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Comparison of pulse wave velocity measured with different devices and the concept of integrated central blood pressure - aortic stiffness risk categories

PhD thesis

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LIST OF ABBREVATIONS

ABPM	ambulatory blood pressure monitoring
ACE-inhibitor	angiotensin-converting enzyme inhibitor
Aix	augmentation index
ARB-blocker	angiotensin receptor blocker
BMI	body mass index
BP	blood pressure
CCB	calcium-channel blocker
cfPWV	carotid-femoral pulse wave velocity
Chol	cholesterol
CI	confidence interval
CKD	chronic kidney disease
cPP	central pulse pressure
cSBP	central systolic blood pressure
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
Framingham CVD	Framingham 10 Year Risk of General Cardiovascular Disease Score
HD	hemodialysis
Hgb	hemoglobin
HR	hazard ratio
HT	hypertension
ICPS	integrated central blood pressure-aortic stiffness
LDL	low-density lipoprotein
MOB	Mobil-O-Graph
MOB 1st hour PWV	Mobil-O-Graph 1st hour pulse wave velocity
MOB 24h PWV	Mobil-O-Graph 24-hour ambulatory pulse wave velocity
n	case number

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PP PWV	pulse wave velocity measured with PulsePen device
PWV	pulse wave velocity
SBP	systolic blood pressure
SD	standard deviation
Tg	triglyceride
WhHT	white-coat hypertension

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1. INTRODUCTION

1.1. Epidemiology of cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading causes of mortality worldwide. According to statistics from 2021, in the European Society of Cardiology's member countries 113 million people live with CVD (1). The risk of CVD is also increased by environmental, lifestyle, and clinical factors. (1-6).

Environmental risk factors include air pollution (6-9), noise pollution (10, 11) and neighborhood characteristics (12-14). Lifestyle risk factors include smoking (15-19), alcohol consumption (1, 20), lack of exercise (1, 21, 22), and excessive calorie and trans fat intake (1, 23-29). Clinical risk factors include hypertension (≥140/90 mmHg) (30-32), dyslipidemia (33-35), obesity (BMI≥30kg/m^2) (1, 36-38), diabetes and psychological factors (1, 38).

The importance of risk factors is determined by the extent to which they can be modified at the individual and population levels, as reducing the risk factors' incidence is the most effective means of reducing the burden of CVD in Europe and worldwide (1-4).

1.2. Cardiovascular risk assesment – arterial stiffness

Arterial stiffness refers the rigidity of the arterial wall. As a result of aging and various risk factors (hypertension, diabetes, chronic kidney disease, and smoking), the wall of the aorta and other large arteries loses elasticity over time, and this process leads to increased arterial stiffness. Several factors contribute to arterial stiffening, including calcification, and inflammation in the arterial wall (39) consisting primarily of arterial wall remodeling due to the degradation of the finely crosslinked network of elastin fibers that are replaced by cross-linked collagen (40, 41).

Pulse waves propagate faster in stiffer arteries, and because of this increased velocity and wave reflection, the backward waves are returned to the left ventricle during systole, leading to hemodynamic changes such as increased central systolic blood pressure and pulse pressure. Consequently, harmful complications emerge on the myocardium due to the increased left ventricular afterload and decreased coronary blood flow. Pulsatility also

generates microvascular damage of small arteries and microcirculation in the high-flow organs (brain, kidney). All these changes lead to increased cardiovascular (CV) risk.

Given that CVDs are still the leading cause of death throughout the world and that a plethora of effective preventive medicines is available, it is essential to predict the risk of cardiovascular diseases accurately in different populations in order to to increase the positive health effects of CV prevention (42, 43). Among diseases which lead to CVD, hypertension is the most important risk factor (44). In addition to hypertension, CV risk is also high in chronic kidney disease (CKD), especially in end-stage renal disease (ESRD), as the CV mortality of patients on maintenance hemodialysis (HD) is more than ten times higher than that of the normal population (45). Therefore, attempts to better identify high-risk patients and more effective preventions are of utmost importance.

What may improve the prediction of CV risk in addition to the usual parameters are measurements describing both the stiffness of the arteries and central hemodynamic status. In the past two decades, these parameters have been widely studied. In the case of hypertension, measuring different arterial stiffness parameters can be beneficial in identifying high-risk patient subpopulations (41, 46); in particular, pulse wave velocity (PWV) predicts the progression of blood pressure and could provide a valuable tool in hypertension risk prediction in young adults (47, 48). In all the stages of CKD (chronic kidney disease), the stiffness of the arteries is a significant risk factor for CV events and death (49).

The measurement of carotid-femoral PWV (with applanation tonometry) in 7.283 participants in the Framingham study was evaluated in a recently published prospective study that found that the measurement of arterial stiffness is of long-term prognostic significance. In multivariable-adjusted models, each standard deviation (SD) increment in carotid-femoral pulse wave velocity was associated with an increased risk of hypertension (hazard ratio [HR]: 1.32 [95% confidence interval [CI]: 1.21-1.44]), diabetes (HR: 1.32 [95% CI, 1.11-1.58]), CKD (HR: 1.19 [95% CI, 1.05-1.34]), dementia (HR: 1.27 [95% CI, 1.06-1.53]), CVD (HR: 1.20 [95% CI, 1.06-1.36]) and its components (coronary heart disease, HR: 1.37 [95% CI, 1.13-1.65]; transient ischemic attack/stroke, HR: 1.24 [95% CI, 1.00-1.53]) and finally, mortality from all causes (HR: 1.29 [95% CI, 1.17-1.43]). The association with heart failure was marginally non-significant (HR: 1.21 [95% CI, 0.98-1.51], P=0.08) (50).

1.2.1. Characteristic parameters of arterial stiffness and their position within guidelines

Arterial stiffness is measured using several methods (41, 51, 52). With the majority of the available devices in parallel with the measurement of PWV, other parameters which correlate with PWV and each other can also be evaluated, but can also reflect on different characteristics of the vasculature. Examples of these parameters are cSBP (central systolic blood pressure) in connection with pressure; cPP (central pulse pressure) with pulsatility; and augmentation index (Aix) with wave reflection.

cfPWV (carotid-femoral pulse wave velocity) was included in the 2007 European Hypertension Guideline as a parameter of target organ damage (53). Based on the growing evidence concerning the role of PWV in predicting target organ damage, pulse wave velocity was given a IIa recommendation in the European guidelines on hypertension in 2007 and 2013 (54, 55). In contrast, the level of recommendation was downgraded to IIb in the 2016 European hypertension guideline (56). The 2018 and 2021 European guidelines on the prevention of CV risk recommended against its use in the assessment of cardiovascular risk within the general population (57, 58). Given this vacillation, it appears that the scientific community is presently less convinced of how useful arterial stiffness measurements for CV risk stratification are in contrast with the beginning of the century.

Among the parameters describing central hemodynamics, cPP (a measure describing pulsatility) and cSBP (a measure of pressure load) appear to be the most promising, since their predictive values are better than those of brachial systolic blood pressure and pulse pressure under some conditions (59-61).

The Aix is a parameter of wave reflection that also measures total peripheral resistance. There is conflicting evidence that Aix serves as an independent predictor of CV outcomes (62), but the results are inconsistent (63, 64).

1.2.2. Methods for measuring pulse wave velocity

Over the last decade, technological developments have resulted in new, simpler alternatives to measuring or estimating PWV; these can potentially replace the operator-dependent measurement of cfPWV.

There are several types of tools available for measuring PWV: devices with piezoelectric mechanotransducers based on simultaneous recording of arterial pulse

waves in the carotid and femoral arteries (Complior device) (65-67); devices operating on the principle of applanation tonometry (high band piezoelectric probes) which sequentially record carotid and femoral arterial pulse waves, synchronizing both signals to the same ECG-R wave (SphygmoCor, PulsePen devices) (68, 69); cuff-based oscillometric devices (Arteriograph, Mobil-O-Graph, Vicorder, BPLab Vasotens) (67, 70-72); and photodiode sensor (pOpmètre) (73) devices assessing brachial-ankle PWV and cardiac-ankle PWV (Omron Healthcare) (67). Besides office measurements, 24-hour monitoring of PWV and central hemodynamic parameters has also become available within the last decade (74).

However, the data measured by a number of validated instruments designed to measure arterial stiffness do not always correlate with one another or provide similar values. In a study of 102 patients, Complior, PulsePen, and ShygmoCor showed strong agreement between the results of invasive aortic PWV measurements and the carotid-femoral PVW measurement ($r>0.83$). The pOpmétre showed only a weak association between invasive aortic recording and non-invasive carotid-femoral PWV measurements ($r<0.33$). Pulse wave velocity as estimated by the Mobile-O-Graph was less consistent with invasive PWV measurement than with cfPWV. Aortic PWV values provided by the BPLab Vasotens and Mobil-O-Graph were entirely dependent on age-squared and peripheral systolic blood pressure (cumulative $r^2=0.98$ and 0.99, respectively). This way, among the evaluated methods evaluated, only those that assess cfPWV (PulsePen, Complior, and SphygmoCor) seem to be reliable methods for the measurement of aortic stiffness (75).

1.2.3. Perspectives

Almost all validation studies are cross-sectional and compare office measurements. Comparative studies are warranted with office and 24-hour devices, and also for evaluating the effects of intervention parameter change differences e.g., lifestyle changes or antihypertensive medications.

Most of the available research on the stiffness of arteries examines the predictive significance of stiffness parameters individually. However, since cSBP, cPP, PWV and Aix can be measured with most available devices within one measurement, and because they each relate to different aspects of the vascular system, it is sensible to integrate these results into one score to predict cardiovascular outcome.

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2. OBJECTIVES

The stiffening of arteries is a substantial contributor to vascular aging. The measurement of the stiffness of arteries and central hemodynamic parameters are candidates which may enhance cardiovascular risk prediction as performed using traditional methods. PWV, regarded as the most accepted biomarker of the stiffening of arteries, can be measured using different methods, and over the last decade the 24-hour monitoring of PWV has also become an available option.

CSBP, cPP and Aix are important additional markers of central hemodynamic properties and pulse wave reflection.

The aims of our study were to:

(1) compare office and ambulatory PWVs with two devices in a cross-sectional design: office cfPWV measured by the tonometric PulsePen device (PP PWV), and first-hour and 24-hour ambulatory oscillometric PWVs evaluated by the Mobil-O-Graph (Study 1);

(2) compare the changes of PWVs in a subgroup of patients after the initiation of lifestyle modifications (in white-coat hypertensive patients) or antihypertensive medication (in hypertensive patients) (Study 1);

(3) create an integrated central blood pressure-aortic stiffness (ICPS) risk score and risk categories – incorporating the predictive potential of identical parameters – to predict cardiovascular events in patients with CKD on conservative therapy (Study 2);

To achieve the above, we aimed to:

- investigate the predictive effectiveness of cSBP, cPP, PWV, and Aix separately for cardiovascular events;
- convert the parameters into scores based on their tertiles;
- establish and test for its cardiovascular prediction ability an integrated parameter formed from the sum of these scores and based and them across different risk categories;
- examine if the integrated score-based risk category concept makes cardiovascular prediction more precise than its components taken separately.

(4) examine the predictive effectiveness of ICPS risk categories on cardiovascular mortality in patients on hemodialysis therapy who have end-stage kidney disease, following the methodology of Study 2 (3) (Study 3).

3. RESULTS

3.1. Cross-sectional comparison of ambulatory and office pulse wave velocity with the help of two methods, and changes in their values after lifestyle or medical interventions in hypertension (Study 1)

A total of 105 Caucasian patients were involved in the cross-sectional segment of the study. ABPM indication was as follows: suspicion of masked hypertension in 7 cases (6.7%), the control of antihypertensive therapy in patients with chronic hypertension in 16 cases (15.2%), confirmation of resistant hypertension in 12 cases (11.4%), diagnosis of new hypertension in 35 cases (33.3%), as well as suspicion of white-coat hypertension in 35 cases (33.3%). Patients with arterial fibrillation were excluded. Control measurements were performed on 22 patients having sustained hypertension and on 22 patients having white-coat hypertension after 3 and 12 months, respectively. **Table 1** shows the laboratory and demographic data of all patients at the time of enrollment, and separately idicates the patients who exhibited new sustained hypertension (HT) or white-coat hypertension (WhHT) and had follow-up data. The cohort consisted mostly of middle-aged subjects. The prevalence of overt CVD and diabetes mellitus was low across the entire population. None of the HT or WhHT patients had overt CVD or diabetes.

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Table 1. Clinical characteristics of the subjects. (76)

	All subjects	HT patients 1.	HT patients 2.	WhHT patients 1.	WhHT patients 2.
N (male/female)	105 (62/43)	22 (15/7)	22 (15/7)	22 (10/12)	22 (10/12)
Age, years	48.3 ± 13.2	47.9 ± 13.5	48.2± 13.5	45 ± 13.2	46 ± 13.2
Diabetes [n (%)]	8 (7.6)	0	0	0	0
CV disease [n (%)]	3 (3.8)	0	0	0	0
Current smoker [n (%)]	19 (18.1)	5 (22.7)	5 (22.7)	4 (18.2)	4 (18.2)
BMI [kg/m^2]	27.4 ± 3.9	27.3 ± 4.5	26.6 ± 4.3	26.4 ± 4.2	26.6 ± 4.5
Blood glucose [mmol/l]	5.3 ± 0.5	5.9 ± 1.7	5.7 ± 1.3	5.3 ± 0.6	5.3 ± 0.5
GFR-EPI [ml/min/1.73m^2]	100.1 ± 14	98.2 ± 14.9	98.2± 14.9	118 ± 18.4	98 ± 16.5
Uric acid [µmol/l]	344.3± 96.3	316.8± 93.1	315 ± 93	313 ± 74	312 ± 79.4
Total cholesterol [mmol/l]	5.7 ± 1.1	6.1 ± 1.1	5.8 ± 1.2	5.6 ± 1.7	5.4 ± 1.1
LDL [mmol/l]	3.6 ± 0.9	3.9 ± 1.0	3.7 ± 1.1	3.6 ± 1.5	3.5 ± 0.9
HDL [mmol/l]	1.1 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.3
Triglyceride [mmol/l]	1.6 ± 0.6	1.7 ± 1.3	1.6 ± 0.9	1.5 ± 1	1.2 ± 0.6
At hypertensive (HT) and white-coat hypertensive (WhHT) patients the 1st columns are baseline data; the 2nd columns are follow-up data. Descriptive data are expressed as mean ± standard deviation or median with interquartile ranges as appropriate. The Kolmogorov-Smirnov test was used to test the normality of continuous parameters.					

3.1.1. Cross-sectional comparison of PulsePen and Mobil-O-Graph pulse wave velocity

Table 2 shows the ambulatory and office hemodynamic as well as PWV data in the entire population, and separately the HT or WhHT patients having follow-up data. During the screening visit, patients' blood pressure was measured by a validated oscillometric device (Omron M3). The Mobil-O-Graph (I.E.M. GmbH, Germany) was used as a 24-hour ambulatory blood pressure monitoring (ABPM) device. The gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy, PP PWV) was used to evaluate cfPWV. Our previous data were recalculated to align with current recommendations suggesting the use of 80% of the direct carotid-femoral distance as the most accurate proxy of the numerator for PWV measurement (77). To calculate PP PWV, we therefore used 80% of the carotid–femoral distance, in accordance with consensus (77). The PulsePen software was used to calculate PP PWV as the ratio of the distance and the pulse pressure wave transit time along the aorta. The amplitude of the pulse wave was calibrated to the brachial mean and diastolic pressure, which were measured immediately before each sequence of pulse wave captures at the two sites. All recordings which had a systolic or diastolic variability of successive waveforms above 10%, or recordings where the amplitude of the pulse wave signal was below 80mV, were disregarded. The interobserver and intraobserver variability of PP PWV measurements which we obtained using the PulsePen device in our laboratory in patients with hypertension were 6.3 and 4.6%, respectively (78).

Ambulatory data on blood pressure, first hour (MOB 1st hour PWV) and 24-hour ambulatory pulse wave velocity (MOB 24h PWV) were evaluated with the Mobil-O-Graph NG unit.

This device is oscillometric, the brachial blood pressure detection unit of which was validated in concordance with standard protocols (79, 80). For the registration of pulse wave curves, and after the registration of brachial blood pressure, the cuff is kept inflated at the level of diastolic blood pressure (DBP) for approximately 8 seconds. The Mobil-O-Graph uses the ARCSolver algorithm with a generalized transfer function to evaluate the aortic pulse waveform, and utilizing a proprietary mathematical algorithm it calculates PWV (81, 82). The device monitored the brachial SBP and DBP, heart rate, and PWV every 15 minutes during the day (07:00 to 22:00 h) and every 30 minutes during the night (22:00 h to 07:00 h) for 24 hours. The measurements were used for the analysis only if

more than 80% of the recordings were valid. MOB first hour PWV and MOB 24h PWV were studied separately. MOB first hour PWV was given by calculating the average of three individual measurements in the first 60 minutes of recording time in accordance with previous literature data (83).

In the entire cohort, PP PWV was higher than MOB first hour PWV (difference: 1.2 (-0.5-2.6) m/s, $p<0.001$) and also higher than MOB 24h PWV (difference: 1.3 (0.3-2.2) m/s, $p<0.001$).

There was no correlation between baseline PP PWV and MOB first hour PWV ($r=0.095$, $p=0.339$), but significant correlation was found between PP PWV and MOB 24h PWV ($r=0.723$, $p<0.001$, **Figure 1**.).

Figure 2 shows the Bland-Altman plots of PP PWV and MOB first hour PWV (**Figure 2A**) and PP PWV and MOB 24h PWV (**Figure 2B**). The results of the Bland-Altman analysis of PP PWV with MOB first hour PWV and MOB 24h PWV were that the 95% limits of accordance between the two methods extended from -4.36 to 6.96 and from -2.01 to 4.83, respectively.

Table 2. Office and ambulatory blood pressure and pulse wave velocity data. (76)

	All subjects	HT patients 1.	HT patients 2.	WhHT patients 1.	WhHT patients 2.
Office systolic BP (mmHg)	140.8 ± 16.8	150.2 ± 15.3	***128.7 ± 13.9***	134.5 ± 12.3	***128.3 ± 16.6***
Office diastolic BP (mmHg)	85.3 ± 9.6	93.3 ± 9.9	***76.9 ± 18.8***	84 ± 6	81.8 ± 5.7
Office heart rate (1/min)	75 (68-86)	84.5 (70.5-88)	73 (70-83)	76.2 (69.5-84.6)	75.6 (66.7-84.8)
1st hour systolic BP (mmHg)	136.8 ± 12.4	137.5 ± 12.5	138.6 ± 14.5	135.5 ± 13.1	***127.4 ± 14.2***
1st hour diastolic BP (mmHg)	89.5 ± 10.5	92.1 ± 9.8	88 ± 11.5	88.5 ± 10.6	86.8 ± 9.1
1st hour heart rate (1/min)	78 (72.6-86.8)	76 (63.2-82.7)	78.3 (73.2-82)	86.3 (76.6-98.2)	81.8 (72.7-91.5)
24-hour systolic BP (mmHg)	128.2 ± 10.2	136.9 ± 7.6	***126 ± 9.7***	123.5 ± 6.3	122.3 ± 5.9
24-hour diastolic BP (mmHg)	81 ± 9.1	88.6 ± 8.3	***79.9 ± 9.6***	78.1 ± 5.2	77.7 ± 4.8
24-hour heart rate (1/min)	73 (68-81)	77 (71.5-84.5)	73.5 (67-81.5)	76.5 (70-83.5)	73 (68.7-80.7)
PulsePen PWV (m/s)	8.7 (7.3-9.9)	8.9(7.9-10.4)	***8.1 (7.1-9.1)***	8 (6.8-9.1)	***7.6 (6.7-8.7)***
Mobil-O-Graph 1st hour PWV (m/s)	7.3 (6.5-8.8)	7.3 (6.6-8.1)	7.3 (5.9-8.6)	7.7 (6.9-8.9)	7.6 (6.1-8.6)
Mobil-O-Graph 24-hour PWV (m/s)	7.4 (6.4-8.8)	7.3 (6.4-8.6)	***6.8 (6.2-7.8)***	6.9 (5.6-7.6)	7 (5.7-7.7)

The total number of participants was 105. For newly diagnosed hypertensive patients (HT; n=22) and white-coat hypertensive patients (WhHT; n=22) the 1st columns are baseline data; the 2nd columns are follow-up data. Descriptive data are expressed as mean ± standard deviation or median with interquartile ranges as appropriate. The Kolmogorov-Smirnov test was used to test the normality of continuous parameters. Hemodynamic parameters and pulse wave velocity evaluated with different methods were compared between baseline and follow-up using paired Student's t-test or dependent samples Wilcoxon Signed Rank test for data failing tests of normality as needed. Italic and bold characters demonstrate significant differences ($p<0.05$) after the follow-up in newly diagnosed hypertensive and white-coat hypertensive patients. BP: blood pressure

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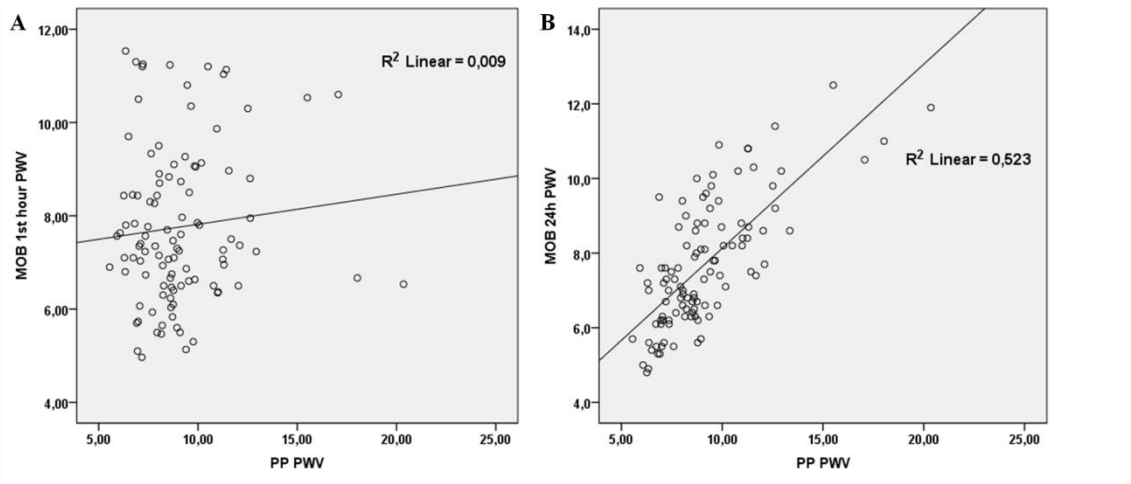

Figure 1. Correlations between PulsePen pulse wave velocity and Mobil-O-Graph 1st hour (A) and 24 h pulse wave velocity (B) in the total population (n=105). Pearson's correlation coefficient was assessed (76).

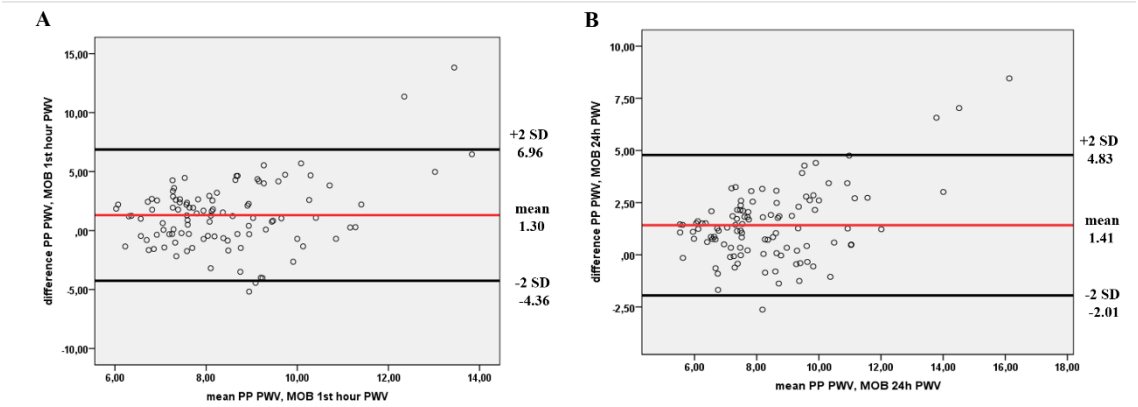

Figure 2. Bland–Altman plots of PulsePen pulse wave velocity and Mobil-O-Graph first hour pulse wave velocity (A) and PulsePen pulse wave velocity and Mobil-O-Graph 24 h pulse wave velocity (B). N=105 (76).

3.1.2. Comparison of changes in pulse wave velocity during follow-up in patients with hypertension and white-coat hypertension

Table 1 also contains the demographic and laboratory data of HT and WhHT patients at the end of follow-up. Laboratory data did not show any changes during the follow-up in either HT or WhHT subjects. At the conclusion of follow-up, 9 HT patients were on monotherapy (40.9%) and 13 HT patients were on dual combination therapy (59.1%). Monotherapies were an angiotensin-converting enzyme inhibitor (ACE-inhibitor) or a calcium-channel blocker (CCB) in 3-3 cases, a beta-blocker in 2 cases, and a centrally-effective drug in 1 case. Ten patients were on an ACE-inhibitor plus CCB, two were on an ACE-inhibitor plus a diuretic, and one patient was on an ARB plus CCB therapy.

Table 2 shows the office and ambulatory hemodynamic and PWV data in patients who were newly diagnosed with HT, also 3 months after starting a treatment of antihypertensive medication and in WhHT patients at the 12-month control. In the case of WhHT patients the average blood pressure was under 140/90 mmHg. In contrast with the screening visit blood pressure data, in more relaxed conditions the values measured were lower in 9 cases within these subjects, and the white-coat effect was not reproduced. Despite this, we left them in the WhHT group and these subjects also received instructions for modifications in lifestyle. Initially, in HT patients PP PWV was significantly higher than MOB first hour and MOB 24h PWV ($p<0.001$), while in WhHT subjects PP PWV was higher than MOB 24h PWV, but the divergence was not significant when compared with MOB first hour PWV. In regards to therapy effectiveness, both office and 24-hour systolic and diastolic blood pressures decreased significantly in HT patients. In the case of WhHT patients, office SBP also became lower in the 12-month control after lifestyle changes. PP PWV decreased significantly both in HT (with 0.9 (0.4-1.5) m/s, $p<0.05$) and WhHT patients (with 0.3 (-0.1-1) m/s, $p<0.05$). MOB first hour PWV did not change significantly either in HT or in WhHT. MOB 24h PWV decreased only in HT patients (with 0.2 (0-0.6) m/s). In comparison with MOB 24 h PWV, PP PWV decreased by a significantly higher amount in both HT and WhHT patients ($p=0.01$ and $p=0.028$, respectively). Compared with MOB first hour PWV, PP PWV decreased by a significantly higher amount only in HT patients ($p=0.032$).

3.1.3. Determinants of the three examined pulse wave velocities

Univariate and multivariate linear regression analyses were conducted to examine the determinants of PP PWV, MOB first hour, and MOB 24 h PWV in baseline and also in the prospective part of the research after the follow-up. In the case of univariate analyses, PP PWV was significantly linked with office brachial SBP and age. MOB first hour PWV was also significantly associated with heart rate and brachial SBP, while MOB 24h PWV was significantly and very strongly linked with age and diabetes, smoking, 24-hour brachial DBP, and 24-hour heart rate **(Table 3)**.

Table 3. Associations with univariate regression analyses of pulse wave velocities measured with PulsePen and with Mobil-O-Graph in 1st hour and 24-hour settings (n=105). (76)

PulsePen PWV					
Variable	**Adjusted R^2**	**B**	**Std. error**	**p**	**95% conf. interval**
Age	0.419	0.113	0.013	>0.001	0.087 - 0.139
Office brachial SBP	0.296	0.082	0.012	>0.001	0.057 - 0.107
Mobil-O-Graph 1st hour PWV					
Variable	**Adjusted R^2**	**B**	**Std. error**	**p**	**95% conf. interval**
1st hour systolic BP	0.046	0.031	0.013	0.017	0.006 - 0.057
1st hour heart rate	0.058	-0.037	0.013	0.008	-0.063 - -0.010
Mobil-O-Graph 24h PWV					
Variable	**Adjusted R^2**	**B**	**Std. error**	**p**	**95% conf. interval**
Age	0.930	0.115	0.003	>0.001	0.108 - 0.120
Diabetes	0.059	1.662	0.603	0.007	0.464 - 2.859
Smoking	0.032	-0.888	0.429	0.041	-1.741 - -0.035
Brachial 24h DBP	0.028	-0.036	0.018	0.047	-0.073 - -0.0004
24h heart rate	0.108	-0.063	0.017	<0.001	-0.097 - -0.0290
SBP: systolic blood pressure; DBP: diastolic blood pressure; MOB: Mobil-O-Graph, PWV: pulse wave velocity.					

Table 4 shows thebaseline results of the multivariate regression analyses. PP PWV variability was determined in 57.5% with the confounders included. MOB 1st hour PWV variability was determined to a considerably lower degree. By contrast, MOB 24h PWV variability was exclusively determined by the included confounders (96.8%).

When we analyzed the associations between changes in BP and PWVs, we found only a tendency to significance in changes in office SBP and 24-hour SBP (adjusted R^2= 0.03, p=0.130). There was a significant association between the drop in office SBP and the PP PWV decrease (adjusted R^2= 0.140, p= 0.010), and we found a robust association between 24-hour SBP change and MOB 24h PWV change (adjusted R^2= 0.952, p<0.001). A significant association was observed between PP PWV and MOB 24h PWV change (adjusted R^2= 0.196, p= 0.002)

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Table 4. Results of multivariate regression analyses for determinants of pulse wave velocities measured with PulsePen and with Mobil-O-Graph in 1st hour and 24-hour settings (n=105). (76)

PulsePen PWV, model adjusted R^2: 0.575				
Variable	**B**	**Std. error**	**p**	**95% conf. interval**
Age	0.095	0.015	>0.001	0.064 - 0.125
Sex	-0.581	0.362	0.112	-1.301 - 0.138
Diabetes	-0.202	0.726	0.782	-1.645 - 1.241
Smoking	0.596	0.456	0.195	-0.311 - 1.504
BMI	-0.675	0.046	0.147	-0.159 - 0.024
LDL	-0.059	0.163	0.718	-0.385 - 0.266
Office brachial SBP	0.067	0.012	>0.001	0.041 - 0.092
Office brachial DBP	-0.023	0.021	0.262	-0.065 - 0.018
Office heart rate	0.023	0.016	0.148	-0.008 - 0.055
Mobil-O-Graph 1st hour PWV, model adjusted R^2: 0.133				
Variable	**B**	**Std. error**	**p**	**95% conf. interval**
Age	0.017	0.013	0.203	-0.009 - 0.044
Sex	0.457	0.353	0.200	-0.264 - 1.161
Diabetes	0.619	0.714	0.388	-0.801 - 2.039
Smoking	-0.168	0.441	0.703	-1.046 - 0.708
BMI	-0.23	0.46	0.616	-0.116 - 0.649
LDL	0.079	0.157	0.615	-0.233 - 0.392
1st hour systolic BP	0.053	0.018	0.005	0.016 - 0.089
1st hour diastolic BP	-0.029	0.021	0.184	-0.072 - 0.014
1st hour heart rate	-0.039	0.014	0.009	-0.069 - -0.010
Mobil-O-Graph 24h PWV, model adjusted R^2: 0.968				
Variable	**B**	**Std. error**	**p**	**95% conf. interval**
Age	0.112	0.002	>0.001	0.107 - 0.117
Sex	-0.201	0.069	0.005	-0.338 - -0.064
Diabetes	0.083	0.135	0.542	-0.186 - 0.352
Smoking	-0.0004	0.093	0.996	-0.187 - 0.186
BMI	-0.009	0.009	0.295	-0.027 - 0.008
LDL	-0.032	0.030	0.292	-0.092 - 0.028
Brachial 24h SBP	.045	0.004	>0.001	0.036 - 0.054
Brachial 24h DBP	-0.023	0.005	>0.001	-0.034 - -0.012
24-hour heart rate	0.0004	0.004	0.915	-0.008 - 0.009
Sex: the influence female is considered; BMI: body mass index; LDL: low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; MOB: Mobil-O-Graph, PWV: pulse wave velocity.				

3.2. Integrated central blood pressure–aortic stiffness (ICPS) risk score for cardiovascular risk stratification in chronic kidney disease (Study 2)

A retrospective cohort study was performed. Patients with CKD in stages 1-5 who were not on dialysis therapy and who signed an informed consent to participate were included. We excluded patients who had atrial fibrillation or frequent ventricular extrasystoles that counteracted with pulse wave analysis. Five of the 108 patients who were found eligible for inclusion refused to participate. In addition, three patients had to be excluded for absent baseline or follow-up data; this left 100 individuals in the analytical sample. Following baseline clinical, laboratory, arterial stiffness and central hemodynamic measurements, the patients were observed in follow-up for a median of 67.6 months (interquartile range: 38.4-82.6).

Blood pressure was measured with a validated BpTru device (VSM Medtech, Vancouver, Canada). The stiffness of the arteries was measured using the tonometric method, employing the PulsePen device (DiaTecne, Milan, Italy, PP PWV).

Table 5 shows baseline characteristics, along with concomitant diseases, as well as traditional and non-traditional cardiovascular risk factors, both metabolic and vascular parameters.

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Table 5. Baseline demographic, clinical and laboratory characteristics (n=100). (84)

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/ 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 (mmHg)	135.50 (120.31-145.44)
DBP (mmHg)	73.12 (9.70)
Heart rate (1/ min)	62.25 (57.50-72.63)
PP (mmHg)	60.38 (50.56-70.38)
PWV (m/s)	11.26 (8.90-14.90)
Aix (%)	21.53 (15.35-26.83)
cSBP (mmHg)	124.33 (14.50)
cPP (mmHg)	48.58 (42.75-60.38)

Categorical parameters are shown as n; numbers can be also regarded as percentages. Continuous data are shown 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; LDL: low-density lipoprotein; n: case number; PP: brachial pulse pressure; PWV: carotid-femoral pulse wave velocity; SBP: brachial systolic blood pressure; Tg: triglyceride.

There were multiple causes of kidney disease (case numbers 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).

Except for one patient, all were given medication for hypertension (number of cases in parentheses): angiotensin receptor blockers (ARB-blockers) or ACE-inhibitors (n = 89), CCB-s (n = 52), diuretics (n = 74), β-receptor blockers (n = 54), α-receptor blockers (n = 18), long-acting nitrate (n = 15), and centrally acting drugs for hypertension (n = 13), either individually or in combination. Aspirin was given to 36 patients in low doses, while 17 individuals were given clopidogrel. Sixty-one of the patients were treated with statin.

Overall, n = 37 patients needed erythropoietin-stimulating agents, n = 35 were given calcitriol, and n = 9 required a therapy of calcium carbonate phosphate binder.

The primary result of the research was the incidence of the combined endpoint of CV events and CV mortality as follows: at the last incidence of a recorded cardiovascular event (heart failure that required hospitalization, acute coronary syndrome, stroke or transient ischemic attack, or peripheral artery disease requiring intervention) or death as a result of the above-mentioned cardiovascular causes.

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

To evaluate the predictive values of the investigated parameters for the primary outcome, multiple-failure-time Cox proportional hazard regression analyses were performed with conditional risk set modeling, which method takes into consideration the possibility of one patient having had more than one event within the follow-up period.

No a priori power calculations were performed for the present analysis, although the sample size for the original study came from the differences we observed and the distribution of one of the measures of arterial stiffness (cPP) ((60)). A post hoc power calculation displayed power values between 0.60 and 0.97 for individual parameters for arterial stiffness (as continuous variables) for predicting cardiovascular events.

We analyzed arterial stiffness central hemodynamic parameters as continuous as well as categorical variables. To improve their comparability, continuous variables were converted into z-scores.

Table 6 shows the link between PWV, cSBP, cPP, and Aix (per one SD change and per tertiles) and cardiovascular outcomes in those models that have been adjusted for age and sex in Model 1 or for the common cardiovascular risk factors in Model 2 (age and sex, LDL-cholesterol, brachial systolic blood pressure, diabetes, current smoking, BMI, known cardiovascular disease, and eGFR). Because there was only one patient without hypertension in the cohort, this variable was excluded from the adjustment.

The four parameters studied were significantly linked to cardiovascular outcomes in Model 1. In Model 2, which was further modified, the association between PWV and cPP diminished to non-significance, whereas cSBP and Aix demonstrated significant associations.

Table 6. Cox models showing cardiovascular mortality and morbidity as outcome and individual arterial stiffness and central hemodynamic parameters as predictors. (84)

				Model 1				**Model 2**			
Variable	**Tertile**	**N**	**Range**	**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**
PWV (m/s)	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 (mmHg)	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 (mmHg)	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

Cox proportional hazard regression analyses were used with conditional risk set modeling. Values in bold show significance when $p < 0.05$. Model 1 is modified for sex and age. Model 2 is modified for sex, age, LDL-cholesterol, brachial systolic blood pressure, diabetes mellitus, current smoking, body mass index, cardiovascular disease, and estimated glomerular filtration rate. Aix: augmentation index; CI: confidence interval; cPP: central pulse pressure; cSBP: central systolic blood pressure; PWV: carotid-femoral pulse wave velocity; SD: standard deviation

Patients were later sorted into tertiles on the basis of their PWV, cSBP, cPP and Aix values. We examined survival with the help of the Kaplan-Meier analysis and Cox-regressions similar to those mentioned above, with the stiffness of arteries and central hemodynamic parameters as predictors, and cardiovascular events or death from cardiovascular diseases as outcomes. We used simple and polynomial contrasts to examine the best scoring for these tertiles. During the analyses of tertiles, PWV and cPP demonstrated a linear relationship with the risk of CV outcomes, and the consecutive tertiles were given 0, 1 and 2 points accordingly. We found a nonlinear association for cSBP, which demonstrated an increased exclusively in the third tertile in Model 1,

adjusted for age and sex. This was assigned 1 point, whereas the first two tertiles, where no increase was shown, were assigned 0 points each. No significant association was found for Aix; consequently, we excluded this parameter from the ICPS score calculation. The associations were substantially lower when further adjustments were made in Model 2 for the most frequent CV risk factors; no risk factors remained significant. Associations that were not adjusted are demonstrated as Kaplan–Meyer curves for every one of the tertiles in all four parameters, as shown in **Figure 3**.

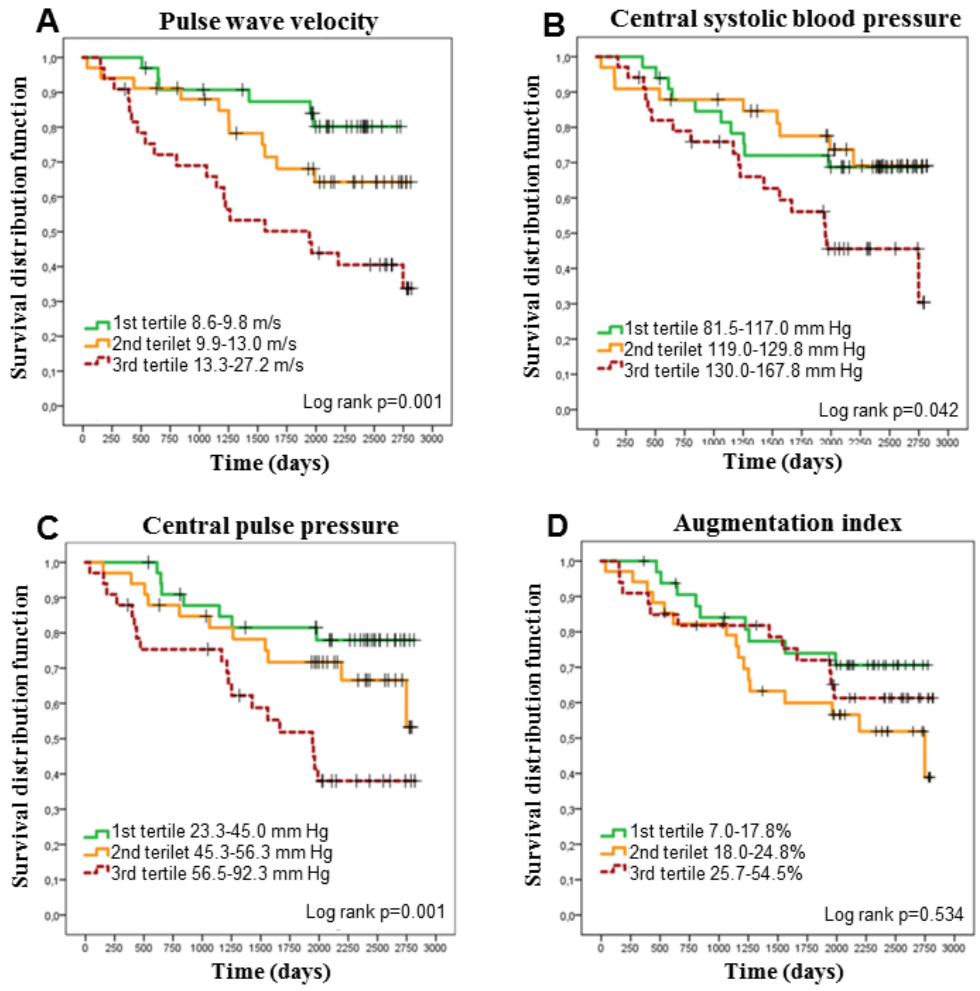

Figure 3. Kaplan–Meier survival curves for every investigated parameter with cardiovascular mortality and cardiovascular events as outcomes. **Panel A:** pulse wave velocity; **Panel B:** central systolic blood pressure; **Panel C**: central pulse pressure; **Panel D**: augmentation index. (84)

The ICPS (integrated central blood pressure-aortic stiffness) score was calculated in the case of each patient by adding the points on the basis of tertiles (range: 0-5 points).

Kaplan-Meier and Cox regression analyses,which were adjusted for age and sex, were used to investigate survival with the ICPS score as predictor and CV event / CV mortality as outcome. Due to our relatively small sample size, the statistical power was limited, thus the patients were put into one of three ICPS risk categories: very high (5 points), high (3-4 points), or average (0-2 points). Kaplan-Meier curves and Cox regressions were used to investigate the predictiveness of these risk categories in Model 1 and Model 2. **Table 7.** shows hazard ratios for CV outcomes with the help of ICPS risk scores as well as ICPS risk categories. Cox models (**Table 7**) and Kaplan–Meier analyses **(Figure 4A)** were used to set up the risk categories by collapsing ICPS scores with similar hazard ratios and sufficient statistical power. Nearly half of the patients were put into the very high- and high-risk categories. **Figure 4B** shows Kaplan–Meier survival curves for each of the three ICPS risk categories.

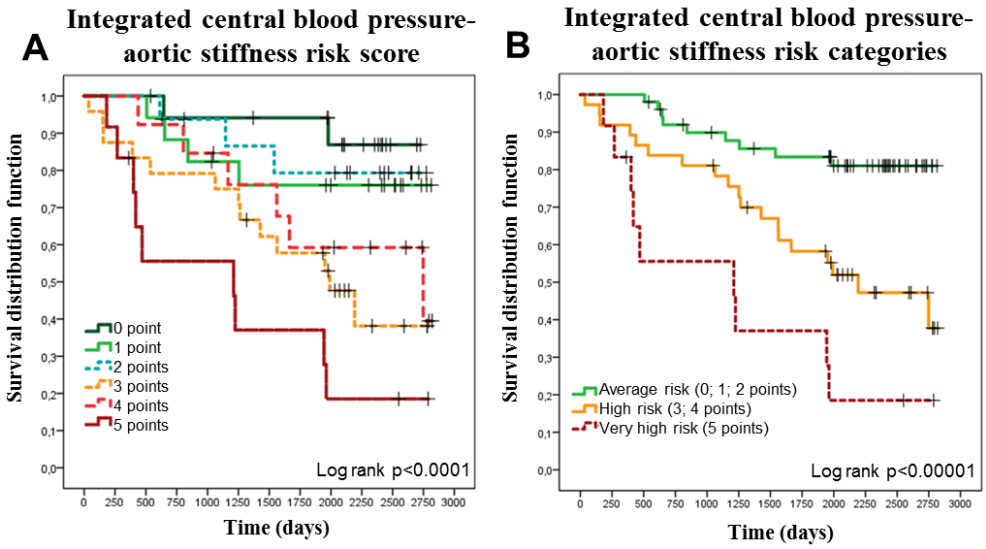

Figure 4. Kaplan–Meier survival curves for risk scores regarding the integrated central blood pressure–aortic stiffness (ICPS) and ICPS risk categories for CV mortality and CV events (cardiovascular events) adjusted for age and sex as outcomes. **Panel A**: ICPS risk score groups; **Panel B**: ICPS risk categories. (84)

Table 7. demonstrates a strong relationship between the ICPS risk categories and CV outcomes even after they were adjusted for traditional cardiovascular risk factors. It is also noteworthy that in the case of Model 2, diabetes and ICPS risk categories were the only predictors that were statistically significant, and had a higher risk in the very high and high ICPS risk categories in comparison with diabetes.

Table 7. The relationship between integrated central blood pressure-aortic stiffness (ICPS) risk score and ICPS risk categories with CV morbidity and mortality on the basis of Cox proportional hazard regression models. (84)

	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**

Values written in bold show significance when p <0.05. Model 1 has been adjusted for age and sex. Model 2 has been adjusted for age, sex, LDL-cholesterol, brachial systolic blood pressure, current smoking, body mass index, diabetes mellitus, cardiovascular disease and eGFR. ICPS: integrated central blood pressure-aortic stiffness.

Lastly, we analyzed the ICPS risk categories and one SD change of each of the components (PWV, cSBP or cPP) in the same Cox-regression model for cardiovascular outcomes. Harrell's concordance statistics were used to examine model discrimination. **Table 8.** shows the results of the comparing the discriminative ability of the ICPS risk categories with one SD change of PWV, cSBP, and cPP. The parameters were all adjusted for age and sex. In the discrimination to PWV and cSBP, ICPS risk categories were superior, and a tendency could be observed in case of cPP, but there was no significant difference.

We found similar results when we repeated all the calculations as a sensitivity analysis at the closure of the follow-up period after the first event, instead of multiple failure time analysis.

Table 8. Comparison of the discriminative ability of the ICPS risk categories with the one standard deviation change of PWV, cSBP and cPP (Harell's C-statistics). (84)

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

Values written in bold show significance when $p < 0.05$. CI: confidence interval; ICPS: integrated central blood pressure-aortic stiffness; PWV: carotid-femoral pulse wave velocity, cSBP: central systolic blood pressue, cPP: central pulse pressure.

3.3. Integrated Central Blood Pressure-aortic Stiffness (ICPS) Risk Categories and Cardiovascular Mortality in End-stage Renal Disease (Study 3)

Study 3 was a retrospective cohort study. In total, 126 ambulatory, chronic (>3 months on HD) ESRD patients treated at the two dialysis units were asked to take part in the study. Of these, seven patients were excluded due to atrial fibrillation and 28 patients refuse to participate, leaving 91 patients for the analytical sample. Patients' follow-up lasted for a median of 29.5 months (interquartile range: 1-51). We had as outcome measure death from a CV event, defined as recorded myocardial infarction, heart failure, stroke, malignant arrythmia leading to death, or sudden cardiac death. The measurements were taken before a midweek HD session; predialysis blood sampling and arterial stiffness measurements were performed on different days within a single week. We measured PWV, Aix, cSBP and cPP with the help of applanation tonometry (PulsePen device; DiaTecne s.r.l. Milan, Italy). Because current recommendations suggest using 80% of the direct carotid-femoral distance as the most precise proxy of the numerator for PWV measurement, we recalculated our previous data accordingly (77). The blood pressure was measured using a validated BpTru device (VSM Medtech, Vancouver, Canada).

Table 9 shows baseline characteristics, including common cardiovascular risk factors, associated diseases, dialysis duration, primary renal disease leading to ESRD, and laboratory and hemodynamic parameters.

Eighty-two patients were given antihypertensive medications (case numbers in parentheses): calcium channel blockers (n = 58), b-receptor blockers (n = 56), renin-angiotensin system inhibitors (n = 51), a-receptor blockers (n = 28), and centrally acting antihypertensive drugs (n = 20), either alone or in combination. In all, n = 58 patients received vitamin D and n = 72 required calcium carbonate phosphate binder therapy.

During follow-up, 31 cardiovascular deaths were documented: eight patients died from heart failure, seven from myocardial infarction, seven from sudden cardiac death, six from stroke, and three from arrythmia.

Predominantly, the flow of statistical analysis followed our previous report (84). We investigated survival using Kaplan-Meier and Cox regression analyses, where ICPS score was the predictor and cardiovascular mortality was the outcome. The stiffness of arteries and central hemodynamic parameters were examined as continuous as well as categorical

variables. Continuous variables were converted into z-scores to enhance their comparability, this way, the associations are indicated for one SD difference in PWV, Aix, cSBP and cPP for the CV outcome (Cox-regression).

Table 9. Baseline demographic, clinical, laboratory and hemodynamic characteristics of participants. (85)

Subjects n	91	**Laboratory results**	
Sex (male, %)	56 (61.5)	Hemoglobin (g/l)	116.0 (103.0-123.0)
Age (years)	63.3 (14.8)	Creatinine (umol/l)	650.0 (516.0-834.0)
Dialysis duration (months)	29.5 (13.7-33.6)	Blood urea nitrogen (mmol/l)	19.6 (16-24.5)
Residual diuresis (ml/day)	650 (100-1300)	Cholesterol (mmol/l)	4.5 (1.2)
BMI (kg/m^2)	25.2 (4.5)	HDL-cholesterol (mmol/l)	1.2 (1.0-1.6)
Smoking n (%)	17 (18.7)	LDL-cholesterol (mmol/l)	2.5 (1.9-3.2)
Diabetes n (%)	38 (41.6)	Triglyceride (mmol/l)	1.7 (1.0-2.7)
Cardiovascular disease n (%)	55 (60.4)	Sodium (mmol/l)	137.0 (135.0-139.0)
Primary renal disease, n (%)		Potassium (mmol/l)	5.2 (0.9)
Diabetic	31 (34.1)	Calcium (mmol/l)	2.3 (2.2-2.4)
Hypertensive	17 (18.7)	Phosphate (mmol/l)	1.6 (1.1-1.9)
Tubulo-interstitial	14 (15.3)	Albumin (g/l)	40.0 (37.6-42.0)
Glomerulonephritis	13 (14.3)	Parathormone (pmol/l)	7.08 (3.88-18.5)
Polycystic	6 (6.6)	25-OH vitamin D (µg/l)	24.7 (18.7-36.5)
Other or unknown	10 (11.0)	CRP (mg/l)	6.7 (4.1-15.1)
Hemodynamic data			
Systolic blood pressure (mmHg)	141.6 (24.7)		
Diastolic blood pressure (mmHg)	77.9 (13.0)		
Heart rate (1/min)	72.4 (12.6)		
Pulse pressure (mmHg)	62.5 (47.0-79.5)		
PWV (m/s)	11.1 (9.3-14.1)		
central SBP (mmHg)	141.9 (23.3)		
central PP (mmHg)	63.5 (47.0-79.0)		
Aix (%)	19.0 (11.0-28.5)		

Categorical parameters are shown as n, numbers can be also regarded as percentages. Continuous data are shown as mean (SD) or median (interquartile range).
Aix: augmentation index; BMI: body mass index; central PP: central pulse pressure; central SBP: central systolic blood pressure; PWV: carotid-femoral pulse wave velocity.

Table 10 shows the relationship between PWV, cSBP, cPP and Aix (per one SD difference, for each tertile) and CV mortality. Model 1 was unadjusted, while Model 2 was adjusted for age, sex, LDL-cholesterol, brachial SBP, current smoking, BMI and history of cardiovascular disease. Only PWV, as a single independent variable, was significantly associated with death from CV events. In the tertile analyses, the 2nd tertile of PWV in Model 1, and the 2nd and 3rd tertiles of cSBP in Model 2 were in association with the outcome. Associations that were not adjusted are displayed as Kaplan–Meyer curves for every tertile of all four parameters in **Figure 5**. This shows non-linear associations: an elevation in the 2nd and 3rd teritle of PWV and cPP and only in the 3rd tertile of cSBP. Because Aix tertiles were not associated with outcome and the curves of the tertiles crossed each other, we excluded this parameter from calculation of the ICPS score.

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Table 10. Cox models with cardiovascular mortality as outcome and individual arterial stiffness and central hemodynamic parameters as predictors. (85)

Variable				Model 1				Model 2			
				Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
PWV (per 1 SD)				1.965	1.322	2.920	**0.001**	1.614	1.069	2.438	**0.023**
cSBP (per 1 SD)				1.223	0.832	1.798	0.305	1.162	0.787	1.716	0.450
cPP (per 1 SD)				1.345	0.942	1.920	0.102	1.066	0.730	1.556	0.740
Aix (per 1 SD)				0.967	0.677	1.381	0.854	1.431	0.929	2.203	0.104
				Model 1				Model 2			
Variable	**Tertile**	**N**	**Range**	**Hazard ratio**	**95% CI**		**P-value**	**Hazard ratio**	**95% CI**		**P-value**
PWV	1st	30	4.7-9.7	1 (ref.)				1 (ref.)			
	2nd	31	9.7-12.8	0.339	0.122	0.943	**0.038**	0.527	0.186	1.49	0.227
	3rd	30	13.3-24.8	0.951	0.439	2.057	0.898	0.913	0.421	1.98	0.818
cSBP	1st	30	88.3-131.8	1 (ref.)				1 (ref.)			
	2nd	31	132.5-152	0.540	0.226	1.287	0.164	0.066	0.009	0.502	**0.009**
	3rd	30	154-200.3	0.524	0.227	1.213	0.131	0.141	0.04	0.494	**0.002**
cPP	1st	30	24-52.3	1 (ref.)				1 (ref.)			
	2nd	31	52.5-73.3	0.567	0.226	1.421	0.226	0.936	0.365	2.399	0.89
	3rd	30	73.5-114.5	0.859	0.384	1.923	0.712	0.982	0.44	2.193	0.964
Aix	1st	31	-0.5-14.5	1 (ref.)				1 (ref.)			
	2nd	30	15.5-23.0	1.020	0.449	2.315	0.963	0.449	0.179	1.122	0.087
	3rd	30	23.5-53.5	0.742	0.298	1.848	0.522	0.445	0.175	1.13	0.089

Model 1 is unadjusted; Model 2 is adjusted for age, sex, current smoking, diabetes, body mass index, cardiovascular disease, brachial systolic blood pressure and LDL-cholesterol. PWV: pulse wave velocity; cSBP: central systolic blood pressure; cPP: central pulse pressure; Aix: augmentation index; SD: standard deviation

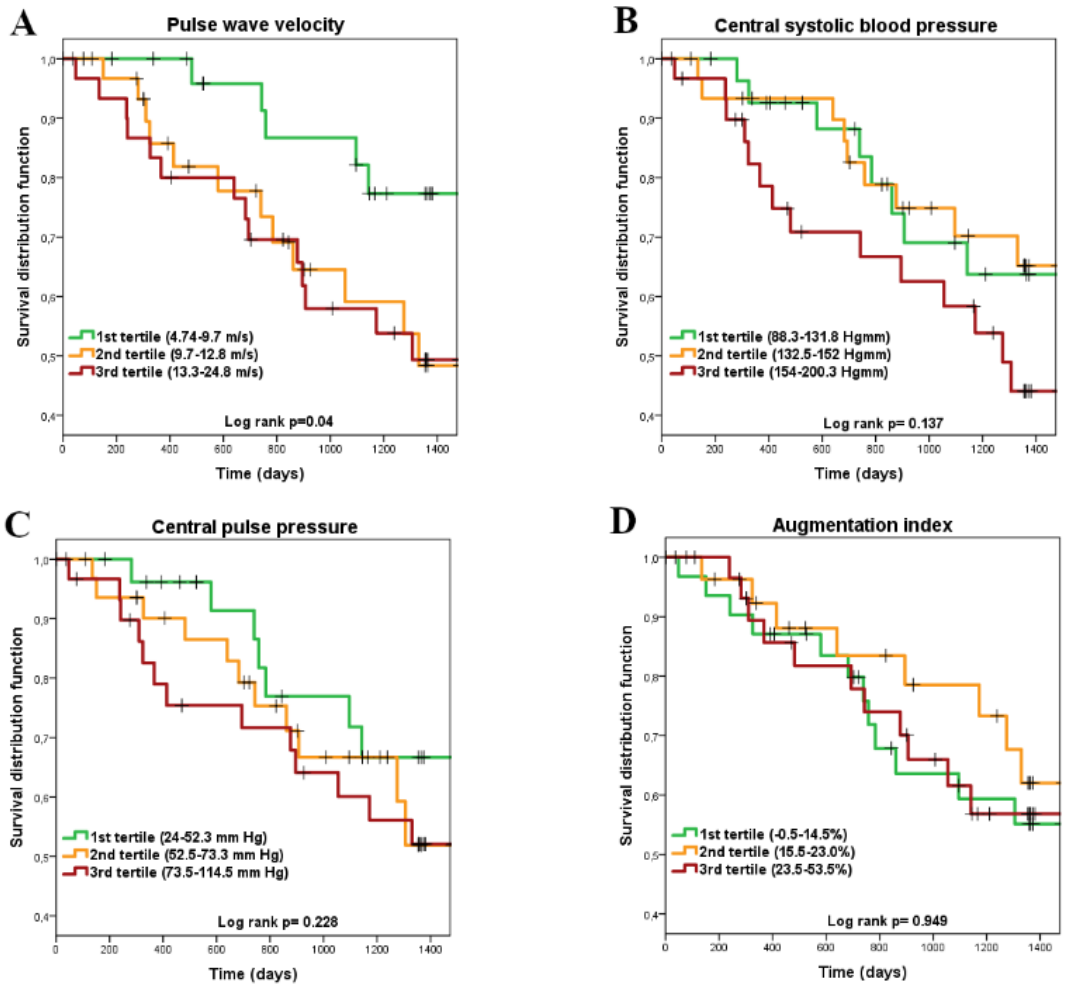

Figure 5. Kaplan–Meier survival curves with cardiovascular mortality as outcome for each integrated central blood pressure-aortic stiffness risk score component. **Panel A**: pulse wave velocity; **Panel B**: central systolic blood pressure; **Panel C**: central pulse pressure; **Panel D**: augmentation index. (85)

For the calculation of the ICPS score, one point was assigned if a patient's cSBP wasin the 3rd tertile, and if PWV or cPP were in the 2nd or 3rd tertiles. We calculated the ICPS score by adding up these points (range: 0-3 points).

Due to our relatively small sample size and hence the limited statistical power, we further reduced the number of risk categories and placed patients into three ICPS risk categories: average (0-1 points), high (2 points) or very high (3 points).

The predictive role of ICPS risk categories was examined with the help of Kaplan-Meier curves and Cox regressions with adjustments for age, sex, LDL-cholesterol,

brachial systolic blood pressure, diabetes, current smoking, BMI, and cardiovascular disease.

Table 11 shows hazard ratios for CV mortality through ICPS scores and risk categories. The risk groups were created on the basis of the results of the Cox-models (Table 11) and the Kaplan–Meier **(Figure 6A)** curves by collapsing ICPS scores with similar hazard ratios to improve statistical power. Nearly two-thirds of the participants were placed in the high and very high-risk groups. **Figure 6B** shows Kaplan–Meier survival curves for each of the three ICPS risk categories.

Table 11 demonstrates that CV mortality risk of those in the very high ICPS risk category was substantially higher and also slightly increased compared with the average through high to very high risk after adjustment for multiple CV risk factors. Besides the very high ICPS risk category in Model 2, older age (HR: 1.05, 95% CI: 1.01–1.09) and lower systemic SBP (HR: 0.97, 95% CI: 0.94– 1.00) continued to be independent predictors of death from CV events.

Finally, so that we could compare the predictive value of all ICPS risk categories and every one of its components (PWV, cSBP and cPP), all parameters were consecutively integrated into a Cox-regression model with death from CV events as the outcome. Harrell's concordance (Harrell's C) statistics were calculated to examine and contrast the discrimination of the various stiffness measures.

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Table 11. The relation of ICPS risk score and ICPS risk categories with cardiovascular mortality on the basis of Cox proportional hazard regression models. (85)

	N	Hazard ratio	95% CI		P-value
ICPS risk score					
Model 1					
0 point	18	1 (ref.)			
1 point	17	1.463	0.327	6.543	0.781
2 points	33	2.323	0.654	8.246	0.869
3 points	23	3.552	1.001	12.598	0.297
Model 2					
0 point	18	1 (ref.)			
1 point	17	0.668	0.131	3.399	0.627
2 points	33	2.112	0.410	10.886	0.371
3 points	23	10.126	1.056	97.110	**0.045**
ICPS risk categories					
Model 1					
Average	35	1 (ref.)			
High	33	1.902	0.748	4.837	0.177
Very high	23	2.910	1.145	7.396	**0.025**
Model 2					
Average	51	1 (ref.)			
High	33	2.622	0.816	8.432	0.106
Very high	23	10.034	1.666	60.425	**0.012**

Model 1 was unadjusted, while Model 2 was adjusted for age, sex, LDL-cholesterol, brachial systolic blood pressure, diabetes, current smoking, body mass index, and CV disease. ICPS: integrated central blood pressure - aortic stiffness

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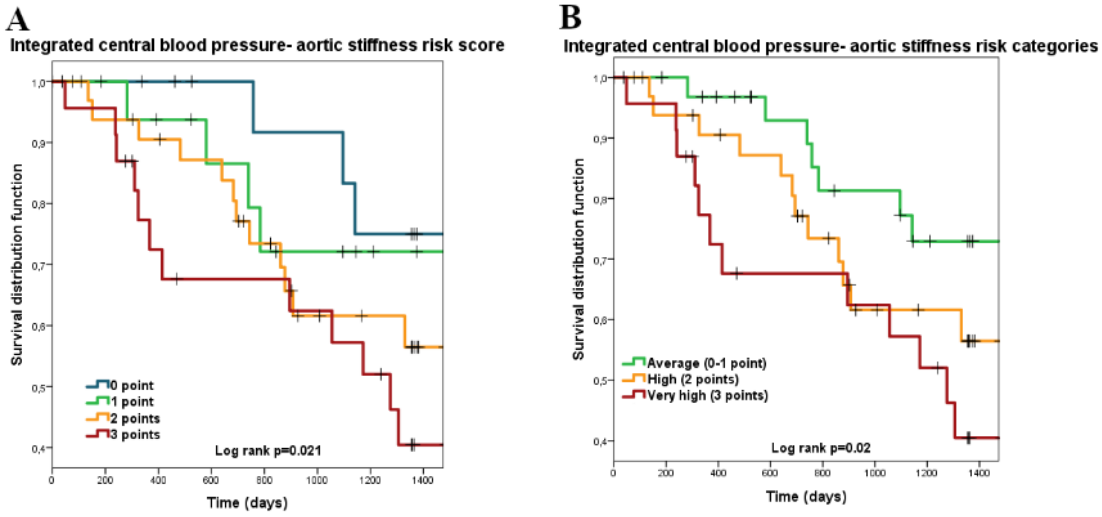

Figure 6. Kaplan–Meier survival curves for the integrated central blood pressure-aortic stiffness (ICPS) risk scores and ICPS risk categories for cardiovascular mortality as outcome. **Panel A:** ICPS risk score groups; **Panel B**: ICPS risk categories (85)

Table 12 shows C-statistics (and differences between C-statistics) for ICPS risk categories and PWV, cSBP, and cPP. All C-values indicate limited discrimination, though discrimination by ICPS risk categories was higher than that of cSBP. We could also see a tendency in the case of cPP, whereas ICPS risk categories and PWV had comparable C-statistics.

Table 12. Harrell's C statistics for ICPS risk categories and arterial stiffness measures and the differences in the C-statistics between ICPS risk categories and arterial stiffness measures. (85)

Variable	Coefficient	Standard error	95% CI		P-value
ICPS risk categories	0.622	0.049	0.525	0.719	**<0.001**
PWV	0.662	0.052	0.558	0.766	**<0.001**
cSBP	0.561	0.052	0.456	0.665	**<0.001**
cPP	0.588	0.05	0.489	0.687	**<0.001**
ICPS risk categories vs PWV	-0.04	0.051	-0.142	0.062	0.438
ICPS risk categories vs cSBP	0.061	0.028	0.006	0.117	**0.031**
ICPS risk categories vs cPP	0.034	0.028	-0.022	0.089	0.226

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

4. DISCUSSION

Evaluation of the stiffness of arteries and central hemodynamic status are possible tools in CV risk assessment. These parameters have been broadly researched in the past two decades, but their examination is not routinely recommended. Several factors play a role in this, including the heterogenity of the parameters, different measurement devices and different values of parameters measured with these devices. Additionally, the current "gold standard" carotid-femoral PWV is time-consuming and operator-dependent. However, arterial stiffness is an important risk factor for CV events and CV mortality in all stages of CKD (49), and in hypertension the evaluation of various arterial stiffness parameters can play a part in the identification of a subpopulation of high-risk patients (41).

Two devices were compared in our first study in hypertensive patients (Study 1): as the gold-standard tonometric method the PulsePen device, and for the 24-hour oscillometric method the Mobil-O-Graph was used. The significant differences observed in the determinants of different PWVs suggest that the examined methods are not interchangeable, and in the case of 24-hour PWV values a lower normality threshold limit should be considered.

With Studies 2 and 3, we developed and tested a concept in which the individual parameters of arterial stiffness and central hemodynamic properties can be integrated. From several parameters characterizing arterial stiffness and central hemodynamics, those with the highest predictive values were selected (cfPWV, cPP, cSBP and Aix) and measured by the gold standard tonometric method. Next, an integrated scoring system (ICPS score) was created on prospective studies of two populations. ICPS risk categories based on the ICPS scoring predicted CV outcome precisely and may thus become an important tool for CV risk assessment.

4.1. Comparison of office and ambulatory pulse wave velocity with PulsePen and Mobil-O-Graph devices (Study 1)

In the cross-sectional part of our study, we found significantly lower office and ambulatory Mobil-O-Graph PWVs when compared with those from the PulsePen device. PP PWV had a significant correlation only with MOB 24h PWV. In the next part of the study, the response of the PWV for antihypertensive therapy was found to be more

prominent with the PulsePen device, and for changes in lifestyle in patients with white-coat hypertension only PP PWV was lower. We found substantial differences between the amount of contribution of determinants of different PWVs.

Earlier validation studies in hypertensive and healthy subjects indicated acceptable agreement between Mobil-O-Graph parameters and the "gold standard" invasive and noninvasive methodologies (71, 82, 86, 87). Nevertheless, until now there have been only three studies available in the literature, where office tonometric PWV was matched against MOB 24h PWV. In accordance with the results of our research, in the study of Luzardo L et al. MOB 24h PWV decreased compared with SphygmoCor office PWV (7.4 ± 1.6 versus 7.9 ± 2.1 m/s, respectively) (70). In the study of Berukstis A et al., SphygmoCor office PWV also proved to be elevated compared with MOB 24h PWV (10.56 ± 2.59 versus 8.72 ± 1.29 m/s, respectively), with the marked difference of 1.84 ± 2.15 m/s (88). In the study of Schwartz JE et al., SphygmoCor PWV proved to be lower than MOB 24h PWV, but the distinction was not considered as significant (7.7 ± 1.7 versus 7.6 ± 1.3 m/s, respectively) (89). In our research the divergence between the oscillometric and tonometric devices was within the range of the values found in the previous studies (1.2 (-0.5-2.6) m/s). In agreement with our findings, in a recent study of Hametner B et al. a correlation coefficient of r=0.70 was found between invasive and MOB office PWV (90), which is nearly the same as our correlation coefficient (r=0.723), which we found between the PulsePen office and MOB 24h PWV. On the basis of these results we can deduce that although there is a strong correlation, MOB 24h PWV values are below office tonometric PWV values; as a consequence, the threshold limit of normality should probably also be adjusted to a lower value (this value now being 10 m/s for office carotid-femoral PWV). The lower 24h PWV values observed, in comparison with office values, are similar to a phenomenon in office and 24-hour ambulatory BP measurement, in which the threshold limit of normality diverge by 10/10 mmHg (140/90 mmHg and 130/80 mmHg, respectively).

The definition of MOB 1st hour PWV came from a study conducted earlier by Matschkal J et al., where 1st hour and 24h MOB PWVs were contrasted in hemodialysis patients; their association with death from all causes was also examined (83). Only MOB 24h PWV was associated independently with the outcome in that study. Utilizing the same methodology, there has been no significant correlation found between MOB 1st hour

PWV and tonometric PP PWV; the values proved to be lower and no change was observed for lifestyle modifications or antihypertensive therapy. It is worth noting that in the case of MOB the 1st hour PWV heart rate acted as an independent predictor, while age did not. The explanation for this result may be that soon after the installation of the Mobil-O-Graph, in the first hour, patients were traveling to their home or workplace, and this could have been the cause of the unusual variability in PWV. From these results we can conclude that MOB 1st hour PWV defined this way has no correlation with office cfPWV and also has unexpected determinants; however, the clinical usefulness of this parameter within different patient groups is yet to be investigated by future research.

In our research for the efficacy of antihypertensive therapy, we found that PWV changes yielded higher values when measured with the PulsePen than with the Mobil-O-Graph. Apart from that, modifications in the lifestyle of patients with white-coat hypertension caused improved PP PWV values, while there was no change in MOB PWVs. This observation might prove to be of clinical importance. In PWV changes can be a marker for the right treatment: in acute stroke patients a decrease in PWV values seemed to be associated with the clinical improvement they showed. (91). In addition, clinical decisions can be influenced by this because in patients on hemodialysis, PWV changes over a 6-month period were associated with death. The authors inferred that in patients showing higher PWV values the treatment of daily dialysis and more extensive cardiovascular intervention by cardiologists should be taken into consideration (92).

It is our assumption that the differences in PWV changes that the two devices measured may be linked with their differing methodologies. The PulsePen, which is considered as one of the the proper devices in the American Heart Association's recommendations for standardizing and improving vascular research on the stiffness of arteries (93), directly measures carotid-femoral PWV. The PulsePen was also used by Salvi P et al. in a comparative study which was performed on patients having Marfan syndrome, and in accordance with our results, PulsePen PWV was higher than Mobil-O-Graph PWV (94). However, that study used the two devices for parallel measurements, not for a comparison of 24-h Mobil-O-Graph and office PulsePen values. Contrary to the PulsePen, the Mobil-O-Graph utilizes a special pulse wave analysis algorithm to measure PWV. In their research, Schwartz JE et al. clearly demonstrated that age uniquely contributed to approximately 75% of the total variation of MOB PWV, while systolic blood pressure

uniquely was responsible for 20%. In all, age and SBP proved to be associated with 99.1% of the total variance of MOB PWV, but only 40.2% of the tonometric cfPWV variance (89). In agreement with their research, we have also observed in the cross-sectional part of our study that age to a large degree as well as SBP are determinants of MOB 24h PWV, while PP PWV is less affected by age and is more related to blood pressure. By contrast, MOB 1st hour PWV is hardly determined by traditional factors. In addition, changes in tonometric PWV depend less on blood pressure and are in all probability linked to a real destiffening of the arteries, while changes in the estimated 24-hour PWV are strongly dependent on changes in blood pressure. In the cross-sectional section of our study, we clearly demonstrated that MOB 24h PWV is mostly determined by age; in short-term follow-up studies only slight changes in it can be predicted, and our results also confirmed this. This is likely one explanation for our finding that in patients with white-coat hypertension, only PulsePen PWV showed decreased values after lifestyle interventions; for antihypertensive therapy the level of PWV improvement was less marked with the Mobil-O-Graph. Lastly, we observed the phenomenon that in both white-coat hypertensive and hypertensive patients, the effect of interventions decreased office blood pressure by a higher amount in comparison with 24-hour blood pressure (21.5/16.4 mmHg versus 10.9/8.7 mmHg in HT and 6.2/2.2 versus 1.2/0.4 mmHg in WhHT patients, respectively) which could also be a contributing factor in the more marked decrease in tonometric PWV. On the basis of these findings, we can conclude that both the threshold limits of normality, and the PWV changes as a result of individual interventions should be considered differently with the two devices mentioned. In prospective studies, more patients should be involved to be able to clarify the role of the independent determinants in inflicting changes in the different PWVs.

In conclusion, the significant deviation observed in the cross-sectional as well as the prospective sections of our study, and also in the determinants of individual PWVs suggests that the investigated methods are not interchangeable, and for 24-hour PWV values a decreased threshold limit of normality should be taken into consideration.

4.2. Integrated central blood pressure-aortic stiffness risk score for cardiovascular risk stratification in patients with chronic kidney disease on conservative therapy or hemodialysis (Study 2 and 3)

Our studies showed that the idea of an integrated score based on arterial stiffness and central hemodynamic parameters (ICPS) is substantially related to incident CV events in patients with chronic kidney disease, whether they receive conservative therapy or hemodialysis. Our results suggest that people classified in the high and very high ICPS risk categories are at an exceptionally high risk for CV outcome. Additionally, in the case of CKD patients who receive conservative therapy, the discriminative ability of ICPS risk scoring is superior to PWV and cSBP and is inclined to be better than cPP, whereas in CKD HD patients it is superior to cSBP, which implies that it is worthwhile to combine the predictive power of these parameters.

In our CKD cohort on conservative therapy (Study 2) high ICPS risk category patients had a significantly higher CV risk in contrast with the average risk group; however, this was not significant in Study 3. In our opinion, this is because of the limited power of Study 3 as the number of events occurring during the follow-up was smaller in comparison with Study 2 (n=31 versus n=49). In Study 2, the follow-up was censored at the last incidence of a recorded CV event (acute coronary syndrome, heart failure with the need of hospitalization, stroke or transient ischemic attack, or peripheral artery disease requiring an intervention) or death as a consequence of any of the above CV causes. However, in Study 3 the outcome measure was death resulting from a CV event, such as documented myocardial infarction, heart failure, stroke, malignant arrythmia causing death, or sudden cardiac death. Non-lethal CV events were not considered.

A consensus statement suggests that CV outcome prediction may be enhanced by the combined assessment of multiple biomarkers (95). In light of this recommendation, the present study examined the combined effect of arterial stiffness and central hemodynamic parameters utilizing a single score that combines the predictive information of individual biomarkers.

Previous studies show inconsistent results in connection with the role of non-invasive markers of functional or morphological arterial wall abnormalities with regard to CV risk, superior to traditional risk factors. In the Rotterdam study’s elderly patients, the evaluation of carotid intima-media thickness (c-IMT), peripheral artery disease, or PWV

slightly enhanced CV risk stratification over Framingham risk factors (96, 97). In comparison, in middle-aged patients from the ARIC study the measured increased c-IMT values and detected plaques in the carotid artery could be associated with a significant ~23% net reclassification index (98).

There are also some accessible data regarding the combined assessment of specific non-invasive hemodynamic biomarkers and their associations with CV outcomes. The results of the study by Wang et al. suggest that central SBP was better at predicting CV outcomes than brachial SBP or central or brachial pulse pressure (99). Holewijn et al. used net reclassification improvement analysis and concluded that CV risk stratification improved in women when they added non-invasive vascular risk markers like Aix, PWV, or cSBP to traditional risk factors. However, the link was found to be weaker in men, and it was only present in men at intermediate risk (100). These results indicate that the combined assessment of different vascular biomarkers may have some potential, but the results can be influenced by age and gender. In the whole of our study, adjustments were made for age and sex, but ICPS risk categories continued to be powerful predictors of CV events.

Niiranen T et al. in the Framingham Heart Study involving 2119 participants combined cfPWV with cPP after dividing their subjects into "high" and "low" groups based on the median values of the two parameters. It was found in the cross-sectional setting that using the low PWV-low cPP group as a reference, patients in the high PWV/high cPP group had a stronger association with left ventricular hypertrophy. Additionally, high PWV/high cPP participants had 52% higher risk of suffering a CV event than participants in the low PWV/low cPP group (101). These results confirm our findings that the combination of different vascular parameters can help to identify high CV risk patients. Unfortunately, this study did not compare the discriminative ability of this simple categorization to the discriminative ability of its components.

In our Study 2’s cohort of CKD patients on conservative therapy, a higher discrimination was observed in the ICPS risk categories over PWV when it came to predicting CV events, whereas it was similar to Study 3 in the ESRD cohort. Presumably, this is probably because PWV predicts CV outcomes much more reliably in ESRD patients on HD compared to CKD patients having conservative therapy (102). Our previous report on this CKD cohort confirms this latter hypothesis (60). This phenomenon

is presumably the consequence of the increased vascular calcification in patients on dialysis, which is firmly associated with mineral-bone disorder (103) and causes increased arterial stiffness and PWV.

The ICPS score concept has many potential advantages. First, PWV, cPP, and cSBP can easily be estimated with most of the accessible devices (e.g., tonometric, oscillometric or mechanotransducer-based) that measure the stiffness of arteries and apply pulse wave analysis. As opposed to traditional risk scores, which require blood sampling, the ICPS score can be determined non-invasively. In line with ICPS risk categories, the recently introduced SCORE2 also defines three risk categories: low-moderate, high and very high (58). Furthermore, with the help of ICPS risk categories the huge problem of diverging methodologies could be solved. Engineers create newer and newer devices which estimate the above-mentioned parameters in simplier manners, but their results are not interchangeable. The tertile-based ICPS scoring system in a certain population could be a universal parameter. Naturally, the tertiles of every parameter must be defined for each device, but presumably equations are not required to convert results between devices. Even though the three parameters we investigated correspond to each other, our results show that it is worth merging them into a single score as this can result in a highly predicting parameter.

In summary, our combined score and the ICPS risk categories we created proved to be strongly associated with CV outcomes in CKD patients who received conservative and HD therapy, highlighting the potential advantages of the integrated measure of arterial stiffness and central hemodynamic parameters for the prediction of CV risks.

4.3. Limitations and future perspectives

There are limitations to our Study 1. Because our patients were not randomly selected, its ability to generalize our findings could be limited; however, as our cohort enlists healthy individuals as well as patients with higher CV risk, it can also have indications of the general population. In addition, the fact that only a small number of patients were involved in the prospective sections of our study restricted the analysis of the confounding factors concerning the changes occurring in different PWVs, and new patients with hypertension and white-coat hypertension were analyzed together. Besides, in our paper

we only compared PWV as measured with the two devices; however, other parameters like cSBP, cPP or Aix can also be measured with both of the studied devices. Following the comparison of PWVs in the present paper, we also plan to examine and publish the findings in conncection with these other parameters in the future.

Our Study 1 discovered that the determinants of tonometric office and formula-based oscillometric 1st hour and 24-hour PWVs are different, and that these parameters change in a different manner for lifestyle changes or antihypertensive medications. The oscillometric 1st hour PWV probably has limited clinical relevance.

We must acknowledge that there are some limitations regarding our Studies 2 and 3. Patients suffering from atrial fibrillation had to be excluded during tonometric arterial stiffness measurements due to some methodological considerations; thus, some patients cannot be included in our new risk stratification method. Because there are few participants and outcome events, our studies are underpowered and we could therefore not define precisely the exact scoring thresholds or the relative contribution of each parameter. Thus, instead of defining the final score, the aim of Studies 2 and 3 was to reveal the possible benefits of this new concept of an amalgamated risk score calculated from arterial stiffness and central hemodynamic parameters. Large databases should serve as the basis for a valid risk score, with a substantially larger number of events, which would make it possible to examine each parameter in the score (104).

Nevertheless, because our ICPS risk categories in their current rudimentary form seem to be substantially stronger predictors than diabetes in our Study 2, we believe that the dissertation of our findings in this form can initiate major discussion and further research. There is great scientific potential in this concept because other cohorts in different races with PWV, cSBP and cPP measurements are available, consequently our results in conncection with ICPS risk categories could easily be extended for different patient populations. Examples of such cohorts include, e.g., the Framingham Heart Study cohort (63) and the Nijmegen Biomedical Study (100).

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5. CONCLUSIONS

The main findings of our studies are as follows:

1. The tonometric PulsePen and the oscillometric Mobil-O-Graph device are not interchangeable, and for 24-hour PWV values a decreased threshold limit of normality should be taken into consideration.

2. The response of PWV response to antihypertensive therapy was more remarkable with the PulsePen device; only PP PWV decreased following lifestyle changes in patients with white-coat hypertension. Substantial differences were found between the extent of the influence of determinants of individual PWVs.

3. Our integrated score and the ICPS risk categories we created showed strong and robust association with cardiovascular outcomes in patients with chronic kidney disease who received conservative therapy (Study 2). This highlights the possible benefits of the merged measured values of arterial stiffness and central hemodynamic parameters for the prediction of cardiovascular risk. Both high and very high ICPS risk categories continued to be independent predictors in a model that had been adjusted for several CV risk factors. ICPS risk categories showed better discrimination than PWV and cSBP, and a tendency of significance has been observed in the case of cPP.

4. Along with our previous results of CKD patients receiving conservative therapy, our study of ESRD patients (Study 3) is the second independent cohort in which our new concept showed encouraging results. Here, we observed a strong gradual association between ICPS risk categories and CV outcomes even after we adjusted them for multiple potential confounders. These ICPS risk categories had a slight discrimination which was significantly better than that of cSBP. The ICPS risk categories may enhance the identification of ESRD patients with a high cardiovascular mortality risk.

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6. SUMMARY

Measuring arterial stiffness and central hemodynamic parameters can improve the prediction of CV risk compared to traditional methods. The aim of our first study was to compare office and ambulatory pulse wave velocities (PWVs). Our aims in the second and third studies were to create an integrated central blood pressure-aortic stiffness (ICPS) risk score and risk categories – incorporating the predictive potential of identical parameters – to predict CV outcome.

In Study 1, office PWV was measured with the tonometric PulsePen device, and 1st hour and 24-hour ambulatory PWVs were evaluated with the oscillometric Mobil-O-Graph device (n=105). The ICPS score development was based on two retrospective cohort studies, where 100 CKD patients on conservative therapy and 91 ESRD patients on hemodialysis therapy were included. Values of PWV, cSBP (central systolic blood pressure), and cPP (central pulse pressure) were measured. Tertiles of PWV, cPP and cSBP were assigned a score on the basis of the ability of each parameter to separately predict CV outcome. We studied as predictors the sum of these scores and three ICPS risk categories. Ultimately, we compared the discriminative ability of the ICPS risk categories with PWV, cSBP and cPP. Then we evaluated the role of ICPS risk categories in the prediction of CV outcomes using Cox proportional hazard regression analysis, and compared its discrimination (Harrell's C) to that of each of its components.

The tonometric PulsePen and the oscillometric Mobil-O-Graph device are not interchangeable, and for 24-hour PWV values a lower threshold limit of normality should be considered. Patients belonging to high and very high ICPS risk categories that had been adjusted for age and sex experienced increased cardiovascular risk. Both high and very high ICPS risk categories continued to be independent predictors in a model that had been adjusted for several CV risk factors. In CKD patients, ICPS risk categories showed better discrimination than PWV and cSBP, and a tendency of significance has been observed in the case of cPP, while in ESRD patients ICPS risk categories had significantly better discrimination than cSBP.

The office and ambulatory PWV measuring devices are not interchangeable. The ICPS risk categories may improve the discerning of CKD and ESRD patients with high and very high CV risk.

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8. BIBLIOGRAPHY OF PUBLICATIONS

Publications related to the thesis:

Batta D, Körösi B, Gyöngyösi H, Nemcsik-Bencze Z, László A, Tislér A, Cseprekál O, Nemcsik J. (2022) Cross-sectional comparison of office and ambulatory pulse wave velocity by two methods, and their changes after lifestyle or medical interventions in hypertension. J Hypertens, 40: 470-477.
impact factor: 4.776

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impact factor: 0.519

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impact factor: 1.113

Publications not related to the thesis:

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

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Background and aims: The aim of this study was to develop an integrated central blood pressure–aortic stiffness (ICPS) risk score to predict cardiovascular events. *Methods:* It was a retrospective cohort study. A total of 100 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 (0–2), cPP (0–2), 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, $p = 0.170$). *Conclusion:* The ICPS score may clinically importantly improve the identification of CKD patients with elevated cardiovascular risk.

Keywords: chronic kidney disease, central blood pressure, central pulse pressure, pulse wave velocity, cardiovascular outcome

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). Measurements of arterial stiffness and central hemodynamic status are contenders that may improve CV risk prediction over and above classical tools. These parameters have been extensively investigated in the past two decades. In all stages of

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chronic kidney disease (CKD), arterial stiffness is an important risk factor for CV 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 was included in 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 the following 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 were hospitalized during baseline investigations. CKD patients at 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.

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Arterial stiffness, central hemodynamic, and blood pressure measurements

All measurements were performed between 10 a.m. and 12 p.m. Patients were allowed to take a non-standardized light breakfast and took their regular medications at least 3 h before the study measurements. They were asked to refrain from smoking on the day of the study and not to consume any caffeine-containing drinks at least 4 h before initiating the measurements. Arterial stiffness measurements and blood sampling were carried out 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-min rest, two consecutive brachial blood pressure measurements were taken 1 min 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-min acclimatization period.

Arterial stiffness was measured with the "gold-standard" tonometric method, above the carotid and femoral sites, using the PulsePen device. We referred our previous publication for the PWV and cPP measurements (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 directly calculated 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 low-density lipoprotein (LDL)-cholesterol were collected at baseline. Routine blood chemistry measurements were carried out directly after blood sampling on a Hitachi auto-analyzer. Baseline estimated glomerular filtration rate was calculated using the four-variable Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical analyses

All data analyses were performed using SPSS 23 (SPSS Inc., Chicago, IL, USA) for Windows (descriptives and Cox regression analyses) or Stata version 13.1 (Harrell's C-statistics). Continuous data are given as mean and standard deviation (SD), 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 CV events and CV 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.

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No a priori power calculations were carried out 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 CV 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 CV 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, CV 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 using 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, five individuals declined participation. Furthermore, three patients were excluded because of missing baseline or follow-up data, leaving 100 subjects in the analytical sample.

Table I displays baseline characteristics, including concomitant diseases, traditional and non-traditional CV risk factors, and metabolic and vascular parameters.

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Table I. 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
eGFR (ml/min per 1.73 m^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 (mmHg)	135.50 (120.31–145.44)
DBP (mmHg)	73.12 (9.70)
HR (L/min)	62.25 (57.50–72.63)
PP (mmHg)	60.38 (50.56–70.38)
PWV (m/s)	11.26 (8.90–14.90)
Aix (%)	21.53 (15.35–26.83)
cSBP (mmHg)	124.33 (14.50)
cPP (mmHg)	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; 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

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

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

Variable	Tertile	*N*	Range	Model 1				Model 2			
				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**
PWV (m/s)	1st	33	6.5–9.8	1 (ref.)				1 (ref.)			
	2nd	34	9.9–13.0	1.867	0.636	5.480	0.256	0.777	0.231	2.618	0.684
	3rd	33	13.2–27.2	4.072	1.400	11.841	**0.010**	1.284	0.386	4.273	0.684
cSBP (mmHg)	1st	33	81.5–117.0	1 (ref.)				1 (ref.)			
	2nd	33	119.0–129.8	0.827	0.325	2.106	0.691	1.052	0.331	3.338	0.932
	3rd	34	130.0–167.8	2.308	1.051	5.071	**0.037**	2.675	0.560	12.772	0.217
cPP (mmHg)	1st	34	23.3–45.0	1 (ref.)				1 (ref.)			
	2nd	33	45.3–56.3	1.608	0.605	4.270	0.341	1.482	0.492	4.469	0.484
	3rd	33	56.5–92.3	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

Bold values demonstrate significance when $p < 0.05$. 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, and GFR-EPI. Aix: augmentation index; CI: confidence interval; cPP: central pulse pressure; cSBP: central systolic blood pressure; PWV: carotid-femoral pulse wave velocity; SD: standard deviation

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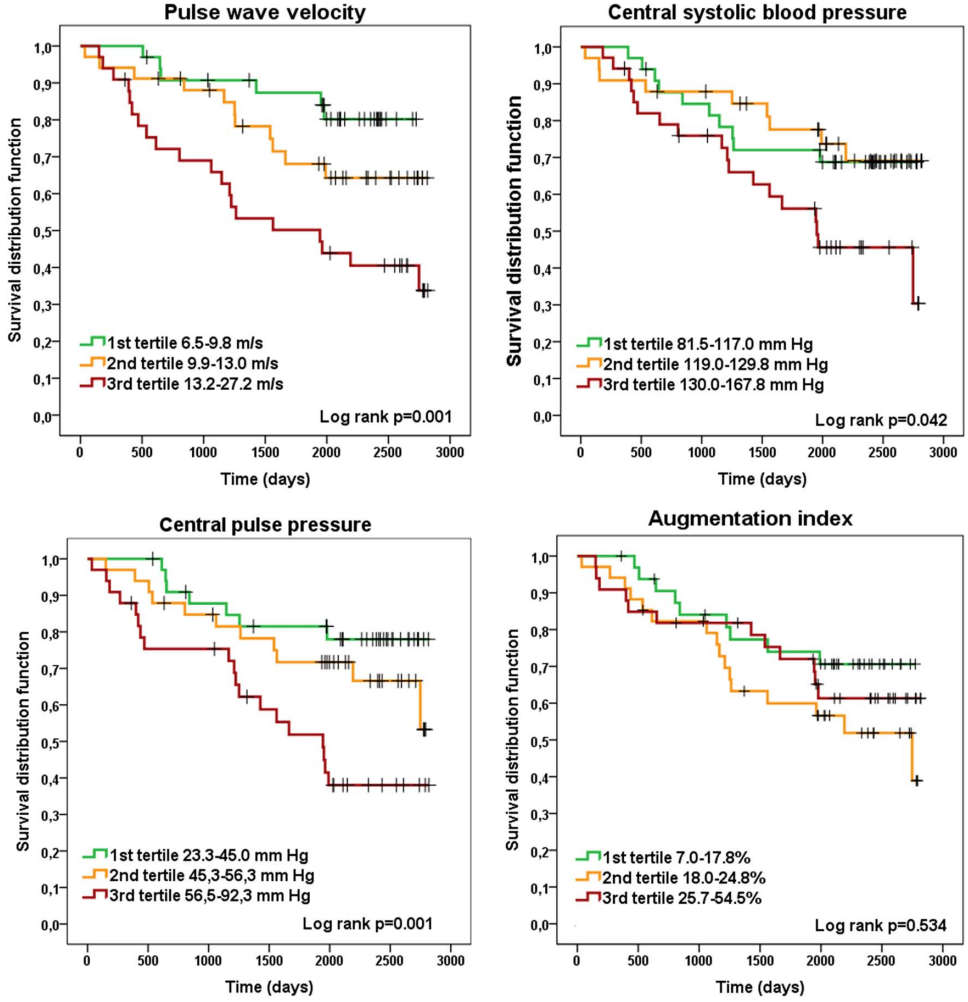

Fig. 1. Kaplan–Meier survival curves for each parameter studied with cardiovascular events (CV mortality and CV events) as outcomes. Panel A: pulse wave velocity; Panel B: central systolic blood pressure; Panel C: central pulse pressure; Panel D: augmentation index

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.

On the whole, $n = 37$ patients required erythropoietin-stimulating agents, $n = 35$ received calcitriol, and $n = 9$ needed calcium carbonate phosphate binder therapy.

During follow-up, $n = 49$ CV events were recorded: $n = 16$ patients died from CV causes (acute coronary syndrome $n = 4$, stroke $n = 3$, heart failure $n = 8$, and 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 II 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

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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 four parameters in Fig. 1.

Table III demonstrates hazard ratios for CV outcomes by ICPS risk scores and ICPS risk categories. The risk categories were derived from Cox models (Table III) and Kaplan–Meier (Fig. 2A) analyses by collapsing ICPS scores with similar hazard ratios and sufficient statistical

Table III. 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**

Bold values demonstrate significance when $p < 0.05$. 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; CI: confidence interval

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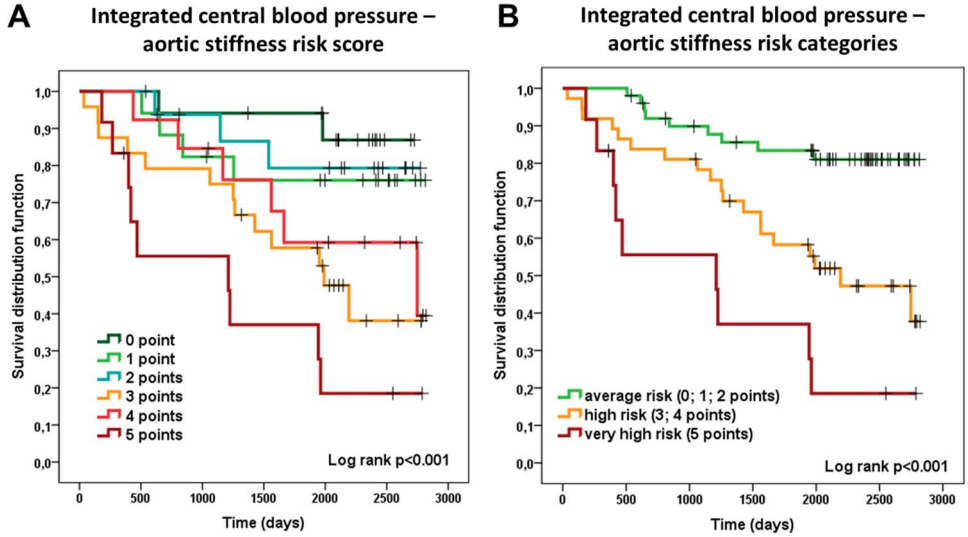

Fig. 2. Kaplan–Meier survival curves for the integrated central blood pressure–aortic stiffness (ICPS) risk scores and ICPS risk categories for cardiovascular events (CV mortality and CV events, adjusted for age and sex) as outcomes. Panel A: ICPS risk score groups; Panel B: ICPS risk categories

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 Fig. 2B.

Table III 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 IV demonstrates the results of the comparison of the discriminative ability of the ICPS risk categories with the one SD change of PWV, cSBP, and cPP. All the parameters

Table IV. 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 (Harrell'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

Bold values demonstrate significance when $p < 0.05$. CI: confidence interval; 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

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were adjusted for age and sex. ICPS risk categories were superior in the discrimination to 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 by request).

Discussion

This study demonstrated that the concept of an integrated score based on arterial stiffness and central hemodynamic parameters (ICPS) is strongly related to incident CV 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. In addition, it is better than PWV and cSBP and tends to be better than cPP, which suggests that it is worth 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, this 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 atherosclerosis risk in communities 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. (16), cSBP was superior in CV outcome prediction compared to brachial systolic blood pressure or brachial or cPP. In the study of Holewijn et al. (3), using net reclassification improvement analysis, CV risk stratification improved by adding non-invasive vascular risk markers, such as 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. These results suggest that the joint evaluation of different vascular biomarkers may have perspectives, but age and sex could influence the results. Although we adjusted for age and sex throughout this study, 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

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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, it is worth integrating 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 enable 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, 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, e.g., the Framingham Heart Study cohort (8) or the Nijmegen Biomedical Study (3).

There are some limitations of this 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, this study is underpowered and thus the exact thresholds for scoring or the relative contribution of individual parameters could not have been exactly defined. Therefore, the aim of this 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 CKD 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 interest

The authors declare no conflict of interest.

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Research Article

Integrated Central Blood Pressure-aortic Stiffness Risk Categories and Cardiovascular Mortality in End-stage Renal Disease

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ABSTRACT

Background: Our aim was to study the predictive power of integrated central blood pressure-aortic stiffness (ICPS) risk categories on cardiovascular (CV) mortality in end-stage renal disease (ESRD) patients.

Methods: This is a secondary analysis of a prospective study of 91 ESRD patients on hemodialysis therapy. At baseline, pulse wave velocity (PWV), central systolic blood pressure (cSBP) and central pulse pressure (cPP) were measured and patients were followed up for CV mortality for a median 29.5 months. Based on the shape of the association of each individual ICPS parameter with the CV outcome, patients were assigned ICPS scores: one point was given, if either the cSBP value was in the 3rd, or if the PWV or cPP was in the 2nd or 3rd tertiles (ICPS range: 0–3). We then evaluated the role of ICPS risk categories (average: 0–1, high: 2, very high: 3 points) in the prediction of CV outcomes using Cox proportional hazard regression analysis and compared its discrimination (Harrell's *C*) to that of each of its components.

Results: We found a strong dose–response association between ICPS risk categories and CV outcome (high risk HR = 2.62, 95% CI: 0.82–8.43, p for trend = 0.106; very high risk HR = 10.03, 95% CI: 1.67–60.42, p = 0.02) even after adjustment for multiple potential confounders. ICPS risk categories had a modest discrimination (*C*: 0.622, 95% CI: 0.525–0.719) that was significantly better than that of cSBP (dC: 0.061, 95% CI: 0.006–0.117).

Conclusion: The ICPS risk categories may improve the identification of ESRD patients with high CV mortality risk.

HIGHLIGHTS

- Integrated evaluation of central blood pressure and stiffness (ICPS) may improve risk prediction.
- ICPS risk categories were developed and tested in end-stage renal disease (ESRD).
- Very high ICPS risk category is a strong predictor of cardiovascular mortality in ESRD.

1. INTRODUCTION

Cardiovascular (CV) diseases are the leading causes of morbidity and mortality in industrialized countries worldwide, despite the availability of highly effective preventive treatments. This phenomenon is even more pronounced in chronic kidney disease (CKD), especially in end-stage renal disease (ESRD), as CV mortality of patients on maintenance hemodialysis (HD) is more than 10-fold higher compared with the normal population [1]. Therefore, attempts in ESRD to better identify high risk patients and their more effective prevention have an outmost importance.

In the past two decades numerous investigations demonstrated that aortic stiffening as measured by carotid-femoral Pulse Wave Velocity (PWV) predicts mortality independently of traditional risk factors. The most striking effect was observed in ESRD patients on maintenance HD, in whom a 3.4 m/s increase in PWV was associated with a threefold rise in the risk for mortality [2]. Based on the accumulating evidence regarding the role of PWV in the prediction of target organ damage, PWV was assigned as IIa recommendation in the European hypertension guidelines in 2007 and 2013 [3,4]. In contrast, the 2016 the European guideline on CV risk prevention advised against its use for CV risk assessment in the general

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population [5] and in the most recent European hypertension guideline the level of recommendation was downgraded to IIb [6]. Given these ups and downs, it seems that the scientific audience is currently less convinced about the usefulness of the measurement of arterial stiffness for CV risk stratification compared to the beginning of the century.

Arterial stiffness can be measured by several methods [7,8]. With most of the available devices parallel with the measurement of PWV, other parameters can also be evaluated, which correlate with PWV and each other, but also reflect on different features of the vasculature. Such parameters are the central systolic blood pressure (cSBP) reflecting on pressure; central pulse pressure (cPP) reflecting on pulsatility; and augmentation index (AIx) reflecting on wave reflection. Recently, we developed an integrated central blood pressure-aortic stiffness (ICPS) risk score and based on it defined three ICPS risk categories in CKD patients on conservative therapy. ICPS risk categories were very strong predictors of CV outcome in CKD patients showing superiority over PWV [9].

In the present study our aim was to test the association between ICPS risk score and ICPS risk categories and CV mortality in a cohort of ESRD patients on HD therapy. We hypothesized that ICPS risk categories would be similarly good predictors of CV outcome in ESRD patients on HD therapy as it was found in CKD patients on conservative therapy.

2. MATERIALS AND METHODS

2.1. Participants and Setting

The details of the methods of this retrospective cohort study were published previously [10–13]. In brief, patients were recruited among ambulatory, chronic (>3 months on HD) ESRD patients of two HD units of a dialysis network. None of the patients were hospitalized at the time of baseline investigations. Patients with atrial fibrillation were excluded, but otherwise all those patients, who gave written informed consent for participation, were included. Patients were considered to have established CV disease if they had a documented history of myocardial infarction, revascularization procedure, stroke or peripheral artery disease. After baseline clinical, laboratory, arterial stiffness and central hemodynamic measurements, patients were followed for a median of 29.5 months (interquartile range: 1–51). Follow-up data were collected between March 2005 and June 2009. All endpoint information was verified by original chart review. Outcome measure was death from a CV event, which was defined as documented myocardial infarction, stroke, heart failure, malignant arrythmia leading to death or sudden cardiac death. The protocol was approved by the Ethics Committee of the dialysis network and was carried out in accordance with the tenets of the Declaration of Helsinki.

2.2. Arterial Stiffness, Central Hemodynamic and Blood Pressure Measurements

All measurements were performed before a midweek HD session, with the patient in the supine position in a temperature-controlled room (24 ± 1°C). Arterial stiffness measurements and predialysis blood sampling were done on separate days within a week.

PWV, AIx, cSBP and cPP were measured by applanation tonometry (PulsePen device; DiaTecne s.r.l. Milan, Italy [14]) using sequential recordings of the arterial pressure wave at the carotid and femoral arteries, and by measurement of the distance between the carotid and the femoral sampling sites. Since current recommendation suggests the use of 80% of the direct carotid-femoral distance as the most accurate proxy of the numerator for PWV measurement, our previous data were recalculated accordingly [15].

All the measured parameters were calculated using the PulsePen software [14]. PWV was defined as the ratio of the distance and the transit time of the pulse pressure wave along the aorta between the sampling sites. Pulse wave amplitude was calibrated to brachial mean and diastolic pressure measured immediately prior to each sequence of pulse wave capture at the two sites. Recordings with a systolic or diastolic variability of consecutive waveforms above 10% or with the amplitude of the pulse wave signal being <80 mV were discarded. All measurements were done three times and their average was used in the calculations. cSBP was calculated directly from the carotid pulse waveform using the calibration considering brachial systolic and diastolic blood pressures. cPP was calculated as the difference between the highest central systolic and diastolic blood pressure values recorded at the carotid sampling site. 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.

Blood pressure and heart rate were recorded in supine position after each arterial stiffness measurement with a validated BpTru device (VSM Medtech, Vancouver, Canada). The two sequential measurements were manually averaged.

2.3. ICPS Score and Risk Categories

To calculate the ICPS score one point was given, if a patient's cSBP was in the 3rd tertile and if PWV or if cPP were in the 2nd or 3rd tertiles. The ICPS score was derived by summing these points (range: 0–3 points).

Given the limited statistical power of our relatively small sample size, the number of risk categories was further reduced and patients were classified into three ICPS risk categories: average (0–1 points), high (2 points) or very high (3 points).

2.4. Epidemiologic and Laboratory Data

Baseline data on current smoking, type and presence of diabetes mellitus, hypertension, coronary artery disease (previous acute myocardial infarction or coronary intervention), chronic heart failure (clinical diagnosis), peripheral arterial disease (documented by angiography or intervention) and cerebrovascular disease (previous stroke or transient ischemic attack) were collected by health record review. Patients were considered to have established CV disease if they had a documented history of myocardial infarction, revascularization procedure, stroke or peripheral arterial disease.

Blood samples for the determination of blood cell counts and hemoglobin, serum cholesterol, triglyceride, LDL-cholesterol, ions, albumin, parathormone and 25-OH vitamin D were collected at

baseline. Routine blood chemistry measurements were done on a Hitachi auto-analyzer, (Japan Care Co. Ltd., Osaka, Japan).

2.5. Statistical Analysis

All data analyses were performed using SPSS 22 for Windows (IBM Ltd., USA) or Stata version 13.1 (StataCorp LLC, USA). Continuous data are given as mean and standard deviation, or in case of evidence against a normal distribution, as a median and interquartile range. In general, the flow of statistical analysis followed our previous report [9].

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, AIx, cSBP and cPP for the CV outcome (Cox regression). Model 1 was unadjusted, while Model 2 was adjusted for age, sex, brachial SBP, LDL-cholesterol, current smoking, diabetes, body mass index and history of CV disease.

Survival was investigated with Kaplan–Meier and Cox regression analyses with ICPS score as the predictor and CV mortality as outcome. The predictive role of ICPS risk categories were investigated in Kaplan–Meier curves and Cox regressions with adjustment for age, sex, brachial SBP, LDL-cholesterol, current smoking, diabetes, body mass index and cardiovascular disease.

Finally, to compare the predictive value of the ICPS risk categories and each of its components (PWV, cSBP and cPP), all parameters were sequentially entered into a Cox-regression model with CV mortality as outcome. To investigate and compare discrimination of the different stiffness measures, Harrell's concordance (Harrell's *C*)-statistics were calculated.

3. RESULTS

Altogether 126 chronic HD patients at the two dialysis units were invited to participate. Of these, 28 patients declined participation and seven were excluded because of atrial fibrillation leaving 91 patients for the analytical sample.

Table 1 displays baseline characteristics including dialysis duration, concomitant diseases, traditional CV risk factors, primary renal disease leading to ESRD, laboratory and hemodynamic parameters.

Eighty-two patients received antihypertensive medication (case numbers in parentheses): renin-angiotensin system inhibitors (n = 51), calcium channel blockers (n = 58), β-receptor blockers (n = 56), α-receptor blockers (n = 28), and centrally acting antihypertensive drugs (n = 20), either alone or in combination.

In all, n = 58 patients received vitamin D and n = 72 needed calcium carbonate phosphate binder therapy.

During follow-up, 31 cardiovascular deaths were recorded: seven patients died from myocardial infarction, seven from sudden cardiac death, three from arrythmia, eight from heart failure and six from stroke.

Table 2 demonstrates the association of PWV, cSBP, cPP and AIx (per one SD difference and for each tertile) with CV mortality in unadjusted (Model 1) and in multiply adjusted models (Model 2). As a single independent variable, only PWV was significantly related to CV mortality. In the analyses by tertiles, the 2nd tertile of PWV in Model 1 and the 2nd and the 3rd tertiles of cSBP in Model 2 were related to the outcome. Unadjusted associations are shown as Kaplan–Meyer curves for each tertile of all four parameters in Figure 1. It demonstrates non-linear associations: showing an increase in the 2nd and 3rd teritle of PWV and cPP and only in the 3rd tertile of cSBP. As AIx tertiles were not related to outcome and the tertile curves crossed each other, this parameter was omitted from the ICPS score calculation.

Table 3 demonstrates hazard ratios for CV mortality by ICPS scores and risk categories. The risk categories were based on the results of the Cox-models (Table 3) and the Kaplan–Meier (Figure 2A) curves by collapsing ICPS scores with similar hazard ratios to improve

Table 1 | Baseline demographic, clinical, laboratory and hemodynamic characteristics of participants

Subjects, *n*	91
Sex (male, %)	56 (61.5)
Age (years)	63.3 (14.8)
Dialysis duration (months)	29.5 (13.7–33.6)
Residual dialysis (ml/day)	650 (100–1300)
BMI (kg/m^2)	25.2 (4.5)
Smoking, *n* (%)	17 (18.7)
Diabetes, *n* (%)	38 (41.6)
CV disease, *n* (%)	55 (60.4)
Primary renal disease, *n* (%)	
Diabetic	31 (34.1)
Hypertensive	17 (18.7)
Tubulo-interstitial	14 (15.3)
Glomerulonephritis	13 (14.3)
Polycystic	6 (6.6)
Other or unknown	10 (11.0)
Laboratory results	
Haemoglobin (g/l)	116.0 (103.0–123.0)
Creatinine (μmol/l)	650.0 (516.0–834.0)
Blood urea nitrogen (mmol/l)	19.6 (16–24.5)
Cholesterol (mmol/l)	4.5 (1.2)
HDL-cholesterol (mmol/l)	1.2 (1.0–1.6)
LDL-cholesterol (mmol/l)	2.5 (1.9–3.2)
Triglyceride (mmol/l)	1.7 (1.0–2.7)
Sodium (mmol/l)	137.0 (135.0–139.0)
Potassium (mmol/l)	5.2 (0.9)
Calcium (mmol/l)	2.3 (2.2–2.4)
Phosphate (mmol/l)	1.6 (1.1–1.9)
Albumin (g/l)	40.0 (37.6–42.0)
Parathormone (pmol/l)	7.08 (3.88–18.5)
25-OH vitamin D (μg/l)	24.7 (18.7–36.5)
CRP (mg/l)	6.7 (4.1–15.1)
Hemodynamic data	
Systolic blood pressure (mmHg)	141.6 (24.7)
Diastolic blood pressure (mmHg)	77.9 (13.0)
Heart rate (1/min)	72.4 (12.6)
Pulse pressure (mmHg)	62.5 (47.0–79.5)
PWV (m/s)	11.1 (9.3–14.1)
Central SBP (mmHg)	141.9 (23.3)
Central PP (mmHg)	63.5 (47.0–79.0)
AIx (%)	19.0 (11.0–28.5)

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; central PP: central pulse pressure; central SBP: central systolic blood pressure; PWV: carotid-femoral pulse wave velocity.

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

Variable				Model 1				Model 2			
				Hazard ratio	95% CI		*p*-value	Hazard ratio	95% CI		*p*-value
PWV (per 1 SD)				1.965	1.322	2.920	0.001	1.614	1.069	2.438	0.023
cSBP (per 1 SD)				1.223	0.832	1.798	0.305	1.162	0.787	1.716	0.450
cPP (per 1 SD)				1.345	0.942	1.920	0.102	1.066	0.730	1.556	0.740
AIx (per 1 SD)				0.967	0.677	1.381	0.854	1.431	0.929	2.203	0.104
Variable	**Tertile**	***N***	**Range**	**Hazard ratio**	**95% CI**		***p*-value**	**Hazard ratio**	**95% CI**		***p*-value**
PWV	1st	30	4.7–9.7		1 (ref.)				1 (ref.)		
	2nd	31	9.7–12.8	0.339	0.122	0.943	0.038	0.527	0.186	1.49	0.227
	3rd	30	13.3–24.8	0.951	0.439	2.057	0.898	0.913	0.421	1.98	0.818
cSBP	1st	30	88.3–131.8		1 (ref.)				1 (ref.)		
	2nd	31	132.5–152	0.540	0.226	1.287	0.164	0.066	0.009	0.502	0.009
	3rd	30	154–200.3	0.524	0.227	1.213	0.131	0.141	0.04	0.494	0.002
cPP	1st	30	24–52.3		1 (ref.)				1 (ref.)		
	2nd	31	52.5–73.3	0.567	0.226	1.421	0.226	0.936	0.365	2.399	0.89
	3rd	30	73.5–114.5	0.859	0.384	1.923	0.712	0.982	0.44	2.193	0.964
AIx	1st	31	−0.5–14.5		1 (ref.)				1 (ref.)		
	2nd	30	15.5–23.0	1.020	0.449	2.315	0.963	0.449	0.179	1.122	0.087
	3rd	30	23.5–53.5	0.742	0.298	1.848	0.522	0.445	0.175	1.13	0.089

Model 1 is unadjusted, Model 2 is adjusted for age, sex, current smoking, diabetes, body mass index, cardiovascular disease, brachial systolic blood pressure and LDL-cholesterol. PWV: pulse wave velocity; cSBP: central systolic blood pressure; cPP: central pulse pressure; AIx: augmentation index; SD: standard deviation.

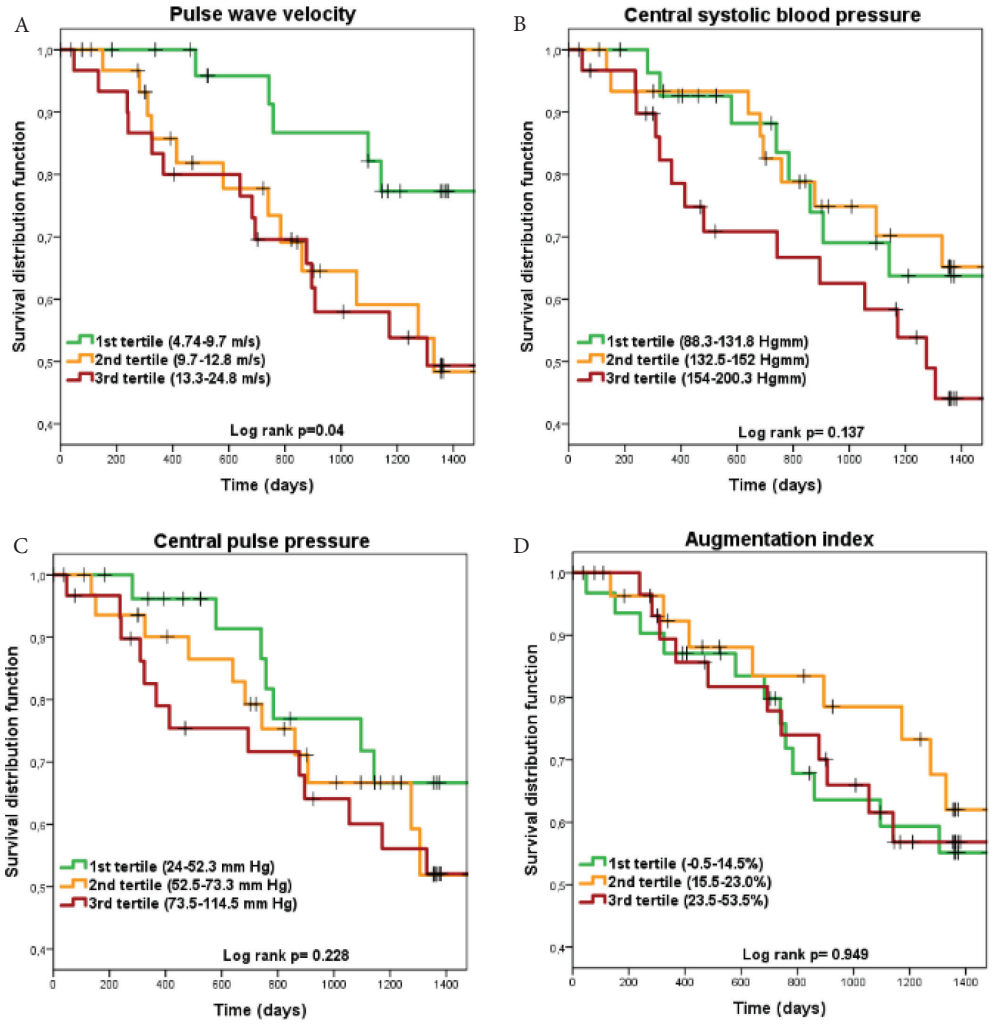

Figure 1 | Kaplan–Meier survival curves with cardiovascular mortality as outcome for each integrated central blood pressure-aortic stiffness risk score component. Panel A: pulse wave velocity; Panel B: central systolic blood pressure; Panel C: central pulse pressure; Panel D: augmentation index.

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Original Article

Cross-sectional comparison of office and ambulatory pulse wave velocity by two methods, and their changes after lifestyle or medical interventions in hypertension

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Objective: Pulse wave velocity (PWV), the most accepted biomarker of arterial stiffening can be measured by different methods and in the past decade, its 24 h monitoring has also become available. The aim of our study was to compare office and ambulatory PWVs and in a proportion of patients to compare the changes of PWVs after the initiation of lifestyle modifications or antihypertensive medication.

Methods: Office carotid–femoral PWV was measured with the tonometric PulsePen device (PP PWV), first hour and 24 h ambulatory oscillometric PWVs were evaluated with Mobil-O-Graph (MOB first hour PWV and MOB 24 h PWV, respectively). In new hypertensive patients, the measurements were repeated 3 months after the initiation of antihypertensive medication. In white-coat hypertensive patients after lifestyle modifications the measurements were repeated at 12 months.

Results: One hundred and five participants were involved with 22 new hypertensive and 22 white-coat hypertensive (WhHT) patients. PP PWV [8.7 (7.3–9.9) m/s] differed from MOB first hour PWV [7.3 (6.5–8.8) m/s] and MOB 24 h PWV [7.4 (6.4–8.8) m/s] as well ($P < 0.05$). PP PWV significantly decreased both in hypertensive [by 0.9 (0.4–1.5) m/s, $P < 0.05$] and WhHT patients [by 0.3 (−0.1 to 1) m/s, $P < 0.05$]. MOB first hour PWV did not change neither in hypertensive patients, nor in WhHT patients. MOB 24 h PWV decreased only in hypertensive patients [by 0.2 (0–0.6) m/s], which was less pronounced compared with PP PWV ($P < 0.05$).

Conclusion: The significant differences observed both in the cross-sectional and in the prospective parts of our study suggests that the two methods are not interchangeable.

Keywords: hypertension, monitoring, oscillometry, pulse wave velocity, tonometry

Abbreviations: CVD, cardiovascular disease; GFR-EPI, glomerular filtration ratio calculated using the four-variable Chronic Kidney Disease Epidemiology Collaboration equation; HDL, high-density lipoprotein; HT, newly diagnosed hypertensive patients; LDL, low-density lipoprotein; MOB 1st hour PWV, first hour oscillometric pulse wave velocity measured with the Mobil-OGraph device; MOB 24 h PWV, average oscillometric pulse wave velocity measured with the Mobil-OGraph device throughout 24 h; PP PWV, office carotid–femoral pulse wave velocity measured with the PulsePen device; PWV, pulse wave velocity; WhHT, white-coat hypertensive patients

INTRODUCTION

Arterial stiffening is a major component of vascular ageing. In hypertension, the measurement of different arterial stiffness parameters can contribute to the identification of high-risk subpopulation of patients [1]. Carotid–femoral pulse wave velocity (cfPWV) has already been incorporated into the 2007 European Hypertension Guideline as a measure of target organ damage [2]. In the next guideline, its measurement was recommended with class IIa evidence [3], however, in the most recent European Hypertension Guideline, it was downgraded to IIb and authors stated that the routine use of cfPWV is not practical and is not recommended for everyday practice [4].

In the past decade, technological developments introduced new, more easy-to-use alternatives to measure or provide approximations of PWV, which potentially can replace the operator-dependent measurement of cfPWV. Amongst others, oscillometric devices were developed and some of them enable the monitoring of 24 h PWV parallel with validated 24 h blood pressure measurement [5]. But the question ensued: are the different methods interchangeable? In a validation study of Berukstis *et al.* [6], only moderate agreement has been found between the office

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measurement with the 'gold standard' tonometric SphygmoCor cfPWV and the 24 h PWV of the oscillometric Mobil-O-Graph.

As Mobil-O-Graph provides an estimate of aortic PWV through mathematical modeling [7], another question arises, does estimated PWV changes parallel with the measured PWV after blood pressure modification?

The aim of our study was to compare the oscillometric first hour and 24 h PWV with office tonometric PWV in a cross-sectional design and to compare the changes of the PWVs in white-coat hypertensive patients after lifestyle modification and in hypertensive patients after medical intervention.

MATERIALS AND METHODS

It was a cross-sectional and prospective study, including Caucasian individuals, who required ambulatory blood pressure monitoring (ABPM) in different indications: diagnosis of newly recognized hypertension (hypertensive), diagnosis of white-coat (WhHT), masked or resistant hypertension, evaluation of the efficacy of medical intervention 3 months after therapy initiation in hypertensive or evaluation of WhHT 12 months after the recommended lifestyle changes.

Patients were recruited in one general practitioner's praxis in Budapest, Hungary, and measurements were performed between February 2015 and March 2019. Convenience sampling was used with consecutive inclusion of those patients, whom ABPM was clinically indicated. Patients with atrial fibrillation were excluded.

WhHT was defined as elevated office blood pressure in the screening visit (>140/90 mmHg), but normal blood pressure values during 24 h ABPM (24 h average <130/80 mmHg, daytime average <135/85 mmHg, night-time average <120/70 mmHg). Hypertension was defined as elevated office blood pressure in the screening visit (>140/90 mmHg), and elevated blood pressure values during 24 h ABPM (24 h average >130/80 mmHg, or daytime average >135/85 mmHg, or night-time average >120/70 mmHg). Resistant hypertension was defined as blood pressure that remains above 140/90 mmHg in the office in spite of the concurrent use of three antihypertensive agents of different classes including a diuretic, or as a controlled blood pressure with use of more than three medications [8].

Antihypertensive treatment was tailored according to the recommendations of the European Society of Hypertension [3]. In hypertensive patients, therapy was optimized by home blood pressure monitoring (HBPM) and a control ABPM and tonometric PWV measurement was appointed 3 months after therapy initiation. In a proportion of patients, within a few weeks after the initiation of the therapy, the dose or the type of the drugs were modified based on the HBPM records. In WhHT patients, lifestyle changes were recommended parallel with HBPM, and an ABPM and tonometric PWV measurement was scheduled after 12 months. Those patients, who required the commencement of medical treatment during this 1-year period, were excluded from the study.

In the screening visit, blood pressure was measured with a validated oscillometric device (Omron M3) and participants were invited into the study. An autoquestionnaire was handed out to the participants for a written informed consent and with a questionnaire for the evaluation of family and personal history. Patients were asked to bring back the autoquestionnaires in the morning of the clinical measurements.

For the involved patients within 2 weeks after the screening visit, an appointment was scheduled for 0700 h. for brachial blood pressure and arterial stiffness (cfPWV) measurement and also for blood sampling, which was taken from the right arm. After the blood pressure and cfPWV measurement and blood sampling, a 24 h ABPM device (Mobil-O-Graph, I.E.M. GmbH, Germany) was fitted with the cuff placed on the left arm. The 24 h ABPM device was brought back on the following day, when its results together with the blood test were discussed with the patient.

Prior to participation, all patients gave written informed consent. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council Hungarian Ministry of Health (ETT TUKEB 570/2014) and was carried out in accordance with the tenets of the Declaration of Helsinki.

Evaluation of office blood pressure

Patients were required to fast overnight and refrain from smoking and drinking caffeine-containing beverages before the procedure but to take their usual blood pressure medication. Upon arrival and after 5 min rest, two brachial blood pressure measurements were taken on each arm in the sitting position with a validated oscillometric blood pressure device (Omron M3). The mean value of the higher side of arms was further taken into account in the calculation as brachial SBP and DBP and heart rate. The participants were next fitted with the tonometric arterial stiffness measurement device and were asked to rest in the supine position for approximately 15 min before being measured.

Tonometric office carotid–femoral pulse wave velocity measurement

First cfPWV was evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy, PP PWV) [9]. The prognostic value of PP PWV was demonstrated previously in our study [10]. In each participant, two sequences of arterial stiffness measurements were performed and their mean were used for statistical analysis. In the PP PWV calculations, 80% of the carotid–femoral distance was used, according the consensus [11]. PP PWV was calculated by the PulsePen software as the ratio of the distance and the transit time of the pulse pressure wave along the aorta. Pulse wave amplitude was calibrated to brachial mean and diastolic pressure measured immediately prior to each sequence of pulse wave capture at the two sites. Recordings with a systolic or diastolic variability of consecutive waveforms above 10% or with the amplitude of the pulse wave signal being less than 80 mV were discarded. The intraobserver and interobserver variability of PP PWV measurements obtained by the PulsePen device in our lab in hypertensive patients was 4.6 and 6.3%, respectively [12].

Ambulatory blood pressure monitoring, oscillometric first hour and 24 h pulse wave velocity measurements

Ambulatory blood pressure data, first hour (MOB first hour PWV) and 24 h ambulatory pulse wave velocity (MOB 24 h

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PWV) were evaluated by the Mobil-O-Graph NG device. This is an oscillometric device, whose brachial blood pressure detection unit was validated according to standard protocols [13,14]. For the registration of pulse wave curves, after the registration of brachial blood pressure, the cuff is kept inflated at the level of DBP for approximately 8 s. Mobil-O-Graph uses the ARCSolver algorithm with generalized transfer function to evaluate aortic pulse waveform and with a proprietary mathematical algorithm it calculates PWV [15,16]. The device was monitoring the brachial SBP and DBP, heart rate and PWV every 15 min during the day (0700 to 2200 h) and every 30 min during the night (2200 h to 0700 h) for 24 h. Measurements were used for the analysis if more than 80% of recordings were valid.

MOB first hour PWV and MOB 24 h PWV were studied separately. MOB first hour PWV was calculated by averaging three single measurements in the first 60 min of recording time according to previous literature data [17]. Although in the original article, the first hour PWV was called 'office' PWV, we found it to be misleading in our conditions as we compare it with office tonometric values, so the definition of MOB first hour PWV is used throughout the article.

Statistical analysis

Descriptive data are expressed as mean ± standard deviation or median with interquartile ranges as appropriate. Normality of continuous parameters was tested with the Kolmogorov–Smirnov test. Correlation was assessed using Pearson's correlation coefficient. PWV readings of the two devices were analyzed according to the method proposed by Bland and Altman [18]. In this, the difference between each pair of measurement is plotted against the mean of the pair, and the number of paired differences that fall outside ± 2 standard deviation boundary of the mean between-device difference is also calculated.

Hemodynamic parameters and pulse wave velocity evaluated with different methods were compared between baseline and follow-up using paired Student's *t* test or dependent samples Wilcoxon Signed Rank test for data failing tests of normality as needed.

Univariate and multivariate linear regression analyses were performed to analyze the determinants of PP PWV, MOB first hour and MOB 24 h PWV in baseline and in the prospective part of the study after the follow-up as well. In multivariate analyses, age, sex, traditional cardiovascular risk factors and hemodynamic parameters were involved into the calculations. As no patient had diabetes in the prospective part of the study, this variable was excluded from the corresponding analyses.

Finally, univariate regression analyses were also performed between first hour and 24 h SBP changes, between different blood pressure changes and PP and MOB 24 h PWV changes and also between PP and MOB 24 h PWV changes.

Data are expressed as mean ± standard deviation or median with interquartile ranges. Two sided $P < 0.05$ was considered to be significant. SPSS 22.0 for Windows (IBM, Armonk, New York, USA) was used for all calculations.

RESULTS

One hundred and five participants were involved into the cross-sectional part of the study. The indication of ABPM was the suspect of masked hypertension in seven cases (6.7%), the control of antihypertensive therapy in chronic hypertensive patients in 16 cases (15.2%), the confirmation of resistant hypertension in 12 cases (11.4%), the diagnosis of new hypertension in 35 cases (33.3%) and the suspect of white-coat hypertension also in 35 cases (33.3%). Twenty-two patients with sustained hypertension and 22 patients with white-coat hypertension had control measurements after 3 or 12 months, respectively.

Cross-sectional comparison of PulsePen and Mobil-O-Graph pulse wave velocity

Table 1 summarizes the demographic and laboratory data of the participants at the time of enrollment. The cohort contained mostly middle-aged participants. The prevalence of diabetes and overt cardiovascular disease was low in the whole cohort. Table 2 summarizes the office and ambulatory hemodynamic and PWV data in the whole cohort. In the whole population, PP PWV was higher than MOB first hour PWV [difference: 1.2 (−0.5 to 2.6) m/s, $P < 0.001$] and MOB 24 h PWV [difference: 1.3 (0.3–2.2) m/s, $P < 0.001$].

TABLE 1. Clinical characteristics of the participants

	All participants	HT patients: 1.	HT patients 2.	WhHT patients 1.	WhHT patients 2.
N (male/female)	105 (62/43)	22 (15/7)	22 (15/7)	22 (10/12)	22 (10/12)
Age (years)	48.3 ± 13.2	47.9 ± 13.5	48.2 ± 13.5	45 ± 13.2	46 ± 13.2
Diabetes [*n* (%)]	8 (7.6)	0	0	0	0
CV disease [*n* (%)]	3 (3.8)	0	0	0	0
Current smoker [*n* (%)]	19 (18.1)	5 (22.7)	6 (27.3)	4 (18.2)	4 (18.2)
BMI (kg/m^2)	27.4 ± 3.9	27.3 ± 4.5	26.6 ± 4.3	26.4 ± 4.2	26.6 ± 4.5
Blood glucose (mmol/l)	5.3 ± 0.5	5.9 ± 1.7	5.7 ± 1.3	5.3 ± 0.6	5.3 ± 0.5
GFR-EPI (ml/min per 1.73 m^2)	100.1 ± 14	98.2 ± 14.9	98.2 ± 14.9	118 ± 18.4	98 ± 16.5
Uric acid (μmol/l)	344.3 ± 96.3	316.8 ± 93.1	315 ± 93	313 ± 74	312 ± 79.4
Total cholesterol (mmol/l)	5.7 ± 1.1	6.1 ± 1.1	5.8 ± 1.2	5.6 ± 1.7	5.4 ± 1.1
LDL (mmol/l)	3.6 ± 0.9	3.9 ± 1.0	3.7 ± 1.1	3.6 ± 1.5	3.5 ± 0.9
HDL (mmol/l)	1.1 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.3
Triglyceride (mmol/l)	1.6 ± 0.6	1.7 ± 1.3	1.6 ± 0.9	1.5 ± 1	1.2 ± 0.6

At hypertensive (HT) and white-coat hypertensive (WhHT) patients the first columns are baseline data, the second columns are follow-up data.

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TABLE 2. Office and ambulatory blood pressure and pulse wave velocity data

	All participants	HT patients 1.	HT patients 2.	WhHT patients 1.	WhHT patients 2.
Office SBP (mmHg)	140.8 ± 16.8	150.2 ± 15.3	***128.7 ± 13.9***	134.5 ± 12.3	***128.3 ± 16.6***
Office DBP (mmHg)	85.3 ± 9.6	93.3 ± 9.9	***76.9 ± 18.8***	84 ± 6	81.8 ± 5.7
Office heart rate (1/min)	75 (68–86)	84.5 (70.5–88)	73 (70–83)	76.2 (69.5–84.6)	75.6 (66.7–84.8)
First hour SBP (mmHg)	136.8 ± 12.4	137.5 ± 12.5	138.6 ± 14.5	135.5 ± 13.1	***127.4 ± 14.2***
First hour DBP (mmHg)	89.5 ± 10.5	92.1 ± 9.8	88 ± 11.5	88.5 ± 10.6	86.8 ± 9.1
First hour heart rate (1/min)	78 (72.6–86.8)	76 (63.2–82.7)	78.3 (73.2–82)	86.3 (76.6–98.2)	81.8 (72.7–91.5)
24 h SBP (mmHg)	128.2 ± 10.2	136.9 ± 7.6	***126 ± 9.7***	123.5 ± 6.3	122.3 ± 5.9
24 h DBP (mmHg)	81 ± 9.1	88.6 ± 8.3	***79.9 ± 9.6***	78.1 ± 5.2	77.7 ± 4.8
24 h heart rate (1/min)	73 (68–81)	77 (71.5–84.5)	73.5 (67–81.5)	76.5 (70–83.5)	73 (68.7–80.7)
PulsePen PWV (m/s)	8.7 (7.3–9.9)	8.9 (7.9–10.4)	***8.1 (7.1–9.1)***	8 (6.8–9.1)	***7.6 (6.7–8.7)***
Mobil-O-Graph first hour PWV (m/s)	7.3 (6.5–8.8)	7.3 (6.6–8.1)	7.3 (5.9–8.6)	7.7 (6.9–8.9)	7.6 (6.1–8.6)
Mobil-O-Graph 24 h PWV (m/s)	7.4 (6.4–8.8)	7.3 (6.4–8.6)	***6.8 (6.2–7.8)***	6.9 (5.6–7.6)	7 (5.7–7.7)

Italic and bold characters demonstrate significant differences ($P < 0.05$) after the follow-up in newly diagnosed hypertensive patients (HT) and in white-coat hypertensive patients (WhHT). At hypertensive (HT) and white-coat hypertensive (WhHT) patients the first columns are baseline data, the second columns are follow-up data. PWV, pulse wave velocity.

Baseline PP PWV and MOB first hour PWV did not correlate with each other ($r = 0.095$, $P = 0.339$) but significant correlation was found between PP PWV and MOB 24 h PWV ($r = 0.723$, $P < 0.001$, Fig. 1).

Figure 2 demonstrates the Bland–Altman plots of PP PWV and MOB first hour PWV (Fig. 2a) and PP PWV and MOB 24 h PWV (Fig. 2b). The Bland–Altman analysis of PP PWV with MOB first hour PWV and MOB 24 h PWV indicate that the 95% limits of agreement between the two methods ranged from −4.36 to 6.96 and −2.01 to 4.83, respectively.

Comparison of hypertensive and white-coat hypertensive patients' pulse wave velocity changes during follow-up

Table 1 summarizes the demographic and laboratory data of hypertensive and WhHT patients at the time of the involvement and at the end of follow-up. None of the hypertensive and WhHT patients suffered from diabetes and overt cardiovascular disease. Laboratory data did not change during the follow-up neither in hypertensive nor in WhHT patients. In case of hypertensive patients at the end of follow-up, nine patients were on monotherapy (40.9%) and 13 patients were on dual combination therapy (59.1%). Monotherapies were calcium-channel blocker (CCB) and ACE-inhibitor both in 3–3 cases, beta-blocker in two cases and centrally effective drug in one case. Ten patients were on ACE-inhibitor with CCB, two on ACE inhibitor with diuretic and one on ARB with CCB therapy.

Table 2 summarizes the office and ambulatory hemodynamic and PWV data in patients with newly diagnosed hypertensive patients before and 3 months after the initiation of antihypertensive medication and in WhHT patients at the diagnosis and at the 12 month control. In WhHT patients, the average blood pressure was under 140/90 mmHg as compared with the blood pressure data of the screening visit, in some of these patients in calmer conditions, lower values were measured and white-coat effect was not reproduced ($n = 9$). However, we left them

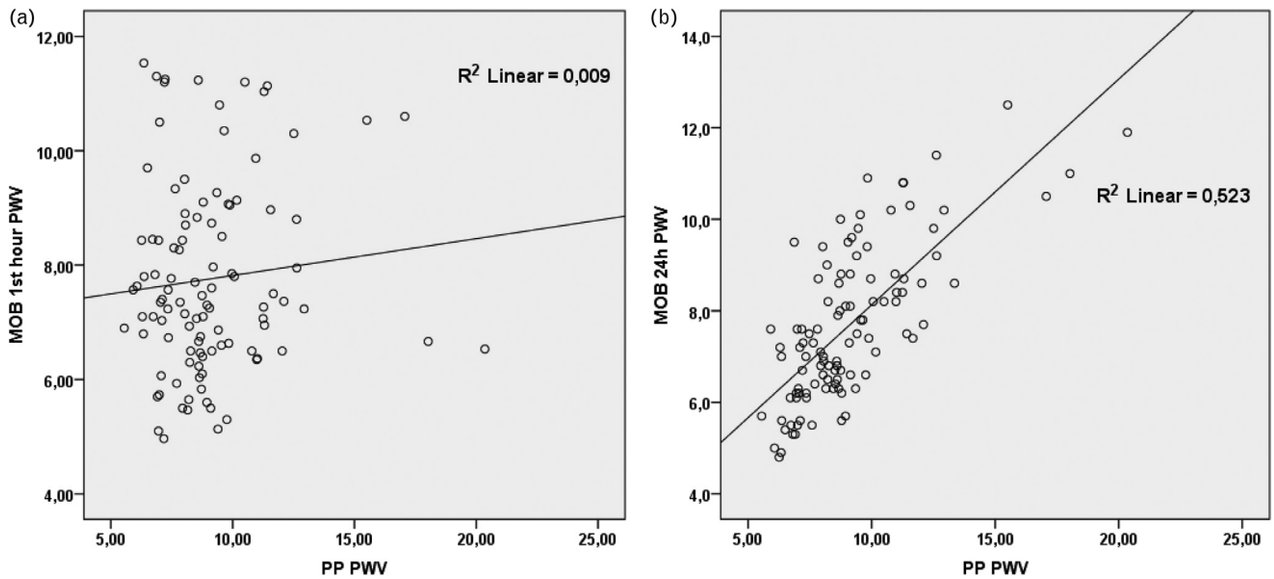

FIGURE 1 Correlations between PulsePen pulse wave velocity and Mobil-O-Graph first hour (a) and 24 h pulse wave velocity (b).

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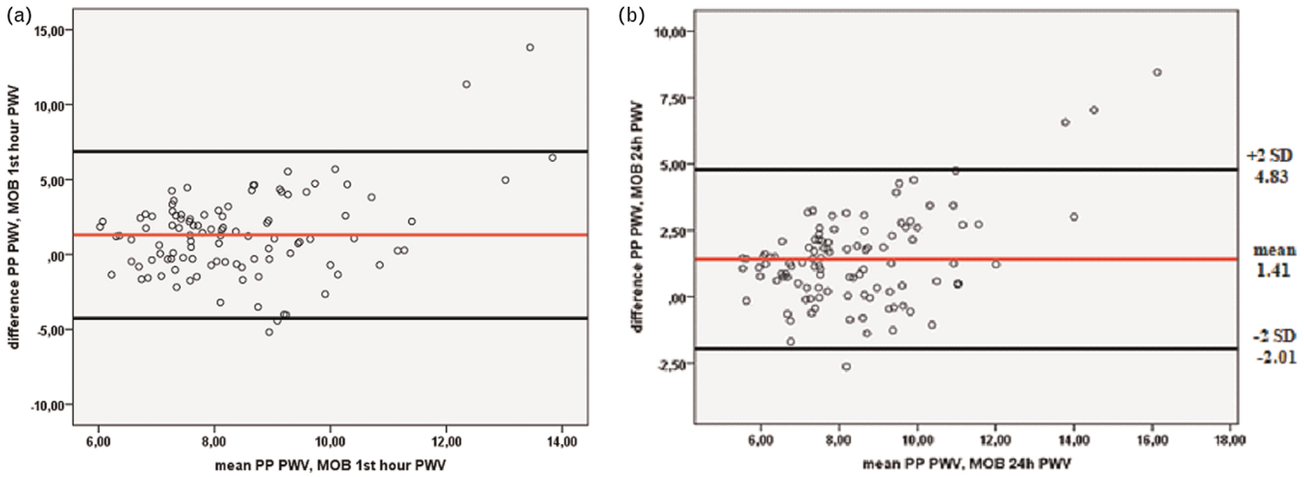

FIGURE 2 Bland–Altman plots of PulsePen pulse wave velocity and Mobil-O-Graph first hour pulse wave velocity (a) and PulsePen pulse wave velocity and Mobil-O-Graph 24 h pulse wave velocity (b).

in the WhHT group and these participants also got instructions for lifestyle modifications. Initially, PP PWV was significantly higher than MOB first hour and MOB 24 h PWV in hypertensive patients ($P < 0.001$), whereas in WhHT patients, PP PWV was higher than MOB 24 h PWV but the difference was not significant compared with MOB first hour PWV. Both office and 24 h SBP and DBPs decreased significantly in hypertensive patients for the effect of therapy. After lifestyle changes, in WhHT patients office SBP also decreased in the 12 month control. PP PWV significantly decreased both in hypertensive (with 0.9 (0.4–1.5) m/s, $P < 0.05$) and WhHT patients [with 0.3 (−0.1 to 1) m/s, $P < 0.05$). MOB first hour PWV did not change significantly neither in hypertensive nor in WhHT. MOB 24 h PWV decreased only in hypertensive patients [with 0.2 (0–0.6) m/s] while an increasing tendency appeared in WhHT patients. Compared with MOB 24 h PWV, PP PWV decreased in significantly higher amount both in hypertensive and WhHT patients ($P = 0.01$ and $P = 0.028$, respectively). Compared with MOB first hour PWV, PP PWV decreased in significantly higher amount only in hypertensive patients ($P = 0.032$).

Determinants of the three studied pulse wave velocities

In univariate analyses, PP PWV was significantly associated with age and office brachial SBP. MOB first hour PWV was significantly associated also with brachial SBP and with heart rate, whereas MOB 24 h PWV was significantly and very strongly associated with age and also with diabetes, smoking, 24 h DBP and 24 h heart rate (Table 3.). Table 4 demonstrates the results of the multivariate regression analyses at baseline. The variability of PP PWV was determined in 57.5% with the included confounders, whereas MOB first hour PWV variability was determined in much lower degree. In contrast, MOB 24 h PWV variability was almost completely determined by the included confounders.

The results of univariate and multivariate regression analyses on the prospective part of our study ($n = 44$) evaluating determinants of PP and MOB PWVs are shown in Supplementary Tables 1–4, http://links.lww.com/HJH/B791. Many similarities were found compared with the cross-sectional part as PP PWV was around 50% determined by age and SBP, MOB first hour PWV was less influenced by

TABLE 3. Significant associations found with univariate regression analyses of pulse wave velocities measured with PulsePen and with Mobil-O-Graph in first hour and 24 h settings ($n = 105$)

Variable	Adjusted R^2	*B*	Standard error	*P*	95% confidence interval
PulsePen PWV					
Age	0.419	0.113	0.013	>0.001	0.087–0.139
Office brachial SBP	0.296	0.082	0.012	>0.001	0.057–0.107
Mobil-O-Graph first hour PWV					
First hour SBP	0.046	0.031	0.013	0.017	0.006–0.057
First hour heart rate	0.058	−0.037	0.013	0.008	−0.063 to −0.010
Mobil-O-Graph 24h PWV					
Age	0.930	0.115	0.003	>0.001	0.108–0.120
Diabetes	0.059	1.662	0.603	0.007	0.464–2.859
Smoking	0.032	−0.888	0.429	0.041	−1.741 to −0.035
Brachial 24 h DBP	0.028	−0.036	0.018	0.047	−0.073 to −0.0004
24 h heart rate	0.108	−0.063	0.017	<0.001	−0.097 to −0.029

Sex: the influence female is considered. LDL, low-density lipoprotein; MOB, Mobil-O-Graph; PWV, pulse wave velocity.

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TABLE 4. Results of multivariate regression analyses for determinants of pulse wave velocities measured with PulsePen and with Mobil-O-Graph in first hour and 24 h settings ($n = 105$)

Variable	*B*	Standard error	*P*	95% confidence interval
PulsePen PWV, model adjusted R^2: 0.575				
Age	0.095	0.015	>0.001	0.064–0.125
Sex	−0.581	0.362	0.112	−1.301 to 0.138
Diabetes	−0.202	0.726	0.782	−1.645 to 1.241
Smoking	0.596	0.456	0.195	−0.311 to 1.504
BMI	−0.675	0.046	0.147	−0.159 to 0.024
LDL	−0.059	0.163	0.718	−0.385 to 0.266
Office brachial SBP	0.067	0.012	>0.001	0.041–0.092
Office brachial DBP	−0.023	0.021	0.262	−0.065 to 0.018
Office heart rate	0.023	0.016	0.148	−0.008 to 0.055
Mobil-O-Graph first hour PWV, model adjusted R^2: 0.133				
Age	0.017	0.013	0.203	−0.009 to 0.044
Sex	0.457	0.353	0.200	−0.264 to 1.161
Diabetes	0.619	0.714	0.388	−0.801 to 2.039
Smoking	−0.168	0.441	0.703	−1.046 to 0.708
BMI	−0.23	0.46	0.616	−0.116 to 0.649
LDL	0.079	0.157	0.615	−0.233 to 0.392
First hour SBP	0.053	0.018	0.005	0.016–0.089
First hour DBP	−0.029	0.021	0.184	−0.072 to 0.014
First hour heart rate	−0.039	0.014	0.009	−0.069 to −0.010
Mobil-O-Graph 24 h PWV, model adjusted R^2: 0.968				
Age	0.112	0.002	>0.001	0.107–0.117
Sex	−0.201	0.069	0.005	−0.338 to −0.064
Diabetes	0.083	0.135	0.542	−0.186 to 0.352
Smoking	−0.0004	0.093	0.996	−0.187 to 0.186
BMI	−0.009	0.009	0.295	−0.027 to 0.008
LDL	−0.032	0.030	0.292	−0.092 to 0.028
Brachial 24 h SBP	0.045	0.004	>0.001	0.036–0.054
Brachial 24 h DBP	−0.023	0.005	>0.001	−0.034 to −0.012
24 h heart rate	0.0004	0.004	0.915	−0.008 to 0.009

Sex: the influence female is considered. LDL, low-density lipoprotein; MOB, Mobil-O-Graph; PWV, pulse wave velocity.

the involved variables, whereas MOB 24 h PWV was robustly determined by age and additionally by SBP.

When the associations between changes of different blood pressures and PWVs were analyzed, we found only a tendency of significance in the changes of office SBP and 24 h SBP (adjusted $R^2 = 0.03$, $P = 0.130$), a significant association between the drop of office SBP and PP PWV decrease (adjusted $R^2 = 0.140$, $P = 0.010$), a robust association between 24 h SBP change and MOB 24 h PWV change (adjusted $R^2 = 0.952$, $P < 0.001$) and also a significant association between PP PWV and MOB 24 h PWV change (adjusted $R^2 = 0.196$, $P = 0.002$).

DISCUSSION

In our cross-sectional part of this study, significantly lower office and ambulatory Mobil-O-Graph PWVs were found compared with the PulsePen device. PP PWV correlated significantly only with MOB 24 h PWV. In the prospective part of our study, the PWV response for antihypertensive therapy was more pronounced with the PulsePen device and for lifestyle changes in white-coat hypertensive patients only PP PWV decreased. Marked differences were found between the amount of contribution of determinants of different PWVs.

Previous validation studies in healthy and hypertensive participants showed acceptable agreement of Mobil-O-Graph parameters with the 'gold standard' noninvasive and invasive methodologies [16,19–21]. However, until now, only three studies are available in the literature, in which office tonometric PWV was compared with MOB 24 h PWV. In line with our results, in the study of Luzardo *et al.* [7], MOB 24 h PWV was lower than SphygmoCor office PWV (7.4 ± 1.6 versus 7.9 ± 2.1 m/s, respectively). In the study of Berukstis *et al.* [6], SphygmoCor office PWV was also higher than MOB 24 h PWV (10.56 ± 2.59 versus 8.72 ± 1.29 m/s, respectively), with the marked difference of 1.84 ± 2.15 m/s. In the study of Schwatz *et al.* [22], SphygmoCor PWV tended to be lower than MOB 24 h PWV but the difference was not significant (7.7 ± 1.7 versus $7.6. \pm 1.3$ m/s, respectively). In our study, the difference between the tonometric and the oscillometric devices was between the values of the previous studies [1.2 (−0.5 to 2.6) m/s]. In line with our results in a recent study of Hametner *et al.* [23], a correlation coefficient of $r = 0.70$ was found between invasive and MOB office PWV, which is almost equal with our correlation coefficient ($r = 0.723$) found between PulsePen office and MOB 24 h PWV. These results suggest, that although strongly correlated, but MOB 24 h PWV values are lower than office tonometric PWV values, so presumably the threshold limit of normality should also be considered to a lower value (which is now 10 m/s for office carotid–femoral PWV). The observed lower 24 h PWV values compared with office values has similarities

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with a phenomenon, which is present in office and 24 h ambulatory blood pressure measurement, where the threshold limit of normality differs by 10/10 mmHg (140/90 and 130/80 mmHg, respectively).

The definition of MOB first hour PWV was based on a previous study of Matschkal *et al.* [17], in which first hour and 24 h MOB PWVs were compared in hemodialysis patients, and their relation with all-cause mortality was also analyzed. In that study, only MOB 24 h PWV was associated independently with the outcome. With the same methodology, we have found no significant correlation of MOB first hour PWV with the tonometric PP PWV, the values were lower and did not change for antihypertensive therapy or lifestyle modifications. Interestingly, in case of MOB first hour PWV, heart rate was an independent predictor whereas age was not. We suppose, the explanation for this finding is that in the first hour after the installation of Mobil-O-Graph, patients were in their way to their workplace or home, and it could cause the unusual variability of PWV. These results suggest, that MOB first hour PWV with this kind of definition does not correlate with office cfPWV and have also unexpected determinants, but the clinical utility of this parameter in different patient populations requires further prospective studies.

In our study for the effect of antihypertensive therapy, the extent of PWV changes was higher measured with PulsePen than with Mobil-O-Graph. Additionally, the lifestyle modifications in white-coat hypertensive patients improved PP PWV, whereas MOB PWVs did not change. This observation might also have clinical importance. Changes of PWV can be the marker of proper treatment, as in acute stroke patients, the clinical improvement was associated with the decrease of PWV [24]. Additionally, it can influence the clinical decisions as in patients on hemodialysis, the changes of PWV in a 6 months period was associated with mortality. The authors concluded that in those patients who demonstrate accelerated PWV values, daily dialysis and more intense cardiovascular analysis by cardiologists should be considered [25].

We assume that the observed differences in PWV changes between the two device maybe associated with the different methodologies. PulsePen, which is listed among the proper devices in the recommendation of the American Heart Association for improving and standardizing vascular research on arterial stiffness [26], directly measures carotid–femoral PWV. It was also used by Salvi *et al.* [27] in a comparative study performed on patients with Marfan syndrome and in line with our results, Mobil-O-Graph PWV was lower than PulsePen PWV. However, in that study, parallel measurements were performed with the two devices, not a comparison of office PulsePen and 24 h Mobil-O-Graph values. In contrast with PulsePen, Mobil-O-Graph employs a proprietary pulse wave analysis algorithm to determine PWV. In the study of Schwartz *et al.*, it was clearly demonstrated that age uniquely accounted for an estimated 75% of the total variation of MOB PWV, whereas SBP uniquely accounted for 20%. Together age and SBP accounted for 99.1% of the total variance of MOB PWV but only 40.2% of the variance of the tonometric cfPWV [22]. In line with this study, we have also found in the cross-sectional part of our study that age in a robust amount and additionally SBP are determinants of MOB 24 h PWV, whereas PP PWV is less influenced by age and more associated with blood pressure. In contrast, MOB first hour PWV is hardly determined by traditional factors. Additionally, changes of the tonometric PWV is less blood pressure-dependent and presumably associated with a real destiffening of the arteries, whereas the changes of the estimated 24 h PWV strongly depends on blood pressure changes. As in the cross-sectional part of our study, it was clearly demonstrated that age is the strongest determinant of MOB 24 h PWV, in short-term follow-up studies only minor changes of it is predictable and it was also confirmed by our results. Probably this is one explanation for our observation, that in white-coat hypertensive patients, only PulsePen PWV decreased for lifestyle interventions and for antihypertensive therapy, the quantity of PWV improvement was less pronounced with Mobil-O-Graph. Finally, the phenomenon that both in hypertensive and white-coat hypertensive patients for the effect of interventions office blood pressure decreased in higher amount compared with 24 h blood pressure (21.5/16.4 mmHg versus 10.9/8.7 mmHg in hypertensive and 6.2/2.2 versus 1.2/0.4 mmHg in WhHT patients, respectively) could also contribute to the more pronounced lowering of the tonometric PWV. These findings suggest that not only the threshold limits of normality but also the PWV changes for different interventions should be judged differently with the two devices. The clarification of the independent determinants of the changes of the different PWVs requires the involvement of higher number of patients in prospective studies.

There are limitations in our study. As we did not randomly select the patients, it can limit the generalizability of our findings but as our cohort contains both healthy individuals and patients with higher cardiovascular risk, it can provide a good reflection of the general population. Additionally, the low number of patients involved in the prospective parts of our study limited the analysis of the confounding factors of the changes of different PWVs and new hypertensive and white-coat hypertensive patients were analyzed together. Moreover, in our manuscript, we provide only the comparison of PWV evaluated with the two devices but there are other parameters as well, like central SBP, central pulse pressure or augmentation index, which also can be measured with both of these devices. After the comparison of PWVs, we also plan to analyze and publish the results of these additional parameters in another article.

In conclusion, the significant differences observed both in the cross-sectional and the prospective parts of our study and also in the determinants of different PWVs suggests that the studied methods are not interchangeable and for 24 h PWV values, a lower threshold limit of normality should be considered.

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Conflicts of interest

There are no conflicts of interest.

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statistical power. Almost two-third participants 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 participants in the very high ICPS risk category had a substantially increased CV mortality risk and also a stepwise increase from average through high to very high risk after adjustment for multiple CV risk factors. In Model 2, besides the very high ICPS risk category older age (HR: 1.05, 95% CI: 1.01–1.09) and lower systemic systolic blood pressure (HR: 0.97, 95% CI: 0.94–1.00) remained independent predictors of CV mortality.

Table 4 shows *C*-statistics (and differences between *C*-statistics) for ICPS risk categories and PWV, cSBP, and cPP. All *C*-values show moderate discrimination, however discrimination by ICPS risk categories was superior to that of cSBP. A tendency may also be seen in the case of cPP, while ICPS risk categories and PWV had similar *C*-statistics.

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

	N	Hazard ratio	95% CI		*p*-value
ICPS risk score					
Model 1					
0 point	18		1 (ref.)		
1 point	17	1.463	0.327	6.543	0.781
2 points	33	2.323	0.654	8.246	0.869
3 points	23	3.552	1.001	12.598	0.297
Model 2					
0 point	18		1 (ref.)		
1 point	17	0.668	0.131	3.399	0.627
2 points	33	2.112	0.410	10.886	0.371
3 points	23	10.126	1.056	97.110	0.045
ICPS risk categories					
Model 1					
Average	35		1 (ref.)		
High	33	1.902	0.748	4.837	0.177
Very high	23	2.910	1.145	7.396	0.025
Model 2					
Average	35		1 (ref.)		
High	33	2.622	0.816	8.432	0.106
Very high	23	10.034	1.666	60.425	0.012

Model 1 was unadjusted, while Model 2 was adjusted for age, sex, brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes, body mass index and CV disease.

4. DISCUSSION

Our study demonstrated that integrated risk categories based on arterial stiffness and central hemodynamic parameters (ICPS) are related to cardiovascular mortality not only in conservatively

Table 4 | Harell's *C*-statistics for ICPS risk categories and arterial stiffness measures and the differences in the *C*-statistics between ICPS risk categories and arterial stiffness measures

Variable	Coefficient	Standard error	95% CI		*p*-value
ICPS risk categories	0.622	0.049	0.525	0.719	**<0.001**
PWV	0.662	0.052	0.558	0.766	**<0.001**
cSBP	0.561	0.052	0.456	0.665	**<0.001**
cPP	0.588	0.05	0.489	0.687	**<0.001**
ICPS risk categories vs. PWV	−0.04	0.051	−0.142	0.062	0.438
ICPS risk categories vs. cSBP	0.061	0.028	0.006	0.117	**0.031**
ICPS risk categories vs. cPP	0.034	0.028	−0.022	0.089	0.226

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

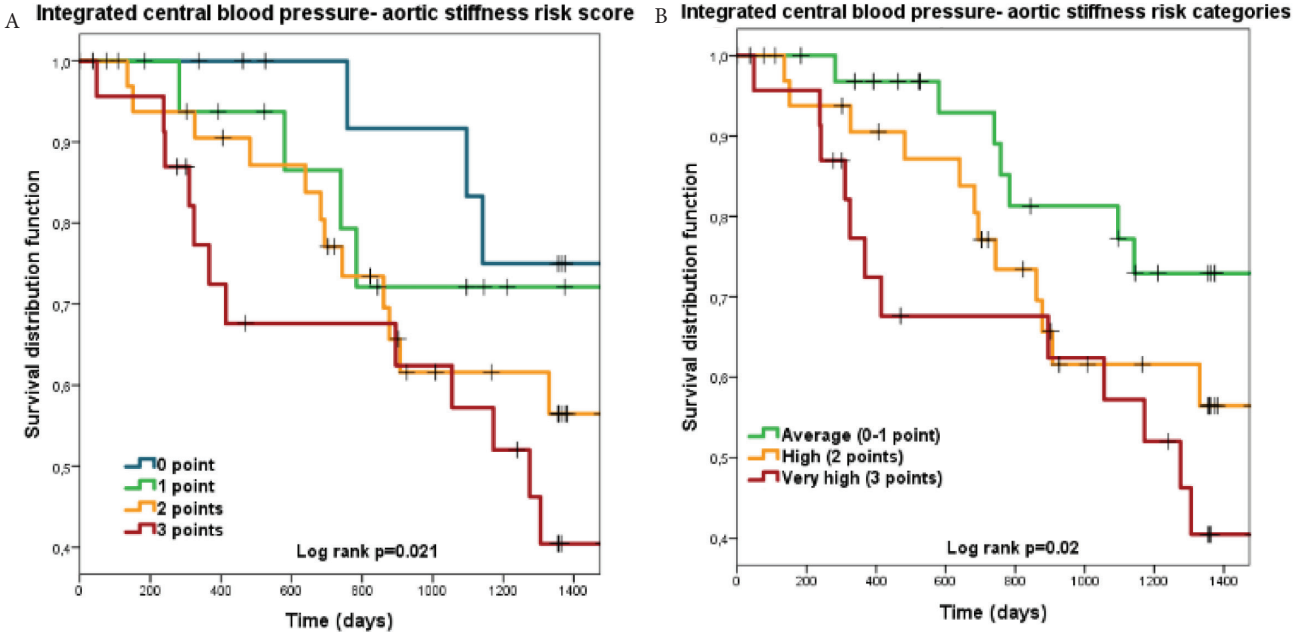

Figure 2 | Kaplan–Meier survival curves for the integrated central blood pressure-aortic stiffness (ICPS) risk scores and ICPS risk categories for cardiovascular mortality as outcome. Panel A: ICPS risk score groups; Panel B: ICPS risk categories.

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treated CKD patients but also in ESRD patients on HD therapy. According to our results, people in the very high ICPS risk category have a remarkably elevated risk of CV mortality, while patients in the high risk category have intermediate risk. ICPS risk categories had a better discriminative ability for CV mortality than cSBP by itself, had a numerically higher *C*-statistics that cPP and similar discrimination to that of PWV.

Recently, we introduced an ICPS risk score and derived three ICPS risk categories based on it, there were strong predictors of CV events in CKD patients on conservative therapy [9]. In that cohort participants in the high ICPS risk category had a significantly elevated CV risk compared with the average risk group. We believe this is due to the limited power of the present study as the number of events during the follow-up was lower in the ESRD compared with the CKD cohort ($n = 31$ vs. $n = 49$) [9].

In our CKD cohort the ICPS risk categories showed superior discrimination over PWV in the prediction of CV events [9], while it was similar in the present ESRD cohort. This is probably due to the fact, that PWV is a much stronger predictor of CV outcomes in ESRD patients on HD compared with that in CKD patients on conservative therapy [2]. This latter hypothesis is supported by our previous report on the CKD cohort [16]. This phenomenon is probably due to the accelerated vascular calcification in dialysis patients, which is strongly associated with mineral-bone disorder [17] and eventuates in elevated arterial stiffness and PWV.

As we highlighted in our previous manuscript, there are multiple potential advantages of the ICPS score concept over the use of its individual components. The required parameters can easily be estimated with most of the commercially available devices, its determination is non-invasive as it requires no blood sampling and it also can bridge the divergent methodologies [9]. A recently published study also supports our concept. Niiranen et al. [18] assessed the prognostic value of the joint evaluation of central pulse pressure and carotid-femoral pulse wave velocity by dividing the population into high and low risk groups based on the categorization of the medians of these values in the Framingham Heart Study. They have found, that patients in "high/high" group had a 52% higher risk of CV events compared with the low/low group [18]. Unfortunately in this study the discriminative ability of this simple categorization was not compared with that of its components.

As the present definition of ICPS risk categories is based on a limited sample, we do not recommend its calculation using the cut-off values from our sample in the general population, not even in ESRD patients on hemodialysis. A valid risk score should be based on much larger samples with an adequate number of CV events that enables the investigation of each parameter involved in the score [19]. However, as our ICPS risk categories in the present simplified form are strong predictors of CV mortality in our cohort, we believe that our pilot report could generate important discussion and further studies.

There are some limitations of our study that has to be acknowledged. As patients with atrial fibrillation are ineligible for tonometric arterial stiffness measurements, they were excluded from the present analysis, the ICPS score cannot be calculated for a substantial proportion of ESRD patients. Due to the low number of participants and events, our study is underpowered and thus the exact thresholds used for scoring or the relative contribution of each components cannot be exactly defined. Given these limitations, our aim with the present report is not to define the final score but to introduce the concept of a combined risk score based on arterial stiffness and central hemodynamic parameters and highlight some of its potential advantages.

In conclusion, our integrated score and the ICPS risk categories derived from it showed a strong association with CV mortality in ESRD patients on hemodialysis therapy. Our findings highlight the potential for a combined measure of arterial stiffness and central hemodynamic parameters for CV prediction. Together with our previous results of CKD patients on conservative therapy, this is the second independent cohort where our new concept demonstrated promising results.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

DB and BK were involved in data curation and visualization. ÁT, BK and JN were involved in formal analysis and writing (review and editing). OC and JE were involved in investigation. OC, JE and JN were involved in methodology. AT and JN were involved in study conceptualization. AT supervised the project. JN was involved in writing (original draft).

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