Relationship of High and Low Ankle Brachial Index to All-Cause and Cardiovascular Disease Mortality

The Strong Heart Study

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Background—The associations of low (<0.90) and high (>1.40) ankle brachial index (ABI) with risk of all-cause and cardiovascular disease (CVD) mortality have not been examined in a population-based setting.

Methods and Results—We examined all-cause and CVD mortality in relation to low and high ABI in 4393 American Indians in the Strong Heart Study. Participants had bilateral ABI measurements at baseline and were followed up for 8.3±2.2 years (36 589 person-years). Cox regression was used to quantify mortality rates among participants with high and low ABI relative to those with normal ABI (0.90≤ABI≤1.40). Death from all causes occurred in 1022 participants (23.3%; 27.9 deaths per 1000 person-years), and of these, 272 (26.6%; 7.4 deaths per 1000 person-years) were attributable to CVD. Low ABI was present in 216 participants (4.9%), and high ABI occurred in 404 (9.2%). Diabetes, albuminuria, and hypertension occurred with greater frequency among persons with low (60.2%, 44.4%, and 50.1%) and high (67.8%, 49.9%, and 45.1%) ABI compared with those with normal ABI (44.4%, 26.9%, and 36.5%), respectively (P<0.0001). Adjusted risk estimates for all-cause mortality were 1.69 (1.34 to 2.14) for low and 1.77 (1.48 to 2.13) for high ABI, and estimates for CVD mortality were 2.52 (1.74 to 3.64) for low and 2.09 (1.49 to 2.94) for high ABI.

Conclusions—The association between high ABI and mortality was similar to that of low ABI and mortality, highlighting a U-shaped association between this noninvasive measure of peripheral arterial disease and mortality risk. Our data suggest that the upper limit of normal ABI should not exceed 1.40. (Circulation. 2004;109:733-739.)

Key Words: epidemiology ■ mortality ■ peripheral vascular disease

Peripheral arterial disease (PAD) is associated with prevalent cardiovascular disease (CVD) and adverse CVD risk factor profiles.1–3 Prospective studies using the ankle brachial index (ABI) have shown that a low ABI predicts fatal and nonfatal CHD and all-cause mortality in people with and without existing coronary artery disease and among people with existing peripheral vascular disease.4–10 Low ABI has been linked with incident stroke in the elderly.11

Epidemiological studies often define the normal range of ABI as 0.90 to 1.50 or focus on persons with ABI <0.90 without defining an upper limit of normal. To our knowledge, no previous studies have evaluated the relationship between high ABI and mortality.

Interest in examining the role of high ABI and mortality stems from the relationship between diabetes and generalized stiffening of blood vessels,12 as well as the observation that medial arterial calcification (MAC), a condition that can result in high ABI measures, is common in diabetes and associated with increased mortality risk.13 American Indians have high rates of both CVD and type 2 diabetes, making this a relevant population in which to compare the effects of low and high ABI on mortality risk.14,15

We hypothesized that compared with participants with 0.90≤ABI≤1.40, those with both low and high ABI would have higher rates of all-cause and CVD mortality, independent of other CVD risk factors.

Methods

Study Population

The Strong Heart Study (SHS) was initiated in 1988 to investigate CVD and its risk factors in American Indians.16 The design and methods of SHS have been reported.16–18 Protocols were approved by the local institutional review boards, and all participants provided informed consent. The SHS cohort consists of 4549 participants aged 45 to 74 at the baseline examination, which was conducted between 1989 and 1992. The second and third examinations were conducted between 1993 to 1995 and 1997 to 1999, respectively.

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Measurement of Ankle and Arm Blood Pressures
At each SHS examination, right arm blood pressures and bilateral ankle blood pressure (posterior tibial artery), measured by handheld Doppler (Imex Medical Systems), were taken with the subject supine. Each measurement was taken twice. If no pulse was palpable or audible with the Doppler, the absent pulse was verified by a second examiner. If the absent pulse was verified, ankle blood pressure measures were taken on the dorsalis pedis. The means of the 2 measurements for each leg and for the arm were used to calculate ABI, and the worse of the 2 values was used to define ABI for each individual.

Definition of ABI Categories
Early PAD studies used a variety of ABI cutoffs, ranging from <0.95 to <0.80, to define PAD.22-23 but most recent studies have used <0.90 as the cutpoint.22,23 An ABI of <0.90 is 95% sensitive and 99% specific for angiographically documented PAD.24-25 This cutpoint has been related to prevalent and incident CVD and all-cause mortality in several studies.1,2,3,5,7,8 and has been used in other studies of American Indians26 and in previous work in the SHS.3 Participants who had an ABI <0.90 in either leg were categorized as having low ABI.

Participants were categorized as having high ABI if either leg had an ABI measure >1.40 or the ankle pressure of either leg could not be obtained during the ABI protocol because of stiffening (pulse could not be obliterated with a pressure of ≥250 mm Hg). Participants were defined as having normal ABI if both ABI measures were ≥0.90 and ≤1.40.

Measurement of CVD Risk Factors
Methods for measurement of CVD risk factors have been published previously.14,15 Cholesterol, triglycerides, and fasting glucose were determined by enzymatic methods using a Hitachi chemistry analyzer and consistent, standardized reagents (Boehringer Mannheim Diagnostics). Fasting glucose (FG), fasting insulin, fibrinogen, and hemoglobin A1c were measured by established methods.27-30 Participants were categorized according to their baseline diabetes status as nondiabetic (FG <110 mg/dL, no report of diabetes, and no use of hypoglycemic medications), impaired fasting glucose (IFG; 110 ≤FG <126 mg/dL), or diabetic (FG ≥126 mg/dL, self-report of diabetes, or use of hypoglycemic medications).31 Participants were considered hypertensive if they were taking antihypertension medication or if they had a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg. Smoking was determined by questionnaire and categorized as ever versus never. Microalbuminuria was defined as a ratio of urinary albumin (mg/mL) to creatinine (g/mL) of 30 to 299 mg/g and macroalbuminuria as a ratio of ≥300 mg/g.

Ascertainment of All-Cause and Cardiovascular Disease Mortality
Deaths were identified through tribal and Indian Health Service hospital records and by direct contact with participants and their families.16,17 Death certificates were obtained from state health departments, and ICD-9 codes were applied centrally by a nosologist.15 Cause of death was investigated using autopsy reports, medical record abstractions, and informant interviews. All materials were reviewed independently by physician members of the SHS Mortality Review Committee to confirm the cause of death.15

Statistical Methodology
We examined the distribution of known and potential CVD risk factors according to vital status at follow-up. We calculated crude death rates attributable to all causes and to CVD and examined these within strata of ABI and diabetes. Cox regression models that examined both low and high ABI in relation to all-cause and CVD mortality were adjusted for potential confounders, including age, gender, diabetes, lipids, hypertension, renal function, and fibrinogen. We selected variables for entry into the model based on their hypothesized biological relationships with ABI and mortality and if findings from descriptive analyses reached a significance level of P<0.1. Follow-up time was calculated through December 31, 1999, as the time between the baseline examination and either (1) date of death, (2) end of study, or (3) date of last SHS examination among those lost to vital status follow-up (0.001%). We tested the proportional hazards assumption by examining hazard curves for the 3 ABI groups against the log of time. There was no evidence that this assumption was violated. Survival analysis was used to examine mortality according to ABI group.

Results
Of the 4549 participants in the SHS cohort, 74 were missing baseline ABI data, and 81 were missing data on baseline diabetes status. One participant had a high ABI in 1 leg and low ABI in the other and was excluded. The sample consists of 4393 participants whose baseline ABI category and diabetes status could be reliably determined. Of these, 216 (4.9%), 3773 (85.9%), and 404 (9.2%) were in the low-, normal-, and high-ABI groups, respectively. Of the 404 participants in the high-ABI group, 179 did not provide a continuous ABI measure because their ankle pressure could not be obtained because of vessel stiffening. During 36 589 person-years (PY) of follow-up, there were 1022 deaths, of which 272 were attributable to CVD.

Table 1 shows baseline characteristics by ABI group. CVD risk factors generally followed a U-shaped pattern with regard to ABI group, with less favorable profiles observed in low and high groups.

Compared with participants with normal ABI at baseline, those with low ABI were significantly older and had more hypertension, higher triglycerides, total and LDL cholesterol, hemoglobin A1c, and fibrinogen and lower HDL cholesterol. People with a low ABI also had higher odds of being diabetic and of having albuminuria. The crude risks of all-cause and CVD mortality among the low- compared with normal-ABI groups were 2.05 (1.98 to 3.04) and 3.76 (2.57 to 5.49), respectively.

Compared with the normal-ABI group, those with high ABI were significantly older and had more hypertension and higher total cholesterol, hemoglobin A1c, fibrinogen, and fasting glucose. The odds ratios for diabetes and albuminuria in the high- compared with normal-ABI groups were markedly higher than those for the low-ABI group. The crude risks of all-cause and CVD mortality in the high- compared with normal-ABI group were 2.19 (1.77 to 2.71) and 2.68 (1.93 to 3.72), respectively.

The rate of all-cause mortality was 53.8 per 1000 PY in the low-ABI group, 61.8 per 1000 PY in the high-ABI group, and 23.6 per 1000 PY in the normal-ABI group (Table 2). The all-cause mortality rate ratio for low:normal ABI was 2.33 (1.87 to 2.90), and the rate ratio for high:normal ABI was 2.76 (2.34 to 3.25).

CVD deaths occurred at a rate of 23.6 per 1000 PY in the low-ABI group, 18.1 per 1000 PY in the high-ABI group, and 5.6 per 1000 PY in the normal-ABI group. The CVD mortality rate ratio for low:normal ABI was 4.28 (3.03 to 6.06), and the rate ratio for high:normal ABI was 3.40 (2.50 to 4.63).

Rates of all-cause mortality generally increased as glucose concentration increased. For instance, in the low-ABI group, all-cause mortality increased from 27.5 to 38.5 to 70.5 deaths per 1000 PY among nondiabetic, IFG, and diabetic participants, respectively. In the low-ABI group, all-cause mortality was 1.59, 2.09, and 2.31 times higher than the normal-ABI.
A U-shaped relationship between baseline ABI and mortality was evident, with risk increasing on the upper end of the distribution, with increased risk appearing at ABI >1.40 (Figures 3A and 3B). Notably, levels of ABI that have been considered in the normal range in previous studies (ABI 0.90 to 1.10) were associated with increased risk of both all-cause and CVD mortality.

When ABI groups were examined in relation to mortality in Cox regression models that adjusted for multiple CVD risk factors, both high- and low-ABI groups were significantly associated with both all-cause mortality and CVD mortality. Low ABI was associated with adjusted all-cause and CVD mortality risk of 1.69 (1.34 to 2.14) and 2.52 (1.74 to 3.64), respectively, and high ABI was associated with all-cause and CVD mortality risk of 1.77 (1.48 to 2.13) and 2.09 (1.49 to 2.94), respectively. Analyses examining the joint effects of ABI category and both albuminuria and diabetes showed no interactions with regard to risk of all-cause or CVD mortality.

**Discussion**

ABI >1.40 predicts mortality with similar strength as ABI <0.90. The U-shaped association between high and low ABI and mortality risk suggests clinically meaningful upper and

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<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Low ABI (&lt;0.90)</th>
<th>Difference in Means or Crude OR*</th>
<th>Normal ABI (0.90 ≤ABI ≤1.40)</th>
<th>Difference in Means or Crude OR*</th>
<th>High ABI (ABI &gt;1.40 or Incompressible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.6</td>
<td>3.7 (2.6 to 4.8)</td>
<td>55.9</td>
<td>1.1 (0.3 to 1.9)</td>
<td>57.1</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>38.0</td>
<td>0.91 (0.69 to 1.22)</td>
<td>40.0</td>
<td>1.44 (1.18 to 1.77)</td>
<td>49.0</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>50.0</td>
<td>1.74 (1.32 to 2.29)</td>
<td>36.5</td>
<td>1.43 (1.16 to 1.76)</td>
<td>45.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.1</td>
<td>−0.9 (−1.8 to −0.5)</td>
<td>31.0</td>
<td>0.2 (−0.5 to 0.8)</td>
<td>31.2</td>
</tr>
<tr>
<td>Triglycerides,† ln(mg/dL)</td>
<td>4.91</td>
<td>0.09 (0.01 to 0.17)</td>
<td>4.82</td>
<td>−0.03 (−0.09 to 0.03)</td>
<td>4.79</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>200</td>
<td>7.7 (2.0 to 13.3)</td>
<td>192</td>
<td>−9.4 (−13.7 to −5.1)</td>
<td>182</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>113</td>
<td>5.7 (1.2 to 10.2)</td>
<td>107</td>
<td>−6.4 (−9.8 to −2.9)</td>
<td>101</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44</td>
<td>−1.9 (−3.8 to −0.05)</td>
<td>46</td>
<td>−0.7 (−2.1 to 0.8)</td>
<td>45</td>
</tr>
<tr>
<td>Hemoglobin A₁c, %</td>
<td>7.2</td>
<td>0.6 (0.3 to 1.0)</td>
<td>6.6</td>
<td>0.9 (0.6 to 1.1)</td>
<td>7.5</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>322</td>
<td>22 (11 to 33)</td>
<td>300</td>
<td>31 (22 to 39)</td>
<td>331</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>164</td>
<td>17 (7 to 27)</td>
<td>147</td>
<td>30 (23 to 31)</td>
<td>177</td>
</tr>
<tr>
<td>Diabetes status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal fasting glucose</td>
<td>31.9</td>
<td>1.0</td>
<td>41.9</td>
<td>1.0</td>
<td>22.5</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>7.9</td>
<td>0.75 (0.43 to 1.29)</td>
<td>13.7</td>
<td>1.31 (0.89 to 1.93)</td>
<td>9.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>60.2</td>
<td>1.77 (1.31 to 2.39)</td>
<td>44.4</td>
<td>2.83 (2.21 to 3.63)</td>
<td>67.8</td>
</tr>
<tr>
<td>Ever smoker,‡ %</td>
<td>73.6</td>
<td>1.12 (0.83 to 1.54)</td>
<td>71.2</td>
<td>0.64 (0.52 to 0.79)</td>
<td>61.4</td>
</tr>
<tr>
<td>Albuminuria,§ %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>55.6</td>
<td>1.0</td>
<td>73.1</td>
<td>1.0</td>
<td>50.1</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>23.2</td>
<td>1.67 (1.18 to 2.37)</td>
<td>18.2</td>
<td>2.04 (1.57 to 2.64)</td>
<td>25.5</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>21.2</td>
<td>3.23 (2.24 to 4.66)</td>
<td>8.7</td>
<td>4.11 (3.12 to 5.42)</td>
<td>24.4</td>
</tr>
<tr>
<td>All-cause mortality, %</td>
<td>41.2</td>
<td>2.05 (1.98 to 3.04)</td>
<td>20.0</td>
<td>2.19 (1.77 to 2.71)</td>
<td>43.8</td>
</tr>
<tr>
<td>CVD mortality, %</td>
<td>18.1</td>
<td>3.76 (2.57 to 5.49)</td>
<td>4.8</td>
<td>2.68 (1.93 to 3.72)</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Data are means and percents for continuous and categorical variables, respectively.

*Crude ORs are presented for comparisons of baseline characteristics. Crude relative risks are presented for mortality.
†Log-transformed to achieve approximate normality.
§Microalbuminuria: ratio of urinary albumin (mg/mL) to creatinine (g/mL) of 30 to 299 mg/g; macroalbuminuria, ratio of urinary albumin (mg/mL) to creatinine (g/mL) ≥300 mg/g.

In the high-ABI group, rates of all-cause mortality were similar in the nondiabetic and IFG groups (≥36 to 37 per 1000 PY) but considerably higher in the diabetic group (75.7 per 1000 PY). In this group, all-cause mortality was 2.10, 2.19, and 2.59 times higher than the normal-ABI group among nondiabetic, IFG, and diabetic participants, respectively. Rates of CVD mortality also generally increased with increasing glucose concentration within each ABI group.

A U-shaped relationship between baseline ABI and mortality was evident, with risk increasing on the upper end of the ABI distribution at ABI >1.40 (Figure 1).

For both all-cause mortality and CVD mortality, rates of survival for the high-ABI (>1.40) and low-ABI (<0.90) groups were significantly worse than for the normal-ABI group (Figures 2A and 2B). Although there was a suggestion of poorer survival for the high-ABI group for all-cause mortality, no statistically significant differences in survival between the low- and high-ABI groups were observed.

Adjusted mortality risk was elevated in an expected manner at the lower end of the ABI distribution, and risk also increased on the upper end of the distribution, with increased risk appearing at ABI >1.40 (Figures 3A and 3B). Notably, levels of ABI that have been considered in the normal range in previous studies (ABI 0.90 to 1.10) were associated with increased risk of both all-cause and CVD mortality.

In previous studies (ABI 0.90 to 1.10) were associated with increased risk of both all-cause and CVD mortality.
lower thresholds for ABI, with increased risk appearing at an upper cutpoint of 1.40. We identified nearly twice as many individuals in the high- as in the low-ABI category, suggesting that individuals with elevated ABI are not rare and that the health impact of high ABI may be larger than for low ABI. High ABI may be of particular importance in populations with a high prevalence of diabetes, such as American Indians and the elderly.

Previous studies of CVD and mortality have demonstrated significant associations between ABI <0.90 relative to a normal-ABI group defined as 0.90 to 1.50, as well as in studies in which no upper limit of normal ABI is specified. Our analyses of ABI increments of 0.10 indicated that mortality risk increases at ABI =1.10 and at ABI =1.40. These findings imply that previous studies of the association between low ABI (where low ABI is defined as ABI <0.90) and mortality may have underestimated the association, because people with ABI 0.90 to 1.10 and those with ABI >1.40 were included in the reference group.7−9

We chose to define the low-ABI group in a manner consistent with most previous studies (<0.90) to facilitate comparison of results across studies. However, defining the low-ABI group as ABI =1.10 results in mortality risk estimates that are similar to those we presented for ABI <0.90, indicating poor outcomes at an ABI cutpoint that is currently considered low to normal. This finding is consistent with preliminary data from the Multi Ethnic Study of Atherosclerosis, showing that individuals with ABI 1.0 to 1.10 have greater subclinical atherosclerosis in the carotid and coronary arteries than those with ABI 1.10 to 1.30.32

Most studies of the relationship between ABI and mortality have focused on those with low ABI, because these individuals are presumed to have atherosclerotic vascular disease that is detectable before a coronary or mortal event.4,6,7 Compared with the normal-ABI group, the adjusted HR for low ABI was 1.69 for all-cause and 2.52 for CVD mortality. The attenuation in the magnitude of mortality risk associated with low ABI compared with the crude estimates is explained by adverse risk factor profiles that are common among people with PAD. However, the significant, multivariable-adjusted relationship between low ABI and increased all-cause and CVD mortality risk supports the utility of ABI as a tool for predicting mortality in individuals with PAD, independent of other factors.

The finding of an independent relationship between low ABI and mortality risk is consistent with findings from other large studies of CVD, and the magnitude of ABI-associated mortality was strikingly similar to several reports. The Edinburgh Artery study8 showed 5-year relative risks of all-cause and CVD mortality of 1.58 and 1.85 for persons
aged 55 to 74 years with an ABI <0.90. Similarly, in a study of older adults without prevalent CVD,\textsuperscript{10} the 6-year relative risk of death associated with an ABI <0.90 was 1.62. In studies with selected patient populations, however, a low ABI may be more strongly predictive of death. For instance, in older adults with systolic hypertension and no baseline CVD,\textsuperscript{7} an ABI <0.90 was associated with a 4-year relative risk of total mortality of 3.0 in men and 2.7 in women. Our results detailing the association between low ABI and risk of mortality extend findings of previous studies to include American Indians, a population with extremely high rates of diabetes\textsuperscript{15} and rates of heart disease that are increasing faster than in other ethnic groups in the United States.\textsuperscript{14}

In addition to the relation of low ABI to mortality, our data demonstrate increased risk of all-cause and CVD mortality among participants with ABI >1.40 or incompressible vessels. The adjusted risk of all-cause mortality in the high-ABI group was 1.77 times that of the normal group, and the HR was 2.09 for CVD mortality. The magnitude of mortality risk associated with high ABI was similar to that of low ABI, highlighting the approximately equal influence of low and high ABI on poor outcomes. We are unaware of other population-based data showing this relationship. It is important to note that this U-shaped relationship cannot be observed by examining mean ABI among survivors and dece-
dents; our data showed only modest differences in mean ABI between groups in descriptive analyses.

Given the high prevalence of obesity in American Indians, we considered the possibility that participants in the high-ABI group with incompressible vessels were incompressible because of obesity rather than rigidity of the vessels and that the obesity, rather than the vascular disease, was responsible for increased mortality risk. We therefore compared body mass index (BMI) between those with incompressible vessels and those with a continuous ABI measure exceeding 1.40. In fact, mean BMI of the incompressible group was slightly, but not significantly, lower than BMI in those with measurable ABI exceeding 1.40 (30.7 versus 31.5).

In both the low- and high-ABI groups, the prevalence of diabetes (60.2% and 67.8%), albuminuria (44.4% and
49.9%), and hypertension (50.0% and 50.0%) was similar. Of particular interest is the fact that both low and high ABI remained significant predictors of mortality after adjustment for CVD risk factors. This raises a question about how to appropriately intervene to reduce PAD-associated mortality. Recent findings from the ABCD trial suggested that among diabetic individuals, intensive blood pressure control was effective in reducing the risk of fatal and nonfatal CVD events.33

Previous research has demonstrated less-favorable outcomes among diabetic persons with PAD compared with nondiabetic persons with PAD.13,34 Despite the increased occurrence of diabetes among persons with both low and high ABI and the suggestion of increasing mortality risk across glucose categories in our descriptive analyses, we observed no significant interaction between diabetes and ABI on mortality risk. This finding is somewhat inconsistent with earlier work in the Pima Indians, which showed a significant interaction between MAC and diabetes.13 The apparent inconsistency in these findings is likely attributable to the fact that ABI is an imperfect surrogate for MAC. It should be emphasized, however, that our data show a significant relationship between high ABI and mortality even among nondiabetic individuals. This finding indicates that the clinical utility of a high ABI is not restricted to persons with diabetes.

The SHS cohort consists entirely of American Indians, and this population is known to have very high rates of diabetes. Although the ethnic homogeneity of the cohort is a limitation with regard to broad generalizations of the role of high ABI on mortality in other ethnic groups, there is no reason to believe that the effects of vascular disease on mortality risk differ mechanistically across ethnic groups. Indeed, many existing clinical practice guidelines for the management of diabetes are based on a longstanding, National Institutes of Health–funded longitudinal study of diabetes in Pima Indians. Although the prevalence of diabetes likely has a direct impact on the prevalence of both high and low ABI, it is likely that the results of this report are equally applicable in populations with a lower prevalence of diabetes.

In summary, our results show a U-shaped association between ABI and mortality, with significantly increased risk in both the <0.90 and >1.40 groups. The U-shaped relationship between ABI and mortality was not fully explained by the increased occurrence of diabetes, hypertension, and renal disease among persons with low and high ABI. Identifying persons at both extremes of the ABI distribution may be a useful method for CVD risk stratification.

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