Original Article

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Association of 24-h central hemodynamics and stiffness with cardiovascular events and all-cause mortality. The VASOTENS Registry

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Objectives: In hemodialysis patients, central hemodynamics, stiffness, and wave reflections assessed through ambulatory blood pressure monitoring (ABPM) showed superior prognostic value for cardiovascular (CV) events than peripheral blood pressures (BPs). No such evidence is available for lower-risk hypertensive patients.

Methods: In 591 hypertensive patients (mean age 58 ± 14 years, 49% males), ambulatory brachial and central BP, pulse wave velocity (PWV), and augmentation index (AIx) were obtained with a validated upper arm cuff-based pulse wave analysis technology. Information on treatment for hypertension (73% of patients), dyslipidemia (27%), diabetes (8%), CV disease history (25%), was collected. Patients were censored for CV events or all-cause death over 4.2 years.

Results: One hundred and four events (24 fatal) were recorded. Advanced age [hazard ratio and 95% confidence interval: 1.03 (1.01, 1.05), $P = 0.0001$], female sex [1.57 (1.05, 2.33), $P = 0.027$], CV disease [2.22 (1.50, 3.29), $P = 0.0001$], increased 24-h central pulse pressure (PP) [1.56 (1.05, 2.31), $P = 0.027$], PWV [1.59 (1.07, 2.36), $P = 0.022$], or AIx [1.59 (1.08, 2.36), $P = 0.020$] were significantly associated with a worse prognosis (univariate Cox regression analysis). The prognostic power of peripheral and central BPs was lower. However, PWV [1.02 (0.64, 1.63), $P = 0.924$], AIx [1.06 (0.66, 1.69), $P = 0.823$], and central PP [1.18 (0.76, 1.82), $P = 0.471$], were not significant predictors in multivariate analyses.

Conclusions: In hypertensive patients, ambulatory central PP, PWV, and AIx are associated with an increased risk of CV morbidity and all-cause mortality. However, this association is not independent of other patient characteristics.

Keywords: ambulatory blood pressure, arterial stiffness, augmentation index, blood pressure telemonitoring, central arterial pressure, hypertension, pulse wave velocity, survival, vascular biomarkers

Abbreviation: AIx, augmentation index; CAP, central arterial pressure; e-CRF, electronic case report form; PWA, pulse wave analysis; PWV, pulse wave velocity; SD, standard deviation; USB, universal serial bus; VASOTENS, vascular health assessment of the hypertensive patients

INTRODUCTION

Ambulatory blood pressure monitoring (ABPM) is the most reliable and accurate tool for obtaining a comprehensive blood pressure (BP) assessment during complex activities occurring over 24-h [1]. A major strength of ambulatory BP lies in predicting health outcomes better than conventional office BP [2].

Following the technological progress achieved in the last two decades, a few upper arm cuff-based ABPM devices now allow combined noninvasive estimation of peripheral BP and relevant vascular biomarkers over the 24-h through pulse wave analysis [3]. Current evidence from cross-sectional studies shows that an increased ambulatory central arterial pressure (CAP) is strongly associated with a higher

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risk of cardiac damage; in contrast, no systematic relationship has been documented with carotid (or vascular) and renal damage [3,4]. Enhanced ambulatory arterial stiffness estimated through pulse wave velocity (PWV) has been associated with increased evidence of hypertension-mediated organ damage, though the strength diminishes when adjustment is made for age and BP levels [3,4].

Recently, a few studies conducted in hemodialysis patients suggested that increased baseline levels of CAP (notably pulse pressure), augmentation index (AIx, an estimate of pulse wave reflection), and above all, PWV are associated with an increased risk of cardiovascular (CV) events and all-cause mortality in the long term, while office and ambulatory brachial BPs or office PWV are not [5–7]. Unfortunately, the high-risk CV profile of patients included in these studies does not guarantee the automatic extrapolation of the findings to other patient groups, particularly to relatively low-risk hypertensive patients most representative of individuals commonly referred to ABPM.

Proof of the prognostic value of pulse wave analysis in ambulatory conditions is mandatory before this technique is recommended for the routine clinical evaluation of hypertensive patients. An attempt to provide supporting evidence for this purpose has been made in recent years by the VASOTENS Registry. The first publications of this study suggested that ambulatory pulse wave analysis may help evaluate the vascular health of individuals at risk for CV disease [4,8]. However, the prognostic role of pulse wave analysis for CV events has yet to be investigated. To close this knowledge gap, we have set to evaluate and compare the prognostic value of ambulatory monitoring of peripheral and central BPs, arterial stiffness, and pulse wave reflection for major CV outcomes and all-cause mortality in the patients of the VASOTENS Registry; this was amongst the secondary objectives of the study, as reported in the original protocol paper [9].

METHODS

Study design and population

The VASOTENS Registry is an international, multicenter, observational, nonrandomized, prospective study, including 24 centers disseminated in five continents. Details about the study protocol are available in a dedicated publication [9]. The study is registered with ClinicalTrials.gov at number NCT02577835 and formally endorsed by the Italian and Russian Societies of Hypertension. Nine of the original 24 centers of the study provided data for this prospective outcome analysis: four centers located in Russia, one in Italy, one in Portugal, one in Australia, one in Argentina, and one in Kazakhstan.

Adults ($\geq$18 years) of either sex with a previous diagnosis of arterial hypertension of any stage or severity or referred to one of the study centers for routine diagnostic evaluation of suspected hypertension and needing an ABPM were eligible to participate in the study. Pregnant women or patients unable to provide reliable automated BP measurements with the oscillometric technique because presenting atrial fibrillation, frequent ectopic beats, or second or third-degree atrioventricular blocks were excluded. In order to obtain accurate BP measurements, patients with a mid-upper arm circumference of $<$22 cm were excluded, while an appropriately sized cuff was used in those with an arm circumference $>$32 cm.

The study followed the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was reviewed and approved by the ethics committees of each participating center. All eligible subjects willing to participate were fully informed about the study design, purposes, and procedures and asked to give written informed consent before enrolment into the study.

The project did not involve any diagnostic evaluation or pharmacological intervention specifically designed for the study, and the Investigator was free to manage the patients included in the Registry according to the requirements of clinical practice and current guidelines. For the purpose of the present analysis, the ABPM performed during the enrolment visit and the associated clinical information were considered. A certified web-based telehealth platform (THOLOMEUS, Biotechmed Ltd, Somma Lombardo, Varese, Italy) was used to ensure data consistency and allow appropriate monitoring of data collection across the centers [10]. Clinical data were entered on the study website's electronic case report form (e-CRF). At the same time, ABPM recordings were uploaded on the telehealth platform and handled as detailed in the next section.

Ambulatory BP measurement

ABPM recordings were performed with the clinically validated electronic, automated upper arm BPLab device (BPLab GmbH, Schwalbach am Taunus, Hessen, Germany) [3,11,12]. Current recommendations were followed [1,13]. In brief, the ABPM device was programmed to measure BP at least every 20 min during the day (providing a minimum of three BP readings per hour) and at least every 30 min during the night (providing a minimum of two BP readings per hour). The monitoring cuff was placed around the nondominant arm. Patients were free to attend their usual daily activities during ABPM. However, they were required to refrain from strenuous exercise and remain motionless during each automated BP measurement. They had to complete a diary in which daily activities, such as time of sleeping, time of meals had to be reported together with the time of unusual events or poor night sleep quality. The patients had to return to the outpatient clinic 24 h after fitting the device and starting the recording to have the monitor removed and the recording uploaded on the web-based telemedicine platform. ABPM data were uploaded and transmitted to the website, where they were analyzed in real-time with the production of an electronic report. Subsequently, the Investigator checked each recording for compliance with quality criteria (see below for details). No additional clinical assessments were done when the ABPM device was removed.

Pulse wave analysis

The oscillometric BPLab device allows simultaneous assessment of brachial BP, arterial stiffness, and central hemodynamics in ambulatory conditions. Vascular measurements were obtained by recording pulsatile pressure inside the cuff placed on the upper arm during step deflation at the average rate of 3–4 mmHg per second, according to the oscillometric BP measurement technique principle. The

web-based telemedicine software processed the signal using proprietary mathematical algorithms. These were based on a specifically developed hemodynamic model to get the PWV and a transfer function to derive the central pressure wave and thus assess CAP and AIx. CAP was estimated relative to measured brachial systolic (SBP) and diastolic BP (DBP), as common for other type I devices. A detailed description of the methodology can be found elsewhere [3,11,12,14]. The accuracy of the BPLab device has been tested and validated in studies against noninvasive measurements of the same parameters obtained with the Sphygmocor device (CAP, PWV, AIx) [11,12] or against intra-arterial recordings (PWV) [15].

Outcome variables

To accomplish this prospective outcome analysis, patients were censored on the date of the first occurrence of the endpoint under study or on the last study visit. As originally mentioned in the study protocol, the study endpoint consisted of a combination of nonfatal and fatal CV and renal events or all-cause death [9]. The outcome variables included transient ischemic attack (TIA) or stroke (ischemic or hemorrhagic), myocardial infarction, angina pectoris or coronary revascularization, heart failure, peripheral vascular disease, and renal failure.

Statistical analysis

Subjects with a valid ABPM at entry and with a valid follow-up visit were included in the analysis. ABPM recordings could be included in the analysis when at least 70% of the expected number of readings was obtained, and at least 20 valid awake and 7 valid asleep readings were available over the 24-h after removal of artifacts, as currently recommended [1,13]. ABPMs matching the aforementioned quality criteria were analyzed to obtain: 24-h mean of brachial SBP, DBP, and pulse pressure (PP, the difference between SBP and DBP); 24-h mean of central SBP, DBP, and PP; 24-h mean of PWV; 24-h mean of AIx. Since AIx depends on heart rate (HR), AIx was normalized to an HR of 75 bpm [16].

Basic demographic and clinical variables were collected for each individual, including treatment for arterial hypertension, dyslipidemia, diabetes mellitus, or a CV disease history.

Descriptive statistics were provided for all demographic, clinical, and hemodynamic variables by calculating absolute and relative frequencies (categorical variables) and mean value ± standard deviation (SD) or 95% confidence interval (continuous variables). The analysis was run according to the occurrence of the composite endpoint (no vs. yes).

To compare differences in the occurrence of the study endpoint based on specific hemodynamic parameters (SBP, DBP, PP, PWV, and AIx), data were categorized into two groups using the median value as reference (below vs. above the median, dichotomized data analysis). Kaplan–Meier curves were drawn, and the log-rank test was used to compare the difference between the two groups in the occurrence or freedom from the study endpoint during the follow-up for central hemodynamics, stiffness, and pulse wave reflection. Univariate Cox regression analyses assessed the impact of major demographic and clinical characteristics and hemodynamic parameters on the composite endpoint. Multivariate Cox regression analysis was applied to each single hemodynamic parameter by adjusting for potential modulators, such as age, sex (female vs. male), treatment for arterial hypertension (yes vs. no), dyslipidemia (yes vs. no), diabetes mellitus (yes vs. no), and preexisting CV disease (yes vs. no). Unadjusted and adjusted hazard ratios and 95% confidence intervals were computed. A multivariate Cox regression analysis was also run by entering all the hemodynamic parameters and modulators into the model at once to weigh the impact of each variable on the outcomes.

Finally, univariate and multivariate Cox regression analyses were also performed on vascular parameters treated as continuous variables; this was meant as a confirmatory analysis (continuous data analysis).

Data management and analysis were done using SPSS for Windows version 25. A $P < 0.05$ was considered the minimum level of statistical significance.

RESULTS

Demographic and clinical data

A total of 663 subjects with an ABPM measurement were initially available. After removing invalid ABPMs, 591 (89.1%) patients were included in the analysis. The mean number of valid hours and readings during the 24 h was 23.3 ± 1.2 (range 18–24) and 60.9 ± 15.6 (range 28–92), respectively. The mean percentage of valid readings over the 24 h was 88.3 ± 7.7%.

The mean patients' age was 58.0 ± 13.9 years; 49.2% were males, 50.8% were females, 73.4% were treated for arterial hypertension, 26.6% for dyslipidemia, and 8.1% for diabetes. A cardiovascular or kidney disease was reported by 24.5% of patients.

As shown in Table 1, 24-h mean central SBP and PP values were lower than brachial ones, the opposite being true for DBP. Twenty-four-hour means of PWV and AIx were 11.3 ± 2.4 m/s and 19.9 ± 19.3%, respectively.

TABLE 1. Demographic and clinical data of patients at baseline

	All ($n = 591$)
Age (years)	58.0 ± 13.9
Sex	
Male	*291 (49.2)*
Female	*300 (50.8)*
Treated hypertension	434 (73.4)
Treated dyslipidemia	157 (26.6)
Treated diabetes	48 (8.1)
Preexisting CV or kidney disease	145 (24.5)
24-h bSBP (mmHg)	129.3 ± 14.1
24-h bDBP (mmHg)	78.7 ± 9.9
24-h bPP (mmHg)	50.5 ± 12.5
24-h cSBP (mmHg)	118.7 ± 12.7
24-h cDBP (mmHg)	80.1 ± 10.0
24-h cPP (mmHg)	38.7 ± 10.9
24-h PWV (m/s)	11.3 ± 2.4
24-h AIx (%)	19.9 ± 19.3

Data are shown as mean values ± standard deviation or absolute (*n*) and relative (%) frequency.
AIx, augmentation index; b, brachial; c, central; CV, cardiovascular; DBP, diastolic blood pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

Occurrence of the study endpoint

The type and frequency of events occurring during a mean follow-up of 4.2 years are shown in Table 2. Overall, 104 events were recorded in as many patients, of which 80 (76.9%) were nonfatal and 24 (23.1%) fatal (including 11 non-CV deaths). Among the CV events, cerebrovascular events (TIA or stroke) were the most represented (29, 27.9% of total events), followed by myocardial infarction, angina pectoris or coronary revascularization (23, 22.1%), and heart failure (21, 20.2%). Peripheral vascular disease and renal failure were reported by 7 (6.7%) and 13 (12.5%) patients, respectively.

Survival according to levels of central hemodynamics and aortic stiffness

Cumulative freedom from study endpoints was 82.1% for patients with a 24-h central SBP above the median vs. 82.8% for patients with values below the median, and 85.1% for patients with a 24-h central DBP above the median vs. 79.6% for patients with values below the median, with no statistically significant difference between the two groups (log rank test $P = 0.756$ for central SBP, Fig. 1a, and $P = 0.101$ for central DBP, Fig. 1b). Cumulative survival was significantly better for patients with a 24-h central PP below the median (85.5%) than those with a mean above the median (79.4%, log rank test $P = 0.025$, Fig. 1c). This was the case also for patients with a lower level of 24-h mean PWV (86.1% below the median vs. 78.8% above the median, log rank test $P = 0.020$, Fig. 1d) and AIx (85.8% below the median vs. 79.9% above the median, log rank test $P = 0.019$, Fig. 1e). No significant difference was observed for cumulative survival free from events for peripheral SBP (81.9% below the median vs. 82.8% above the median, log rank test $P = 0.902$), DBP (79.3% vs. 85.1%, $P = 0.087$) or PP (85.1% vs. 79.8%, $P = 0.119$).

Factors associated with survival in the dichotomized data analysis

In the univariate Cox regression analysis (Table 3), factors significantly associated with the worst prognosis were an advanced age [hazard ratio and 95% confidence interval: 1.03 (1.01, 1.05), $P = 0.0001$], female sex [1.57 (1.05, 2.33), $P = 0.027$], a preexisting CV disease [2.22 (1.50, 3.29), $P = 0.0001$], higher values of 24-h central PP [1.56 (1.05, 2.31), $P = 0.027$], PWV [1.59 (1.07, 2.36), $P = 0.022$] or AIx [1.59 (1.08, 2.36), $P = 0.020$]. Peripheral and central SBPs, as well as DBPs, were not significantly associated with a higher risk of events.

In the multivariate analysis adjusted for modulators, PWV, AIx, and central PP, were not significantly associated with event occurrence (Table 3).

In a multivariate Cox regression analysis entering all major demographic and clinical variables and central hemodynamics and arterial stiffness variables at once in the same model, statistically significant hazard ratios were achieved by preexisting CV disease and age only (Fig. 2).

TABLE 2. Number and type of events that occurred during the follow-up in the study population

	N (%)
Nonfatal events	
TIA or stroke (ischemic or hemorrhagic)	24 (23.1)
Myocardial infarction, angina pectoris, or oronary revascularization	19 (18.3)
Heart failure	17 (16.3)
Peripheral vascular disease	7 (6.7)
Renal failure	13 (12.5)
Fatal events	
TIA or stroke (ischemic or hemorrhagic)	5 (4.8)
Myocardial infarction, angina pectoris, or coronary revascularization	4 (3.8)
Heart failure	4 (3.8)
Other causes of death	11 (10.6)
Total	104

Data are shown as absolute (*n*) and relative (%) frequency.
TIA, transient ischemic attack.

Factors associated with survival in the continuous data analysis

As shown in Table 4, no statistically significant difference was observed in average peripheral and central SBPs at enrolment in the two groups of the study (patients without vs. patients with an event at follow-up). Average peripheral and central DBPs were significantly lower, and PP, PWV, and AIx were significantly higher in patients with an event.

The univariate Cox regression analysis considering vascular parameters as continuous variables returned results substantially in line with those observed for dichotomized analysis (Table 4): central PP, PWV, and AIx showed a significant association with the risk of future events; peripheral and central DBP showed a significant inverse relationship with the risk of future events, peripheral and central SBPs had no significant prognostic value. As for the dichotomized analysis, the associations were not statistically significant in the multivariate analysis.

DISCUSSION

In the present prospective cohort study of treated and untreated hypertensive patients, in Kaplan-Meyer analysis, survival free from CV events or all-cause death after approximately four years of follow-up was significantly better in patients with lower 24-h ambulatory central PP, PWV, and AIx levels at enrolment. The risk of achieving the combined study endpoint was not significantly different according to levels of peripheral BPs and central SBP and DBP: this may be in contradiction with previous findings based on ABPM without pulse wave analysis (as it will be further discussed) or may suggest independent prognostic values of central PP, PWV, and AIx from SBP and DBP, at least in our cohort of subjects. However, when Cox regression analysis was adjusted with multivariate models including common risk factors at baseline (age, sex, treatment for arterial hypertension, dyslipidemia, or diabetes, and preexisting CV disease), the prognostic power of PWV, AIx, and to a less extent, central PP disappeared, indicating that these parameters were not independently associated with poor survival.

The strong relation between increased CAP, PWV, and AIx, and CV outcomes and the prognostic value of these parameters assessed in resting conditions in various patient groups and populations have been well established in several longitudinal studies [17–20]. On the contrary, the

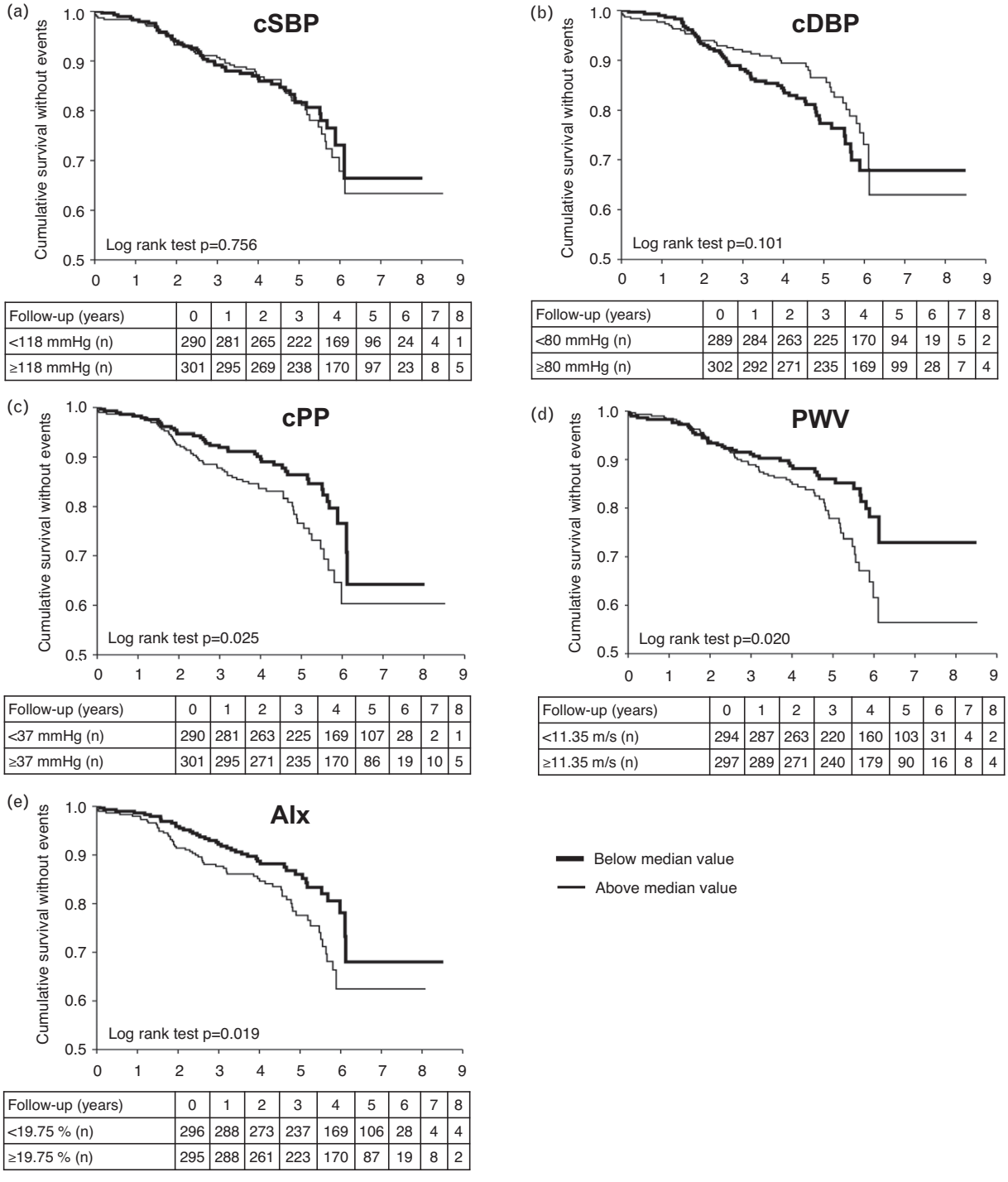

FIGURE 1 Kaplan–Meier survival curves and life tables for the occurrence of fatal and nonfatal events according to levels of (a) central systolic blood pressure, (b) central diastolic blood pressure, (c) central pulse pressure, (d) pulse wave velocity, and (e) augmentation index. For each parameter, patients were classified into two groups according to the level of the baseline value (above or below the median value). The *P*-value for the log rank test is shown in each panel. AIx, augmentation index; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; PWV, pulse wave velocity.

evidence of a prognostic value for future CV events of the same vascular indices obtained in ambulatory conditions over the 24-h, is limited to three studies, all conducted in high-risk patients with end-stage renal disease using a device (Mobil-O-Graph) different from that (BPLab) used in our study [5–7]. In the first study, the authors examined 170 hemodialysis patients undergoing an initial 48-h ABPM and followed them up for 2.5 years. In this study, increasing levels of ambulatory central PP, PWV, and AIx at baseline were associated with an increased risk of CV events and mortality at follow-up: such a relation was not observed for office and ambulatory peripheral BP and ambulatory central SBP and DBP levels. In multivariate Cox regression analyses, ambulatory PWV was the only vascular parameter independently associated with the combined endpoint of all-cause mortality, myocardial infarction, or stroke. Further

TABLE 3. Hazard ratio and 95% confidence interval resulting from univariate and multivariate Cox regression analysis for the occurrence of events during the follow-up in the study population

Univariate analysis	HR (95% CI)	*P*-value
Age (years)	1.03 (1.01, 1.05)	0.0001
Sex (female vs. male)	1.57 (1.05, 2.33)	0.027
Treated hypertension (yes vs. no)	1.01 (0.66, 1.55)	0.959
Treated dyslipidemia (yes vs. no)	0.99 (0.63, 1.55)	0.965
Treated diabetes (yes vs. no)	0.87 (0.43, 1.74)	0.701
CV disease (yes vs. no)	2.22 (1.50, 3.29)	0.0001
24-h bSBP (above vs. below the median)	0.98 (0.66, 1.44)	0.902
24-h bDBP (above vs. below the median)	0.71 (0.49, 1.05)	0.088
24-h bPP (above vs. below the median)	1.36 (0.92, 2.02)	0.121
24-h cSBP (above vs. below the median)	1.06 (0.72, 1.56)	0.757
24-h cDBP (above vs. below the median)	0.72 (0.49, 1.07)	0.103
24-h cPP (above vs. below the median)	1.56 (1.05, 2.31)	0.027
24-h PWV (above vs. below the median)	1.59 (1.07, 2.36)	0.022
24-h AIx (above vs. below the median)	1.59 (1.08, 2.36)	0.020
Multivariate analysis[a]	**HR (95% CI)**	***P*-value**
24-h bSBP (above vs. below the median)	1.05 (0.71, 1.56)	0.800
24-h bDBP (above vs. below the median)	0.92 (0.61, 1.38)	0.671
24-h bPP (above vs. below the median)	1.17 (0.78, 1.77)	0.468
24-h cSBP (above vs. below the median)	1.12 (0.75, 1.63)	0.606
24-h cDBP (above vs. below the median)	0.92 (0.61, 1.38)	0.686
24-h cPP (above vs. below the median)	1.18 (0.76, 1.82)	0.471
24-h PWV (above vs. below the median)	1.02 (0.64, 1.63)	0.924
24-h AIx (above vs. below the median)	1.06 (0.66, 1.69)	0.823

P-values indicating the statistical significance of the results are also reported.
Aix, augmentation index; b, brachial; c, central; CI, confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; HR, hazard ratio; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
[a]Adjustment for modulators including age, sex, treated hypertension, treated dyslipidemia, treated diabetes, and CV disease.

analyses of the same study revealed that patients with a weaker within-individual association of ambulatory BP with ambulatory PWV had a higher risk of death and CV events, suggesting that arterial stiffness may promote adverse outcomes in chronic kidney disease patients independently from BP [6]. In the ISAR Study (risk stratification in end-stage renal disease) that enrolled 344 hemodialysis patients and followed them up for 36 months, after adjustment for common risk factors, 24-h ambulatory but not office PWV significantly predicted the risk for all-cause mortality [7].

In all the prospective studies conducted in hemodialysis patients, the strength of the association of ambulatory central hemodynamics, arterial stiffness, and pulse wave reflections with CV events and all-cause mortality weakened or disappeared in adjusted or multivariate models: ambulatory PWV was the only vascular parameter with independent prognostic power. Similarly, in our study following multivariate Cox regression analyses, the prognostic power of PWV and AIx, and to a lesser extent central PP, disappeared. However, it must be recognized that, unlike the aforementioned studies, our study included relatively low-risk hypertensive patients, as documented by the small proportion of individuals with a history of CV disease (25%) or diabetes (8%) at enrolment.

As mentioned above, the finding of the lack of association between peripheral or central SBP and DBP and prognosis may contradict previous evidence. However, Sarafidis *et al.* also reported similar evidence [5]. There may be a few explanations for this finding. First, in our cohort, the mean levels of peripheral (129/79 mmHg) and central BPs (119/80 mmHg) were only mildly elevated and assimilable to borderline or high-normal office BP values [21,22]: this may have limited the long-term impact of BP on prognosis. Second, the lack of difference in baseline SBP between the two study groups and the fact that DBP was lower in patients with an event during the follow-up may have also contributed to our finding; however, PP indirectly assessed as the

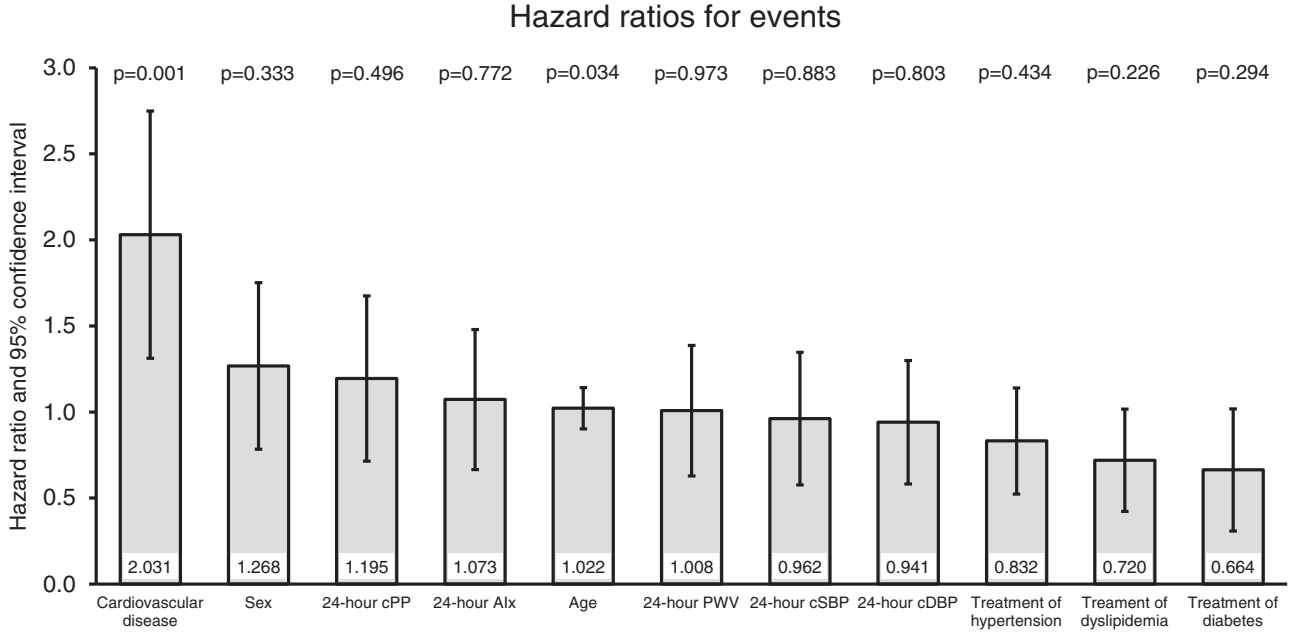

FIGURE 2 Hazard ratios (and 95% confidence intervals) from multivariate Cox regression analysis for the occurrence of events during the follow-up in the study population. *P*-values indicating the statistical significance of the results are also reported. AIx, augmentation index; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; PWV, pulse wave velocity.

TABLE 4. Comparison of vascular parameters summarized by means and standard deviations in patients without or with an event at follow-up and hazard ratio and 95% confidence interval resulting from univariate and multivariate Cox regression analysis for the occurrence of events during the follow-up in the study population

					Univariate analysis		Multivariate analysis[a]	
Vascular parameter	Events - ($n = 487$)	Events + ($n = 104$)	*P*-value	Association with events	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
24-h bSBP	129.3 ± 13.6	129.3 ± 16.1	0.980	24-h bSBP (per mmHg increase)	1.00 (0.99, 1.01)	0.949	1.00 (0.99, 1.02)	0.747
24-h bDBP	79.2 ± 9.7	76.4 ± 10.4	0.008	24-h bDBP (per mmHg increase)	0.98 (0.96, 0.99)	0.013	0.99 (0.97, 1.01)	0.417
24-h bPP	50.0 ± 12.0	52.9 ± 14.7	0.032	24-h bPP (per mmHg increase)	1.01 (0.99, 1.03)	0.067	1.00 (0.99, 1.01)	0.615
24-h cSBP	118.6 ± 12.3	119.3 ± 14.5	0.619	24-h cSBP (per mmHg increase)	1.00 (0.99, 1.02)	0.581	1.00 (0.99, 1.02)	0.440
24-h cDBP	80.6 ± 9.8	77.7 ± 10.5	0.008	24-h cDBP (per mmHg increase)	0.98 (0.96, 0.99)	0.013	0.99 (0.97, 1.01)	0.401
24-h cPP	38.1 ± 10.3	41.6 ± 13.1	0.002	24-h cPP (per mmHg increase)	1.02 (1.00, 1.04)	0.004	1.00 (0.99, 1.02)	0.413
24-h PWV	11.1 ± 2.3	11.9 ± 2.4	0.003	24-h PWV (per m/s increase)	1.16 (1.06, 1.27)	0.001	1.02 (0.89, 1.16)	0.774
24-h AIx	18.7 ± 18.4	25.5 ± 22.5	0.001	24-h AIx (per % increase)	1.02 (1.01, 1.03)	0.001	1.00 (0.99, 1.02)	0.374

Vascular parameters are represented as continuous variables. *P*-values indicating the statistical significance of the results are also reported.
AIx, augmentation index; b, brachial; c, central; CI: confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
[a]Adjustment for modulators including age, sex, treated hypertension, treated dyslipidemia, treated diabetes, and CV disease.

difference between SBP and DBP showed a prognostic value, particularly when estimated at a central level. Third, given the observational nature of our study, we could not record information relevant to changes in pharmacological treatment over time and at the study end that may have impacted peripheral and central BPs. We also did not assess ambulatory vascular measurements after baseline.

Study strengths and limitations

Our results should be considered in light of potential strengths and limitations. Our study is the first outcome study based on ambulatory pulse wave analysis that was not specifically conducted in hemodialysis patients; rather, it enrolled hypertensive patients with a risk profile common to most patients usually referred to routine ABPM. Furthermore, our study may represent an important step forward compared to previous studies because of the larger sample of subjects examined (591 vs. 170–344) and the longer follow-up (4.2 vs. 2.3–3 years) than previous studies.

The accuracy of noninvasive CAP, PWV, and AIx measurements by oscillometry has sometimes been questioned. However, the device and technique used in our study have been properly validated against gold standards [11,12,15]. Additionally, results obtained with the same device in normotensive and hypertensive patients support the technique's validity for general clinical use [4,8,23,24]. As previously mentioned, in studies performed in hemodialysis patients, a device (Mobil-O-Graph) different from that used in our study (BPLab) was employed [5]: this may limit comparability on one side but increase generalizability on the other.

CONCLUSION

In our cohort of relatively low-risk hypertensive patients, ambulatory central hemodynamics (PP), arterial stiffness (PWV), and pulse wave reflections (AIx) showed a statistically significant association with increased risk of CV events and all-cause mortality in a Kaplan–Meyer analysis and univariate Cox regression analysis. However, this association was not significant in a multivariate analysis considering major modulators such as age, sex, CV risk factors, and preexisting CV disease. This finding suggests that, despite central PP, PWV, and AIx obtained in ambulatory conditions potentially having some role, their prognostic power is not statistically independent of other patient characteristics.

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Authors' contribution: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. S.O. ran the analysis, drew the pictures and tables, and drafted the manuscript. All authors critically revised and approved the final manuscript.

Data availability: The data underlying this article are available in the article.

Conflicts of interest

S.O. has received honoraria as scientific consultant from Biotechmed Ltd, provider of telemedicine services. All other authors declare no conflicts of interest regarding the publication of this paper.

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