Integrated central blood pressure- aortic stiffness risk score for cardiovascular risk stratification in chronic kidney disease

Running title: ICPS risk score for CV risk stratification in CKD

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Abstract

Background and aims: Our objective was to develop an integrated central blood pressure-aortic stiffness (ICPS) risk score to predict cardiovascular events.

Methods: It was a retrospective cohort study. One hundred chronic kidney disease (CKD) patients on conservative therapy were included. Pulse wave velocity (PWV), central systolic blood pressure (cSBP) and central pulse pressure (cPP) were measured. A score was assigned to tertiles of PWV (0 to 2), cPP (0 to 2) and cSBP (0 to the first and second and 1 to the third tertile) based on each parameter's ability to individually predict cardiovascular outcome. The sum of these scores and three ICPS risk categories as predictors were studied. Finally, we compared discrimination of the ICPS risk categories with PWV, cSBP and cPP.

Results: Adjusted for age and sex, patients in high and very high ICPS risk categories had increased cardiovascular risk (HR: 3.52, 95%CI: 1.65-7.49, HR: 7.56, 95%CI: 3.20-17.85, respectively). High and very high ICPS risk categories remained independent predictors in a model adjusted for multiple CV risk factors (HR: 4.58, 95%CI: 1.65-7.49, HR: 8.56, 95%CI: 3.09-23.76, respectively). ICPS risk categories (Harrell's C: 0.723, 95%CI: 0.652-0.795) showed better discrimination than PWV (Harrell's C: 0.659, 95%CI: 0.586-0.732, p=0.028) and cSBP (Harrell's C: 0.660, 95%CI: 0.584-0.735, p=0.008) and there has been a tendency of significance in case of cPP (Harrell's C:0.691, 95%CI: 0.621-0.761, p=0,170).

Conclusions: The ICPS score may clinically importantly improve the identification of CKD patients with elevated cardiovascular risk.

Keywords: chronic renal failure, central blood pressure, central pulse pressure, pulse wave velocity, survival analysis

Introduction

Given that cardiovascular (CV) diseases are still the leading causes of mortality worldwide and that an armamentarium of effective preventive medications is available, it is of utmost importance to accurately predict CV risk in different populations to increase the health benefits of CV prevention (5). One group of contenders that may improve CV risk prediction over and above the classical parameters are measurements that describe arterial stiffness and central hemodynamic status. These parameters have been extensively investigated in the past two decades. In all stages of chronic kidney disease (CKD) arterial stiffness is an important risk factor for cardiovascular events and mortality (13).

The most important marker of arterial stiffness is the carotid-femoral pulse wave velocity (PWV). It was found to be predictive in different patient populations and is included in the European hypertension guidelines since 2007. However, the most recent European guideline on CV risk prevention advised against its use for CV risk assessment in the general population (12).

Among parameters describing central hemodynamics, central systolic blood pressure (cSBP, a measure of pressure load) and central pulse pressure (cPP, describing pulsatility) seem to be the most promising, as they have better predictive values compared to brachial systolic and pulse pressure in some conditions (1, 7), although no additional advantage was found compared to brachial pressure in the Framingham Heart Study (8).

Another measure, the augmentation index (Aix) is a wave reflection parameter that also describes total peripheral resistance. It has also been reported to be an independent predictor of CV outcomes (6), but results are conflicting (8, 11).

Although most available literature on arterial stiffness investigates the predictive power of stiffness parameters individually, given that PWV, cSBP, cPP and Aix can be obtained with most available devices at a single measurement, and that they reflect different aspects of the vasculature, it seems reasonable to combine their results into a single score to predict vascular events.

Our aims were to investigate in CKD patients on conservative therapy (1) the predictive power of PWV, cSBP, cPP and Aix individually for CV events, (2) to translate these parameters into simple scores based on their tertiles, (3) to establish and test for CV prediction an integrated parameter as the sum of these scores and based and these scores,

different risk categories and (4) to test whether the integrated score-based risk category concept improves CV prediction compared with its components separately.

Methods

It was a retrospective cohort study. Scientific results from this cohort were published previously (1, 10). Patients were recruited from two tertiary care nephrology outpatient clinics. Convenience sampling was used with the consecutive inclusion of CKD patients. None of the patients was hospitalized at the time of baseline investigations. CKD patients in stages 1-5, not on dialysis therapy, who gave written informed consent for participation, were included. Patients with atrial fibrillation or with frequent ventricular extrasystoles counteracting with pulse wave analysis were excluded. After baseline clinical, laboratory, arterial stiffness and central hemodynamic measurements, patients were followed for a median of 67.6 months (interquartile range: 38.4-82.6). Follow-up data were collected between April 2007 and July 2014 by yearly telephone interviews either with the patients, their general practitioners or treating physicians. All endpoint information was verified by original chart review. Follow-up was censored at the last occurrence of a documented CV event (acute coronary syndrome, heart failure requiring hospitalization, stroke or transient ischemic attack or peripheral artery disease with the need for an intervention) or death due to the above CV causes.

The protocol was approved by the local ethical committees of the participating hospitals and was carried out in accordance with the tenets of the Declaration of Helsinki. All patients gave written informed consent before participation.

Arterial stiffness, central hemodynamic and blood pressure measurements

All measurements were performed between 10-12 a.m. Patients were allowed to take a non-standardized light breakfast and took their regular medications at least 3 hours before the study measurements. Patients were asked to refrain from smoking on the day of the study and not to consume any caffeine-containing drinks at least 4 hours before the start of the measurements. Arterial stiffness measurements and blood sampling were done on separate days within a week.

Arterial stiffness measurements were carried out in a temperature-controlled room (24±1°C). Upon arrival after a 5-minute rest, two consecutive brachial blood pressure measurements were taken one minute apart on each arm in the sitting position with a validated BpTru device (VSM Medtech, Vancouver, Canada). The mean value was calculated for each arm, and the higher of these was further taken as brachial systolic and diastolic blood pressure and heart rate. Subjects were then set in the supine position for a 10-minute acclimatization period.

Arterial stiffness was measured with tonometric method, using the PulsePen device. About the PWV and cPP measurements we refer our previous publication (1). Aix was measured by automatic identification of the '1st shoulder' (inflexion point) on the averaged carotid pulse signal by the PulsePen software. The pressure amplitude following this point divided by the pulse pressure provided the Aix. CSBP was calculated directly from the carotid pulse waveform using the calibration considering brachial systolic and diastolic blood pressures.

Epidemiologic and Laboratory data

Baseline data on current smoking, any type of diabetes mellitus, hypertension, coronary artery disease (previous acute myocardial infarction or coronary intervention), chronic heart failure (previous diagnosis), peripheral arterial disease (documented by angiography or intervention) and cerebrovascular disease (previous stroke or transient ischemic attack) were collected by health record review.

Blood samples for the determination of blood cell count and hemoglobin, serum cholesterol, triglyceride, and LDL-cholesterol were collected at baseline. Routine blood chemistry measurements were done directly after blood sampling on a Hitachi auto-analyser. Baseline eGFR was calculated using the four-variable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Statistical analysis

All data analyses were performed using SPSS 23 for Windows or Stata version 13.1. Continuous data are given as mean and standard deviation, or in case of evidence against a normal distribution, as a median and interquartile range.

The primary outcome of the study was the occurrence of the combined endpoint of cardiovascular events and cardiovascular mortality, as defined above.

To assess the predictive values of the studied parameters for the primary outcome multiple failure times Cox proportional hazard regression analyses were used with conditional risk set modeling. This method accommodates for the fact that one patient may have had more than one event during follow-up.

No a priori power calculations were done for the current analysis, however the sample size for the original study was based on the observed differences and the distribution of one of the arterial stiffness measures (cPP) (1). A post hoc power calculation showed power values ranging from 0.60 to 0.97 for individual arterial stiffness parameters (as continuous variables) for the prediction of cardiovascular events.

Arterial stiffness and central hemodynamic parameters were analyzed both as continuous and categorical variables. For the former, these variables were transformed into z-scores to improve their comparability and thus the associations are given for one SD differences in PWV, cSBP, cPP and Aix for the CV outcome. Model 1 was adjusted for age and sex, Model 2 was further adjusted for brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes, body mass index, known cardiovascular disease and GFR-EPI. As in the cohort all but one patient had hypertension, we omitted this variable from the adjustment.

Next, patients were divided into tertiles based on their PWV, cSBP, cPP and Aix values, respectively. Survival was investigated using Kaplan-Meier analysis and Cox-regressions similar to the ones described above, with arterial stiffness and central hemodynamic parameters as predictors and CV events or CV mortality as outcome. Polynomial and simple contrasts were performed to investigate the best scoring for these tertiles. According to these results, Aix was not related to CV outcome and was excluded from further analysis. There was a linear association between PWV and cPP and CV outcomes, and accordingly 0, 1 and 2 points were given to the consecutive tertiles. As the risk of CV events or CV mortality only increased in the third tertile of cSBP, 0 points were given to the first two tertiles and 1 point to the third.

The integrated central blood pressure- aortic stiffness (ICPS) score was calculated for each patient by summing the points based on tertiles (range: 0-5 points). Survival was investigated with Kaplan-Meier and Cox regression analyses (adjusted for age and sex) with ICPS score as the predictor and CV event or CV mortality as outcome. Given the limited statistical power of our relatively small sample size, patients were classified into three ICPS risk categories:

average (0-2 points), high (3-4 points) or very high (5 points). The predictive role of these risk categories were investigated in Kaplan-Meier curves and Cox regressions with adjustment (1) for age and sex and (2) with further adjustment for brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes, body mass index, cardiovascular disease and GFR-EPI.

Finally, the ICPS risk categories and one SD change of each of its components (PWV, cSBP and cPP) were analyzed in the same Cox-regression model for CV outcomes. To investigate model discrimination, Harrell's concordance statistics were utilized.

As sensitivity analysis, all of the measurements were performed with Cox regression analyses considering the occurrence of the first CV event instead of multiple failure time analysis as well.

Results

Of the 108 patients eligible for inclusion 5 individuals declined participation. Further 3 patients were excluded because of missing baseline or follow-up data, leaving 100 subjects in the analytical sample.

Table 1 displays baseline characteristics, including concomitant diseases, traditional and nontraditional CV risk factors, metabolic and vascular parameters.

The causes of kidney disease were heterogeneous (number of cases in parentheses): glomerulonephritis (n=14), diabetic nephropathy (n=29), hypertensive nephrosclerosis (n=17), chronic tubulointerstitial nephritis (n=18), vascular cause (n=6), polycystic kidney disease (n=6), tumor (n=1) and unknown (n=9).

All but one patient received antihypertensive medication (case numbers in parentheses): angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n=89), calcium channel blockers (n=52), diuretics (n=74), β-receptor blockers (n=54), α-receptor blockers (n=18), long-acting nitrate (n=15) and centrally acting antihypertensive drugs (n=13), either alone or in combination. Low dose aspirin was taken by n=36 patients, whereas n=17 individuals took clopidogrel. Sixty-one patients were on statin therapy.

In all, n=37 patients required erythropoietin-stimulating agents, n=35 received calcitriol and n=9 needed calcium carbonate phosphate binder therapy.

During follow-up, n=49 cardiovascular events were recorded: n=16 patients died from CV causes (acute coronary syndrome n=4, stroke n=3, heart failure n=8, peripheral artery disease n=1) and there were n=33 additional CV events (acute coronary syndrome n=8, stroke n=6, heart failure n=12 and peripheral artery disease n=7).

Table 2 demonstrates the association of PWV, cSBP, cPP and Aix (per one SD change and per tertiles) with CV outcomes in models adjusted for age and sex or for traditional CV risk factors. All the four studied parameters were significantly related to CV outcomes in Model 1. In the further adjusted Model 2, the association of PWV and cPP was attenuated to non-significance, while cSBP and Aix showed significant associations. In the analyses of tertiles, PWV and cPP showed a linear association with the risk of CV outcomes, while for cSBP the association was non-linear: showing an increase only in the third tertile in Model 1 adjusted for age and sex. For Aix, no significant association was found, so this parameter was omitted from the ICPS score calculation. Further adjustment for traditional CV risk factors in Model 2 substantially attenuated the associations and none of them remained significant. Unadjusted associations are shown as Kaplan-Meyer curves for each tertile of all 4 parameters in **Figure 1**.

Table 3 demonstrates hazard ratios for CV outcomes by ICPS risk scores and ICPS risk categories. The risk categories were derived from Cox-models (**Table 3**) and Kaplan-Meier (**Figure 2A**) analyses by collapsing ICPS scores with similar hazard ratios and sufficient statistical power. Almost half of the patients were classified into the high and very high-risk categories. Kaplan-Meier survival curves for the three ICPS risk categories are shown in **Figure 2B**.

Table 3 shows that the ICPS risk categories are strongly related to the CV outcomes even after adjustment for traditional CV risk factors. It is also notable, that in Model 2 ICPS risk categories and diabetes were the only statistically significant predictors, with a higher risk in the high and very high ICPS risk categories compared to diabetes.

Table 4 demonstrates the results of the comparison of the discriminative ability of the integrated central pressure-stiffness risk categories with the one standard deviation change of PWV, cSBP and cPP. All the parameters were adjusted for age and sex. ICPS risk categories were superior in the discrimination than PWV and cSBP and a tendency was also present in case of cPP, but the difference was not significant.

When, as sensitivity analysis all the calculations were repeated with the closure of follow-up at the first event instead of multiple failure time analysis, similar results were found (data are available from authors for request).

Discussion

Our study demonstrated that the concept of an integrated score based on arterial stiffness and central hemodynamic parameters (ICPS) is strongly related to incident cardiovascular events in CKD patients. According to our results, people in high and very high ICPS risk categories are at a remarkably high risk for CV events and have a risk that is stronger than that related to diabetes, the strongest single predictor among traditional risk factors in our cohort. Additionally, it is better than PWV and cSBP and tends to be better than cPP which suggests that it is worth to adding together the predictive power of these parameters.

A recent consensus statement suggests that the combined assessment of more than one biomarker may improve CV outcome prediction (15). In line with this recommendation, our study investigated the combined effect of arterial stiffness and central hemodynamic parameters using a simple score that integrates the predictive information of individual biomarkers.

Available studies have conflicting results regarding the role of non-invasive markers of morphological or functional abnormalities of the arterial wall in relation to CV risk. In elderly patients of the Rotterdam study, the evaluation of carotid intima-media thickness (c-IMT), peripheral artery disease or PWV marginally improved CV risk stratification over Framingham risk factors (4, 14). In contrast, in middle-aged subjects from the ARIC study the detection of increased c-IMT and carotid artery plaques was associated with a significant ~23% net reclassification index (9).

There are also some data available about the joint evaluation of different non-invasive hemodynamic biomarkers and their relation to CV outcomes. In the study of Wang et al., central systolic blood pressure was superior in CV outcome prediction compared with brachial systolic blood pressure or brachial or central pulse pressure (16). In the study of Holewijn et al., using net reclassification improvement analysis, CV risk stratification improved by adding non-invasive vascular risk markers, like PWV, Aix or cSBP to traditional risk factors in women, however the association was weaker in men and was limited to men at intermediate risk (3). These results suggest that the joint evaluation of different vascular biomarkers may have perspectives, but age and sex could influence the results. Throughout

our study, we adjusted for age and sex and however ICPS risk categories still remained robust predictors of CV events.

There are multiple potential advantages of the ICPS score concept. First, PWV, cSBP and cPP can easily be estimated with most of the available devices (e.g. tonometric, mechanotransducer-based or oscillometric) that measure arterial stiffness and use pulse wave analysis. The ICPS score is determined in a non-invasive manner without blood sampling, which is required for traditional risk scores. Furthermore, it could help to bridge the huge problem of diverging methodologies. Thanks to creative engineers newer and newer devices are marketed that estimate these parameters in simpler ways, but the actual results of these devices are not interchangeable. Our ICPS score based on tertiles in a given population could be a universal parameter. Of course, the tertiles of each parameter should be defined for each device, but probably no equations are required to translate results between devices. Although our studied three parameters correlate with each other, but our results demonstrate, that it is worth to integrate them into one score as it can produce a very strong predictor parameter.

As the ICPS score is based on a limited sample of CKD patients, we do not recommend its calculation using the cutoff values from our sample, not even on CKD patients on conservative therapy. A valid risk score should be based on large databases with a much higher number of events that enables the investigation of each parameter involved in the score (2). However, as our ICPS risk categories in the present rudimentary form are much stronger predictors than diabetes in our cohort, we think that the publication of our results in this form can generate important discussion and further studies. A great scientific potential of this concept is related to the fact that there are other cohorts in divergent races with available PWV, cSBP and cPP measurements, so our finding on ICPS risk categories could easily be broaden for different patient populations. Such cohorts are for example the Framingham Heart Study cohort (8) or the Nijmegen Biomedical Study (3).

There are some limitations of our study that has to be acknowledged. During tonometric arterial stiffness measurements patients with atrial fibrillation are excluded because of methodological considerations, so a proportion of patients cannot be involved into our new risk stratification method. Due to the low number of participants and outcome events, our study is underpowered and thus the exact thresholds for scoring or the relative contribution of individual parameters could not have been exactly defined. So, the aim of the present study is

not to define the final score but to report the possible advantages of this new concept of a combined risk score based on arterial stiffness and central hemodynamic parameters.

In conclusions, our integrated score and the constructed ICPS risk categories provided strong and robust association with CV outcomes in chronic kidney disease patients on conservative therapy, which highlights the possible advantages of the combined measure of arterial stiffness and central hemodynamic parameters for CV risk prediction.

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Conflict of interests

The Authors declare that there is no conflict of interest.

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Figure legends

Figure 1.

Kaplan-Meier survival curves for each parameter studied with cardiovascular events (CV mortality plus CV events) as outcome. Panel A: pulse wave velocity; Panel B: central systolic blood pressure; Panel C: central pulse pressure; Panel D: augmentation index.

Figure 2.

Kaplan-Meier survival curves for the integrated central pressure-stiffness (ICPS) risk scores and ICPS risk categories for cardiovascular events (CV mortality plus CV events, adjusted for age and sex) as outcomes. Panel A: ICPS risk score groups; Panel B: ICPS risk categories.

Table 1. Baseline demographic, clinical and laboratory characteristics (n=100).

Male n	48
Age (years)	66.00 (58.25-75.00)
BMI (kg/m^2)	27.63 (25.24-30.49)
Current smoker	12
Diabetes mellitus	44
Baseline cardiovascular disease	64
Coronary artery disease	13
Chronic heart failure	19
Cerebrovascular disease	24
Peripheral artery disease	53
Framingham CVD score (point)	22.89 (13.09)
eGFR (ml/ min per 1.73m^2),	35.74 (23.15-49.43)
Hgb (g/l)	126.89 (14.32)
Chol (mmol/l)	4.81 (4.28-5.33)
Tg (mmol/l)	1.80 (1.15-2.60)
LDL (mmol/l)	2.57 (0.84)
SBP (mm Hg)	135.50 (120.31-145.44)
DBP (mm Hg)	73.12 (9.70)
HR (1/ min)	62.25 (57.50-72.63)
PP (mm Hg)	60.38 (50.56-70.38)
PWV (m/s)	11.26 (8.90-14.90)
Aix (%)	21.53 (15.35-26.83)
cSBP (mm Hg)	124.33 (14.50)
cPP (mm Hg)	48.58 (42.75-60.38)

Categorical parameters are presented as n, numbers can be also considered as percentage.
Continuous data are presented as mean (SD) or median (interquartile range).
Aix: augmentation index; BMI: body mass index; Chol: cholesterol; cPP: central pulse pressure; cSBP: central systolic blood pressure; DBP: brachial diastolic blood pressure; eGFR: estimated glomerular filtration rate; Framingham CVD: Framingham 10 Year Risk of General Cardiovascular Disease Score; Hgb: hemoglobin; HR: heart rate; LDL: low-density lipoprotein; n: case number; PP: brachial pulse pressure; PWV: carotid-femoral pulse wave velocity; SBP: brachial systolic blood pressure; Tg: triglyceride.

Table 2. Cox models with cardiovascular morbidity and mortality as outcome and individual arterial stiffness and central hemodynamic parameters as predictors.

				Model 1				Model 2			
Variable				**Hazard ratio**	**95% CI**		**P-value**	**Hazard ratio**	**95% CI**		**P-value**
PWV	**(per 1 SD)**			1.467	1.182	1.821	**<0.001**	1.227	0.865	1.740	0.253
cSBP	**(per 1 SD)**			1.452	1.054	2.001	**0.023**	2.935	1.342	6.418	**0.007**
cPP	**(per 1 SD)**			1.636	1.183	2.262	**0.003**	1.539	0.980	2.416	0.061
Aix	**(per 1 SD)**			1.381	1.067	1.788	**0.014**	1.399	1.041	1.879	**0.026**
				Model 1				**Model 2**			
Variable	**Tertile**	**N**	**Range**	**Hazard ratio**	**95% CI**		**P-value**	**Hazard ratio**	**95% CI**		**P-value**
PWV	1st	33	6.5-9.8 m/s	1 (ref.)				1 (ref.)			
	2nd	34	9.9-13.0 m/s	1.867	0.636	5.480	0.256	0.777	0.231	2.618	0.684
	3rd	33	13.2-27.2 m/s	4.072	1.400	11.841	**0.010**	1.284	0.386	4.273	0.684
cSBP	1st	33	81.5-117.0 mmHg	1 (ref.)				1 (ref.)			
	2nd	33	119.0-129.8 mmHg	0.827	0.325	2.106	0.691	1.052	0.331	3.338	0.932
	3rd	34	130.0-167.8 mmHg	2.308	1.051	5.071	**0.037**	2.675	0.560	12.772	0.217
cPP	1st	34	23.3-45.0 mmHg	1 (ref.)				1 (ref.)			
	2nd	33	45.3-56.3 mmHg	1.608	0.605	4.270	0.341	1.482	0.492	4.469	0.484
	3rd	33	56.5-92.3 mmHg	3.712	1.492	9.235	**0.005**	3.697	0.988	13.830	0.052
Aix	1st	33	7.0-17.8%	1 (ref.)				1 (ref.)			
	2nd	34	18.0-24.8%	1.897	0.853	4.219	0.117	1.758	0.701	4.406	0.229
	3rd	33	25.7-54.5%	1.658	0.665	4.132	0.278	2.049	0.708	5.928	0.186

Model 1 is adjusted for age and sex.

Model 2 is adjusted for age, sex, brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes mellitus, body mass index, cardiovascular disease, hypertension, GFR-EPI.

Aix: augmentation index; CI: confidence intervals; cPP: central pulse pressure; cSBP: central systolic blood pressure; PWV: carotid-femoral pulse wave velocity. Bold values demonstrate significance when $p<0.05$.

Table 3. The relation of integrated central blood pressure- aortic stiffness (ICPS) risk score and ICPS risk categories with cardiovascular morbidity and mortality based on Cox proportional hazard regression models.

	N	Hazard ratio	95% CI		P-value
ICPS risk score					
Model 1					
0	18	1 (ref.)			
1	17	1.831	0.339	9.876	0.482
2	16	1.528	0.233	10.018	0.659
3	24	5.719	1.298	25.208	**0.021**
4	13	4.236	0.849	21.131	0.078
5	12	11.105	2.366	52.120	**0.002**
ICPS risk categories					
Model 1					
Average	51	1 (ref.)			
High	37	3.517	1.650	7.494	**0.001**
Very high	12	7.559	3.201	17.850	**<0.001**
Model 2					
Average	51	1 (ref.)			
High	37	4.583	1.867	11.253	**0.001**
Very high	12	8.563	3.086	23.758	**<0.001**
Diabetes	44	3.073	1.680	5.621	**<0.001**

Model 1 is adjusted for age and sex.

Model 2 is adjusted for age, sex, brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes mellitus, body mass index, cardiovascular disease and GFR-EPI.

ICPS: integrated central blood pressure- aortic stiffness. Bold values demonstrate significance when $p<0.05$.

Table 4. Comparison of the discriminative ability of the integrated central blood pressure-aortic stiffness risk categories with the one standard deviation change of pulse wave velocity, central systolic blood pressure and central pulse pressure (Harell's C-statistics).

Variable	Coefficient	Standard error	95% CI		P-value
ICPS risk categories	0.723	0.036	0.652	0.795	**<0.001**
PWV	0.659	0.037	0.586	0.732	**<0.001**
cSBP	0.660	0.038	0.584	0.735	**<0.001**
cPP	0.691	0.035	0.621	0.761	**<0.001**
ICPS risk categories vs PWV	0.065	0.029	0.007	0.122	**0.028**
ICPS risk categories vs cSBP	0.064	0.024	0.017	0.110	**0.008**
ICPS risk categories vs cPP	0.032	0.023	-0.014	0.079	0.170

CI: confidence intervals; ICPS risk categories: integrated central blood pressure- aortic stiffness risk categories; PWV: carotid-femoral pulse wave velocity; cSBP: central systolic blood pressure; cPP: central pulse pressure. Bold values demonstrate significance when $p<0.05$.

Figure 1.

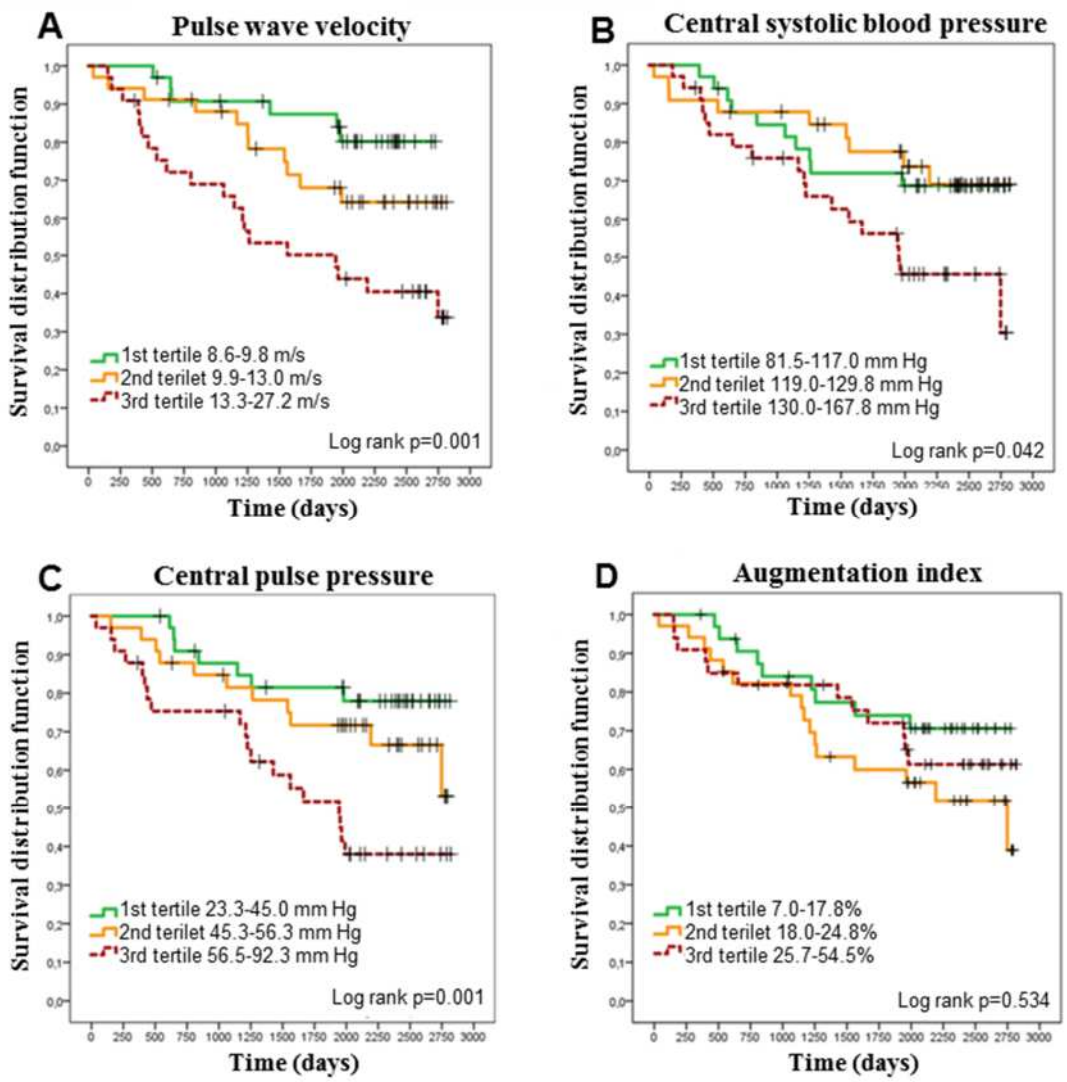
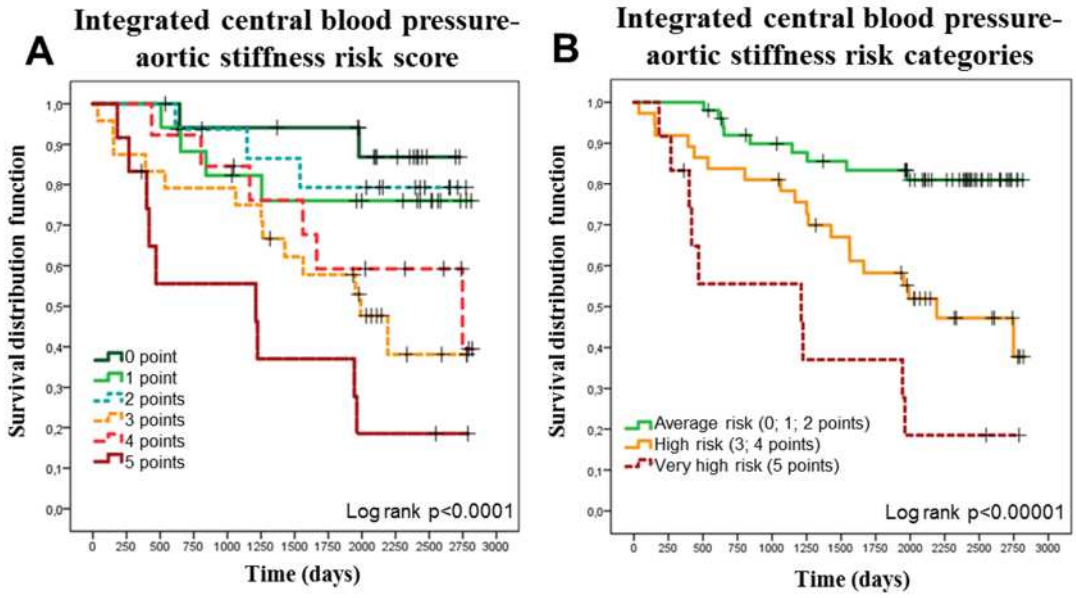

A
Pulse wave velocity
Survival distribution function
1st tertile 8.6-9.8 m/s
2nd terilet 9.9-13.0 m/s
3rd tertile 13.3-27.2 m/s
Log rank p=0.001
Time (days)
B
Central systolic blood pressure
Survival distribution function
1st tertile 81.5-117.0 mm Hg
2nd terilet 119.0-129.8 mm Hg
3rd tertile 130.0-167.8 mm Hg
Log rank p=0.042
Time (days)
C
Central pulse pressure
Survival distribution function
1st tertile 23.3-45.0 mm Hg
2nd terilet 45.3-56.3 mm Hg
3rd tertile 56.5-92.3 mm Hg
Log rank p=0.001
Time (days)
D
Augmentation index
Survival distribution function
1st tertile 7.0-17.8%
2nd terilet 18.0-24.8%
3rd tertile 25.7-54.5%
Log rank p=0.534
Time (days)

Figure 2.


A
Integrated central blood pressure-aortic stiffness risk score
Survival distribution function
0 point
1 point
2 points
3 points
4 points
5 points
Log rank p<0.0001
Time (days)
B
Integrated central blood pressure-aortic stiffness risk categories
Survival distribution function
Average risk (0; 1; 2 points)
High risk (3; 4 points)
Very high risk (5 points)
Log rank p<0.00001
Time (days)