The Ankle-Brachial Index as a Biomarker of Cardiovascular Risk
It’s Not Just About the Legs

Todd S. Perlstein, MD, MMSc; Mark A. Creager, MD

The ankle-brachial index (ABI) is widely accepted as a diagnostic test used to evaluate the presence of lower extremity peripheral artery disease (PAD) in patients with symptoms of intermittent claudication or rest ischemia. However, the majority of patients with PAD are asymptomatic; therefore, measurement of the ABI only when prompted by symptoms will result in most cases of PAD going unrecognized.

The measurement of the ABI in patients without symptoms of PAD is controversial. In 2005, the United States Preventative Services Task Force assigned a “D” recommendation to screening for PAD, a grade indicating minimal benefit and possible harm. This recommendation was based on evaluation of limb outcomes such as claudication, amputation, and impaired ambulation. However, most patients with PAD do not go on to have major adverse limb outcomes. They do, however, have an excessively high burden of cardiovascular morbidity and mortality. In this issue of Circulation, Diehm and colleagues make an important contribution to the mounting evidence that screening for PAD in asymptomatic individuals be considered in terms of cardiovascular and not limb outcomes. They report 5-year outcomes in the German Epidemiological Study on Ankle Brachial Index (getABI), an ongoing prospective observational cohort study on the prognosis of elderly (aged ≥65 years) individuals with a low ABI compared with those with a normal ABI. Twenty-one percent of subjects screened had PAD, and the presence of PAD was associated with a >2-fold adjusted risk of death or severe vascular events. In persons with PAD, the risk of death or a severe coronary or cerebral vascular event was 3-fold that of a peripheral vascular event. Their findings reinforce the concept that the measurement of the ABI in selected patients as part of primary care practice would identify a significant number of persons at heightened risk for cardiovascular morbidity and mortality and that limb events are infrequent relative to total cardiovascular events in patients with PAD.

Thus, the greatest relevance of the ABI may not be for the limb but rather as a biomarker of cardiovascular risk.

The ABI as a Biomarker of Cardiovascular Risk

A National Institutes of Health working group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.” The ABI meets this definition as an objectively measured indicator of a pathogenic process.

The ABI satisfies many of the general features of a desirable cardiovascular disease biomarker (Table). It measures a specific pathology (ie, systemic atherosclerosis) because the cumulative prevalence of nonatherosclerotic causes of a low ABI (eg, giant cell arteritis) is very low. It adds to clinical assessment because the history and physical examination are often insufficient to correctly diagnose or rule out PAD. The ABI is acceptable to the patient because it causes only mild discomfort and poses no risk such as radiation exposure. Most often, a single measure is sufficient to diagnose PAD. It is applicable to men and women of all ages and has been tested in numerous ethnicities. The measurement is standardized, and it is both accurate and precise. The ABI has known reference limits; an ABI ≤0.90 has been validated as both a sensitive and a specific marker of PAD. Its specificity is not only for the presence of PAD but also for adverse cardiovascular outcomes, making it unlikely to mislabel or harm asymptomatic individuals. It has been tested in healthy individuals as well as in persons with varying severity of cardiovascular disease. The measurement takes only a few minutes, it does not require specialized equipment or a specialized technician, and has immediate turnaround. A previous report from the getABI group demonstrated that the ABI determination is highly reproducible and reliable when done in a primary care setting by physicians and nonphysicians with little training.

The ABI meets another important requirement for a cardiovascular disease biomarker: There is a consistent series of prospective epidemiological studies indicating that an abnormal ABI predicts cardiovascular disease. A systematic review and meta-analysis including 7 population-based studies with a total of 28,679 subjects found a consistent relationship between a low ABI and an adverse cardiovascular prognosis. The specificity of low ABI for coronary heart disease, stroke, and cardiovascular mortality was 92.7%, 92.2%, and 87.9%, respectively. The adjusted relative risk for cardiovascular mortality ranged from 2.0 to 6.3. A more recent
Table. Characteristics of the ABI as a Cardiovascular Biomarker

<table>
<thead>
<tr>
<th>Question</th>
<th>Characteristic</th>
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<tr>
<td>Can the clinician measure the biomarker?</td>
<td>ABI measurement is accurate and reproducible.</td>
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<td>ABI is acceptable to physicians and patients, presenting no risk including no ionizing radiation.</td>
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<td>Equipment necessary is widely available, and little training is required.</td>
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<td>The turnaround time is immediate.</td>
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<td>There is little to no cost.</td>
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<td>Does the biomarker add new information?</td>
<td>There is a strong and consistent association between low ABI and cardiovascular morbidity and mortality.</td>
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<td>The ABI adds to existing risk stratification scheme (Framingham Risk Score).</td>
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<td>Decision limits are validated in &gt;1 study: An ABI of ≤0.9 is diagnostic of PAD.</td>
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<td>Evaluation includes data from community-based populations.</td>
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<td>Will the biomarker help the clinician to manage patients?</td>
<td>A clinical trial is warranted to address this question.</td>
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Based on Morrow and de Lemos.8

There Is No Definitive Proof That Measurement of the ABI in Asymptomatic Individuals Will Benefit Cardiovascular Disease Outcomes

The overall expectation of a cardiovascular disease biomarker is to enhance the ability of the clinician to optimally manage the patient.10 One could plausibly argue that the detection of PAD in an asymptomatic patient with atherosclerotic risk factors mandates intensified therapy to mitigate cardiovascular events. It is not known, however, whether antiplatelet therapy and aggressive treatment of hypercholesterolemia and hypertension improve cardiovascular outcomes in patients with an abnormal ABI who do not have clinically manifest atherosclerosis. A meta-analysis by the Antithrombotic Trialists’ Collaboration reported that antiplatelet therapy reduces adverse cardiovascular events in symptomatic PAD.16 The 1 trial performed exclusively in asymptomatic PAD found no benefit of aspirin, a result that may have been due to coexisting diabetes mellitus.16,17 The Heart Protection Study found that statin therapy, compared with placebo, reduced the risk of adverse cardiovascular events in patients with symptomatic PAD, but no study has evaluated the efficacy of intensive lipid lowering in patients with asymptomatic PAD.18 Another trial suggested that aggressive antihypertensive therapy improves cardiovascular outcomes in patients with diabetes mellitus and a low ABI, but it is not known whether this would apply to all patients with PAD.19 The paucity of clinical trial data to inform clinical practice for patients with PAD needs to be addressed.20 The U.S. Preventive Services Task Force has just issued a statement on the use of nontraditional risk factors in coronary heart disease risk assessment of asymptomatic persons.21 The ABI was assigned a grade of “I”, indicating that evidence was insufficient to assess the benefits and harms. A high priority was given to determining the net clinical benefit of aggressive treatment of persons reclassified from intermediate to high risk on the basis of additional information obtained from the ABI.

We propose a trial to determine whether altering treatment strategy on the basis of an abnormal screening ABI would improve cardiovascular outcomes. Individuals at risk for PAD but without clinically established atherosclerotic vascular disease would have an ABI performed. Those with an ABI ≤0.9 would be eligible for enrollment. Subjects would be randomized to a strategy of maximal secondary prevention measures or routine clinical care. The primary outcome could be the combination of myocardial infarction, stroke, or death (ie, not a limb outcome).

It’s not just about the legs: In asymptomatic individuals, the ABI should be thought of as a biomarker of cardiovascular disease risk. Diehm and colleagues8 have cemented the platform on which to initiate a clinical trial examining the potential benefits of screening ABI and application of aggressive secondary preventive measures on cardiovascular outcomes. Until such a trial is completed, we recommend that high-risk persons be screened with an ABI and that those diagnosed with PAD be treated with intensive risk reduction therapies.
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References


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