The toe-brachial index in the diagnosis of peripheral arterial disease

Christian Høyer, MD,a,b Jes Sandermann, MD,c,d and Lars J. Petersen, MD, DMSc,e,f Viborg, Aalborg, and Aarhus, Denmark

Background: Peripheral arterial disease (PAD) can be diagnosed noninvasively by segmental blood pressure measurement and calculating an ankle-brachial index (ABI) or toe-brachial index (TBI). The ABI is known to be unreliable in patients with vascular stiffness and fails to detect the early phase of arteriosclerotic development. The toe vessels are less susceptible to vessel stiffness, which makes the TBI useful. However, the diagnostic limits used in guidelines, clinical settings, and experimental studies vary substantially. This review provides an overview of the evidence supporting the clinical use of the TBI.

Methods: A review of the literature identified studies reporting the use of the TBI regarding guideline recommendations, normal populations, correlations to angiographic findings, and prognostic implications.

Results: Eight studies conducted in a normal population were identified, of which only one study used imaging techniques to rule out arterial stenosis. A reference value of 0.71 was estimated as the lowest limit of normal based on the weighted average in studies with preheating of the limbs. A further seven studies showed correlations of the TBI with angiographic findings. The TBI had a sensitivity of 90% to 100% and a specificity of 65% to 100% for the detection of vessel stenosis. Few studies investigated the value of the TBI as a prognostic marker for cardiovascular mortality and morbidity, and no firm conclusions could be made. Studies have, however, shown correlation between the TBI and comorbidities such as kidney disease, diabetes, and microvasculature disease.

Conclusions: In contrast to the well-defined and evidence-based limits of the ABI, the diagnostic criteria for a pathologic TBI remain ambiguous. Although several guidelines and reviews of PAD diagnostics recommend a TBI <0.70 as cutoff, it is not strictly evidence-based. The current literature is not sufficient to conclude a specific cutoff as diagnostic for PAD. The current studies in normal populations and the correlation with angiography are sparse, and additional trials are needed to further validate the limits. Large-scale trials are needed to establish the risk of morbidity and mortality for the various diagnostic limits of the TBI. (J Vasc Surg 2013;58:231-8.)

Peripheral arterial disease (PAD) is a manifestation of generalized arteriosclerotic disease and leads to a range of clinical conditions from asymptomatic disease to critical ischemia.1 According to intersociety consensus guidelines, PAD can be diagnosed noninvasively using segmental blood pressure measurements by obtaining an ankle-brachial index (ABI) or a toe-brachial index (TBI).1,2 The diagnostic limits of the ABI have been validated in several large-scale studies, and an ABI cutoff of ≤0.90 has been shown to be a strong predictor of cardiovascular morbidity and mortality,3,4 even in the absence of traditional risk factors.5 In addition, the diagnostic limits of the ABI have been shown to correspond to angiographic findings, although studies have reported diverging diagnostic accuracy for detecting vessel stenosis in the lower limb.6

Conditions associated with media calcification, such as diabetes, chronic kidney disease, or advanced age, can lead to falsely elevated or falsely normal ankle pressures due to vessel stiffness.7,9 The toe vessels, however, are less susceptible to vessel stiffness, which makes the TBI useful.10,11 In addition, the ABI has been shown to underestimate the presence of media calcification compared with findings from imaging techniques.12

Screening is the key to detecting early-stage disease and allows the initiation of optimal preventive medical treatment, which may reduce modifiable risk factors for patients at risk for arteriosclerotic disease.13 In the current screening algorithms, the most frequently used primary testing procedures include the Doppler-derived ABI, patient history, and clinical examination. The TBI is usually limited to patients who are expected to have vessel stiffness because of relevant comorbidities or who have an elevated ABI.1 This approach is well known to underestimate the true prevalence of PAD in the population, and in particular, fails to detect the early phase of arteriosclerotic development.14 In addition, studies have shown that 14% to 27% of patients referred for distal pressure measurements have a low TBI but a normal ABI.7,14,15 Approximately 60% of these patients were not diagnosed with a disease associated with vessel
stiffness, and therefore, would not have been diagnosed with PAD according to the current screening algorithms. Implementation of the TBI as the standard test for PAD could potentially allow detection of PAD patients who remain undiagnosed by current standards.

Reliable measurement of the TBI has historically been limited to vascular laboratories due to the expensive and cumbersome techniques. Hand-held Doppler-based methods are the primary tools for PAD diagnostics but are less useful for the measurement of toe pressures. However, recently developed methods have been introduced that allow access to bedside assessment of the TBI. Early results are promising.

In contrast to the well-defined and evidence-based limits of the ABI, the diagnostic criteria for having a pathologic vs a normal ABI remain ambiguous. Several guidelines and reviews of PAD diagnostics recommend a TBI < 0.70 as a cutoff, but other different limits are widely used in observational studies and clinical settings. This may reflect the lack of evidence regarding the prognostic implication of various TBI cutoffs and the correlation to angiographic findings. The purpose of this review is to provide an overview of the evidence supporting the various limits used for the TBI-based diagnosis of PAD.

GUIDELINE RECOMMENDATIONS

Ferket et al identified eight major guidelines in a systematic review of PAD screening. The guidelines were evaluated with an Appraisal of Guidelines, Research and Evaluation in Europe (AGREE) rigor score varying from 33% to 81%. We reviewed the same guidelines for statements regarding the use of TBI in the diagnosis of PAD. These guidelines recommended an ABI < 0.90 or ABI ≤ 0.90 as the diagnostic limit, and only two of these guidelines included statements for the use of the TBI. The TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) defined a TBI < 0.70 as an abnormal finding, but the guidelines did not include references to support this. They emphasized that the importance of toe pressures cannot be underestimated in diabetic patients with ulcers due to the possibility of falsely elevated ankle pressures.

The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) stated in the ACCF/AHA 2011 guidelines that the TBI should be used to establish the lower extremity PAD diagnosis in patients in whom the condition is suspected, and when the ABI test is not reliable due to noncompressible vessels (longstanding diabetes or advanced age). The evidence supporting this was graded as level B evidence. They did not specify diagnostic cutoff levels in these guidelines. The ACCF/AHA 2005 guidelines defined a TBI < 0.7 as diagnostic for PAD; however, none of the studies cited to support this cutoff value advocated the use of a TBI < 0.7 as a diagnostic limit.

NORMAL RANGE

A limited number of studies have examined the normal range of TBI in populations without vascular disease and showed normal lower limits of TBI ranging from 0.49 to 0.74 (Table I). According to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) recommendations for quality grading in diagnostic accuracy studies, it is imperative to minimize the risk of bias by appropriate patient selection, using correct reference standard, and adequately displaying data.

Regarding patient selection, all studies except for one (Williams et al, 2006) were established without using imaging techniques to rule out arterial stenosis. The high prevalence of PAD and the fact that > 50% of PAD patients are asymptomatic are important factors to consider when assessing a reliable normal patient population. This issue may be primarily relevant for normal values in elderly populations. Arveschough et al, however, added blood sample screening to exclude patients with arteriosclerotic risk factors. In general, the recruitment process for healthy volunteers for the normal populations for all studies was insufficiently described and included coworkers, etc.

Regarding the appropriate use of reference standards, all studies reported the use of pretest limb heating, except the studies by Williams et al, Muro et al, and Brooks et al. The lack of pretest heating could partly explain the relatively low average TBI found in these studies. The failure to include standardized pretest limb heating can compromise reproducibility and lead to the measurement of falsely low toe pressures.

A number of different techniques are currently used for the assessment of toe pressures in vascular laboratories, including laser Doppler flowmetry, photo plethysmography, oscillometric plethysmography, and mercury-in-silastic strain gauge plethysmography. These methods are not fully interchangeable due to the differences in measurement technologies and end points (DC or AC signals). For example, photoplethysmography has been shown to produce lower pressure readings than strain-gauge plethysmography and laser Doppler flowmetry.

Age and sex could be important factors, and different reference values have been proposed for different age groups. In the Fig, the mean age is plotted against TBI findings from available sources. The data do not reveal an evident discrepancy in the TBI across different age groups, although the studies cannot be directly compared due to the major differences in pretest preparation and technologies applied.

Overall, the primary limitations of the existing studies include the lack of imaging techniques to exclude PAD, small study sample sizes, inclusion of cohorts with inappropriate age distributions, and the use of different and likely not directly comparable techniques. Finally, the general acceptance of the limits stated as the mean ± two standard deviations is based on the assumption of a normal distribution of the TBI, which remains to be documented.

CORRELATION OF TBI TO ANGIOGRAPHIC FINDINGS

Various methods, including duplex ultrasound imaging, have been validated against contrast angiography for the
detection of vessel stenosis. Although the limit of ABI ≤0.90 is considered robust in PAD diagnostics, a recent systematic review showed a sensitivity ranging from 15% to 79% and a specificity from 83% to 100% for detecting >50% vessel stenosis in the lower limb. The sensitivity was particularly low in elderly patients and in patients with diabetes. A number of studies have included the TBI as well as angiographic findings, but the primary end points in most of these studies were not to assess the diagnostic accuracy of the TBI, which can lead to heterogeneous data. The extracted studies are reported in Table II. Most of the studies used highly selected populations, which does not allow generalization due to the different prevalence of PAD in the varying groups.

According to the QUADAS-2 grading on the quality of diagnostic accuracy studies, there is a risk of introducing a systematic bias when enrolling inappropriate study populations. As it was the case with the studies of normal populations, the reference standard for the TBI is performed by different methods and with inconsistent use of pretest limb heating. A falsely low TBI would increase the reported sensitivity.

In addition to appropriate patient selection and the use of a correct reference standard, the QUADAS-2 recommendations emphasize the importance of adequately displaying the data. In several instances, the publications only partially presented key data. Another problem is that the extracted studies focused on PAD diagnosis on a limb basis only and not on a patient basis.

In the 1971 study by Carter et al, a key study in the determination of TBI reference values, the results from a normal population (Table I) were transferred to 135 patients with known PAD. They concluded that a TBI <0.64 was abnormal. By using this cutoff, 121 of the 135 limbs with angiographically verified stenosis had a TBI below the lower limit of normal. This study remains one of the most frequently quoted studies regarding TBI limits.

Only one study was identified that included a subgroup of patients not primarily suspected of having PAD. In this 2005 study, Williams et al enrolled 88 patients with diabetes and a control population of 41 without diabetes. They performed color duplex imaging to diagnose stenosis of lower limb vessels and concluded that a TBI <0.75 was an optimal cutoff with a high sensitivity and specificity for detecting PAD for both patient groups (Table II). In comparison, the Doppler-based ABI showed a sensitivity of 83% for controls, 100% for diabetic patients without peripheral neuropathy, and 53% for diabetic patients with peripheral neuropathy when using an ABI <0.9 or ABI >1.15 as the limit. The correspondent numbers for the specificity were 100% for controls, 88% for diabetic patients without peripheral neuropathy, and 95% for diabetic patients with peripheral neuropathy.

Weinberg et al performed contrast angiography in 116 limbs of 92 patients with an ABI >1.40; of whom,
67% had diabetes and 19% required hemodialysis. A TBI <0.7 was found in 92% of patients with PAD confirmed by angiography. Suominen et al\(^\text{29}\) studied 1762 patients suspected of PAD that were referred to a vascular center and performed digital subtraction angiography in two subsets of these patients. The first part, including 69 patients with an ABI >1.3, all showed vessel stenosis involving >50% of the lumen, of which only one patient had TBI >0.6. In the second subset, which included 47 patients with a normal ABI but a TBI <0.6, the researchers confirmed the presence of significant stenosis in 44 patients (94%) by angiography. Park et al\(^\text{58}\) performed infrapopliteal angiography in both limbs in patients with diabetic gangrene and suspected arterial insufficiency. They included patients with reduced TBI (<0.6) or ABI (<0.9) in at least one limb. Among this group, 13 of the 30 limbs presented with a pathologic TBI. The TBI showed a sensitivity of 100% and a specificity of 100% for detecting a vessel stenosis per limb requiring subsequent intervention. In contrast, the ABI showed a sensitivity of 38% and a specificity of 88% in this highly selective cohort. It was not reported whether the observers were blinded to the results of the reference or the index test, or both, which is a key issue in studies of diagnostic accuracy and may introduce a source of bias.\(^\text{59}\)

**ASSOCIATION OF TBI TO MORBIDITY AND MORTALITY**

Cardiovascular disease and mortality. So far, only a few studies have described the prognostic effect on cardiovascular disease and mortality of having a pathologic TBI and a normal ABI. In the San Diego Population Study, Criqui et al\(^\text{60-64}\) performed PAD screening on a geographically defined population of 624 individuals as a part of a study on dyslipidemia. By using an ABI ≤0.8 and a TBI ≤0.7 as diagnostic limits and diagnosis based on pulse reappearance time, 14% of the population presented with isolated low toe pressures.\(^\text{61}\) A 10-year follow-up of this small study sample of 90 revealed a 2.6 times increased risk of cardiovascular death in patients with an isolated reduced TBI compared with those with normal pressure indices.\(^\text{64}\) Nonetheless, they showed that patients with a low TBI but a normal ABI were epidemiologically distinct from patients with a low ABI because they had a lower frequency of smokers, were less likely to be obese, had a lower fasting glucose levels, and were younger.\(^\text{60}\)

In comparison, Suominen et al\(^\text{7}\) conducted an analysis of patients referred to a vascular clinic with suspicion of PAD. A total of 27% in the cohort had a TBI <0.6 and an ABI >0.9; of these, >40% were reported to have chronic kidney failure or diabetes. PAD diagnosed by TBI was independently associated with all-cause and cardiovascular mortality in patients with an ABI >1.3. In a study of 309 patients with a TBI <0.10 and a low-pulse amplitude, an increased risk of the overall and cardiovascular 5-year death rate was reported.\(^\text{42}\) Regarding cardiovascular disease, Papanas et al\(^\text{65}\) showed an association with the TBI and coronary artery stenosis confirmed on coronary angiography.

**Normal ABI but low TBI.** The prevalence of having a low TBI but a normal ABI ranges from 9% to 27% in different large-scale studies (n > 100; Table III). The findings are, however, not comparable due to the heterogeneous study populations, different diagnostic limits used, and substantial methodologic differences. Three studies included patients suspected of PAD and showed a normal ABI but a low TBI in 16% to 27%. In these studies, a high pretest likelihood of having the disease was expected, as was the case in studies of patients with diabetes or chronic kidney disease.

**Disease progression.** Bird et al\(^\text{15}\) performed repeated distal pressure assessments in 755 limbs in 423 patients referred to a vascular laboratory at the San Diego Veterans Administration Medical Center, with a mean follow-up of 4.6 years. They identified 106 patients (14%) with

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**Table II. Sensitivity and specificity of the toe-brachial index (TBI) for detecting peripheral arterial disease (PAD) with imaging technique as reference tests\(^a\)**

<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>Year</th>
<th>Population</th>
<th>Limbs, No.</th>
<th>Low TBI, No. (%)</th>
<th>Stenosis, No. (%)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>TBI limits</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams(^48)</td>
<td>2005</td>
<td>Nondiabetic controls</td>
<td>41</td>
<td>18 (44)</td>
<td>13 (32)</td>
<td>100</td>
<td>81</td>
<td>72</td>
<td>100</td>
<td>&lt;0.75</td>
<td>PP</td>
</tr>
<tr>
<td>Williams(^48)</td>
<td>2005</td>
<td>Diabetes</td>
<td>88</td>
<td>43 (49)</td>
<td>22 (25)</td>
<td>91</td>
<td>65</td>
<td>47</td>
<td>96</td>
<td>&lt;0.75</td>
<td>PP</td>
</tr>
<tr>
<td>Weinberg(^56)</td>
<td>2012</td>
<td>ABI &gt;1.4</td>
<td>100</td>
<td>92 (92)</td>
<td>100 (100)</td>
<td>92</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>&lt;0.7</td>
<td>PP</td>
</tr>
<tr>
<td>Carter(^57)</td>
<td>1971</td>
<td>Known PAD</td>
<td>135</td>
<td>121 (90)</td>
<td>135 (100)</td>
<td>90</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>&lt;0.64</td>
<td>SGP</td>
</tr>
<tr>
<td>Suominen(^29)</td>
<td>2008</td>
<td>ABI &gt;1.3</td>
<td>69</td>
<td>68 (99)</td>
<td>69 (100)</td>
<td>99</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>&lt;0.6</td>
<td>PP</td>
</tr>
<tr>
<td>Suominen(^29)</td>
<td>2008</td>
<td>ABI 0.9 to &lt;1.3</td>
<td>47</td>
<td>47 (100)</td>
<td>44 (94)</td>
<td>…</td>
<td>…</td>
<td>94</td>
<td>…</td>
<td>&lt;0.6</td>
<td>PP</td>
</tr>
<tr>
<td>Park(^58)</td>
<td>2012</td>
<td>Diabetic gangrene</td>
<td>30</td>
<td>13 (43)</td>
<td>13 (43)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>&lt;0.6</td>
<td>PP</td>
</tr>
</tbody>
</table>

\(\text{ABI, Ankle-brachial index; NPV, negative predictive value; PP, photoplethysmography; PPV, positive predictive value; SGP, strain-gauge plethysmography.}\)

\(^a\)Sensitivity, specificity, and predictive values are based on values or calculations based on data presented in the listed studies with each included limb analyzed separately.

\(^b\)Number of included limbs with a low TBI and the percentage of the total. All findings were confirmed by contrast angiography, except Williams et al\(^48\) who used color duplex imaging.
a modified disease criterion based on a TBI <0.7, ABI >0.9, and normal posterior tibial flow velocity. At follow-up, 41 (39%) had a normal TBI and ABI, 30 (28%) had an unchanged isolated low TBI, and 35 (33%) had a low ABI. Aboyans et al66 did a similar follow-up study (mean, 4.6 years) of 403 patients from the same vascular laboratory using the same diagnostic limits. They defined a decline of −0.27 for the TBI and −0.30 for the ABI (highest decile) as an indicator of major progression. They showed that cigarette smoking, lipids, and inflammation contributed to progression in patients with a low ABI, whereas diabetes was a significant predictor of patients with an isolated low TBI.

**Diabetes.** The presence of diabetes is a well-described risk factor for the development of arteriosclerosis, and the ABI is considered less reliable than the TBI in this population due to the high prevalence of media calcification.1,12 A large study with >500 patients showed a linear relationship between the TBI and the ABI in nondiabetic patients but had an inverted J-shaped relationship in diabetic patients.67 This indicated that a high ABI in diabetic patients masked the presence of lower limb ischemia. A similar conclusion was asserted in a study using an isotope-washout technique.68 These studies consistently showed that the ABI underestimated the severity of PAD in patients with diabetes. Furthermore, studies have shown that the TBI is more closely associated with estimated glomerular filtration rate, the degree of albuminuria,69 and the presence of peripheral neuropathy50 in patients with diabetes.

Sahli et al47 screened a diabetic population for PAD and showed that 9% of the included limbs had an isolated low TBI. On the basis of their own normal population data (Table I), they applied a TBI <0.74 and an ABI <0.90 as diagnostic limits. They showed that the TBI is independently associated with the fasting blood glucose, smoking status, age, and the duration of diabetes. A 10-year follow-up was planned, but no data have yet been presented in the public domain.

**Chronic kidney disease.** Patients with chronic kidney disease have a high risk of developing generalized atherosclerosis and a high prevalence of media calcification.70 Morimoto et al71 identified that 11% of patients with chronic kidney failure on hemodialysis (n = 220) had an ABI ≥0.9 and a TBI <0.6. They did not analyze outcomes regarding mortality; however, they showed that a finding of an isolated low TBI was associated with risk factors such as diabetes and excess body weight. Moreover, studies have shown that TBI is a predictor of outcome after kidney transplantation.72

**Microvascular disease.** Some authors have considered the TBI as a marker of the early phase of arteriosclerotic development and low ABI as a manifestation of an advanced arteriosclerotic condition.73 In support of this argument, studies have shown the TBI has a stronger association than the ABI with diseases involving the microvasculature such as erectile dysfunction74 and systemic sclerosis.49 Another study showed that tissue plasminogen activator activity, which is an indicator of vascular injury, was associated with having a TBI <0.74.75

**DISCUSSION**

The measurement of absolute toe pressures is well validated in the diagnosis of critical limb ischemia and is a prognostic marker for wound healing.42,43,75 However, this review shows that the use of the TBI for the diagnosis of PAD remains ambiguous, as summarized in Table IV. On the basis of the available clinical information on normal populations, correlation to angiographic findings, mortality, and comorbidities, it is evident that a substantial divergence exists regarding specific TBI limits. Although several guidelines and reviews of PAD diagnostics24-27 recommend a TBI of <0.70 as the cutoff, this recommendation is not strictly evidence based. In addition, other limits are frequently used in observational studies and clinical settings, among them TBI <0.75,44 <0.74,47 <0.65,72 <0.64,18,76,77 <0.60,7,10,29,65,71 or ≤0.54.28 The use of different and not fully interchangeable measuring techniques and non-standardized measurements, such as pretest heating, are important issues that may compromise generalizability of these studies.50 The extracted normal material is sparse and includes limited use of imaging techniques to exclude the PAD diagnosis. The studies on the correlation with angiographic findings are mainly performed in highly selected patient populations. Nonetheless, these studies suggest a high sensitivity of 90% to 100% for the detection of vessel stenosis, regardless of the diagnostic limit used.

The current literature is not sufficient to conclude a specific cutoff as diagnostic for PAD. We estimated

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**Table III. Prevalence of patients with a low toe-brachial index (TBI) and a normal ankle-brachial index (ABI)**

<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>Year</th>
<th>No.</th>
<th>Low TBI, normal ABI, %</th>
<th>Diagnostic limits</th>
<th>Population</th>
<th>Method</th>
<th>Pretest limb heating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahli47</td>
<td>2004</td>
<td>303</td>
<td>9*</td>
<td>ABI &gt;0.9, TBI &lt;0.74</td>
<td>Diabetic patients</td>
<td>PP, Yes</td>
<td></td>
</tr>
<tr>
<td>Bird15</td>
<td>1999</td>
<td>423</td>
<td>14*</td>
<td>ABI &gt;0.9, TBI ≤0.7</td>
<td>Patients suspected of PAD</td>
<td>PP, No</td>
<td></td>
</tr>
<tr>
<td>Høyer16</td>
<td>2012</td>
<td>204</td>
<td>17</td>
<td>ABI &gt;0.9, TBI &lt;0.7</td>
<td>Patients suspected of PAD</td>
<td>SGP, Yes</td>
<td></td>
</tr>
<tr>
<td>Crique14,60</td>
<td>1985</td>
<td>613</td>
<td>16</td>
<td>ABI &gt;0.8, TBI ≤0.7</td>
<td>Screening population</td>
<td>SGP, No</td>
<td></td>
</tr>
<tr>
<td>Morimoto71</td>
<td>2009</td>
<td>115</td>
<td>11</td>
<td>ABI &gt;0.9, TBI ≤0.6</td>
<td>Patients in hemodialysis</td>
<td>OP, No</td>
<td></td>
</tr>
<tr>
<td>Suominen7</td>
<td>2010</td>
<td>2159</td>
<td>27</td>
<td>ABI &gt;0.9, TBI ≤0.6</td>
<td>Patients suspected of PAD</td>
<td>PP, No</td>
<td></td>
</tr>
</tbody>
</table>

*Each limb diagnosed independently.
a reference value of 0.71 as the lowest limit of normal based on the weighted average in studies with preheating of the limbs. The exact limits await properly conducted diagnostic accuracy studies performed in accordance with the current methodologic requirements. In comparison, the diagnostic boundaries of the ABI are not defined by a normal population but by the association with angiographic findings and hard end points such as cardiovascular morbidity and mortality. As mentioned earlier, a systematic review has shown a large discrepancy in the reported diagnostic value for an ABI to detect arterial stenosis in the lower limb, which questions the use of an ABI \( \leq 0.90 \) as the cutoff. An ABI of 0.91 to 1.00 has been suggested to constitute a borderline abnormal finding due to the increased mortality compared with patients with an ABI of 1.00 to 1.30. It could be hypothesized that borderline classification is also required for the TBI, although this remains speculative. Studies have shown that approximately one-third of the patients with a TBI < 0.7 and a normal ABI progress to an abnormal ABI after a 4.6-year follow-up, which would imply that these patients should receive additional vascular control. Some have proposed that a low TBI in the setting of a normal ABI reflects small-vessel disease, whereas patients with a low ABI have large-vessel disease. However, the pathophysiology is most likely more complex than the dichotomous answer of PAD/not PAD. For instance, a proportion of patients in the subgroup with vessel stiffness would produce a falsely normal ABI and mask the presence of true large-vessel disease. Another subgroup of patients could have vessel stenosis below the ankle level and have minor vessel disease. Moreover, because the toe vessels are known to be susceptible to vasoconstriction, patients without PAD could falsely be classified as having a low TBI. This effect can be minimized by measuring the TBI under standardized conditions, such as using rooms with stable temperatures and implementing pretest limb heating. Under standardized conditions, the day-to-day variation of toe pressures seems comparable to that of ankle pressures.

Methods used for measurement of toe blood pressures use different detection systems. Systematically biased values of the TBI among systems should be taken into account when assessing the diagnostic and prognostic effect of such measurements. Such considerations have been highlighted for ABI measurements as well. The influence of experimental conditions, such as skin temperature, may differ among systems, and it would be advisable for each vascular laboratory to establish quality criteria for experimental conditions and reproducibility to optimize the diagnostic accuracy and precision.

CONCLUSIONS

Regardless of the ambiguous definition of diagnostic limits, there is an interesting correlation between the TBI and comorbidities, such as kidney disease and diabetes, which suggests that the TBI, in some aspects, is more valid than the ABI. This shows that the TBI has a place in vascular diagnostics, although the exact role remains to be clarified. In the current screening algorithms, the TBI is primarily applied in selected patient cohorts where vascular stiffness is suspected. However, studies have indicated that a large subset of patients have a low TBI and a normal ABI, even in patients not suspected of vascular stiffness. The TBI could be used alone or combined with the ABI to select patients eligible for a full vascular examination. Implementing the TBI as a primary gatekeeper in screening algorithms could thus allow for detection of patients with PAD who remain undetected by the current algorithms. However, large-scale trials are needed to establish the risk of morbidity and mortality for the various diagnostic limits of the TBI. The current studies of normal populations and the correlation with angiography are few in numbers, and additional trials according to the recommendations of Standards for Reporting of Diagnostic Accuracy Studies and Cochrane Diagnostic test accuracy are needed to further validate the limits. This is particularly relevant with the introduction of new methods for PAD screening, that are based on the TBI, which may supplement or even substitute for the ABI.

AUTHOR CONTRIBUTIONS

Conception and design: CH, JS, LP
Analysis and interpretation: CH, JS, LP
Data collection: CH, JS, LP
Writing the article: CH, JS, LP
Critical revision of the article: CH, JS, LP
Final approval of the article: CH, JS, LP
Statistical analysis: CH, JS, LP
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Overall responsibility: CH

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