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Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease

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Long-term visit-to-visit blood pressure (BP) variability predicts a high risk for cardiovascular events in patients with essential hypertension. Whether long-term visit-to-visit BP variability holds the same predictive power in predialysis patients with chronic kidney disease (CKD) is unknown. Here we tested the relationship between long-term visit-to-visit office BP variability and a composite end point (death and incident cardiovascular events) in a cohort of 1618 patients with stage 2–5 CKD. Visit-to-visit systolic BP variability was significantly and independently related to baseline office, maximal, and average systolic BPs, age, glucose, estimated glomerular filtration rate, and albumin, and to the number of visits during the follow-up. Both the standard deviation of systolic BP (hazard ratio: 1.11, 95% confidence interval: 1.01–1.20) and the coefficient of variation of systolic BP (hazard ratio: 1.15, 95% confidence interval: 1.02–1.29) were significant predictors of the combined end point independent of peak and average systolic BP, cardiovascular comorbidities, Framingham risk factors, and CKD-related risk factors. Antihypertensive treatment (β-blockers and sympatholytic drugs) significantly abrogated the excess risk associated with high systolic BP variability. Thus, large visit-to-visit systolic BP variability in patients with CKD predicts a higher risk of death and nonfatal cardiovascular events independent of underlying BP levels.

Kidney International (2013) **84,** 381–389; doi:10.1038/ki.2013.132; published online 24 April 2013

KEYWORDS: BP variability; cardiovascular risk; chronic kidney disease

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Received 12 July 2012; revised 24 January 2013; accepted 7 February 2013; published online 24 April 2013

Chronic kidney disease (CKD) is now recognized as a strong cardiovascular (CV) and renal risk amplifier[1,2] that imposes high and rising costs to health systems of economically developed[3] and developing[4] countries alike. Hypertension is the most relevant treatable risk factor for the prevention of CV events and progression to kidney failure in patients with CKD.[5,6] The main determinant of blood pressure (BP)–related renal and CV risk derives from vessels barotrauma, and it is prevailing opinion that this barotrauma is best captured by the usual BP,[7] i.e., by the average of several office or home BP measurements or by the average of the several BP measurements made during 24-h ambulatory monitoring (ABPM).[8] These concepts are formally endorsed by current guidelines such as KDOQI Clinical practice guidelines on hypertension in CKD[9] and by other guidelines developed by public health agencies and scientific societies.[10]

In general, long-term visit-to-visit BP variability is considered as a random fluctuation and as a phenomenon without clinical implications when not as a factor interfering with the correct estimation of usual BP.[11] In the same vein, it was remarked that in CKD patients ABPM[12,13] but neither conventional office[13] nor standard standardized measurements of BP[12] hold predictive power for death and CV events. Recently, the concept that visit-to-visit BP variability does not convey meaningful clinical information has been challenged by Rothwell *et al.*[14] On the basis of a series of new analyses of major clinical trials in essential hypertensive subjects,[15–17] these authors showed that high visit-to-visit variability and episodic hypertension entail a high risk for vascular events notwithstanding good control of average BP. Given the peculiar risk profile of CKD[2] and the pervasive nature of hypertension in this population, the question whether high, long-term, visit-to-visit BP variability holds prognostic value in CKD patients is of paramount relevance.

With this background in mind, we tested the relationship between long-term, visit-to-visit BP variability, death, and

CV events in a large cohort of stages 3 and 4 CKD patients with a long follow-up.

RESULTS

The main demographic and clinical characteristics of the study cohort ($n = 1618$) are summarized in Table 1. Fifty-nine percent were men, and the mean age was 64 years. On average, the estimated glomerular filtration rate (eGFR) was 35 ± 13 ml/min per 1.73 m^2. Median proteinuria was 0.5 g per 24 h. One thousand and ninety-nine patients (68%) had proteinuria $\leqslant 1$ g per 24 h and 104 patients (6%) had proteinuria > 3 g per 24 h. One-hundred and eighty-nine patients (12%) were current smokers, 480 (30%) had type-2 diabetes, and 1089 (67%) had hypercholesterolemia. Four-hundred and twelve patients had previous CV disease (25%). Office BP at first visit was $137 \pm 18/79 \pm 11$ mm Hg. BP variability during follow-up was on average $11 \pm 6/7 \pm 4$ mm Hg (coefficient of variations: $8.0 \pm 4.3\%$ for systolic BP (SBP) and $8.5 \pm 4.7\%$ for diastolic BP (DBP)). The mean value of individual average BP and peak (maximal) BP during follow-up were $134 \pm 13/78 \pm 7$ and $147 \pm 17/86 \pm 9$ mm Hg, respectively. During the study, only 12% of patients had BP persistently below 130/80 mm Hg. The vast majority of patients (1514, 94%) were on antihypertensive treatment: 23% were treated with one drug, 34% with two drugs, and 43% with three or more drugs. One-thousand and two-hundred and sixty-two patients were treated with angiotensin-converting enzyme inhibitors and/or angiotenstin II blockers either alone or in combination with diuretics and other antihypertensive drugs, and the remaining 252 patients were treated with calcium channel blockers, sympathetic blockers, and β-blockers either as single agents or with drug combinations including diuretics.

Table 1 | Main demographic, somatometric, and clinical characteristics of the study population

	Whole group ($n = 1618$)
Age (years)	64 ± 12
BMI (kg/m^2)	27.9 ± 4.8
Male sex, *n* (%)	950 (59%)
Current smokers, *n* (%)	189 (12%)
Diabetics, *n* (%)	480 (30%)
With cardiovascular comorbidities, *n* (%)	412 (25%)
With hypercholesterolemia, *n* (%)	1089 (67%)
Baseline SBP (mmHg)	137 ± 18
Baseline DBP (mmHg)	79 ± 11
Visit-to-visit SBP variability (mmHg)	11 ± 6
Visit-to-visit DBP variability (mmHg)	7 ± 4
Coefficient of variation of SBP (%)	8.0 ± 4.3
Coefficient of variation of DBP (%)	8.5 ± 4.7
Average SBP (mmHg)	134 ± 13
Average DBP (mmHg)	78 ± 7
Max SBP (mmHg)	147 ± 17
Max DBP (mmHg)	86 ± 9
Creatinine (mg/dl)	2.1 ± 0.9
eGFR-$MDRD_{186}$ (ml/min per 1.73 m^2)	35 ± 13
24-h urinary protein (g per 24 h)	0.5 (0.2–1.2)
Glucose (mg/dl)	111 ± 45
Hemoglobin (g/dl)	12.8 ± 1.8
Total cholesterol (mg/dl)	194 ± 42
Triglycerides (mg/dl)	152 ± 82
Albumin (g/dl)	4.0 ± 0.5
On treatment with statins, *n* (%)	599 (37%)
On antihypertensive therapy, *n* (%)	1514 (94%)
On β-blockers/sympatholytic agents, *n* (%)	578 (36%)
On treatment with ACE inhibitors and/or angiotensin II blockers, *n* (%)	1262 (78%)
On treatment with calcium antagonists, *n* (%)	704 (44%)
On treatment with diuretics, *n* (%)	763 (47%)
Number of antihypertensive drugs	2 ± 1

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MDRD, Modified Diet in Renal Disease; SBP, systolic blood pressure.
Data are expressed as mean ± s.d., median, and interquartile range or as percent frequency, as appropriate.

Associations of BP variability with other BP components and risk factors

SBP variability was very weakly explained by the number of visits ($r^2 = 0.006$, 0.6%, $P < 0.001$) and by the total number of antihypertensive drug classes ($r = 0.13$, $r^2 = 0.017$, 1.7%) (Figure 1). SBP variability expressed in terms of s.d. was more strongly associated ($P < 0.001$) with maximal BP ($r = 0.64$, $P < 0.001$) than with average ($r = 0.31$, $P < 0.001$) or office SBP and pulse pressure at first visit ($r = 0.35$ and $r = 0.29$; $P < 0.001$). Although to a much weaker extent, SBP variability (s.d.) was also associated in a direct manner with age ($r = 0.13$, $P < 0001$), antihypertensive treatment (untreated: 9.1 ± 4.4 mm Hg; treated: 10.9 ± 6.1 mm Hg; $P < 0.001$), CV comorbidities (without CV comorbidities: 10.6 ± 5.8 mm Hg; with CV comorbidities: 11.4 ± 6.8 mm Hg; $P = 0.02$), body mass index ($r = 0.08$, $P < 0.001$), 24-h proteinuria ($r = 0.07$, $P < 0.001$), C-reactive protein (CRP; $n = 750$, $r = 0.07$, $P = 0.049$), and heart rate variability ($n = 750$, $r = 0.13$, $P < 0.001$), and in an inverse manner with smoking ($r = -0.12$, $P < 0.001$), serum albumin ($r = -0.10$, $P < 0.001$), hemoglobin (Hb; $r = -0.10$, $P < 0.001$), and the eGFR ($r = -0.07$, $P = 0.01$). The relationships of visit-to-visit SBP variability with baseline, maximal, and average SBP, number of visits, age, glucose, eGFR, and albumin remained significant (all $P \leqslant 0.05$) also in a multiple regression model (Table 2) including all univariate correlates of SBP variability (s.d.) (see above). By introducing into the model baseline office SBP or average SBP instead of max SBP both baseline SBP ($\beta = 0.33$, $P < 0.001$) and average SBP ($\beta = 0.27$, $P < 0.001$) resulted to be independently associated with visit-to-visit SBP variability, but these associations were much weaker as compared with that of max SBP.

The same analyses carried out with the coefficient of variation of SBP as a dependent variable provided similar results (data not shown). In a multiple linear regression analysis restricted to patients with available data of CRP and heart rate variability ($n = 750$), these two variables failed to independently predict visit-to-visit SBP variability (both $P =$ nonsignificant).

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