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The ability of the toe-brachial index to predict the outcome of treadmill exercise testing in patients with a normal resting ankle-brachial index.

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5 **The ability of the toe-brachial index to predict the outcome of**
6 **treadmill exercise testing in patients with a normal resting**
7 **ankle-brachial index.**
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50 Abstract

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52 Objective

53 Peripheral arterial disease (PAD) in the presence of a normal ankle-brachial index (ABI) can be
54 diagnosed noninvasively by measuring a postexercise ABI or by measuring the toe-brachial index
55 (TBI).

56 Methods

57 This was a prospective comparative study. Over a period of 30 months, a total of 415 patients who
58 were referred with the suspicion of vascular claudication and resting values of $0.91 \leq \text{ABI} < 1.40$ were
59 further evaluated for the resting TBI and postexercise ABI by treadmill testing.

60 Results

61 A total of 325 (39%) of the 830 investigated limbs had a low TBI (≤ 0.70), and 505 (61%) had a
62 normal TBI. Of the limbs with a low TBI, 160 (49%) had PAD according to a postexercise ABI
63 versus 165 (33%) of the limbs with normal TBI. The overall agreement in PAD classification
64 between the two methods was 500/830 (60%) with a Cohen's kappa = 0.166 (95% CI: 0.096-0.232).
65 The data showed an inverse correlation between the magnitude of the TBI decrease, as well as the
66 resting ABI, and the probability of an abnormal postexercise ABI. On average, limbs with a low
67 TBI had a lower resting ABI than patients with a normal TBI (1.07 ± 0.09 vs. 1.13 ± 0.10 , $P < .001$).
68 The groups with a low TBI had a significantly higher ratio of abnormal test results than patients
69 with a normal TBI, in limbs with ABI (0.96-1.00) and ABI > 1.10 ($P \leq .022$ for both), but there
70 were no statistically significant differences found in other ABI intervals ($P > .200$ for all).

71 Conclusions

72 The magnitude of the TBI reduction correlates with an increased probability of an abnormal
73 postexercise ABI. However, this is due in part to limbs with a low TBI having a lower resting ABI
74 on average than limbs with a normal TBI, which also correlates with the probability of an abnormal

75 exercise test result. This study shows that the TBI and the postexercise ABI are not interchangeable
76 for establishing a PAD diagnosis.

77

78 Keywords: Ankle brachial index (MeSH), Toe brachial index (MeSH), Diagnostic test (MeSH),
79 Peripheral arterial disease (MeSH), Postexercise ABI.

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119 **1. Introduction**

120 Arteriosclerosis in the lower limbs is a common condition affecting 15-20% of persons older than
121 70-years.¹ The presence and severity of peripheral arterial disease (PAD) can be diagnosed by
122 measuring the ankle-brachial index (ABI) at rest. Having an $ABI \leq 0.90$ is indicative of the presence
123 of arterial disease and is associated with an increased risk of cardiovascular mortality and
124 morbidity. However, a normal resting ABI does not rule out the presence of PAD.²

125
126 The normal physiological response to leg exercise, such as walking, is an increase in the central
127 systolic pressure along with vasodilation in the exercising muscles, thus reducing peripheral
128 vascular resistance. In cases with occlusive PAD, this can lead to a significant drop in ankle
129 pressure or ABI post exercise.³ The resting ABI can be unreliable in conditions related to medial
130 arterial calcinosis such as diabetes, chronic kidney insufficiency, or age, which can lead to falsely
131 elevated, or even falsely normal ankle pressures.⁴

132
133 In addition to the ABI, PAD can be diagnosed by measuring the toe-brachial index (TBI), which is
134 less prone to medial arterial calcinosis.⁵ Previous studies have shown that approximately 20% of
135 patients suspected of PAD have normal ankle pressures but low TBI.⁶ However, this subset of
136 patients consists of both patients with masked large vessel disease, and small vessel disease with
137 lesions below the ankle level. The aim of the current study is to test the ability of the toe-brachial
138 index to predict the outcome of treadmill testing, and establish whether a normal TBI would render
139 a supplementary treadmill testing redundant.

140

141 **2. Materials and Methods**

142 **2.1 Design**

143 This was a prospective study.

144 **2.2 Subjects**

145 Over a 30 month inclusion period from 2015-2018, patients who were referred to the Department of
146 Nuclear Medicine at Aalborg University Hospital for distal blood pressure measurements and
147 clinically suspected of vascular claudication were screened for enrollment. The inclusion criteria
148 were patients with $0.91 \leq \text{ABI} < 1.40$ who were able to participate in standardized treadmill testing.
149 The study protocol was approved by the Northern Danish Regional Committee on Biomedical
150 Research Ethics and the Danish Data Protection Agency. The study complied with the Helsinki II
151 declaration.

152 **2.3 Experimental procedure**

153 The patients rested in a supine position for at least 15 minutes prior to the measurements. Adequate
154 limb temperatures were maintained at 35-40°C using heating overlays prior to testing (Dorcas
155 Activator Pack, ProTerapi, Ballerup, Denmark). Toe- and ankle pressures were assessed by
156 photoplethysmography (Falcon PRO, Viasonix, Ra'anana, Israel).⁷ Appropriately sized pneumatic
157 occlusion cuffs were positioned at the site of measurement. The photoplethysmographic sensors were
158 positioned distal to the cuff and measured changes in light absorption upon illumination of the skin.
159 The cuff deflated automatically with the sensor detecting flow throughout the deflation period. The
160 brachial blood pressure was measured simultaneously with each toe or ankle pressure (automatic
161 digital blood pressure monitor M6, Omron Healthcare Europe, Hoofddorp, Netherlands), with the
162 side with the highest systolic pressure selected as the reference for the ABI and TBI calculations.

163 **2.4 Exercise test**

164 Following the assessment of the resting ABI and TBI, the patients underwent standardized treadmill
165 testing at a set speed of 4 kilometers per hour (2.5 miles per hour), and at a fixed inclination (10%)
166 for 5 minutes or until they were unable to continue due to symptoms (MedTrack CR60, Quinton
167 Instrument, Washington, USA). Immediately following completion of the treadmill exercise, the
168 patients were repositioned in a supine position, and ankle and brachial measurements were repeated
169 until the normalization of the ABI. The observers were not blinded to the outcome of the TBI
170 measurements.

171

172 **2.5 Diagnostic classification**

173 A resting ABI was considered within the normal range between $0.91 \leq \text{ABI} < 1.40$, and $\text{TBI} > 0.70$
174 according to criteria set by the American College of Cardiology/American Heart Association
175 (ACC/AHA).^{1,2} An abnormal postexercise ABI was defined according to the AHA scientific
176 statement by one of the two following criteria: a postexercise ABI decrease of more than 20% or a
177 postexercise ankle pressure decrease of more than 30 mmHg.³ An abnormal postexercise increase
178 in ABI was defined as an ABI increase in either of the two limbs.⁸ This was, however, not deemed
179 an abnormal test result.

180 **2.6 Statistical analysis**

181 The data are presented as the mean \pm standard deviation. The differences in hemodynamic and
182 demographic variables between the two groups were analyzed using an unpaired t-test, in the case
183 of quantitative variables and a chi-square test (χ^2) in the case of categorical variables. Agreement in
184 diagnostic classification (PAD/not PAD) was analyzed by Cohen's kappa (κ). A P-value < 0.05 was
185 considered to be statistically significant, and the statistical analysis was performed using SPSS
186 software version 20.0 (SPSS Inc., Illinois, USA).

187 **3 Results**

188 **3.1 Patients and data sampling**

189 During the 30 month inclusion period, a total of 4020 distal pressure measurements were performed
190 at the department, of which 432 patients met the inclusion criteria. A total of 18 patients were
191 excluded due to incomplete exercise tests (n=15) or failure to obtain toe pressures (n=3), leaving
192 415 patients/830 limbs eligible for further analysis. Of these patients, 210 (51%) had a resting
193 $TBI \leq 0.70$, and 205 (49%) had a resting $TBI > 0.70$. Patient demographics for the two groups are
194 presented in Table I. The parameters derived from pretest ankle and toe pressure assessment are
195 presented in Table II, along with postexercise measurements. Overall, the patients with low TBIs
196 had lower pre- and post-exercise mean ankle pressures, and mean ABI than patients with a normal
197 TBI (all $P \leq .002$).

198 **3.2 Diagnostic Agreement**

199 A total of 117 (28%) of the 415 patients had PAD according to the outcome of the exercise testing
200 and the TBI and 128 (31%) had normal test results for both evaluations according to AHA/ACC
201 criteria. Another 93 (22%) patients had a low TBI but a normal treadmill testing result, and 77
202 (19%) patients had a normal TBI but PAD according to the treadmill testing. The overall agreement
203 in the diagnostic classification was 245/415 (59%) with a Cohen's kappa (κ) = 0.181 (95% CI:
204 0.087-0.276). When analysing the agreement on a limb basis, 160 (49%) of the 325 limbs with low
205 TBI had an abnormal exercise test, whereas 165 (33%) of the 505 limbs with a normal TBI had an
206 abnormal exercise test. The overall agreement on a limb basis was 500/830 (60%) with a Cohen's
207 kappa (κ) = 0.166 (95% CI: 0.096-0.232). The diagnostic outcome for the exercise testing on a limb
208 basis is displayed in Table III and on a patient basis in Table IV. The sensitivity, specificity,
209 positive and negative predictive values for the TBI with postexercise ABI as reference are shown in
210 Table V. There were no significant differences in the ratio of abnormal tests within the two major

211 groups when comparing patients who were able to complete the full 5 minutes of the treadmill
212 testing to the subgroups that were only able to complete less than 3 minutes or 3 to 5 minutes,
213 respectively (all $P \geq .481$). There were no significant differences in the ratio of abnormal exercise
214 test results in the subgroup of patients with diabetes (49% abnormal tests) or chronic kidney failure
215 (54% abnormal tests) compared to the other groups ($P \geq .144$ for both).

216

217 **3.3 The ABI and TBI versus outcome of exercise test**

218 The probability of an abnormal treadmill testing result increased with the magnitude of the TBI
219 reduction, as shown in Fig. 1 ($P < .005$). The same was true for pre-exercise ABI (Fig. 2), with a
220 borderline reduced ABI (0.91-1.00) having a higher probability (52%) of an abnormal exercise test
221 than limbs with an ABI > 1.00 (36%) ($P < .0001$). The groups with a low TBI had a significantly
222 higher ratio of abnormal test results than patients with a normal TBI, in limbs with ABI (0.96-1.00)
223 and ABI > 1.10 ($P \leq .022$ for both). However, there were no statistically significant differences in
224 the remaining groups ($P \geq .200$ for all). The correlation between the pretest ABI and the TBI is
225 shown in Fig. 3. A receiver operator curve for ABI and TBI was constructed and showed an area
226 under the curve of 0.564 (95% CI: 0.509-0.619) for the ABI and 0.580 for the TBI (95% CI: 0.525-
227 0.634), and no clear diagnostic cut-off was determined for the prediction of the outcome of exercise
228 test (Fig. 4).

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237 **4 Discussion**

238 This study shows that the TBI and postexercise ABI are not interchangeable methods for the
239 diagnosis of PAD, with agreement in only 59% of cases. Although we found a correlation between
240 the magnitude of the TBI decrease and the probability of an abnormal exercise test result, this could
241 be partially explained by the known correlation between the resting ABI and TBI within the
242 investigated pressure range.⁹ The lower the resting ABI, the higher the probability of obtaining an
243 abnormal test result, as was also indicated by this study.¹⁰ Since limbs with a low TBI have a lower
244 ABI in average than limbs with a normal TBI, there is a logical increase in the probability of an
245 abnormal test result in that group. Accordingly, we did not detect a significant difference between
246 patients with a normal TBI and low TBI within most of the ABI subgroups.

247

248 Having a reduced resting ABI is a well established indicator of increased risk of cardiovascular
249 morbidity and mortality.³ Furthermore, studies have shown that an abnormal postexercise ABI in
250 the presence of a normal resting ABI, is an independent predictor of mortality and is related to a
251 higher incidence of revascularization.^{11,12} The TBI has also been shown to be an independent risk
252 marker for mortality, although this remains to be verified in large-scale trials.^{5,13,14} It has been
253 hypothesized that a reduced TBI in the presence of a normal ABI reflects small vessel disease, and
254 the TBI has been shown to have a superior correlation to prognostic markers in comorbidities such
255 as diabetes, kidney disease and microvascular disease than the ABI.⁵ However, the group of patients
256 with a low TBI and normal ABI likely contains a mixture of patients with masked large vessel
257 disease (e.g., due to vessel stiffness), patients with small vessel disease, or the use of flawed
258 diagnostic limits for the TBI. The treadmill testing could in theory offer a way to discriminate these

259 subgroups, as significant large vessel stenosis would result in a postexercise ABI decrease.¹⁵
260 Patients with diabetes are more prone to develop distal lesions, whereas smokers or young patients
261 are more prone to develop proximal lesions.¹⁶ However, we did not find any significant difference
262 in the probability of an abnormal test result for patients with suspected microvascular disease, such
263 as patients with diabetes or chronic kidney failure, although these subgroups were too small to
264 allow any firm conclusions to be made.

265
266 Large-scale studies have shown, that a supranormal ABI is associated with increased mortality due
267 to vessel stiffness.¹⁷ Recently, Hammand and coworkers found that patients with an abnormal
268 increase in ABI following an exercise test also have an increased risk of mortality, although this
269 finding needs to be verified.⁸ It could be hypothesized that this is a reflection of increased vessel
270 stiffness which compromises the arterial windkessel function, leading to an alteration of the
271 pressure curve.¹⁸ However, we did not find any discrepancies in the ratio of patients with an
272 abnormally high postexercise ABI between patients with a low or normal TBI.

273
274 In the 2016 ACC/AHA guidelines on the management of patients with lower extremity PAD, the
275 postexercise ABI is recommended for patients with exertional nonjoint related symptoms and
276 resting ABI within the range of 0.91-1.40 for the PAD diagnosis.² On the other hand, it is also
277 stated that PAD can be diagnosed by measuring a TBI ≤ 0.70 , and this method is recommended in
278 patients with a supranormal ABI (>1.40) or patients with nonhealing wounds or gangrene. In other
279 words, the methods are used more or less interchangeably to establish a PAD diagnosis. The
280 findings in our study highlight that there is substantial disagreement between the two diagnostic
281 modalities, likely due to differences in the sites of the vessel lesions. The treadmill testing primarily
282 offers information on lesions proximal to the ankle, whereas patients with a reduced TBI are a

283 heterogeneous group including both patients with masked large vessel disease and patients with
284 distal vessel lesions.¹⁶ Another possible reason for the discrepancy is the limited evidence for the
285 diagnostic limits in use for both methods.^{5,19}. There is a substantial need for additional large-scale
286 trials that correlate these methods to angiographically verified vessel stenoses and cardiovascular
287 morbidity and mortality to clarify this.

288 **5 Conclusion**

289 The results of the present study show that the magnitude of the TBI reduction correlates with an
290 increased probability of an abnormal postexercise ABI with 49% of limbs with a low TBI having an
291 abnormal test result vs. 33% of the limbs with normal TBI. However, this was due in part to limbs
292 with a low TBI having a lower resting ABI on average than limbs with a normal TBI, as the level of
293 the resting ABI also relates to the probability of an abnormal exercise test result. This study shows
294 that the TBI and the postexercise ABI are not interchangeable for establishing a PAD diagnosis, and
295 likely reveal different entities of peripheral arteriosclerotic disease.

296 **6 Acknowledgements**

297 We would like to thank the laboratory technicians for their contributions to this study. This study
298 received no financial support.

299 **7 Conflict of Interest Statement**

300 The authors report no conflicts of interest.

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307 **8 References**

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- 353

Table I: Demographics.

	Normal TBI (n=205)	Low TBI (n=210)	P-value
Age [years]	61.0 ± 12.4	65.9 ± 11.4	< .001
Height [cm]	173.5 ± 9.1	172.9 ± 9.7	.526
Weight [kg]	86.4 ± 18.5	82.6 ± 19.1	.043
Diabetes Mellitus	26 (13%)	32 (15%)	.453
Myocardial Infarction	21 (10%)	31 (15%)	.165
Chronic Kidney Insufficiency	7 (3%)	10 (5%)	.489
Arterial Hypertension	106 (52%)	107 (51%)	.878
Hypercholesterolemia	97 (47%)	107 (51%)	.459
Smokers	56 (27%)	48 (23%)	.295

Abbreviations: Data shown as mean (± standard deviation) or total (percentage).

Table II: Hemodynamic variables.

	Normal TBI (n=205)	Low TBI (n=210)	P-value
Pre-test resting values			
Brachial pressure [mmHg]	135 ± 16	136 ± 19	.534
Right ankle pressure [mmHg]	152 ± 21	146 ± 24	.002
Left ankle pressure [mmHg]	152 ± 22	146 ± 22	.005
Right ABI	1.13 ± 0.10	1.07 ± 0.09	< .001
Left ABI	1.12 ± 0.09	1.07 ± 0.09	< .001
Right toe pressure [mmHg]	113 ± 18	87 ± 21	< .001
Left toe pressure [mmHg]	114 ± 18	87 ± 20	< .001
Right TBI	0.84 ± 0.09	0.63 ± 0.12	< .001
Left TBI	0.84 ± 0.09	0.64 ± 0.12	< .001
1-minute post-exercise			
Brachial pressure [mmHg]	172 ± 26	176 ± 29	.182
Right ankle pressure [mmHg]	167 ± 39	150 ± 51	< .001
Left ankle pressure [mmHg]	167 ± 40	149 ± 48	< .001
Right ABI	0.98 ± 0.19	0.85 ± 0.24	< .001
Left ABI	0.97 ± 0.19	0.85 ± 0.23	< .001

Abbreviations: Data shown as mean (± standard deviation) or total (percentage).

Table III: Exercise testing on a limb basis.

	Normal TBI (n=505 limbs)	Low TBI (n=325 limbs)	P-value
≥30 mmHg decrease in ankle pressure	43 (9%)	59 (18%)	.0003
≥20% decrease in ABI	165 (33%)	160 (49%)	.002
≥30 mmHg decrease in ankle pressure or ≥20% decrease in ABI	165 (33%)	160 (49%)	.002
Postexercise increase in ABI	80 (16%)	47 (14%)	.644
Postexercise ABI drop 0-19%	260 (51%)	119 (37%)	.009

Abbreviations: Data shown as the mean (\pm standard deviation) or total (percentage).

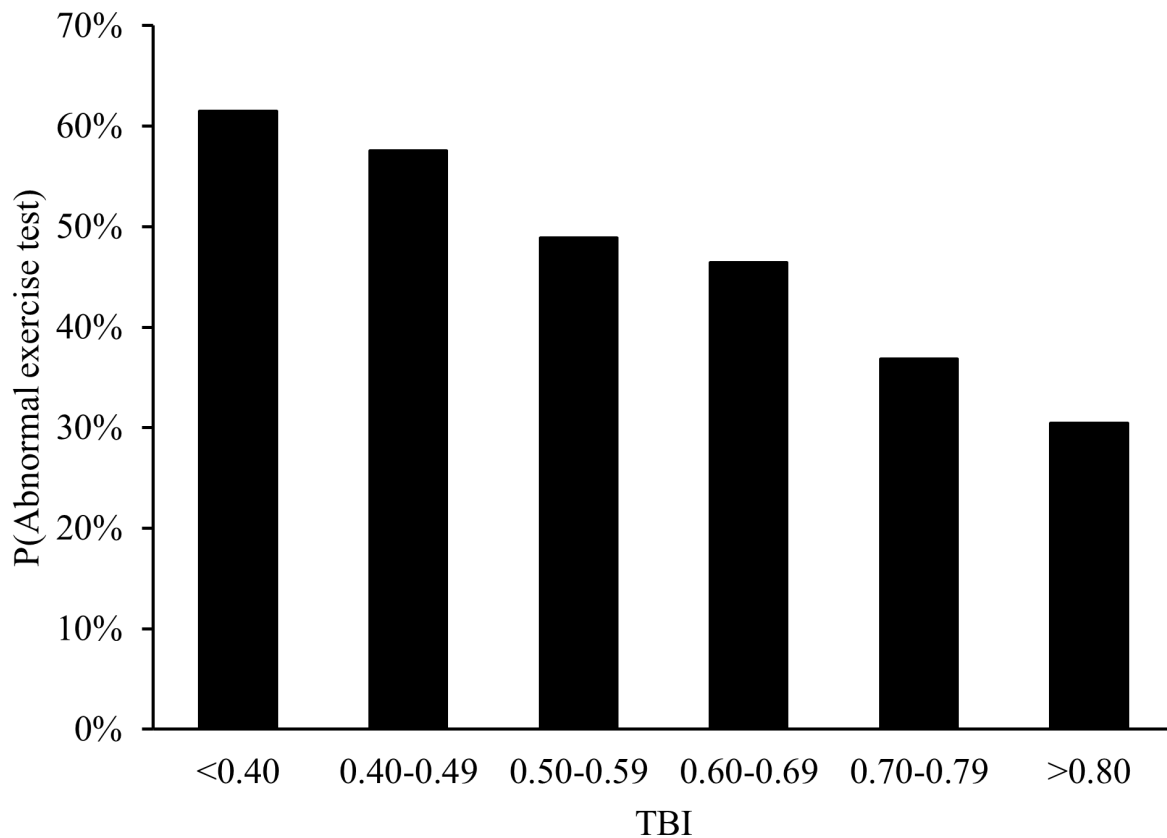
Table IV: Exercise testing on a patient basis.

	Normal TBI (n=205)	Low TBI (n=210)	P-value
≥30 mmHg decrease in ankle pressure	24 (12%)	48 (23%)	.003
≥20% decrease in ABI	77 (38%)	117 (56%)	.0002
≥30 mmHg decrease in ankle pressure or ≥20% decrease in ABI	77 (38%)	117 (56%)	.0002
Postexercise increase in ABI	43 (21%)	39 (19%)	.539
Postexercise ABI drop 0-19%	87 (42%)	56 (27%)	.001

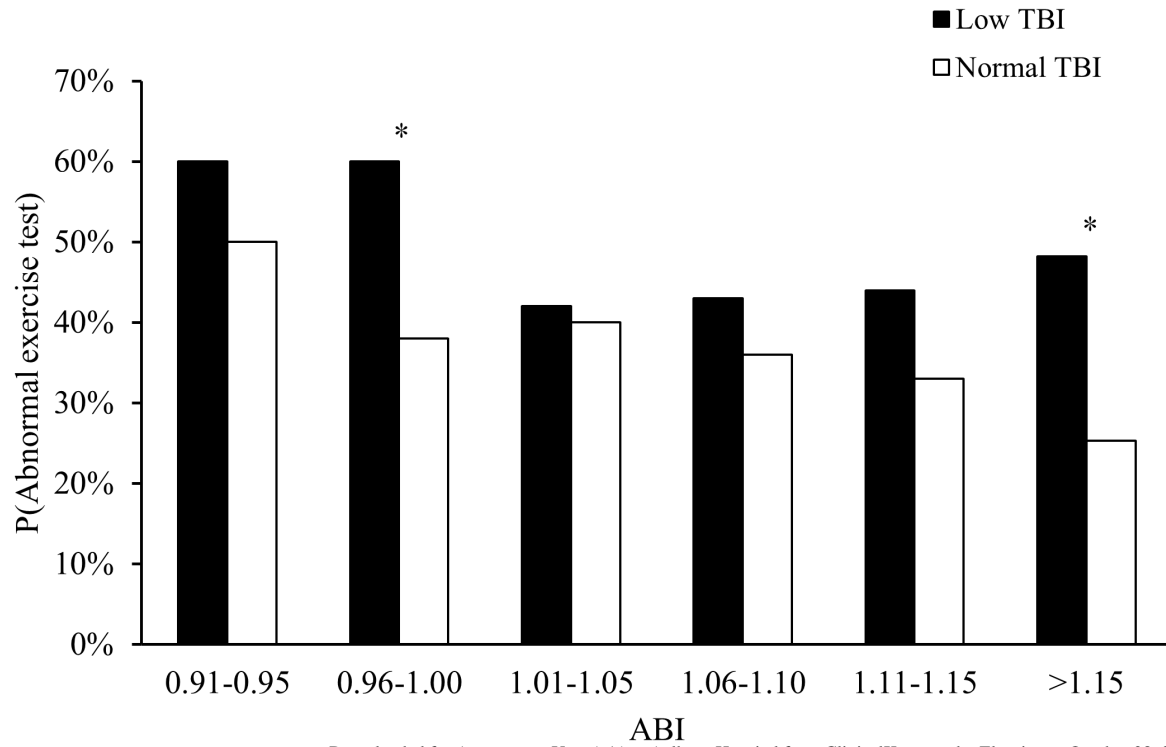
Abbreviations: Data shown as the mean (\pm standard deviation) or total (percentage).

Table V: Test accuracy of the TBI with postexercise ABI as reference.

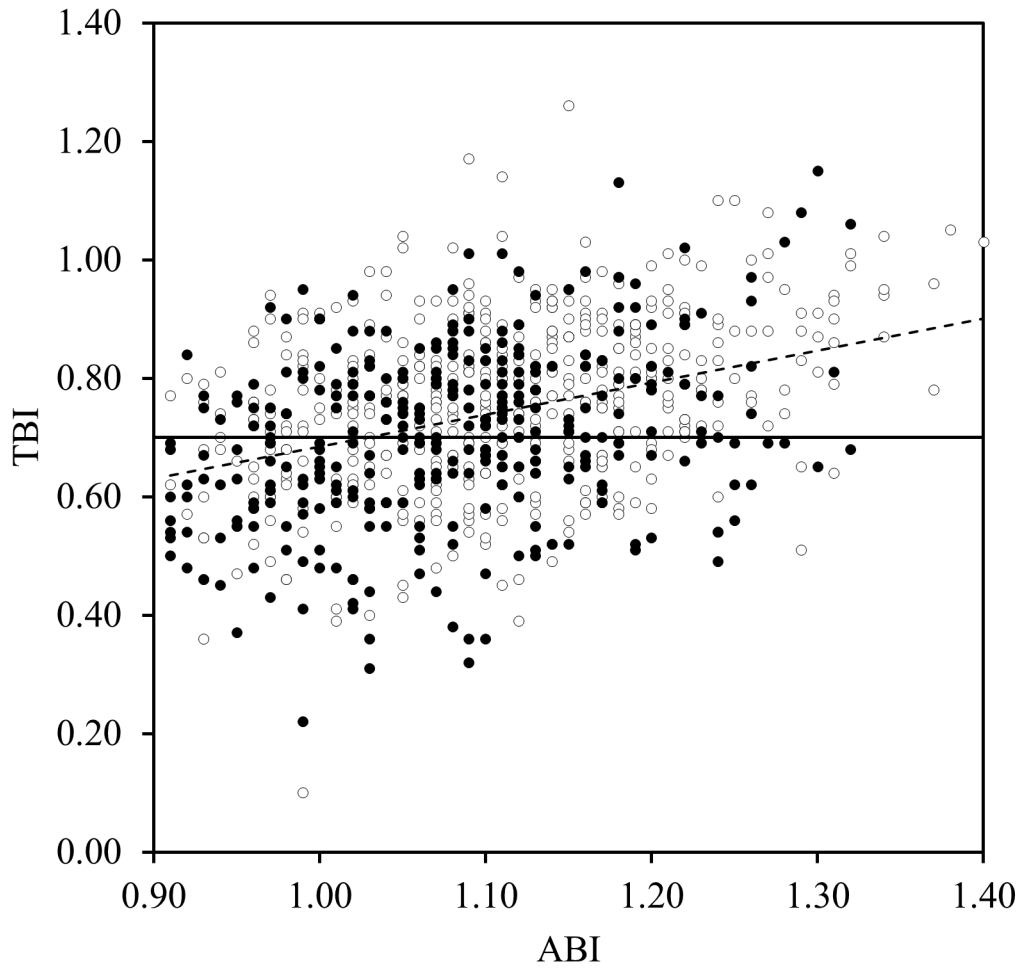
	On a patient basis (n=415)	On a limb basis (n=830)
Sensitivity	60.3%	49.2%
Specificity	57.9%	67.3%
Positive predictive value	55.7%	49.2%
Negative predictive value	62.4%	67.3%



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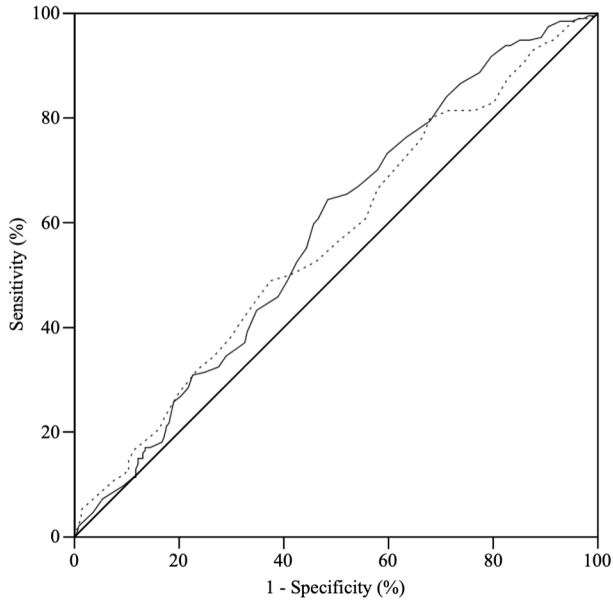


Figure 1: The probability of an abnormal exercise test vs. the TBI on a limb basis.

Figure 2: The probability of an abnormal exercise test vs. the ABI on a limb basis. *) Denotes $P \leq .022$

Figure 3: The correlation between TBI and pre-test ABI. The equation for the linear regression line (dotted line) were $y = 0.63x + 0.01$ ($R^2 = 0.173$). Full dots indicate patients with an abnormal exercise test and hollow dots patients with a normal exercise test.

Figure 4: Receiver operator characteristics (ROC) curve for various TBI (full line) and pretest ABI (dotted line) cut-offs.