The Effect of Post-Exercise Ankle-Brachial Index on Lower Extremity Revascularization

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ABSTRACT

OBJECTIVES The purpose of this study was to investigate the effect of post-exercise ankle-brachial index (ABI) on the incidence of lower extremity (LE) revascularization, cardiovascular outcomes, and all-cause mortality in patients with normal and abnormal resting ABI.

BACKGROUND The clinical and prognostic value of post-exercise ABI in the setting of normal or abnormal resting ABI remains uncertain.

METHODS A total of 2,791 consecutive patients with ABI testing between September 2005 and January 2010 were classified into group 1: normal resting (NR)/normal post-exercise (NE); group 2: NR/abnormal post-exercise (AE); group 3: abnormal resting (AR)/NE; and group 4: AR/AE. Abnormal post-exercise ABI was defined as a drop of >20% from resting ABI as per the American College of Cardiology/American Heart Association guidelines. The primary endpoint was incidence of LE revascularization. Secondary endpoints were major adverse cardiovascular events (MACE) and all-cause mortality. Associations between post-exercise ABI and outcomes were adjusted using multivariable Cox proportional hazard and propensity analyses.

RESULTS Compared with group 1 (NR/NE), group 2 (NR/AE) had increased LE revascularization (propensity-matched adjusted hazard ratio [HR]: 6.63, 95% confidence interval [CI]: 3.13 to 14.04; p < 0.001) but no differences in MACE or all-cause mortality. When resting ABI was abnormal, group 4 (AR/AE) compared with group 3 (AR/NE), abnormal post-exercise ABI was still associated with increased LE revascularization (adjusted HR: 1.59, 95% CI: 1.11 to 2.28; p = 0.01), which persisted after propensity matching (adjusted HR: 2.32, 95% CI: 1.52 to 3.54; p < 0.001). Compared with group 1 (NR/NE) and after propensity matching, group 4 (AR/AE) had a significant increase in MACE (adjusted HR: 1.44, 95% CI: 1.09 to 1.90; p = 0.009) and a trend toward increased all-cause mortality (adjusted HR: 1.37, 95% CI: 0.99 to 1.88; p = 0.052); however, group 3 (AR/NE) did not.

CONCLUSIONS Post-exercise ABI appears to offer both clinical (lower extremity revascularization) and prognostic information in those with normal and abnormal resting ABI. (J Am Coll Cardiol Intv 2015;8:1238–44) © 2015 by the American College of Cardiology Foundation.
However, patients with PAD commonly present with exercise-induced symptoms (claudication); therefore, it is unclear whether post-exercise ABI measurement would have an effect on clinical decision making (LE revascularization rate) beyond that of normal or abnormal resting ABI (6). Furthermore, there are limited data on the prognostic implications of post-exercise ABI beyond that of resting ABI (6–9).

**METHODS**

**STUDY POPULATION.** This was a retrospective cohort study of 2,791 patients who underwent both resting and post-exercise ABI testing at a large tertiary care center between September 2005 and January 2010. Consistent with current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, abnormal resting (AR) ABI was defined as a resting ABI <0.90 and abnormal post-exercise (AE) ABI was defined as a >20% decrease from resting ABI (10). On the basis of these definitions, each leg for each patient was classified into one of these 4 groups: group 1: normal resting (NR)/normal post-exercise (NE); group 2: NR/AE; group 3: AR/NE; and group 4: AR/AE. Each patient was then assigned to the worst group of the 2 legs. Those with no audible Doppler sounds were classified as group 4. We excluded those with missing ABI measurements, prior lower extremity revascularization or amputation (n = 1), or incompressible vessels in both legs, defined as ABI at resting >1.4 (n = 50).

**ABI MEASUREMENT, ENDPOINTS, AND DATA COLLECTION.** Resting and post-exercise ABI data were obtained from the institutional Non-Invasive Vascular Laboratory database. All exercise ABI studies were performed in an accredited vascular laboratory (Intersocietal Accreditation Commission) by a registered vascular technologist. Prior to the test, patients were instructed to rest quietly for at least 5 min in the supine position. Subsequently, systolic blood pressure was measured in all 4 extremities using a Doppler device. Resting ABI was calculated by dividing the higher of the 2 ankle systolic blood pressures in each leg (dorsalis pedis or posterior tibial artery) by the higher of the 2 brachial artery systolic blood pressures. Post-exercise ABI was recalculated after remeasuring systolic blood pressures immediately post fixed-workload exercise protocol on a motorized treadmill. The standardized protocol is walking for 5 min at a 12.5% grade at 2.0 miles/h or until symptoms forced the patient to stop. In general, for post-exercise ABI calculation, the arm that has the higher resting brachial pressure along with the higher of the dorsalis pedis or posterior tibial artery ankle pressure are used to record the post-exercise measurement. Our protocol requires obtaining the post-exercise pressure measurements as promptly as possible once exercise has been terminated to reflect the hemodynamic changes produced by exercise most accurately. AE ABI was defined as a >20% decrease from resting ABI according to the ACC/AHA guidelines.

Lower extremity revascularization was selected as the primary endpoint to examine the effect of post-exercise ABI on clinical decision making, whereas major adverse cardiovascular outcomes (MACE) and all-cause mortality were the secondary endpoints. MACE was defined as a composite of all-cause mortality, stroke, myocardial infarction, and major lower extremity amputation. Stroke was defined as documented new or worsening focal neurological symptoms that persisted for >24 h and confirmed by neuroimaging. Both embolic and hemorrhagic strokes were included. Myocardial infarction was defined as documented positive cardiac enzymes plus electrocardiographic changes or symptoms consistent with myocardial ischemia. Baseline characteristics and outcomes were collected for all patients via electronic medical record review and were supplemented by the Social Security Death Index (SSDI) with a censoring date of September 30, 2011.

**STATISTICAL ANALYSIS.** Categorical variables were presented as number (percentage) and compared using the chi-square test or Fisher exact test when frequency was <10. Continuous variables were presented as mean ± SD and compared using the t test (for parametric variables) or Wilcoxon rank sum test (for nonparametric variables). Data with missing values, only 4 variables (Online Table 1), were imputed using the R package “mice 2.22” (11) under fully conditional specification, where 10 datasets were imputed and one complete dataset was selected at random for further analysis.

 Survival analysis was performed by Kaplan-Meier curves and the log-rank comparison. Groups were compared using unadjusted and multivariable-adjusted (for all variables in Table 1) Cox proportional hazard regression models. In a separate analysis, propensity score matching was performed for all baseline characteristics in Table 1, utilizing a greedy matching algorithm in a 1:1 fashion (12). Outcomes were then analyzed between propensity
Patients were referred for ABI testing by a number of different specialties: 25% by vascular medicine, 20% by vascular surgery, 20% by cardiology, 18% by primary care, and 17% by others. Approximately 46% had classic symptoms of intermittent claudication (the most common presentation in groups 2, 3, and 4), 53% had atypical or no symptoms (the most common presentation in group 1), and 1% had critical limb ischemia (Online Table 2).

A total of 1,462 (52%) patients were classified in group 1 (NR/NE), 350 (13%) patients in group 2 (NR/AE), 219 (8%) in group 3 (AR/NE), and 759 (27%) in group 4 (AR/AE). Baseline characteristics for all 4 groups are presented in Table 1. There were significant differences with regard to baseline comorbidities and medical treatment between ABI groups (Table 1). When comparing group 1 (i.e., patients without PAD) with the other groups (i.e., patients with PAD), patients in group 1 (NR/NE) were more likely to be nonsmokers, and were less likely to have coronary artery disease, prior stroke, or diabetes. Patients in group 1 were also less likely to be on baseline aspirin, clopidogrel, or statin therapy, which is reflective of the fact that patients with PAD (groups 2, 3, and 4) often have other comorbidities (13-15).

**UNADJUSTED AND MULTIVARIABLE-ADJUSTED ANALYSIS.** In unadjusted analysis, there were significant differences in the incidence of LE revascularization, MACE, and all-cause mortality between the ABI groups (p < 0.001 for all comparisons) (Table 2, Figures 1 to 3). The majority of revascularizations occurred within the first 6 months of ABI testing, reflecting practice pattern or persistent symptoms after 3 months of conservative therapy. After multivariable Cox proportional hazard adjustment (for all variables in Table 1), abnormal post-exercise ABI (group 2 [NR/AE] vs. group 1 [NR/NE]) was associated with increased LE revascularization (adjusted hazard ratio [HR]: 8.35, 95% confidence interval [CI]: 4.96 to 14.06; p < 0.001), but did not have a significant increase in MACE or all-cause mortality (Online Table 3). Similarly, when comparing group 4 (AR/AE) to group 3 (AR/NE), an abnormal post-exercise ABI was also associated with an increased rate of LE revascularization (adjusted HR: 1.59, 95% CI: 1.11 to 2.28; p = 0.01) but no differences in MACE or all-cause mortality (Online Table 4). Patients were more likely to undergo lower extremity revascularization if the referring physician was a vascular surgeon, a vascular medicine specialist, or a cardiologist compared with a primary care physician (Online Table 5) or if the patients presented with intermittent claudication or

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**TABLE 1** Baseline Characteristics According to Resting and Post Exercise ABI

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(NR/NE)</td>
<td>(NR/AE)</td>
<td>(AR/NE)</td>
<td>(AR/AE)</td>
</tr>
<tr>
<td>n</td>
<td>1,463</td>
<td>350</td>
<td>219</td>
<td>759</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>61.7 ± 13.1</td>
<td>63.6 ± 11.0</td>
<td>69.1 ± 11.7</td>
<td>67.0 ± 10.7</td>
</tr>
<tr>
<td>Female</td>
<td>703 (48)</td>
<td>115 (33)</td>
<td>104 (47)</td>
<td>252 (33)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.6 ± 8.4</td>
<td>29.0 ± 5.5</td>
<td>27.9 ± 6.2</td>
<td>28.2 ± 5.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>782 (53)</td>
<td>196 (56)</td>
<td>158 (72)</td>
<td>442 (58)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>368 (25)</td>
<td>116 (33)</td>
<td>86 (39)</td>
<td>269 (35)</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>78 (5)</td>
<td>24 (7)</td>
<td>24 (11)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>470 (32)</td>
<td>153 (44)</td>
<td>103 (47)</td>
<td>339 (45)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>27 (2)</td>
<td>7 (2)</td>
<td>11 (5)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>Coronary bypass grafting</td>
<td>100 (7)</td>
<td>46 (13)</td>
<td>31 (14)</td>
<td>108 (14)</td>
</tr>
<tr>
<td>Stroke</td>
<td>267 (18)</td>
<td>107 (31)</td>
<td>84 (38)</td>
<td>260 (34)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>645 (44)</td>
<td>286 (82)</td>
<td>185 (84)</td>
<td>669 (88)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>184 (13)</td>
<td>115 (33)</td>
<td>53 (24)</td>
<td>255 (34)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>716 (49)</td>
<td>214 (61)</td>
<td>152 (69)</td>
<td>523 (69)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>219 (15)</td>
<td>97 (28)</td>
<td>55 (25)</td>
<td>221 (29)</td>
</tr>
<tr>
<td>Statin</td>
<td>650 (44)</td>
<td>212 (61)</td>
<td>117 (53)</td>
<td>468 (62)</td>
</tr>
<tr>
<td>Creatine clearance, ml/min</td>
<td>92.3 ± 41.7</td>
<td>87.1 ± 37.9</td>
<td>78.7 ± 41.4</td>
<td>80.8 ± 38.3</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dl</td>
<td>54.1 ± 17.3</td>
<td>49.7 ± 16.8</td>
<td>52.5 ± 17.6</td>
<td>47.8 ± 15.8</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dl</td>
<td>100.5 ± 39.4</td>
<td>92.1 ± 38.4</td>
<td>97.9 ± 34.7</td>
<td>100.3 ± 40.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

Abbreviations: ABI = ankle-brachial index; AR = abnormal ankle-brachial index post exercise; AE = abnormal ankle-brachial index at resting; NE = normal ankle-brachial index post exercise; NR = normal ankle-brachial index at resting.

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**TABLE 2** Incidence of Lower Extremity Revascularization, MACE, and All-Cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(NR/NE)</td>
<td>(NR/AE)</td>
<td>(AR/NE)</td>
<td>(AR/AE)</td>
</tr>
<tr>
<td>n</td>
<td>1,463</td>
<td>350</td>
<td>219</td>
<td>759</td>
</tr>
<tr>
<td>Lower extremity revascularization</td>
<td>22 (2)</td>
<td>50 (14)</td>
<td>36 (16)</td>
<td>241 (32)</td>
</tr>
<tr>
<td>MACE</td>
<td>134 (9)</td>
<td>57 (16)</td>
<td>51 (23)</td>
<td>152 (20)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>33 (2)</td>
<td>21 (6)</td>
<td>20 (9)</td>
<td>41 (5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>21 (1)</td>
<td>6 (2)</td>
<td>11 (5)</td>
<td>29 (4)</td>
</tr>
<tr>
<td>Amputation</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>94 (6)</td>
<td>38 (11)</td>
<td>34 (16)</td>
<td>114 (15)</td>
</tr>
</tbody>
</table>

Values are n (%). Statistical significance determined by chi-square testing at p < 0.05.

MACE = major adverse cardiovascular events; other abbreviations as in Table 1.
rest pain compared with those who presented with atypical or no symptoms (Online Table 6).

**PROPENSITY-ADJUSTED ANALYSIS.** Propensity score matching was successful in 700 patients between groups 1 and 2 (350 from each group), 438 patients between groups 1 and 3 (219 from each group), 1,518 patients between groups 1 and 4 (759 from each group), and 438 patients between groups 3 and 4 (219 from each group) resulting in similar baseline characteristics between each of the matched groups (Online Tables 7 to 10). After propensity matching, among patients with a normal resting ABI, an abnormal post-exercise ABI remained predictive of LE revascularization (Table 3). Importantly, when resting ABI was abnormal, comparing group 4 (AR/AE) to group 3 (AR/NE), abnormal post-exercise ABI was still associated with an increased LE revascularization rate (adjusted HR: 2.32, 95% CI: 1.52 to 3.54; \( p < 0.001 \)) but not all-cause mortality or MACE (Table 4).

**DISCUSSION**

We found that abnormal post-exercise ABI testing is associated with increased incidence of lower extremity revascularization among individuals with normal or abnormal resting ABI. Furthermore, when compared with patients with normal resting and post-exercise ABI, patients with both abnormal resting and post-exercise ABI had a trend toward higher all-cause mortality, as well as a significant increase in the rate of major cardiovascular outcomes. In this retrospective study, post-exercise ABI appears to offer clinical and prognostic information beyond normal and abnormal resting ABI.

The majority of patients who undergo revascularization for PAD present with claudication, typically defined as pain, tightness, or discomfort in the calf muscles upon walking that resolves with resting. However, when evaluating patients with exercise-induced claudication, resting ABI alone is typically performed and recommended (10). This approach has many limitations, including the well-known documented normal ABI in patients with aortoiliac or inflow disease that drops with exercise only (16,17). Accordingly, the ACC/AHA guidelines have suggested post-exercise ABI when suspicion for PAD is high but resting ABI is normal (10). However, another important question not currently addressed by the guidelines is the incremental clinical and prognostic value of post-exercise ABI among all patients presenting with claudication. We showed that the presence of abnormal post-exercise ABI increases the likelihood

![FIGURE 1 Unadjusted Kaplan-Meier Curves in All 4 ABI Groups for Lower Extremity Revascularization](image1)

The log-rank test revealed a statistically significant difference between the lower extremity revascularization rates across all 4 groups over time (\( p < 0.001 \)). ABI = ankle-brachial index; AE = abnormal ankle-brachial index post exercise; AR = abnormal ankle-brachial index at resting; NE = normal ankle-brachial index post exercise; NR = normal ankle-brachial index at resting.

![FIGURE 2 Unadjusted Kaplan-Meier Curves in All 4 ABI Groups for MACE](image2)

The log-rank test revealed a statistically significant different MACE rates across all 4 groups over time (\( p < 0.001 \)). MACE = major adverse cardiovascular events; other abbreviations as in Figure 1.
of LE revascularization ×7 among those with normal resting ABI and ×2 among those with abnormal resting ABI.

Post-exercise ABI, compared with resting ABI alone, better reflects limb perfusion when patients are symptomatic with claudication. Therefore, it may help physicians to objectively and more accurately identify the severity of malperfusion and correlate that with the patient’s symptoms. For example, a resting ABI of 0.8 would be considered mild PAD, but a post-exercise ABI of 0.3 in the same patient would identify severe disease that may not be amenable to medical management alone and may require further evaluation or revascularization.

Therefore, post-exercise ABI is clinically valuable among those with either a normal or abnormal resting ABI, and thus should be considered in all patients presenting with symptoms of claudication.

To our knowledge, this is only the second study (6) to explore the clinical effect of abnormal post-exercise ABI on LE revascularization, and one of few studies (6–9) to investigate the prognostic implications of abnormal post-exercise ABI. Further, we used strict criteria to define PAD following the current ACC/AHA guidelines (10), including a resting ABI of ≤0.9 and a 20% drop in resting ABI post exercise as the cutoff for abnormal post-exercise ABI.

Diehm et al. (6) examined the implications of post-exercise ABI in an outpatient primary care setting and found that patients with normal resting ABI but abnormal post-exercise ABI were at higher risk for LE revascularization and MACE but with no difference in all-cause mortality. Overall, the study population was low risk, with the highest-risk group (AR/AE) having only 50 (8%) LE revascularization events compared with 241 (32%) events in our study, and both rates are lower than that reported by Ferina et al. (18) which may reflect different practice settings and patterns. Despite this, our study extends the findings of Diehm et al. (6) to the in-hospital setting and confirms the clinical value of post-exercise ABI even after adjusting for multiple comorbidities including medication use, and propensity matching.

Sheikh et al. (7) investigated the association of post-exercise ABI with all-cause mortality alone from 1990 to 2000 and found that patients with an isolated abnormal post-exercise ABI were at higher risk for all-cause mortality compared with those with both normal resting and post-exercise ABI. This study used 0.85 as the cutoff for both abnormal resting and post-exercise ABI, which is not consistent with the current

![FIGURE 3 Unadjusted Kaplan-Meier Curves in All 4 ABI Groups for All-Cause Mortality](image)

The log-rank test revealed statistically significant different all-cause mortality rates across all 4 ABI groups over time (p < 0.001). Abbreviations as in Figure 1.
guidelines and may have biased results in favor of post-exercise ABI. Additionally, data related to baseline medication use, LE revascularization, and MACE were not collected. Other publications (8,9) in this area have been withdrawn due to concerns about publication integrity (19).

We also noted that a total of 761 patients in group 1 (NR/NE) and 84 patients in group 3 (AR/NE) had similar or an increase in their ABI post exercise. Although the exact mechanism for this is unknown, similar findings have been described by others (6,9). Factors such as collateral flow, hyperemia, endothelial dysfunction, or measurement error could potentially explain this. Additionally, if valid, the clinical significance of this finding should be evaluated.

**STUDY LIMITATIONS.** Despite the large initial study population, the post-propensity matching samples size was relatively small. Additionally, outcomes such as stroke, myocardial infarction, and LE revascularization performed at other centers may not have been captured, but only 75 (3%) of patients were lost to follow-up. More specifically, only 35 (3%) patients in groups 2, 3, and 4 had no follow-up post-ABI testing at our institution and may have had revascularization at other centers; however, this would most likely further strengthen the association between post-exercise ABI and outcomes. Although there was no formal adjudication of outcomes, we doubt that this had created any systematic bias, as the classification of the patients into 4 ABI groups occurred only after the completion of data collection. Furthermore, it is possible that endpoints such as myocardial infarction and stroke were under-reported. Our data is from a tertiary care referral center, and our results may not be generalizable to other populations; however, the current study encompasses our main medical center and all of its associated 8 satellite community hospitals. There may have been heterogeneity in exercise ABI; however, in general, we used a standard protocol for most patients with minor modifications in grade or speed if necessary for safety purposes. Our sample size may be biased; however, the decision to perform post-exercise testing was made on the basis of the ordering physician’s discretion, and furthermore, the prevalence of intermittent claudication and critical limb ischemia in our population was similar to that of patients with PAD in the general population (20).

**CONCLUSIONS**

The current ACC/AHA guidelines do not recommend post-exercise ABI measurement when the resting ABI is abnormal; however, in this analysis, post-exercise ABI was associated with a 2-fold increase in lower extremity revascularization even among these patients. Post-exercise ABI can be performed in the office setting, is relatively safe, and provides objective perfusion assessment at the time of claudication symptoms. Future properly conducted prospective studies should confirm the diagnostic and prognostic utility of exercise ABI; however, at the present time, our results support the utilization of this test among patients with suspected PAD, even when resting ABI is abnormal.

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**PERSPECTIVES**

**WHAT IS KNOWN?** The current ACC/AHA guidelines do not recommend post-exercise ABI measurement when the resting ABI is abnormal; however, post-exercise ABI, unlike resting ABI, may more accurately represent blood flow at the time when patients experience claudication.

**WHAT IS NEW?** In our analysis, post-exercise ABI was associated with a 2-fold increase in lower extremity revascularization rate even among patients with abnormal resting ABI.

**WHAT IS NEXT?** Future properly conducted prospective studies should confirm the diagnostic and prognostic utility of post-exercise ABI.
REFERENCES


KEY WORDS all-cause mortality, exercise ankle-brachial index, lower extremity revascularization, peripheral artery disease, prognosis

APPENDIX For supplemental tables, please see the online version of this article.