The impact of visit-to-visit systolic blood pressure variability on residual renal function and left ventricular hypertrophy in peritoneal dialysis patients

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Background/aim: Blood pressure (BP) variability is more closely associated with adverse outcomes than 'usual' BP in the general population. Residual renal function (RRF) and left ventricular hypertrophy (LVH) are thought to be predictors of poor outcome in dialysis patients. However, only a few studies have focused on BP variation and its link to RRF, LVH, and outcome in peritoneal dialysis (PD) patients. Therefore, we aimed to explore the effect of visit-to-visit BP variability on RRF and LVH in continuous ambulatory PD (CAPD) patients.

Materials and methods: We performed an observational study that included all prevalent PD patients between 1 February 2006 and 31 January 2007. All patients underwent BP measurements, pulse wave velocity (PWV), cardiac ultrasound, and biochemical examination during the 1-year observation. Patients were divided into the HBPV group (higher BP variability) and LBPV group (lower BP variability) based on the standard deviation of systolic BP (SBP).

Results: There were 70 patients recruited for the final analysis. Patients with HBPV had a higher SBP as compared to patients with LBPV at baseline. Renal Kt/V decreased significantly from 0.50 ± 0.49 to 0.32 ± 0.35 (P < 0.01) in HBPV group (but not in the LBPV group) during follow-up. Patients with HBPV also showed a higher left ventricular mass index (LVMI) and PWV than those with LBPV at the end of follow-up.

Conclusion: Our study suggests that BP variability may affect RRF in PD patients. PD patients with HBPV had a faster decline in RRF and higher PWV and LVH.

Key words: Blood pressure, variability, residual renal function, left ventricular hypertrophy, peritoneal dialysis

1. Introduction

Cardiovascular disease is the leading cause of death in end-stage renal disease (ESRD) patients (1). Hypertension is a major risk factor for cardiovascular disease and is highly prevalent in ESRD patients, although hypertension, unlike in the general population, is not always linearly associated with adverse outcomes (2).

Recently, blood pressure (BP) variability has been found to be more closely associated with adverse outcomes in patients with vascular disease than that of 'usual' BP (3) and may play a causal role in the progression of organ damage and in triggering a vascular event (4,5). Some studies demonstrated that visit-to-visit BP variability was a novel risk factor for stroke (3), cardiovascular events (3), and all-cause mortality in the general population (6). It is reported that visit-to-visit BP

variability also predicted cardiovascular events and all-cause mortality in patients with chronic kidney disease (7,8) and hemodialysis (5,9–14). Note, however, that different dialysis modalities should have different effects on BP due to the intermittent nature of hemodialysis and continuous nature of peritoneal dialysis (PD). To date, only a few studies have focused on BP variation and outcome in PD patients (15–17).

There are many studies indicating that residual renal function (RRF) is a powerful predictor of morbidity and mortality in PD patients (18–20). Yokota et al. reported that visit-to-visit BP variability was associated with renal function decline in nondiabetic chronic kidney disease (21). Therefore, the aim of the present study was to investigate the relationships between visit-to-visit BP variability, RRF, and cardiovascular status in continuous ambulatory PD (CAPD) patients.

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2. Materials and methods

2.1. Patients

We performed an observational study in prevalent PD patients in the PD Center of Peking University Third Hospital, People's Republic of China between 1 February 2006 and 31 January 2007. All PD patients aged 18 years and older, and who had been on CAPD therapy for at least 3 months in our PD center were eligible for participating in this study. The patients were clinically stable and visited our clinic regularly with BP measurements at each clinical visit. None of patients had atrial fibrillation. Patients that suffered an acute cardiovascular event [stroke, transient ischemic attack, myocardial infarction, angina, or heart failure (NYHA class III to IV)] prior to the study were not included. Patients that died during the observation period were excluded from the present analysis. All demographic data were obtained through patient chart review.

All patients received repeated BP measurements during the 1-year observation. Patients were evaluated for clinical and biochemical data, dialysis adequacy at baseline and at the end of 1-year observation. Measurements were performed during a scheduled visit. The first measurement, at least 3 months after the initiation of dialysis between 1 February 2006 and 31 January 2007 was taken as baseline. Echocardiographic evaluation and measurement of pulse wave velocity were done at the end of the 1-year observation.

The ethical committee of Peking University approved the study protocol and informed consent was obtained from each patient.

2.2. Dialysis therapy

PD patients were treated by 3–4 exchanges per day, using standard glucose-based dialysate solutions (Baxter China Ltd., Guangzhou, China).

2.3. Blood pressure measurements

BP measurements were performed during a scheduled monthly visit. BP was measured in a supine position after a 15-min rest using a mercury sphygmomanometer with a cuff of appropriate size. Phases I and V of the Korotkoff sound were taken as systolic BP (SBP) and diastolic BP (DBP), respectively. Three consecutive measurements were performed in every patient and the arithmetic mean of these measurements was used. Pulse pressure (PP) was calculated as SBP minus DBP.

Visit-to-visit systolic BP variability (VTV-SBPV) was defined as the standard deviation (SD) of all SBP values recorded during the baseline visit and the following visits during the study period. The SD of at least 5 visits' BP readings was used for the analyses in each patient (22). Patients were then divided into HBPV (higher BP variability) group and LBPV (lower BP variability) group, according to the mean BP variation (23).

2.4. Blood biochemistry and dialysis adequacy

Fasting venous blood samples were taken from all study participants for evaluation of biochemical parameters. Biochemical parameters such as hemoglobin, urea, creatinine, serum glucose, triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, serum sodium, serum calcium, and phosphate were analyzed by standard procedures. Serum albumin was measured using the bromocresol green method. Intact parathyroid hormone (PTH) levels and sensitive C-reactive protein (SCRP) were determined using a commercial enzyme linked immunosorbent assay. Dialysis adequacy was assessed by urea clearance, Kt/V (K, clearance; t, treatment time; V, volume of urea distribution) (24). Peritoneal Kt/V and renal Kt/V were measured separately; total Kt/V was the sum of peritoneal Kt/V and renal Kt/V. Urea distribution volume was calculated according to Watson's formula (25). Renal Kt/V was used as an indicator of RRF.

2.5. Echocardiography

Echocardiograms were examined using an ultrasound machine (Sonoline G50 ultrasound system, Siemens Medical Solutions Inc., Issaquah, WA, USA) equipped with a 2–4-MHz probe. Patients were in a supine or left lateral decubital position with the limb lead electrocardiogram connected. Echocardiography parameters, including interventricular septum diastolic thickness (IVSDT), left ventricular posterior wall diastolic thickness (LVPWDT), and left ventricular end-diastolic diameter (LVEDD) were measured at end-diastole. Ventricular dimensions were assessed through 2-D guided M-mode tracings according to American Society of Echocardiography (ASE) recommendations (26). Left ventricular mass (LVM) was calculated by the Devereux formula: (27) LVM (g) = 0.8 × 1.04 [(LVEDD + IVSDT + LVPWDT)^3 – (LVEDD)^3] + 0.6. LVM index (LVMI) was derived by dividing the calculated LVM by body surface area. LVH was diagnosed according to the Framingham criteria (28) (males, LVMI > 131 g/m^2; females, LVMI > 100 g/m^2). Left ventricular ejection fraction (LVEF) was determined by Simpson's method.

2.6. Measurement of pulse wave velocity (PWV)

Aortic PWV was measured by an automatic device, the Complior (Colson SG, Garges les Gonesses, France) (29). Common carotid artery and femoral artery pressure wave forms were first noninvasively recorded using a TY-306 Fukuda pressure sensitive transducer (Fukuda Ltd., Tokyo, Japan). Measurements were performed consecutively over 10 cardiac cycles, and the mean value of these measurements was used. The distance traveled by the pulse wave (D) was measured over the body surface as the distance between the two recording sites, while pulse transit time (t) was automatically determined by the Complior. PWV was calculated as PWV = D/t. Details, as well as validation of

Table 2. Baseline characteristics of patients grouped according to BP variability.

	LBPV group (n = 39)	HBPV group (n = 31)	P-value
Age (years)	58.9 ± 13.2	61.3 ± 13.6	0.461
Sex (male/female)	12/27	16/15	0.077
BMI (kg/m^2)	23.1 ± 4.2	24.6 ± 3.0	0.103
Diabetes mellitus (%)	12.8	25.8	0.165
Time on dialysis (months)	9.9 (3.2, 64.5)	10.4 (3.3, 99.0)	0.607
Follow-up time (months)	9.3 ± 2.2	10.0 ± 1.7	0.176
Antihypertensive medication			
ACEI/ARBs (%)	14 (35.9)	17 (54.8)	0.113
Calcium-channel blockers (%)	22 (56.4)	24 (77.4)	0.066
b-blockers (%)	22 (56.4)	17 (54.8)	0.895
Diuretics (%)	6 (15.4)	1 (3.2)	0.123
Others (%)	2 (5.1)	5 (16.1)	0.228
SBP (mmHg)	137.4 ± 20.8	148.7 ± 25.8	**0.046**
DBP (mmHg)	80.9 ± 12.2	82.4 ± 15.1	0.649
PP (mmHg)	56.5 ± 16.8	66.3 ± 24.6	0.052
SD of SBP	10.3 ± 2.9	20.5 ± 4.6	**< 0.001**
SD of DBP	7.2 ± 1.8	9.6 ± 3.2	**< 0.001**
Hemoglobin (g/L)	118.7 ± 20.1	115.6 ± 24.3	0.570
Serum albumin (g/L)	36.9 ± 5.0	37.4 ± 3.2	0.667
Serum glucose (mmol/L)	6.0 ± 2.2	6.6 ± 3.1	0.383
TG (mmol/L)	2.14 ± 1.50	2.29 ± 0.73	0.740
Total CHOL (mmol/L)	5.00 ± 1.29	5.28 ± 0.98	0.506
LDL-C (mmol/L)	3.37 ± 0.93	3.47 ± 1.04	0.772
HDL-C (mmol/L)	1.49 ± 0.55	1.26 ± 0.34	0.168
Serum calcium (mmol/L)	2.22 ± 0.35	2.14 ± 0.31	0.350
Serum phosphorus (mmol/L)	1.68 ± 0.66	1.61 ± 0.43	0.600
Parathormone (pg/mL)	182.8 ± 114.6	219.6 ± 178.0	0.494
SCRP (mg/L)	1.3 (0.1, 1.5)	3.6 (0.2, 1.7)	0.222

Table 3. Changes in selected clinical and biochemical variables in PD patients with intragroup and intergroup comparisons.

	LBPV group			HBPV group			P_1-value	P_2-value
	Baseline	Follow-up	P value	Baseline	Follow-up	P-value		
Peritoneal Kt/V	1.14 ± 0.52	1.33 ± 0.59	0.047	1.35 ± 0.51	1.54 ± 0.44	0.002	0.097	0.104
Renal Kt/V	0.74 ± 0.68	0.54 ± 0.53	0.051	0.50 ± 0.49	0.32 ± 0.35	0.001	0.107	0.039
Total Kt/V	1.87 ± 0.81	1.87 ± 0.50	0.978	1.84 ± 0.30	1.86 ± 0.30	0.740	0.838	0.909
Urine volume (mL/day)	765.1 ± 529.6	518.7 ± 482.2	< 0.001	532.9 ± 482.4	351.3 ± 350.4	0.003	0.062	0.110
Ultrafiltration volume (mL/day)	537.2 ± 548.9	504.3 ± 465.9	0.626	773.1 ± 460.0	651.7 ± 380.2	0.122	0.068	0.172

Note: P_1-value referred to comparison between the two groups at baseline; P_2-value referred to comparison between the two groups at the end of follow-up.

from 1.35 ± 0.51 to 1.54 ± 0.44 (P < 0.01). Urine volume was also significantly decreased (P < 0.01). However, there were no significant changes in ultrafiltration volume.

Patients with higher VTV-SBPV showed a decreased renal Kt/V compared to those with lower VTV-SBPV at the end of follow-up (P < 0.05).

3.4. Comparisons of cardiac structure and function between the two groups at the end of follow-up

Patients' IVSDT, LVPWDT, LVMI, prevalence of LVH, and PWV were significantly higher in the HBPV group than those in the LBPV group (P < 0.01) (Table 4).

4. Discussion

In the present study, we found that renal Kt/V obviously decreased in the HBPV group at the end of follow-up, whereas it did not differ in the LBPV group. Patients with higher VTV-SBPV showed a decreased renal Kt/V than those with lower VTV-SBPV, indicating a possible association of BP variability with RRF in PD patients.

Some previous studies suggest that RRF could predict mortality in ESRD patients (18–20). Rocco et al. found from a multicenter prospective cohort study of 1446 prevalent PD patients that for each 10 L/week/1.73 m² increase in renal CrCl there was a 40% reduced risk of death, and that for each increase in weekly renal Kt/V of 0.1 there was a 12% reduction in the risk of death (19). The ADEMEX study reported that each increase of 0.1 in renal Kt/V was associated with a 6% decrease in mortality (20). Thus, considerable efforts have been put into finding ways to prevent the loss of RRF in PD patients.

Recently, BP variability is thought to be a parameter reflecting cardiovascular outcome (14,30). It can be quantified over both the short-term, using 24-h ambulatory BP measurements, and long-term variability using visit-to-visit BP readings. The SD of BP is a measure of the mean absolute distance between the observed measurements and their mean. It is often used in many studies and can reflect BP fluctuation (7,14). Thus, SD of SBP was adopted in our study. The association of BP variability with RRF in our study encourages us to seek new ways to help this patient population. In fact, Yokota et al. reported that VTV-BPV was associated with renal function decline in nondiabetic chronic kidney disease (21), but not in diabetic chronic kidney disease (31). Okada et al. found that diabetic patients with higher VTV-SBPV had a great risk of developing albuminuria (32). Jo et al. demonstrated that VTV-SBPV was an independent risk factor for the rapid loss of RRF in PD patients (16). Mancia et al. suggest that BP variability is a more critical determinant of glomerular damage than the BP level (33).

Our study found that patients with higher BP variability showed a higher IVSDT, LVPWDT, LVMI, and a higher prevalence of LVH. It was consistent with Atas et al.'s reports (15). We also investigated the changes in PWV, a parameter that reflects arterial stiffness, which plays a cushioning role on BP. We found that PWV was significantly increased in the HBPV group. Thus, we speculated that PWV may be involved in the pathogenesis of the effect of BP and BP variability on RRF and cardiovascular outcome.

It was thought that different antihypertensive medication may have different effects on RRF. In Jo et al.'s study, more calcium channel blockers and diuretics were prescribed in patients with higher VTV-SBPV (16). A recent meta-analysis of randomized clinical trials showed that the interblood pressure variability was higher with the use of ACEI/ARBs and beta-blockers, and lower with the use of calcium channel blockers (34). However, there was no significant difference in antihypertensive

Table 4. Comparison of cardiac structure and function between the two groups at the end of follow-up.

	LBPV group	HBPV group	P-value
IVSDT (mm)	11.5 ± 2.3	13.5 ± 2.1	< 0.001
LVPWDT (mm)	9.6 ± 1.3	11.0 ± 1.6	< 0.001
LVEDD (mm)	45.2 ± 6.1	47.3 ± 5.9	0.165
LVMI (g/m²)	110.5 ± 36.2	139.8 ± 39.5	0.002
LVH (%)	39.5	74.2	0.004
LVEF (%)	67.1 ± 10.7	68.0 ± 9.8	0.726
PWV (m/s)	10.5 ± 2.1	12.4 ± 2.2	0.001

Abbreviations: IVSDT, interventricular septum diastolic thickness; LVPWDT, left ventricular posterior wall diastolic thickness; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; PWV, pulse wave velocity.

medication between the two groups in our study, similar to the observation reported by Chang et al. (9). The effect of antihypertensive drugs on BP variability and RRF needs further study.

Some weaknesses of the present study should also be discussed. Firstly, as the study is observational and retrospective in nature, cause and effect cannot be separated. Secondly, the present study involved a relatively small number of patients; further prospective study in a larger dialysis population is needed. Thirdly, baseline data on echocardiography and arterial stiffness were in absence in our study. In addition, we attempted to describe the use of antihypertensive medication clearly; however, the long-term effects of administered drugs cannot be accurately gauged.

In summary, our study suggests that BP variability may affect RRF in PD patients. PD patients with higher BP variability showed a decrease in RRF and a higher LVH and PWV. Decreasing BP variability may help prevent the loss of RRF in PD patients and needs further studies.

References

1. Sharma R, Pellerin D, Brecker SJ. Cardiovascular disease in end stage renal disease. Minerva Urol Nefrol 2006; 58: 117-131.

2. Chang TI. Systolic blood pressure and mortality in patients on hemodialysis. Curr Hypertens Rep 2011; 13: 362-369.

3. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010; 375: 895-905.

4. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010; 375: 938-948.

5. Selvarajah V, Pasea L, Ojha S, Wilkinson IB, Tomlinson LA. Pre-dialysis systolic blood pressure-variability is independently associated with all-cause mortality in incident haemodialysis patients. PloS One 2014; 9: e86514.

6. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. Hypertension 2011; 57: 160-166.

7. Di Iorio B, Pota A, Sirico ML, Torraca S, Di Micco L, Rubino R, Guastaferro P, Bellasi A. Blood pressure variability and outcomes in chronic kidney disease. Nephrol Dial Transpl 2012; 27: 4404-4410.

8. Mallamaci F, Minutolo R, Leonardis D, D'Arrigo G, Tripepi G, Rapisarda F, Cicchetti T, Maimone I, Enia G, Postorino M et al. Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease. Kidney Int 2013; 84: 381-389.

9. Chang TI, Flythe JE, Brunelli SM, Muntner P, Greene T, Cheung AK, Chertow GM. Visit-to-visit systolic blood pressure variability and outcomes in hemodialysis. J Hum Hypertens 2014; 28: 18-24.

10. Flythe JE, Brunelli SM. Blood pressure variability and dialysis: variability may not always be the spice of life. J Am Soc Nephrol 2014; 25: 650-653.

11. Di Iorio B, Di Micco L, Torraca S, Sirico ML, Guastaferro P, Chiuchiolo L, Nigro F, De Blasio A, Romano P, Pota A et al. Variability of blood pressure in dialysis patients: a new marker of cardiovascular risk. J Nephrol 2013; 26: 173-182.

12. Flythe JE, Inrig JK, Shafi T, Chang TI, Cape K, Dinesh K, Kunaparaju S, Brunelli SM. Association of intradialytic blood pressure variability with increased all-cause and cardiovascular mortality in patients treated with long-term hemodialysis. Am J Kidney Dis 2013; 61: 966-974.

13. Rossignol P, Cridlig J, Lehert P, Kessler M, Zannad F. Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL. Hypertension 2012; 60: 339-346.

14. Flythe JE, Brunelli SM. Blood pressure variability among chronic dialysis patients: recent advances in knowledge. Curr Opin Nephrol Hy 2015; 24: 163-169.

15. Atas N, Erten Y, Okyay GU, Inal S, Topal S, Onec K, Akyel A, Çelik B, Tavil Y, Bali M et al. Left ventricular hypertrophy and blood pressure control in automated and continuous ambulatory peritoneal dialysis patients. Ther Apher Dial 2014; 18: 297-304.

16. Jo HA, An JN, Lee JP, Oh KH, Lim CS, Oh YK. Visit-to-visit variability in systolic blood pressure is a risk factor for rapid loss of residual renal function in peritoneal dialysis patients. Tohoku J Exp Med 2015; 235: 295-304.

17. Shigenaga A, Tamura K, Dejima T, Ozawa M, Wakui H, Masuda S, Azuma K, Tsurumi-Ikeya Y, Mitsuhashi H, Okano Y et al. Effects of angiotensin II type 1 receptor blocker on blood pressure variability and cardiovascular remodeling in hypertensive patients on chronic peritoneal dialysis. Nephron Clin Pract 2009; 112: 31-40.

18. Nongnuch A, Assanatham M, Panorchan K, Davenport A. Strategies for preserving residual renal function in peritoneal dialysis patients. Clinical Kidney Journal 2015; 8: 202-211.

19. Rocco M, Soucie JM, Pastan S, McClellan WM. Peritoneal dialysis adequacy and risk of death. Kidney Int 2000; 58: 446-457.

20. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S, Mexican Nephrology Collaborative Study Group. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 2002; 13: 1307-1320.

21. Yokota K, Fukuda M, Matsui Y, Hoshide S, Shimada K, Kario K. Impact of visit-to-visit variability of blood pressure on deterioration of renal function in patients with non-diabetic chronic kidney disease. Hypertens Res 2013; 36: 151-157.

22. Whittle J, Lynch AI, Tanner RM, Simpson LM, Davis BR, Rahman M, Whelton PK, Oparil S, Muntner P. Visit-to-visit variability of BP and CKD outcomes: results from the ALLHAT. Clin J Am Soc Nephro 2016; 11: 471-480.

23. Hassan AKM, Abd-El Rahman H, Mohsen K, Dimitry SR. Impact of in-hospital blood pressure variability on cardiovascular outcomes in patients with acute coronary syndrome. J Clin Hypertens 2017; 19: 1252-1259.

24. Nolph KD, Moore HL, Prowant B, Meyer M, Twardowski ZJ, Khanna R, Ponferrada L, Keshaviah P. Cross sectional assessment of weekly urea and creatinine clearances and indices of nutrition in continuous ambulatory peritoneal dialysis patients. Periton Dialysis Int 1993; 13: 178-183.

25. Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females estimated from simple anthropometric measurements. Am J Clin Nutr 1980; 33: 27-39.

26. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072-1083.

27. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57: 450-458.

28. Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J 3rd, Feinleib M, Castelli WP. The spectrum of left ventricular hypertrophy in a general population sample: the Framingham Study. Circulation 1987; 75: 26-33.

29. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995; 26: 485-490.

30. Mallamaci F, Tripepi G. Blood pressure variability in chronic kidney disease patients. Blood Purificat 2013; 36: 58-62.

31. Yokota K, Fukuda M, Matsui Y, Kario K, Kimura K. Visit-to-visit variability of blood pressure and renal function decline in patients with diabetic chronic kidney disease. J Clin Hypertens 2014; 16: 362-366.

32. Okada H, Fukui M, Tanaka M, Inada S, Mineoka Y, Nakanishi N, Senmaru T, Sakabe K, Ushigome E, Asano M et al. Visit-to-visit variability in systolic blood pressure is correlated with diabetic nephropathy and atherosclerosis in patients with type 2 diabetes. Atherosclerosis 2012; 220: 155-159.

33. Mancia G, Parati G. The role of blood pressure variability in end-organ damage. J Hypertens 2003; 21: 17-23.

34. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 2010; 375: 906-915.