Arterial stiffness and 5-year mortality in patients with peripheral arterial disease

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Abstract:	Arterial stiffness (AS) is a risk factor which coexist in high-risk populations including peripheral arterial disease (PAD). However, the prognostic impact of arterial stiffness in PAD remains to be defined. We investigated whether aortic Pulse Wave Velocity (aPWV) and Augmentation index normalized to 75 beats/min (Aix @75HR) predict total mortality (all-cause and cardiovascular mortality) in patients with PAD. In 231 PAD with ABI ≤0.9 at rest or with a positive Treadmill test performed on the borderline group (ABI=0.91-0.99) and 167 No-PAD (ABI ≥ 0.91<1.3) patients aPWV and Aix @75HR were evaluated using arterial tonometry and ABI were obtained using an 8-MHz Doppler probe. Total mortality rates in relation to ABI, aPWV and Aix@75HR were analyzed using Cox regression model. During a mean follow-up of 5.4±2 years 39 (16.9%) deaths occurred in PAD patients and 8 (4.8%) in those No-PAD. In the PAD group, the aPWV was associated with increased risk for total mortality (HR=1.14, 95% CI, 1.03-1.26; p=0.016) independent of cardiovascular risk factors and CAD history. In conclusion, in PAD patients aPWV is also an indicator of total mortality that could be useful for risk stratification.

Arterial stiffness and 5-year mortality in patients with peripheral arterial disease

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Arterial stiffness (AS) is a risk factor which coexist in high-risk populations including peripheral arterial disease (PAD). However, the prognostic impact of arterial stiffness in PAD remains to be defined. We investigated whether aortic Pulse Wave Velocity (aPWV) and Augmentation index normalized to 75 beats/min (Aix @75HR) predict total mortality (all-cause and cardiovascular mortality) in patients with PAD. In 231 PAD with ABI ≤0.9 at rest or with a positive Treadmill test performed on the borderline group (ABI=0.91-0.99) and 167 No-PAD (ABI ≥ 0.91<1.3) patients aPWV and Aix @75HR were evaluated using arterial tonometry and ABI were obtained using an 8-MHz Doppler probe. Total mortality rates in relation to ABI, aPWV and Aix@75HR were analyzed using Cox regression model**.** During a mean follow-up of 5.4±2 years 39 (16.9%) deaths occurred in PAD patients and 8 (4.8%) in those No-PAD. In the PAD group, the aPWV was associated with increased risk for total mortality (HR=1.14, 95% CI, 1.03-1.26; p=0.016) independent of

cardiovascular risk factors and CAD history. In conclusion, in PAD patients aPWV is also an indicator of total mortality that could be useful for risk stratification.

INTRODUCTION

Peripheral arterial disease (PAD) is a cardiovascular disease highly prevalent in the elderly and in individuals with conventional cardiovascular risk factors (diabetes type 2, smoking history and hypertension). [1] The Ankle-brachial index (ABI) represents the primary noninvasive screening test for the diagnosis of PAD. [2] The ABI (≤0.9) is also an indicator of generalised atherosclerosis, as it has been associated with higher rates of concomitant coronary and cerebrovascular disease. [3] PAD patients with and without leg ischaemic symptoms have a three-fold increase in risk of myocardial infarction, stroke and all-cause and cardiovascular mortality compared to those without PAD. [4-6] The increase in PAD-associated mortality may be mediated, through generalized atherosclerotic disease [7] that directly contributes to the development of arterial stiffness. [8-11] To our knowledge however, the impact of arterial stiffness on mortality remains to be demonstrated. [12] The aim of our study was to investigate whether aortic Pulse Wave Velocity (aPWV) and Augmentation index, normalized to 75 beats/min (Aix@75HR), predict total mortality (all-cause and cardiovascular mortality) in patients with PAD beyond traditional risk factors and coronary artery disease (CAD) history.

METHODS

Study Population

A total of 722 subjects referred to the Angiology Unit, Research Center on Vascular Diseases, University of Milan L. Sacco Hospital were evaluated for non-invasive vascular tests: the Pulse Wave Analysis (PWA), was used to measure the Augmentation index, normalized to 75 beats /min (Aix@75HR), and aortic Pulse Wave Velocity (aPWV) to evaluate aortic stiffness. The Ankle-brachial index (ABI) at rest was performed to diagnose PAD (ABI ≤0,90) at rest or with a positive Treadmill test performed on the borderline group (ABI=0.91-0.99). [2] We excluded patients with

known cancer, recent myocardial infarction and or stroke, (during the past 6 months), critical limb ischemia (CLI) and subjects with high ABI (≥1,3) that suggested poorly compressible, calcified arteries and in those without palpable femoral pulses, that indicated the presence of bilateral iliac disease which could cause inaccurate aPWV measurements.[13] Patients with cardiac dysrhythmias, such as atrial fibrillation, pacemakers and frequent extra systole were also excluded. The final study group included a total of 398 subjects age range (40-95 years), divided into 2 groups: the first was composed of 231 patients with PAD (ABI ≤0.9) and the second of 167 No-PAD (ABI ≥ 0.91 ≤1.3). All participants had been informed about the study protocol and gave their informed consent to participate in the study. Participants were followed up between July 2008 and July 2017.

Risk factors PAD CAD and CVD definitions

For data collection, history was taken and medical records were reviewed. Traditional cardiovascular risk factors were assessed: age, gender, smoking history, hypertension, diabetes type 2, dyslipidemia. Arterial hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at the time of the visit (mean of two readings) or history of hypertension or use of antihypertensive medication (diuretics, α-blockers, β-blockers, Angiotensin-converting enzyme inhibitors, AT2-blockers or Ca-antagonists). Type 2 diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL or history of diabetes or of use of diabetes medication (insulin or oral hypoglycemic agents). Dyslipidemia was defined as total serum cholesterol >200 mg/dL or in treatment with statins and/or fibrates. Patients with intermittent claudication (IC) or with a history of lower limb revascularization (arterial bypass, angioplasty or stenting) were also considered as having PAD. [2] Asymptomatic PAD was defined as a resting ABI ≤0,9 with an absence of prior lower-extremity peripheral vascular events or clinical symptoms indicative of intermittent claudication. Critical limb ischemia (CLI) was defined as limb pain that occurs at rest and that may be accompanied by tissue loss (ischemic ulcer or gangrene). Coronary artery disease (CAD) and Cerebrovascular disease (CVD) were assessed by clinical history

(myocardial infarction, stroke) or interventions. Patients with asymptomatic carotid stenosis were not classified as CVD. Height and weight were measured and body mass index was calculated as weight to height squared (kg/h²). The primary endpoint was total mortality (all-cause and cardiovascular mortality).

Arterial stiffness and ABI measurement protocol

Pharmacologic treatment was suspended (when possible) 12 hours before the measurements. Patients rested in a supine position for 5-10 minutes in a quiet room in a comfortable environment at a temperature of 22±1° C. The protocol of sequential measurements in the laboratory included: Brachial blood pressure measurement in the dominant arm using a standard mercury sphygmomanometer. Three readings were taken separated by 2-minute intervals, and the average was used for analysis. Peripheral pulse pressure (PP) was calculated as the difference between SBP and DBP. Arterial tonometry was performed using the SphygmoCor device (AtCor Medical, Sydney, Australia) in radial, carotid, and femoral arteries. [14] Radial pressure waveform was calibrated to brachial SBP and DBP measurements (obtained with the sphygmomanometer). The mean arterial pressure (MAP) was calculated integrating the calibrated radial pressure wave. Central pressure was determined using a transfer function from the radial artery pressure waveform. [15] Augmentation pressure (AP) was defined as the difference between the second and the first systolic peak, of the derived aortic pressure waveform. The augmentation index (Aix) was defined as the difference between the second and first systolic peaks of the central arterial waveform, expressed as a percentage of the central pulse pressure. In addition, as Aix is influenced by heart rate, it was normalized for a standard heart rate of 75 bpm (Aix@75) in accordance with Wilkinson et al. [16] Aortic pulse wave velocity (aPWV) was measured by sequentially recording electrocardiography (ECG)-gated carotid and femoral artery waveforms. Wave transit time was calculated by software using the R wave of a simultaneously recorded ECG as a reference frame. The distance between the carotid and the femoral sampling sites was measured above the surface of the body with a tape. aPWV was determined by dividing the distance between the two recording

sites by the wave transit time. All measurements were made by one investigator (GS) in duplicate and mean values were used for the final analysis. Immediately after measurement of the arterial stiffness variables, the ankle systolic BP measurements for ABI calculation was obtained by two operators using an 8-MHz Doppler probe and a BP cuff after 10 minutes of rest with the patient in a supine position. The systolic pressure was measured on either the posterior tibial or dorsalis pedis artery. ABI was calculated by dividing the higher of the two ankle systolic blood pressures in each leg by the higher of the two brachial systolic blood pressures. The higher of the two brachial pressures was used as the denominator to account for the possibility of subclavian artery stenosis, which can decrease the blood pressure in the upper extremity. Peripheral arterial disease was defined as ABI ≤0,9 at rest or after Treadmill test performed on the borderline group (ABI=0.91-0.99) to confirm PAD. The lowest ABI values were used for statistical analysis.

Follow-Up

Follow-up time was defined by the time from the baseline visit until the event date was censored at the last contact date. Information on events were obtained through follow-up visits, phone interviews and familial contacts. All deaths included in analysis were validated by research doctors who were unaware of the patient's arterial stiffness tests using source data. Death as result of acute myocardial infarction, stroke, or heart failure was defined as a cardiovascular death.

Statistical analysis

Statistical analyses were performed using the statistical software JMP, version 10.0, SAS Institute Inc. 2012. Continuous variables were reported as mean ± SD, categorical variables as percentages for all patients. The statistical assessment of data was performed by Student t-test for numeric data and Pearson χ^2 for categorical data. Prognostic factors of mortality were identified by use of Cox proportional hazards regression model ABI, aPWV, Aix@75 were included as a continuous variables in the adjusted statistical model, along with the risk factors (age, sex, diabetes type 2,

dyslipidemia, hypertension, smoking history and CAD history). Survival curves were estimated by use of the Kaplan-Meier method and compared by using the Log-rank test. Variables were considered prognostic when they were found to be statistically significant (P<0.05).

RESULTS

Baseline characteristics

The study group was composed of 398 subjects: 231 PAD patients and 167 No-PAD (Tables I). Referring to No-PAD, PAD patients showed a higher prevalence of common risk factors: hypertension (p<.0001), smoking history (p<.0001), type 2 diabetes mellitus (p=0.015) and CAD history (p=0.0016). In PAD patients the ABI was lower (p<.0001), SBP-brachial artery, PP-brachial artery aPWV and Aix@75 were higher (p<.0001), (p<.0001), (p=0.002); (p=0.010).

71% of PAD patients were found to be asymptomatic Pharmacological treatment with anti-platelets, calcium-channel-blockers, ACE-I, β-blockers, ARBs, diuretics, statins and antidiabetics was significantly higher in PAD patients.

All-cause and CV mortality in PAD and No-PAD groups

During a mean follow-up of 5.4±2 years we observed 39 (16.9%) deaths of 231 PAD and 8 (4.8%,) of 167 No-PAD. Table 2 shows that when PAD and No-PAD groups were examined the age and aPWV was directly associated with total mortality (p=0.009) (p=<.0001) while ABI was inversely associated (p=0.018). In the analysis carried out in PAD patients alone the aPWV was directly associated with total mortality (p=0.011). Table 3 shows the results of a Cox multivariate regression model adjusted for multiple CV risk factors, (age, hypertension, diabetes type 2, smoking history, dyslipidemia) and previous CAD history. The aPWV, age and ABI were associated with a significant increase in total mortality risk: (p= 0.001), (p= 0.009) (p= 0.018) respectively, while Aix @75HR did not (p= 0.844). A separate analysis carried out in PAD patients showed that aPWV was associated with total mortality (p=0.016). In PAD and No-PAD total mortality was from all-cause

(77%-75%) while CV mortality (myocardial infarction, stroke) was respectively 23% - 25%.(Figure 1). In both groups the most frequent cause of death was due to cancer (ie, lung, gastric, colon, leukemia/lymphoma and renal), followed by chronic obstructive pulmonary disease (COPD) and renal failure.

Survival analysis for PAD and Non-PAD groups

Figure 2 shows the survival distribution of the two ABI groups for total mortality. In particular, the Kaplan-Meier survival curves showed that the survival rate was lower in the PAD group (Log-rank p=0.0003). In PAD patients, (Figure 3) the survival in the third tertile of aPWV (≥11,5 m/s) is statistically lower (Log-rank test p=0.0005) with respect to the first tertile (≤9,3m/s). Table 4 shows that in PAD no-survivors with respect to survivors age and aPWV were higher (p=0.0001), (p<.0001) while the ABI and the use of cardiovascular drugs (antiplatelet, lipid-lowering, anti-hypertensives) were comparable.

DISCUSSION

In both sexes the presence of PAD is regarded as a marker of atherosclerosis in other vascular beds, and many epidemiological studies support the finding that PAD is a strong prospective predictor of all cause and cardiovascular mortality. [4-7] Our results have confirmed that these findings were also true for individuals referred to our vascular center for the evaluation of PAD. In particular, our analysis revealed that after further adjustment for potential confounders, a low (≤0.9) ABI value was strongly and inversely correlated with total mortality (Table 2) and the Kaplan-Meier survival curves showed that the survival rate was significantly lower in the PAD group compared with the normal ABI group (Figure 2). It has been hypothesized that increased PAD-associated mortality may be mediated by presence of systemic atherosclerosis that leads to arterial stiffening [17] thus the question addressed in this study was whether higher arterial stiffness is associated with total mortality (all cause and CV mortality). The results of the present study show that aPWV, considered the "gold standard" of arterial stiffness, but not Aix@75HR, is associated with total mortality in overall subjects. This predictive value of aPWV remained significant in PAD patients. independently of classic risk factors (hypertension, smoking history, type 2 diabetes, dyslipidemia) and CAD history often present in such patients. These observations are in accordance with the conclusions drawn in previous longitudinal studies, where the aPWV was proven to be an independent predictor of all-cause and cardiovascular mortality in the general population, [18,19] in patients with risk factors and conditions associated with PAD such as: type 2 diabetes, [20] hypertension [21] end-stage renal disease (ESRD). [22] To the best of our knowledge, only a recent study by Kals et al examined the predictive role of aPWV and Aix in PAD patients. [12]

The same Authors in a cohort of 117 men (aged 62,3±7,7 years) symptomatic PAD patients prospectively recruited between 2002 and 2010 reported 32 fatal events during the follow-up period (mean 4.1±2.2 years). In this study, decreased small artery elasticity was an independent predictor of all-cause and CVD mortality; in contrast aPWV and Aix were not. The reasons for this discrepancy in results are. not clear however, we believe that the characteristics found in the

patients in the Kals et al study may explain the different results from our current study. In other words, the study by Kals et al had patients with a lower average ABI of 0.40 and of the 117 patients studied, 75 had stage II, 29 stage III, and 13 stage IV chronic ischemia as defined by Fontaine, while our study had an average ABI value of 0.68 and 71% were asymptomatic (stage I Fointaine), indicating a less severe population of PAD. It has been reported that in patients with severe PAD the aPWV measurement can result falsely low [13,23] and this could condition the predictive result of the aPWV. How the aortic stiffness is associated with a decreased survival rate in PAD patients did not readily identifiable in our study. However it is possible that the overlapping of common vascular risk factors (aging, smoking, diabetes, obesity, metabolic syndrome or insufficient physical activity) and the existence of common pathogenetic mechanisms (chronic inflammation, increased oxidative stress) [24] may contribute to aortic stiffening, atherosclerosis, and risk for the development of several malignancies (eg, lung cancer). [25,26]

Potential implications

It has been widely documented that ABI has a prognostic role identifying patients with very high risk of mortality, independently of the presence or absence of symptoms. Compared to other diagnostic methods, ABI is superior because of its simplicity, being very easy to routinely determine in all patients and because it is a non-invasive test. Our observation that aPWV is associated with total mortality could have important implications. Compared to PAD survivors, PAD No-Survivors showed no differences in average ABI values (p=0.324) but a higher average aPWV (p=0.0001) (Table 4) and the Kaplan-Meier curves showed that survival in the third tertile of aPWV was significantly lower (Log-rank test p=0.0005) with respect to the first tertile (Figure 3). Therefore, aPWV measurement in a less severe population of PAD could be useful to stratify risk of mortality [27,28] in patients with known atherosclerotic disease.

Study limitations

The present study must be interpreted within the context of its potential limitations. First, this study consisted of patients with mean age 68±8 years and less severe PAD, and thus the results may not apply to young PAD populations or to severe PAD patients.

CONCLUSIONS

This study provides further evidence in support of previous studies that have demonstrated an independent association between aPWV and mortality expanding understanding of the prognostic importance of arterial stiffness in atherosclerotic PAD patients. Even though it is very likely, further studies are required to confirm these results and to evaluate whether along with ABI, routine evaluation of aPWV could be helpful for risk stratification.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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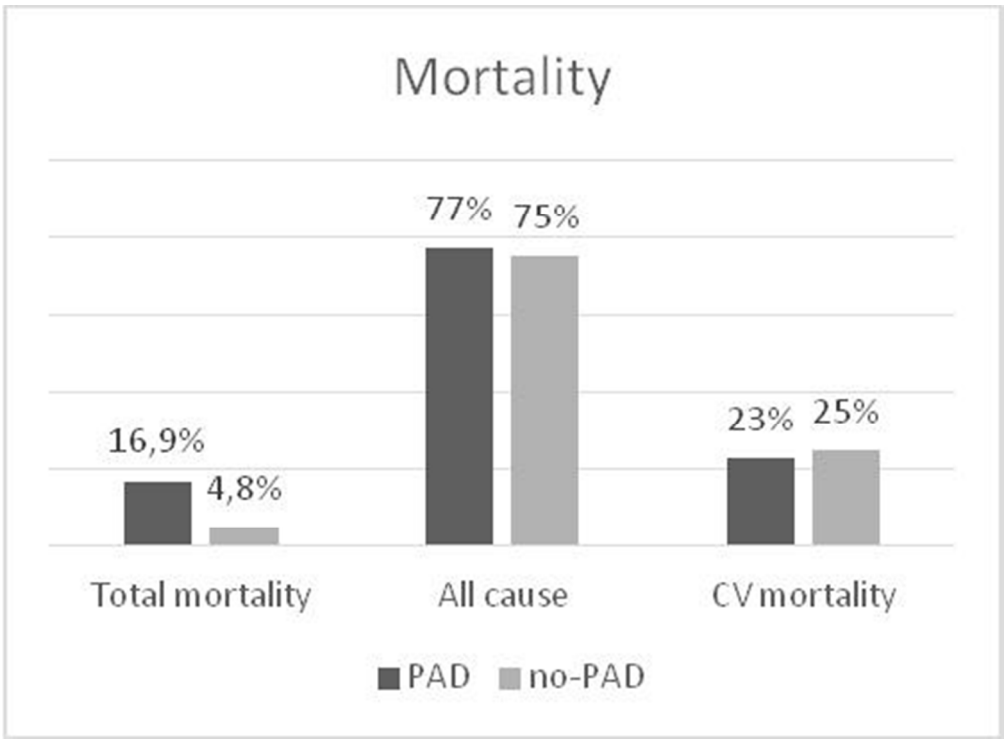

All-cause and CV mortality in PAD and No-PAD

133x97mm (96 x 96 DPI)

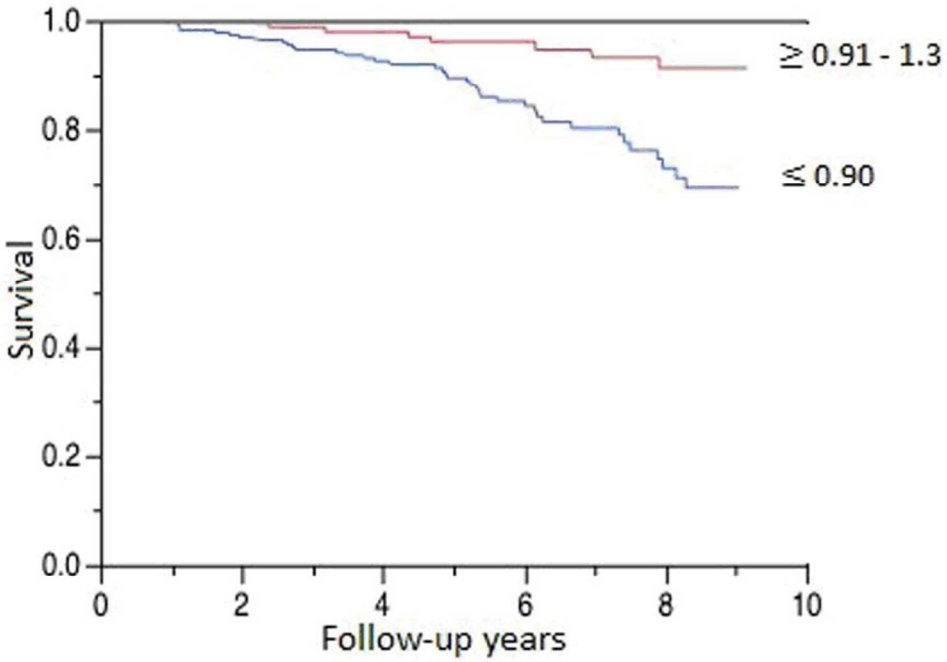

Figure 2. Kaplan-Meier survival curves from total mortality in the population study according to the level of ABI.Comparison between survival curves were statistically significant (Log-rank test (p=0.0003).

250x171mm (96 x 96 DPI)

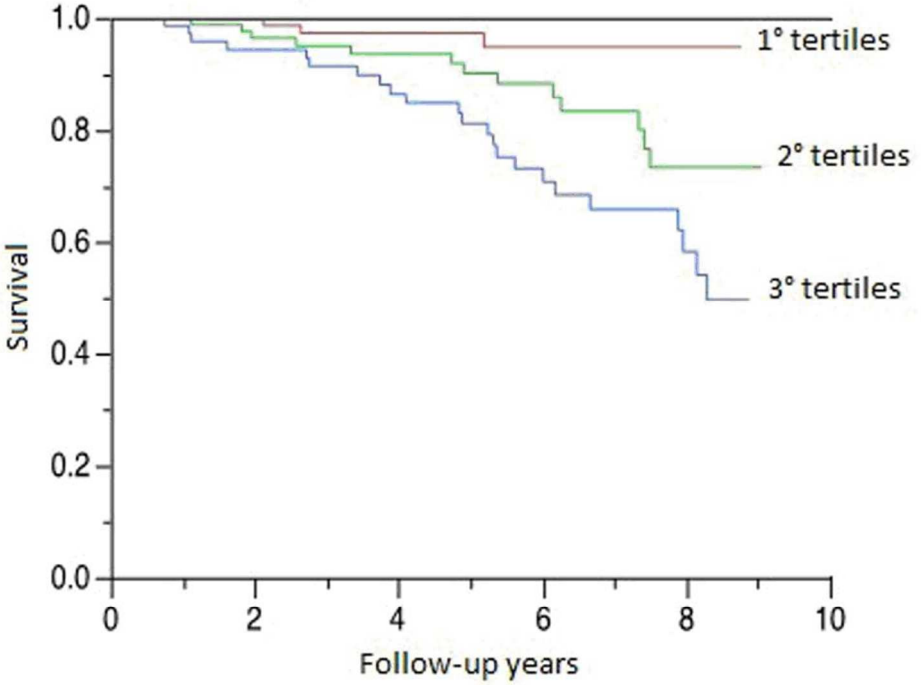

Figure 3. Kaplan-Meier survival curves from total mortality in the PAD according to the level of aPWV divided into teriles.Comparison between survival curves were statistically significant (Log-rank test (p=0.0005)

273x193mm (96 x 96 DPI)

Table 1 - Clinical and demographic characteristic of study population

Parameters	Overall n°398	PAD n°231	No-PAD n°167	p-value
Age (years) - Mean (SD)	68±9	69±9	68±7	0.221
Sex male, n %	294 (74)	169 (73)	125 (75)	0.704
Height (cm) - Mean (SD)	164±9	164±9	165±9	0.234
Weight (kg) - Mean (SD)	74±12	74±12	75±12	0.361
BMI (kg/m^2) - Mean (SD)	27±4	27±4	27±4	0.970
Hypertension - n (%)	280 (70)	190 (82)	90 (54)	<.0001
Type 2 diabetes - n (%)	149 (37)	98 (42)	51 (31)	0.015
Dyslipidaemia - n (%)	259 (65)	158 (68)	101 (60)	0.122
Smoking history – n (%)	214 (54)	164 (71)	50 (30)	<.0001
CAD history - n (%)	96 (24)	69 (30)	27 (16)	0.0016
CVD history - n (%)	16 (4)	12 (5)	4 (2)	0.160
Anti-Platelets, n (%)	187 (47)	139 (60)	48 (29)	<.0001
Calcium-channel-blockers, n (%)	68 (17)	53 (23)	15 (9)	0.0007
ACE-I, n (%)	91 (23)	68 (29)	23 (14)	0.0002
β-blockers, n (%)	89 (21)	60 (26)	29 (17)	0.041
ARBs, n (%)	82 (21)	60 (26)	22 (13)	0.001
Diuretics, n (%)	34 (9)	26 (11)	8 (5)	0.022
Statins, n (%)	130 (33)	96 (42)	34 (20)	<.0001
Antidiabetics, n (%)	98 (25)	68 (29)	30 (18)	0.008
SBP - brachial artery (mmHg)	138±21	142±21	132±20	<.0001
DBP - brachial artery (mmHg)	80±10	79±10	80±10	0.084
PP - brachial artery (mmHg)	58±19	63±19	52±16	<.0001
Mean Arterial Pressure (mmHg)	100±13	101±12	99±13	0.206
Heart rate (bpm)	68±11	68±11	68±11	0.425
Aix @75HR (%)	28±8	29±8	27±9	0.010
aPWV	10,4±2,6	10,8±2,6	9,9±2,2	0.002
Ankle Brachial Index	0,85±0,2	0,68±0,2	1,06±0,1	<.0001

BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular disease; ACE-I: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, PP: Pulse Pressure; Aix @75HR: aortic augmentation index corrected for heart rate 75; c-fPWV: carotid-femoral Pulse Wave Velocity.

Table 2 - Multivariate regression analysis in overall subjects and PAD patients

	Variables	Estimate	95% CI	P value
Overall subjects	aPWV (m/s)	0.160	0.065 - 0.252	<.0001
	Age	0.056	0.013 - 0.100	0.009
	ABI	-1.673	-3.060 - 0.285	0.018
	Aix @75HR (%)	-0.002	0.042 - 0.036	0.887
PAD	aPWV (m/s)	0.136	0.031 - 0.236	0.011
	Age	0.042	-0.001 - 0.089	0.061
	Aix @75HR (%)	-0.016	-0.065 - 0.034	0.530

Table 3 - Hazards Ratio Analyses of total mortality in overall subjects and PAD patients

	Variables	Hazard Ratio	95 % CI	P value
Overall subjects	aPWV	1.17	1.06 - 1.28	0.001
	Age	1.05	1.01 - 1.10	0.009
	ABI	0.18	0.04 - 0.75	0.018
	Aix@75HR	0.99	0.95 - 1.04	0.844
PAD	aPWV	1.14	1.03 - 1.26	0.016
	Age	1.04	0.99 - 1.09	0.061
	Aix@75HR	0.98	0.93 - 1.03	0.530

Adijusted for age, sex, hypertension, diabetes, dislypidemia, smoking history, CAD history. CI, confidence interval.

Table 4 - Clinical characteristic of Survivors and Non-survivors PAD patients

Parameters	Survivors (192)	No-survivors (39)	p-value
Age (years) - Mean (SD)	68±10	73±6	0.0001
aPWV	10,3±2,6	12,6±2,9	<.0001
Ankle Brachial Index	0,69±0,2	0.66±0,2	0.324
Aix @75HR (%)	29±8	28±6	0.528
Sex male, n (%)	138 (72)	31 (79)	0.328
BMI (kg/m^2) - Mean (SD)	28±4	27±3	0.800
Hypertension, n (%)	155 (81)	35 (90)	0.179
Type 2 diabetes, n (%)	76 (40)	22 (56)	0.052
Dyslipidaemia, n (%)	135 (70)	22 (56)	0.089
Smoking history, n (%)	141 (73)	23 (59)	0.069
CAD history, n (%)	56 (29)	13 (33)	0.064
CVD history, n (%)	9 (5)	3 (8)	0.440
Anti-Platelets, n (%)	121 (63)	18 (46)	0.049
Lipid lowering therapy	82 (43)	14 (36)	0.431
Anti - hypertensives therapy	134 (70)	25 (64)	0.484