Vascular prediction: Just an illusion?
Or
Does Preclinical Atherosclerosis improve risk stratification?

The “Good Old” ABI

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Disclosure Statement of Financial Interest

I currently have, or have had over the last four years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

Affiliation/Financial Relationship
• Grant/Research Support
• Consulting Fees/Honoraria
• Major Stock Shareholder/Equity
• Royalty Income
• Ownership/Founder
• Intellectual Property Rights
• Other Financial Benefit

Company
• Astra Zeneca, BMS, Sanofi aventis
• Astra zeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi, Sankyo, GE, MSD, Pfizer, Philips, Servier, Zambon
• none
• none
• none
• none
• none
The old ABI


  – Systolic pressures can be measured easily in the limbs with arterial occlusive disease using blood pressure cuffs. Pulse pick-ups, ultrasonic flow detector, spectroscope, or visual “flush” technique may be used to detect the end point. ….The pressures were abnormal in all limbs with complete proximal occlusion and in the majority of limbs with proximal stenosis. …..The described techniques should find wide clinical application, particularly since the measurements can be carried out easily at bedside and in the physician's office.
The good ABI

- **ABI allows an accurate diagnosis of PAD**
  - Sensitivity and specificity respectively, 79% and 96%.
  - For diagnosis in primary care:
    - an ABI, 0.8 or the mean of three ABIs, 0.90 had a positive predictive value of ≥95%;
    - an ABI, 1.10 or the mean of three ABIs, 1.00 had a negative predictive value of ≥99%.

- **Simple, painless, accurate, highly reproducible**
  - Needs only a continuous wave handheld Doppler (2-300 €)

How to measure ABI

- Patient resting supine for 5-10 minutes
- Measure Systolic BP in both arms
  - Higher value is denominator of ABI
- Measure Systolic BP in DP and PT
  - Higher value is numerator of ABI
# Interpretation of the ABI

<table>
<thead>
<tr>
<th>ABI</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.29</td>
<td>Check for diabetes</td>
</tr>
<tr>
<td>1.00–1.29</td>
<td>Normal</td>
</tr>
<tr>
<td>0.91–0.99</td>
<td>Equivocal</td>
</tr>
<tr>
<td>0.41–0.90</td>
<td>Mild-to-moderate PAD</td>
</tr>
<tr>
<td>0.0–0.40</td>
<td>Severe PAD</td>
</tr>
</tbody>
</table>

Event free Survival

Hirsch AT et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease
ABI identifies people with a high risk of cardiovascular events

11 Studies comprising 44,590 subjects from six different countries

A low ABI (<0.9) was associated with an increased risk of subsequent CV events

Heald CL et al. Atherosclerosis 2006;189:61–69
Risk of a cardiac event by ABI

Adjusted odds of cardiac event by ABI
Moderate blood pressure control – ABCD normotensive cohort reference group:
baseline ABI=1.0

Odds of MI, stroke, or CV death

Baseline ABI

Norgren L, Hiatt WR (eds) et al. Eur J Vasc Endovasc Surg 2007;33(suppl 1):S1–S75
ABI and mortality: a linear relationship

Baseline ABI: mean participant follow-up 8.3 years

The PATHOS study analysed 1,758 patients from 49 centres in Italy: abnormal ABI was seen in 27.3% of CVD patients and 33.5% of CAD patients.

Abnormal ABI ($\leq 0.9$) is seen in one third of patients hospitalised for acute coronary or cerebrovascular events and predicts poor outcome at 1 year.

ABI and prediction of the risk in “so call” healthy people

- Risk evaluation relies highly on prediction models
  - Framingham
  - SCORE
  - => over prediction in low risk and under prediction in high risk
- FRS does not fully explain CVR
  - 20 % MI without RF
  - 60-80 % of CHD in low or intermediate risk groups

ABI in patients with non-high cardiovascular risk
The PANDORA Study

- Male aged ≥45 years or female aged ≥55 years (CVD risk factor)
- At least another risk factor for CVD, among the following:
  - cigarette smoking (any cigarette smoking in the past month);
  - hypertension (arterial blood pressure ≥140/90 mmHg or taking antihypertensive medication);
  - low HDL cholesterol (<40 mg/dL) or high LDL cholesterol (≥130 mg/dL), within 3 months of study entry;
  - family history of premature CHD (clinical CHD or sudden death in father or other male first-degree relative <55 years of age; CHD in mother or other female first-degree relative <65 years of age);
  - elevated waist circumference (≥102 cm for male; ≥88 cm for female);

- Exclusion
  - Symptoms of PAD
  - Diabetes Mellitus

The Pandora Study

9816 pts in primary care in 6 EU countries

Prevalence of low ABI by country

Nb of RF and risk of low ABI

Framingham 10-year CHD risk score ranges (%) by ABI value

- ABI > 0.90
  - <10%: 35.2%
  - 10%-20%: 46.45%
  - >20%: 18.35%

- ABI <= 0.90
  - <10%: 43.46%
  - 10%-20%: 27.98%
  - >20%: 28.56%

- All subjects
  - <10%: 34.02%
  - 10%-20%: 45.91%
  - >20%: 20.07%

N=9,816

IPSILON

- 5679 pts in primary care
- 2077 with at least 2 RF => 10.4 % of PAD

Is ABI independent of the risk scores to predict CV events and mortality?

The ABI Collaboration

• 16 studies – 48294 participants of any age, sex and derived from general population

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Individuals in Studies in the Ankle Brachial Index (ABI) Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Weatherley et al, 2007</td>
</tr>
<tr>
<td>Komiter et al, 1995</td>
</tr>
<tr>
<td>Newman et al, 1999</td>
</tr>
<tr>
<td>Lang et al, 1996</td>
</tr>
<tr>
<td>Murabito et al, 2002</td>
</tr>
<tr>
<td>Fowler et al, 2002</td>
</tr>
<tr>
<td>Abbott et al, 2000</td>
</tr>
<tr>
<td>Jager et al, 1999</td>
</tr>
<tr>
<td>McDermott et al, 2004</td>
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<tr>
<td>Hooi et al, 2004</td>
</tr>
<tr>
<td>Cron et al, 1990</td>
</tr>
<tr>
<td>Van der Meeren et al, 2004</td>
</tr>
<tr>
<td>Croqui et al, 1992</td>
</tr>
<tr>
<td>Hiatt et al, 1995</td>
</tr>
<tr>
<td>Resnick et al, 2004</td>
</tr>
<tr>
<td>McDermott et al, 2000</td>
</tr>
</tbody>
</table>

Ankle Brachial Index Collaboration, JAMA 2008;300:197-208.
Low ABI adds significantly to the risk of mortality in men and women.
ABI collaboration

- Low ABI (≤ 0.9) doubles the risk of total mortality, cardiovascular mortality and major coronary events in all FRS category
- 19 % of men and 36 % of women are changing risk category

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Table 8. 10-Year Total Coronary Heart Disease (CHD) Rates in Men and Women by Framingham Risk Score (FRS) Category and Ankle Brachial Index (ABI) at Baseline for All Studies Combined in the ABI Collaboration

<table>
<thead>
<tr>
<th>FRS Category</th>
<th>Total</th>
<th>≤0.90</th>
<th>0.91-1.10</th>
<th>1.11-1.40</th>
<th>&gt;1.40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. in FRS Category</td>
<td>CHD, %</td>
<td>No. in FRS Category</td>
<td>CHD, %</td>
<td>No. in FRS Category</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>5643</td>
<td>5</td>
<td>76</td>
<td>8</td>
<td>1076</td>
</tr>
<tr>
<td>Intermediate (10%-19%)</td>
<td>7392</td>
<td>13</td>
<td>245</td>
<td>16</td>
<td>2069</td>
</tr>
<tr>
<td>High (≥20%)</td>
<td>8398</td>
<td>23</td>
<td>1149</td>
<td>40</td>
<td>3406</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>15,505</td>
<td>11</td>
<td>1083</td>
<td>21</td>
<td>6192</td>
</tr>
<tr>
<td>Intermediate (10%-19%)</td>
<td>5563</td>
<td>13</td>
<td>558</td>
<td>25</td>
<td>2429</td>
</tr>
<tr>
<td>High (≥20%)</td>
<td>1418</td>
<td>27</td>
<td>200</td>
<td>44</td>
<td>598</td>
</tr>
</tbody>
</table>

Ankle Brachial Index Collaboration, JAMA 2008;300:197-208.
ABI adds accuracy to the Framingham score risk (men)

- The greatest effect occurred in men categorised as high-risk according to Framingham score
  - Addition of ABI reduced risk level to intermediate
- Overall, 19% of men were reclassified

<table>
<thead>
<tr>
<th>FRS category</th>
<th>ABI</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.90</td>
<td>0.91–1.10</td>
<td>1.11–1.40</td>
<td>&gt;1.40</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>N CHD (%)</td>
<td>N CHD (%)</td>
<td>N CHD (%)</td>
<td>N CHD (%)</td>
<td>N CHD (%)</td>
</tr>
<tr>
<td></td>
<td>76   8</td>
<td>1076 5</td>
<td>4255 4</td>
<td>236 5</td>
<td></td>
</tr>
<tr>
<td>Intermediate (10–19%)</td>
<td>245 16</td>
<td>2069 12</td>
<td>4815 12</td>
<td>263 8</td>
<td></td>
</tr>
<tr>
<td>High (≥20%)</td>
<td>1149 40</td>
<td>3406 21</td>
<td>3668 18</td>
<td>175 14</td>
<td></td>
</tr>
</tbody>
</table>

Addition of ABI to Framingham risk score adds accuracy, and treatment should therefore be optimised to patients’ new risk level

ABI adds accuracy to the Framingham score risk (women)

- Adding ABI changed women with abnormal ABI in the Framingham low-risk category to intermediate or high risk.
- Women with abnormal ABI in the Framingham intermediate category became high risk.
- Overall, 36% of women changed category.

<table>
<thead>
<tr>
<th>FRS category</th>
<th>ABI</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.90</td>
<td>0.91–1.10</td>
<td>1.11–1.40</td>
<td>&gt;1.40</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>CHD (%)</td>
<td>N</td>
<td>CHD (%)</td>
<td>N</td>
<td>CHD (%)</td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>1083</td>
<td>21</td>
<td>6192</td>
<td>10</td>
<td>7909</td>
</tr>
<tr>
<td>Intermediate (10–19%)</td>
<td>558</td>
<td>25</td>
<td>2429</td>
<td>12</td>
<td>2433</td>
</tr>
<tr>
<td>High (≥20%)</td>
<td>200</td>
<td>44</td>
<td>598</td>
<td>21</td>
<td>577</td>
</tr>
</tbody>
</table>

Addition of ABI to Framingham risk score adds accuracy, and treatment should therefore be optimised to patients’ new risk level.

Is ABI independent of the risk scores to predict CV events and mortality? Data from the ARIC study

- 11594 individuals; 45 – 64 yrs old
- 270 abnormal ABI, 10 yrs FU => 659 CVE
- RF are related to ABI
- Low ABI X 2 risk in individuals with low FRS (from 5.6% to 11.0%)
- High FRS X3 the average risk compared with low FRS (5.6% to 14.4%).
- High FRS and abnormal ABI => adj 10-year risk of CVD is 32.2%

Is ABI independent of the risk scores to predict CV events and mortality? Data from the ARIC study

- **Reclassification**
  - When incorporating ABI with FRS in a model
    - 28 participants reclassified upwards
    - 26 participants reclassified downwards

- **Two-steps process**
  - Sensitivity FRS alone = 14.4%.
  - Adding ABI => 16.7

=> Modest contribution of ABI to risk assessment, over threshold adjustment

<table>
<thead>
<tr>
<th></th>
<th>FRS only</th>
<th>FRS +ABI (2 step)</th>
<th>FRS modified threshold**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.144</td>
<td>0.167</td>
<td>0.171</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.970</td>
<td>0.963</td>
<td>0.963</td>
</tr>
<tr>
<td>PPV</td>
<td>0.224</td>
<td>0.212</td>
<td>0.218</td>
</tr>
<tr>
<td>NPV</td>
<td>0.950</td>
<td>0.950</td>
<td>0.951</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.923</td>
<td>0.917</td>
<td>0.918</td>
</tr>
<tr>
<td>Adjusted % correct (Youden’s index)</td>
<td>0.114</td>
<td>0.130</td>
<td>0.134</td>
</tr>
</tbody>
</table>

- **But:** one side ABI by oscillometric technique ??

**Annals of Internal Medicine**

**USING NONTRADITIONAL RISK FACTORS IN CORONARY HEART DISEASE RISK ASSESSMENT CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic men and women with no history of coronary heart disease (CHD), diabetes, or any CHD risk equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>I statement: Insufficient Evidence</td>
<td>No recommendation because of Insufficient evidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>This recommendation applies to adult men and women classified at intermediate 10-year risk for CHD (10% to 20%) by traditional risk factors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importance</td>
<td>Coronary heart disease (CHD) is the most common cause of death in adults in the United States. Treatment to prevent CHD events by modifying risk factors is currently based on the Framingham risk model. If the classification of individuals at intermediate risk could be improved by using additional risk factors, treatment to prevent CHD might be targeted more effectively. Risk factors not currently part of the Framingham model (nontraditional risk factors) include high-sensitivity C-reactive protein (hs-CRP), ankle–brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima–media thickness, coronary artery calcification score on electron-beam computed tomography, homocysteine level, and lipoprotein(a) level.</td>
</tr>
<tr>
<td>Rationale for No Recommendation</td>
<td>There is insufficient evidence to determine the percentage of intermediate-risk individuals who would be reclassified by screening with nontraditional risk factors, other than hs-CRP and ABI. For individuals reclassified as high-risk on the basis of hs-CRP or ABI scores, data are not available to determine whether they benefit from additional treatments. Little evidence is available to determine the harms of using nontraditional risk factors in screening. Potential harms include lifelong use of medications without proven benefit and psychological and other harms from being misclassified in a higher risk category.</td>
</tr>
<tr>
<td>Considerations for Practice</td>
<td>Clinicians should continue to use the Framingham model to assess CHD risk and guide risk-based preventive therapy. Adding nontraditional risk factors to CHD assessment would require additional patient and clinical staff time and effort. Routinely screening with nontraditional risk factors could result in lost opportunities to provide other important health services of proven benefit.</td>
</tr>
<tr>
<td>Relevant USPSTF Recommendations</td>
<td>USPSTF recommendations on risk assessment for CHD, the use of aspirin to prevent cardiovascular disease, and screening for high blood pressure can be accessed at <a href="http://www.preventiveservices.ahrq.gov">www.preventiveservices.ahrq.gov</a>.</td>
</tr>
</tbody>
</table>

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov).
16. Recommendation for Measurement of Ankle-Brachial Index

**CLASS IIa**

1. Measurement of ankle-brachial index is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (47). *(Level of Evidence: B)*
## 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease

### Table 2. Recommendations for Ankle-Brachial Index, Toe-Brachial Index, and Segmental Pressure Examination

<table>
<thead>
<tr>
<th>Class I</th>
<th>2005 Recommendations</th>
<th>2011 Focused Update Recommendations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with exertional leg symptoms, with nonhealing wounds, who are 70 years and older or who are 50 years and older with a history of smoking or diabetes. <em>(Level of Evidence: C)</em></td>
<td>1. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes <em>(G–I)</em>. <em>(Level of Evidence: B)</em></td>
<td>Modified recommendation (age modified and level of evidence changed from C to B).</td>
</tr>
<tr>
<td></td>
<td>The ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower extremity PAD and establish a baseline <em>(12–14)</em>. <em>(Level of Evidence: B)</em></td>
<td>1. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes <em>(G–I)</em>. <em>(Level of Evidence: B)</em></td>
<td>2005 recommendation remains current in 2011 focused update.</td>
</tr>
<tr>
<td></td>
<td>The toe-brachial index should be used to establish the lower extremity PAD diagnosis in patients in whom lower extremity PAD is clinically suspected but in whom the ABI test is not reliable due to noncompressible vessels (usually patients with long-standing diabetes or advanced age) <em>(15–19)</em>. <em>(Level of Evidence: B)</em></td>
<td>1. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes <em>(G–I)</em>. <em>(Level of Evidence: B)</em></td>
<td>2005 recommendation remains current in 2011 focused update.</td>
</tr>
<tr>
<td></td>
<td>Leg segmental pressure measurements are useful to establish the lower extremity PAD diagnosis when anatomic localization of lower extremity PAD is required to create a therapeutic plan <em>(20–23)</em>. <em>(Level of Evidence: B)</em></td>
<td>1. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes <em>(G–I)</em>. <em>(Level of Evidence: B)</em></td>
<td>2005 recommendation remains current in 2011 focused update.</td>
</tr>
<tr>
<td></td>
<td>2. ABI results should be uniformly reported with noncompressible values defined as greater than 1.40, normal values 1.00 to 1.40, borderline 0.91 to 0.99, and abnormal 0.90 or less <em>(24)</em>. <em>(Level of Evidence: B)</em></td>
<td>1. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes <em>(G–I)</em>. <em>(Level of Evidence: B)</em></td>
<td>New recommendation</td>
</tr>
</tbody>
</table>

*ABI: Ankle-Brachial Index, PAD: Peripheral Artery Disease*
Box 2. Subclinical organ damage in total cardiovascular risk stratification

1. In hypertension, assessment of total cardiovascular risk is important to optimize the decision about treatment initiation, intensity and goals.

2. Quantification of total cardiovascular risk must include a search for subclinical organ damage, which is common in hypertension and has independent prognostic significance.

3. In patients with hypertension, the presence of subclinical organ damage usually brings cardiovascular risk into the high range. Subclinical organ damage alone may not be sufficient to bring normotensive individuals into the high-risk category, although this may occur with multiple organ damage and the metabolic syndrome.

4. As detailed in the 2007 ESH/ESC guidelines, several measures of renal, cardiac and vascular damage can be considered for total cardiovascular risk quantification. Because of their simplicity, wide availability and limited cost measures based on urinary protein excretion (including microalbuminuria), eGFR (MDRD formula), and ECG are suitable for routine use. Cardiac and vascular ultrasounds are more and more easily available in Europe, and their use in the evaluation of the hypertensive patient can be encouraged.

5. Subclinical organ damage should be assessed both at screening and during treatment because a number of treatment-induced changes in organ damage relate to cardiovascular and renal outcomes, thereby offering information on whether the selected treatment is protecting patients from progressing organ damage and potentially from cardiovascular events.

6. Several other measures of subclinical organ damage have been shown to have prognostic significance, but their complexity, low availability, and high cost prevent their routine clinical use. It is likely that technological progress will make use of some of these measurements more common in the future. Any measure, however, should be considered only if it adds to the overall precision of cardiovascular risk quantification.
Box 6 Laboratory investigations

Routine tests
- Fasting plasma glucose
- Serum total cholesterol
- Serum LDL-cholesterol
- Serum HDL-cholesterol
- Fasting serum triglycerides
- Serum potassium
- Serum uric acid
- Serum creatinine
- Estimated creatinine clearance (Cockcroft-Gault formula) or glomerular filtration rate (MDRD formula)
- Haemoglobin and haematocrit
- Urinalysis (complemented by microalbuminuria via dipstick test and microscopic examination)
- Electrocardiogram

Recommended tests
- Echocardiogram
- Carotid ultrasound
- Quantitative proteinuria (if dipstick test positive)
- Ankle-brachial BP Index
- Fundoscopy
- Glucose tolerance test (if fasting plasma glucose >5.6 mmol/L (100 mg/dL)
- Home and 24 h ambulatory BP monitoring
- Pulse wave velocity measurement (where available)

Extended evaluation (domain of the specialist)
- Further search for cerebral, cardiac, renal and vascular damage. Mandatory in complicated hypertension
- Search for secondary hypertension when suggested by history, physical examination or routine tests: measurement of renin, aldosterone, corticosteroids, catecholamines in plasma and/or urine; arteriographies; renal and adrenal ultrasound; computer-assisted tomography; magnetic resonance imaging
CVD is a global disease with a long asymptomatic course

Conclusion
Conclusion

• ABI is simple, fast to perform, cheap, accurate…..
• Just do it !..................
• Even if it remains unclear whether the prognosis will really be improved.

« The truth is that there is no truth… »

Pablo Neruda