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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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# Abstract

## Objective

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

## Methods

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

## Results

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

## Conclusions

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

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

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

## 1. Introduction

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

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

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

## 2. Materials and Methods

### 2.1 Design

This was a prospective study.

### 2.2 Subjects

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

### 2.3 Experimental procedure

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

### 2.4 Exercise test

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

### 2.5 Diagnostic classification

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

### 2.6 Statistical analysis

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

## 3 Results

### 3.1 Patients and data sampling

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

### 3.2 Diagnostic Agreement

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

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

### 3.3 The ABI and TBI versus outcome of exercise test

The probability of an abnormal treadmill testing result increased with the magnitude of the TBI reduction, as shown in Fig. 1 (P<.005). The same was true for pre-exercise ABI (Fig. 2), with a borderline reduced ABI (0.91-1.00) having a higher probability (52%) of an abnormal exercise test than limbs with an ABI >1.00 (36%) (P<.0.001). The groups with a low TBI had a significantly higher ratio of abnormal test results than patients with a normal TBI, in limbs with ABI (0.96-1.00) and ABI >1.10 (P ≤ .022 for both). However, there were no statistically significant differences in the remaining groups (P ≥ .200 for all). The correlation between the pretest ABI and the TBI is shown in Fig. 3. A receiver operator curve for ABI and TBI was constructed and showed an area under the curve of 0.564 (95% CI: 0.509-0.619) for the ABI and 0.580 for the TBI (95% CI: 0.525-0.634), and no clear diagnostic cut-off was determined for the prediction of the outcome of exercise test (Fig. 4).

## 4 Discussion

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

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

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

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

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

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

## 5 Conclusion

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

## 6 Acknowledgements

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## 7 Conflict of Interest Statement

The authors report no conflicts of interest.

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**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 (± standard deviation) or total (percentage).

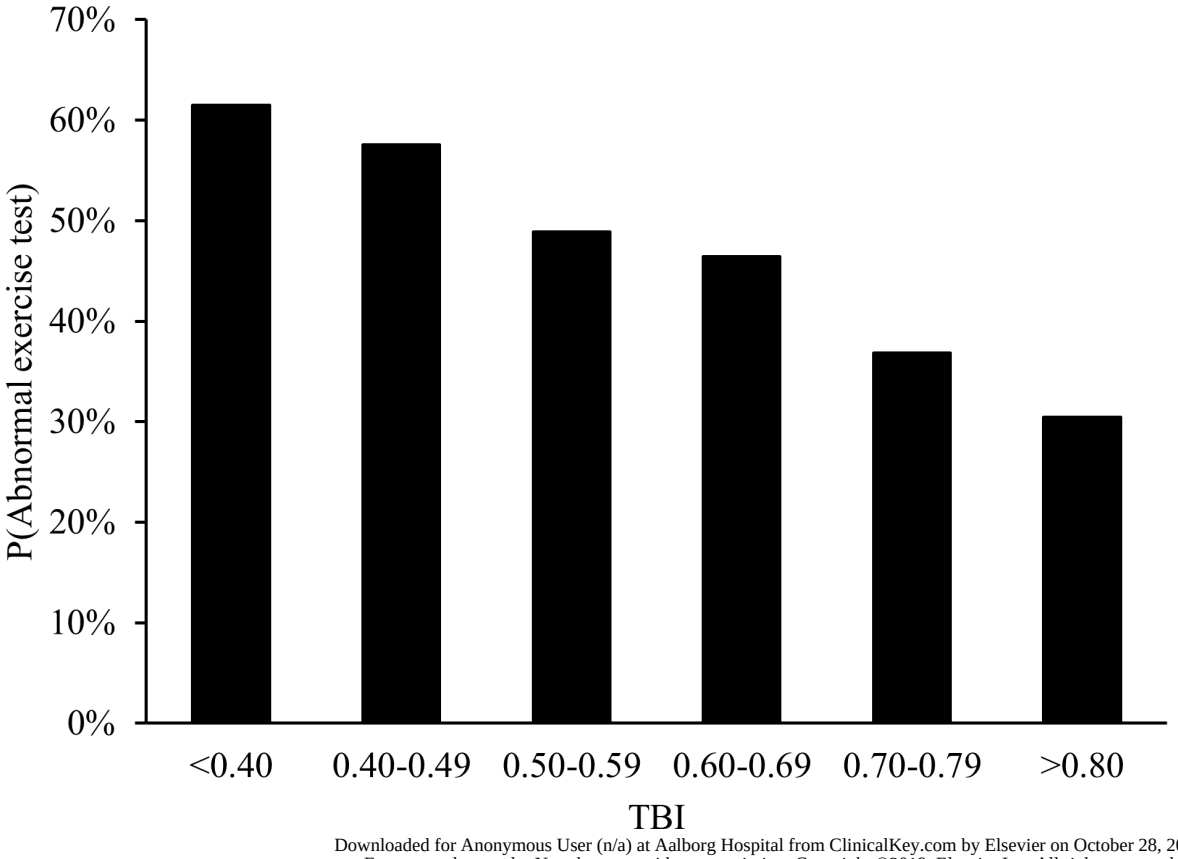
**Table IV:** Exercise testing on a patient basis.

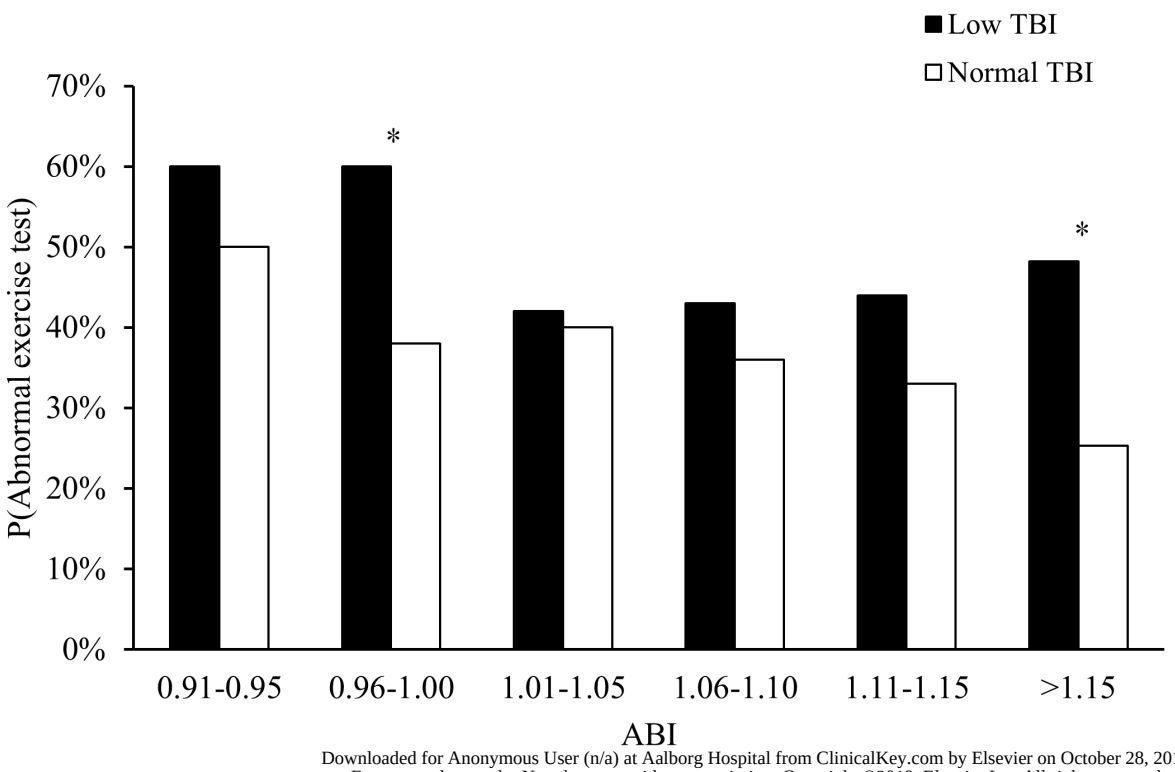
| | Normal TBI (n=205) | Low TBI (n=210) | P-value |
|---|---|---|---|
| ≥30 mmHg decrease in ankle pressure | 24 (12%) | 48 (23%) | .003 |
| ≥20% decrease in ABI | 77 (38%) | 117 (56%) | .0002 |
| ≥30 mmHg decrease in ankle pressure or ≥20% decrease in ABI | 77 (38%) | 117 (56%) | .0002 |
| Postexercise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

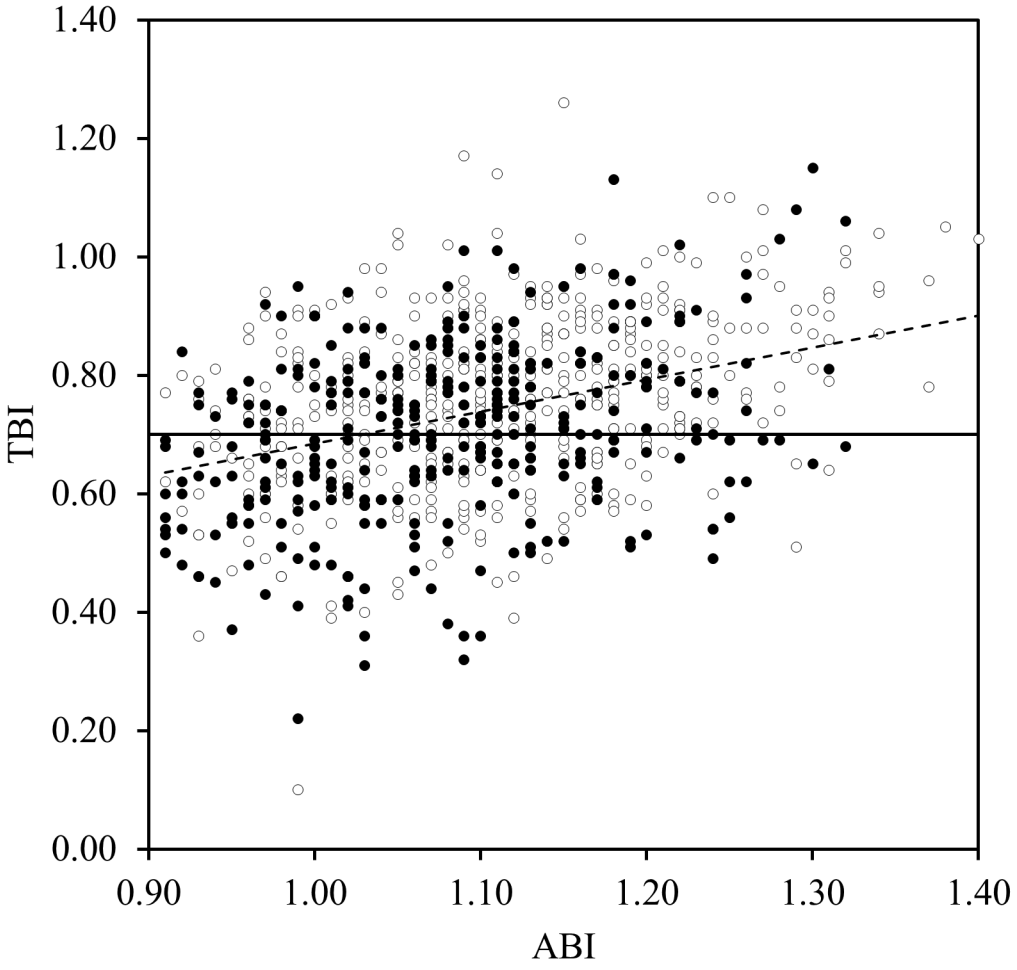
*Abbreviations:* Data shown as the mean (± standard deviation) or total (percentage).

**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% |







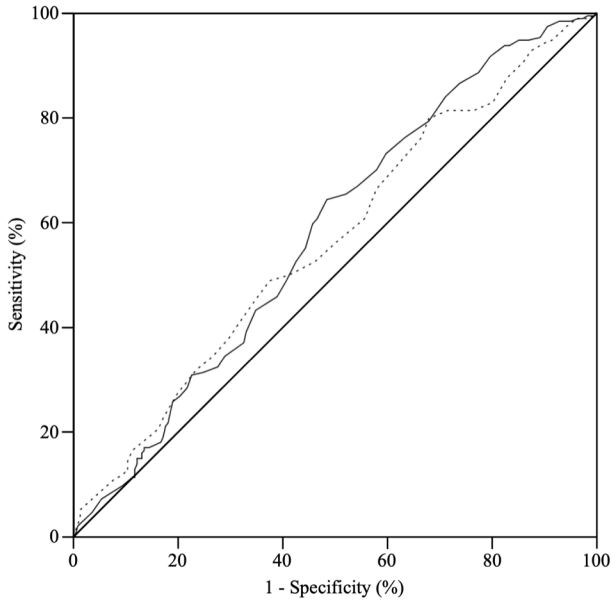


**Figure 1:** The probability of an abnormal exercise test vs. the TBI on a limb basis.

**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.