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ORIGINAL RESEARCH

Ankle-Brachial Index and Subsequent Risk of Severe Ischemic Leg Outcomes: The ARIC Study

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BACKGROUND: Ankle-brachial index (ABI) is used to identify lower-extremity peripheral artery disease (PAD). However, its association with severe ischemic leg outcomes (eg, amputation) has not been investigated in the general population.

METHODS AND RESULTS: Among 13 735 ARIC (Atherosclerosis Risk in Communities) study participants without clinical manifestations of PAD (mean age, 54 [SD, 5.8] years; 44.4% men; and 73.6% White) at baseline (1987–1989), we quantified the prospective association between ABI and subsequent severe ischemic leg outcomes, critical limb ischemia (PAD with rest pain or tissue loss) and ischemic leg amputation (PAD requiring amputation) according to discharge diagnosis. Over a median follow-up of ≈28 years, there were 221 and 129 events of critical limb ischemia and ischemic leg amputation, respectively. After adjusting for demographics, ABI ≤0.90 versus 1.11 to 1.20 had a ≈4-fold higher risk of critical limb ischemia and ischemic leg amputation (hazard ratios, 3.85 [95% CI, 2.09–7.11] and 4.39 [95% CI, 2.08–9.27]). The magnitude of the association was modestly attenuated after multivariable adjustment (hazard ratios, 2.44 [95% CI, 1.29–4.61] and 2.72 [95% CI, 1.25–5.91], respectively). ABI 0.91 to 1.00 and 1.01 to 1.10 were also associated with these severe leg outcomes, with hazard ratios ranging from 1.7 to 2.0 after accounting for potential clinical and demographic confounders. The associations were largely consistent across various subgroups.

CONCLUSIONS: In a middle-aged community-based cohort, lower ABI was independently and robustly associated with increased risk of severe ischemic leg outcomes. Our results further support ABI ≤0.90 as a threshold diagnosing PAD and also suggest the importance of recognizing the prognostic value of ABI 0.91 to 1.10 for limb prognosis.

Key Words: amputation ■ ankle-brachial index ■ peripheral artery disease ■ prognosis

Lower-extremity peripheral artery disease (PAD) affects over 200 million people worldwide and increases the risk of cardiovascular mortality and morbidity.[1] Despite its prevalence and prognostic importance, PAD is often underrecognized and underdiagnosed.[2] The ankle-brachial index (ABI), the ratio of ankle to brachial systolic blood pressure, is an important noninvasive method for identifying PAD.[3] An ABI ≤0.90 is considered PAD.[3] ABI ≤0.90 has been also associated with increased risk of mortality and cardiovascular events.[4,5]

However, to the best of our knowledge, no studies have investigated the association of ABI with subsequent risk of severe ischemic leg outcomes such as amputation in the general population. This is a critical knowledge gap with potential implications for the management and care of individuals with low ABI values.

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CLINICAL PERSPECTIVE

What Is New?

- In community-dwelling middle-aged adults, we found that low (≤0.90) ankle-brachial index (ABI) versus 1.11 to 1.20 were associated with 2.4 to 2.7 times the risk of critical limb ischemia and ischemic leg amputation, after accounting for potential confounders.
- Even ABI 0.91 to 1.00 (borderline low) and 1.01 to 1.10 demonstrated adjusted hazard ratios of 1.7 to 2.0 for these severe leg outcomes.

What Are the Clinical Implications?

- Our results further confirm ABI ≤0.90 as a threshold for peripheral artery disease diagnosis.
- Clinicians should recognize the elevated risk of severe leg events in those with ABI 0.91 to 1.00 and 1.01 to 1.10.
- The discussion about the value of peripheral artery disease screening using ABI has been mainly based on its contribution to cardiovascular risk prediction, but its association with severe leg outcomes should be considered.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
CLI	critical limb ischemia

Therefore, we examined the association between ABI and severe ischemic leg outcomes, independently of potential confounders, in a community-based cohort, the ARIC (Atherosclerosis Risk in Communities) study, with a median follow-up of 28 years. We also assessed whether ABI 0.91 to 1.00 (currently considered borderline low) and ABI >1.30 (indicative of uncompressible artery) were associated with severe ischemic leg outcomes.[6]

METHODS

The data and materials from the ARIC study are publicly available from the National Heart, Lung, and Blood Institute or can be requested to its coordinating center at the University of North Carolina.[7,8]

Study Participants

The ARIC study is a prospective cohort study, which enrolled 15 792 middle-aged participants from 4 US communities (Forsyth County, North Carolina; Washington County, Maryland; Jackson, Mississippi; and suburbs of Minneapolis, Minnesota) during 1987 to 1989 (visit 1).[9] Using visit 1 data, we excluded participants who identified themselves as non-White or non-Black because of the small sample size (n=48) and those with clinical manifestations of PAD (ie, self-reported history of leg revascularization or intermittent claudication based on the Rose questionnaire) at baseline (n=146). We also excluded participants with missing data on ABI, covariates, and outcomes of interest (n=1863). The excluded participants were more likely to have diabetes, hypertension, prevalent coronary heart disease, and prevalent heart failure compared with the participants we included in the study (Table S1). The resulting study population was composed of 13 735 participants. The institutional review boards at each field location approved the study, and all participants gave informed consent.

ABI Measurement

ABI measurements were taken according to a standardized protocol.[10] Specifically, a self-calibrating automated oscillometric device, Dinamap Model 1846 SX, was used to measure the blood pressure of the upper and lower extremities.[10] Ankle systolic blood pressure was taken in a randomly selected leg, wrapping the blood pressure cuff around the ankle. After calibrating the device for occlusion pressure, 2 measurements of the ankle blood pressure were taken. Brachial blood pressure was measured every 5 minutes when the participant was in the supine position. This was usually done in the right arm. At least 2 measurements of brachial blood pressure were recorded for each individual.[10] ABI was calculated as the average ankle systolic blood pressure divided by the average brachial systolic blood pressure.

Outcomes: Severe Ischemic Leg Outcomes

For severe ischemic leg outcomes, we included critical limb ischemia (CLI) (PAD with rest pain or tissue loss) and ischemic leg amputation (PAD requiring amputation) that occurred by December 31, 2018. CLI was defined as hospitalization with the following *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes (and corresponding *International Classification of Diseases, Tenth Revision* [*ICD-10*] codes)[11,12]: atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); or cases with the combination of tissue loss (leg amputation [84.1x], lower extremity ulcer [707.1x], and gangrene [785.4]) plus PAD (other atherosclerosis of native arteries of the extremities [440.29]; atherosclerosis of bypass graft of the extremities [440.3];

atherosclerosis of other specified arteries [440.8]; peripheral vascular disease, unspecified [443.9]; leg artery revascularization [38.18, 39.25, 39.29, 39.50]). Ischemic leg amputation was defined as coexistence of both leg amputation (84.1x) and PAD (as defined above).

Covariates

Sociodemographic covariates, including age, race, sex, and education level were self-reported.[13] Lifestyle factors such as smoking status and alcohol habit were assessed through questionnaires administered by interviewers.[11] Body mass index was calculated as weight (kg) divided by the square of height (m). Enzymatic methods were used to measure cholesterol. Seated blood pressure was measured 3 times, and the average of the last 2 was used for the analysis. The use of antihypertensive or cholesterol-lowering drugs was based on self-report and the inspection of medication containers.[14,15] Kidney function was assessed through estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[16] Diabetes was defined as a self-reported physician diagnosis of diabetes, fasting glucose of ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or use of antidiabetic medications.[13] Prevalent heart failure was determined based on the Gothenburg criteria.[15] Prevalent coronary heart disease was self-reported on the basis of previous diagnosis of myocardial infarction by a physician or coronary revascularization. Prevalent stroke was also self-reported according to prior physician diagnosis.[14]

Statistical Analysis

We summarized participant characteristics, mean (SD) or median (interquartile interval) for continuous

Table 1. Participant Characteristics by ABI Categories

	Overall	ABI category					
		≤0.90	0.91 to 1.00	1.01 to 1.10	1.11 to 1.20	1.21 to 1.30	>1.30
n	13 735	390	1197	3218	4407	3115	1408
Age, y	54.1 (5.8)	55.8 (5.7)	53.7 (5.8)	53.7 (5.7)	53.9 (5.7)	54.3 (5.8)	55.1 (5.7)
White, %	10 111 (73.6)	260 (66.7)	873 (72.9)	2325 (72.2)	3229 (73.3)	2331 (74.8)	1093 (77.6)
Male, %	6105 (44.4)	135 (34.6)	286 (23.9)	1092 (33.9)	2009 (45.6)	1721 (55.2)	862 (61.2)
Education level, %							
Grade school or no formal education	1269 (9.2)	64 (16.4)	112 (9.4)	279 (8.7)	405 (9.2)	280 (9.0)	129 (9.2)
High school, but no degree	1877 (13.7)	82 (21.0)	216 (18.0)	458 (14.2)	605 (13.7)	355 (11.4)	161 (11.4)
High school graduate	4459 (32.5)	109 (27.9)	436 (36.4)	1112 (34.6)	1453 (33.0)	909 (29.2)	440 (31.2)
Vocational school	1178 (8.6)	40 (10.3)	77 (6.4)	261 (8.1)	361 (8.2)	301 (9.7)	138 (9.8)
At least some college	3574 (26.0)	72 (18.5)	278 (23.2)	810 (25.2)	1105 (25.1)	908 (29.1)	401 (28.5)
Graduate school or professional school	1378 (10.0)	23 (5.9)	78 (6.5)	298 (9.3)	478 (10.8)	362 (11.6)	139 (9.9)
BMI, kg/m^2	27.6 (5.3)	27.9 (6.4)	28.3 (6.2)	27.6 (5.6)	27.4 (5.0)	27.4 (4.9)	28.1 (5.4
Systolic blood pressure, mm Hg	121.0 (18.8)	126.0 (22.8)	122.9 (21.2)	121.9 (20.0)	120.5 (18.4)	119.8 (17.1)	119.6 (16.3)
Current smoker, %	3546 (25.8)	193 (49.5)	378 (31.6)	879 (27.3)	1106 (25.1)	705 (22.6)	285 (20.2)
Current drinker, %	7743 (56.4)	178 (45.6)	654 (54.6)	1800 (55.9)	2495 (56.6)	1821 (58.5)	795 (56.5)
HDL cholesterol, mg/dL	52.1 (17.1)	50.2 (17.0)	53.4 (17.0)	53.8 (17.5)	52.3 (17.3)	50.9 (16.6)	49.8 (16.4)
LDL cholesterol, mg/dL	137.2 (39.1)	146.8 (45.3)	138.5 (39.3)	137.7 (40.2)	136.7 (39.2)	135.9 (37.5)	136.5 (37.4)
Total cholesterol, mg/dL	214.1 (41.2)	224.2 (47.5)	217.2 (41.4)	216.1 (42.2)	213.5 (40.9)	211.7 (39.8)	211.7 (40.0)
Diabetes, %	1519 (11.1)	87 (22.3)	149 (12.4)	363 (11.3)	470 (10.7)	293 (9.4)	157 (11.2)
Hypertension, %	3917 (28.5)	164 (42.1)	389 (32.5)	975 (30.3)	1246 (28.3)	778 (25.0)	365 (25.9)
Antihypertension medication, %	3376 (24.6)	157 (40.3)	336 (28.1)	847 (26.3)	1069 (24.3)	646 (20.7)	321 (22.8)
Cholesterol medication, %	378 (2.8)	21 (5.4)	40 (3.3)	94 (2.9)	109 (2.5)	73 (2.3)	41 (2.9)
eGFR, ml/min/1.73m^2	103.2 (94.9–111.5)	102.3 (91.4–112.5)	104.2 (95.9–111.9)	103.9 (95.4–112.3)	103.2 (94.9–111.6)	102.9 (94.9–111.1)	101.4 (93.6–109.3)
Prevalent coronary heart disease, %	636 (4.6)	43 (11.0)	73 (6.1)	131 (4.1)	177 (4.0)	138 (4.4)	74 (5.3)
Prevalent heart failure (%)	619 (4.5)	36 (9.2)	79 (6.6)	168 (5.2)	178 (4.0)	113 (3.6)	45 (3.2)
Prevalent stroke, %	248 (1.8)	8 (2.1)	22 (1.8)	64 (2.0)	89 (2.0)	42 (1.3)	23 (1.

ABI indicates ankle-brachial index; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein and LDL, low-density lipoprotein. Values indicate mean (SD), median (IQI), or count (%).

variables and proportion for categorical variables, according to ABI categories of ≤0.90, 0.91 to 1.00, 1.01 to 1.10, 1.11 to 1.20, 1.21 to 1.30, and >1.30, based on the previous literature.[4,6] We used the Kaplan-Meier method to evaluate the cumulative incidence of CLI and ischemic leg amputation.

We used Cox regression models to quantify the association between ABI and the outcomes after accounting for potential confounders. Model 1 adjusted for age, race, sex, and study site. Model 2 was further adjusted for education level, body mass index, total cholesterol, high-density lipoprotein cholesterol, cholesterol-lowering drugs, systolic blood pressure, antihypertensive drugs, smoking status, drinking status, diabetes, kidney function, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke. The 1.11 to 1.20 ABI category was used as the reference since it was the most prevalent group and has been used as the reference category in prior studies.[4] The proportional hazards assumption was checked and verified by using Schoenfeld residuals. We also modeled ABI as a restricted cubic spline, with knots at ABI 0.94, 1.10, 1.19, and 1.35, which correspond to the 5th, 35th, 65th, and 95th percentiles, respectively. The reference was set at ABI 1.15 (midpoint of the reference ABI category 1.11–1.20).[17]

As a sensitivity analysis, we stratified the study sample by age, sex, race, smoking status, and the presence/absence of diabetes, hypertension, and prevalent coronary heart disease at baseline. Wald tests for interaction were used to determine whether there were significant differences in the association between a linear term of ABI and ischemic leg outcomes across each subgroup. Two-sided *P* values of <0.05 were considered statistically significant. All statistical analyses were completed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Among the 13 735 participants, the mean age was 54 years, with 73.6% being White and 44.4% men (Table 1). There were 390 individuals (2.8%) with ABI ≤0.90, 1197 (8.7%) with ABI 0.91 to 1.00, and 3218 (23.4%) with ABI 1.01 to 1.10. Participants with lower ABI were more likely to be Black and smokers and have traditional risk factors for PAD, such as diabetes, hypertension, and prevalent coronary heart disease. Those with ABI >1.30 had a higher body mass index and prevalence of coronary heart disease compared with the reference ABI of 1.11 to 1.20.

Risk of CLI and Ischemic Leg Amputation

Over a median of 27.7 and 28.2 years of follow-up, there were 221 and 129 events of CLI and ischemic leg amputation, respectively. Participants with ABI ≤0.90 had the highest cumulative incidence of CLI and ischemic leg amputation, followed by ABI 0.91 to 1.00 and then ABI 1.01 to 1.10 (Figure S1). Participants with

Table 2. Incidence and Hazard Ratios of Severe Ischemic Leg Outcomes According to ABI Categories

ABI range	Individuals	Incidence per 1000 person-years	Model 1	Model 2
Critical limb ischemia				
≤0.90	390	1.82	3.85 (2.09–7.11)*	2.44 (1.29–4.61)*
0.91 – 1.00	1197	0.95	2.35 (1.46–3.77)*	1.76 (1.09–2.85)*
1.01 – 1.10	3218	0.90	1.94 (1.35–2.79)*	1.85 (1.29–2.66)*
1.11 – 1.20	4407	0.50	Ref.	Ref.
1.21 – 1.30	3115	0.64	1.21 (0.82–1.79)	1.38 (0.93–2.05)
>1.30	1408	0.39	0.71 (0.39–1.31)	0.86 (0.46–1.59)
Ischemic leg amputation				
≤0.90	390	1.24	4.39 (2.08–9.27)*	2.72 (1.25–5.91)*
0.91 – 1.00	1197	0.68	2.92 (1.64–5.19)*	2.02 (1.13–3.63)*
1.01 – 1.10	3218	0.49	1.82 (1.13–2.92)*	1.73 (1.07–2.79)*
1.11 – 1.20	4407	0.30	Ref.	Ref.
1.21 – 1.30	3115	0.31	0.97 (0.57–1.65)	1.15 (0.68–1.97)
>1.30	1408	0.21	0.61 (0.27–1.38)	0.69 (0.30–1.58)

Model 1 – Adjusted by race, age, sex, and study site.

Model 2 – Adjusted for race, age, sex, study site, education level, adiposity, total cholesterol, HDL cholesterol, cholesterol-lowering drugs, systolic blood pressure, antihypertensive drugs, smoking status, drinking status, diabetes, kidney function, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

ABI indicates ankle-brachial index; and HDL, high-density lipoprotein.

ABI ≤0.90 category includes ABI range 0.42<ABI≤0.90.

*Values represent significant hazard ratios.

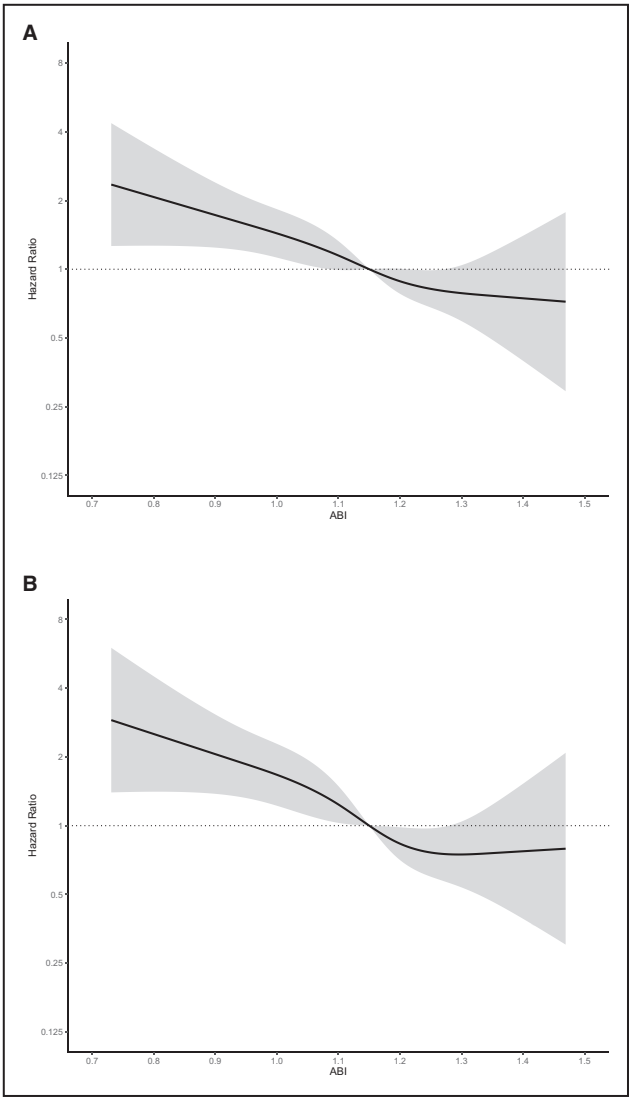

Figure 1. Adjusted hazard ratio of (A) critical limb ischemia and (B) ischemic leg amputation over ≈28 years according to ABI using cubic splines.

Hazard ratios in reference to ABI of 1.15 and adjusted for race, age, sex, study site, education level, adiposity, total cholesterol, HDL cholesterol, cholesterol-lowering drugs, systolic blood pressure, antihypertensive drugs, smoking status, drinking status, diabetes, kidney function, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke. Restricted cubic spline created with knots at the 5th, 35th, 65th, and 95th percentiles of ABI. The figure is trimmed at the 0.5th and 99.5th percentiles of ABI (0.73 and 1.47, respectively). ABI indicates ankle-brachial index; and HDL, high-density lipoprotein.

high ABI (>1.30) had the lowest incidence of these 2 outcomes.

ABI categories were associated with CLI and amputation after adjusting for demographic factors (Model 1 in Table 2). Low ABI (≤0.90) showed the strongest association, with hazard ratio (HR) 3.85 (95% CI, 2.09–7.11) for CLI and HR 4.39 (95% CI, 2.08–9.27) for ischemic leg amputation. Borderline low ABI (0.91–1.00) showed a robust association as well. For CLI, the HR was 2.35 (95% CI, 1.46–3.77) and for ischemic leg amputation, 2.92 (95% CI, 1.64–5.19). Even ABI 1.01 to 1.10 showed a significant relationship, with HRs 1.8 to 1.9. High ABI (>1.30) did not show increased risk for either outcome.

Additional adjustment for clinical factors attenuated the associations; however, all ABI groups ≤1.10 were associated with significantly elevated risk of both leg outcomes (Model 2 in Table 2). The greatest risk for both CLI and ischemic leg amputation was in ABI ≤0.90, with HR 2.44 (95% CI, 1.29–4.61) and 2.72 (95% CI, 1.25–5.91), respectively. ABI 0.91 to 1.00 and 1.01 to 1.10 had HR ≈1.7 to 2.0 for both outcomes. There was no risk for either outcome with high ABI. The results were largely consistent when we updated several covariates over time (Table S2). We confirmed the dose-response association between ABI and ischemic leg outcomes when ABI was modeled continuously in model 2 (Figure 1).

Subgroup Analyses

In the subgroups of race, smoking status, hypertension, and prevalent coronary heart disease, the results were consistent among both CLI and ischemic leg amputation (Figure 2). There were significantly stronger associations shown in men versus women and in no diabetes versus diabetes for both leg outcomes. We observed significant interaction by age for ischemic leg amputation (Figure 2B), with a stronger association in older versus younger participants.

DISCUSSION

In this large community-based study of middle-aged adults at baseline, we found that individuals with low ABI (≤0.90), borderline low ABI (0.91–1.00), and ABI 1.01 to 1.10 had elevated risks of severe leg outcomes of CLI and ischemic leg amputation relative to people with normal ABI (1.11–1.20). The association was largely consistent across demographic and clinical subgroups, although the association with both outcomes was weaker in women and participants with diabetes compared with their counterparts. High ABI >1.30 was not associated with elevated risk of these adverse leg outcomes. We confirmed graded associations between lower ABI and the 2 leg outcomes when ABI was modeled continuously with cubic spline terms.

Although the association of lower ABI with severe leg outcomes (eg, amputation) has been shown in selected clinical populations (ie, patients with PAD[18,19] or people with diabetes[20]), there are several unique aspects of our study. To the best of our knowledge, this is the first study demonstrating this association in the general population (Table S3). Thus, our findings are

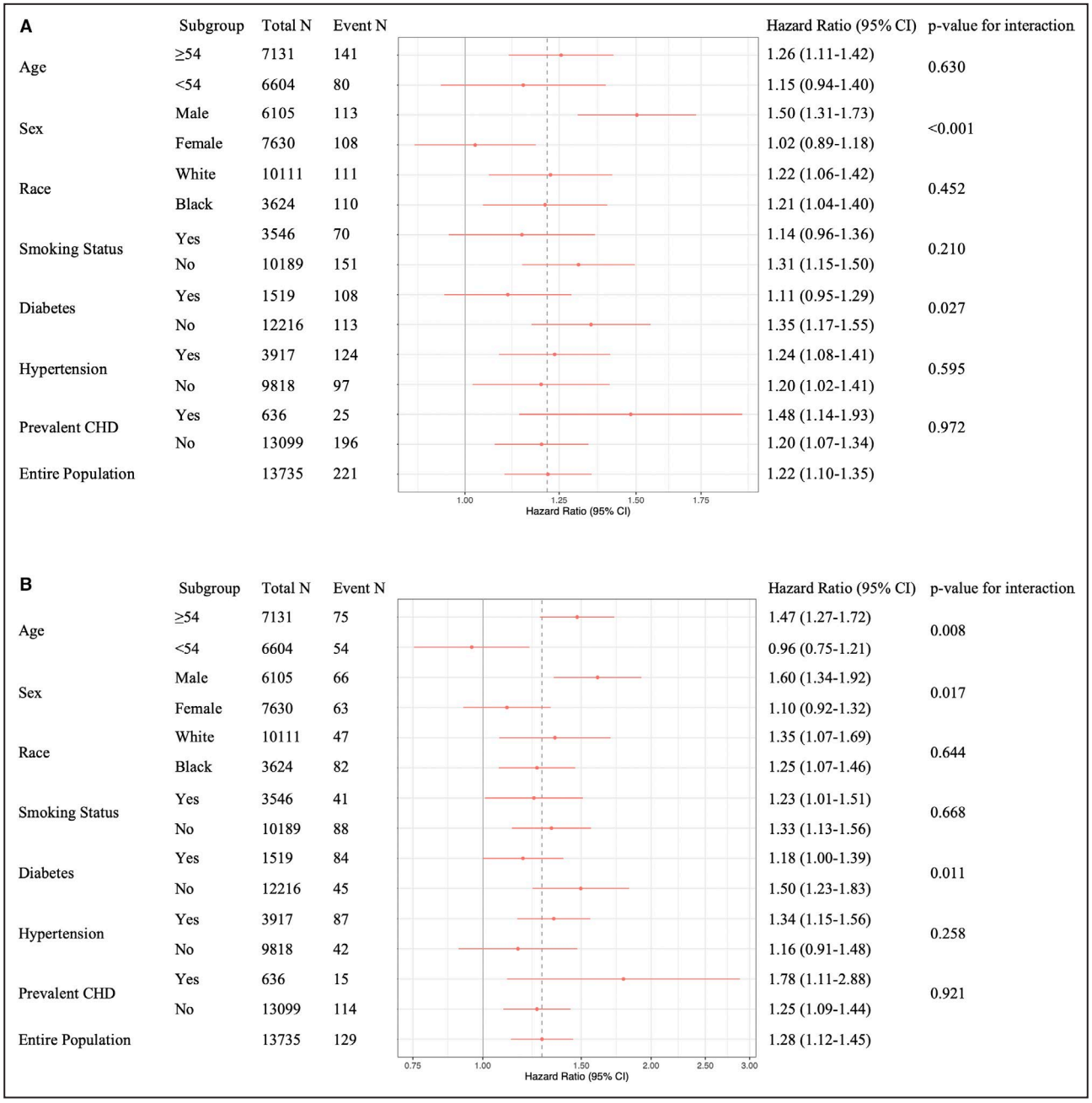

Figure 2. Hazard ratios of (A) critical limb ischemia and (B) ischemic leg amputation for 0.1 decrement of ABI by subgroups. ABI indicates ankle-brachial index; and CHD, coronary heart disease. Adjusted for race, age, sex, study site, education level, adiposity, total cholesterol, high-density lipoprotein cholesterol, cholesterol-lowering drugs, systolic blood pressure, antihypertensive drugs, smoking status, drinking status, diabetes, kidney function, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

likely to be more generalizable than previous studies. Also, reflecting the distribution of ABI in the general population, we uniquely observed elevated risk of severe leg outcomes for borderline low ABI (0.91–1.00) and even for ABI 1.01 to 1.10. Moreover, leveraging large sample size and long follow-up of ≈28 years, we confirmed overall consistent results across major demographic and clinical subgroups.

The lack of elevated risk of leg outcomes in high ABI in our study differs from a few previous reports based on patients with CLI and diabetes.[20–23] This discrepancy may be explained by the focus on diabetes mellitus in these other studies. Diabetes is a known risk factor of medial arterial calcification, which has been shown to increase ABI as well as the risk of amputation.[6,24] Indeed, most patients (>70%) in these previous

reports showing the positive association of high ABI and severe leg outcomes had diabetes.[21,23] In contrast, the prevalence of diabetes among those with ABI >1.30 in our study was ≈11%.

The statistically significant interactions for both ischemic leg outcomes by diabetes status and sex deserve some discussion. Medial arterial calcification may play a role here as well for the observed weaker association in diabetes than in no diabetes, since, as mentioned earlier, medial arterial calcification is common in people with diabetes and can result in misclassification of ABI.[25,26] Indeed, a few studies have shown that ABI is less prognostic in diabetes than in non–diabetes.[25,27] We are not sure about potential mechanisms behind a weaker association in women than in men. Of interest, a study has previously shown that ABI was more strongly associated with plasma fibrinogen, a known risk factor for cardiovascular outcomes,[28,29] in men than in women.[30] Nonetheless, we should keep in mind that this subgroup analysis was performed without any prespecified hypotheses and should be interpreted as hypothesis generating rather than hypothesis testing.

Our results have several clinical implications. These findings address a critical knowledge gap between ABI and leg outcomes since for various clinical diagnostic tests, their associations with their most relevant outcome(s) have guided how to interpret those tests (eg, glomerular filtration rate and its association with end-stage renal disease and glycated hemoglobin and its relation to diabetic complications).[31,32] Our results support ABI ≤0.90 as a threshold for diagnosing PAD. The robust association of ABI 0.91 to 1.00 with severe leg outcomes in our study is in line with a recent recognition of this range as borderline low ABI.[33] It is notable that even ABI 1.00 to 1.10 conferred ≈80% elevated risk of CLI and ischemic amputation after adjusting for potential confounders. Thus, it would be suboptimal if clinicians interpret this ABI range simply as normal. As of 2018, the US Preventive Services Task Force stated that there was insufficient information to determine the effectiveness of using ABI to screen for PAD in asymptomatic adults, mainly on the basis of the improvement of cardiovascular risk prediction by adding ABI to traditional predictors.[34] Given the purpose of ABI (ie, detecting leg atherosclerotic disease, PAD), it seems reasonable for future iterations of US Preventive Services Task Force to discuss any implications of ABI on leg outcomes. To enrich that discussion, further studies are needed to evaluate whether any interventions can reduce the risk of major ischemic leg outcomes in people with low ABI. In this regard, a few studies have shown that statins, already recommended in people with PAD regardless of leg symptoms,[3] may reduce the risk of major adverse limb events.[35,36]

There are several limitations of this study that should be considered. The ABI measurement was based on an oscillometer device. Additionally, the ABI measurements were obtained on a single, randomly selected leg. Nonetheless, any nondifferential misclassification of ABI should bias the results toward null. Finally, ARIC participants were mainly composed of middle-aged White and Black individuals; thus, the generalizability of these findings may be limited in other race or age groups.

In conclusion, lower ABI was independently and robustly associated with increased risk of CLI and ischemic leg amputation among this community-based cohort of middle-aged participants. Our results further support ABI ≤0.90 as a threshold for the diagnosis of PAD and also suggest the importance of recognizing the prognostic value of ABI 0.91 to 1.10 for limb prognosis.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Table S1-–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Excluded Participant Characteristics by ABI Categories.

		ABI Category					
	Overall	**≤0.90**	**0.91-1.00**	**1.01-1.10**	**1.11-1.20**	**1.21-1.30**	**>1.30**
n	2009	74	134	315	431	318	166
Age, years	54.5 (5.8)	58.1 (5.1)	54.8 (5.9)	54.3 (5.8)	54.2 (5.7)	54.6 (5.9)	54.8 (5.5)
White (%)	1367 (68.0)	51 (68.9)	85 (63.4)	204 (64.8)	286 (66.4)	226 (71.1)	128 (77.1)
Male (%)	954 (47.5)	37 (50.0)	48 (35.8)	135 (42.9)	214 (49.7)	177 (55.7)	79 (47.6)
Education Level (%)							
Grade School or No Formal Education	257 (13.0)	12 (16.2)	25 (18.7)	42 (13.8)	63 (14.8)	42 (13.3)	17 (10.5)
High School, but No Degree	351 (17.7)	20 (27.0)	34 (25.4)	52 (17.1)	68 (16.0)	52 (16.5)	29 (17.9)
High School Graduate	618 (31.2)	18 (24.3)	32 (23.9)	116 (38.2)	137 (32.2)	101 (32.1)	53 (32.7)
Vocational School	147 (7.4)	5 (6.8)	14 (10.4)	15 (4.9)	32 (7.5)	9 (2.9)	14 (8.6)
At Least Some College	426 (21.5)	16 (21.6)	26 (19.4)	61 (20.1)	78 (18.4)	68 (21.6)	36 (22.2)

Graduate School or Professional School	184 (9.3)	3 (4.1)	3 (2.2)	18 (5.9)	47 (11.1)	43 (13.7)	13 (8.0)
BMI, kg/m^2	28.6 (5.7)	28.4 (4.6)	29.1 (6.1)	29.0 (5.8)	28.0 (5.4)	28.5 (4.9)	29.0 (5.4)
Systolic Blood Pressure, mmHg	124.1 (20.1)	133.8 (22.9)	126.0 (19.7)	125.5 (20.7)	123.7 (20.0)	121.2 (17.0)	121.4 (18.2)
Current Smoker (%)	571 (28.7)	33 (45.2)	50 (37.3)	80 (25.8)	117 (27.5)	78 (24.7)	40 (24.1)
Current Drinker (%)	999 (51.6)	38 (53.5)	62 (47.3)	156 (51.3)	210 (50.5)	159 (52.5)	80 (50.3)
HDL, mg/dl	47.5 (16.6)	43.4 (14.1)	46.6 (16.9)	46.7 (17.3)	47.2 (18.5)	44.7 (15.2)	46.8 (14.7)
LDL, mg/dl	142.0 (41.2)	158.3 (40.0)	144.2 (41.4)	144.7 (45.2)	139.8 (39.7)	142.5 (42.0)	139.9 (36.5)
Total Cholesterol, mmol/L	5.7 (1.2)	6.3 (1.3)	5.9 (1.4)	5.8 (1.3)	5.7 (1.2)	5.7 (1.2)	5.7 (1.2)
Diabetes (%)	348 (18.7)	24 (33.8)	24 (19.7)	65 (23.0)	72 (18.1)	61 (21.2)	21 (14.1)
Hypertension (%)	723 (37.7)	33 (46.5)	54 (40.9)	124 (41.9)	145 (35.9)	123 (40.9)	57 (37.5)
Antihypertension Medication (%)	622 (32.4)	30 (42.3)	49 (37.4)	110 (37.3)	120 (29.7)	102 (33.9)	51 (33.6)

Cholesterol Medication (%)	74 (3.9)	6 (8.3)	3 (2.4)	14 (4.9)	16 (4.1)	14 (4.7)	5 (3.3)
eGFR [IQI]	102.9 [94.2, 111.9]	95.2 [76.2, 105.8]	103.2 [94.8, 113.4]	103.8 [94.9, 112.0]	103.3 [95.7, 111.8]	102.1 [94.7, 111.6]	102.0 [92.0, 110.3]
Prevalent Coronary Heart Disease (%)	129 (7.7)	13 (20.3)	7 (6.3)	24 (9.9)	21 (6.4)	26 (10.4)	9 (7.1)
Prevalent Heart Failure (%)	132 (7.7)	11 (16.4)	17 (14.0)	27 (10.4)	19 (5.6)	12 (4.7)	12 (9.0)
Stroke (%)	38 (2.3)	6 (8.6)	2 (1.8)	4 (1.6)	11 (3.3)	5 (2.1)	2 (2.0)

*ABI = ankle-brachial index, BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, eGFR = estimated glomerular filtration rate, IQI = interquartile interval

Table S2. Summary of Previous Epidemiological Reviews on Ankle-Brachial Index and Severe Ischemic Leg Outcomes among Selected Clinical Populations.

Paper Reference	Cohort	Cohort Description	N	Exposure	Main Outcomes	Findings of Interest
Moussa Pacha H, Mallipeddi VP, Afzal N, Moon S, Kaggal VC, Kalra M, Oderich GS, Wennberg PW, Rooke TW, Scott CG, Kullo IJ, McBane RD, II, Nishimura RA, Chaudhry R, Liu H, Arruda-Olson AM. Association of ankle-brachial indices with limb revascularization or amputation in patients with	Rochester Epidemiology Project	PAD patients from Olmsted County, Minnesota	1413	-Severe PAD (ABI <0.5) -Other ABI values (0.5≤ ABI ≤0.9) -Poorly compressible arteries (ABI ≥1.4)	Limb revascularization or amputation	-Severe PAD was associated with an elevated risk of limb revascularization (HR 2.69, 95% CI [2.15-3.37], P <.001) -Poorly compressible arteries did not confer a higher risk of limb revascularization -The poorly compressible arteries group had an increased risk of

peripheral artery disease. JAMA Network Open. 2018;1:e185547-e185547						limb amputation compared to the reference group (HR 3.12, 95% CI [2.16-4.50], P <.001) -Severe PAD did not have a significant association with limb amputation in the fully adjusted model
Miyata T, Higashi Y, Shigematsu H, Origasa H, Fujita M, Matsuo H, Naritomi H, Matsuda H, Nakajima M, Yuki S, Awano H. Evaluation of risk factors for limb-specific peripheral	Surveillance of Cardiovascular Events in Antiplatelet-treated Arterioscleros is Obliterans Patients in	Patients seen at medical clinics in Japan	6565	-Abnormal (ABI <0.90) -Borderline (0.9≤ ABI ≤1.0) -Normal (ABI ≥1.0)	Lower limb-specific peripheral vascular events, peripheral vascular events, composite	-Those with an abnormal ABI had an increased risk of any vascular event, any peripheral vascular event (including CLI and amputation), and all-cause death compared to

vascular events in patients with peripheral artery disease: A post hoc analysis of the SEASON Prospective Observational study. Angiology. 2019;70:506-514	Japan (SEASON)				vascular events, other SEASON events, all-cause death	normal ABI -Borderline ABI did not confer a statistically significant risk for limb-specific peripheral vascular events compared to normal ABI
Boyko EJ, Seelig AD, Ahroni JH. Limb- and person-level risk factors for lower-limb amputation in the prospective Seattle Diabetic Foot study. Diabetes Care. 2018;41:891-898	Prospective Seattle Diabetic Foot Study	Male patients with diabetes without foot ulcer seen at Department of Veterans Affairs (VA) Puget Sound Health	1461	-ABI ≤0.5 -0.5< ABI ≤0.9 -0.9< ABI <1.3 -ABI ≥1.3	Lower-limb amputation	-In the fully adjusted models, ABI ≤0.5, 0.5< ABI ≤0.9, and ABI ≥1.3 all conferred significantly elevated risks of lower-limb amputation compared to the reference of 0.9< ABI <1.3 -The highest risk of

		Care System - Seattle Division				amputation was seen in the ABI ≤0.5 group

*PAD = peripheral artery disease, ABI = ankle-brachial index, HR = hazard ratio, CI = confidence interval, CLI = critical limb ischemia

Table S3. Hazard Ratios of Severe Ischemic Leg Outcomes according to ABI Categories with Time Dependent Covariates.

	Critical Limb Ischemia	Ischemic Leg Amputation
ABI ≤ 0.90	**1.57 (1.10-2.25)**	1.52 (0.95-2.45)
ABI 0.91-1.00	**1.50 (1.15-1.95)**	**1.90 (1.37-2.62)**
ABI 1.01-1.10	**1.61 (1.33-1.95)**	**1.60 (1.23-2.08)**
ABI 1.11-1.20	Ref.	Ref.
ABI 1.21-1.30	**1.37 (1.11-1.68)**	1.19 (0.89-1.59)
ABI > 1.30	0.74 (0.53-1.04)	0.68 (0.43-1.06)

*Adjusted for race, age, sex, study site, education level, time dependent adiposity, total cholesterol, HDL cholesterol, time dependent cholesterol-lowering drugs, time dependent systolic blood pressure, time dependent antihypertensive drugs, smoking status, drinking status, diabetes, time dependent kidney function, prevalent coronary heart disease, prevalent heart failure, and stroke

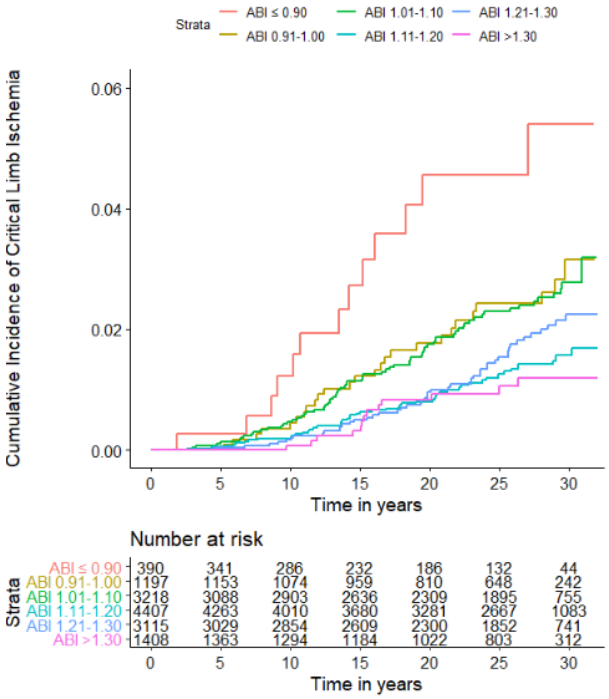
†Bolded values represent significant hazard ratios

‡ABI = ankle-brachial index, HDL = high-density lipoprotein

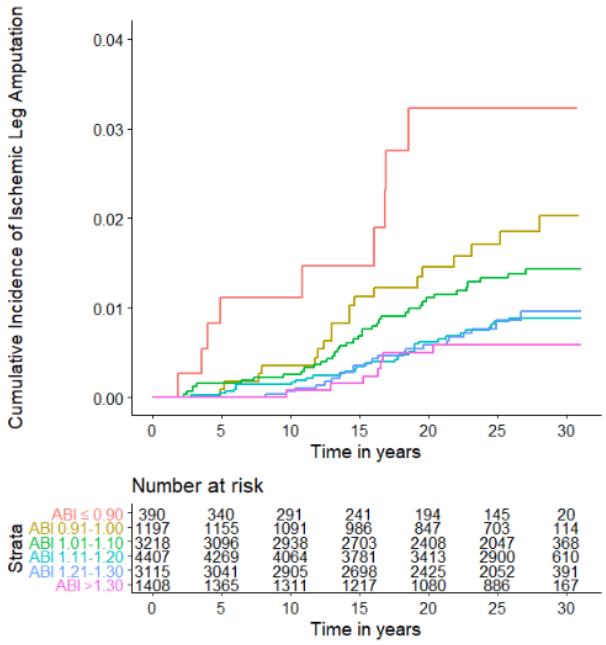
§A third measurement of systolic blood pressure was not available at Visit 4, so the average of measurements 1 and 2 was used

Figure S1. Cumulative Incidence of A) Critical Limb Ischemia and B) Ischemic Leg Amputation.

A)



B)



*ABI = ankle-brachial index