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Blood pressure variability and outcomes in chronic kidney disease

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Abstract

Background. We investigated the effects of visit-to-visit systolic blood pressure variability (SBPV) on both mortality and dialysis inception in a cohort of chronic kidney disease (CKD) patients not requiring dialysis therapy. Furthermore, we also explored the carry-over effect of visit-to-visit SBPV on mortality after dialysis initiation.

Methods. We conducted a longitudinal retrospective, observational, multi-centre study in three tertiary care nephrology outpatient clinics. All the ambulatory CKD patients admitted to the outpatient clinics from 1 January 2004 to 31 December 2005 were screened for study eligibility. We selected all consecutive patients older than 18 years of age with a mean estimated glomerular filtration rate of <60 mL/min/m^2, free from cardiovascular disease. SBPV was defined as the ratio of the SD to the mean SBP of five values recorded during a run-in phase of 4–5 months. Data on dialysis inception and mortality were recorded through 31 December 2010.

Results. Overall, we selected a cohort of 374 elderly (median age: 79 years) subjects. A total of 232 (62%) and 103 (29%) patients were male and had diabetes, respectively. A significant association between SBPV and the risk of death but not of CKD progression to dialysis was noted at univariate and after multivariable adjustments (hazard ratio for all-cause mortality per 1% increase in SBPV: 1.05; 95% confidence interval: 1.02–1.09; P = 0.001). Notably, no lethal event was recorded after dialysis initiation.

Conclusions. Current findings suggest that SBPV may be of use for risk stratification in CKD patients.

Keywords: chronic kidney disease; death; dialysis inception; systolic blood pressure variability

Introduction

Advanced stages of chronic kidney disease (CKD), including end-stage renal disease requiring renal replacement therapies (RRTs), are characterized by high rates of adverse cardiovascular (CV) outcomes [1]. Hypertension is one of the major causes of left ventricular hypertrophy, congestive heart failure, coronary heart disease, arrhythmias and cerebrovascular events in the general population [2, 3]. Analogously, elevated blood pressure (BP) is one of the most frequent complications of CKD [3], promotes renal function impairment [4–8] and is associated with a substantial increase in the CV risk of CKD subjects [6, 9, 10]. Thus, BP control represents a major therapeutic goal in general as well as in non-dialysis-dependent CKD individuals.

Recently, Rothwell *et al*. [11–14] investigated the importance of BP variability (BPV) as a predictor of CV events and demonstrated that both visit-to-visit BPV and the highest SBP value recorded during the visits were strong predictors of stroke, independently of mean SBP. However, in spite of a growing body of evidence suggesting that BPV portends a poor CV prognosis in subjects without renal disease [15–18], data on patients with CKD or on maintenance dialysis are not available [19–21]. Similarly, to the best of our knowledge, no study has ever investigated the relationship between visit-to-visit BPV and progression of CKD in patients free from CV disease. Accordingly, the objective of this study was to investigate the effects of visit-to-visit systolic BPV on both mortality and dialysis inception in a cohort of CKD patients not requiring dialysis therapy. Furthermore, we also explored the carry-over effect of visit-to-visit systolic BPV on mortality after dialysis initiation.

Materials and methods

We conducted a longitudinal retrospective, observational, multi-centre study in three tertiary care nephrology outpatient clinics. The respective local medical ethics committees approved the study.

All ambulatory CKD patients admitted to the outpatient clinics from 1 January 2004 to 31 December 2005 were screened for study eligibility. Demographic, clinical and laboratory characteristics, medications as well as data on dialysis inception or death were collected. CKD was defined as mean estimated glomerular filtration rate (eGFR) <60 mL/min/m^2. Diabetes mellitus was defined on the basis of having an 8-h fasting plasma glucose level of >126 mg/dL, a non-fasting plasma glucose level of >200 mg/dL or if the subject reported having diabetes or was taking diabetes medications. Chronic obstructive pulmonary disease (COPD)

was defined if the subject reported having COPD. Cardiovascular disease (CVD) was defined as a history of cerebral vasculopathy, ischaemic heart disease or chronic heart failure (Class III and IV).

For the proposes of the study, we selected all consecutive patients older than 18 years of age with five consecutive outpatient visits during a period of 4–5 months. Over this run-in phase, eGFR and BP were repeatedly assessed via the four-variable Modification of Diet in Renal Disease Study (MDRD) equation and averaging all assessments available over a period of 3 months to exclude an acute kidney function impairment at the time of the first outpatient visit. An eGFR change of >15% during this 3 months window period was considered an exclusion criterion. Furthermore, all of the patients with CVD, neoplasia, cachexia, COPD, pregnancy and inflammatory chronic diseases at the time of the first visit at the outpatient clinic were also excluded.

From the original cohort of 730 patients identified, 111 were excluded because of the presence of any of the exclusion criteria [more than one criterion maybe concurrently present: eGFR variation of >15% during the run-in period ($n = 34$), neoplasia ($n = 12$), cachexia ($n = 15$), COPD ($n = 18$), pregnancy ($n = 3$), inflammatory chronic diseases ($n = 29$), CVD ($n = 63$)]. Finally, 245 were excluded because of data incompleteness (missing data on BP, medications, laboratory variables, lost-to-follow-up, transferred to other nephrology clinic).

All the patients received three or more complete nephrological evaluations per year. All medications, including anti-hypertensive drugs, were maintained or changed by the attending physician according to the National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) clinical guidelines available at the time of the visit.

At each outpatient clinic involved in the study, BP was routinely measured in the sitting position after 5 min rest with the use of a validated, semi-automated oscillometric device. BPV was defined as the ratio of the SD to the mean BP of all values recorded during the baseline visit and the following visits during the run-in phase. The coefficient of the visit-to-visit BP variation is expressed as a percent, multiplying the ratio by 100.

Data on dialysis inception and mortality were recorded through 31 December 2010. The date of dialysis inception was identified through the Italian Registry of Dialysis or, alternatively, by the renal unit where the patient started the RRT. Any fatal event among cohort members was identified by the renal unit where the patient attended for the renal care. Finally, to investigate the carry-over effect of BPV after dialysis initiation, mortality data on the dialysis status were recorded until study completion independently. We calculated the minimal detectable hazard ratio (HR) comparing individuals in the highest with the lowest quartile of systolic blood pressure variability (SBPV) [HR: 2.01; 95% confidence interval (CI): 1.31–3.07; P = 0.001] under the following assumption: (i) a two-tailed type-I error of 5%, (ii) a median survival time of 24 months (iii) an accrual time of 24 months and (iv) a fixed sample size of $n = 374$ patients. Under these assumptions, we would have 66% statistical power to detect a HR for all-cause mortality of 1.31.

Statistical analysis

Data are expressed as mean ± SD or frequencies as appropriate. To identify factors associated with systolic BPV, the study cohort was stratified according to quartiles of the systolic BPV coefficient. Trends across quartile of BPV were compared using analysis of variance for continuous variables and χ^2 tests for discrete variables. Survival analyses were used to gauge the association between SBPV and the risk of death or dialysis inception at follow-up. We used the Kaplan-Meier method to obtain the cumulative mortality curves according to SBPV. Next, unadjusted and multivariable-adjusted HRs were calculated by SBPV as a continuous variable. Thus, we initially adjusted for age and sex. Subsequent models included additional adjustment for the case-mix (diabetes mellitus, renal function, systolic and diastolic BP) as well as laboratory and treatment parameters (serum haemoglobin and phosphorous at study entry, low-protein diet). Finally, a stepwise procedure was used to identify the most parsimonious models to predict outcomes. A P-value of <0.05 was considered statistically significant. All analyses were completed using R version 2.9.2 (2009-08-24—the R Foundation for Statistical Computing).

Results

Table 1 shows clinical characteristics and laboratory data of the 374 patients recruited for the analyses. Overall, we selected a cohort of elderly (median age: 79 years; interquartile range 71–85 years) subjects. A total of 232 (62%) and 103 (29%) patients were male and had diabetes, respectively.

Table 1. Main demographic, clinical and laboratoristic characteristics of the study cohort according to quartiles of SBPV

	Overall ($n = 374$)	Quartiles of SBP variability				P-trend
		I quartile ($n = 91$), <6.67	II quartile ($n = 107$), 6.92–9.67	III quartile ($n = 104$), 6.92–9.67	IV quartile ($n = 72$), >12.59	
Males (%)	62	51	68	63	65	0.11
Diabetes (%)	27	29	23	31	28	0.39
Age, years	76 ± 11	72 ± 12	75 ± 11	76 ± 11	80 ± 8	<0.001
Low-protein diet (%)	24	29	20	20	33	0.23
Creatinine (mg/dL)	2.3 ± 1.3	2.3 ± 1.4	2.5 ± 1.6	2.1 ± 1.2	2.1 ± 1.1	0.50
Serum urea	84 ± 40	78 ± 33	96 ± 45	81 ± 39	80 ± 37	0.71
eGFR	33 ± 15	33 ± 14	33 ± 16	37 ± 17	33 ± 11	0.66
Sodium (mmol/L)	141 ± 4	140 ± 4	140 ± 4	141 ± 3	141 ± 4	0.63
Phosphorus (mg/dL)	3.6 ± 0.7	3.6 ± 0.9	3.6 ± 0.5	3.6 ± 0.7	3.6 ± 0.8	0.72
Haemoglobin (g/dL)	12.5 ± 1.6	12.4 ± 1.4	12.1 ± 1.7	13.1 ± 1.5	12.3 ± 1.8	0.55
Albumin (g/dL)	3.9 ± 0.6	4.0 ± 0.8	3.9 ± 0.5	4.0 ± 0.4	4.0 ± 0.4	0.93
SBP (mmHg)	137 ± 19	141 ± 19	132 ± 17	138 ± 20	137 ± 22	0.40
DBP (mmHg)	74 ± 11	77 ± 12	72 ± 11	75 ± 10	76 ± 10	0.79
ACE-I (%)	46	49	36	58	43	0.55
ARB (%)	55	58	47	49	75	**0.03**
β-blockers (%)	38	57	33	23	43	0.08
CCB (%)	44	52	46	48	26	**0.02**
Diuretics (%)	60	65	65	46	68	0.94
N anti-hypertensive drugs	3 (0–6)	3 (1–5)	2 (0–5)	2 (1–5)	3 (1–6)	0.07

eGFR, estimated glomerular filtration rate, calculated via the abbreviated MDRD equation; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); ACE-I, Ace inhibitor; ARB, angiotensin receptor blocker; B-blockers, beta blockers; CCB, calcium channel blockers.

At the beginning of the study, an overall adequate BP control was noted. Nonetheless, in spite of a mean systolic (137 ± 19 mmHg; median 140 mmHg; range: 80–200 mmHg) and diastolic (74 ± 11 mmHg; median 80 mmHg; range: 50–110 mmHg) BP below 140/90 mmHg, ∼50% of the study cohort did not meet the recommended BP targets. More than 50% of the study cohort took at least three anti-hypertensive drugs (Table 1). No significant correlation between SBPV and systolic (P = 0.40), diastolic (P = 0.79) or pulse pressure (P = 0.61) BP was detected.

When the study cohort was stratified according to quartiles of SBPV, only age and the use of angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) were associated with higher SBPV. Indeed, patients in the forth quartile of SBPV were, on average, older, more likely to be prescribed an ARB and less likely to be prescribed a CCB (Table 1).

During a mean follow-up of 33 (SD: 21) months, 209 patients (55.8%) died and 34 (9.0%) started dialysis. When the observation was extended beyond dialysis inception (mean follow-up: 39; SD: 20 months) no more fatal events were recorded.

As documented by the Kaplan–Meier curves, a significant association was noted between systolic BPV (SBPV) and the risk of death but not of CKD progression to dialysis (Figure 1A and B). Of note, no further fatal event was recorded when the follow-up was extended after dialysis inception (Figure 1C). We further tested the association between BPV and the risk of death or dialysis inception with different Cox models adjusted for demographics, case-mix and laboratory variables (Table 2). In spite of the multivariable adjustments, the associations between systolic BPV and the risk of all-cause mortality remained significant (HR: 1.05; 95% CI: 1.02–1.09; P = 0.001). On the contrary, no association with the risk of dialysis initiation could be detected (HR 1.04; 95% CI: 0.94–1.16; P = 0.39) (Table 2). Notably, stratification for mean BP change during the run-in phase (to account for the effect of a poor BP control prior to nephrology clinic appearance) did not seem to affect these results (data not shown).

Finally, we looked for the most parsimonious model to predict the risk of death and dialysis inception (Table 3). The SBPV was taken as a significant and independent predictor of death but not dialysis inception. As depicted in Figure 2, the higher the SBPV, the greater the risk of death at follow-up.

Discussion

The major finding of the current study is the independent association of SBPV and the risk of death but not of CKD progression among CKD patients not receiving dialysis. Though limited by the small sample size and by the lack of fatal events after dialysis initiation, these results

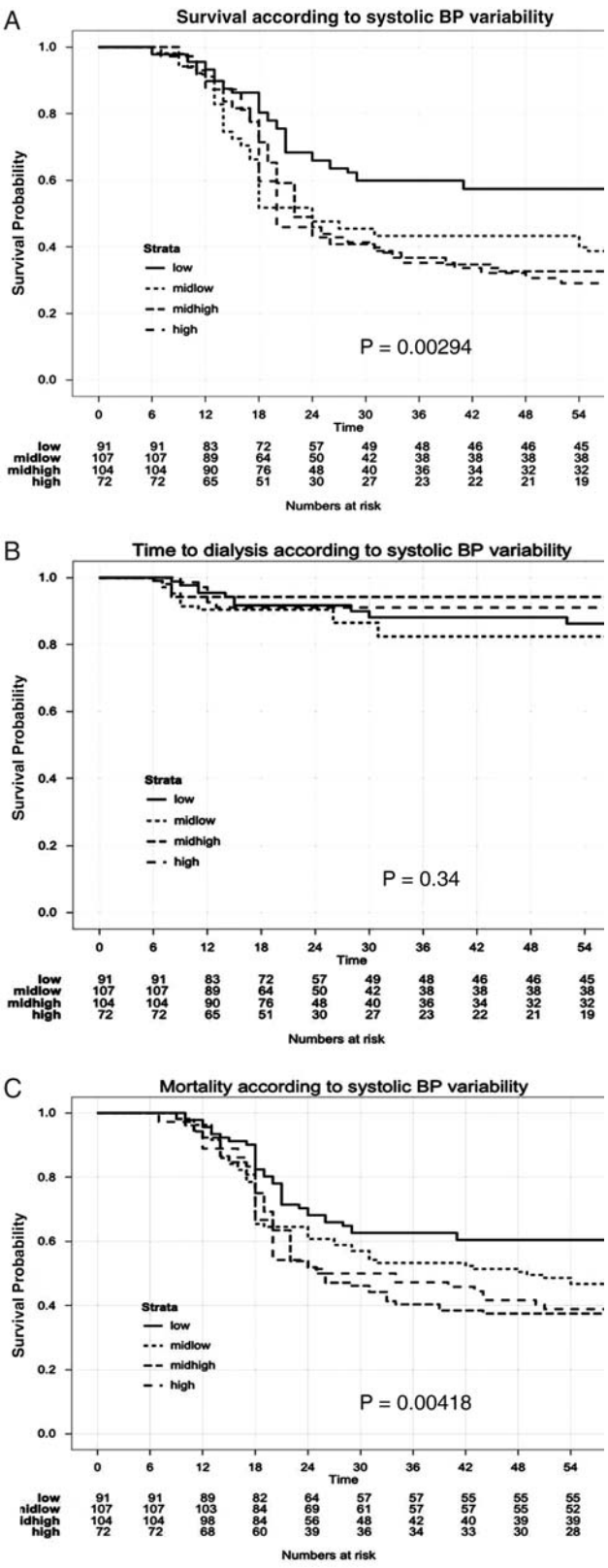

Fig. 1. Time-to-death (**A**), dialysis (**B**) and death even after dialysis (carry-over effect) initiation (**C**) according to the systolic BPV.

Table 2. Association between SBPV and the risk of all-cause mortality, dialysis inception and mortality even after dialysis inception (carry-over effect)

Model	HR	95% CI	P-value
Risk of all-cause mortality before dialysis entry			
Model 1: unadjusted	1.058	1.026–1.091	<0.001
Model 2: adjusted for age, sex	1.051	1.017–1.087	0.002
Model 3: model 2 + SBP + DBP + diabetes + eGFR	1.050	1.015–1.085	0.003
Model 4: model 3 + phosphorous + haemoglobin + low-protein diet + albumin	1.055	1.020–1.091	0.001
Risk of dialysis inception			
Model 1: unadjusted	0.962	0.883–1.049	0.384
Model 2: adjusted for age, sex and body weight	1.042	0.947–1.146	0.394
Model 3: model 2 + SBP + DBP + diabetes + eGFR	1.021	0.922–1.130	0.687
Model 4: model 3 + phosphorous + haemoglobin + low-protein diet + albumin	1.047	0.940–1.168	0.398
Risk of death even after dialysis inception (carry-over effect)			
Model 1: unadjusted	1.059	1.026–1.093	<0.001
Model 2: adjusted for age, sex and body weight	1.044	1.010–1.080	0.010
Model 3: model 2 + SBP + DBP + diabetes + eGFR	1.047	1.012–1.083	0.007
Model 4: model 3 + phosphorous + haemoglobin + low-protein diet + albumin	1.048	1.013–1.085	0.006

eGFR, estimated glomerular filtration rate, calculated via the abbreviated MDRD equation; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg).

Table 3. Predictors of all-cause mortality, dialysis inception and mortality even after dialysis initiation (carry-over effect) selected according to the stepwise procedure

Variable	HR	95% CI	P-value
Risk of all-cause mortality before dialysis entry			
Systolic BP variability (%, increase)	1.046	1.013–1.081	0.005
Age (year, increase)	1.009	0.996–1.022	0.174
Body weight (kg, increase)	1.000	1.000–1.000	0.281
Diabetes mellitus (yes versus no)	0.801	0.580–1.001	0.161
Serum creatinine (mg/dL, increase)	1.263	1.125–1.418	<0.001
Serum albumin (g/dL, increase)	0.762	0.580–1.001	0.051
Risk of dialysis inception			
Age (year, increase)	0.950	0.929–0.971	<0.001
Body weight (kg, increase)	0.987	0.963–1.013	0.337
Systolic BP (mmHg, increase)	0.983	0.966–1.001	0.051
eGFR (mL/min/1.73 m^2, increase)	0.899	0.871–0.927	<0.001
Albumin (g/dL, increase)	0.197	0.099–0.392	<0.001
Risk of death even after dialysis inception (carry-over effect)			
Systolic BP variability (%, increase)	1.046	1.013–1.081	0.006
Age (year, increase)	1.018	1.004–1.031	0.009

BP, blood pressure (mmHg); eGFR, estimated glomerular filtration rate, calculated via the abbreviated MDRD equation.

suggest that the excessive risk of death associated with SBPV is not altered by dialysis initiation.

BP control aims at reducing BP levels and more importantly at preventing future CV events. Recent studies in the general population suggest that exaggerated BPV is a risk factor for CV events in hypertensive adult patients independently of systolic (SBP) or diastolic (DBP) BP levels [22, 23]. However, data supporting the prognostic value of BPV as an independent risk factor for CV events have yet to be confirmed mainly because of the study limitations of the existing body of evidence [24, 25]. Indeed, the prognostic value of BPV has not yet been tested in properly designed longitudinal trials and the few studies available are limited by the small study size, short follow-up or by the use of surrogate markers (progression of left ventricular hypertrophy or arterial wall thickening) rather than hard end-points, such as CV or all-cause events [26].

Little is known about the CV risk connected to BPV in patients with CKD receiving or not receiving dialysis [19–21]. In light of a great BPV and the peculiar U-shaped relationship between BP and the CV risk observed among CKD patients [19], we sought to investigate the impact of SBPV on CKD progression and the risk of death in a large historical cohort of CKD patients receiving renal care in three different tertiary care nephrology outpatient clinics in Italy. In spite of the retrospective nature of the study, we were able to select a large cohort of consecutive patients followed longitudinally until dialysis inception or death of any cause. Notably, all the patients received care according to the KDOQI and the Italian guidelines on CKD management available at the time patients were referred to the nephrologists.

Similar to what was previously reported on patients on maintenance dialysis [19–21], we noted that CKD

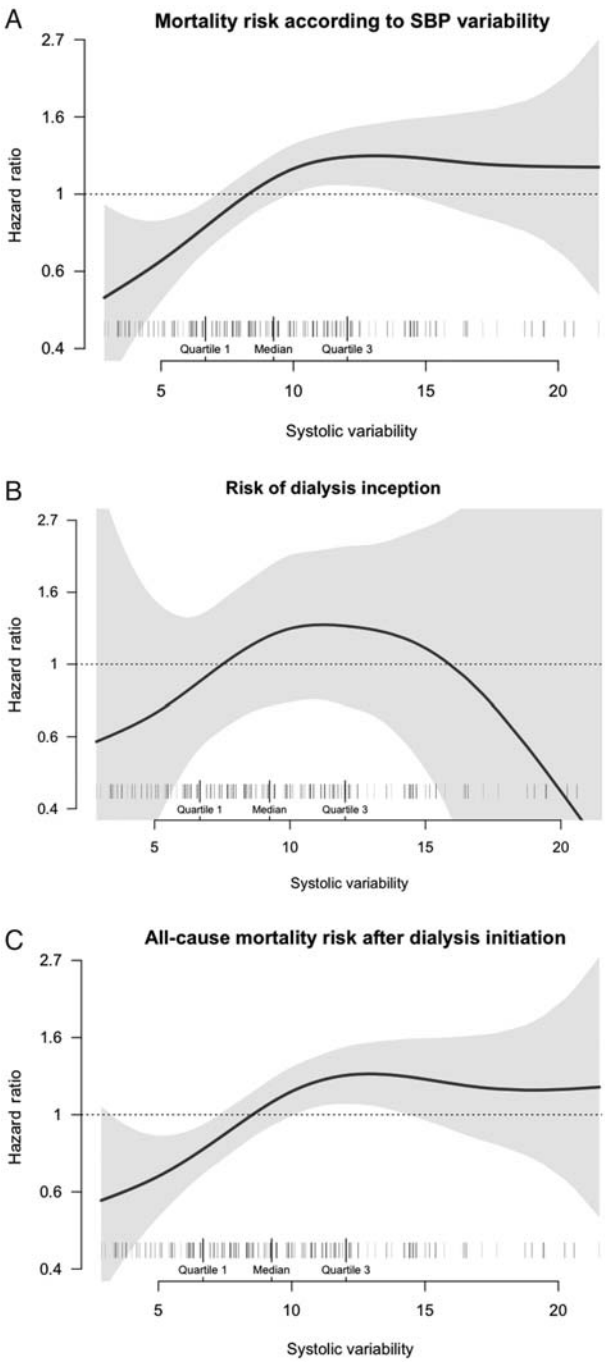

Fig. 2. Risk of death (**A**), dialysis inception (**B**) and death even after dialysis initiation (carry-over effect) (**C**) according to systolic BP variability (SBPV expressed as percent). All the models represented are models selected via the stepwise procedure. The solid line represents the HR according to SBPV; the light-blue area represents the 95% CI.

patients tended to exhibit a greater within-patient variability in SBPV than that observed in the general population. However, unlike the general population [27], SBPV does not correlate with systolic (P = 0.40), diastolic (P = 0.79) or pulse pressure (P = 0.61) in CKD subjects. Notably, only advanced age and the use of angiotensin II receptor blockers (P = 0.03) as well as CCBs (P = 0.02) were significantly associated with SBPV (Table 1).

Whether the association between SBV and different anti-hypertensive medications reflects a poor patient compliance with treatment more than cardiac or vascular abnormalities is currently unclear. Nonetheless, a previous study has shown that CCBs compared with β-blockers reduce visit-to-visit systolic BPV and the risk of future CV complications in non-renal patients [12]. Mitsuhashi *et al.* [21] documented a lower short-term BPV and CV remodelling in forty hypertensive patients on haemodialysis treated with losartan [21].

To the best of our knowledge, this is the first report on an independent association between SBPV and mortality but not CKD progression in a sizable CKD cohort. Notably, this association was not attenuated by adjustment for systolic, diastolic and mean blood pressure, as well as a few other commonly accepted predictors of poor outcomes in CKD.

Though the lack of association between SBPV and CKD progression might be explained by the small number of patients incident to dialysis, multiple potential mechanisms may explain the association between SBPV and increased risk of death. Indeed, inflammation, especially in those subjects with high SBPV, may induce cardiac remodelling and dysfunction via the activation of the cardiac angiotensin II system and inducing resistance to the angiotensin receptor blockade [4, 24]. BPV has also been associated with other different markers of CV disease such as arterial stiffness [2], left ventricular hypertrophy [26] and endothelial dysfunction [27]. Finally, at least in non-CKD individuals, a significant interaction between age and BPV has been described, making older individuals more susceptible to BP fluctuations [29].

The present study must be interpreted within the context of the potential limitations. First, we recruited predominantly old white Italian and diabetic patients free from CVD only, and the results might not be generalized to every CKD subject. Second, the high mortality rate observed in the study cohort might, to some extent, limit the external validity of the findings. Third, the quality of the measurement procedure could have affected BPV, although BP is usually measured under relatively controlled conditions. Fourth, visit-to-visit BPV is a rough estimate of BPV. Nonetheless, such heterogeneity should dilute the effect and bias our results towards the null. Fifth, the small number of patients progressing to dialysis may have resulted in the lack of association between SBPV and renal function decline. Nonetheless, the relatively low statistical power of the mortality analyses suggests that future *ad hoc* prospective studies are deemed to confirm these associations. Finally, the observational and retrospective nature of the study does not allow us to assess the causal relationship between SBPV and mortality, so future prospective studies should confirm this observation and test whether SBPV attenuation improves survival in CKD patients.

In conclusion, current findings suggest that SBPV may be of use for risk stratification in CKD patients. Nonetheless, prospective trials are necessary to evaluate whether BPV reduction should be regarded as a

therapeutic goal for antihypertensive treatment of CKD patients.

Conflict of interest statement. None declared.

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BLOG COMMENTARY

Blood Pressure Variability and outcomes in Chronic Kidney Disease

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Systolic Blood Pressure Variability (SBVP) has been shown in the publication by Iorio and colleagues from Italy to be associated with increased risk of death over a 2 year observation period in a retrospective cohort of elderly individuals with CKD (eGFR < 60ml/min). Of interest, SBPV was not associated with a faster rate of eGFR decline or a higher incidence of ESRD.

This is the first time such an observation is made in CKD patients confirming those made in the general population linking SBVP to higher risk of CVD and mortality (1).

It is becoming increasingly apparent that casual and office BP measurements are mostly unreliable in predicting outcomes in view of their inaccuracies as well as inherent variability of BP measurements as well as inconsistencies of standardization of measurement procedures (2). Office BP recording is also confounded by white-coat

hypertension when BP is elevated in the office and normal outside it. Home BP recording has come to age with home BP recording outperforming office recordings in terms of prognosis and prediction of end-organ damage such as left ventricular hypertrophy, atherosclerosis and death (3). Unfortunately, data is limited in patients with CKD but the overall impression is that BP measured at home is a better predictor of CVD but also progression to ESRD when compared to office BP (4).

The NDT$^{ERA\text{-}EDTA}$ OLA readers may be interested to learn more from the authors of this very interesting article about:

(1) Whether they would like to speculate as to how and why SBPV would increase the risk of CVD and death. What is the pathophysiological underpinning of SBPV and is it merely a reflection of a poorly compliant vascular system?

(2) Is the association between SBPV and mortality is independent of systolic blood pressure categories per se, as one would speculate that the higher the SBP the higher the likelihood of variability? It is somewhat surprising that in that analysis SBP in itself was not a predictor of mortality, thus raising concern over the possible inaccuracies of BP recording in that population.

(3) It would be interesting to know whether the SBVP impact on outcomes varies depending on whether those elderly individuals with CKD have age-related decline in kidney function or whether they have more significant CKD. One would expect, that in individuals with decreased eGFR + albuminuria, SBVP may impact on the progression to ESRD and incident dialysis. On the other hand, in those with age-related CKD3a and in the absence of albuminuria, the decline in eGFR would be too slow to lead to ESRD. Along similar lines, it would be intriguing to know whether individuals with eGFR < 45ml/min (CKD3b) have a faster rate of eGFR decline with higher level of SBPV?

(4) Finally, the authors put emphasis on the clinical applicability of such measure. It is unclear how SBPV would change the clinician's management that is already based on optimization of BP control. Would a raised SBPV affect the choice of anti-hypertensive agents?

Undoubtedly, this study will raise considerable interest highlighting once more the limitations of office BP recording in terms of predicting all cause mortality, cardiovascular disease as well as CKD progression and ESRD. Alternative measures of BP recording are called upon to improve diagnosis and prognosis of hypertension in CKD. Is SBPV the answer?

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