Association of Peripheral Artery Disease With Incident Atrial Fibrillation: The ARIC (Atherosclerosis Risk in Communities) Study

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Background—Although peripheral artery disease as defined by ankle-brachial index (ABI) is associated with incident atrial fibrillation (AF), questions remain about the risk of AF in borderline ABI (>0.90 to <1.0) or noncompressible arteries (>1.4). We evaluated the association of borderline ABI and ABI >1.4 in the ARIC (Atherosclerosis Risk in Communities) study, a population-based prospective cohort study.

Methods and Results—We included 14 794 participants (age, 54.2±5.8 years, 55% women, 26% blacks) with ABI measured at the baseline (1987–1989) and without AF. AF was identified from hospital records, death certificates, and ECGs. Using Cox proportional hazards, we evaluated the association between ABI and AF. During a median follow-up of 23.3 years, there were 2288 AF cases. After adjustment for cardiovascular risk factors, hazard ratio (HR) (95% confidence interval) for AF among individuals with ABI <1.0 compared with ABI 1.0 to 1.4, was 1.13 (1.01–1.27). ABI >1.4 was not associated with increased AF risk. ABI ≤0.9 and borderline ABI were associated with a higher risk of AF compared with ABI 1.0 to 1.4. Demographics-adjusted HRs (95% confidence interval) were 1.43 (1.17–1.75) and 1.32 (1.16–1.50), respectively. However, the associations of ABI ≤0.9 and borderline ABI with AF were attenuated after adjusting for cardiovascular risk factors (HR [95% confidence interval], 1.10 [0.90–1.34] and 1.14 [1.00–1.30]), respectively.

Conclusions—Peripheral artery disease indicated by low ABI, including borderline ABI, is a weak risk factor for AF. ABI >1.4 is not associated with an increased AF risk. The relationship between peripheral artery disease and AF appears to be mostly explained by traditional atherosclerotic risk factors. (***J Am Heart Assoc***. 2018;7:e007452. DOI: 10.1161/JAHA.117.007452.)

Key Words: ankle-brachial index • atherosclerosis • atrial fibrillation • peripheral artery disease • risk factors

A trial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time.[1] AF is associated with an increased risk of stroke,[2] heart failure,[3] and death.[4,5] AF is more prevalent in patients with peripheral artery disease (PAD) compared with the general population.[6–8] Data from the Reduction of Atherothrombosis for Continued Health (REACH) registry

have demonstrated the high co-prevalence of PAD and AF, and the additive risk of these 2 clinical syndromes.[7,8] In the REACH registry, there was an 11.5% prevalence of AF among patients with PAD compared with an estimated prevalence of 2.3% and 5.9% in the general population aged ≥40 and ≥65 years, respectively.[8,9] PAD is associated with incident clinical AF regardless of age, sex, race, and cardiovascular risk factors among postmenopausal women[10] and the general population.[11,12]

Although there is evidence to support an association of PAD with AF, no study has examined whether the association (as measured by the ankle-brachial index [ABI]) is different for ABI >1.4 versus ABI <1.0. Further, it is unknown what effect the severity of PAD (as measured by the ankle-brachial index [ABI]) has on AF incidence; specifically, whether borderline ABI (>0.9–<1.0) has a similar association as ABI ≤0.9 with AF incidence.

The aim of this study was to evaluate the longitudinal association of PAD (ABI <1.0 or >1.40), including borderline ABI (>0.9–<1.0) with AF incidence among participants in the ARIC (Atherosclerosis Risk in Communities) study.

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Clinical Perspective

What Is New?

- This study used American Heart association/American College of Cardiology clinical-guideline defined categories for ankle-brachial index to determine the relationship between peripheral artery disease and incident atrial fibrillation.

What Are the Clinical Implications?

- Both ankle-brachial index ≤0.9 and borderline ankle-brachial index were associated with a 13% increase in the risk of atrial fibrillation, indicating that borderline ankle-brachial index is not benign.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data underlying our work can be obtained through 2 mechanisms. First, interested investigators can contact the ARIC Coordinating Center at the University of North Carolina—Chapel Hill. Details about the procedures for data request can be found online.[13] Second, most ARIC data can be also obtained from BioLINCC, a repository maintained by the National Heart, Lung, and Blood Institute. The BioLINCC website[14] includes detailed information about the available data and the process to obtain such data. Any interested researcher could obtain a de-identified, minimal data set needed to replicate or reprove the study findings pending ethical approval following any of the 2 mentioned mechanisms.

Study Population

The ARIC study has been previously described.[15] Briefly, the ARIC study is a population-based prospective study of cardiovascular disease (CVD) in a cohort of 15 792 participants aged 45 to 64 years at enrollment (1987–1989) sampled from 4 US communities: suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. Only blacks were recruited in Jackson. The baseline visit (visit 1) and 4 follow-up visits—1990 to 1992 (visit 2), 1993 to 1995 (visit 3), 1996 to 1998 (visit 4), and 2011 to 2013 (visit 5), included interviews, laboratory measurements, and clinical examinations, including an ECG that was centrally read for AF. Participants were also contacted annually by phone to obtain medical updates. We included participants who had ABI information, free of prevalent AF, had a readable ECG and available covariates. Participants who had race other than white or black, along with non-whites in the Minneapolis and Washington County

field centers were excluded because of small numbers (Figure 1). The ARIC study protocol was approved by the institutional review boards of each participating center, and informed consent was obtained from each study participant.

ABI Measurement

Details of ABI measurement in the ARIC study have been previously described.[16,17] Briefly, resting ankle and brachial pressures were measured by a standardized protocol using a DINAMAP™ 1846 SX automated oscillometric device (Critikon, Tampa, FL). Ankle blood pressure was measured with the individual in a prone position, in only one leg, which was selected based on the fifth digit of the ARIC ID. If the number was even, the right leg was used; if the number was odd the left leg was used. Following a first manually triggered measurement to calibrate the occlusion pressure, 2 readings of ankle blood pressure were taken 5 to 8 minutes apart. Two brachial blood pressure measurements were then measured in the supine position, 5 minutes apart. The ankle-brachial index was calculated as the average of the 2 resting ankle systolic pressure readings divided by the average of the 2 resting brachial systolic pressure readings. The correlation between the duplicate blood pressure readings has been described[16] and was found to be 0.92 in the leg, and 0.90 in the arm. The mean difference between the duplicate readings was 0.5 mm Hg (95% confidence interval [CI]: 0.3–0.6) in the leg and 3.0 mm Hg (95% CI: 2.8–3.2) in the arm. The reliability of the single measure of ABI in ARIC has also been described.[18] The reliability coefficient was 0.68 (95% CI: 0.57–0.77) for the ankle blood pressure and 0.74 (95% CI: 0.62–0.83) for the brachial blood pressure. The reliability for the ABI based on single ankle and arm systolic blood pressures (SBPs) was 0.61 (95% CI: 0.50–0.70) and was similar to the estimated reliability of the ABI measured from 2 ankle pressures and 2 arm pressures (0.70).

Ascertainment of Incident AF

The methods used for AF ascertainment in ARIC have previously been described in detail.[19,20] AF was identified through hospital discharge diagnosis codes, death certificates, or study visit ECGs, when *International Classification of Diseases, Ninth Revision, clinical modification* (*ICD-9-CM*) code 427.31 or 427.32 or *ICD-10* code I48, was listed in any position. All study visit ECGs coded by ECG software as AF were visually re-checked by a cardiologist or trained coder to confirm the diagnosis.

Ascertainment of Covariates

Covariates were obtained at baseline and included age at study entry, sex, race, education level, ARIC field center,
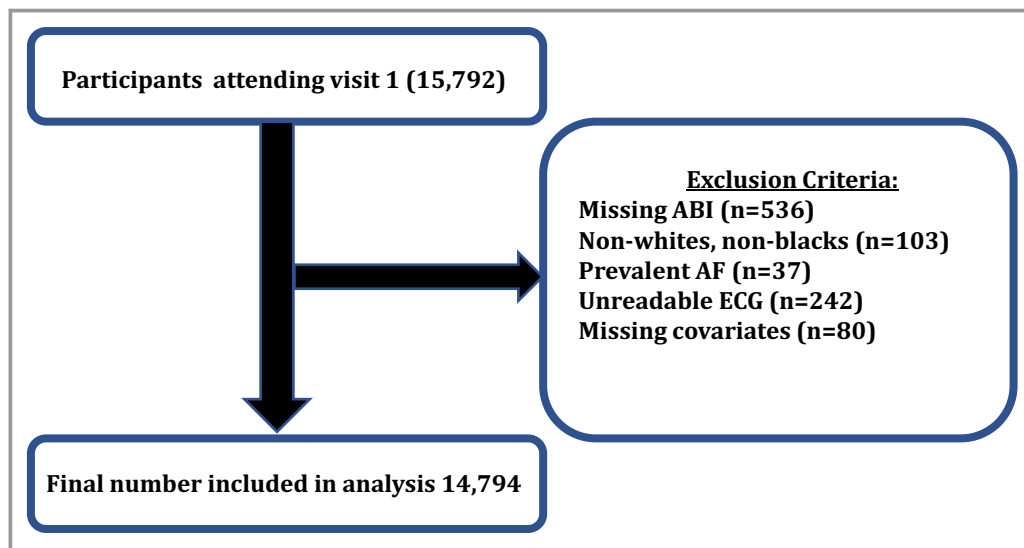
Figure 1. Inclusion and exclusion criteria. ABI indicates ankle-brachial index; AF, atrial fibrillation.

smoking status, body mass index, systolic blood pressure, diabetes mellitus, coronary heart disease, heart failure, use of antihypertensive medications, and left ventricular ejection fraction. Race was based on self-report, and combined with study center to create a 5-level variable. Hypertension was defined as use of medication to treat high blood pressure in the previous 2 weeks, and confirmed by medications brought to the visit by the participant, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as a self-reported physician's diagnosis of diabetes mellitus, use of diabetic medications, nonfasting serum glucose levels ≥200 mg/dL, or fasting serum glucose levels ≥126 mg/dL. Heart failure at baseline was defined as the reported use of medications to treat heart failure in the previous 2 weeks or the clinical presence of heart failure. Heart failure at follow-up visits was defined as the presence of *ICD-9-CM* code 428 in any hospitalization during follow-up. Prevalent coronary heart disease (CHD) was defined as self-reported, physician-diagnosed CHD or the presence of a previous myocardial infarction (MI) by ECG. Questionnaires during study visits assessed self-reported smoking status (current, former, never) and smoking amount.

Statistical Analyses

ABI measurements at ARIC visit 1 were used in this analysis. ABI was evaluated according to guideline-defined categories of PAD diagnosis: ABI values of 1.00 to 1.40 being normal, ≤0.90 abnormal, >0.9 to <1.0 borderline, and values >1.40 indicating noncompressible arteries.[21] We first explored the relationship between PAD and AF using restricted cubic splines adjusted for age, race, and sex.[22] To estimate the association of PAD with incident AF, we calculated hazard

ratios (HRs) and 95% confidence intervals (CIs) using multivariable Cox proportional hazard models. Person-years at risk were calculated from ABI measurement until date of diagnosis of AF, death, loss to follow up, or end of follow up (December 2012), whichever occurred first. The first multivariable model was adjusted for age, sex, race/ARIC field center. The second model additionally adjusted for education level, smoking status, body mass index, SBP, use of antihypertensive medication, statin use, diabetes mellitus, coronary heart disease, heart failure, cigarette years among smokers, diastolic blood pressure (DBP), and height. Incidence rates per 1000 person-years were also calculated. We adjusted for age and sex because AF incidence and prevalence increase with age[1,20] and are different between men and women.[20] We additionally adjusted for race/ARIC field center because blacks have a lower incidence of AF compared with whites,[20] therefore there are differences in incidence rates of AF in the various ARIC field centers.

Subgroup analyses were performed with stratification of the cohort according to sex, race, diabetes mellitus and CHD status. We performed additional analyses evaluating the association of baseline ABI with the risk of death among individuals with incident AF. Statistical analyses were performed with SAS v 9.3 (SAS Inc, Cary, NC).

Results

Table 1 shows selected clinical and socioeconomic characteristics of study participants overall, and by PAD status. There were 8169 (55%) female participants and 3900 participants (26%) were black. Compared with ABI 1.0 to 1.40, participants with ABI <1.0 were more likely to be female and have higher prevalence of traditional atherosclerotic risk factors.

Table 1. Baseline Participant Characteristics by ABI, ARIC Study, 1987–1989

Characteristics	ABI				P Value for Comparison
	Total (N=14 794)	<1.0 (n=2232)	1.0 to 1.40 (n=12 182)	>1.40 (n=379)	
Age, mean (SD), y	54.2 (5.8)	55.7 (5.9)	54.1 (5.7)	55.1 (5.7)	<0.0001
Female	8169 (55%)	1559 (69%)	6448 (53%)	162 (43%)	<0.0001
Black	3900 (26%)	624 (28%)	3207 (26%)	69 (18%)	0.003
Education level					<0.0001
<High school	3477 (24%)	645 (29%)	2748 (23%)	84 (22%)	
Completed high school	6073 (41%)	934 (42%)	4985 (41%)	154 (41%)	
Some college	5244 (35%)	653 (29%)	4449 (36%)	141 (37%)	
Cigarette smoking					<0.0001
Current	3838 (26%)	722 (32%)	3034 (25%)	82 (22%)	
Former	4781 (32%)	637 (29%)	4014 (33%)	130 (34%)	
Never	6175 (42%)	873 (39%)	5134 (42%)	167 (44%)	
Cigarette years of smoking, mean (SD)	315.3 (434.8)	488.9 (556.7)	308.3 (426.8)	287.4 (439.2)	<0.0001
Body mass index, mean (SD), kg/m^2	27.7 (5.3)	28.0 (6.1)	27.6 (5.3)	29.1 (5.9)	<0.0001
Height, mean (SD), cm	168.5 (9.3)	165.7 (8.7)	168.6 (9.3)	170.3 (9.5)	<0.0001
Diabetes mellitus	1731 (12%)	327 (15%)	1354 (11%)	50 (13%)	<0.0001
Use of hypertension medications*	4501 (30%)	825 (37%)	3545 (29%)	131 (35%)	<0.0001
Alpha-beta blockers	1380 (9%)	259 (12%)	1076 (9%)	45 (12%)	<0.0001
Calcium blockers	515 (3%)	93 (4%)	400 (3%)	22 (6%)	0.005
Antihypertensive (including beta blockers and combination medications)	1427 (10%)	277 (12%)	1116 (9%)	34 (9%)	<0.0001
Diuretics	2607 (18%)	490 (22%)	2041 (17%)	76 (20%)	<0.0001
Use of statins	84 (0.6%)	24 (1.1%)	57 (0.5%)	3 (0.8%)	0.002
Systolic blood pressure, mm Hg	121.2 (18.8)	125.8 (21.5)	121.1 (18.8)	118.7 (16.4)	<0.0001
Diastolic blood pressure, mm Hg	73.6 (11.2)	72.7 (12.1)	73.7 (11.2)	71.6 (10.7)	0.0001
Coronary heart disease	710 (5%)	145 (7%)	537 (4%)	28 (7%)	<0.0001
Heart failure	676 (5%)	160 (7%)	500 (4%)	16 (4%)	<0.0001

ABI indicates ankle-brachial index; ARIC, Atherosclerosis Risk in Communities.
Values are mean (SD) or n (%).
*Some participants have >1 medication.

There were 2288 (15%) incident AF events among 14 794 participants during a median (25th and 75th percentile) follow-up time of 23.3 (16.4–24.4) years. Age-, race-, and sex-adjusted restricted cubic spline models of the relationship between PAD (based on ABI categories) and AF are shown in Figure 2. The restricted cubic splines supported using the clinically-relevant categories in our analyses, supported both by the population distribution in ABI values and the significant linear association with AF in those with ABI <1.0 and then the non-significant associations and linear relationships in the other 2 categories. The P value for trend was non-linear based on using the categorical variable as a continuous term. There was a U-shaped relationship, with higher hazard ratios for AF seen in ABI <1 (including borderline ABI) as well as ABI >1.4.

After adjustment for age, sex, race/ARIC field center (model 1), ABI <1 was associated with a higher risk of AF compared with those with ABI 1.0 to 1.4: HR (95% CI) 1.35 (1.21–1.51). ABI >1.4 (noncompressible arteries) was not associated with increased AF risk (Table 2). The association of ABI <1 with incident AF was attenuated after additional adjustment for variables in model 2, but an increased risk of AF persisted: HR (95% CI) 1.13 (1.01–1.27). A post hoc power calculation was performed to determine whether the non-significant association among individuals with an ABI >1.4 was related to a small sample size. With a type I error of 0.05,
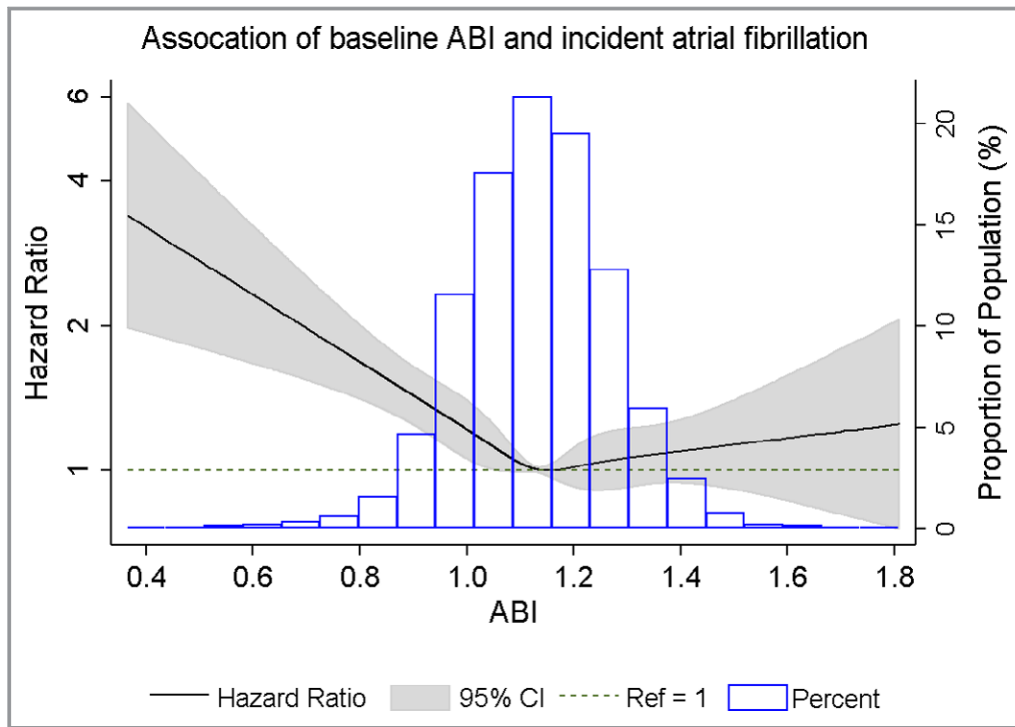
Figure 2. Age, race, and sex adjusted restricted cubic spline of the relationship between PAD and AF. *P* value for a linear relationship <0.001. Indicating it is not a linear association. ABI indicates ankle-brachial index; AF, atrial fibrillation; PAD, peripheral artery disease.

a sample of 379 participants in the ABI >1.4 group, a sample of 12 183 participants in the reference group, and AF incident proportion of 15% in the reference group, we had 37% and 86% power to detect a HR of 1.2 and 1.4, respectively, for incident AF. Therefore, the non-significant association between ABI >1.4 and incident AF might have been because of inadequate power.

When borderline ABI was assessed as a separate category, it was also found to be associated with higher risk of AF. After adjustment for age, sex, race/field center (model 1), both ABI ≤0.9 and ABI >0.9 to <1.0 were associated with a higher risk of AF compared with ABI 1.0 to 1.4 (Table 3). After additional multivariable adjustment (model 2), the associations were attenuated (ABI ≤0.9: HR [95% CI], 1.10 [0.90–1.34]; ABI >0.9 to <1.0: HR [95% CI], 1.14 [1.00–1.30]). In subgroup analysis, there was no interaction of the relationship between PAD and AF by sex (*P*=0.88), race (*P*=0.86), diabetes mellitus (*P*=0.80), or CHD status (*P*=0.54).

Table 2. Cox Regression Models, Assessing the Association Between PAD (Based on ABI Category) and Presence of Atrial Fibrillation, ARIC Study, 1987–2012

	ABI		
	<1.0 (n=2232)	1.0 to 1.4 (n=12 183)	>1.40 (n=379)
# Incident atrial fibrillation	373 (17%)	1846 (15%)	69 (18%)
Person-years	44 572	244 365	7581
Incidence rate (95% CI)*	8.4 (7.5–9.3)	7.6 (7.2–7.9)	9.1 (7.1–11.5)
HR (95% CI), model 1[†]	1.35 (1.21–1.51)	1 (ref.)	1.02 (0.81–1.30)
HR (95% CI), model 2[‡]	1.13 (1.01–1.27)	1 (ref.)	0.96 (0.75–1.23)

ABI indicates ankle-brachial index; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR hazard ratio.
*Incidence rate per 1000 person-years.
[†]Model 1: adjusted for age, sex, and race/study center.
[‡]Model 2: Model 1+education level, smoking status, body mass index, systolic blood pressure (SBP), use of antihypertensive medication, statin use, diabetes mellitus, coronary heart disease, heart failure, cigarette years of smoking, diastolic blood pressure (DBP), and height.

Table 3. Cox Regression Models, Assessing the Association Between PAD (Based on ABI Category Including Borderline ABI) and Presence of Atrial Fibrillation, ARIC Study, 1987–2012

	ABI			
	≤0.90 (n=620)	>0.90 to <1.0 (n=1612)	1.0 to 1.4 (n=12 183)	>1.40 (n=379)
# Incident atrial fibrillation	103 (17%)	270 (17%)	1846 (15%)	69 (18%)
Person-years	10 371	31 201	244 365	7581
Incidence rate (95% CI)*	9.9 (8.1–12.0)	8.7 (7.7–9.7)	7.6 (7.2–7.9)	9.1 (7.1–11.5)
HR (95% CI), model 1†	1.43 (1.17–1.75)	1.32 (1.16–1.50)	1 (ref.)	1.02 (0.81–1.30)
HR (95% CI), model 2‡	1.10 (0.90–1.34)	1.14 (1.00–1.30)	1 (ref.)	0.96 (0.76–1.23)

ABI indicates ankle-brachial index; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR hazard ratio; PAD, peripheral artery disease.
*IR per 1000 person-years.
†Model 1: adjusted for age, sex, and race.
‡Model 2: Model 1+education level, smoking status, body mass index, systolic blood pressure (SBP), use of antihypertensive medication, statin use, diabetes mellitus, coronary heart disease, heart failure, cigarette years of smoking, diastolic blood pressure (DBP), and height.

Among individuals with incident AF, with ABI 1.0 to 1.4 as the reference group, HR (95% CI) of all-cause mortality in individuals with borderline ABI was 1.37 (1.16–1.62). It was 1.48 (1.16–1.89) for those with PAD (ABI ≤0.90), compared with those with normal ABI. The risk of all-cause mortality among those with ABI >1.4 was non-significant (1.02 [0.73–1.44]) (Table 4). Among individuals who did not develop AF, HR (95% CI) for all-cause mortality was 1.42 (1.25–1.61) for those with ABI ≤0.9 and 1.16 (1.05–1.28) for those with ABI >0.90 to <1.0.

Discussion

In this biracial middle-aged cohort with long follow-up, PAD was associated with incident AF. After adjustment for atherosclerotic risk factors, both ABI ≤0.9 and borderline ABI were associated with a 13% increase in the risk of AF. ABI >1.4 was not associated with an increased risk of AF. Among individuals with incident AF, those with borderline ABI as well as those with PAD, have an increased risk of all-cause

mortality compared with those with normal ABI. These findings add to the growing body of evidence which indicates that borderline ABI is not benign.

Prior studies that have evaluated the relationship of PAD to AF have defined PAD as ABI <1.0 or >1.4.[10,11] In a report by O'Neal and colleagues using data from the MESA (Multi-Ethnic Study of Atherosclerosis) Study,[11] the associations between high (>1.4) and low (<1.0) ABI values with AF were examined separately. They were individually found to be in the same direction as the association between PAD (defined as both ABI <1.0 and ABI >1.4 grouped together) and AF. The adjusted HR (95% CI) for ABI <1.0 was 1.5 (1.1–2.0); ABI >1.4, adjusted HR 1.8 (0.65–4.8). The non-significant result for ABI values >1.4 was attributed to the small number of participants in this group (n=40) and small number of AF cases (n=4).

By contrast, in our study (which included 379 participants with ABI >1.4 and 69 incident AF cases in this group), we did not observe any association between ABI >1.4 and incident AF (HR 0.97 [0.76–1.23]). Although the absence of an association in our study is most likely because of a small

Table 4. Cox Regression Models, Assessing the Risk of Death Within Strata of AF Status, ARIC Study, 1987–2012

	ABI			
	≤0.90 (n=620)	>0.90 to <1.0 (n=1612)	1.0 to 1.4 (n=12 183)	>1.40 (n=379)
Those who developed AF				
HR (95% CI), model 1*	1.92 (1.51–2.44)	1.52 (1.28–1.79)	1 (ref.)	0.90 (0.64–1.25)
HR (95% CI), model 2†	1.48 (1.16–1.89)	1.37 (1.16–1.62)	1 (ref.)	1.02 (0.73–1.44)
Those who did not develop AF				
HR (95% CI), model 1*	2.09 (1.84–2.37)	1.38 (1.25–1.52)	1 (ref.)	0.90 (0.74–1.10)
HR (95% CI), model 2†	1.42 (1.25–1.61)	1.16 (1.05–1.28)	1 (ref.)	0.95 (0.77–1.16)

ABI indicates ankle-brachial index; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio.
*Model 1: adjusted for age, sex, and race.
†Model 2: Model 1+education level, smoking status, body mass index, systolic blood pressure (SBP), use of antihypertensive medication, statin use, diabetes mellitus, coronary heart disease, heart failure, cigarette years of smoking, diastolic blood pressure (DBP), and height.

sample size, there are other explanations to consider. Noncompressibility is related to the presence of medial arterial calcification which is more common in the elderly and diabetics.[23] This is in contrast to low ABI where atherosclerosis is the primary mechanism. The different underlying pathophysiology may have some bearing on the prognostic significance of ABI <1.0 versus ABI >1.4. Some studies have found an association between ABI >1.4 with higher risk of cardiovascular risk factors or outcomes, whereas others have not. Lilly et al[23] found that ABI ≤0.9, as well as ABI ≥1.4, were independently associated with increased coronary artery calcium compared with ABI 0.91 to 1.3. Arain et al,[24] also found that individuals with ABI ≥1.4 along with those with ABI ≤0.9, have higher all-cause mortality than those with normal ABI. On the other hand, other reports have shown that high ABI was not consistently associated with worse outcomes. For example, Hendriks et al,[16] evaluated the association of high ABI (≥1.4) with adverse outcomes in a high-risk population. They found that although ABI ≥1.4 was associated with an increased risk of myocardial infarction; there was no association with stroke, all-cause mortality or vascular mortality, compared with ABI 0.9 to <1.4.

The association of borderline ABI with higher incidence of AF is noteworthy. The study population was middle aged at the time of ABI measurement (mean age 54 years). Previous reports have shown that borderline ABI is associated with increased CVD risk. Menke and colleagues[25] reported a 10-year CHD risk of ≥20% in individuals with borderline ABI. In addition, CHD, stroke, and CVD prevalence were higher among individuals with borderline PAD compared with those with normal ABI: OR (95% CI) for age, sex and race/center-adjusted and multivariable-adjusted models were 2.03 (1.25–3.31) and 1.45 (0.80–2.63) respectively. Further, McDermott et al[26] investigated associations between ABI and subclinical atherosclerosis in the MESA study. They found that borderline ABI was associated with higher coronary calcium (CAC) score: OR (95% CI) for Agatston CAC score >20 for males with borderline ABI compared with those with normal ABI was 1.72 (1.12–2.63). In addition, in the ARAPACIS Study,[27] Italian investigators followed 2027 patients with AF for a median of 34.7 months and found that ABI ≤0.9 was associated with an increased risk of vascular death (HR: 2.047, 95% CI: 1.255–3.338; *P*=0.004) and MI (HR: 2.709, 95% CI: 1.485–5.083; *P*=0.001) in these patients. In our study, among individuals with incident AF, all-cause mortality was 1.37 times higher in those with borderline ABI and 1.48 times higher in those with PAD, compared with individuals with normal ABI. Among individuals without AF, PAD was associated with a 42% increased risk of all-cause mortality and borderline ABI was associated with a 16% increased risk of all-cause mortality. This indicates that even in the absence of AF, borderline ABI is linked to adverse outcomes.

The link between borderline ABI and CVD may be related to endothelial dysfunction in individuals with subclinical atherosclerosis. In a 2011 paper,[28] Finnish investigators evaluated endothelial function among individuals with borderline ABI. Assessment of endothelial function was performed by measuring the reactive hyperemia index at the fingertips of these individuals. The investigators detected endothelial dysfunction, defined as reactive hyperemia index <1.67 in one quarter of the subjects, and this finding did not differ based on their cardiovascular risk factors. To our knowledge, our study is the first to show that borderline ABI is an independent risk factor for another cardiovascular outcome, namely AF.

Another important finding of our study was the weaker association of PAD and AF compared with what has been previously described. The WHI analysis[10] showed an HR (95% CI) 1.53 (1.37–1.72). Of 81 892 women, 8252 developed AF over a mean follow up of 9.8 years. The WHI paper, however, suffered from an important limitation: PAD was self-reported. In the MESA analysis,[11] 301 of 6568 participants developed AF over a median follow up of 8.5 years. The HR (95% CI) for the association between PAD and AF was 1.5 (1.1–2.0). Our analysis had 2288 incident AF events among 14 794 participants, during a median (25th percentile and 75th percentile) follow-up time of 23.3 (16.4–24.4) years. Overall, our analysis has a larger sample size, more than double the follow up time, and an objective assessment of PAD status.

Our study has some limitations. Ankle blood pressure was measured only in one leg which may underestimate PAD prevalence since the disease is often unilateral. Thus, the associations of ABI with prevalent atherosclerotic disease may have been underestimated. Previous reports have however demonstrated that ABI measurements in ARIC have comparable reliability to ABI measured from two ankle pressures and two arm pressures.[18] Since only one measure of ABI was used in this analysis, individuals who developed PAD afterwards, may have been missed. Most of our AF cases are identified from hospitalizations, which may not account for AF managed in outpatient setting. Also, as AF is often transient, asymptomatic patients may have been missed. Therefore, there is likely an under ascertainment of incident AF cases. However, AF cases through hospitalizations in ARIC have been validated, with a sensitivity of 84% and sensitivity of 98%.[20] Despite these limitations, this study has important strengths, including the large sample size, availability of information on potential confounders, and extended follow-up.

Conclusion

In this large population-based cohort of middle-aged adults with long follow up and objective assessment of PAD, guideline-defined PAD indicated by low ABI, is a weak risk

factor for AF. This includes borderline ABI. Borderline ABI is a marker of subclinical atherosclerosis, and is not benign. ABI >1.4 is not associated with an increased AF risk. The relationship of PAD and AF appears to be mostly explained by traditional atherosclerotic risk factors.

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None.

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