Prognostic Impact of Arterial Stiffness in Patients with Symptomatic Peripheral Arterial Disease

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WHAT THIS PAPER ADDS

Only a few studies have estimated associations between vascular function and prognosis in the setting of peripheral arterial disease (PAD). Whether changes in arterial stiffness can predict all-cause and cardiovascular disease mortality in patients with symptomatic PAD has never been investigated. The present study is the first to demonstrate a direct independent relationship between small artery elasticity and all-cause and cardiovascular disease mortality in a cohort of symptomatic patients with advanced atherosclerosis. This finding further supports the relevance of arterial dysfunction in progression of cardiovascular disease and suggests that symptomatic PAD patients with reduced small artery elasticity continue to be at an increased risk for all-cause and cardiovascular disease mortality.

Objectives: Arterial stiffness (AS) is increasingly recognized as an independent risk factor in different high-risk populations. Whether changes in AS can predict prognosis in patients with symptomatic peripheral arterial disease (PAD) has never been investigated. The aim of the present study was to test the hypothesis that AS is an independent predictor of all-cause and cardiovascular disease (CVD) mortality in patients with symptomatic PAD.

Methods: A cohort of 117 symptomatic PAD patients (aged 62.3 ± 7.7 years) were prospectively recruited from the Department of Vascular Surgery, Tartu University Hospital, between 2002 and 2010. The AS was measured using pulse wave analysis and assessment of pulse wave velocity (PWV).

Results: During the follow-up period (mean 4.1 ± 2.2 years) there were 32 fatal events. Kaplan—Meier analysis showed that the probability of all-cause and CVD mortality decreased with increasing small artery elasticity (SAE), as estimated by the log-rank test (p = .004; p = .005, respectively). By contrast, large artery elasticity, augmentation index, and aortic and brachial PWV were not significantly related to mortality. In a Cox proportional hazard model, SAE above the median was associated with decreased all-cause and CVD mortality after adjustment for confounding factors: relative risk (RR), 0.37; 95% confidence interval (CI), 0.17–0.81; p = .01; RR, 0.11; 95% CI, 0.01–0.86; p = .04, respectively.

Conclusions: This study provides the first evidence, obtained from an observational study, that decreased small artery elasticity is an independent predictor of all-cause and CVD mortality in patients with symptomatic PAD.

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INTRODUCTION

Lower extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis with a prevalence of 2.7–3% in a population aged 45–49 years, increasing to 18.2% in persons aged 60–90 years.1–3 The association of PAD with increased future cardiovascular disease (CVD) events and mortality, and total mortality has been demonstrated in numerous studies.4,5 Possible explanations for the PAD patients’ poor prognosis lie in accumulation of classical CVD risk factors and in functional impairment and progression of the disease.6,7 However, the exact mechanisms by which PAD is associated with increased risk are not fully understood. Therefore, identification of novel prognostic markers for PAD may improve understanding of the mechanisms of atherosclerosis, which may ultimately lead to new and better therapies.8

Altered arterial wall properties, such as arterial stiffness (AS), might be one potential cause of poor prognosis in
patients with PAD. Increased AS is an important independent determinant of CVD events, mortality and total mortality, and also plays an important role in atherosclerosis. Arterial stiffening may induce arterial remodeling, wall thickening, and development of atheroma. Moreover, AS may contribute to ulceration and rupture of atherosclerotic plaques.

Pulse wave analysis (PWA) and assessment of brachial and aortic pulse wave velocity (PWV) are well established methods for measuring AS. Increased aortic PWV and augmentation index (AIx), and decreased small (SAE) and large artery elasticity (LAE) were independently associated with all-cause and CVD mortality in patients with PAD who have been demonstrated. Large-scale studies have shown that increased aortic PWV and AIx, and decreased SAE are independent predictors of CVD, CVD events and mortality. Moreover, lower SAE and higher AIx were associated with ankle-brachial index (ABI), which is the most powerful indicator in PAD and is linked to survival.

Only a few studies have estimated associations between vascular function and prognosis in the setting of PAD. Endothelial dysfunction predicts postoperative and long-term CVD events in PAD patients. Furthermore, whether changes in AS can predict all-cause and CVD mortality in patients with symptomatic PAD has never been investigated. The aim of the present study was to test the hypothesis that AS is an independent predictor of all-cause and CVD mortality in symptomatic PAD patients after controlling for the classic CVD risk factors.

METHODS

Subjects and study design

This study was conducted within the framework of an ongoing prospective study comparing vascular phenotype and biomarkers in PAD patients living in Estonia. Patients with PAD (Fontaine stages II-IV) were prospectively recruited from the Department of Vascular Surgery, Tartu University Hospital, Estonia, between October 2, 2002 and May 24, 2010. The primary end point of this cohort study was mortality (all-cause and CVD). The subjects were all male with angiographically proven PAD defined by occlusion or stenosis of the arteries of the lower extremities. The ABI was less than 0.90 (range 0.1–0.89). The patients’ exclusion criteria included (based on clinical examination, ECG, and blood tests): any concomitant acute or chronic inflammatory disease, myocardial infarction, coronary revascularization or cerebrovascular events during the past 6 months, earlier revascularization procedures of the lower limb, upper limb occlusive arterial disease, cardiac arrhythmias, or valve pathologies, diabetes mellitus, malignancies, and renal failure. Demographic data including the risk factors for CVD, were collected on the study entry day when the AS indices, brachial and aortic PWV, AIx, SAE, and LAE, were measured. Smoking status was defined as current or past versus never. This study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the ethics committee, University of Tartu. Informed written consent was obtained from each participant.

Study protocol

The subjects were studied and the plasma samples were collected after an overnight fast and abstinence from any medications, tobacco, alcohol, and tea or coffee. After 15 min of rest in a quiet, temperature-controlled room, ABI, blood pressure and PWV were measured and PWA was performed. All hemodynamic recordings were made in duplicate for each time point. Thereafter, venous blood samples were drawn from the antecubital fossa for measurement of glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, high-sensitivity C-reactive protein (hsCRP), creatinine, oxidized LDL-C (oxLDL), hemoglobin, and red blood cells (RBC) count. Height and weight were recorded, and body mass index (BMI) was calculated.

Measurement of arterial stiffness and ABI

Peripheral blood pressure (BP) was measured from the both arms using a validated oscillometric technique (OMRON M4-I; Omron Healthcare Europe BV, Hoofddorp, The Netherlands). The arterial waveform was measured in the dominant arm by a Cardiovascular Profiling Instrument (HDI/Pulse Wave CR-2000, Hypertension Diagnostics Inc, Eagan, USA). This method of vascular assessment is based on a modified 2-element Windkessel model that allows calculation of SAE and LAE.

The AIx and central hemodynamics were assessed by systolic PWA using an SphygmoCor apparatus (SphygmoCor; AtCor Medical, Sydney, Australia). Pulse pressure (PP) amplification (PPA) was expressed as the percentage increase of PP in the peripheral (brachial) artery (PPP) relative to central (aortic) PP (CPP), according to the formula: PPA = 100 × (PPP-CPP)/CPP. Aortic and brachial PWV were measured by sequentially recording ECG-gated carotid and femoral or radial artery waveforms (SphygmoCor; AtCor Medical, Sydney, Australia). The ABI was measured using the Bidirectional Doppler MD 6 (D. E. Hokanson Inc, Bellevue, WA, USA). The mean of the two BP readings (from the arm of which the BP values were higher) and the lower ABI value of the two legs were included in statistical analysis.

Biochemical analysis

The blood samples were centrifuged and the plasma was divided into aliquots and stored at −70 °C until analysis. The plasma content of oxLDL was analyzed using a competitive enzyme-linked immunoassay (ELISA) kit. Plasma levels of glucose, hsCRP, total cholesterol, LDL-C, HDL-C, triglyceride and creatinine, hemoglobin level, RBC count, and glomerular filtration rate were determined by standard laboratory methods.

Mortality

The follow-up period ended in August 4, 2011 (mean follow-up, 4.1 ± 2.2 years). The deceased subjects were identified from Estonia mortality records and death was confirmed from the death certificate. All other subjects were...
considered to be alive at the end of the follow-up period. The causes of death were taken from the death certificate, or by telephone interview with the subjects’ general practitioner or relatives, and were coded in accordance with the International Classification of Disease (tenth revision). Death as a result of acute myocardial infarction, non-hemorrhagic stroke, or exacerbation of heart failure was defined as a CVD death.

Population for analysis

Of the 123 subjects with a measurement of AS parameters, five were excluded from the analyses because of poor quality of the AS index recordings, leaving 118 subjects. One subject was excluded with unknown cause of mortality, leaving 117 subjects for analyses.

Statistical analysis

Power calculation is based on the expected 20% difference in PAD survival according to the SAE value. This implies that about 120 subjects have to be included (two sided test, $\beta = .2$ at $\alpha = .05$; RR $= 0.3$). Data were collected and analyzed using the software R, version 2.15.2 for Windows. All data were tested for normality of distribution, and log transformation and/or nonparametric tests were used where appropriate. Continuous data are expressed as mean $\pm$ SD if distributed normally, or otherwise, as median with the 25% and 75% percentiles. Dichotomous variables are given as prevalence in number and percentage. Relationships of the AS parameters and potential confounders with all-cause and CVD survival were estimated using the chi-square test for categorical variables and the Student t test or the Mann-Whitney test for continuous variables that had a normal or skewed distribution, respectively. Survival was assessed by the Kaplan—Meier curves and was compared by the log-rank test according to the median of the AS parameters. For the AS parameters, additional adjustments were made for MAP and heart rate. To evaluate whether oxLDL levels or RBC count added to the predictive value of AS, the study population was divided into eight groups: patients with SAE higher than the median and oxLDL or RBC count lower than the median, those with both SAE and oxLDL or RBC count higher than their respective median values, those with both SAE and oxLDL or RBC count lower than their respective median values, and those with SAE lower than the median value and oxLDL or RBC count higher than the median value. A Cox proportional hazards regression model was then used to control for the confounders identified by univariate analysis (inclusion criteria $p < .1$). The proportional hazards assumptions were satisfied. Receiver-operating characteristic (ROC) curves were employed to compute the discriminatory power of different sets of prognostic factors. Differences in the discriminatory power between models were estimated by a nonparametric approach to the analysis of areas under the ROC curves using the theory on generalized $U$ statistics.

RESULTS

Patients with PAD

In the 117 patients studied, 75 had stage II, 29 stage III, and 13 stage IV chronic ischemia as defined by Fontaine. Forty-six patients (39.3%) with arterial hypertension and 23 patients (19.7%) with coronary artery disease as the co-morbidity were included in the study. A non-significant proportion of the patients used concomitant medications: 46 patients used pentoxifylline; 31 patients, aspirin; 14 patients, statins; 18 patients, angiotensin-converting enzyme inhibitors; 19 patients, calcium channel blockers; 11 patients, angiotensin-receptor blockers; eight patients, beta-blockers; and five patients, diuretics. The mean duration of the follow-up period was 4.1 $\pm$ 2.2 years. During that time there were 32 fatal events: 10 (31.3%) patients had a CVD death; two (6.3%) died because of acute myocardial infarction, one (3.1%) had a fatal ischemic stroke, and seven (21.9%) patients died because of exacerbation of chronic heart failure. The baseline clinical and biochemical characteristics of the survivors and non-survivors are presented in Table 1. As is evident, the non-survivors have lower BMI, hemoglobin, and RBC count, and higher oxLDL values. The non-survivors also had a lower glucose value; however, the glucose level is within a normal range in both groups.

Arterial stiffness and all-cause and cardiovascular disease mortality

The AS parameters for the survivors and non-survivors are presented in Table 2. By univariate analysis, lower SAE and PPP, and higher Alx and Alx@75 were associated with increased all-cause mortality. The LAE, brachial and aortic PWV, AP, and CPP for the study groups were comparable. Lower PPA showed a trend to association with higher all-cause mortality ($p = .08$). As the Kaplan—Meier survival curves demonstrate (Fig. 1), the incidence of all-cause (left) and CVD (right) deaths during follow-up was higher in PAD patients with SAE below the median value than in those with SAE above the median value. In the log-rank test, all-cause but not CVD mortality was related to Alx@75 ($p = .04$; $p = .89$, respectively). The oxLDL was related to CVD mortality ($p = .01$), but remained with borderline significance for all-cause mortality ($p = .08$). Conversely, when the population was divided according to the median value of LAE, brachial and aortic PWV and Alx, all-cause survival probability was not associated with AS ($p = .19$, $p = .89$, $p = .73$, $p = .24$, respectively). The variables that met the entry criterion ($p = .1$ in univariate analysis) were included in the Cox proportional hazard model: BMI, peripheral systolic BP, glucose, hemoglobin, RBC count, oxLDL, SAE, Alx, Alx@75, PPP, and PPA. The independent significant predictors of all-cause and CVD mortality were SAE and RBC count (Table 3).

The results of an additional Kaplan—Meier analysis for the four subgroups of PAD patients divided according to the median values of SAE and oxLDL or RBC count are shown in Fig. 2. The analysis revealed that oxLDL and RBC slightly
improved the prognostic value of SAE, which was confirmed by Cox analysis. Compared with patients with SAE above the median value and oxLDL below the median value, those with both SAE and oxLDL above the median value showed a 1.8-fold increase in the all-cause mortality risk (95% CI 0.45–7.32, p = .41). Also, patients with both SAE and oxLDL below the median value showed a 2.7-fold increase in the risk (95% CI 0.59–11.99, p = .20). The highest risk for future all-cause mortality was observed in patients with SAE below the median value and oxLDL above the median value (RR 4.6, 95% CI 1.3–16.0, p = .02). Compared with patients with both SAE and RBC count above the median value, those with SAE above the median and RBC below the median value had a 1.9-fold increase in risk (95% CI 0.48–7.7, p = .36). Patients with SAE below the median value and RBC above the median value had a 4.1-fold increase in risk (95% CI 1.13–14.89, p = .03). The highest risk for future all-cause mortality was observed in patients with both SAE and RBC count below the median value (RR 4.6, 95% CI 1.3–16.0, p = .02).

The area under the ROC curve (Fig. 3) was 0.70 for the model on the basis of age, BMI, smoking, total cholesterol, HDL-C, glucose, mean arterial pressure (MAP), heart rate, and ABI. When SAE and oxLDL were added to this model, the discriminatory power improved up to 0.82 (p = .006).

**DISCUSSION**

The present study is the first to evaluate the prognostic impact of AS in patients with symptomatic PAD. The main

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**Table 1. Clinical and biochemical characteristics of the study population.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors (n = 85)</th>
<th>Non-survivors (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.8 ± 8.1</td>
<td>62.9 ± 6.5</td>
<td>.43</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 ± 4.1</td>
<td>23 ± 2.9</td>
<td>.001</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>17 (20)</td>
<td>6 (19)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>31 (36)</td>
<td>15 (47)</td>
<td>.42</td>
</tr>
<tr>
<td>Smoking (past + current), n (%)</td>
<td>83 (98)</td>
<td>31 (97)</td>
<td>1.0</td>
</tr>
<tr>
<td>Peripheral systolic BP (mmHg)</td>
<td>141 (128–158)</td>
<td>135 (128–142)</td>
<td>.08</td>
</tr>
<tr>
<td>Peripheral diastolic BP (mmHg)</td>
<td>78 (73–84)</td>
<td>80 (74–83)</td>
<td>.62</td>
</tr>
<tr>
<td>Central systolic BP (mmHg)</td>
<td>129 (119–142)</td>
<td>126 (121–133)</td>
<td>.35</td>
</tr>
<tr>
<td>Central diastolic BP (mmHg)</td>
<td>79 (75–85)</td>
<td>80 (75–85)</td>
<td>.65</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>99 (93–109)</td>
<td>98 (92–106)</td>
<td>.53</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>66 (59–72)</td>
<td>67 (61–74)</td>
<td>.79</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>0.5 (0.3–0.6)</td>
<td>0.4 (0.1–0.5)</td>
<td>.17</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.9 ± 1.2</td>
<td>5.9 ± 1.1</td>
<td>.92</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.3 (1–1.4)</td>
<td>1.3 (1.1–1.4)</td>
<td>.31</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>4.2 ± 1.1</td>
<td>4 ± 1.2</td>
<td>.36</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.6 (1.3–2.1)</td>
<td>1.4 (1.2–1.7)</td>
<td>.16</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.5 (4.9–5.9)</td>
<td>5 (4.8–5.4)</td>
<td>.009</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>2.9 (1.1–7.7)</td>
<td>4.6 (2–7.7)</td>
<td>.16</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>78 (68–85)</td>
<td>72 (64–82)</td>
<td>.25</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>97 (85–111)</td>
<td>100 (88–116)</td>
<td>.61</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>149.5 ± 14.9</td>
<td>141.4 ± 16.7</td>
<td>.02</td>
</tr>
<tr>
<td>Red blood cells count (x 10¹²/L)</td>
<td>4.9 (4.5–5.1)</td>
<td>4.7 (4–4.9)</td>
<td>.009</td>
</tr>
<tr>
<td>oxLDL (U/L)</td>
<td>78 (57–111)</td>
<td>128 (95–177)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Values are mean (±SD), median (with 25% and 75% percentiles) or prevalence (%). BP, blood pressure; hsCRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate; oxLDL, oxidized low-density lipoprotein cholesterol.

* Values are available for 113 patients.

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**Table 2. Arterial stiffness parameters of the study population.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors (n = 85)</th>
<th>Non-survivors (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAE index (mL/mmHg × 10)</td>
<td>12.1 (8.8–15.6)</td>
<td>12.4 (10–15.1)</td>
<td>.73</td>
</tr>
<tr>
<td>SAE index (mL/mmHg × 100)</td>
<td>2.9 (2.3–3.8)</td>
<td>2.1 (1.8–2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Augmentation index (%)</td>
<td>32 (26–39)</td>
<td>38 (31–41)</td>
<td>.03</td>
</tr>
<tr>
<td>Augmentation index@75 (%)</td>
<td>28.1 ± 8.5</td>
<td>31.7 ± 7.2</td>
<td>.03</td>
</tr>
<tr>
<td>Aortic PWV (m/s)</td>
<td>10 ± 2.5</td>
<td>10.2 ± 2.1</td>
<td>.78</td>
</tr>
<tr>
<td>Brachial PWV (m/s)</td>
<td>8.8 ± 1.4</td>
<td>8.7 ± 1</td>
<td>.77</td>
</tr>
<tr>
<td>Augmentation pressure (mmHg)</td>
<td>16.5 ± 6.9</td>
<td>17.7 ± 5.5</td>
<td>.31</td>
</tr>
<tr>
<td>Peripheral pulse pressure (mmHg)</td>
<td>61 (53–70)</td>
<td>58 (51–62)</td>
<td>.04</td>
</tr>
<tr>
<td>Central pulse pressure (mmHg)</td>
<td>50 (43–57)</td>
<td>47 (42–52)</td>
<td>.20</td>
</tr>
<tr>
<td>Pulse pressure amplification</td>
<td>23 (16–30)</td>
<td>20 (13–24)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Values are mean (±SD), median (with 25% and 75% percentiles) or prevalence (%). LAE, large artery elasticity; SAE, small artery elasticity; PWV, pulse wave velocity.
The present results are in good agreement with previous data. Wan et al. demonstrated that the probability of a CVD event or CVD death in patients with coronary artery disease increased with a decrease in SAE.22 A prospective analysis of participants who were initially free from symptomatic CVD demonstrated that SAE provided predictive information about myocardial infarction, coronary heart death, angina, heart failure, stroke, and PAD.23 Lower SAE was incrementally associated with the incidence of hypertension among normotensive adults free from CVD24 and CVD events independently of age.24 Both SAE and LAE were associated with subclinical coronary atherosclerosis in a multi-ethnic middle-aged cohort free from CVD.25

Although patients with PAD are at an increased CVD risk compared with age-matched controls, only a few studies have been conducted to demonstrate associations between vascular function and outcome in PAD patients. Impaired brachial artery endothelial function independently predicts postoperative17 and long-term CVD events,18,19 as well as adding to the prognostic value of ABI in PAD patients.20 Increased AS has been reported in patients with PAD compared with age-matched controls,12,13 and there is a link between increased AS and atherosclerotic complications.9 However, there are no data about an association between AS and outcome in PAD patients. The main novel finding in this study that lower SAE predicts all-cause and CVD mortality in PAD patients after adjustment for potential confounders, emphasizes the pathophysiological link between AS and clinical outcome in patients with systemic atherosclerosis.

Several mechanisms can account for the association between increased AS and worse outcome in patients with PAD. The AS may favor fatal cardio- and cerebrovascular events through acceleration of atherosclerosis and increase of CPP.26 Elevated PP may also induce arterial remodeling by increasing wall thickness, and promoting development of plaques.10 Higher PP is independently associated with arterial plaque ulceration in patients with symptomatic carotid stenosis, supporting the hypothesis that cyclical hemodynamic forces are important determinants of plaque rupture.11 Elevated central BP and thromboembolism, subsequent to plaque rupture caused by stiff arteries, may explain the association between increased AS and poor outcome in patients with atherosclerosis.

Wilkins et al. demonstrated that decreased SAE was significantly associated with lower ABI values in apparently healthy persons, whereas LAE was less strongly associated with ABI.15 The ABI also correlated with SAE in patients with PAD but its association with LAE was only borderline.27 Although PAD is primarily a disease of the large muscular arteries, it is clear that SAE is an important determinant of CVD risk in patients with symptomatic PAD.
arteries, the observation that prognosis was associated with SAE, which represents the oscillatory or reflective component of the small muscular arteries and arterioles, indicates a specific link between changes in the distal vascular bed and global and CVD mortality risk. The flow of blood into the lower extremities depends not only on the severity of atherosclerosis but also on the regulatory mechanisms that govern the microcirculatory blood flow, including modulation of vasodilator and vasoconstrictor activity in skeletal muscle. In the advanced stages of PAD, microvascular abnormalities become more prominent, representing inadequate compensatory collateral circulation, and may contribute to the symptomatology of the disease. \(^2\) Stiffening of the small arteries alters the magnitude and timing of reflected waves and increases central BP and left ventricular afterload. Thus, a decrease of SAE, rather than changes in the mechanical properties of the large muscular arteries supplying the lower extremity exerts a stronger impact on the association of vascular dysfunction with severity and outcome in patients with PAD.

Abnormal large artery stiffness is associated with major CVD end points, including heart disease, stroke, and chronic kidney disease. However, this study failed to find an association between LAE and aortic PWV, the gold standard measure of AS, in PAD patients’ prognosis. Nor did the recent PARTAGE study find significant association between aortic PWV and total mortality or major CVD events, while only lower PPA was associated with poor prognosis in the very elderly. \(^2\) Brand et al. showed that aortic PWV was markedly attenuated in patients with advanced PAD and an index of the central PP/aortic PWA mismatch predicted the presence of critical limb ischemia better than alternative vascular indices. \(^3\) This study demonstrated that RBC count itself predicts all-cause and CVD mortality, and RBC count as well as oxLDL adds to the predictive value of SAE in determining the risk for all-cause mortality in patients with PAD. Previous studies have shown that oxLDL is a predictor

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**Figure 2.** Left, Kaplan–Meier survival curves for a subgroup of patients showing higher or lower than the median values of small artery elasticity (SAE) and oxidized LDL (oxLDL). A combination of lower than median SAE and higher than median oxLDL is associated with the highest risk for future all-cause mortality. Right, Kaplan–Meier survival curves for a subgroup of patients showing higher or lower than the median values of small artery elasticity (SAE) and red blood cells (RBC) count. Patients with SAE below the median value and RBC count above the median value had a significantly increased risk of future all-cause mortality. The highest risk was observed in patients with both SAE and RBC count below the median value.

**Figure 3.** Receiver-operating characteristic (ROC) analysis of the conventional risk factors (age, BMI, smoking, total cholesterol, HDL-C, glucose, MAP, heart rate, ABI), small artery elasticity (SAE) and a combination of SAE and oxidized LDL (oxLDL). The area under the ROC curve for 4.1-year mortality is the lowest for only the conventional risk factors (0.70, 95% CI 0.60–0.80 (model 1)), followed by a combination of the conventional risk factors with SAE (0.78, 95% CI 0.68–0.87 (model 2)), and the highest for a combination of the conventional risk factors with SAE and oxLDL (0.82, 95% CI 0.73–0.92 (model 3)). Model 1 vs. Model 2 (p = .03); Model 1 vs. Model 3 (p = .006); Model 2 vs. Model 3 (p = .14).
of all-cause mortality and improves the reclassification capacity of Framingham-derived risk functions. Anemia is also a common and an independent prognostic factor for mortality in CVD patients. There are several limitations to the present study. First, the study examined male subjects with established atherosclerosis and the findings may not be generally applicable. Second, a limitation of this study is the potential confounding effect of smoking and medications on AS. Third, measures of central hemodynamics, arterial stiffness, and Windkessel-derived arterial elasticity indices may be subject to substantial under- or overestimation in patients with PAD caused by luminal stenosis in various arterial segments. Fourth, the cause of death was obtained from death certificates using a telephone interview with the patients’ general practitioners or relatives. A recent systematic review emphasizes the need to improve global methodologies of mortality measurement, because of long-held discrepancies between clinical and postmortem diagnosis. Finally, the small number of subjects is also a potential limitation of the study.

CONCLUSIONS

This study provides the first evidence, obtained from an observational study, that decreased small artery elasticity is an independent predictor of all-cause and CVD mortality in patients with symptomatic PAD. This finding further supports the relevance of arterial dysfunction in progression of CVD and suggests that symptomatic PAD patients with stiffer arteries are at an increased risk of all-cause and CVD mortality. Non-invasive arterial phenotype testing might improve prediction of prognosis and have clinical utility for management of patients with systemic atherosclerosis.

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CONFLICT OF INTEREST

None.

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