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Prognostic Significance of Declining Ankle-brachial Index Values in Patients with Suspected or Known Peripheral Arterial Disease

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Background. *Peripheral arterial disease (PAD) is a risk factor for cardiovascular events. This study assessed the prognostic significance of repeated ankle-brachial index (ABI) measurements at rest and after exercise in patients with PAD receiving conservative treatment.*
Methods. *In a cohort study of 606 patients (mean age 62 ± 12 years, 68% male), ABI at rest and after exercise was measured at baseline and after 1 year. Patients with reductions in ABI were divided into three equally-sized groups (minor, intermediate and major reductions) and were compared to patients without reductions. During a mean follow-up of 5 ± 3 years, all-cause mortality, cardiac events, stroke and progression to kidney failure were noted.*
Results. *Death was recorded in 83 patients (14%) of which 49% were due to cardiac causes. Non-fatal myocardial infarction occurred in 38 patients (6%), stroke in 46 (8%) and progression to kidney failure in 35 (6%). By multivariate analysis, patients with major declines in resting (>20%) and post-exercise (>30%) ABI were at increased risk of all-cause mortality (HR: 3.3, 95% CI: 1.5–7.2, HR: 3.0, 95% CI: 1.4–6.4, respectively), cardiac events (HR: 3.1, 95% CI: 1.3–7.2, HR: 2.4, 95% CI: 1.1–5.6, respectively), stroke (HR: 4.2, 95% CI: 1.6–10.4, HR: 3.9, 95% CI: 1.4–10.2, respectively) and kidney failure (HR: 2.7, 95% CI: 1.1–7.5, HR: 6.9, 95% CI: 1.5–31.5, respectively), compared to patients with no declines in ABI.*
Conclusions. *This study shows that major 1-year declines in resting and post-exercise ABI are associated with all-cause mortality, cardiac events, stroke and kidney failure in patients with PAD.*

Keywords: Peripheral arterial disease; Ankle-brachial index; Prognosis.

Introduction

Peripheral arterial disease (PAD) is associated with an increased risk of vascular morbidity and mortality despite medical treatment.[1–3] In the Netherlands, the combined prevalence of symptomatic and asymptomatic PAD in the population of 55 years and older is 19%.[4] In the United States, prevalence rates for PAD have been reported that range from 4% in patients aged 40 years and older to 29% in patients aged 70 years and older.[1,5–8] Therefore, the identification of patients with PAD who are at increased risk of late events is necessary for disease control and selection of appropriate treatment strategies.[3,9,10]

The ankle-brachial index (ABI) is a simple, inexpensive and non-invasive test used for the assessment of lower extremity arterial obstruction and for screening of patients with suspected PAD.[8–10] A resting ABI of less than 0.90 has been associated with a 2- to 7-fold increased risk of overall mortality and a 2- to 4-fold increased risk of cardiovascular mortality, compared to a resting ABI higher than 0.90.[11–17] The prognostic value of declines in ABI over time is not well known. In this study, we assessed the association between changes in resting and post-exercise ABI over time and long-term outcome in patients with known or suspected PAD who are receiving conservative (non-surgical) treatment. We hypothesized that a larger decline in both resting and post-exercise ABI would identify patients at increased risk of all-cause mortality, cardiac events, stroke and end-stage renal disease, irrespective of baseline ABI values and clinical risk factors.

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Methods

Study participants

We have prospectively included consecutive patients with suspected or known lower extremity PAD who were referred to our university clinic of vascular surgery for the evaluation and management of their disease between January 1996 and January 2005. Patients with known PAD had a resting or post-exercise ABI $\leq$0.90. In patients with suspected PAD, the diagnosis was based on a typical history of intermittent claudication or other symptoms of chronic arterial insufficiency, including ulceration of the foot, hair loss or reduced capillary refill. Patients unable to perform exercise, patients who underwent previous vascular surgery and patients who had foot or leg amputations were not included. We further considered patients with ABI values greater than 1.50 to have calcified atherosclerosis, resulting in high ABI readings. These patients were also not included in the study. The hospital's Medical Ethical Committee approved the study protocol and patients who fulfilled the inclusion criteria agreed to participate in the study.

Co-morbidities

Based on hospital records and personal interviews at the time of the visit, a medical history was recorded including details of a previous myocardial infarction, angina pectoris, coronary artery revascularization, congestive heart failure, previous stroke or transient ischemic attack, diabetes mellitus, hypertension, smoking, hypercholesterolemia and renal dysfunction. Diabetes mellitus was recorded if patients presented with a fasting glucose level of $\geq$7.0 mmol/L, or in those who required medical treatment. Hypertension was recorded if patients presented with a blood pressure $\geq$140/90 mmHg or if patients received antihypertensive treatment. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level $\geq$5.5 mmol/L, or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level $\geq$2.0 mg/dL (177 μmol/L) or in those who required dialysis. Patients were assessed for chronic cardiac medication use. A baseline 12-lead electrocardiography was obtained and the ABI at rest and after exercise was measured in each patient.

Measurement of the ankle-brachial index

Trained technicians, using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT + Vascular Doppler, Miami Medical, USA), measured systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibial artery. The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used when a discrepancy in systolic blood pressure between the two arteries was measured. If no pressure in the dorsalis pedis artery was obtained due to an absent dorsalis pedis artery, the pressure in the posterior tibial artery was used. The ABI at rest was measured after the participants had been resting in the supine position for at least 10 minutes. Measurements were then repeated at both sides with the patient in the supine position, after 5 minutes of walking on a treadmill with a speed of 2.5 miles/hour. No inclining plane or graded inclines were used with treadmill testing, and the treadmill tests were performed without continuous electrocardiographic monitoring before, during and after testing. Inter- and intra-observer agreement for resting ABI was 97% and 98%, respectively and for post-exercise ABI 96% and 97%, respectively.

Conservative versus surgical management

The decision for conservative management or surgical intervention was at the discretion of the treating physician. In general, surgical treatment was indicated when a significant improvement of symptoms could be expected and when the expected benefits would outweigh the risk of surgery. In patients who received conservative treatment, i.e. walking exercise and/or pharmacotherapy, ABI measurements were repeated at least every year after enrollment. Patients who died before the second ABI measurement and in whom an ABI change over time could not be determined were excluded from the study ($n = 13$).

Follow-up

Follow-up ended at the date of the last visit or the date of death. Information about the patient's vital status was obtained at the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were reviewed. For patients who died outside our hospital, general practitioners were approached to ascertain the cause of death. A cardiac cause of death was defined

as death caused by acute myocardial infarction (post-mortem evidence of acute myocardial infarction or definite criteria for myocardial infarction within the four weeks before death), cardiac arrhythmias, congestive heart failure, or sudden death. Details on non-fatal myocardial infarction, stroke and end-stage renal disease were obtained by regularly scheduled follow-up visits. Additional information was obtained by approaching the general practitioners or referring clinicians. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level >190 U/L and CK-MB >14 U/L, or CK-MB fraction >6% of total CK, or cardiac troponin T > 0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Stroke was diagnosed when patients presented with typical neurological symptoms lasting for more than 24 hours. In all cases of stroke, the diagnosis was established by a neurologist. End-stage renal disease was defined as an estimated glomerular filtration rate less than 15 ml/min per 1.73 m^2 or a need to start kidney replacement therapy, which included dialysis or renal transplantation. The estimated glomerular filtration rate was calculated using the following equation: glomerular filtration rate (ml/min/1.73 m^2) = 186 × (serum creatinine level)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if of African descent).[18]

Statistical analysis

Continuous data are expressed as mean (+/− SD) or median (+/− interquartile range) and compared using the Student t test or Mann-Whitney U test as appropriate. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test with Yates' correction. Comparisons of categorical variables with continuous measures were calculated with analysis-of-variance techniques. Initially, we compared patients receiving conservative treatment ($n = 606$) to patients receiving lower extremity surgical revascularization ($n = 974$). We then focused our analysis on the 606 patients receiving conservative treatment to assess the prognostic value of declines in ABI. The change of the serial ABI measurements was calculated in each leg and expressed as a percentage value. Of the changes in ABI obtained in each leg, the lower was used in all analyses. Although repeat ABI measurements were obtained annually, the change in ABI was calculated over the first year and expressed as both percentage and absolute change. Only 1-year changes were used in our analysis. Patients with declining ABI were compared to patients with no declines in ABI. Patients with declining ABI were further divided into minor, intermediate and major decline according to the tertiles as cut-off value (5% and 20% for the decline in resting ABI and 6% and 30% for the decline in post-exercise ABI). For the prediction of a major decline in ABI, a final set of baseline variables was identified by multivariate analysis with stepwise deletion of the least significant variable. Only variables with a $p \leq 0.20$ were retained in the final model. The primary endpoints were overall mortality and cardiac events (cardiac death or non-fatal myocardial infarction). Secondary endpoints were stroke and progression to end-stage renal disease. For the outcome analysis, we used univariate and multivariate Cox proportional hazard regression models to analyze the association between ABI decline and outcome. In multivariate analyses, all clinical variables were entered, irrespective of the significance level in univariate analysis. Hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

Conservative treatment versus surgical treatment

Baseline characteristics of patients receiving either conservative or surgical treatment are presented in Table 1. Patients receiving surgical treatment were more likely to present with hypercholesterolemia, hypertension, angina pectoris, chronic pulmonary disease and lower resting ABI values. Mean follow-up was 5.3 ± 3.3 years. In patients receiving surgical and conservative treatment, death was recorded in 293 patients (30%) and 83 patients (14%), respectively. As shown in Fig. 1, survival was significantly lower in patients receiving surgical treatment.

Declines in ABI

In the 606 patients receiving conservative treatment, the mean baseline ABI at rest (the lower of the right and left ABI) was 0.69 ± 0.23. A resting ABI >0.90 in both legs was measured in 99 patients (16%). The mean ABI measured after exercise (the lower of the right and left ABI) was 0.48 ± 0.29. A post-exercise ABI >0.90 in both legs was observed in 59 patients (10%). A total of 29 patients (5%) had both a resting and post-exercise ABI of more than 0.90. These

Table 1. Baseline characteristics of patients with peripheral arterial disease receiving conservative management ($n = 606$) and patients receiving lower extremity revascularization surgery ($n = 974$)

Characteristic	Conservative management ($n = 606$)	Surgical treatment ($n = 974$)	*P* value
Age (years), mean +/− SD	62 ± 12	63 ± 12	0.2
Male gender, No. (%)	414 (68)	709 (73)	0.06
Angina pectoris, No. (%)	112 (18)	250 (26)	0.001
Previous myocardial infarction, No. (%)	200 (33)	351 (36)	0.2
History of heart failure, No. (%)	40 (7)	64 (7)	0.9
History of stroke, No. (%)	51 (8)	101 (10)	0.2
Diabetes mellitus, No. (%)	112 (19)	155 (16)	0.054
Hypercholesterolemia, No. (%)	147 (24)	292 (30)	0.02
Hypertension, No. (%)	222 (37)	470 (48)	<0.001
Current smoking, No. (%)	169 (28)	289 (30)	0.5
Renal dysfunction, No. (%)	31 (5)	59 (6)	0.5
Chronic pulmonary disease, No. (%)	57 (9)	145 (15)	0.002
Rest ankle-brachial index, mean +/− SD	0.69 ± 0.23	0.65 ± 0.24	0.03
Post-exercise ankle-brachial index, mean +/− SD	0.48 ± 0.29	0.46 ± 0.29	0.3
Aspirin, No. (%)	179 (30)	297 (30)	0.7
Angiotensin-converting enzyme inhibitors, No. (%)	174 (29)	290 (30)	0.7
β-blockers, No. (%)	193 (32)	355 (36)	0.07
Statins, No. (%)	218 (36)	329 (34)	0.4

29 patients all had a typical history of claudication and signs of arterial insufficiency, including weak peripheral pulses and reduced capillary refill. A total of 459 patients (76%) had declining ABI values at rest and 456 patients (75%) had declining ABI values after exercise. Declining ABI values at rest were observed in 67 (68%) out of 99 patients with a normal resting ABI (ABI >0.90). Declining ABI values after exercise were observed in 40 (68%) out of 59 patients with normal post-exercise ABI (ABI >0.90). The median change in resting ABI in patients with no declining ABI was +13% and in patients with declining ABI −12%. The median change in post-exercise ABI in patients with no declining ABI was +21% and in patients with declining ABI − 17%.

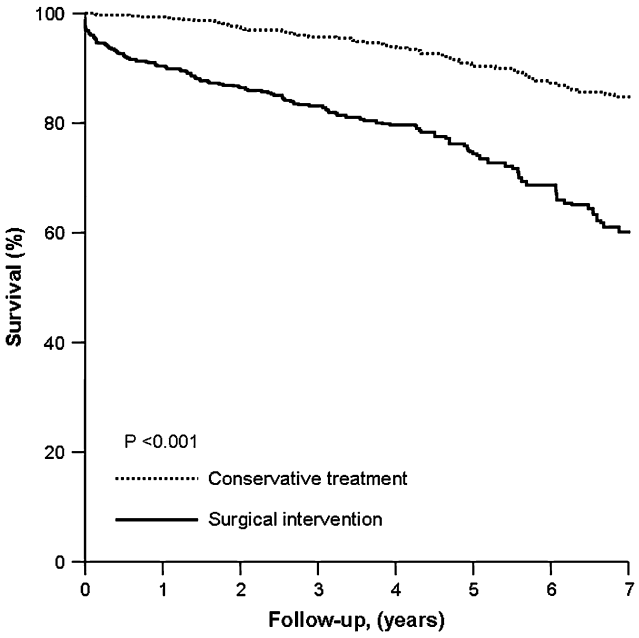


Fig. 1. Kaplan-Meier survival curves in 1580 patients with peripheral arterial disease according to conservative treatment or surgical intervention.

Predictors of declines in ABI values

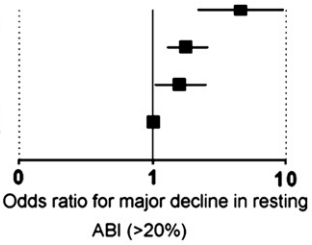
Significant predictors of major declines in resting ABI values (>20%) were age ($p = 0.003$), cigarette smoking ($p < 0.001$), history of stroke ($p < 0.001$) and a previous myocardial infarction ($p = 0.042$) (Fig. 2). Significant predictors of major declines in post-exercise ABI values (>30%) were age ($p < 0.001$), diabetes mellitus ($p < 0.001$), cigarette smoking ($p < 0.001$) and a history of stroke ($p = 0.031$) (Fig. 2).

Predictive value of declines in ABI

Of the 83 patients receiving conservative treatment who died during follow-up, 49% were due to cardiac causes (41 patients). Non-fatal myocardial infarction occurred in 38 patients (6%), stroke in 46 patients (8%) and progression to end-stage renal disease in 35 patients (6%). Fig. 3 shows the incidence of overall mortality, cardiac events, stroke and progression to end-stage renal disease in patients with no, minor, intermediate and major declines in resting and post-exercise ABI. By univariate analysis, patients with major declines in resting and post-exercise ABI had the highest hazard of all-cause mortality, cardiac events, stroke and end-stage renal disease (Table 2). Patients with intermediate declines in resting and post-exercise ABI were also at significantly increased risk of death and cardiac events (Table 2). After adjustment for baseline clinical variables, baseline ankle-brachial index values, β-blockers, statins, aspirin and angiotensin-converting enzyme inhibitors, major declines in resting and post-exercise ABI remained significantly associated with all-cause mortality, cardiac events, stroke and kidney failure (Table 2). Intermediate declines remained significantly associated with death and cardiac events (Table 2). As demonstrated in Table 3, absolute declines in ABI (per 0.10 decline) were significantly associated with all-cause mortality, cardiac events, stroke and end-stage renal disease.

Predictors of a major decline in resting ABI (>20%)	Hazard ratio (95% CI)	p value	β-coefficient
History of stroke	4.6 (2.2–9.6)	<0.001	1.53
Current cigarette smoking	1.8 (1.3–2.6)	<0.001	0.59
Previous myocardial infarction	1.6 (1.02–2.5)	0.042	0.46
Age (per year increase)	1.03 (1.01–1.05)	0.003	0.03

Chi-square: 32.9, p <0.0001



Predictors of a major decline in postexercise ABI (>20%)	Hazard ratio (95% CI)	p value	β-coefficient
Diabetes mellitus	3.0 (1.9–4.9)	<0.001	1.11
History of stroke	2.3 (1.1–4.7)	0.031	0.81
Current cigarette smoking	1.9 (1.3–2.8)	<0.001	0.68
Age (per year increase)	1.05 (1.03–1.07)	<0.001	0.05

Chi-square: 38.7, p <0.0001

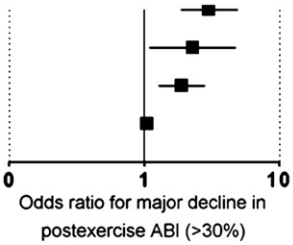


Fig. 2. Baseline clinical variables associated with a major 1-year decline in resting ankle-brachial index (ABI) (decline of more than 20%) and post-exercise ankle-brachial index (decline of more than 30%) in patients with peripheral arterial disease receiving conservative management.

Discussion

The current study found that major declines in resting and post-exercise ABI values are significantly associated with increased long-term mortality, cardiac events, stroke and progression to end-stage renal disease. These findings were independent of baseline ABI values, established clinical risk factors and cardiovascular therapy.

Given the fact that the presence of PAD should be regarded as a marker of atherosclerosis in other vascular beds, it is not surprising that many of these patients die due to cardiovascular disease, stroke or renal dysfunction.[10] The management of PAD comprises of walking exercise, aggressive management of risk factors, life-style modifications, antiplatelet therapy and statins.[19] Patients who have extensive functional disability, who are unresponsive to exercise or pharmacotherapy, and who have a reasonable likelihood of symptomatic improvement may benefit from surgical intervention.[19] The higher mortality rate in patients undergoing surgery in relation to conservative management may be explained by the presence of more co-morbidities. The high prevalence and associated morbidity and mortality of PAD in the general population warrants the identification of patients at increased risk so that preventive measures can be applied to reduce the incidence of atherosclerosis related complications.

Large cohort studies have consistently demonstrated that lower ABI values are associated with increased mortality and cardiovascular events. In a study of Leng and colleagues, a significant linear increase in mortality across decreasing ABI categories was observed using resting ABI cut-off values of 1.10, 1.00, 0.90 and 0.70.[17] We have previously demonstrated that the adjusted risk for overall mortality increased by 8% for every 0.10 decrease of the resting ABI, and by 9% for every 0.10 decrease of the post-exercise ABI. The adjusted risk for cardiac death increased by 12% and 15% for every 0.10 decrease of the resting ABI and post-exercise ABI, respectively.[20] The concept that PAD is a marker of generalized atherosclerosis has been reflected by the fact that ABI values correlate with the extent of angiographic coronary artery disease.[21] The prognostic value of post-exercise ABI has been supported by the view that a healthy person can maintain ankle systolic

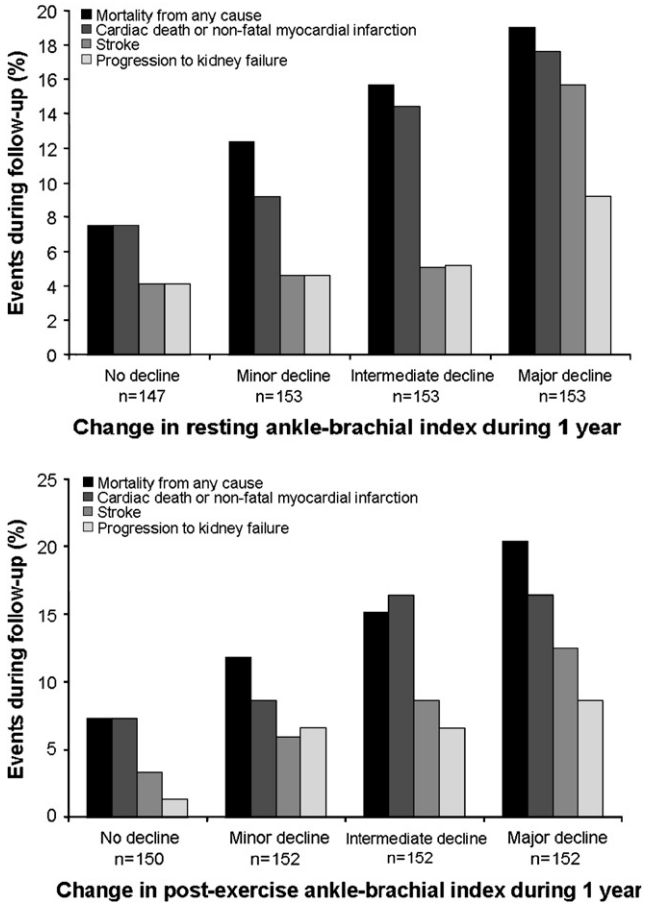


Fig. 3. Absolute event rate during follow-up according to the 1-year decline in resting (minor decline: 1–5%, intermediate decline: 6–20%, major decline: >20%) and post-exercise ankle-brachial index (minor decline: 1–6%, intermediate decline: 7–30%, major decline: >30%) in patients with peripheral arterial disease receiving conservative medical management.

pressures at normal levels during modest workloads, but that larger falls in systolic pressure in the legs are measured during low levels of workload in patients with more extensive PAD.[22–24] Based on the greater accuracy of the postexercise ABI to detect PAD, the American College of Cardiology/American Heart Association has recommended its use, especially in patients with suspected PAD who have normal resting ABI values.[19]

Important predictors of declining ABI values in our study included advanced age and smoking. Our results are supported by the Cardiovascular Health study, which found that advanced age, smoking, male gender, hypertension and higher LDL-cholesterol concentrations were risk factors for declines in ABI.[25] Smoking was also identified as a strong predictor of large vessel peripheral arterial disease in a study by Aboyans and colleagues.[26] We found that diabetes only predicted

Table 2. The long-term prognostic value of percentage declines in ankle-brachial index values in multivariate analysis in patients with peripheral arterial disease receiving conservative management

	Number of patients	HR (95% CI) for all-cause mortality		HR (95% CI) for cardiac events		HR (95% CI) for stroke		HR (95% CI) for end-stage renal disease	
		Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Total population									
ABI at rest									
No decline**	147	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Minor decline (1–5%)	153	1.8 (0.9–3.7)	2.0 (0.9–4.6)	1.4 (0.6–3.0)	1.5 (0.6–3.8)	1.1 (0.4–3.4)	1.2 (0.4–3.5)	1.1 (0.4–3.4)	1.2 (0.4–3.7)
Intermediate decline (6–20%)	153	2.4 (1.2–4.8)	3.0 (1.3–6.7)	2.3 (1.1–4.8)	2.5 (1.03–5.8)	1.5 (0.5–4.2)	1.5 (0.5–4.2)	1.3 (0.4–3.8)	1.4 (0.5–4.1)
Major decline (>20%)	153	2.5 (1.2–4.9)	3.3 (1.5–7.2)	2.4 (1.2–4.7)	3.1 (1.3–7.2)	4.3 (1.7–11.0)	4.2 (1.6–10.4)	2.4 (1.1–3.4)	2.7 (1.1–7.5)
Post-exercise ABI									
No decline**	150	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Minor decline (1–6%)	152	1.2 (0.5–2.7)	1.4 (0.6–3.2)	1.7 (0.8–3.7)	1.0 (0.4–2.6)	1.8 (0.6–5.5)	1.7 (0.6–5.4)	5.2 (1.2–24.2)	4.8 (1.01–22.8)
Intermediate decline (6–30%)	152	2.4 (1.2–5.2)	2.1 (1.03–4.8)	2.3 (1.1–4.8)	2.2 (1.05–5.2)	2.7 (0.9–7.8)	2.7 (0.9–7.9)	5.1 (1.1–22.9)	4.7 (1.01–22.6)
Major decline (>30%)	152	2.6 (1.3–5.8)	3.0 (1.4–6.4)	3.2 (1.6–6.7)	2.4 (1.1–5.6)	4.2 (1.5–11.4)	3.9 (1.4–10.2)	6.9 (1.5–31.2)	6.9 (1.5–31.5)

ABI = ankle-brachial index.
* Adjusted for age, gender, coronary artery disease, history of heart failure, history of stroke, diabetes, hypercholesterolemia, hypertension, smoking, renal dysfunction, baseline ankle-brachial index values and cardioprotective medication.
** Reference category.

Table 3. The long-term prognostic value of absolute declines in ankle-brachial index values in multivariate analysis in patients with peripheral arterial disease receiving conservative management

	Resting ABI per 0.10 decline	Postexercise ABI per 0.10 decline
All-cause mortality		
• Unadjusted Hazard Ratio (95% CI)	1.12 (1.01–1.26)	1.12 (1.02–1.25)
• Adjusted Hazard Ratio (95% CI)*	1.13 (1.01–1.26)	1.11 (1.01–1.23)
Cardiac events		
• Unadjusted Hazard Ratio (95% CI)	1.17 (1.05–1.31)	1.15 (1.03–1.30)
• Adjusted Hazard Ratio (95% CI)*	1.18 (1.05–1.33)	1.17 (1.04–1.33)
Stroke		
• Unadjusted Hazard Ratio (95% CI)	1.30 (1.14–1.48)	1.24 (1.09–1.40)
• Adjusted Hazard Ratio (95% CI)*	1.35 (1.18–1.55)	1.22 (1.06–1.38)
End-stage renal disease		
• Unadjusted Hazard Ratio (95% CI)	1.20 (1.02–1.41)	1.19 (1.03–1.38)
• Adjusted Hazard Ratio (95% CI)*	1.20 (1.03–1.41)	1.18 (1.02–1.36)

* Adjusted for age, gender, coronary artery disease, history of heart failure, history of stroke, diabetes, hypercholesterolemia, hypertension, smoking, renal dysfunction, baseline ankle-brachial index values and cardioprotective medication.

major declines in post-exercise ABI in contrast to resting ABI. Similarly, diabetes was not a significant predictor of ABI decline,[25] of large vessel PAD progression[26] and of declines in post-exercise ABI.[27] In the current study, however, a significant correlation between diabetes and major declines in post-exercise ABI was found. Concomitant arterial wall stiffening, medial calcinosis and higher ankle systolic pressures in diabetic patients may mask arterial occlusive disease, leading to pseudo-normal resting ABI values. We speculate that the value of postexercise ABI lies in its ability to measure larger decreases in ankle systolic pressures in the presence of atherosclerotic obstructive lesions, and that obstructive arterial disease can become more evident after exercise in diabetic patients.

To our knowledge, the current study is the first to describe the association between declines in ABI and prognosis in patients with PAD receiving conservative treatment. Declines in ABI may reflect active and progressive atherosclerosis, precipitating acute coronary and cerebrovascular events. The association between progression in atherosclerosis and progression to kidney failure is less well-defined. The Atherosclerosis Risk in Communities Study showed that patients with an ABI of 0.90–0.99 and <0.90 were at increased risk of serum creatinine increases over a 3-year time period, compared to patients with ABI values above 1.00.[28] It has been proposed that atherosclerosis has indirect effects on the kidney because of atherosclerotic lesions in the renal artery and that atherosclerosis or atherogenic factors may induce directly intrarenal microvascular disease and renal injury.[29]

Repeated measurements of resting and post-exercise ABI values are simple, inexpensive and non-invasive. Results from this study suggest that repeated ABI measurements at rest and after exercise may be incorporated among other tools for identifying patients at increased risk of late events. Either resting and post-exercise ABI declines after 1 year can identify a subgroup of patients at increased risk. Post-exercise ABI testing may be useful in patients with no declines in serial resting ABI. Therefore, both methods may be recommended.

Patients with major declines in ABI values may be referred for further cardiovascular, cerebrovascular or renal evaluation and may subsequently benefit from preventive pharmacologic and non-pharmacologic interventions.

Several limitations of this study should be addressed. It should be emphasized that the event rate in the groups of patients with different declines in ABI was relatively small which may have affected the statistical power of the study. However, the hazard of adverse events was consistently increased in those with major declines in resting and post-exercise ABI. Secondly, the results apply to patients referred to a university hospital. These patients may have a higher risk profile compared to patients with suspected or known PAD in the general population.

In conclusion, this observational cohort study of patients with PAD receiving conservative treatment shows that major declines in resting and post-exercise ABI are associated with late overall mortality, cardiac events, stroke and end-stage renal disease. The results support the view that progression of atherosclerosis in the lower extremities is associated with morbidity in the coronary, cerebrovascular and renal circulation. Repeated measurements of resting and post-exercise ABI are simple and non-invasive and should be considered in the follow-up of patients with PAD receiving conservative treatment for identifying those at increased risk of adverse events and for enabling optimal prevention of complications.

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