Visit-to-visit SBP variability and cardiovascular disease in a multiethnic primary care setting: l0-year retrospective cohort study

Yook Chin Chia[a,b], Siew Mooi Ching[c,d], and Hooi Min Lim[a]

Objectives: The current study aims to determine the relationship of long-term visit-to-visit variability of SBP to cardiovascular disease (CVD) in a multiethnic primary care setting.

Method: This is a retrospective study of a cohort of 807 hypertensive patients over a period of 10 years. Three-monthly clinic blood pressure readings were used to derive blood pressure variability (BPV), and CVD events were captured from patient records.

Results: Mean age at baseline was 57.2 ± 9.8 years with 63.3% being women. The BPV and mean SBP over 10 years were 14.7 ± 3.5 and 142 ± 8 mmHg, respectively. Prevalence of cardiovascular event was 13%. In multivariate logistic regression analysis, BPV was the predictor of CVD events, whereas the mean SBP was not independently associated with cardiovascular events in this population. Those with lower SBP and lower BPV had fewer cardiovascular events than those with the same low mean SBP but higher BPV (10.5 versus 12.8%). Similarly those with higher mean SBP but lower BPV also had fewer cardiovascular events than those with the same high mean and higher BPV (11.6 versus 16.7%). Other variables like being men, diabetes and Indian compared with Chinese are more likely to be associated with cardiovascular events.

Conclusion: BPV is associated with an increase in CVD events even in those who have achieved lower mean SBP. Thus, we should prioritize not only control of SBP levels but also BPV to reduce CVD events further.

Keywords: blood pressure, blood pressure variability, cardiovascular disease, cohort, events, long term, Malaysia, multiethnic, primary care, visit-to-visit

Abbreviations: α-blocker, alpha-blocker; β-blocker, beta-blocker; BPV, blood pressure variability; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular event; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system

INTRODUCTION

In recent years, there has been an increasing interest in blood pressure variability (BPV), and studies have reported that it is an independent risk factor for end-organ damage as well as all-cause mortality and cardiovascular morbidity, particularly of strokes and coronary events [1–7]. However, the prognostic significance of BPV remains controversial and has been deemed inferior to mean SBP in the causation of cardiovascular events [8–10]. Whether the impact of BPV in patients at the primary care level, who generally have better and lower mean SBP, is different from those in specialist clinics who usually have higher mean SBP, still remains unclear.

BPV occurs over both short-term and long-term basis. Short-term BPV occurs because of external factors like temperature, weather or emotional disturbance and physical activity [1,11]. Long-term BPV may occur over months and years and between clinics visits and are likely to be mediated by different mechanisms. Older age [12,13], female sex [4,13], higher mean SBP [13], use of beta-blockers (β-blockers) [1,3,13,14], prior history of cardiovascular disease (CVD) [4], renal impairment [4], diabetes mellitus [15,16] and sedentary lifestyle [4] have been reported as factors associated with long-term BPV. Long-term BPV could also be due to poor adherence and improper dosing or titration of antihypertensive agents in those who are on treatment for hypertension [17].

Questions have been raised about the prognostic significance of BPV as most of the studies on BPV were either post-hoc analyses of clinical trials that followed strict protocols [18,19], or involved specific high-risk populations [3,15,20] and usually of a shorter duration of follow-up [20]. As such, the impact of BPV may not be perceived or deemed to be so applicable in real-life clinical practice, particularly at the primary care level in which most of the patients have lower cardiovascular risk and lower mean

Journal of Hypertension 2017, 35 (Suppl 1):S50–S56

[a]Department of Primary Care Medicine, University of Malaya Primary Care Research Group (UMPCRG), Faculty of Medicine, University of Malaya, Kuala Lumpur, [b]Sunway Institute for Healthcare Development, Sunway University, Petaling Jaya, [c]Department of Family Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia and [d]Malaysian Research Institute on Ageing, Universiti Putra Malaysia, Serdang, Malaysia

Correspondence to Yook Chin Chia, Department of Primary Care Medicine, University of Malaya Primary Care Research Group (UMPCRG), Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Tel: +60 3 7949 2620; fax: +60 3 7957 7941; e-mail: chiayc@um.edu.my

Received 25 August 2016 **Revised** 23 January 2017 **Accepted** 10 February 2017

DOI:10.1097/HJH.0000000000001333

SBP. Furthermore, to our knowledge, BPV has not been studied much in the Asia-Pacific region, especially in a multiethnic population. Malaysia has a multiethnic population of estimated 31.7 million in 2016, with Malays (68.6%) being the major ethnic group, followed by Chinese (23.4%) and Indians (7.0%) [21]. Studies have reported that Asian Indians were at greatest risk of coronary heart disease (CHD) [22]. Thus, our study aimed to examine long-term BPV and its determinants as well as its association with CVD events in a randomly selected representative sample from a multiethnic primary care setting.

METHODS

Setting

We examined long-term BPV in a randomly selected cohort of hypertensive patients in an urban primary care clinic of a teaching hospital. Random numbers were generated by computer based on the patient's registration number with the clinic. This selected sample consists of adult hypertensive patients aged 30 years and older on long-term follow-up in our primary care clinic. Our study population consists of three main ethnic groups, namely the Malays, Chinese and Indians [23]. As this was a retrospective study based on patient records, and as all data entry, analysis and results output were anonymized, no informed consent, verbal or written, was obtained. Ethics approval for our study, based on this study design and methodology, was obtained and granted by the Ethics Committee of our institution. (University of Malaya Medical Centre Ethics Committee/IRB Reference Number 691.1).

Study population

Inclusion criteria

A total of 883 out of 1525 in the original cohort were hypertensive in the baseline year of 1998 [24]. After excluding 56 patients with a total SBP reading less than seven, nine patients who were not contactable or traceable from hospital records and 11 foreigners, 807 patients were eligible and entered into our analysis.

Data collection

The sample was randomly selected using a computer-generated number based on the patient's unique registration number with the clinic. All patient records were in paper form. We manually extracted the patients' information at baseline (1998) and at the end of 10 years (2007) from their records according to a predetermined proforma (clinical report form) that included the patient's sociodemography, blood pressure (BP) and use of antihypertensive agents. This was then entered into an electronic Excel spreadsheet and then converted to SPSS format for analysis using SPSS (SPSS IBM New York, United States) version 21.

The data were captured by a trained and experienced research assistant, and accuracy of data entry was checked by the investigators themselves.

Patients' BP readings that were measured by the attending doctors as part of daily clinical practice were captured from the medical records. Patients with hypertension were defined as those who had been diagnosed to have hypertension (BP $\geq$ 140/90 mmHg) or were on antihypertensive medications at baseline. Diagnosis of hypertension in our clinics is made in accordance with standard recommendations, that is based on at least two BP measurements at least 2 weeks apart [25].

Diabetes mellitus was based on the doctors' diagnosis or the use of hypoglycemic agents or both as stated in the medical records. Serum creatinine was obtained from patient records. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-epi) [26,27]. Antihypertensive drug use was also captured and classified into the following classes: renin–angiotensin system (RAS) inhibitors encompassing angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, calcium channel blocker (CCB), diuretics and alpha-blockers (α-blockers).

Definition

Visit-to-visit SBP variability

Over a 10-year clinic visit, serial SBP readings were captured, with a maximum of four readings per year (each year was divided into 3 monthly intervals with one BP reading per 3 months). Visit-to-visit variability (VVV) is the variability of the SBP over all the visits. We used SD and coefficient of variation as a measure of VVV of systolic BPV. SD of systolic BPV is calculated as

$$\frac{\sqrt{\left[\text{sum (individual SBP readings} - \text{sample mean SBP})^2\right]}}{\text{Total number of visits}}$$

Coefficient of variation is derived as SD divided by the individual's mean SBP $\times$ 100.

To examine the interaction of BPV and mean SBP on CVD event, we categorized the patients into different groups of high and low means based on the entire cohort mean SBP and BPV. We used less than 142 mmHg as the cutoff point for low mean SBP and at least 142 mmHg as high mean SBP. We also used 14.7 mmHg, the mean BPV of the entire cohort as the cutoff point to define high or low BPV.

Subsequently, we grouped them into those with low mean SBP low BPV as group 1, low mean SBP high BPV (group 2), high mean SBP low BPV (group 3) and high mean SBP high BPV (group 4).

We then examined the differences in cardiovascular events across these groups. Thus, the four groups represented patients whose mean SBP was either in the lower or higher range or with either a greater or a lower degree of fluctuations of BP over the 10-year follow-up.

Cardiovascular disease events

CVD events are defined as fatal and nonfatal CHD, fatal and nonfatal strokes, heart failure and peripheral artery disease. This information was also obtained and verified from medical records. We traced and examined patients' case records from the main hospital to determine the CVD status for those who did not complete their subsequent 10-year

follow-up at our clinic. For those patients who did not continue their follow-up at our clinic or hospital, we contacted the patients or their family individually to find out their CVD status for any fatal or nonfatal CVD events.

Statistical analysis

All statistical analyses were done using the Statistical Package for Social Sciences (SPSS) version 21. Continuous data are described as mean and SD if the distribution is normal. When the data were a skewed distribution, median and interquartile range (25th–75th percentiles) was used. Categorical data are reported as proportions (percentage) or chi-square test. Multiple linear regression models were used to look for the predictors of BPV. The independent variables were age, female sex, eGFR, use of RAS blockers, α-blockers, mean SBP and a diabetes status.

Multiple logistic regression was used to adjust the variables to look for the predictors of CVD events. All variables with the *P* value less than 0.05 in the univariate analyses as well as clinically significant variables were entered into the multiple logistic regression analysis. The dependent variable was cardiovascular event (yes or no). The independent variables were age, sex, presence of diabetes, ethnicity, mean SBP over 10 years, mean BPV over 10 years, smoking status and total and HDL cholesterol. We compared the cardiovascular event rate according to the four groups of mean SBP and BPV. All analyses were done with 95% confidence intervals (CI), and the level of significance was set at *P* less than 0.05.

TABLE 1. Sociodemographic and clinical characteristics of the study population at baseline (*n* = 807)

Variables	Year 1998	Year 2007
Age [year (mean ± SD)]	57.2 ± 9.8	67.2 ± 9.8
Men, *n* (%)	296 (36.7)	296 (36.7)
Race, *n* (%)		
Malays	215 (26.6)	215 (26.6)
Chinese	404 (50.1)	404 (50.1)
Indians	188 (23.3)	188 (23.3)
Current smoker, *n* (%)	50 (6.2)	50 (6.2)
SBP [mmHg (mean ± SD)]	145.8 ± 18.2	136.3 ± 16.4
DBP [mmHg (mean ± SD)]	87.5 ± 10.0	79.9 ± 8.6
BPV of SBP in SD [mmHg (mean ± SD)]	8.7 ± 5.3	10.3 ± 2.3
BPV of SBP in CV [% (mean ± SD)]	7.3 ± 1.6	6.2 ± 4.5
Types of antihypertensive agents used, *n* (%)		
RAS	88 (10.9)	348 (43.1)
β-Blockers	423 (52.4)	399 (49.4)
CCB	342 (42.4)	479 (59.4)
Diuretics	100 (12.4)	278 (34.4)
α-Blockers	45 (5.6)	36 (4.5)
Diabetes mellitus, *n* (%)	262 (32.5)	393 (48.7)
HbA1C [% (mean ± SD)]	7.4 ± 1.7	7.3 ± 1.6
Use of lipid-lowering medication, *n* (%)	58 (7.2)	527 (65.3)
Total cholesterol [mmol/l (mean ± SD)]	6.0 ± 1.1	4.9 ± 0.9
LDL cholesterol [mmol/l (mean ± SD)]	3.5 ± 1.0	3.0 ± 0.8
HDL cholesterol [mmol/l (mean ± SD)]	1.2 ± 0.4	1.3 ± 0.3
Triglyceride [mmol/l (mean ± SD)]	1.7 ± 1.2	1.5 ± 0.81
eGFR by Cockcroft–Gault [ml/min/1.73 m^2 (mean ± SD)]	79.1 ± 18.7	71.8 ± 22.5
CKD Stage 3A and higher, *n* (%)	65 (8.1)	93 (11.5)

α-Blockers, alpha-blockers; β-blockers, beta-blockers; BP, blood pressure; BPV, blood pressure variability; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA1C, Haemoglobin A H1c; RAS, renin–angiotensin system.

RESULTS

A total of 807 patients were eligible and were entered into our analysis. The characteristics of patients at baseline are shown in Table 1. The mean age of the participants at baseline was 57.2 ± 9.8 years, and two-thirds were women (63.3%). The ethnic distribution was 50.1% Chinese, 26.6% Malays and 23.3% Indians. In our study, the mean number of SBP readings was 32 ± 5 and ranged from 10 to 40 readings. Mean BP at baseline was 145/88 mmHg, and 136/80 mmHg at the end of 10-year follow-up. At the end of 10 years, 48.7% were people with diabetes, 11.5% had CKD stage 3A or higher and 65.3% were on lipid-lowering agents.

The mean SD and coefficient of variation of systolic BPV for the entire cohort over a 10-year period was 14.7 ± 3.5 mmHg and 10.3 ± 2.3%, respectively. The mean SBP over 10 years was 142 ± 8 mmHg.

Table 2 shows the univariate analysis of the BPV over 10 years. Women had higher VVV compared with men ($P = 0.01$). There is no difference in BPV among the different ethnicities. Among all the antihypertensive agents, patients who were prescribed RAS blockers and α-blockers have the highest BPV (10.8 and 10.9 mmHg, respectively) ($P < 0.05$).

Table 3 shows the adjusted general linear model analyses. There was significant relationship between BPV and mean SBP, being women and worsening of renal function. For every 1-mmHg increase in mean SBP, the BPV is expected to increase by 0.20 mmHg. On the other hand, for every 1-ml/min/1.73 m^2 reduction in eGFR, the BPV is expected to increase by 0.11 mmHg. Being female sex is expected to increase BPV by 0.11 mmHg.

Table 4 compares the clinical variables of patients with and without history of CVD. The overall prevalence of cardiovascular event was 13% (six had fatal CHD, 72 had nonfatal CHD, two had fatal stroke and 33 had nonfatal strokes, six had heart failure and two had peripheral artery disease). Those clinical variables that have significant association with CVD events on univariate analysis are age, being women, having underlying diabetes, ethnicity group and BPV. However, the mean SBP is on the threshold of significance ($P = 0.052$).

Table 5 shows the determinants of the cardiovascular events. According to multiple logistic regression analyses, being men [odds ratio (OR) 2.47, 95% CI 1.34–4.53] and presence of diabetes (OR 2.65, 95% CI 1.45–4.82) are more likely to be associated with cardiovascular events. Being Indian (OR 3.06, 95% CI 1.52–6.18) is more likely to be associated with cardiovascular events compared with Chinese. Increase per 1 mmHg of BPV is associated with higher odds of getting cardiovascular events in this population (OR 1.06, 95% CI 1.00–1.13). However, the mean SBP, which was of borderline significance on univariate analysis, is no longer significantly associated with the CVD events on multivariate analysis.

Figure 1 shows the CVD events in the four groups according to their mean SBP and BPV. Those with the same mean SBP, whether high or low, but who also have higher BPV have more events than those with lower BPV. Those

TABLE 2. Univariate analysis of the blood pressure variability over 10 years ($n = 807$)

Variables	*r*	*P* value
Age in 1998 (year)	0.15	<0.001
Mean SBP in 10 years (mmHg)	0.23	<0.001
eGFR in 1998 (ml/min/1.73 m^2)	−0.09	0.02
HbA1C in 1998 (%)	−0.06	0.31
Total cholesterol (mmol/l)	0.04	0.26
HDL (mmol/l)	0.10	0.02
LDL (mmol/l)	−0.92	0.45
Triglyceride (mmol/l)	−0.05	0.19

Categorical data	Mean BPV (mmHg)	*P* value
Sex		
Male	10.1 ± 2.4	0.01
Female	10.5 ± 2.2	
Ethnicity at baseline		
Malays	10.5 ± 2.3	0.19
Chinese	10.2 ± 2.2	
Indians	10.5 ± 2.4	
Smokers		
Yes	10.2 ± 2.2	0.67
No	10.3 ± 2.3	
Diabetes		
Yes	10.6 ± 2.4	0.04*
No	10.2 ± 2.2	
Chronic kidney disease		
Yes	10.5 ± 2.4	0.19
No	10.2 ± 2.2	
Lipid-lowering agents		
Yes	10.6 ± 2.8	0.36
No	10.9 ± 2.2	
Antihypertensive agents at baseline		
RAS inhibitors		
Yes	10.8 ± 2.7	0.04*
No	10.2 ± 2.2	
Calcium channel blockers		
Yes	10.2 ± 2.1	0.40
No	10.4 ± 2.4	
β-Blockers		
Yes	10.4 ± 2.2	0.49
No	10.3 ± 2.3	
α-Blockers		
Yes	10.9 ± 2.6	0.07
No	10.3 ± 2.2	
Diuretics		
Yes	10.0 ± 2.3	0.92
No	10.4 ± 2.2	

α-Blockers, alpha-blockers; β-blockers, beta-blockers; BPV, blood pressure variability; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system.
*$P \leq 0.05$.

with the lower SBP and lower BPV had fewer cardiovascular events than those with the same low mean SBP but higher BPV (10.5 versus 12.8%). Similarly, those with higher mean SBP but lower BPV also had fewer cardiovascular events than those with the same high mean and higher BPV (11.6 versus 16.7%).

One unanticipated finding was that patients with low mean SBP but high BPV have nearly the same events than those patients with high mean SBP but low BPV (12.8 versus 11.6%), suggesting BPV had a greater impact and hence more important than the mean SBP in causing CVD events in our cohort.

TABLE 3. Factors associated with SBP variability using multiple linear regression

		95.0% CI		
	Beta	Lower bound	Upper bound	Sig.
Age in 1998	0.053	−0.01	0.035	0.28
Mean SBP of 10 years	0.202	0.031	0.076	<0.001*
eGFR in 1998	−0.109	−0.025	−0.002	0.026*
HDL cholesterol in 1998	0.057	−0.179	0.869	0.196
Women	0.114	0.121	0.937	0.011*
Diabetes in 1998	0.038	−0.228	0.594	0.382
RAS inhibitors in 1998	0.083	−0.006	1.145	0.052
Alpha-blockers in 1998	0.068	−0.148	1.47	0.109

CI, confidence interval; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system.
*$P \leq 0.05$.

TABLE 4. Comparison of baseline clinical variables of patients with and without cardiovascular disease events

Variables	No CVD	CVD	*P* value
Age in 1998 in year (mean ± SD)	56.8 ± 9.7	60.2 ± 10.3	0.001*
Sex			
Male, *n* (%)	242 (81.8)	54 (18.2)	0.001*
Female, *n* (%)	460 (90.0)	51 (10.0)	
Having diabetes			
Yes, *n* (%)	209 (79.8)	53 (20.2)	<0.001*
No, *n* (%)	493 (90.6)	51 (9.4)	
Race			
Malay, *n* (%)	185 (86.0)	30 (14.0)	0.001*
Chinese, *n* (%)	367 (90.8)	37 (9.2)	
Indian, *n* (%)	150 (79.8)	38 (20.2)	
Antilipid agent			
Yes, *n* (%)	46 (82.8)	10 (17.2)	0.32
No, *n* (%)	654 (87.3)	95 (12.7)	
RAS blocker			
Yes, *n* (%)	71 (80.7)	17 (19.3)	0.06
No, *n* (%)	631 (87.8)	88 (12.2)	
β-Blocker			
Yes, *n* (%)	379 (89.6)	44 (10.4)	0.02*
No, *n* (%)	323 (84.1)	61 (15.9)	
Calcium channel blocker			
Yes, *n* (%)	291 (85.1)	51 (14.9)	0.17
No, *n* (%)	411 (88.4)	54 (11.6)	
Diuretics			
Yes, *n* (%)	91 (91.0)	9 (9.0)	0.20
No, *n* (%)	611 (86.4)	96 (13.6)	
α-Blockers			
Yes, *n* (%)	38 (84.4)	7 (15.6)	0.60
No, *n* (%)	664 (87.1)	98 (12.9)	
Smoking			
Yes, *n* (%)	42 (85.7)	7 (14.3)	0.86
No, *n* (%)	498 (86.6)	77 (13.4)	
Mean BPV over year 10 in mmHg (mean ± SD)	14.6 ± 3.4	15.6 ± 3.9	0.003*
Mean SBP over year 10 (mmHg)	141.9 ± 8.4	143.7 ± 9.0	0.05
Total cholesterol [mmol/l (mean ± SD)]	6.0 ± 1.1	5.9 ± 1.0	0.47
HDL cholesterol [mmol/l (mean ± SD)]	1.2 ± 0.4	1.1 ± 0.4	0.57
LDL cholesterol [mmol/l (mean ± SD)]	3.5 ± 1.0	4.0 ± 0.7	0.18
Triglyceride [mmol/l (mean ± SD)]	1.7 ± 1.3	1.7 ± 0.9	0.82

α-Blockers, alpha-blockers; BPV, blood pressure variability; RAS, renin–angiotensin system.
*$P \leq 0.05$.

TABLE 5. Predictors of cardiovascular events

	OR	95% CI Lower	95% CI Upper	*P* value
Age	1.022	0.99	1.055	0.176
Sex				
Male	2.468	1.344	4.532	0.004*
Female	1			
Diabetes				
Yes	2.646	1.452	4.823	0.001*
No	1			
Ethnicity				0.007*
Indian	3.064	1.519	6.179	0.002
Malay	1.691	0.799	3.576	0.170
Chinese	1			
BPV 10-year	1.065	1.003	1.129	0.038*
Mean SBP 10-year	0.999	0.961	1.038	0.950
Smoking				
Yes	0.599	0.183	1.961	0.397
No	1			
HDL cholesterol	1.061	0.462	2.435	0.889
Total cholesterol	0.871	0.641	1.184	0.379

BPV, blood pressure variability; CI, confidence interval; OR, odds ratio.
*Statistically is significant as the *P* value is <0.05 after adjusted for age, sex, diabetes, ethnicity, mean BPV, mean SBP over 10 years, smoking, HDL and total cholesterol.

DISCUSSION

The mean SD and coefficient of variation of systolic BPV across this study was 14.7 ± 3.5 mmHg and $10.3 \pm 2.3\%$, respectively. This is higher than that reported in the National Health and Nutrition Examination Survey (NHANES III) study, in which the mean SD and coefficient of variation of SBP was 7.7 mmHg and 6.1%, respectively [4]. This difference could be due to the different population studied. NHANES was a community-based health survey, whereas our study was only on patients with hypertension [3]. However, in a study on elderly patients with hypertension in Japan, the reported coefficient of variation of BPV was 10.6% [28], which is similar to our study (10.3%).

Our study found that being woman is associated with greater BPV, and this is consistent with findings of other studies [4,29]. Our study also shows that there is a negative relationship between eGFR and BPV after adjustment for confounding factors. This is also similar with the other studies [30,31]. We also found that mean BPV was associated with mean SBP level, again consistent with other studies [13].

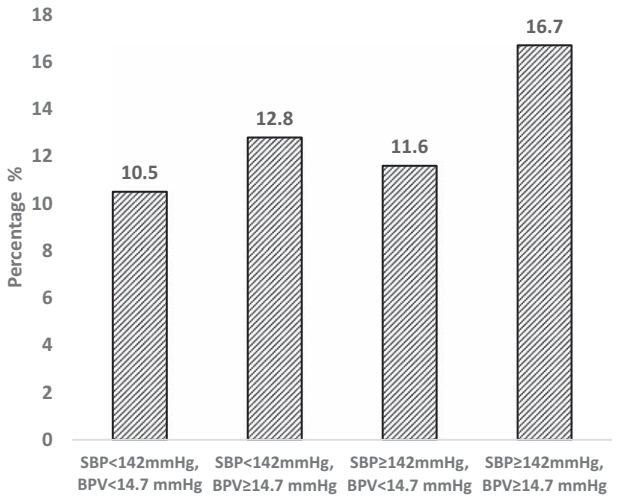

FIGURE 1 Percentage of CVD events in the 4 different groups according to mean SBP and BPV.

In our study, ACEI/ARB, α-blocker and β-blockers, CCBs or diuretics did not have any relationship with BPV. This is consistent with a post-hoc analysis of the European Lacidipine Study on Atherosclerosis [32], which also did not find any significant difference between β-blockers and CCBs on BPV. However, with the Anglo-Scandinavian Cardiac Outcome Trial and the Medical Research Council Trial of Treatment of Hypertension in Older Adults, different antihypertensive drug classes were found to be associated with BPV [18].

Although Indians have more cardiovascular events than the Chinese and Malays both in other reported studies [22] as well as our current study, BPV was not different between the three races suggesting that BPV by itself may not have much impact on the incidence of cardiovascular events between ethnicities. In our study, we reconfirmed determinants of CVD events that have been reported in previous studies.

Surprisingly, age is no longer a significant predictor of CVD events after adjustment in logistic regression analysis. This could partially be explained by the bigger number of smokers (8.5%) in the younger age group of under 57 years compared with 7.3% in older age group of over 57 years. This was seen when we ran an analysis to look for interaction between smoking and age as it was found to be significant with *P* value of 0.04.

Furthermore in our study, those with both low mean SBP and low BPV have the lowest CVD events. Conversely, those with both high mean SBP and high BPV have highest CVD events. In fact, those with the same mean BP, whether high or low, but who also had higher BPV have more events than those with lower BPV. One unanticipated finding was that patients with low mean SBP but high BPV have nearly the same events than those patients with high mean SBP but low BPV (12.8 versus 11.6%), suggesting that BPV had a greater impact and hence more important than the mean SBP in causing CVD events in our cohort. This could be due to the overall better SBP control in our study population in which the mean SBP was 145 mmHg in 1998 and 136 mmHg in 2007, and overall mean SBP over 10 years was 142 mmHg. Our findings differ from a previous study that showed that the mean SBP was more important than BPV in causing an increase in white matter densities on MRI [33]. However, the population of that study was mainly elderly, and only three BP readings had been taken to derive BPV values.

Although the difference in CVD events among the four groups was not statistically significant ($P = 0.18$), it nevertheless warrants further study to elucidate this matter more clearly as our findings of nonsignificance could have been due to the small sample size in each of the four groups in our study cohort.

Strength and limitations

Our current study has several strengths and some limitations. The strength of our study is that it reflects real-life clinical practice in a primary care setting in which most patients with hypertension are managed, whereas other studies were either community-based [4] or a post-hoc

analysis of randomized controlled trials [3]. Furthermore, very few studies have been done in primary care. Second, our sample of 807 patients is a substantial size. We have a mean of 32 BP readings, whereas other studies have only three BP readings as a measure of long-term BPV [4]. We also have a longer duration of follow-up compared with the other studies [4,34], and this is more reflective of patients with hypertension who need to be treated over a period of long time. A limitation of our study is that it was a retrospective study; therefore, missing data is not unexpected. However, the number of missing value is very small, and this will not affect our findings in any substantial way.

CONCLUSION

BPV is associated with an increase in CVD events even in those who have achieved lower mean SBP. Thus, we should prioritize not only control of SBP levels but also BPV to reduce CVD events further. Long-term visit-to-visit BPV could be another target in the management of patients with hypertension.

ACKNOWLEDGEMENTS

The author would like to acknowledge Department of Primary Care at the University of Malaya for providing the support during the data collection, and University of Malaya (UMRG 116/09HTM) and Malaysia Society of Hypertension for funding the research.

University of Malaya Research Grant – 116/09HTM.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Floras JS. Blood pressure variability: a novel and important risk factor. *Can J Cardiol* 2013; 29:557–563.
2. Pringle E, Phillips C, Thijs L, Davidson C, Staessen JA, de Leeuw PW, *et al.* Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 2003; 21:2251–2257.
3. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; 375:895–905.
4. 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.
5. Mancia G, Parati G. Importance of smooth and sustained blood pressure control in preventing cardiovascular morbidity and mortality. *Blood Press Suppl* 2001; 3:26–32.
6. Parati G. Blood pressure variability: its measurement and significance in hypertension. *J Hypertens Suppl* 2005; 23:S19–S25.
7. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, *et al.* Prognostic significance of blood pressure and heart rate variabilities: the Ohasama Study. *Hypertension* 2000; 36:901–906.
8. Schutte AE, Schutte R, Huisman HW, van Rooyen JM, Fourie CM, Malan NT, Malan L. Blood pressure variability is significantly associated with ECG left ventricular mass in normotensive Africans: the SABPA Study. *Hypertens Res* 2011; 34:1127–1134.
9. Schutte R, Thijs L, Liu YP, Asayama K, Jin Y, Odili A, *et al.* Within-subject blood pressure level – not variability – predicts fatal and nonfatal outcomes in a general population. *Hypertension* 2012; 60:1138–1147.
10. Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, *et al.* Prognostic value of reading-to-reading blood pressure variability over 24 h in 8938 subjects from 11 populations. *Hypertension* 2010; 55:1049–1057.
11. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol* 2013; 10:143–155.
12. Cao H, Wu S, Li S, Zhao H, Ruan C, Wu Y, *et al.* Characterization and influencing factors of visit-to-visit blood pressure variability of the population in a northern Chinese industrial city. *Chin Med J (Engl)* 2014; 127:1022–1026.
13. Schutte R, Thijs L, Liu YP, Asayama K, Jin Y, Odili A, *et al.* Within-subject blood pressure level – not variability – predicts fatal and nonfatal outcomes in a general population. *Hypertension* 2012; 60:1138–1147.
14. Mancia G, Messerli F, Bakris G, Zhou Q, Champion A, Pepine CJ. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension* 2007; 50:299–305.
15. Hsieh YT, Tu ST, Cho TJ, Chang SJ, Chen JF, Hsieh MC. Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: a 5.5-year prospective analysis. *Eur J Clin Invest* 2012; 42:245–253.
16. Okada H, Fukui M, Tanaka M, Inada S, Mineoka Y, Nakanishi N, *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.
17. Parati G, Ochoa JE, Salvi P, Lombardi C, Bilo G. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes. *Diabetes Care* 2013; 36 (Suppl 2): S312–S324.
18. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, *et al.* Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010; 9:469–480.
19. Webb AJ, Rothwell PM. Effect of dose and combination of antihypertensives on interindividual blood pressure variability a systematic review. *Stroke* 2011; 42:2860–2865.
20. Eguchi K, Ishikawa J, Hoshide S, Pickering TG, Schwartz JE, Shimada K, Kario K. Night time blood pressure variability is a strong predictor for cardiovascular events in patients with type 2 diabetes. *Am J Hypertens* 2009; 22:46–51.
21. Current Population Estimates, Malaysia, 2014-2016. Last modified on July 2016. https://www.statistics.gov.my/index.php?r=column/cthemeByCat&cat=155&bul_id=OWlxdEVoYlJCS0hUZzJyRUcvZEYxZz09&menu_id=L0pheU43NWJwRWVSZklWdzQ4TlhUUT09. Accessed on 10 December 2016.
22. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore Cardiovascular Cohort Study. *Int J Epidemiol* 2001; 30:983–988.
23. Demographics of Malaysia. Last modified on 13 February 2017. https://en.wikipedia.org/wiki/Demographics_of_Malaysia. Accessed on 10 December 2016.
24. Chia YC, Gray SY, Ching SM, Lim HM, Chinna K. Validation of the Framingham general cardiovascular risk score in a multiethnic Asian population: a retrospective cohort study. *BMJ Open* 2015; 5:e007324.
25. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.* The seventh report of the joint National Committee on Prevention, Detection, Evaluation, and treatment of high Blood pressure: the JNC7report. *JAMA* 2003; 289:2560–2572.
26. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604–612.
27. Chin CY, Mooi CS. Concordance of serum creatinine to estimated glomerular filtration rate in determining early chronic kidney disease in Malaysia. *Life Sci J* 2012; 9:453–457.
28. Eto M, Toba K, Akishita M, Kozaki K, Watanabe T, Kim S, *et al.* Impact of blood pressure variability on cardiovascular events in elderly patients with hypertension. *Hypertens Res* 2005; 28:1–7.
29. Chen SH, Liu YH, Cai J, Wang AT, Ma YJ, Li XL, *et al.* Impact of systolic blood pressure on visit-to-visit blood pressure variability in middle-aged and elderly people. *Zhonghua Xin Xue Guan Bing Za Zhi* 2013; 41:219–223.
30. Lasserson DS, Scherpbier de Haan N, de Grauw W, van der Wel M, Wetzels JF, O'Callaghan CA. What is the relationship between renal function and visit-to-visit blood pressure variability in primary care? Retrospective cohort study from routinely collected healthcare data. *BMJ Open* 2016; 6:e010702.

31. Chia YC, Lim HM, Ching SM. Long-term visit-to-visit blood pressure variability and renal function decline in patients with hypertension over 15 Years. *J Am Heart Assoc* 2016; 5:e003825.
32. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment. *J Hypertens* 2012; 30:1241–1251.
33. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, *et al*. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010; 67:564–569.
34. Aalbers J. Reduced blood pressure variability in ASCOT-BPLA trial favours use of amlodipine/perindopril combination to reduce stroke risk. *Cardiovasc J Afr* 2010; 21:115.