause of amputations in individuals with diabetes.

The ankle brachial index (ABI) has been the principal screening tool for PAD for over 40 years, and reflects the ratio of systolic blood pressure in the ankle relative to the arm. However, its use is complicated in individuals with diabetes. In addition to the high prevalence of flow-limiting atherosclerotic PAD, individuals with diabetes also 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 (5). MAC contributes to arterial stiffening, which results in vessels that are more difficult to occlude in the ankle, artificially elevating the ankle blood pressure relative to the arm and leading to falsely high ABI readings. 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 (5) the toe arteries are usually spared. (6) The toe brachial index (TBI) uses similar principals 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 less affected by the presence or absence of MAC and may therefore be useful to detect atherosclerotic PAD even in individuals who have MAC. Given concerns that the ABI may miss PAD in individuals with diabetes, both the American Heart Association and the American Diabetes Association have recommended using TBI measurements to evaluate atherosclerotic PAD in individuals with

incompressible ankle arteries, or when the ABI is very high (> 1.30). While low ABI measurements are known to predict CVD events in individuals with and without diabetes, it is uncertain whether the nature of the association differs by diabetes status, and whether or not the TBI measurement may provide useful information about CVD risk irrespective of MAC.

We hypothesized 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 covariate data (n=31, 6%), resulting in final analytic sample of 469 participants. (8,9)

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 (8,10). 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 and the great toe for TBI measurements, and Doppler ultrasonography was used to detect blood flow in the dorsalis pedis and posterior tibial artery for the ABI. The ABI and TBI were computed using the arm with the higher systolic pressure due to the strong correlation between PAD and subclavian stenosis (11).

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, race, 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/m^2 . 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 race in the 4-variable Modification and Diet in Renal Disease equation to estimate glomerular filtration rate (eGFR). (16)

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. Pearson correlations were used to evaluate the unadjusted

correlation between the ABI and TBI measurements. 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. A sequence of adjustment models was developed. The initial model was unadjusted. A subsequent model adjusted for demographics and traditional CVD risk factors (age, sex, race, 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 values < 0.05 were considered statistically significant for all analyses including interaction terms.

Results

The mean age of the 469 study participants was 68 ± 9 years. Four hundred and seventeen (87%) 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 .

Baseline characteristics by ABI categories are shown in Table 1. Compared to participants with an ABI score between 0.90-1.30, those with higher and lower ABI measurements were more likely to be male, to have diabetes, hypertension, lower HDL cholesterol, and lower TBI measurements. In contrast, only those with lower ABI scores, but not those with higher ABI scores were older and a higher total cholesterol.

Figure 1 depicts the distribution of TBI measurements as a function of ABI measurements. The Pearson correlation between ABI and TBI measurements was 0.63 ($p < 0.001$). While lower ABI scores were generally associated with lower TBI scores, the distribution of TBI scores was much more variable at higher ABI levels.

We created TBI categories to assign similar numbers of participants to each group as were assigned to the corresponding ABI categories. During 7.0 years median follow-up, there were 158 CVD deaths. Seventy-five (47%) occurred in patients with diabetes. 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 0.002). Figure 2 A and B show Kaplan Meier survival curves of ABI 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 this

group, no events were observed in the group with ABI > 1.30. In contrast, among participants with diabetes, the group with ABI levels between 0.90-1.30 had the lowest risk, whereas those with lower, or higher ABI had 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 scores contributed to the statistical effect modification by diabetes status, we conducted a sensitivity analysis excluding subjects with ABI scores > 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 0.17; Figure 2C and 2D). In both diabetic and non-diabetic participants, a 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).

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 increase in CVD risk in non-diabetics, but a U-shaped relationship was not demonstrated between ABI scores and CVD death in diabetics. In contrast, the association of TBI categories with CVD event risk was linear irrespective of diabetes status. These findings may have important implications for screening for PAD among individuals with diabetes.

Diabetes is a well-established risk factor for MAC (17), and MAC may falsely elevate the ABI. (18) Prior studies by our group in cohorts with both ABI measurements and lower limb x-rays have demonstrated that nearly all diabetics with ABI measurements > 1.30 have MAC. (19) We found that individuals with diabetes and at the highest 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 hypothesize that, when present, MAC may decrease the sensitivity of the ABI for detection of PAD, and may therefore 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 subjects 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. While the mechanisms for this finding are uncertain, they suggest that MAC may be co-present and 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. Thus, our findings support current recommendations of the ADA and AHA, 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, if these findings are confirmed, they suggest that diabetic patients with normal or low ABI scores may still benefit from additional vascular testing with the TBI. Some such individuals may have more severe PAD and higher risk for CVD death than would be recognized relying on the ABI alone, likely because concomitant MAC is leading to higher ABI scores than they would have otherwise.

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 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.(12, 22) 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. (20) While the test-retest correlation of the TBI is less well studied, (21) 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 lead to weaker associations of the TBI with CVD mortality relative to the ABI with the same outcome. (14, 12, 15)

Strengths of this study include its relatively large sample size and long-term follow-up, concurrently available 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 many of the subjects were male. While we have demonstrated that high ABI scores have high specificity for MAC in diabetic subjects in prior studies (19), lower limb imaging confirming the presence of MAC were 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 diabetics and linear in non-diabetics.. 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 even when ABI measurements are normal or elevated..

References:

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and Trends in Obesity Among US Adults, 1999-2000. *JAMA* 2002; 288(14): 1723-1727.
2. Gregg, E.W., et al., *Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey*. *Diabetes Care*, 2004. 27(7): p. 1591-7.
3. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, Ix JH, Burke GL, Liu K, Shea S. The Ankle-Brachial Index and Incident Cardiovascular Events in the MESA (Multi-Ethnic Study of

Atherosclerosis), *Journal of the American College of Cardiology* 2010; 56(18): 1506-1512.

4. McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik JM, Liao Y, Criqui MH. Decline in Functional Performance Predicts Later Increased Mobility Loss and Mortality in Peripheral Arterial Disease. *Journal of the American College of Cardiology*. 2011; 57(8): 962-970.
5. Everhart, J.E., et al., *Medial arterial calcification and its association with mortality and complications of diabetes*. *Diabetologia*, 1988. 31(1): p. 16-23.
6. Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia*. 1993; 36(7): 615-21.
7. A.T. Hirsch, Z.J. Haskal and N.R. Hertzler *et al.*, ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease), *J Am Coll Cardiol* 2006; 47: 1239–1312.
8. Bird CE, Criqui MH, Fronck A, Denenberg JO, Klauber MR, Langer RD. Quantitative and qualitative progression of peripheral arterial disease by non-invasive testing. *Vasc Med* 1999; 4:15-21.

9. Aboyans V, Criqui MH, Denenberg JO, Knoke JD, Ridker PM, Fronck A. Risk factors for progression of peripheral arterial disease in large and small vessels. *Circulation* 2006; 113:2623-9.
10. Carter, S.A, Lezack, J.D. *Digital systolic pressures in the lower limb in arterial disease*. *Circulation*. 1971; 43:905-914.
11. Shadman R, Criqui MH, Bundens WP, et al. Subclavian artery stenosis: prevalence, risk factors, and association with cardiovascular diseases. *J Am Coll Cardiol* 2004;44:618 –23.
12. Orchard, T., et al *Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Diabetes Association and the American Heart Association September 18- 20, 1992 New Orleans, Louisiana*. *Circulation*,1993;88;819-828.
13. Fowkes FG, Housley, E, Macintyre CC, Prescott RJ, Ruckley CV. Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. *J Epidemiol Community Health* 1988; 42: 128-133.
14. Lezack JD, Carter SA. Systolic pressures in the extremities of man with special reference to the toes. *Can J Physiol Pharmacol* 1970; 48: 469-74.
15. Sawka AM, Carter SA. Effect of temperature on digital systolic pressures in lower limb in arterial disease. *Circulation* 1992; 85: 1097-101.
16. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. *J Am Soc Nephrol*. 2001;11:A0828.

17. Lachman AS, Spray TL, Kerwin DM, Shugoll GI, Roberts WC. Medial calcinosis of Mockenberg. A review of the problem and a description of patient with involvement of peripheral, visceral and coronary arteries. *Am J Med* 1977;63:615-22.
18. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. *J Vasc Surg.* 2008; 48(5):1197-203.
19. Ix JH, Miller RG, Criqui MH, Orchard TJ. Test characteristics of the ankle-brachial index and ankle-brachial difference for medial arterial calcification on X-ray in type 1 diabetes. *J Vasc Surg.* 2012; 56(3):721-7.
20. McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik JM, Liao Y, Criqui MH. Decline in Functional Performance Predicts Later Increased Mobility Loss and Mortality in Peripheral Arterial Disease. *Journal of the American College of Cardiology.* 2011; 57(8): 962-970.
21. Suominen V, Rantanen T, Venermo M, Saarinen J, Salenius J. Prevalence and Risk Factors of PAD among Patients with Elevated ABI. *Eur J Vasc Endovasc Surg.* 2008; 35(6):709-14.
22. Johnston KW, Hosang MY, Andrews DF. Reproducibility of noninvasive vascular laboratory measurements of the peripheral circulation. *J Vasc Surg* 1987; 6: 147-51.

Table 1. Baseline Characteristics by Ankle Brachial Index Categories

	ABI Categories				P-value
	< 0.60	0.60-0.89	0.90-1.30	> 1.30	
N					
(%)	106 (22%)	160 (34%)	189 (40%)	14 (3%)	
Age	70 ± 8	70 ± 8	66 ± 10	65 ± 9	0.002
Female	9 (8%)	17 (11%)	26 (14%)	0 (0%)	0.28
Black	5 (5%)	8 (5%)	5 (3%)	0 (0%)	0.55
Diabetes	49 (46%)	55 (34%)	52 (27%)	12 (86%)	< 0.001
Hypertension	90 (85%)	131 (81%)	128 (68%)	13 (92%)	0.01
Smoking					0.02
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	0.01
Toe brachial index	0.38 ± 0.12	0.54 ± 0.16	0.78 ± 0.22	0.69 ± 0.24	< 0.001

Data show mean ± SD or number (%).

Table 2. Number of Participants and Number of Deaths in Each ABI and TBI Category Overall and Stratified by Diabetes Status

	All Participants		Diabetes		No Diabetes	
	# Participants (%)	# Dead (%)	# Participants (%)	# Dead (%)	# Participants (%)	# Dead (%)
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 (33%)	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%)

Table 3. Relationship of ABI Categories with Cardiovascular Mortality Overall and Stratified by Diabetes Status.

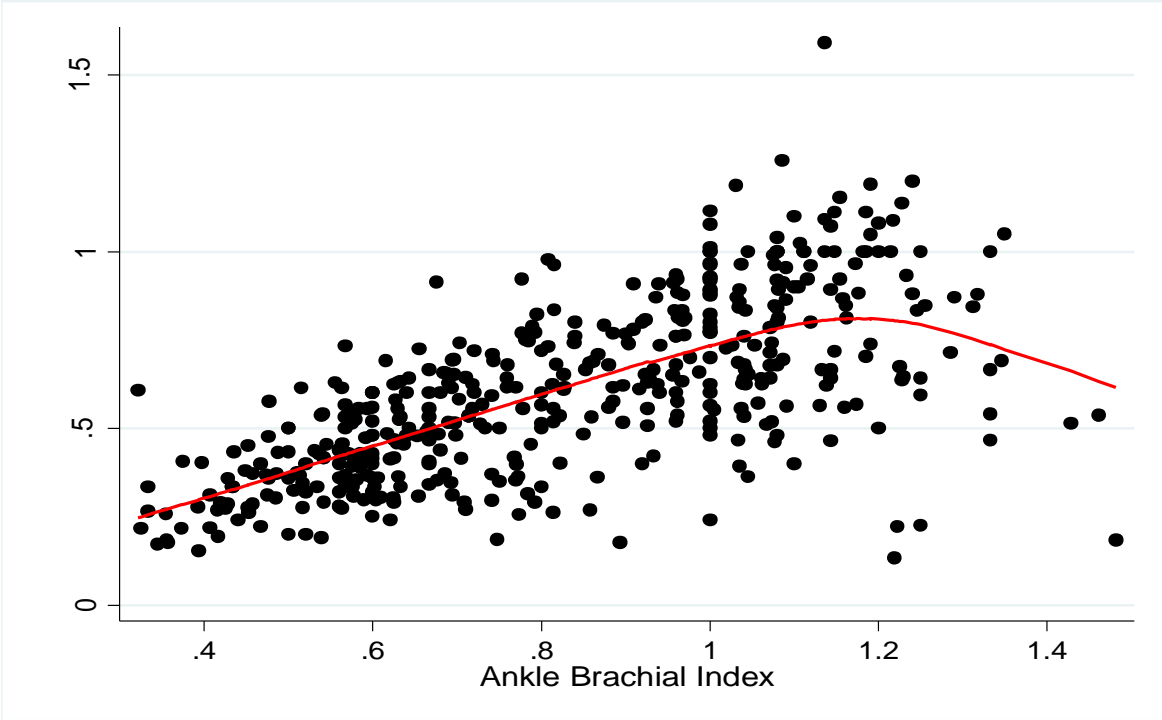
	All Participants		Diabetes†		No Diabetes‡	
	Age and Sex Adjusted HR (95% CI)	Fully Adjusted* HR (95% CI)	Age and Sex Adjusted HR (95% CI)	Fully Adjusted* HR (95% CI)	Age and Sex Adjusted HR (95% CI)	Fully Adjusted* HR (95% CI)
ABI						
Categories						
> 1.30	2.99 (1.33, 6.74)	1.81 (0.77, 4.24)	2.47 (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						
> 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)
0.40-1.61	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)

* Adjusted for age, sex, race, diabetes, smoking (current, former, never), systolic blood pressure, blood pressure medication use, total cholesterol, hdl cholesterol, lipid medication use, eGFR, and body mass index.

† p interaction by diabetes status in the fully adjusted model = 0.002

‡ p interaction by diabetes status in the fully adjusted model = 0.17

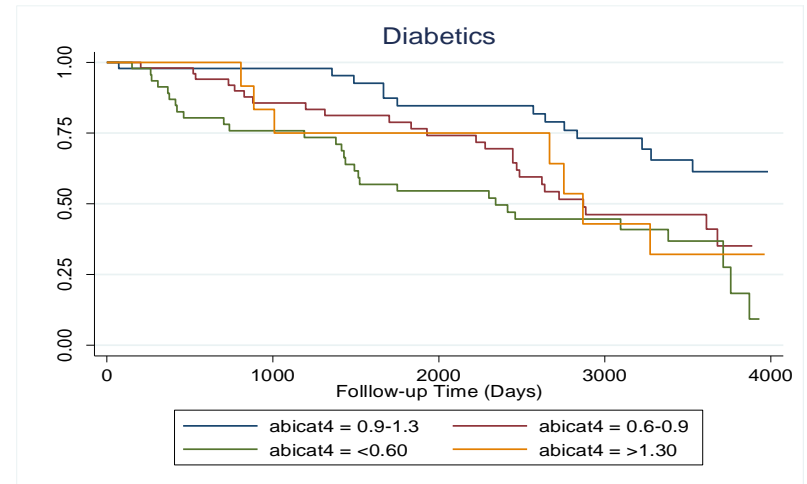
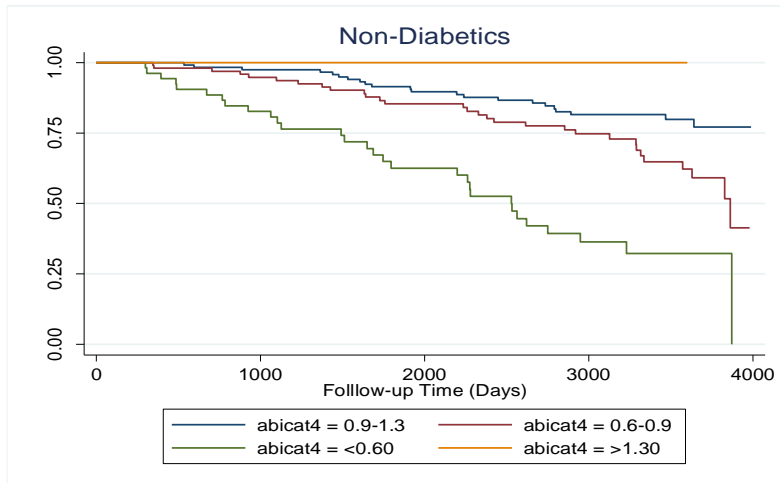
Figure 1. Distribution of Toe Brachial Index Measurements by Ankle Brachial Index Measurements



Legend: Figure shows the distribution of toe brachial index measurements as a function of ankle brachial index measurements. The Pearson correlation (r) = 0.63. The line depicts a lowess plot to demonstrate the nature of the relationship.

Figure 2. Kaplan-Meier Curves of ABI and TBI Categories with Cardiovascular Disease Mortality Stratified by Diabetes Status

ABI Categories



TBI Categories

