Sensitivity and Specificity of the Ankle–Brachial Index to Predict Future Cardiovascular Outcomes: A Systematic Review

Anand V. Doobay, Sonia S. Anand

Objective—The ankle–brachial index is the ratio of the ankle and the brachial systolic blood pressure and is used to assess individuals with peripheral arterial disease. An ankle–brachial index <0.90 suggests the presence of peripheral arterial disease and is a marker of cardiovascular risk. The objective of this review is to determine the sensitivity and specificity of an ankle–brachial index <0.90 to predict future cardiovascular events, including coronary heart disease, stroke, and death.

Methods and Results—We conducted a systematic review of the literature and included studies that used an ankle–brachial index cutoff between 0.80 and 0.90 to classify patients with or without peripheral arterial disease, followed patients prospectively, and recorded cardiovascular outcomes (ie, myocardial infarction, stroke, or mortality). Data were combined using a random-effects model meta-analysis to determine the sensitivity, specificity, relative risks, and likelihood ratios of a low ankle–brachial index to predict future cardiovascular disease. A total of 22 studies were identified, 13 were excluded, and 9 studies were included in the meta-analysis. The sensitivity and specificity of a low ankle–brachial index to predict incident coronary heart diseases were 16.5% and 92.7%, for incident stroke were 16.0% and 92.2%, and for cardiovascular mortality were 41.0% and 87.9%, respectively. The corresponding positive likelihood ratios were 2.53 (95% CI, 1.45 to 4.40) for coronary heart disease, 2.45 (95% CI, 1.76 to 3.41) for stroke, and 5.61 (95% CI, 3.45 to 9.13) for cardiovascular death.

Conclusion—The specificity of a low ankle–brachial index to predict future cardiovascular outcomes is high, but its sensitivity is low. The ankle–brachial index should become part of the vascular risk assessment among selected individuals. (Arterioscler Thromb Vasc Biol. 2005;25:1463-1469.)

Key Words: atherosclerosis • cardiovascular disease • ankle–brachial index • diagnostic test • systematic review

Cardiovascular disease is the leading cause of death in North America and all developed nations. As the population ages, the burden of cardiovascular disease is expected to increase. Although the primary determinants of cardiovascular disease have been clearly established and are used to predict future cardiovascular risk, simple, noninvasive, and inexpensive tests that aid in vascular risk prediction are useful.

Individuals with peripheral arterial disease of the lower extremities are among the highest-risk vascular patients. The presence of peripheral arterial disease is an indicator of widespread atherosclerosis in other vascular territories such as the coronary, carotid, and cerebrovascular arteries. There is substantial evidence that peripheral arterial disease is a predictor of future cardiovascular outcomes such as myocardial infarction, stroke, and death.

The ankle–brachial index (ABI) is the ratio of the ankle to brachial systolic blood pressure, and a value of <0.90 indicates the presence of flow-limiting arterial disease affecting the limb. The ABI is used in the diagnosis of peripheral arterial disease of the extremities in symptomatic patients and in the assessment of vascular risk in asymptomatic patients. The ABI is a simple and noninvasive test that can be performed in the office or clinic setting. The intraobserver variability of the test in trained observers is low at \( \approx 7\% \). The validity of the ABI for detecting \( \geq 50\% \) stenosis in the leg arteries is high (90% sensitivity and 98% specificity).

Although the ABI has been promoted as an adjunct to the office-based assessment of cardiovascular risk, to our knowledge, there have been no systematic reviews evaluating the sensitivity and specificity of the ABI used in this way. To determine the validity of a low ABI to predict future cardiovascular outcomes, we conducted a systematic review of all available studies in which the ABI was measured at baseline and the incidence of cardiovascular events was reported.

Methods

We attempted to identify all studies published before January 2004 by searching the MEDLINE database and reviewing reference lists.
Demographics and Risk Factors

Combining data from 2674 individuals from the 2 high-risk cohort studies, the mean age was 68.4 years, 48.8% were women, 66.3% reported some exposure to tobacco, 30.5% had diabetes, and 48.1% had hypertension. A total of 72.3% of individuals (1934 of 2674) had a low ABI at baseline, and the average duration of follow-up of the cohort was 10 years (Table 1).

CHD and Stroke Incidence

Two of the 9 studies reported data on CHD incidence, and both were population-based studies (Table 2; n=7131). Three of the 9 studies reported stroke incidence, and all were population based (n=21341). For CHD incidence, the sensitivity of a low ABI was 16.5% (95% CI, 12.8 to 20.2), and the specificity was 92.7% (95% CI, 92.1 to 93.3). The positive likelihood ratio for CHD incidence was 2.53 (95% CI, 1.45 to 4.40). For stroke incidence, the sensitivity of a low ABI was 16.0% (95% CI, 12.9 to 19.1), the specificity was 92.2% (95% CI, 91.9 to 92.5), and the positive likelihood ratio was 2.45 (95% CI, 1.76 to 3.41).

All-Cause Mortality

Five studies reported information on all-cause mortality (n=8908), and 4 of these studies were population based (n=6978). Combining data from the population-based studies for all-cause mortality, the sensitivity of a low ABI was 31.2% (95% CI, 27.8 to 34.6), and the specificity was 88.9% (95% CI, 88.2 to 89.6). The likelihood ratio of a low ABI predicting all-cause mortality was 3.97 (95% CI, 3.17 to 4.96). Among 1 high-risk cohort, the sensitivity of a low ABI for all-cause mortality was 85.0% (95% CI, 82.1 to 87.5), the specificity was 30.1% (95% CI, 27.6 to 32.7), and the positive likelihood ratio was 1.22 (95% CI, 1.16 to 1.28).


###TABLE 2. Incident CHD and Stroke by ABI Category

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>No./Total (%)</th>
<th>Relative Risk (95% CI)</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHD</strong></td>
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<tr>
<td>Population-based cohorts</td>
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<tr>
<td>Newman et al, 199911</td>
<td>33/409 (8.1)</td>
<td>1.93 (1.26–2.74)</td>
<td>85.2% (95% CI, 76.9–90.8)</td>
<td>90.8 (89.9–91.7)</td>
</tr>
<tr>
<td>Abbott et al, 200012</td>
<td>31/181 (17.1)</td>
<td>2.14 (1.32–3.47)</td>
<td>87.9% (95% CI, 85.5–90.4)</td>
<td>92.1 (91.9–92.5)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td>Population-based cohorts</td>
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<tr>
<td>Newman et al, 199911</td>
<td>35/409 (8.6)</td>
<td>3.34 (2.12–5.34)</td>
<td>59.9% (95% CI, 51.6–68.8)</td>
<td>90.8 (89.9–91.7)</td>
</tr>
<tr>
<td>Abbott et al, 200112</td>
<td>20/322 (6.2)</td>
<td>3.61 (2.02–6.48)</td>
<td>80.1% (95% CI, 75.0–84.2)</td>
<td>90.4 (89.5–91.3)</td>
</tr>
</tbody>
</table>

*This study used an ABI cutoff of 0.80; for CHD incidence, positive predictive value was 10.9% (95% CI, 8.3–13.4), negative predictive value was 95.1% (95% CI, 94.5–95.6), and positive likelihood ratio was 2.53 (95% CI, 1.45–4.40); for stroke incidence, positive predictive value was 6.4% (95% CI, 5.0–7.9), negative predictive value was 97.6% (95% CI, 97.9–97.7), and positive likelihood ratio was 2.45 (95% CI, 1.76–3.41); adjusted relative risk ratios are shown for studies that calculated the incremental effect of a low ABI on the risk of incident CHD or stroke after statistical adjustment for cardiovascular mortality, diabetes, hypertension, alcohol intake, fibrinogen, fasting glucose, body mass index, distance walked per day, and atrial fibrillation.

###Cardiovascular Mortality

Five studies collected data on mortality from cardiovascular causes such as myocardial infarction or stroke (n=77227,10,11,23,28). Four of these studies were population based (n=69782,10,11,28).

Combining data from the population-based studies, for cardiovascular mortality, the sensitivity of a low ABI was 41.0% (95% CI, 33.8–48.2), the specificity was 87.9% (95% CI, 87.2 to 88.6), and the positive likelihood ratio was 5.61 (95% CI, 3.45–9.13). Using data from 1 high-risk cohort, the sensitivity was 85.2% (95% CI, 76.9 to 90.8), the specificity was 38.4% (95% CI, 34.7 to 42.2), and the positive likelihood ratio was 1.38 (95% CI, 1.25 to 1.53) for predicting cardiovascular mortality.

###Discussion

The ABI is a simple, noninvasive, and inexpensive test that can be used to identify individuals who are at high risk of developing cardiovascular disease (Table 5). Among population-based cohorts, the ABI is highly specific but not sensitive for predicting cardiovascular disease. In other words, a low ABI helps to “rule in” a high-risk patient, but a normal ABI does not “rule out” a high-risk patient.

Ideally, screening tests that are highly sensitive can “rule out” disease if the test is normal (eg, serum ferritin for iron deficiency anemia). Therefore, if the sensitivity of a test is high, it can be applied broadly in the population. However, if the sensitivity is low, a normal test cannot “rule out” the

###TABLE 3. All-Cause Mortality by ABI Category

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>No./Total (%)</th>
<th>Unadjusted Relative Risk (95% CI)</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
</tr>
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<tbody>
<tr>
<td>Population-based cohorts</td>
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<tr>
<td>Ciri et al, 199229</td>
<td>22/50 (44.0)</td>
<td>3.50 (2.32–5.30)</td>
<td>3.10 (1.8–5.3)</td>
<td>32.4 (21.2–43.5)</td>
<td>92.0 (89.1–94.8)</td>
</tr>
<tr>
<td>Vogt et al, 19937</td>
<td>11/51 (21.6)</td>
<td>5.26 (2.87–9.64)</td>
<td>3.10 (1.5–6.7)</td>
<td>21.6 (10.3–22.1)</td>
<td>95.4 (94.7–97.2)</td>
</tr>
<tr>
<td>Newman et al, 199710</td>
<td>52/298 (17.4)</td>
<td>3.19 (2.23–5.47)</td>
<td>2.70 (1.88–4.13)</td>
<td>49.5 (40.0–59.1)</td>
<td>78.8 (76.5–81.2)</td>
</tr>
<tr>
<td>Newman et al, 199911</td>
<td>104/409 (25.4)</td>
<td>2.91 (2.40–3.54)</td>
<td>1.62 (1.24–2.12)</td>
<td>23.6 (19.6–27.5)</td>
<td>92.0 (91.2–92.9)</td>
</tr>
<tr>
<td>Total (population-based)</td>
<td>6978</td>
<td>276/1388 (20.1)</td>
<td>3.23 (2.68–3.88)</td>
<td>31.2 (27.8–34.6)</td>
<td>88.9 (88.2–89.6)</td>
</tr>
<tr>
<td>High-risk cohorts</td>
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</tr>
<tr>
<td>Vogt et al, 19934</td>
<td>577/1452 (39.7)</td>
<td>1.86 (1.55–2.24)</td>
<td>—</td>
<td>85.0 (82.1–87.5)</td>
<td>30.1 (27.6–32.7)</td>
</tr>
</tbody>
</table>

*This study used an ABI cutoff of 0.80; * for population-based cohorts, positive predictive value was 23.4% (95% CI, 20.5–26.3), negative predictive value was 92.3% (95% CI, 91.6–93.0), the positive likelihood ratio was 3.97 (95% CI, 3.17–4.96), and disease incidence was 9.5%. ¥for the high-risk cohort, positive predictive value was 39.7%; negative predictive value was 78.7%; positive likelihood ratio was 1.22 (95% CI, 1.16–1.28), and disease incidence was 35.2%; adjusted relative risk ratios are shown for studies that calculated the incremental effect of a low ABI on the risk of all-cause mortality after statistical adjustment for cardiovascular risk factors including age, gender, race, smoking, diabetes, total cholesterol, hypertension, fasting glucose, body mass index, waist-hip ratio, fibrinogen, physical activity, history of coronary heart disease, amputation, CHD, or cardiovascular disease.
TABLE 4. Cardiovascular Mortality by ABI Category

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>No./Total (%)</th>
<th>Relative Risk (95% CI)</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>% Sensitivity of ABI (95% CI)</th>
<th>% Specificity of ABI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based cohorts</td>
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<tr>
<td>Criqui et al, 1992*</td>
<td>12/50 (24.0)</td>
<td>5.86 (2.91–11.8)</td>
<td>6.3* (2.6–15.0)</td>
<td>44.4 (25.7–63.2)</td>
<td>90.2 (87.3–93.2)</td>
</tr>
<tr>
<td>Vogt et al, 1993</td>
<td>6/51 (11.8)</td>
<td>12.76 (4.72–34.35)</td>
<td>4.5* (1.5–6.7)</td>
<td>40.0 (15.2–64.8)</td>
<td>95.6 (94.3–96.8)</td>
</tr>
<tr>
<td>Newman et al, 1997</td>
<td>19/298 (6.4)</td>
<td>3.86 (2.01–7.41)</td>
<td>3.2* (1.67–6.49)</td>
<td>54.3 (37.8–70.8)</td>
<td>77.4 (75.0–79.7)</td>
</tr>
<tr>
<td>Newman et al, 1999</td>
<td>28/409 (6.8)</td>
<td>3.94 (2.57–6.06)</td>
<td>2.0* (1.22–3.37)</td>
<td>29.5 (20.3–38.6)</td>
<td>90.9 (90.0–91.7)</td>
</tr>
<tr>
<td>Total (population-based)*</td>
<td>65/808 (8.0)</td>
<td>5.09 (3.30–7.88)</td>
<td>—</td>
<td>41.0 (33.8–48.2)</td>
<td>87.9 (87.2–88.6)</td>
</tr>
<tr>
<td>High-risk cohorts</td>
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<tr>
<td>McKenna et al, 1991</td>
<td>86/482 (17.8)</td>
<td>3.12 (1.84–5.28)</td>
<td>2.0* (1.34–3.02)</td>
<td>85.2 (76.9–90.8)</td>
<td>38.4 (34.7–42.2)</td>
</tr>
</tbody>
</table>

*This study used an ABI cutoff of 0.80; £this study used an ABI cut-off of 0.85; ¥for population-based cohorts, positive predictive value was 8.0% (95% CI, 6.2–9.9); negative predictive value was 98.3% (95% CI, 98.0–98.6); positive likelihood ratio was 5.61 (95% CI, 3.45–9.13); and disease incidence was 2.5%; ¥for the high-risk cohort, positive predictive value was 17.8%, negative predictive value was 94.3%, positive likelihood ratio was 1.38 (1.25–1.53), and disease incidence was 13.6%; €adjusted relative risk ratios are shown for studies that calculated the incremental effect of a low ABI on the risk of all-cause mortality after statistical adjustment for ≥1 cardiovascular risk factors including age, gender, race, smoking, diabetes, total cholesterol, hypertension, fasting glucose, body mass index, waist-hip ratio, fibrinogen, physical activity, history of coronary heart failure, amputation, CHD, or cardiovascular disease.

disease, and if the pretest probability is high, further testing is needed. Because of its low sensitivity (yet high specificity), the ABI cannot be used as a generic screening test. Rather, it must be used in a focused manner, choosing individuals for whom the yield of the test is expected to be higher.

When applying the results of a diagnostic test practically, using likelihood ratios is superior to using the specificity and sensitivity because likelihood ratios are less likely to change with the prevalence of the disorder. They can be calculated for several levels of the symptom/sign or test, they can be used to combine the results of multiple diagnostic tests, and they can be used to calculate post-test probability for a target disorder. They are particularly valuable when the test is used to screen individuals with a low pretest probability for a disease, because its associated with a significantly increased risk of mortality (eg, pretest to post-test probability changes from 9.5% to 28.0%).

It is important to determine whether a low ABI provides additional risk information over and above the assessment of conventional cardiovascular risk factors. The finding of a low ABI indicates the presence of flow-limiting atherosclerosis in a peripheral artery and likely reflects the presence of generalized atherosclerosis. Furthermore, the ABI should be used as an adjunct to a global risk assessment, which considers conventional cardiovascular risk factors as being additive in their predictive power. This is in contrast to the use of single risk factors to assess vascular prognosis (ie, low-density lipoprotein cholesterol) because on their own, they have poor predictive accuracy. A low ABI is more prevalent in patients with cardiovascular risk factors such as smoking, diabetes, and hypertension and is inversely correlated with other measures of vascular disease, including microalbuminuria and carotid intimal-medial thickness. Several studies have demonstrated that adding a low ABI to conventional cardiovascular risk factors, a low ABI is an independent predictor of cardiovascular risk. Murabito et al, using the Framingham data set, demonstrated that CHD prevalence remains associated with a low ABI after adjusting

TABLE 5. Summary Table of Population-Based Studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sensitivity of Low ABI (95% CI)</th>
<th>Specificity of Low ABI (95% CI)</th>
<th>Positive Likelihood Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD11,33</td>
<td>16.5 (12.8–20.2)</td>
<td>92.7 (92.1–93.3)</td>
<td>2.53 (1.45–4.40)</td>
</tr>
<tr>
<td>Stroke11–13</td>
<td>16.0 (12.9–19.1)</td>
<td>92.2 (91.9–92.5)</td>
<td>2.45 (1.76–3.41)</td>
</tr>
<tr>
<td>All-cause mortality7,10,11,28</td>
<td>31.2 (27.8–34.6)</td>
<td>88.9 (88.2–89.6)</td>
<td>3.97 (3.17–4.96)</td>
</tr>
<tr>
<td>Cardiovascular mortality7,10,11,28</td>
<td>41.0 (33.8–48.2)</td>
<td>87.9 (87.2–88.6)</td>
<td>5.61 (3.45–9.13)</td>
</tr>
</tbody>
</table>
for conventional risk factors, indicating that there is some incremental value of a low ABI in this setting.27 Using the likelihood ratio of a low ABI for predicting incident CHD derived in our analysis (2.53), together with the pretest probability that a patient will experience future CHD, can assist a clinician in determining the post-test probability of future CHD. For example, a 55-year-old male smoker on an antihypertensive medication with a high-density lipoprotein cholesterol of 38.5 mg/dL is at a 20% risk of developing clinical CHD in the next 10 years by conventional risk assessment. If his ABI is 0.90, the likelihood ratio of 2.53 increases his post-test probability of developing CHD to 42%. This information will help inform the clinician that the patient is at much higher risk than that derived from standard risk assessments and may influence his/her choice of diagnostic and therapeutic strategies for this patient.

The American Heart Association (AHA) Prevention Conference V described the ABI as a strong and independent risk factor for cardiovascular mortality and recommended it be used to detect subclinical disease in the prevention of cardiovascular mortality and stroke.19,40 AHA recommended that the ABI might be a useful addition to the assessment of CHD risk in selected populations, especially among people ≥50 years of age or among those who appear to be at intermediate or higher risk for cardiovascular disease on the basis of traditional risk factor assessment, such as cigarette smokers or individuals with diabetes mellitus. Their recommendation takes into account that the prevalence of a low ABI increases significantly with age and is 4 to 5× higher among individuals >70 years of age compared with those <50 years of age.41 In our analysis, the mean age of individuals was 68 years, and the prevalence of a low ABI was ~13%; accepting that the prevalence of a low ABI is ~4× lower among individuals aged 50, this is consistent with an expected prevalence of 3% in this age group. Although the prevalence of a low ABI may be lower in a younger population, the relative impact of this finding on their cardiovascular prognosis would be expected to be quantitatively similar. This suggests that although identifying younger individuals is important, advocating routine screening of all adults with the ABI is beyond the scope of primary care practice. Thus, the AHA recommendation to streamline the use of the ABI by age or the presence of cardiovascular risk factors is reasonable.

This model was tested in the Partners Program42 involving 350 primary care practices across the United States in which ABI screening was performed if subjects were ≥70 years of age or if they were 50 to 69 years of age and had a history of smoking or diabetes. After exclusion of individuals with established diagnosis of peripheral arterial disease or previous cardiovascular disease, a low ABI was identified in 13.1% of individuals screened. In primary care settings, it seems reasonable to expand the Partners approach to screen people ≥70 years of age or among those aged 50 to 69 years who have ≥1 cardiovascular risk factor (ie, elevated serum cholesterol, hypertension, dysglycemia, tobacco exposure, or a family history of atherosclerotic vascular disease; Figure). Among patients with established vascular disease, there is clear evidence that supports aggressive risk factor control and treatment with antiplatelet agents,43–45 statins,46–48 and angiotensin-converting enzyme (ACE) inhibition,49,50 and routine screening with the ABI would not alter drug treatment. However, the ABI may be useful in identifying certain high-risk patients before their first event. Many of these patients would normally not receive treatment with antiplatelets, statins, and ACE inhibitors because most clinical trials have focused on patients with previous cardiovascular events. Future prospective studies are needed to determine the cost and effectiveness of a screening program using the ABI, followed by early aggressive medical treatment among individuals with a low ABI to determine whether such an approach significantly improves cardiovascular prognosis.

The major limitation of the present analysis is our inability to determine the exact incremental value of the ABI over and above conventional risk factors because individual data were not available to us. Therefore, our weighted estimates of
sensitivity, specificity, relative risk, and positive likelihood ratios are unadjusted for conventional risk factors such as age, gender, hyperlipidemia, hypertension, smoking, and diabetes. However, many of the included studies, but not all, showed an increased relative risk of CHD, stroke, and mortality in subjects with a low ABI even after adjustment of these risk factors (Tables 2 through 4). Therefore, an essential contribution to the current understanding of ABI and cardiovascular risk prediction would be a large-scale study adequately powered to assess the predictability of ABI after adjusting for all conventional risk factors such as diabetes, hypertension, smoking, and hyperlipidemia. Conducting such a study is the only reliable way to show conclusively that low ABI has an incremental predictive value over traditional methods of risk assessment. A second limitation is the variation in measurement technique of the ABI across studies. Some investigators used the average ABI of the 2 lower extremities, some used the lower of the 2 measured values, whereas others used the lowest pressure found among multiple points in the leg. However, despite variations in measurement technique between studies, no systematic bias in the classification of low versus normal ABI would have occurred.

Conclusion
A low ABI is highly specific but not sensitive for predicting future vascular risk. Given that it is simple to perform, noninvasive, and inexpensive, among selected individuals, the ABI is a useful vascular risk prediction tool.

Acknowledgments
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