Ambulatory Pulse Wave Velocity Is a Stronger Predictor of Cardiovascular Events and All-Cause Mortality Than Office and Ambulatory Blood Pressure in Hemodialysis Patients

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See Editorial Commentary, pp 27–29

Abstract—Arterial stiffness and augmentation of aortic blood pressure (BP) measured in office are known cardiovascular risk factors in hemodialysis patients. This study examines the prognostic significance of ambulatory brachial BP, central BP, pulse wave velocity (PWV), and heart rate–adjusted augmentation index [AIx(75)] in this population. A total of 170 hemodialysis patients underwent 48-hour ambulatory monitoring with Mobil-O-Graph-NG during a standard interdialytic interval and followed-up for 28.1±11.2 months. The primary end point was a combination of all-cause death, nonfatal myocardial infarction, and nonfatal stroke. Secondary end points included: (1) all-cause mortality; (2) cardiovascular mortality; and (3) a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, coronary revascularization, or hospitalization for heart failure. During follow-up, 37(21.8%) patients died and 46(27.1%) had cardiovascular events. Cumulative freedom from primary end point was similar for quartiles of predialysis-systolic BP (SBP), 48-hour peripheral-SBP, and central-SBP, but was progressively longer for increasing quartiles for 48-hour peripheral-diastolic BP and central-diastolic BP and shorter for increasing quartiles of 48-hour central pulse pressure (83.7%, 71.4%, 69.0%, 62.8% [log-rank P=0.024]), PWV (93.0%, 81.0%, 57.1%, 55.8% [log-rank P<0.001]), and AIx(75) (88.4%, 66.7%, 69.0%, 62.8% [log-rank P=0.014]). The hazard ratios for all-cause mortality, cardiovascular mortality, and the combined outcome were similar for quartiles of predialysis-SBP, 48-hour peripheral-SBP, and central-SBP, but were increasing with higher ambulatory PWV and AIx(75). In multivariate analysis, 48-hour PWV was the only vascular parameter independently associated with the primary end point (hazard ratios, 1.579; 95% confidence intervals, 1.187–2.102). Ambulatory PWV, AIx(75), and central pulse pressure are associated with increased risk of cardiovascular events and mortality, whereas office and ambulatory SBP are not. These findings further support that arterial stiffness is the prominent cardiovascular risk factor in hemodialysis. **(*Hypertension*. 2017;70:148-157. DOI: 10.1161/HYPERTENSIONAHA.117.09023.)** ● **Online Data Supplement**

Key Words: ambulatory ■ arterial stiffness ■ augmentation index ■ cardiovascular events ■ hemodialysis ■ mortality ■ pulse wave velocity

Patients undergoing hemodialysis have higher mortality and lower life expectancy compared not only to general population but also to patients with diabetes mellitus, cardiovascular disease, or cancer.[1] Although the mortality rate in hemodialysis patients gradually decreased over the years, in 2013 it was 169 deaths/1000 patient-years in United States.[2] The leading causes of mortality is cardiac and cerebrovascular events, as they account for >50% of deaths of known causes.[1] This may be to a great extend attributed to accelerated arteriosclerosis and increased arterial stiffness, which is the predominant arterial abnormality in end-stage renal disease (ESRD),[3] in elevated systolic blood pressure (SBP) levels, increased pulse pressure (PP), left ventricular (LV) hypertrophy, and diastolic cardiac dysfunction.[4] Other factors proposed to contribute to high cardiovascular mortality in hemodialysis patients include excessive interdialytic weight

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gain and intradialytic weight loss, uncontrolled hyperparathyroidism and nonadherence to the prescribed hemodialysis regimen.[5]

The first direct evidence of the prognostic significance of arterial stiffness markers in hemodialysis patients was suggested by a previous cohort study in which increased predialysis pulse wave velocity (PWV) was an independent determinant of cardiovascular and all-cause mortality.[6] Similarly, a study associating wave reflections with adverse outcomes showed that every 10% increase in augmentation index (AIx) was related to 1.5-fold higher risk of cardiovascular events or death,[7] and another one showed that increased PP is also independently associated with mortality.[8] A previous study examined the response of prehemodialysis PWV over a mean follow-up of 50 months in hemodialysis patients who had stable prehemodialysis BP within normal limits or, if hypertensive, received nonpharmacological interventions and antihypertensive drugs to decrease BP; in patients who survived during follow-up, a decrease in PWV parallel to the decline in BP levels was noted, whereas nonsurvivors had a steady increase in PWV despite a similar reduction in BP,[9] an observation that brought forward the hypothesis that modification of arterial stiffness and not BP is the factor that mainly determines mortality decrease.

In hemodialysis patients predialysis and postdialysis BP display a J- or U-shaped association with cardiovascular events and survival, a fact most likely reflecting the low accuracy of relevant measurements, as high BP measured with ambulatory BP monitoring is clearly associated with increased mortality.[10,11] Elevated aortic stiffness, as indicated by increased PWV levels, is generally associated with higher BP levels and increased PP during the interdialytic intervals.[12] To the best our knowledge, only a previous study from our group examined the ambulatory pattern of arterial stiffness and central BP indexes in hemodialysis patients. AIx decreased during hemodialysis and gradually increased during interdialytic intervals, this increase being 30% higher at the end of the 3-day compared with the end of the 2-day interval.[13] However, PWV displayed only a minimal increase over time that reached again statistical significance at the end of the 3-day interval.[13] All devices measuring arterial stiffness and central BP indexes use brachial BP for calibration of the aortic waveforms[14]; such measurements are subject to errors inserted by predialysis or postdialysis office BP readings, which are known to be highly inaccurate and poorly reflect the true BP load due to numerous factors, such as the white-coat effect, patient frustration to start dialysis and leave the unit quickly, anxiety for correct arteriovenous fistula needling, and truly high BP variability during the intra- and interdialytic periods.[11] We have, therefore hypothesized that ambulatory estimates of arterial stiffness and central BP parameters may have stronger associations with cardiovascular events and mortality in this population. Thus, the aim of this study was to evaluate and compare the prognostic value of ambulatory recording of peripheral and central BP, arterial stiffness and wave reflection parameters for major cardiovascular outcomes and all-cause mortality in hemodialysis patients.

Methods

Study Population

This is a prospective cohort study including hemodialysis patients from 5 affiliated hemodialysis centers in northern Greece. Adult patients (>18 years) were eligible to participate to the study if they (1) had ESRD treated with hemodialysis for >3 months, (2) were following a standard thrice-weekly hemodialysis schedule, and (3) provided an informed written consent. Exclusion criteria were as follows: (1) chronic atrial fibrillation or other arrhythmia; (2) nonfunctional arteriovenous fistula in the contralateral brachial arm area of the one used for vascular access; (3) modification of dry weight or antihypertensive treatment during 1 month before enrollment; (4) myocardial infarction (MI), angina pectoris, and ischemic stroke during 1 month before study initiation; (5) congestive heart failure class III to IV based on the New York Heart Association (NYHA) classification; and (6) history of malignancy or any other condition with poor prognosis. The study protocol was approved by the Ethics Committee of School of Medicine, Aristotle University of Thessaloniki.

Study Procedures and Ambulatory BP Monitoring

A total 170 hemodialysis patients who met the aforementioned criteria and had valid 48-hour BP recordings between February 2013 and March 2016 were included in this analysis. Baseline evaluation included full medical history, physical examination, and standard laboratory tests to capture demographic, anthropometric, and dialysis-related parameters, as well as comorbidities. Study participants were instructed to arrive to their hemodialysis unit 1 hour before a midweek dialysis session; for example, the second or the third weekly session. Prehemodialysis BP was evaluated with the use of a validated oscillometric device, at the level of brachial artery in the nonfistula arm, after 5 minutes of rest and with 2 measurements per occasion taken 2 minutes apart, according to the European Society of Hypertension 2013 guidelines.[15] Venous blood specimens were acquired for routine hematologic and biochemical laboratory testing. After blood sampling, the Mobil-O-Graph monitor with a cuff of appropriate size was fitted in the nonfistula arm and ambulatory BP monitoring was started, as described below. Subsequently, all participants underwent their regular dialysis session, during which volume withdrawal was programmed on the basis of their prespecified dry weight, according to standard clinical criteria. Patients were instructed to follow their usual activities until the next session.

Ambulatory brachial and aortic BP, indices of wave reflection [AIx, defined as the ratio of augmentation pressure to aortic PP and heart rate-adjusted AIx (AIx(75))], and PWV were estimated with the Mobil-O-Graph NG device, an oscillometric ambulatory BP monitoring device, whose brachial BP-detection unit was validated according to standard protocols[16,17] and was shown to provide practically identical values with a widely used ambulatory BP monitor.[18] Immediately after recording brachial BP, the cuff reinflates at the level of the diastolic BP (DBP) where it records the brachial pulse waves for ≈10 s with a high-fidelity pressure sensor (MPX5050, Freescale, Tempe, AZ).[13,19,20] For calibration of the brachial pulse waveforms, the system uses the brachial SBP and DBP. Then, the aortic pulse waveform is generated with the use of the ARCSolver algorithm with generalized transfer function; the software also performs wave separation analysis by decomposing the aortic pulse waveform into forward and backward waves, as described elsewhere.[19,20] Among various indexes, the device calculates augmentation pressure and AIx, as well as aortic SBP, DBP, and PP. The device was monitoring the above parameters every 20 minutes during the day (7 AM to 11 PM) and every 30 minutes during the night (11 PM to 7 AM) for 48 hours until the next dialysis session. Measurements were used for the analysis if >80% of recordings were valid with ≤2 nonconsecutive day-hours with <2 valid measurements, and ≤1 night-hour without valid recording.[21] All prespecified measurements automatically obtained during the 48-hour period were used to calculate the average values of each studied parameter for each patient, whereas measurements performed manually were excluded. Previous validation studies in hypertensive and healthy volunteers showed acceptable agreement between Mobil-O-Graph–derived parameters and

invasive and noninvasive measurements.[20,22–24] In hemodialysis patients, Mobil-O-Graph provided comparable estimates of office aortic SBP, AIx, and PWV with that obtained by Sphygmocor (ArtCor, Sydney, Australia), which is the most widely applied method for noninvasive assessment of these parameters.[14]

End Points

In this analysis, we censored patients on the date of the first occurrence of the end points under study or on August 15, 2016. The primary end point was a combination of all-cause death, nonfatal MI, and nonfatal stroke. Secondary end points included: (1) all-cause mortality, (2) cardiovascular mortality defined as fatal MI (death by any cardiovascular mechanism within 30 days after an MI related to the immediate consequences of the MI) or fatal stroke (death within 30 days after a stroke that is either a direct consequence of the stroke or a complication of the stroke) or sudden death, and (3) a combined outcome of cardiovascular death, nonfatal MI, nonfatal stroke resuscitation after cardiac arrest, coronary revascularization procedure or hospitalization for heart failure.

Statistical Analysis

Statistical analysis was performed with Statistical Package for Social Sciences 23 (SPSS Inc, Chicago, IL). Shapiro–Wilk test was applied to examine the normality of distribution for continuous variables. Quantitative variables are presented as mean±SD or median with range according to the normality of distribution, whereas qualitative variables are presented as frequencies and percentages (n, %). To compare differences in occurrence of study end points among the different levels of each studied parameter, data were categorized in ascending order to quartiles of patients. Kaplan–Meier curves were created, and the log-rank test was applied to compare the differences among the quartiles in the occurrence or freedom from the studied end points during follow-up. Univariate and multivariate Cox regression analyses were performed to evaluate the impact of various demographic and clinical characteristics, ambulatory central BP, wave reflection and arterial stiffness parameters on all-cause mortality. Variables were tested for interactions and included in the multivariate model if $P<0.2$ in univariate analysis. The adjusted hazard ratios (HR) are reported with 95% confidence intervals (CI) and values of $P<0.05$ (2-tailed) were considered statistically significant.

Results

Baseline Characteristics and Outcomes of Interest

Baseline demographic, anthropometric, clinical and routine laboratory characteristics are presented in Table 1. A total of 170 hemodialysis patients (101 men and 69 women), with mean age of 63.76±14.32 years and median hemodialysis vintage 26 (3–180) months were included in this study. The prevalence of main cardiovascular risk factors and target-organ damage was 31.8% for diabetes mellitus, 82.9% for hypertension, 27.1% for dyslipidemia, 6.5% for peripheral vascular disease, 22.4% for coronary heart disease, 8.2% for heart failure, and 8.8% for previous stroke. Participants were prospectively followed for 28.09±11.16 months. The frequencies for the study end points are presented in Table 2. During follow-up, 37 (21.8%) patients died, 5 (2.9%) due to MI, 4 (2.4%) due to stroke, 19 (11.2%) patients experienced sudden death and 9 (5.3%) due to noncardiac causes; (ie, infective endocarditis, sepsis, pancreatitis, cachexia, or cancer).

Primary End Point

Figure 1 depicts the Kaplan–Meier curves of freedom from the primary end point for quartiles of 48-hour central SBP, 48-hour central PP, 48-hour PWV and 48-hour AIx(75). Figure 2

Table 1. Baseline Demographic, Anthropometric, Clinical, and Routine Laboratory Characteristics of the Population Studied

Parameter	Value
n	170
Age, y	63.76±14.32
Mean follow-up, mo	28.09±11.16
Female, n (%)	69 (40.6)
Weight, kg	73.04±14.93
Height, cm	168.16±8.93
BMI, kg/m^2	26.06±5.76
Dialysis vintage, mo	26 (3–180)
Diabetes mellitus, n (%)	54 (31.8)
Hypertension, n (%)	141 (82.9)
Dyslipidemia, n (%)	46 (27.1)
Peripheral vascular disease, n (%)	11 (6.5)
Coronary heart disease, n (%)	38 (22.4)
Heart failure, n (%)	14 (8.2)
Stroke history, n (%)	15 (8.8)
Smoking, n (%)	29 (17.1)
Serum urea nitrogen, mmol/L	23.26±6.22
Serum creatinine, μmol/L	729.5±214.0
URR, %	68.83 (40.41–85.71)
Serum calcium, mmol/L	2.25±0.18
Serum phosphate, mmol/L	1.75±1.06
Parathormone, ng/L	295.07±210.26
Hemoglobin, g/L	113.1±12.7
Albumin, g/L	40.2±3.9
RAAS blockers, n (%)	
ARBs	32 (18.8)
ACEIs	12 (7.1)
Renin inhibitors	1 (0.6)
Aldosterone blockers, n (%)	2 (1.2)
CCBs, n (%)	89 (52.4)
Loop diuretics, n (%)	65 (38.2)
β-Blockers, n (%)	87 (51.2)
Central active, n (%)	33 (19.4)
Erythropoietin, n (%)	134 (78.8)
Statins, n (%)	72 (42.4)
Pre-HD SBP, mm Hg	145.2±23.09
48h pSBP, mm Hg	133.2±17.0
48h pDBP, mm Hg	78.9±11.1
48h cSBP, mm Hg	120.9±14.8
48h cDBP, mm Hg	80.4±11.27
48h pPP, mm Hg	54.3±13.2
48h cPP, mm Hg	40.5±9.5

(*Continued*)

Table 1. Continued

Parameter	Value
48h heart rate, bpm	73±10
48h PWV	9.4±2.2
48h AIx(75)	26.7±7.5
UF rate, mL/h per kg	7.38±4.07

ACEIs indicates angiotensin-converting enzyme inhibitors; AIx, augmentation index; ARBs, angiotensin II receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; DBP, diastolic blood pressure; HD, hemodialysis; p, peripheral; PP, pulse pressure; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure; UF, ultrafiltration; and URR, urea reduction rate.

presents HR of the primary end point for quartiles of predialysis SBP, and ambulatory 48-hour brachial SBP, central SBP, central PP, PWV and AIx(75). Quartile 1 was the reference group in all comparisons. As shown in Figure 2, no significant differences between quartiles of predialysis BP or ambulatory brachial SBP were evident, whereas ambulatory brachial DBP was inversely related with the risk of the primary end point. With regards to central SBP (Figure 1A), cumulative freedom from primary end point was 65.1% for patients in quartile 1, 69.0% for patients in quartile 2, 76.2% for patients in quartile 3 and 76.7% for patients in quartile 4 (log-rank P=0.324), and for central DBP cumulative freedom from primary end point was 55.8% for patients in quartile 1, 73.8% for patients in quartile 2, 76.2% for patients in quartile 3 and 81.4% for patients in quartile 4 (log-rank P=0.024, Figure 1B). Cumulative survival was different for quartiles of 48-hour central PP (83.7%, 71.4%, 69.0% and 62.8% for quartiles 1–4 ; log-rank P=0.024, Figure 1C). Moreover, cumulative freedom was significantly different for quartiles of ambulatory PWV (93.0%, 81.0%, 57.1% and 55.8% for quartiles 1 to 4 (log-rank P<0.001, Figure 1D) and HR of freedom from the primary end point were 7.874 (95% CI, 2.317–26.764) and 8.709 (95% CI, 2.570–29.507) for quartiles 3 and 4 compared to quartile 1 (Figure 2). Similarly, cumulative freedom was significantly different for quartiles of ambulatory AIx(75) (88.4%, 66.7%, 69.0%. and 62.8% for quartiles 1–4; log-rank P=0.014, Figure 1E) and HR of freedom from the primary end point were 3.022 (95% CI, 1.077–8.480) and 3.784 (95% CI, 1.386–10.336) for quartiles 3 and 4 compared with quartile 1 (Figure 2).

Table 2. Outcomes of Interest and Study End Points During Follow-Up in the Total Population

Parameter	Value
Myocardial infarction, n (%)	
Fatal	5 (2.9)
Nonfatal	7 (4.1)
Stroke, n (%)	
Fatal	4 (2.4)
Nonfatal	7 (4.1)
Sudden death, n (%)	19 (11.2)
Resuscitation after cardiac arrest, n (%)	2 (1.2)
Coronary revascularization procedure, n (%)	5 (2.9)
Hospitalization for acute decompensated heart failure, n (%)	9 (5.3)
All-cause death, n (%)	37 (21.8)
Cardiovascular death, n (%)	28 (16.5)
All-cause death or nonfatal MI or nonfatal stroke, n (%)	48 (28.2)
Cardiovascular death or nonfatal MI or nonfatal stroke, n (%)	39 (22.9)
Cardiovascular death, or nonfatal MI or nonfatal stroke or resuscitation after cardiac arrest or coronary revascularization or hospitalization for heart failure, n (%)	46 (27.1)

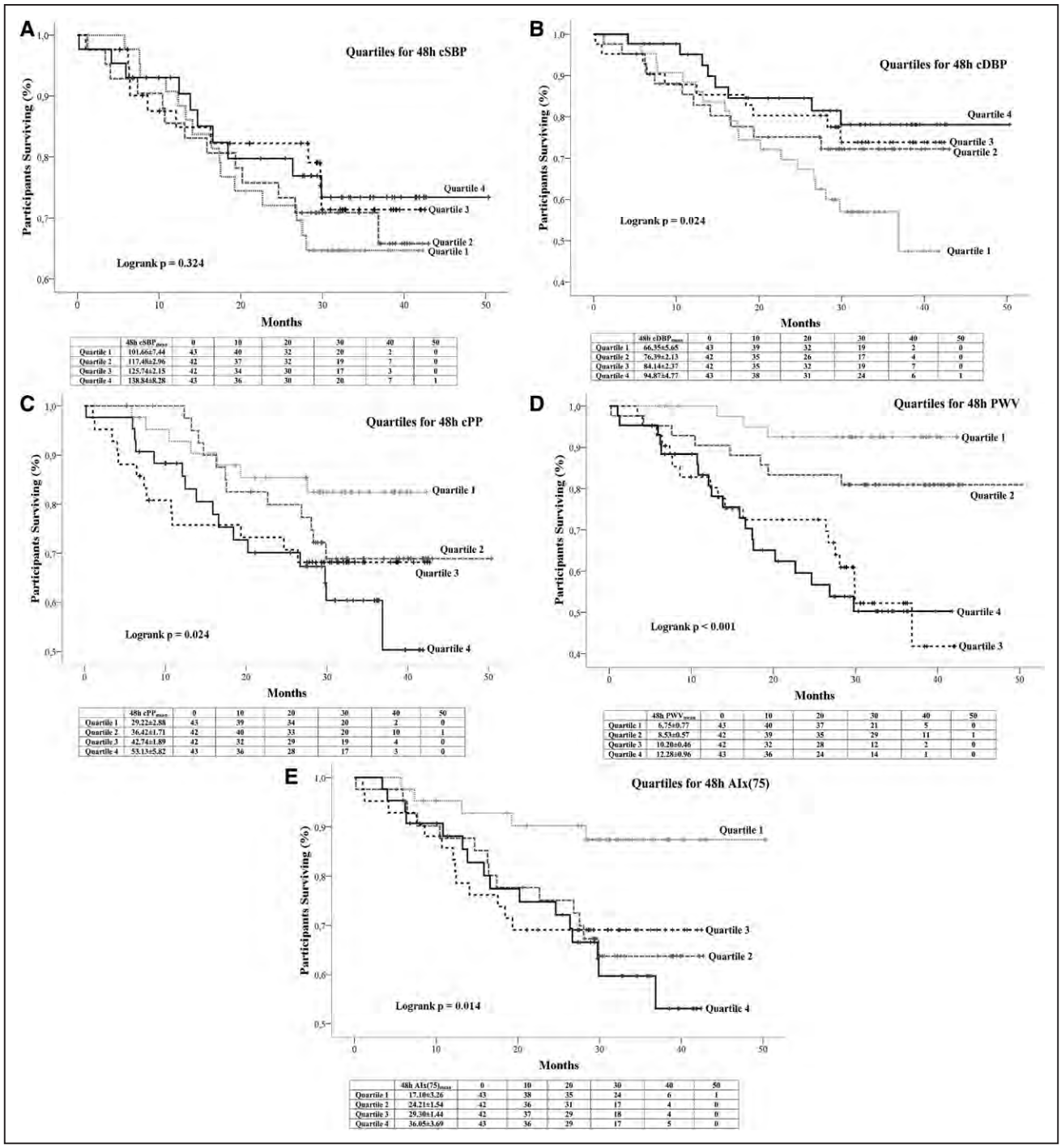
MI indicates myocardial infarction.

Secondary End Points

As shown in Figure 3, no significant differences in the future risk of death between quartiles of predialysis BP or ambulatory brachial SBP and DBP were evident. With regards to central SBP and DBP (Figure 3), no significant differences in the HR for all-cause mortality were noted. Future risk of death was marginally different for quartiles of 48-hour central PP, as HR was 1.895 (95% CI, 0.689–5.214) for quartile 3 and 2.216 (95% CI, 0.831–5.907) for quartile 4 (log-rank P=0.089). In contrast, future risk was significantly different for quartiles of ambulatory PWV 10.417 (95% CI, 2.392–45.360) and 8.495 (95% CI, 1.912–37.740) for quartiles 3 and 4 compared with quartile 1. In the same context, HR of all-cause mortality for quartiles of ambulatory AIx(75) were gradually increasing; that is, 3.189 (95% CI, 1.015–10.021) and 3.732 (95% CI, 1.217–11.449) for quartiles 3 and 4 compared with quartile 1. Similarly, no significant differences in the future risk of cardiovascular death between quartiles of predialysis SBP, and ambulatory brachial SBP and DBP, central SBP and DBP, and central PP were evident (Figure S1 in the online-only Data Supplement). With regards to ambulatory PWV, the HR of cardiovascular mortality was significantly higher for patients in quartile 3 (HR, 7.935; 95% CI, 1.773–35.518) and quartile 4 (HR, 6.745; 95% CI, 1.472–30.912) compared with those in quartile 1. The relevant risk was also higher for patients in quartile 4 (HR, 4.230; 95% CI, 1.180–15.167) compared with those in quartile 1 of AIx(75). Finally, the risk of the last combined cardiovascular outcome (Figure S2 in the online-only Data Supplement) was not different between quartiles of predialysis BP, ambulatory brachial SBP, and ambulatory central SBP and DBP, but progressively lower with higher quartiles of brachial ambulatory DBP and higher with higher quartiles of ambulatory central PP, ambulatory PWV, and ambulatory AIx(75).

Factors Associated With Occurrence of Death, MI, or Stroke

Table 3 presents the univariate and multivariate Cox regression analyses including the primary end point as the dependent variable and various demographic, clinical and laboratory factors possibly affecting mortality as independent variables. Ambulatory parameters were examined as continuous variables in this analysis. In univariate analysis age >75 years (HR, 3.110; 95% CI, 1.757–5.503), body mass index (HR, 0.914; 95% CI, 0.854–0.979), hemoglobin (HR, 0.700; 95% CI, 0.556–0.881), serum albumin (HR, 0.377; 95% CI,



	48h cSBP$_{mean}$	0	10	20	30	40	50
Quartile 1	101.66±7.44	43	40	32	20	2	0
Quartile 2	117.48±2.96	42	37	32	19	7	0
Quartile 3	125.74±2.15	42	34	30	17	3	0
Quartile 4	138.84±8.28	43	36	30	20	7	1

	48h cDBP$_{mean}$	0	10	20	30	40	50
Quartile 1	66.35±5.65	43	39	32	19	2	0
Quartile 2	76.39±2.13	42	35	26	17	4	0
Quartile 3	84.14±2.37	42	35	32	19	7	0
Quartile 4	94.87±4.77	43	38	31	24	6	1

	48h cPP$_{mean}$	0	10	20	30	40	50
Quartile 1	29.22±2.88	43	39	34	20	2	0
Quartile 2	36.42±1.71	42	40	33	20	10	1
Quartile 3	42.74±1.89	42	32	29	19	4	0
Quartile 4	53.13±5.82	43	36	28	17	3	0

	48h PWV$_{mean}$	0	10	20	30	40	50
Quartile 1	6.75±0.77	43	40	37	21	5	0
Quartile 2	8.53±0.57	42	39	35	29	11	1
Quartile 3	10.20±0.46	42	32	28	12	2	0
Quartile 4	12.28±0.96	43	36	24	14	1	0

	48h AIx(75)$_{mean}$	0	10	20	30	40	50
Quartile 1	17.10±3.26	43	38	35	24	6	1
Quartile 2	24.21±1.54	42	36	31	17	4	0
Quartile 3	29.30±1.44	42	37	29	18	4	0
Quartile 4	36.05±3.69	43	36	29	17	5	0

Figure 1. Kaplan–Meier survival curves and life tables for occurrence of the primary end point (all-cause death or myocardial infarction or stroke) and (**A**) 48-hour ambulatory central systolic blood pressure (48h cSBP), (**B**) 48-hour ambulatory central diastolic blood pressure (48h cDBP) (**C**) 48-hour ambulatory central pulse pressure (48h cPP), (**D**) 48-hour ambulatory pulse wave velocity (48h PWV), and (**E**) 48-hour ambulatory heart rate–adjusted augmentation index [48h AIx(75)].

0.181–0.788; per g/dL increase), 48-hour central DBP (HR, 0.968; 95% CI, 0.944–0.993; per mm Hg increase), 48-hour PWV (HR, 1.410; 95% CI, 1.225–1.623) and 48-hour AIx(75) (HR, 1.046; 95% CI, 1.009–1.085; per % increase) were associated with mortality. However, in multivariate analysis, only 3 parameters were independently associated with the primary end point in the population studied; that is, body mass index (HR, 0.900; 95% CI, 0.834–0.971; per kg/m^2 increase), hemoglobin (HR, 0.970; 95% CI, 0.945–0.995; per g/L increase) and 48-hour PWV (HR, 1.579; 95% CI, 1.187–2.102; per m/s increase).

Discussion

This prospective cohort study was designed to examine the prognostic role of ambulatory peripheral and central SBP, PP, PWV, and AIx recordings for cardiovascular events and

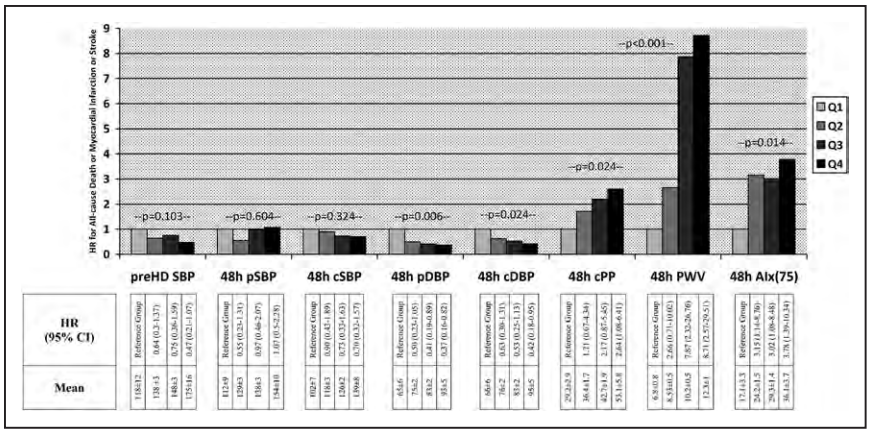


Figure 2. Hazard ratios (HRs) of all-cause death or myocardial infarction or stroke for quartiles of predialysis SBP 48-hour peripheral SBP (48h pSBP), 48-hour central SBP (48h cSBP), 48-hour central pulse pressure (48h cPP), 48-hour pulse wave velocity (48h PWV), and 48-hour heart rate-adjusted augmentation index (48h AIx(75)]. Quartile 1 was the reference group for all comparisons. *P* values are those reported for linear trend. CI indicates confidence interval.

mortality in hemodialysis patients. The main finding was that cumulative freedom from primary end point was significantly shorter with higher quartiles of ambulatory PWV and AIx(75), but was not different for quartiles of predialysis SBP, 48-hour peripheral SBP, and 48-hour central SBP. Similarly, the HR for all-cause mortality, cardiovascular mortality and the combined outcome of cardiovascular events were similar for quartiles of predialysis SBP, 48-hour peripheral SBP and 48-hour central SBP, but were progressively increasing with higher quartiles of ambulatory PWV and ambulatory AIx(75). Increasing quartiles of 48-hour central PP displayed higher HR for primary end point, but nonsignificant trends toward increased cardiovascular events and mortality. In multivariate Cox-regression analysis 48h-ambulatory-PWV was the only vascular parameter independently associated with mortality.

PWV is the most common way to measure arterial stiffness, as it determines the pressure wave propagation velocity from the aorta toward peripheral arterial branches.[25] Arterial stiffness, due to aortic geometry changes, lumen-narrowing and arterial wall alternations, creates an impedance mismatch. This happens because reflections of the forward pressure waves arrive back to the aorta earlier and amplify aortic pressures during systole, while they reduce aortic pressures during diastole.[26] These changes inevitably result in: (1) opposition to LV ejection which induces LV afterload increase and thus in LV remodeling and failure, (2) reduction of aortic diastolic pressure which may affect coronary blood flow and cause myocardial ischemia, and (3) excessive penetration of pulsatile pressure into peripheral organs, particularly in those with decreased precapillary resistance, such as brain and kidney.[3,26–28] The consequence of these pathophysiological changes in patients with extreme arterial stiffness, such as those with ESRD, is higher occurrence of LV hypertrophy, cardiovascular and cerebrovascular events, and death.[3]

Preliminary studies indicate a strong association between arterial stiffness parameters and all-cause or cardiovascular mortality, based on office evaluations.[25] In a cohort of 241 hemodialysis patients, PWV values >12.0 m/s, measured with Doppler ultrasonography, were independently associated with all-cause mortality (HR, 5.4; 95% CI, 2.4–11.9) and cardiovascular mortality (HR, 5.9; 95% CI, 2.3–15.5), during a mean follow-up of 72 months.[6] In another study including 150 hemodialysis patients, and prehemodialysis BP levels <160/90 mm Hg were targeted by dry weight probing or initiation of drug treatment and PWV changes were monitored. During 51±38 months of follow-up, a mean of 15 mm Hg decrease in SBP was achieved; however, a significantly higher risk for mortality (HR, 2.59; 95% CI, 1.51–4.43) and cardiovascular complications (HR, 2.35; 95% CI, 1.23–4.41) were present in patients with the absence of concomitant PWV decrease, suggesting that lowering BP in hemodialysis patients that cannot modify the wall properties of their aorta and major arteries may not be beneficial.[9] Results from a third study including 242 hemodialysis patients, showed that patients with higher PWV values compared with nomograms established from subjects without ESRD had a 3-fold higher risk for all-cause

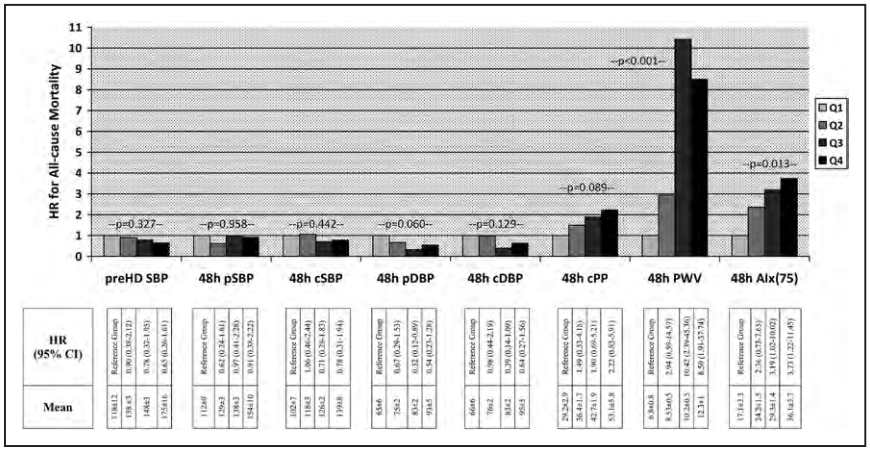


Figure 3. Hazard ratios (HRs) of all-cause mortality for quartiles of predialysis SBP (preHD SBP), 48-hour peripheral SBP (48h pSBP), 48-hour central SBP (48h cSBP), 48-hour central pulse pressure (48h cPP), 48-hour pulse wave velocity (48h PWV), and 48-hour heart rate-adjusted augmentation index [48h AIx(75)]. Quartile 1 was the reference group for all comparisons. *P* values are those reported for linear trend. CI indicates confidence interval.

Table 3. Univariate and Multivariate Cox Regression Analysis for Occurrence of the Primary End Point (All-Cause Death or Myocardial Infarction or Stroke) in the Total Studied Population

	Univariate Analysis			Multivariate Analysis		
Parameter	Unadjusted Hazard Ratio	95% CIs	*P* Value	Adjusted Hazard Ratio	95% CIs	*P* Value
Age >75 y	3.110	1.757–5.503	<0.001	0.437	0.152–1.252	0.123
Female	1.341	0.761–2.363	0.310			
BMI, per kg/m^2 increase	0.914	0.854–0.979	0.011	0.900	0.834–0.971	0.006
Dialysis vintage, per month increase	0.990	0.981–1.000	0.052	0.996	0.986–1.006	0.444
Diabetes mellitus	1.918	1.083–3.397	0.026	1.752	0.825–3.721	0.144
Hypertension	1.025	0.480–2.191	0.949			
Dyslipidemia	0.785	0.400–1.541	0.482			
Heart failure	1.187	0.486–3.306	0.742			
Coronary heart disease	1.781	0.967–3.280	0.064	1.573	0.752–3.290	0.229
Peripheral vascular disease	1.848	0.732–4.669	0.194	2.428	0.723–8.160	0.151
History of stroke	0.931	0.334–2.591	0.891			
Smoking	0.891	0.393–2.020	0.783			
Hemoglobin, per g/L increase	0.965	0.943–0.987	0.002	0.970	0.945–0.995	0.020
Serum albumin, per g/L increase	0.907	0.843–0.976	0.009	0.947	0.871–1.030	0.202
Serum parathormone, per ng/L increase	1.000	0.998–1.001	0.599			
preHD SBP, per mm Hg increase	0.993	0.981–1.005	0.261			
48h peripheral MAP, per mm Hg increase	0.990	0.968–1.013	0.402			
48h central SBP, per mm Hg increase	0.994	0.975–1.013	0.531			
48h central DBP, per mm Hg increase	0.968	0.944–0.993	0.012	0.976	0.941–1.012	0.186
48h central PP, per mm Hg increase	1.027	0.999–1.055	0.058	0.951	0.901–1.005	0.075
48h heart rate, per bpm increase	0.991	0.962–1.020	0.542			
48h PWV, per m/s increase	1.410	1.225–1.623	<0.001	1.579	1.187–2.102	0.002
48h AIx(75), per % increase	1.046	1.009–1.085	0.015	0.998	0.943–1.055	0.940
Use of antihypertensive medications	0.608	0.303–1.220	0.162	0.691	0.308–1.547	0.368

AIx indicates Augmentation index; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HD, hemodialysis; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; and SBP, systolic blood pressure.

or cardiovascular mortality than in patients with lower PWV values.[29] We have previously shown that PWV-recorded office values with the Mobilograph NG device is strongly correlated to that recorded with Sphygmocor, the most widely used device for PWV measurements currently.[14] Our study expands the prognostic role of office PWV in hemodialysis patients, by showing that that increasing 48-hour ambulatory PWV was independently associated with shorter survival and displayed markedly higher HRs for cardiovascular events and death.

A previous seminal cohort study of 180 hemodialysis patients indicated that increased AIx, assessed with applanation tonometry, was independently associated with all-cause (HR, 1.51; 95% CI, 1.23–1.86, per 10% increase) and CV mortality (HR, 1.48; 95% CI, 1.16–1.90, per 10% increase).[7] In contrast, a study including 92 patients failed to prove that wave reflections is an independent predictor, as during 61 months of follow-up, no significant differences were noted in cumulative survival among quartiles of AIx (log-rank *P*=0.780).[30] The findings of this study clarify these issues, as we found that 48-hour ambulatory AIx(75) was significantly associated with higher risk of all-cause mortality or cardiovascular outcomes. Arterial stiffness and wave reflections are generally closely correlated with each other in the general population.[31] However, the unique pattern of changes in cardiovascular parameters during the interdialytic and intradialytic periods in hemodialysis patients is also affecting this association. We have previously shown by office and ambulatory recordings that during the interdialytic intervals central SBP, and AIx gradually increased (this increase being about 30% higher during the 3-day interval), but PWV follows a rather steady pattern.[32,33] In the same context, we have shown that although hemodialysis acutely reduces central SBP and AIx, PWV remained unchanged.[34] In this study, ambulatory PWV was the only vascular parameter independently predicting

mortality, a finding probably related to the fact that PWV is the most direct estimate of arterial stiffness and that this analysis included the average 48-hour values of these parameters and not their variability, which in the case of AIx(75) could also be a factor affecting cardiovascular disease.

Most of the available studies in the field indicate a significant association of PP with adverse outcomes in hemodialysis populations, although PP is indirectly estimated as the difference between SBP and DBP.[35,36] In a prospective cohort of 190 hemodialysis patients, increased central PP measured directly with arterial tonometry was also independently associated with lower survival.[8] In the only study with ambulatory PP, in 57 hypertensive hemodialysis patients, 24-hour PP was significantly associated with cardiovascular mortality (HR, 1.85; 95% CI, 1.28–2.65, per 10 mm Hg increase).[37] Our results suggest a trend for increased adverse outcomes with higher 48-hour PP, with the exception of the combined outcome of cardiovascular death, nonfatal MI, nonfatal stroke, resuscitation after cardiac arrest, coronary revascularization, or hospitalization for heart failure, where a significantly increased risk was noted.

The prognostic value of peridialytic BP, home BP and ambulatory BP recordings in hemodialysis populations is a field of major interest in recent years.[10] In a cohort of 326 hemodialysis patients, 44-hour SBP levels between 110 and 120 mm Hg displayed significant lower mortality than higher levels, while BP measurements acquired before and after dialysis were not predictive of mortality.[38] Similarly, in 150 hemodialysis patients levels of 44-hour SBP >145 mm Hg were associated with a 2-fold higher risk for all-cause and cardiovascular mortality compared with lower levels, but predialysis and postdialysis BP had no prognostic relations.[39] In our study, we confirmed the absence of association between predialysis SBP and cardiovascular events and mortality; this was also evident, however, for 48-hour peripheral and central SBP, a finding contrasting the above. Although this could be attributed to residual risk, a possible explanation could be that doctors caring for the patients in this cohort were aware of the above[38,39] and other studies[40] on the association of ambulatory BP with outcome; thus the results of the single ambulatory BP recording were added on the other clinical findings and home BP measurements to guide nonpharmacological (ie, dry weight reductions) and pharmacological measures to reduce BP to goal. Another important finding in this study concerned ambulatory DBP, for which an increase was related with lower risk of some of the outcomes studied, resembling the J-curve phenomenon.[41] The J-curve is by many considered to be an epiphenomenon related to the increased mortality of severely diseased patients, including those with cachexia or advanced heart failure,[42] which are not uncommon among the hemodialysis population. However, it is also possible that in our cohort, truly low DBP in the absence of terminal disease or low SBP has led to adverse cardiovascular effects. This is relevant to our other findings, as one of the major consequences of increased arterial stiffness is reduced aortic DBP that may affect coronary blood flow.[41] These findings associating low DBP with events may mirror those in the general hypertensive population, where a corresponding association of increased PP with outcome, explained some of the DBP-related mortality.[43] Herein, the univariate inverse associations of ambulatory DBP with outcome were abolished in multivariate analysis, where PWV was the only vascular parameter independently associated with the primary outcome. In this regard, our study of a cohort with doctors continuously aiming in proper BP control could resemble previous observations, were improvement in BP levels was not associated with improved outcomes, unless concomitant improvements in PWV were evident during follow-up.[9] These results may overall be reflective of the strong prognostic value of arterial stiffness, which, apart from BP is affected by several additional factors in hemodialysis patients.[3]

Our study has strengths and limitations. To our knowledge, this study is the first to evaluate the effect of ambulatory recordings of arterial stiffness and wave reflections parameters on cardiovascular events and mortality in hemodialysis patients. We have included a complete 48-hour period to cover a full standard interdialytic interval; 48-hour recordings are always a difficult task, much more in hemodialysis patients. In this context, the population size must be considered high as few studies with ambulatory BP monitoring in hemodialysis included higher number of patients. Furthermore, our study included information over most of the factors affecting mortality and cardiovascular complications in patients with ESRD. However, the mean follow-up of the study was less than 2.5 years. A longer follow-up period may have led to a higher number of events, but given the trends presented in our analysis this would rather not affect the main conclusions, with the exception of the associations of ambulatory central PP which were marginally significant. Finally, this study included a unique evaluation of factors of interest (ambulatory BP, PWV, and AIx) at baseline and, thus, their levels overtime and at study-end were not recorded; this is however, a common limitation of relevant cohort studies.

In conclusion, this study showed that ambulatory PWV and ambulatory AIx(75) are independently associated with the risk of cardiovascular events and all-cause mortality in hemodialysis patients. In this cohort, both office BP and ambulatory peripheral and central BP did not had prognostic use for cardiovascular events and mortality. Ambulatory PWV is probably the most prominent of these factors, as it was the only vascular parameter predicting mortality in multivariate analysis.

Perspectives

Patients with ESRD have extremely high rates of cardiovascular events and mortality. Arterial stiffness and augmentation of the aortic BP component measured in office conditions are established cardiovascular risk factors in hemodialysis patients. To date, all devices measuring arterial stiffness and central BP indexes use brachial BP for calibration of the aortic waveforms, thus are subjected to errors inserted by office BP measurements. This is the first study to evaluate the prognostic significance of ambulatory PWV and ambulatory AIx(75) in hemodialysis patients, suggesting that it is much higher than that of office and ambulatory BP. These findings add

to the evidence suggesting that arterial stiffness is probably the most prominent cardiovascular risk factor in hemodialysis. Whether therapeutic measures to modify arterial stiffness and wave reflection parameters would result in beneficial long-term effects in hemodialysis populations remains to be answered.

Disclosures

None.

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Novelty and Significance

What Is New?

- This study is the first to evaluate the association of ambulatory arterial stiffness and wave reflection parameters with future cardiovascular events and mortality in hemodialysis patients.

What Is Relevant?

- Peridialytic blood pressure measurements display ambiguous associations with outcome. Office arterial stiffness measurements based on these readings are subjected to relevant errors.
- Ambulatory blood pressure has a better association with cardiovascular events in hemodialysis; this study examines the prognostic significance of ambulatory peripheral and central systolic blood pressure, pulse pressure, pulse wave velocity, and augmentation index (AIx) in hemodialysis patients.

Summary

Ambulatory pulse wave velocity, AIx(75), and central pulse pressure were significantly associated with cardiovascular events and mortality in the population studied, in contrast to office and ambulatory blood pressure. Arterial stiffness, estimated with ambulatory pulse wave velocity, seems the most prominent cardiovascular risk factor for patients undergoing hemodialysis.