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Number of blood pressure measurements needed to estimate long-term visit-to-visit systolic blood pressure variability for predicting cardiovascular risk: a 10-year retrospective cohort study in a primary care clinic in Malaysia

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ABSTRACT

Objective To determine the reproducibility of visit-to-visit blood pressure variability (BPV) in clinical practice. We also determined the minimum number of blood pressure (BP) measurements needed to estimate long-term visit-to-visit BPV for predicting 10-year cardiovascular (CV) risk.

Design Retrospective study

Setting A primary care clinic in a university hospital in Malaysia.

Participants Random sampling of 1403 patients aged 30 years and above without any CV event at baseline.

Outcomes measures The effect of the number of BP measurement for calculation of long-term visit-to-visit BPV in predicting 10-year CV risk. CV events were defined as fatal and non-fatal coronary heart disease, fatal and non-fatal stroke, heart failure and peripheral vascular disease.

Results The mean 10-year SD of systolic blood pressure (SBP) for this cohort was 13.8±3.5 mm Hg. The intraclass correlation coefficient (ICC) for the SD of SBP based on the first eight and second eight measurements was 0.38 (p<0.001). In a primary care setting, visit-to-visit BPV (SD of SBP calculated from 20 BP measurements) was significantly associated with CV events (adjusted OR 1.07, 95% CI 1.02 to 1.13, p=0.009). Using SD of SBP from 20 measurement as reference, SD of SBP from 6 measurements (median time 1.75 years) has high reliability (ICC 0.74, p<0.001), with a mean difference of 0.6 mm Hg. Hence, a minimum of six BP measurements is needed for reliably estimating intraindividual BPV for CV outcome prediction.

Conclusion Long-term visit-to-visit BPV is reproducible in clinical practice. We suggest a minimum of six BP measurements for calculation of intraindividual visit-to-visit BPV. The number and duration of BP readings to derive BPV should be taken into consideration in predicting long-term CV risk.

Strengths and limitations of this study

- This study was conducted in real-life clinical setting, which reflects the visit-to-visit blood pressure variability (BPV) in routine clinical practice.
- This study was carried out in primary care setting where the patients are at a lower cardiovascular (CV) risk and different CV profile from those in secondary care.
- Ten-year duration of follow-up allows capturing of adequate visit-to-visit BP readings for analysis.
- There was no time of onset of CV event in this cohort study due to missing data.
- Majority of patients in this cohort study were on antihypertensive medications at the end of 10 years, which may reduce the CV risk and BPV.

INTRODUCTION

Recent studies have shown that visit-to-visit blood pressure variability (BPV) is not merely random 'noise' that affects the estimation of mean blood pressure (BP). It is reproducible and has prognostic significance for adverse cardiovascular (CV) events, all-cause mortality and decline in renal function.[1–7] Visit-to-visit BPV has been shown to be an independent predictor of CV events and has an even stronger association than mean systolic blood pressure (SBP).[3 8] In real-world clinical practice, BP measurements vary from visit to visit depending on measurement method, BP device used, different healthcare workers who measure the BP, duration in between visits, number of visits, number of measurements in each visit and adherence to medication. All these differences are believed to lead to higher variability in BP. During clinic

consultation, the BP measurements recorded in previous clinical visits can be used to calculate a patient's visit-to-visit BPV. However, the question remains as to whether the visit-to-visit BPV calculated retrospectively using clinical measurement is reliable to predict future CV events.

The number of BP measurements used to calculate BPV varied between studies and even within the same study. The number of BP measurements is important as unreliable estimates of visit-to-visit BPV will lead to underestimation or overestimation of cardiovascular disease (CVD) outcome risk.[9] However, current evidence has yet to suggest the optimal number of BP measurements needed to reliably estimate visit-to-visit BPV. Two studies have suggested that reproducibility of seven measurements is higher than four measurements.[10 11] In this present study, the goal is to examine the reproducibility and reliability of visit-to-visit BPV when BP is measured in routine clinical practice in an outpatient setting. We aimed to determine the number of BP measurements needed to calculate reliable visit-to-visit BPV for predicting CV events in primary care setting.

METHODS

Study population

This is a retrospective cohort study of 1403 patients in a primary care clinic. The original study cohort was used to validate the Framingham general CVD risk score and pooled cohort risk score in Malaysia.[12 13] This study was conducted in an outpatient primary care clinic at University Malaya Medical Centre, a teaching hospital in Kuala Lumpur, Malaysia. In this study, 1536 patients were randomly selected from all patients registered with the clinic in the year 1998. Patients aged 30 years and above who attended the primary care clinic were included in the cohort study. Those patients who had any CV events at baseline (1998) were excluded, that is, myocardial infarction, angina, heart failure, stroke and peripheral vascular disease because the objective of the present study is to examine the occurrence of the first CV event. For this present study, we excluded 25 patients whose CV event was not ascertained as of 2007. We further excluded 108 patients who had less than seven BP readings.

Data collection

In the original cohort study, the patients were randomly selected using a computer-generated number based on the patients' clinic registration numbers. Sociodemographic and clinical data were extracted from paper-based medical records manually. Diabetes mellitus was defined as documented by the attending doctors or the use of antidiabetic agents or both. The use and types of antihypertensive medications and diabetes medications were captured from the medical records. Smoking is defined as those patients who were still actively smoking while non-smokers were those who never smoked or were ex-smokers. Lipid profile including total cholesterol and low-density lipoprotein (LDL) cholesterol was captured together with the use of lipid-lowering medications. All blood tests were performed by the chemical laboratory in the hospital which is certified by the Royal College of Pathologists of Australasia standards. Serum creatinine levels were captured and were used for calculation of estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease (CKD) Epidemiology Collaboration Equation.[14] CKD was defined as eGFR <60 mL/min/1.73 m^2 in accordance with the staging by Kidney Disease Improving Global Outcomes 2012.[15]

Blood pressure data

BP was measured by the attending doctors using mercury sphygmomanometer during routine clinical practice without any structured measurement protocol. For the patients in this study, their recorded BP readings over the 10-year period (four per year, three- monthly) were retrieved by trained research staff.

Cardiovascular disease outcome

CVD events occurring any time from year 1998 to 2007 were captured from the patients' medical records. These included fatal myocardial infarction, non-fatal myocardial infarction and angina, fatal and non-fatal stroke, heart failure and peripheral vascular disease. The CV outcome is counted for the first occurrence only for a patient. For patients who did not complete their 10-year follow-up in this clinic, their hospital records were traced to ascertain their CV status. For those who had died, the cause of death was captured from the patient's hospital records where a diagnosis of the cause of death was made. If the cause of death was a CV event, it was counted as a CV event. For those who did not continue to be seen at our hospital, the patient or the family were called to ascertain the patient's status. Some were well without any CV events but had decided to be followed up at a clinic closer to their own homes. For those who had died, verbal autopsies were conducted to ascertain the cause of death as certified by the attending doctors.

As this was a retrospective study based on patient records, data analysis and results were anonymised.

Statistical analysis

In this study, to evaluate visit-to-visit BPV, four metrics were used: SD of SBP, coefficient variation (CV) of SBP, peak size and average real variability (ARV). A previous study has shown that using many more metrics to evaluate BPV will not provide additional information on the association with outcome.[16] For overall variability, SD and CV of SBP were used. Peak size, defined as the difference between the maximum and mean BP, was used to determine extreme value. ARV was used to examine the variability of consecutive visits (see online supplementary S1 for formulae). BPV of diastolic blood pressure (DBP) was not included in this present analysis because mean DBP and SD of DBP were not significantly associated with CV outcome in this present study (mean DBP OR 1.0, 95% CI 0.94 to 1.0, p=0.16; SD of DBP OR 1.14, 95% CI 1.0 to

1.31, p=0.06).[7] Furthermore, visit-to-visit variability of SBP is more often investigated than DBP.[17 18] Thus, only SD of SBP was analysed and reported in this study.

Visit-to-visit BPV metrics were calculated for the first four and the second four BP measurements and again for the first eight and the second eight BP measurement. BP measurements were done every three-monthly (four readings per year) during their clinic follow-up. Hence, analysing the reproducibility using four and eight BP readings was based on the estimated BP measurement for 1 year (four readings) vs 2 years (eight readings) duration. Intraclass correlation coefficients (ICC) for mean SBP and each metric was calculated to determine the reproducibility.

We were only able to ascertain the time to CV event for 89 patients (49.4%) out of the 180 patients with CV events over the 10-year period due to missing data. The logistic regression analysis was used to determine the association between SD of SBP and CV risk. SD of SBP is known to be associated with CV outcomes.[2 8] Multiple logistic regression was used to examine the association of SD of SBP and risk of CVD events. The OR was calculated for each cumulative number of BP measurements, adjusted for age, sex, race, presence of diabetes mellitus, use of antihypertensive medications, haemoglobin A1c (HbA1c), total cholesterol, LDL cholesterol, smoking, CKD and mean SBP. The variables used for the multiple logistic regression model were based on the data collected over the 10-year study period. The prognostic information contributed by SD of SBP based on different BP measurements was considered accurate if the adjusted OR remained significant (p≤0.05). As the number of BP measurements increased, the number of patients decreased. This was because patients who had CV event or died would have lesser BP readings. Also, there were patients who defaulted clinic visits or had less than four visits per year.

The median BP measurements for each patient was 32 readings with IQR (IQR 27–36 readings, range 7–40 readings). In this present study, SD of SBP calculated from 20 readings was 13.5±3.8 mm Hg and it was significantly associated with CV events. To determine the number of BP measurements needed for the calculation of reliable BPV, we used the SD calculated from 20 measurements as a reference for comparison with SD calculated with reduced number of visits because SD of SBP calculated from >20 readings onwards was significantly associated with risk of CV event. We quantified concordance between SD calculated from the full 20 measurements with fewer measurements using Pearson's correlation coefficient and ICC. Higher correlation coefficient indicates higher concordance. According to Koo and Li, ICC values of <0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.90 indicate good reliability and values >0.90 indicate excellent reliability.[19] All statistical analyses were carried out using Statistical Package for Social Sciences (V.21).

Table 1 Sociodemographic and clinical characteristics of the study population (n=1403)

	Year 1998	Year 2007
Age, year (mean±SD)	56.4±10.1	66.4±10.1
Female (n, %)	917 (65.4)	
Race (n, %)		
Malay	351 (25.0)	
Chinese	607 (43.3)	
Indian	426 (30.4)	
Others	17 (1.3)	
Weight, kg (mean±SD)	65.8±13	64.9±13.6
Systolic BP, mm Hg (mean±SD)	140.3±19	135.0±16.7
Diastolic BP, mm Hg (mean±SD)	84.9±10	79.1±8.3
Treatment of hypertension (n, %)	819 (58.5)	1131 (80.6)
Types of antihypertensive agents used (n, %)		
ACEi/ARB	93 (6.6)	581 (44.3)
β-Blockers	434 (30.9)	504 (38.4)
CCB	335 (25.3)	606 (46.2)
Diuretics	108 (7.7)	372 (28.4)
α-Blockers	47 (3.3)	39 (3.0)
Diabetes mellitus (n, %)	621 (44.3)	788 (60.8)
Haemoglobin A1c, % (mean±SD)	7.81±1.89	7.67±1.81
Types of diabetic medications used (n, %)		
Metformin	340 (24.2)	581 (44.4)
Sulfonylurea	501 (35.7)	553 (42.2)
Insulin	17 (1.2)	157 (12.0)
Use of statins (n, %)	113 (8.1)	846 (64.5)
Total cholesterol, mmol/L (mean±SD)	5.98±1.12	4.92±1.0
LDL cholesterol, mmol/L (mean±SD)	3.67±1.09	2.98±0.83
Smoking (n, %)	97 (6.9)	97 (6.9)
Cardiovascular events (n, %)	0	180 (12.8)
Chronic kidney disease stage 3 and above	158 (11.3)	285 (20.3)

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; LDL, lower-density lipoprotein.

Patient and public involvement

Patients were not involved in setting the research questions or planning the study.

RESULTS

The sociodemographic and clinical characteristics of the 1403 patients in this study are shown in table 1. The mean age at baseline was 56.4 years and 65.4% of patients were female; 58.5% (n=819) of patients at baseline were on antihypertensive medication and the number increased to 80.6% (n=1131) over the 10-year period. There was 5 mm Hg reduction in the mean SBP

Table 2 The intraclass correlation of each measure of BP variability

Metrics of BPV	First four readings (n=1403)	Second four readings (n=1403)	ICC (95% CI)	P value
Mean SBP, mm Hg	140.2±14.1	140.6±13.2	0.79 (0.77 to 0.82)	<0.001
Maximum SBP, mm Hg	153.7±17.9	153.4±17.5	0.71 (0.68 to 0.74)	<0.001
Peak size, mm Hg	13.5±7.9	12.7±8.0	0.19 (0.89 to 0.27)	<0.001
SD of SBP, mm Hg	12.1±6.0	11.4±6.0	0.25 (0.17 to 0.33)	<0.001
CV of SBP, %	8.5±4.0	8.0±4.0	0.16 (0.06 to 0.25)	<0.001
ARV, mm Hg	13.8±8.2	12.8±7.7	0.14 (0.04 to 0.23)	0.04
	First eight readings (n=1399)	**Second eight readings (n=1399)**	**ICC (95% CI)**	**P value**
Mean SBP, mm Hg	140.5±12.4	140.3±11.7	0.82 (0.80 to 0.84)	<0.001
Maximum SBP, mm Hg	159.9±17.6	159.0±17.1	0.69 (0.65 to 0.72)	<0.001
Peak size, mm Hg	19.4±9.2	18.7±9.4	0.20 (0.11 to 0.29)	<0.001
SD of SBP, mm Hg	12.8±4.8	12.3±4.6	0.38 (0.31 to 0.45)	<0.001
CV of SBP, %	9.0±3.1	8.7±3.0	0.26 (0.18 to 0.34)	<0.001
ARV, mm Hg	13.4±5.7	13.1±5.7	0.24 (0.15 to 0.32)	<0.001

ARV, average real variability; BPV, blood pressure variability; CV, coefficient of variation; ICC, intraclass correlation coefficient; SBP, systolic blood pressure.

from 140.3 to 135 mm Hg at the end of 10 years in 2007; 60.8% of patients had diabetes mellitus in 2007. There was a significant incremental use of lipid-lowering medication from 8.1% in 1998 to 64.5% in 2007 contributing to the improvement of lipid profile. There was total of 180 patients with CV events in this 10-year period (1998–2007). The CVD events included 10 fatal myocardial infarction, 12 non-fatal myocardial infarction, 112 angina, 9 heart failure, 3 fatal stroke, 45 non-fatal stroke and 4 peripheral vascular disease. Among those in whom we had ascertained the time of CV events (n=89, 49.4%), there was no difference in the SD of SBP before and after the onset of CV event (13.8 vs 13.4 mm Hg, p=0.60).

Reproducibility of visit-to-visit SBP in clinical practice

Table 2 shows the ICC between the first four versus the second four measurements and the first eight versus the second eight measurements of mean SBP and visit-to-visit BPV metrics. Generally, the visit-to-visit BPV values were slightly higher for the first four measurements compared with the second four measurements. The same pattern was observed in the analysis with eight readings. Mean SBP has good reproducibility with ICC 0.79 for first four versus second four measurements and 0.82 for first eight versus second eight measurements. BPV metrics have much lower reproducibility compared with mean SBP. Among the visit-to-visit BPV metrics, the ICC values for SD of SBP were higher (0.25 for comparing the first four and the second four measurements; 0.38 for comparing first eight and second eight readings, p<0.001) compared with CV and ARV of SBP. Overall, the ICC values for SBP and BPV metrics were higher for eight measurements compared with four measurements.

Number of readings for visit-to-visit BPV and risk of cardiovascular event

Table 3 shows the association between SD of SBP and risk of CV events based on the number of BP measurements. The association of visit-to-visit BPV with risk of CV events was significant with SD of SBP calculated from 20 measurements onwards (adjusted OR 1.07, 95% CI 1.02 to 1.13, p=0.009), after adjusting for age, sex, race, presence of diabetes, on antihypertensive treatment, HbA1c, total cholesterol, LDL cholesterol, smoking, presence of CKD and mean SBP. Multiple comparison analysis was performed using a false recovery rate of 5%.[20] Based on this, the largest p value that was less than the Benjamini-Hochberg value was with 20 measurements (see online supplementary S2).

We used SD of SBP calculated from 20 readings as a reference to determine the minimum number of BP measurement needed to reliably estimate intraindividual BPV (table 4). The SD of SBP increased when more numbers of BP measurements were added into the calculation of SD. As shown in table 4, compared with 20 BP measurements, the ICC values increased with increasing number of BP measurements, starting from ICC value of 0.45 with 3 BP measurements to ICC value of 0.97 with 16 BP measurements. In this study, the ICC of 0.75 is reached at six BP measurement with the 95% CI between 0.71 and 0.77. The difference in mean SBP between 6 and 20 measurements was of 0.8 mm Hg. The median duration for completing the six SBP measurements was 1.75 years (IQR 1.5–2.25 years); 73.9% (n=1037) of the patients had six BP measurements within 2 years.

Table 3 Association of SD of SBP with risk of cardiovascular event, based on number of blood pressure measurement (n=1403)

Number of measurement	Mean SD of SBP, mm Hg	Adjusted OR (95% CI)*	P value	Number of patients
8	12.8±4.7	1.00 (0.96 to 1.05)	0.88	1403
12	13.1±4.2	1.01 (0.96 to 1.06)	0.76	1396
16	13.3±4.0	1.02 (0.96 to 1.08)	0.50	1381
20	13.5±3.8	1.07 (1.02 to 1.13)	0.009	1344
24	13.6±3.6	1.09 (1.03 to 1.15)	0.002	1249
28	13.7±3.5	1.09 (1.02 to 1.16)	0.008	1096
32	13.9±3.3	1.11 (1.04 to 1.19)	0.003	853
36	14.3±3.3	1.10 (1.00 to 1.19)	0.04	483
40	14.5±3.2	1.04 (0.67 to 1.61)	0.88	65

*Adjusted for age, sex, race, presence of diabetes mellitus, on antihypertensive treatment, HbA1c, total cholesterol, LDL cholesterol, smoking, chronic kidney disease and mean SBP.
HbA1c, haemoglobin A1c; LDL, low-density lipoprotein; SBP, systolic blood pressure.

To examine if more frequent visits made a difference in BPV, we compared the mean SD of SBP values of the first 10 consecutive measurement (approximately 2.5 years) with that of 10 measurement taken once a year, over the 10-year period (figure 1). In the analysis, the SD of SBP from the first 10 consecutive SBP measurements was lower than that from 10 BP measurements taken once per year (13.1 vs 14.2 mm Hg, p<0.001).

DISCUSSION

Studies have stressed that the number of BP measurements is very important in the calculation of visit-to-visit BPV for prediction of outcome risk.[9 21] However, comparison of BPV between studies was difficult due to variations in the number of measurements used for calculation of the BPV. Two systematic reviews and meta-analysis studies on visit-to-visit BPV and CVD risk have pointed out the need for standardisation of the number of visits when defining visit-to-visit BPV.[17 18] Our study added to the evidence showing the effect of the number of BP measurements in calculating visit-to-visit BPV. Our study has shown that SD of SBP increased with more number of BP measurements included for the calculation of BPV. Too few BP measurements will inadvertently suggest a smaller BPV and this might not predict the outcome risk, although some studies managed to report the association with CV event with only three BP measurements.[8 22] There is still a question of the optimal number of visit-to-visit BP measurements that can sufficiently and reliably estimate BPV. Our study reports that SD of SBP derived from 6 measurements was concordant to SD of SBP calculated from 20 measurements with only a small difference (<1 mm Hg) in

Table 4 Concordance between SD of SBP from 3 to 20 SBP measurements

Number of BP measurement	Mean SD of SBP, mm Hg	Delta, mm Hg	r	ICC (95% CI)	P value	Number of patients
20	13.4±3.7	Ref	Ref	Ref	Ref	1344
16	13.3±4.0	0.1	0.94	0.97 (0.96 to 0.97)	<0.001	1381
12	13.1±4.2	0.3	0.82	0.90 (0.89 to 0.91)	<0.001	1396
10	12.9±4.4	0.5	0.77	0.87 (0.85 to 0.88)	<0.001	1399
9	12.9±4.5	0.5	0.74	0.84 (0.82 to 0.86)	<0.001	1401
8	12.8±4.7	0.6	0.71	0.82 (0.80 to 0.84)	<0.001	1403
7	12.7±4.9	0.7	0.66	0.78 (0.76 to 0.80)	<0.001	1403
6	12.6±5.2	0.8	0.62	0.74 (0.71 to 0.77)	<0.001	1403
5	12.6±5.6	0.8	0.56	0.68 (0.65 to 0.72)	<0.001	1403
4	12.2±6.0	1.2	0.47	0.60 (0.55 to 0.64)	<0.001	1403
3	11.5±6.9	1.9	0.34	0.45 (0.39 to 0.51)	<0.001	1403

Delta, difference in SD of SBP compared with SD of SBP calculated from 20 BP measurements; ICC, intraclass correlation coefficient; r, Pearson's coefficient; SBP, systolic blood pressure.

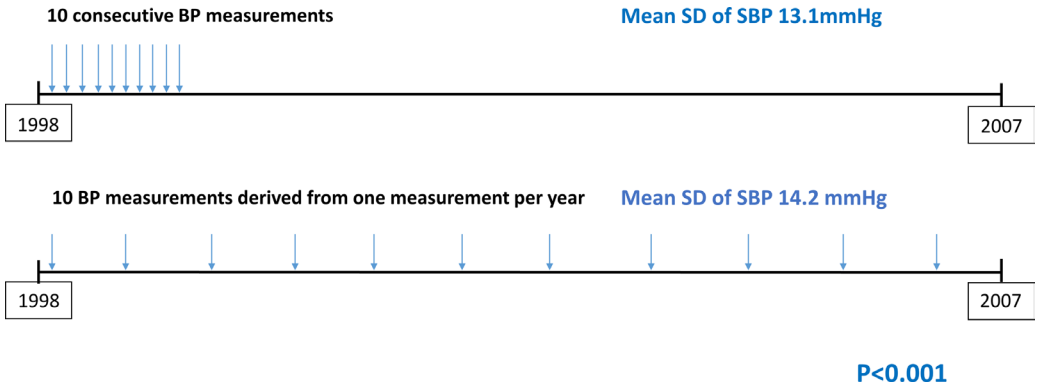

Figure 1 Effect of duration of clinic visits on visit-to-visit blood pressure variability. BP, blood pressure; SBP, systolic blood pressure.

mean SBP. The study by Levitan *et al* showed that the SD of SBP of 7 visits (automated measurements) and 6 visits (manual measurements) also had only a small difference of ≤1 mm Hg when compared with the SD of SBP from 18 measurements (automated measurements 7.5 mm Hg for 7 visits vs 8.5 mm Hg for 18 visits; manual measurements 6.7 mm Hg from 6 visits vs 7.7 mm Hg from 18 visits).[9] To date, there is no 'correct' answer to the optimal number of BP measurements needed to calculate visit-to-visit BPV. Our present study estimated that a minimum of six BP measurements in a real-life clinical setting may suffice to estimate a reliable visit-to-visit BPV. Additionally, our study showed that SD of SBP for 10 consecutive measurements to be lower than 10 BP measurements taken once per year (13.1 vs 14.2 mm Hg). This implies that frequent BP measurement makes a difference in BPV and in the number of measurements. As ageing is a factor associated with higher BPV, longer duration of measurements may potentially cause higher BPV, contributing to a significant rise in outcome risk.[8]

Our present study shows reproducibility of visit-to-visit BPV in real-life clinical practice. Our data were retrospectively retrieved from patient medical records and BP measurements may not be as consistently done as BP measurements in clinical trials or prospective cohort studies. In spite of this, the visit-to-visit BPV in our study was still found to be reproducible and not at all random. Muntner *et al* also showed the visit-to-visit BPV is reproducible in a cohort study among older patients with hypertension.[11] Despite both Muntner *et al* and our study showed significant results in the reproducibility of SD of SBP, we have to be aware of the low ICC for SD of SBP compared with mean SBP. This is consistent with a study which showed that the mean SBP still remains to be more superior to BPV in prognosticating CV events.[23] With the use of electronic medical records in current clinical practice, previous visit-to-visit BP readings are easily retrievable for calculation of BPV. Reproducibility of visit-to-visit BPV in clinical practice is important to test if BPV is associated with the outcome risk. Low reliability of SD of SBP may contribute to regression dilution bias, which could underestimate the outcome risk.[24 25] Reliability was lower when fewer number of measurements were used in BPV calculation implying that the attenuation of bias would be increased when more BP measurements are used in BPV calculation.

The utility of visit-to-visit BPV as a predictor for CV risk in clinical setting is presumed to be imprecise because of the variation in methods of BP measurement, seasonal changes, treatment adherence and duration between visits, added to the pre-existing intraindividual BPV.[26] However, this present study shows that visit-to-visit BPV is associated with 10-year CV risk. As this study was conducted in a lower risk primary care setting, where patients did not have any CVD events at the baseline, smaller OR for SD of SBP in predicting risk of CV event is not unexpected. The significance of SD of SBP in predicting CV risk was established in this present cohort study, although the overall mean BP was well controlled, reducing from 140.3 to 135 mm Hg in the 10-year period. Despite improvement in mean SBP over 10 years, visit-to-visit BPV was seen to be increasing with longer periods of measurements.

Studies have assessed the long-term visit-to-visit BPV using root-mean-square error (RMSE), which calculates the SD of the residuals from the linear regression of the SBP measurements.[27–29] This residual SD is different from the conventional BPV metrics such as SD, CV and ARV because residual SD is less influenced by the BP level change over time compared with SD; however, this is based on the assumption that a patient's BP increases in a linear pattern over time.[30] So far, there was no consensus on a gold standard approach to measure and report the visit-to-visit BPV.[30] For this present study, SD of SBP was used as the main BPV metric for analysis because SD of SBP was more commonly reported in studies examining association of visit-to-visit BPV and CVD compared with RMSE.[17 18] As shown in a systematic review by Diaz *et al*, among 37 studies on visit-to-visit BPV and CVD, 22 studies reported using SD while only 2 studies reported using RMSE.[17] Another systematic review on visit-to-visit BPV and CVD by Wang *et al* excluded those studies reporting RMSE in their systematic review.[18] Diaz *et al* reported that huge variation in the number of BP measurements used in visit-to-visit BPV studies, ranging from 3 to 256 visits.[17]

Hence, SD of SBP was used in our study to calculate BPV with the aim to draw the attention of researchers and clinicians on the effect of number of BP measurements in calculating SD of BPV and the least number of BP measurement required for a reliable intraindividual BPV. For implementation of visit-to-visit BPV in clinical practice, SD of SBP may be an easier measure for clinicians to obtain.[30]

There are several limitations in this study that should be considered when interpreting these results. We did not have the time of onset of CV events for all patients because of unavoidable missing data inherent in a retrospective study. The BP measurements after the onset of CV events were included into the calculation of SD of SBP. However, when we analysed the SD of SBP before and after the CV events for the 89 patients (49.4%) in whom we had the time of onset of events, we did not find any significant difference of SD of SBP before and after the CV events; in fact, the SD of SBP after the event was even lower than the SD of SBP before the event. This could have been due to the treatment effect and better medication adherence. However, we have included the use of antihypertensive medications as one of the variables in the multiple logistic regression for analysis of the OR of CV event. The major strength of our study is that it was conducted in a real-life clinical setting with big sample size. Our study was conducted in a primary care setting on a population with lower risk compared with most of the visit-to-visit BPV studies that were done in high-risk population. It is important for primary care physicians to know whether the effects of BPV is similar and applicable in primary care setting for prevention of CV events. There was no effects of seasonal changes on visit-to-visit BPV in this study as Malaysia is a tropical country with hot and humid environment throughout the year.

CONCLUSIONS

Visit-to-visit BPV was reproducible in a low-risk population in a primary care clinical setting. Our study reports a significant association of visit-to-visit BPV with risk of CV events when 20 measurements (median period 5.5 years) were used for SD of SBP calculation. We suggest that a minimum of six BP measurements (median period 1.75 years) is sufficient to reliably estimate intraindividual SD of SBP. Visit-to-visit BPV was influenced by the number and duration of measurements. Attention should be paid to these aspects when examining the association of long-term visit-to-visit BPV and outcome risk.

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