The Ankle-Brachial Index and Incident Cardiovascular Events in the MESA (Multi-Ethnic Study of Atherosclerosis)

Michael H. Criqui, MD, MPH,* Robyn L. McClelland, PtiD,† Mary M. McDermott, MD,‡ Matthew A. Allison, MD, MPH,* Roger S. Blumenthal, MD,§ Victor Aboyans, PtiD,‖ Joachim H. Ix, MD, MAS,* Gregory L. Burke, MD, MS,¶ Kaing Liu, PtiD,‡ Steven Shea, MD, MS#

La Jolla, California; Seattle, Washington; Chicago, Illinois; Baltimore, Maryland; Limoges, France; Winston-Salem, North Carolina; and New York, New York

Objectives
The purpose of this study was to examine the association of both a low and a high ankle-brachial index (ABI) with incident cardiovascular events in a multiethnic cohort.

Background
Abnormal ABIs, both low and high, are associated with elevated cardiovascular disease (CVD) risk. However, it is unknown whether this association is consistent across different ethnic groups, and whether it is independent of both newer biomarkers and other measures of subclinical atherosclerotic CVD.

Methods
A total of 6,647 non-Hispanic white, African-American, Hispanic, and Chinese men and women age 45 to 84 years from free-living populations in 6 U.S. field centers and free of clinical CVD at baseline had extensive measures of traditional and newer biomarker risk factors, and measures of subclinical CVD, including the ABI. Incident CVD, defined as coronary disease, stroke, or other atherosclerotic CVD death, was determined over a mean follow-up of 5.3 years.

Results
Both a low (≤1.00) and a high (>1.40) ABI were associated with incident CVD events. Sex- and ethnic-specific analyses showed consistent results. Hazard ratios were 1.77 (p < 0.001) for a low and 1.85 (p = 0.050) for a high ABI after adjustment for both traditional and newer biomarker CVD risk factors, and measures of subclinical CVD, including the ABI. Incident CVD, defined as coronary disease, stroke, or other atherosclerotic CVD death, was determined over a mean follow-up of 5.3 years.

Conclusions
In this study, both a low and a high ABI were associated with elevated CVD risk in persons free of known CVD, independent of standard and novel risk factors, and independent of other measures of subclinical CVD. Further research should address the cost effectiveness of measuring the ABI in targeted population groups. (J Am Coll Cardiol 2010;56:1506–12) © 2010 by the American College of Cardiology Foundation

Peripheral artery disease (PAD) is prevalent worldwide and in all ethnic groups in the U.S. (1). It can be accurately diagnosed with the ankle-brachial index (ABI), and low values of the ABI are strongly predictive of incident cardiovascular disease (CVD) events and CVD, as well as total mortality (2–5). These associations hold true in both sexes and are independent of traditional CVD risk factors and extent CVD at baseline (2,4,5). Recently, a meta-analysis of 16 general population studies worldwide demonstrated that as opposed to the conventional definition of a normal ABI as >0.90, the true normal range of the ABI appears to be 1.00 to 1.40, with both higher and lower values associated with increased risk of CVD events (5). Second, the risk associated with an abnormal ABI contributed incremental information to the Framingham Risk Score (FRS), and the risk of a CVD event with an abnormal ABI was present at every level of the FRS. Third, the ABI increased the area under the receiver-operating characteristic (ROC) curve beyond the FRS predic-
tion. However, the questions of whether the ABI provides incremental risk information beyond newer biomarkers, or beyond other measures of subclinical CVD, or in ethnic groups other than non-Hispanic white (NHW), have not previously been addressed.

In the MESA (Multi-Ethnic Study of Atherosclerosis), multiple newer biomarkers were measured as well as the standard CVD risk factors, and in addition to the ABI, additional tests of subclinical cardiovascular disease were performed (6). Participants had measurements of coronary artery calcium (CAC) by computed tomography (CT), carotid intimal medial thickness (CIMT) by ultrasound, and major electrocardiographic (ECG) abnormalities. CAC in MESA showed strong predictive power for incident CVD events (7), and CIMT was also significantly associated with CVD events, though less so than CAC (8). Here, we explored the ethnic-specific associations of the ABI with CVD events, and whether the predictive power of the ABI was independent of newer biomarkers as well as standard CVD risk factors, and independent of other subclinical measures in MESA (i.e., CAC, CIMT, and major ECG abnormalities).

**Methods**

**Participants.** Details of the study design and protocol have been published (6). In brief, between July 2000 and August 2002, 6,814 NHW, African-American, Hispanic, or Chinese men and women 45 to 84 years of age and free of clinically apparent CVD were recruited from 6 communities and participated in the baseline examination.

**Data collection.** At the baseline examination, standardized questionnaires were used to obtain demographic information and level of education, annual household income, smoking history, and medication usage for high blood pressure, high cholesterol, or diabetes. Cigarette smoking was calculated in pack-years and also defined as current, former, or never. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic resting blood pressures were measured in seated participants.

**Laboratory.** Total and high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein cholesterol was calculated by the Friedewald equation. Diabetes was defined as fasting glucose ≥126 mg/dl or use of hypoglycemic medication. Using fasting blood samples from the baseline visit, the following analytes were selected based on their association with the ABI in prior analyses: high-sensitivity plasma C-reactive protein (CRP), fibrinogen, interleukin (IL)-6, d-dimer, estimated glomerular filtration rate (eGFR), and homocysteine (9). The laboratory methodology for these variables has been published (10).

**ABI protocol.** Systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a hand-held Doppler instrument with a 5-mHz probe. To avoid potential bias from subclavian stenosis, the higher of the brachial artery pressures was used as the denominator (11). For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. The leg cuff was inflated to a maximum of 300 mm Hg, and if a pulse was still detected at this level, the ABI was classified as “incompressible.” A subset of 384 MESA participants had replicate ABI measurements that showed excellent reproducibility. Participants were classified into 1 of 3 ABI categories: “normal” when both legs had values 1.00 ≤ ABI < 1.4; “low” when at least 1 leg had a value <1.00; and “high” when at least 1 leg was ≥1.40 or incompressible and the other leg was high/incompressible or normal.

**Subclinical CVD assessment.** Scanning centers assessed CAC by CT using either a cardiac-gated electron-beam CT scanner or a multidetector CT system (11,12). The mean phantom-adjusted Agatston score was used in all analyses (13). Trained technicians performed B-mode ultrasonography of the right and left near and far walls of the internal carotid and common carotid arteries (13). Three 12-lead recordings were obtained using a Marquette MAC-PC instrument (Marquette Electronics, Milwaukee, Wisconsin) and read using Novacode criteria (14).

**CVD follow-up.** Follow-up went from the baseline examination until the first CVD event, loss to follow-up, death, or the sixth follow-up call, for a follow-up median of 4.8 and a mean of 5.3 years (maximum, 6.5 years). For this report, we defined incident CVD as coronary heart disease (CHD) (definite and probable MI, definite CHD death, resuscitated cardiac arrest, and definite angina), stroke (fatal or nonfatal), or other atherosclerotic CVD death. Details of CVD event ascertainment have been published (7).

**Statistical analysis.** From the 6,814 MESA participants, we excluded 167 with missing ABI values, leaving 6,647 participants for analysis. Age-, sex-, and ethnicity-adjusted means and percentages of potential risk factors by ABI group were computed using either linear or logistic regression models. A natural log (ln) transformation was used for highly skewed variables. For CVD outcome analyses, we
utilized the 3 levels of ABI (normal, low, high) for categorical analyses, and also employed ABI as a continuous variable, excluding participants with an ABI ≥1.40. Cox proportional hazard regression was used to estimate hazard ratios (HRs). We performed tests for nonproportional hazards across ABI categories using Schoenfeld residuals (15); all results were nonsignificant. Additionally, interactions between time and ABI category were also nonsignificant. In order to examine the independence of the ABI with increasing levels of adjustment, 4 separate Cox models were run. Model 1 was adjusted for age, sex, and ethnicity. Model 2 added education, income, and the traditional CVD risk factors noted in Table 1, that is, smoking (never/former/current and pack-years), BMI, diabetes, systolic and diastolic blood pressure, antihypertensive medications, total cholesterol to HDL ratio, log triglycerides, and lipid-lowering medications. Model 3 added the newer biomarkers: CRP, IL-6, fibrinogen, D-dimer, eGFR, and homocysteine. Model 4 added CAC (none, 1 to 100, and >100 Agatston units), both common and internal CIMT values as continuous variables, and major ECG abnormalities, in order to provide maximum adjustment for any confounding by other subclinical CVD. Model 3 was employed in evaluating the association of ABI category with coronary disease and stroke events separately. Separate models were also run within ethnic groups adjusted for age and sex. Kaplan-Meier event curves were drawn for the 3 ABI categories, and CVD event rates per 1,000 person-years at risk were calculated for the ABI categories stratified by CAC levels (0, 1 to 100, and >100 Agatston units). The incremental value of ABI to the prediction of events in MESA was evaluated both by the improvement in the area under the ROC curve and the “integrated discrimination improvement” (IDI) (16). All analyses were performed using STATA version 10.1 (StataCorp, College Station, Texas) statistical software.

Results

Table 1 shows first the distribution of age, sex, and ethnicity across the low, normal, and high ABI groups. Both low and high ABI groups were somewhat older than the normal groups, with lower rates of smoking overall and fewer Pack-years of smoking. Similarly, diabetes was less common in the high ABI group. There were also differences in lipids, with the low ABI group having a lower HDL cholesterol to total cholesterol ratio and lower lipid-lowering medications. In contrast, high ABI groups had higher systolic and diastolic blood pressure, antihypertensive medications, total cholesterol to HDL ratio, and lipid-lowering medications. Additionally, there were differences in inflammation markers, with higher CRP and IL-6 in the higher ABI categories. There were also differences in other markers, such as fibrinogen and D-dimer, which were higher in the high ABI group. Overall, these differences suggest that the ABI is associated with a higher risk of CVD events in the high ABI group compared to the normal group.
group, and women were more common in the low and men more common in the high ABI groups. Compared to NHWs, African Americans were more likely to be in the low ABI group, whereas Hispanics and Chinese were less likely. Chinese were also less likely to be in the high ABI group. Because of these differences, the baseline risk factor levels in the remainder of Table 1 were adjusted for age, sex, and ethnicity.

Education and income levels were lower in the low ABI group. With the exception of BMI, traditional CVD risk factors were uniformly significantly higher in the low ABI group, whereas only BMI and diabetes were higher in the high ABI group. Among the 6 novel biomarkers, hs-CRP, IL-6, and homocysteine were all significantly higher in both the low and high ABI groups. Fibrinogen and D-dimer were higher, and eGFR borderline lower, in the low ABI group.

There were 317 first CVD events during follow-up, 226 CHD events, 89 strokes (including 7 who also had CHD events), and 9 “other” atherosclerotic CVD deaths. CVD event rates per 1,000 person-years in men for NHW, African Americans, Hispanics, and Chinese were 14.9, 14.5, 16.1, and 10.2, respectively, and for women 8.4, 7.4, 6.4, and 3.7, respectively. Figure 1 shows Kaplan-Meier event curves illustrating the similarly increased hazard of CVD events for both a low and a high ABI over time compared with a normal ABI. Table 2 shows the results of the proportional hazards analysis. Adjusted for age, sex, and ethnicity (model 1), a low ABI was associated with a HR of 2.30 (p < 0.001) for CVD events. Adjustment for traditional CVD risk factors in addition (model 2) attenuated the HR to 1.78 (p < 0.001). Further adjustment (model 3) for newer biomarkers produced no change (HR: 1.77, p < 0.001). Finally, adjustment for multiple subclinical CVD measures, CAC, both common and internal CIMT, and major ECG abnormalities attenuated the HR somewhat to 1.46, but the association remained significant (p = 0.021).

A high ABI was also associated with an increased risk, and after multiple adjustment (model 3), the HR was 1.85, p = 0.050, which was a similar effect size as for the low ABI. Additional adjustment for CAC, common and internal CIMT, and major ECG abnormalities attenuated the HR somewhat to 1.69, p = 0.099. Tests of the these models for sex–ABI interactions were not significant. After model 2 adjustment for the categorical ABI analysis, the area under the ROC curve was 0.78 without and 0.79 with the ABI, p = 0.022 for the difference, and the IDI index showed that the ABI contributed significantly (p = 0.003) to improving classification of events and non-events. Table 2 shows that results were similar for analyses with ABI as a continuous variable (excluding ABIs ≥1.40), and a generalized additive model fit to examine potential nonlinearity indicated that after covariate adjustment there was little deviation from a linear inverse relationship across the ABI values.

Figure 2 illustrates the risk of CVD events by ABI group within strata of CAC. In those without any CAC, incidence rates were quite low irrespective of ABI group. In the groups with nonzero CAC, ABI showed a U-shaped association within CAC groups. As a continuous variable, ABI was
inversely and significantly related to the CVD event rate among those with any CAC (data not shown). Models limited to “hard” CVD events (i.e., excluding angina and “other” CVD deaths) showed similar results except for reduced statistical power (data not shown).

Additional models evaluated the association of the ABI defined continuously (excluding ABIs >1.40) within ethnic groups, adjusted for age and sex. The HRs were quite similar: 0.74 for NHWs, 0.80 for Hispanics, 0.83 for Chinese, and 0.87 for African Americans. Although power was insufficient to analyze the ABI categorically within ethnic groups, an additional Cox model was run including an interaction term for ABI group × ethnicity. The p value for the interaction term was 0.71, confirming the similar effect size for ABI within ethnic groups.

Models were also run for CHD and stroke events separately, using model 2 adjustments. For CHD end points, the low and high ABIs again showed similar hazard ratios, 1.87 (p = 0.001) and 2.15 (p = 0.029). However, the results appeared to differ for stroke, where high ABI was associated with a HR of 2.69, p = 0.06, whereas low ABI showed a weaker association, HR: 1.56, p = 0.10.

Discussion

Using updated and more accurate definitions of a normal, low and high ABI (5), this study confirmed the independent association of both a low and high ABI with future CVD events in an ethnically diverse community dwelling population of men and women without symptomatic CVD at baseline. Addition of the ABI to risk factors resulted in minor but significant improvement in the area under the ROC curve. However, this statistic has been criticized as not providing the full potential discriminating value of a risk marker, since a marker producing only modest change in the ROC curve can nonetheless substantially improve risk classification, as was the case here (17). Several studies have reported higher risks than those shown here, but such studies included persons with known CVD at baseline, and were thus enriched with higher-risk persons with lower ABIs on average than for this primary prevention cohort. This study demonstrates that in a healthy population with careful exclusion for any known CVD at baseline that both a low and a high ABI predict incident CVD events.

Analysis of CHD and stroke events separately demonstrated that a high ABI was more strongly associated with stroke (HR: 2.69) than a low ABI (HR: 1.56), and despite the small numbers, the p value for the high ABI was borderline statistically significant (p = 0.06). This is unlikely to be a chance finding, since it has been reported previously (18,19). A high ABI is thought to represent stiff arterial walls, potentially including medial arterial calcification. That is, the value for the ankle artery is not an accurate measure of intra-arterial pressure but rather a falsely high value due to stiffness in the arterial wall. Thus, whether such persons have PAD cannot be determined with the ABI, though one-half or more may have PAD (20,21). Thus,
many persons in the high ABI group could have the CVD risk associated with PAD, but may have a separate stroke-specific risk as well. The reason for this is unclear, though a specific link between arterial stiffening and microvascular disease in the brain has been suggested (22), and prior studies using other measures of vascular stiffness such as pulse wave velocity have also shown stronger associations with stroke than with other CVD events (23).

Although it has been well established that African Americans have considerably higher, and Hispanics and Asians slightly lower, prevalence rates of PAD compared with NHWs (9,24,25), previous studies have not explored potential differences in the predictive value of the ABI for incident CVD within ethnic groups. The findings here were similar for each of the 4 ethnic groups considered separately.

Earlier studies, including the ABI Collaboration meta-analysis (5), in general did not adjust for newer biomarkers. Table 1 shows that indeed such newer biomarkers were associated with both a low and a high ABI. However, adjustment for these newer biomarkers resulted in little change.

In the MESA, CAC showed high HRs and significant improvement in the area under the ROC curve over traditional CVD risk factors alone (7). Here, the association of either a low or a high ABI with CVD events was only modestly attenuated after adjustment for CAC, both common and internal CIMT, and major ECG abnormalities (Table 2). Thus, the predictive value of an abnormal ABI remained independent of other measures of subclinical atherosclerosis.

The evidence to date suggests that both CIMT (8), and here, the ABI have independent predictive power beyond risk factors and CAC burden. However, it is much easier, quicker, less expensive, and safer to measure the ABI than CAC or CIMT. The data here are the first, to our knowledge, to show the risk of a subclinical measure (ABI) adjusted for traditional and novel risk factors, and for multiple other subclinical measures, simultaneously.

Considering that fewer than 10% of persons with PAD in a general population have ischemic leg pain (26), this suggests the potential benefit of identifying such high-risk individuals with targeted ABI screening (27). Although specific ABI screening criteria have been endorsed by multiple national societies (28), to date a cost-effectiveness analysis of such targeted screening has not been published.

**Study strengths and limitations.** Strengths of our study include standardized and validated protocols in a large multiethnic population, measurement of traditional as well as novel risk factors, and assessment of subclinical CVD in a population free of clinical CVD at baseline. Our study also has limitations. The ABI was measured only once at baseline. However, test/retest reliability is good, with a mean error of about 9% within and between observers (29), and nonsystematic misclassification of the ABI at baseline would have been biased toward the null hypothesis. Participants were alerted to low (but not high) ABIs, and thus persons with low ABIs may have differentially received new or more aggressive cardiovascular therapy. Here again, any such bias would be toward the null hypothesis. There were only 11 CVD events in the high ABI group, and numbers were inadequate to evaluate the ethnic-specific risk of a high ABI, so these results must be interpreted cautiously.

**Conclusions**

In a primary prevention population, both a low ABI, diagnostic for PAD, and a high ABI, indicative of medial arterial calcification and possible PAD, were associated with incident CVD events. A high ABI was more strongly associated with stroke than was a low ABI. These associations were largely independent of standard CVD risk factors, newer biomarkers, CAC, CIMT, and major ECG abnormalities, and did not vary by ethnic group. Given the simplicity and low cost of measuring the ABI, cost-effectiveness analyses for the use of ABI in targeted groups should be a research priority.

**Reprint requests and correspondence:** Dr. Michael H. Criqui, University of California–San Diego School of Medicine, 9500 Gilman Drive, MC 0607, La Jolla, California 92039-0607. E-mail: mcriqui@ucsd.edu.

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