Visit-to-visit Systolic Blood Pressure Variability and Stroke Risk: A Systematic Review and Meta-analysis*

Han WANG[1, 3], Min LI[2], Shu-hua XIE[2], Ye-tong OYANG[2], Min YIN[2], Bing BAO[3], Zhi-ying CHEN[3#], Xiao-ping YIN[3#]
[1]*Department of Outpatient, The First Affiliated Hospital of Nanchang University, Nanchang 330000, China*
[2]*Department of Neurology, The Second Affiliated Hospital of Nanchang University, Nanchang 330000, China*
[3]*Department of Neurology, The Affiliated Hospital of Jiujiang University, Jiujiang 332000, China*

Summary: Visit-to-visit variability in systolic blood pressure (SBP) may have an important additional role in increasing the risk of vascular complications, including stroke. We conducted a meta-analysis to assess the relationship between visit-to-visit SBP variability (SBPV) and stroke risk. PubMed, EMBASE, and the Cochrane library databases were searched for cohort studies with data on visit-to-visit SBPV and stroke risk. Studies that reported adjusted relative risks (RRs) with 95% CIs of stroke associated with SBPV were included. Fourteen cohort studies met the inclusion criteria and were included in our meta-analysis. After adjustment for age, sex, and existing vascular risk factors, the analysis showed that the risk of stroke in patients with SBPV was significantly increased compared with patients with a small baseline SBPV [SD (RR=1.20, 95% CI=(1.07–1.35), *P*=0.0005), CV (RR=1.12, 95% CI=(1.00–1.26), *P*=0.008)]. In addition, follow-up variations of more than 5 years were associated with a higher risk of stroke than those of less than 5 years [RR=1.08, 95% CI=(1.04–1.11)]. Visit-to-visit SBPV was associated with an increased risk of stroke, especially in terms of the time of variation. Taken together, SBPV data may be useful as a preventative diagnostic method in the management of stroke.
Key words: blood pressure; blood pressure variability; meta-analysis; stroke; systematic review; visit-to-visit systolic blood pressure

Stroke is one of the leading causes of death globally, which accounts for 11.1% of all causes of death[1]. Blood pressure variability (BPV) reflects the degree of blood pressure fluctuations over a certain period of time, and visit-to-visit variability is defined as the standard deviation (SD) about the participant's mean systolic blood pressure across visits[2]. The relationship between stroke and blood pressure was first described in 1932 by Gunewardene *et al*[3], the study of which indicated that cerebral hemorrhage does not seem to occur with diastolic blood pressure under 115 mmHg (whatever may be the systolic), indicating that stroke is associated with blood pressure. It has also been noted in the latest American Heart Association/ American Stroke Association (AHA/ASA) guidelines for management of hemorrhagic stroke that early intensive lowering of blood pressure (BP) is safe and feasible and that surviving patients show modestly better functional recovery, with a favorable trend seen toward a reduction in the conventional clinical end points of major disability and/or death[4]; however, these recent guidelines did not indicate the association of the risk of stroke with visit-to-visit SBPV.

Pringle *et al*[5] first proposed the relationship between SBPV and stroke risk, suggesting that increased night-time SBPV is an independent risk factor for stroke. Later, Shimbo *et al*[2] found that greater visit-to-visit variability (VVV) of SBP in postmenopausal women was associated with increased risk of stroke, especially in the lowest range of the mean SBP. In a large cohort of the United Kingdom Transient Ischemic Attack Aspirin Trial (TIA; UK-TIA Aspirin Trials) and a broad population of patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA), Rothwell *et al*[6] reported that visit-to-visit SBPV and maximum SBP were strong predictors of stroke. In addition, many reports have demonstrated that VVV in SBP is significantly correlated with stroke[7–9]. Since then, more reports have been published on the association of SBPV with stroke and have included different proposed

Han WANG, E-mail: wanghanwangbuhan@126.com
#Corresponding authors, Zhi-ying CHEN, E-mail: 13767263459 @126.com; Xiao-ping YIN, E-mail: xiaopingbuxiao@126.com
*The study was supported by grants from the National Natural Science Foundation of China (No. 81760221 and No. 81660209), National Science & Technology Foundational Resource Investigation Program of China (No. 2018FY100900), the Major Program of the Natural Science Foundation of Jiangxi Province (No. 2016ACB20015).

viewpoints. In the analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial[10], visit-to-visit SBP variability was clearly associated with myocardial infarction and cardiovascular death, but not with stroke. In contrast, Tully *et al*[11] concluded that BPV is generally not associated with the incidence of stroke.

Therefore, the relationship between SBPV and stroke risk has remained inconsistent. Hence, it is unclear whether it is useful to monitor BPV in the general population to detect and reduce the risk of stroke. The objective of the present study was to obtain a more comprehensive estimate of the association between SBPV and the risk of stroke.

1 MATERIALS AND METHODS

1.1 Search Strategy

Systematic review and meta-analysis were carried out in line with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[12]. Comprehensive searches were conducted in PubMed, Medline, Embase, and the Cochrane Library (including the Cochrane Central Register of Controlled Trials). The methodology was in accordance with the Cochrane Handbook for Interventional Systematic Reviews[13] and was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14]. We searched PubMed, Embase and Cochrane Library databases (i.e., including reports from 1950 to the first week of May 2018) using combinations of the search terms "meta(-)analysis" and "visit-to-visit systolic blood pressure AND stroke" or other comparable terms (Data S1); only studies written in Chinese or English were considered. Additionally, we reviewed the references included in each study to supplement possible clinical studies that may be missed from our database searches. A prospective protocol was registered on PROSPERO (https://www.crd.york.ac.uk/prospero/) with the identification number CRD42017078880.

1.2 Study Eligibility

Studies were included if the following criteria were fulfilled: (1) cohort design, including prospective cohort (PC) group or retrospective cohort (RC); (2) the exposure of interest was mean SBP at baseline; (3) the outcome included any types of stroke (fatal, nonfatal, ischemic, or hemorrhagic stroke); and (4) quantitative estimates of the multivariate-adjusted RR and 95% CI for stroke associated with visit-to-visit SBP were reported. Studies that gave insufficient detail on BP measurements or BPV calculations were excluded. A study was also excluded if the inclusion or exclusion criteria of the study were unclear or unreasonable, or if there was a loss of follow-up or the follow-up time was not consistent with the study design.

1.3 Extraction of Data

Data were extracted from all of the articles using data tables generated by two review authors. Discrepancies in data abstraction were resolved by discussion and by a third investigator. When literature was in doubt or there was a lack of information, the original authors were consulted for supplementary information. Data extraction of studies included study characteristics (the first author's name, country where the study was performed, publication year, study type, single-center or multicenter design, duration of follow-up, sample size, criterion of stroke, subtypes of stroke), patient characteristics, mean of SBP, the adjusted OR, hazard ratios (HR), 95% CIs and possible biases.

1.4 Assessment of Study Quality

The Newcastle-Ottawa scale (NOS) for cohort studies[15] was used to evaluate study quality because all of the included studies consisted of cohorts. Studies were assessed from three aspects: selection of study groups (score of 0–4), comparability of groups (score of 0–2), and assessment of outcome in the cohorts (score of 0–3). A higher score represented a better quality of study, and studies with more than six stars were considered to be of high quality.

1.5 Data Synthesis and Statistical Analysis

All of the statistical analyses were conducted with the Review Manager version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and Stata version 12 (Stata Corporation, College Station, USA). HRs were pooled using a random effects model. In the selected cohort study, due to some studies involving living information, RR≈HR was considered as roughly equivalent (i.e., RR and HR were merged directly). The heterogeneity test between studies was evaluated using the Cochran's Q χ^2 test with the I^2 statistic being as follows: 0–40% indicated little or no heterogeneity; 30%–60% indicated moderate heterogeneity; 50%–90% indicated substantial heterogeneity; and 75%–100% indicated considerable heterogeneity. If there was evidence of heterogeneity, stratified syntheses and sensitivity analyses were employed to explain what contributed to the heterogeneity. We performed stratified analyses according to sex (females *versus* males), follow-up duration (≤5 years *versus* >5 years), study design (PC *versus* RC), and history of stroke (yes *versus* no). We calculated the linear *P* for trend and P for interaction for stratified analysis. Potential publication bias was assessed by the Egger's test and the symmetry of the funnel plot. The level of statistical significance for the two-tailed test of each hypothesis was set at $P<0.05$.

2 RESULTS

2.1 Basic Characteristics of The Selected Studies

Searches identified 3538 references (detailed flow

diagram of selection strategy in fig. 1), of which 3487 references were excluded for duplicate records and/or reporting of findings of articles that did not fulfill our inclusion criteria. After reviewing the abstracts and the full text, all of the articles were screened by two authors. The authors identified 20 possible research-related articles, six of which were excluded due to BP variability being predefined as ineligible. The remaining 14 articles were used for our systematic review and meta-analysis[2, 6, 16–27]. Among them, one article[6] included four population-based cohort studies. Table 1 presents the characteristics of the included articles. The sample sizes of the studies varied from 281[18] to 114 900[22] participants. The follow-up durations varied from one year[22] to 15 years[19], with a median of 5.4 years. Additionally, all of the investigations provided adjusted risk estimates (age, sex, body mass index, hypertension, diabetes; table 1). We also conducted the Newcastle-Ottawa Quality Assessment for the articles, and from the histogram we can see the distribution of all included NOS scores.

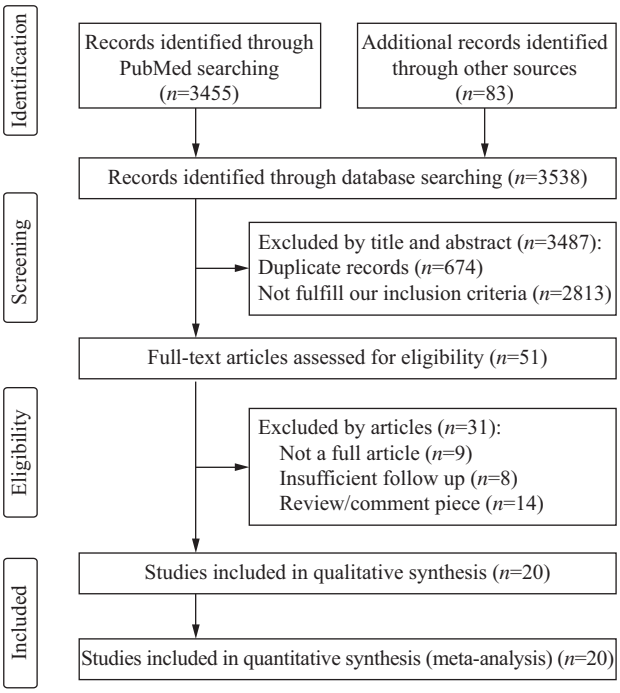

Fig. 1 Flow chart of selection strategy

2.2 Association Between VVV and the Risk of Stroke

VVV in SBP was defined by using SD and the coefficient of variation (CV; defined as SD/mean). After extracting data from 14 included articles, 11 SD values and five CV values were extracted for subgroup analysis. After adjustment for age, sex, and existing vascular risk factors, the analysis revealed the following. The risk of stroke in patients with SBPV was significantly increased compared with that of patients with a low baseline SBPV [SD (RR=1.20, 95% CI=(1.07–1.35), P=0.0005), CV (RR=1.12, 95% CI=(1.00–1.26), P=0.008); fig. 2]. Additionally, there was evidence of significant heterogeneity in the magnitude of the association across studies [SD (I^2=68%), CV (I^2=71%)].

2.3 Stratifying Analysis

One of the 14 selected articles included four studies, and the specific study could not be combined. Therefore, stratifying analysis of gender and follow-up years excluded this article temporarily. We conducted a subgroup analysis of the remaining 13 articles (table 2) using different sex, follow-up years, and statistical measures as different effects (CV and SD, preferred SD). In most subgroups, SBPV was associated with stroke. Stratified by sex, the association between SBPV and the risk of stroke was similar to the association between males and females. The pooled RR of stroke was 1.07 (95% CI 1.04–1.11). We then stratified by study design and whether the included patients had a history of stroke in the past. The pooled RRs of stroke were 1.20 (95% CI 1.01–1.58) in SD, 1.12 (95% CI 1.00–1.26) in CV, and 1.15 (95% CI 1.06–1.24) in pre-stroke. Stratified by follow-up years, no association between SBPV and the risk of stroke was observed in patients with follow-up time within five years [RR=1.06, 95% CI: 0.98–1.14].

2.4 Bias and Sensitivity Analysis

We used Stata version 12 for Bias and Sensitivity Analysis. There was no evidence of publication bias by inspection of the funnel plot, and Egger's linear regression test of publication bias of SD also suggested that there was no publication bias (t=–1.39, P=0.299) in the literature included in the meta-analysis. Also, the value of the CV of Egger's test further confirmed that there was no publication bias (t=0.85, P=0.459) in the literature included in the meta-analysis. These conclusions remained consistent when the SBP and stroke-risk-assessment results were converted to RR values from the HR values. Additionally, when the 16 values selected from the 14 studies were each deleted, the results of the meta-analysis remained essentially unchanged, indicating that the meta-analysis was stable.

3 DISCUSSION

The results from this meta-analysis provided new evidence that, after adjustments for stroke and cardiovascular risk factors, great visit-to-visit SBPV in patients may indicate an increased risk of stroke. The above analysis showed that gender difference and patient past history did not yield any significant differences in the risk of stroke. Blood pressure variation in patients with more than five years of stroke risk was associated with SBPV, whereas this was not significant in patients with less than five years of stroke risk. When CV was considered, the association between SBPV and stroke

Table 1 Baseline characteristics of studies included in meta-analysis

First author, publication (Year)	Country	Sample size (% male)	Follow-up duration (Years)	Mean age or age range (Years)	Study design	Stroke subtypes	Adjustment for covariates	Pre-stroke excluded
Rothwell *et al* (2010)	United Kingdom	7732	–	–	–	Any type of stroke	Age, sex, BSRF, mean blood pressure during the measurement period	Yes
Poortvliet *et al* (2012)	Scotland, Ireland, Netherlands	1808 (48.5)	7.1	70–82	RC	Any type of stroke	Age, sex, DM, BMI, randomized treatment, country, mean DBP, smoking, CVD, HDL, LDL, history of hypertension	No
Schutte *et al* (2012)	Belgium	2944 (49.3)	12	44.9	PC	Any type of stroke	Age, sex, BMI, heart rate, smoking and alcohol intake, HDL-C, plasma glucose, mean SBP and an index of SBP variability, history of previous CVD, use of β-blockers	Yes
Hata *et al* (2013)	20 countries from Asia, Australasia, Europe, and North America	8811 (58)	2.4	66	PC	Any type of stroke	Age, sex, BMI, DM, HR, smoking and alcohol intake, randomized BP-lowering intervention, randomized glucose control intervention, region of residence, total cholesterol, triglycerides, use of β-blockers, and use of calcium-channel blockers, mean SBP during the measurement period	Yes
Suchy-Diecy *et al* (2013)	US	3852 (41.0)	9.9	≥65	RC	Any type of stroke	Age, sex, DM, BMI, white race, clinics, smoking, HDL-C, LDL-C , intraindividual SBP mean and slope	No
Yinon *et al* (2013)	Bangladesh	11153 (57.6)	6.5	37	PC	Any type of stroke	Age, sex, BMI, DM, CVD, education, smoking status, baseline SBP and DBP, betel leaf use	No
McMullan *et al* (2014)	Europe or North America	2739 (75)	4.45	30–70	PC	Any type of stroke	Age, sex, smoker, trial, treatment assignment, race, mean glomerular filtration rate, mean SBP, mean log-transformed urine albumin-creatinine ratio	No
Lau *et al* (2014)	China	281 (52.3)	6.5	70±10	PC	IS or HS	Age, sex, DM, BMI, smoking, hyperlipidemia, mean SBP, CVD, ischemic stroke, congestive heart failure, peripheral vascular disease, anti-hypertensive medications	Yes
Gao *et al* (2014)	Not stated	2906 (4)	≤15	67.7	PC	Any type of stroke	Age, sex, BMI, race, smoking	No
Muntner *et al* (2015)	United States, Canada, Puerto Rico, the U.S. Virgin Islands	25814 (51.7)	2.3	≥55	RC	Any type of stroke	Age, sex, DM, BMI, Race, randomization assignment, smoking, total cholesterol levels, AF, HDL-C, LDL-C, education, history of CVD, MI or stroke, aspirin use, statin use, useof blood pressure medications, classes of antihypertensive medication being received, mean SBP	Yes
Men *et al* (2017)	China	19248 (40.7)	4.5	45–75	RC	IS or HS or US	Age, sex, center, treatment group, BSRF	Yes
Shimbo *et al* (2013)	US	58228 (0)	5.4	50–79	RC	IS or HS	Age, sex, DM, BMI, high cholesterol, smoking, education level, prior hormone therapy use, physical activity, mean SBP, mean heart rate, history of CHD, history of atrial fibrillation, temporal trend of SBP	Yes
Chang (2016)	California	114900 (41.3)	1	74.4	RC	IS or HS	Age, sex, race, smoking, SBP, number of blood pressure measurements, CVD, MI, AF, DM, hospitalized stroke or TIA, peripheral arterial disease, hypertension, dyslipidemia, diagnosed dementia, diagnosed depression, chronic liver disease, chronic lung disease, cancer, hospitalized bleed, documented proteinuria, GFR, drug	Yes
Dai *et al* (2017)	China	54650 (76.9)	3	18–98	RC	IS or HS	Age, sex, BMI, smoking, alcohol intake, education level, physical activity, heart rate, DM, dyslipidemia, serum uric acid, high-sensitivity CRP after logarithmic transformation, history of MI, family history of stroke, the use of antihypertensive drugs, mean SBP and DBP	Yes

RC, retrospective cohort; PC, prospective cohort; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CHF, congestive heart failure; US, undetermined stroke, BSRF, baseline stroke risk factors (baseline systolic blood pressure, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, homocysteine, creatinine, smoking status, alcohol consumption and body mass index); MI, myocardial infarction; DBP, diastolic blood pressure; AF, atrial fibrillation; CRP, C-reactive protein; HR, heart rate; TIA, transient ischemic attack; GFR, glomerular filtration rate

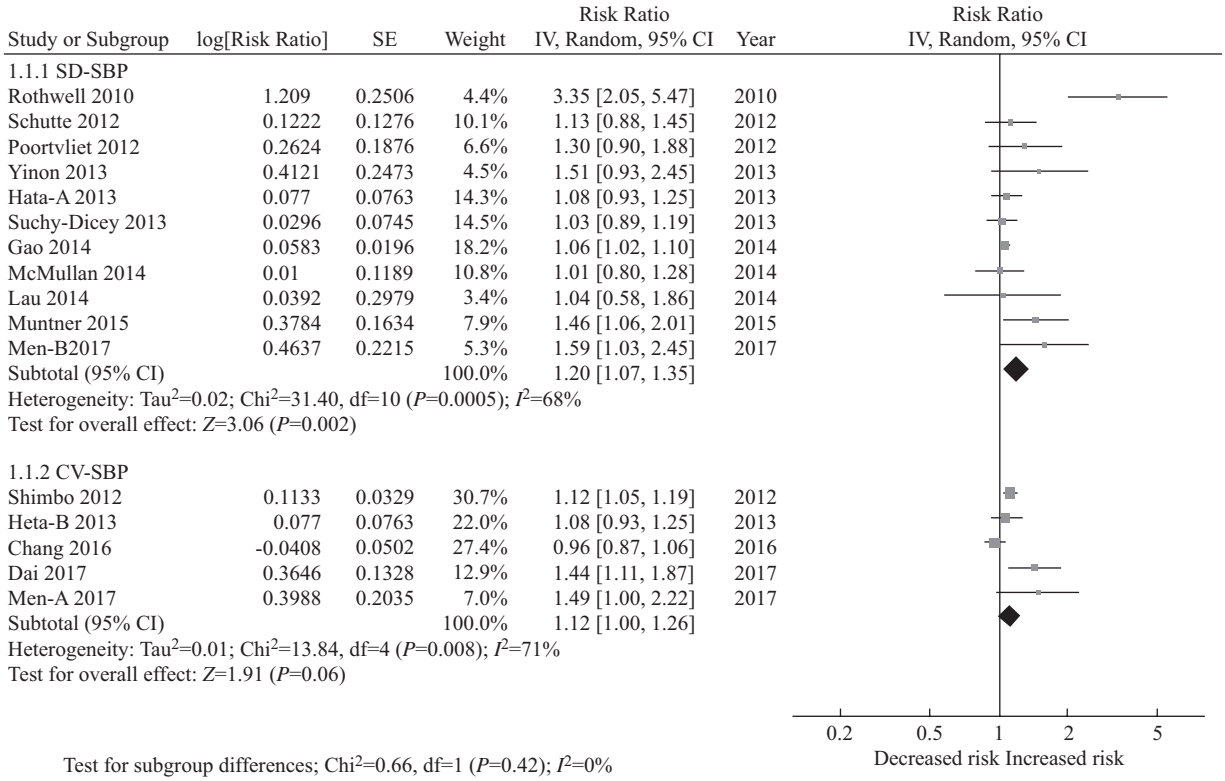

Fig. 2 Forest plot comparing SBPV and risk of stroke
The diamond indicates the overall summary estimate for the analysis. The center of the diamond represents the point estimate and the width represents 95% confidence interval (CI).

Table 2 Subgroup analysis of SBPV and stroke

	Sub-group	Studies, No.	*P* value	RR (95%CI)	Heterogeneity		
					χ^2	*P* value	I^2 (%)
Sex*	Total		<0.00001	1.07 [1.04, 1.11]	22.3	0.03	46
	Male	6	0.003	1.17 [1.05, 1.29]	8.12	0.15	38
	Female	7	<0.0001	1.07 [1.03, 1.10]	11.48	0.07	48
Follow-up duration*	Total		<0.00001	1.07 [1.04, 1.11]	22.3	0.03	46
	≤5	6	0.08	1.06 [0.98, 1.14]	16.62	0.005	70
	>5	7	<0.00001	1.08 [1.04, 1.11]	5.46	0.49	0
SD-SBP	Total		0.002	1.20 [1.01, 1.58]	31.4	0.0005	68
	SD-PC	7	0.03	1.20 [1.02, 1.41]	23.35	0.0007	74
	SD-RC	4	0.04	1.26 [1.01, 1.58]	6.88	0.08	56
CV-SBP	Total		0.06	1.12 [1.00, 1.26]	13.84	0.008	71
	CV-PC	1	0.31	1.08 [0.93, 1.25]	–	–	–
	CV-PRC	4	0.08	1.15 [0.98, 1.34]	13.83	0.003	78
Pre-stroke excluded	Total		0.0007	1.15 [1.06, 1.24]	42.84	<0.0001	70
	Yes	9	0.002	1.24 [1.08, 1.43]	37.34	<0.00001	79
	No	5	0.001	1.06 [1.02, 1.10]	3.54	0.47	0

*Fixed effect was used.

risk was not stable; this result may have been due to the number of included studies with small sample sizes. Additionally, in the included CV studies [Chang *et al*[22] (2016) (NOS: 7), Hata *et al*[26] (2013) (NOS: 7)], two articles with low NOS scores may also be relevant.

Furthermore, in this meta-analysis, heterogeneity might have arisen from several sources, among which study design and the status of having or not having a prior stroke were the most prominent sources. In the present meta analyses, the sample size of each study was different, which caused divergent power; thus, heterogeneity varied immensely. Relatively small sample sizes, incomplete matching, and insufficient representative samples generated from a single center constitute some limitations that may have caused additional heterogeneity. Certainly, the observed

heterogeneity could be attributable to differences in behavioral factors, the country of origin, and methodological factors concerning the study design.

This is the only meta-analysis that has reported association of SBPV and the risk of stroke. In the past, systematic reviews on the association of SBPV and stroke have been published[28], but the number of samples and the total number of studies were smaller (n=8) than those in our present meta-analysis. As such, these past studies may have been insufficient to achieve statistical significance, may not have made a detailed stratified analysis, and did not carry out publication-bias and stratification analysis. Past reviews mainly described the relationship between SBPV and cardiovascular disease, while our present analysis was mainly focused on the relationship between stroke and SBPV.

The mechanism by which abnormal SBPV leads to target organ damage may be attributed to direct damage to the vascular endothelium, activation of the renin-angiotensin system (RAS), activation of inflammatory responses, greater BPV, and more substantial damage to the heart and brain[29]. Taken together, an increase in VVV in SBP seems to be a sign of many cardiovascular and cerebrovascular diseases, and some articles reported that variability in pulse pressure (but not diastolic blood pressure or SBP) is associated with a long-term risk of stroke[24]. In addition, BP variability contributes to the development of hemorrhagic transformation following acute ischemic stroke. Therefore, visit-to-visit BPV has received considerable attention recently, and our present study further describes the important role of SBPV in stroke.

There are several limitations in the current study. First, dynamic blood-pressure monitoring has found that human blood pressure has circadian fluctuations. Most daytime diastolic blood pressure is higher than the lowest point of night systolic blood pressure, and the average difference between daytime and nighttime systolic and diastolic BPs is 10%–20%[30]. As such, differences in the time points of blood-pressure measurements may lead to biases in results. Second, methodological factors—including different regions, number of visits, time intervals between visits, duration of follow-ups, measurement indicators, and assessments provided by different doctors—may have affected the VVV of BP outcomes. Third, some of the included studies on the assessment standards of SBP of variability were not detailed. Moreover, the included studies did not analyze the complications, morbidity, mortality, and hemorrhagic transformations of stroke.

The results of our present study also suggest that the treatment of hypertension should not only control blood pressure levels, but also prevent abnormal fluctuations in blood pressure to restore normal rhythms of blood pressure. In future clinical work, clinicians could monitor the degree of SBPV in clinical patients. However, few studies have been reported on BPV, so there are no recognized diagnostic criteria or normal reference values, which limits its guiding significance for current clinical practice. As such, more clinical studies are needed to investigate the safety of blood pressure variability and to determine more effective management of blood pressure variability in the clinic to reduce the incidence of stroke or other vascular events.

Taken together, this systematic review and meta-analysis demonstrated that VVV of SBP is an independent predictor of stroke incidence. In particular, patients with variability of blood pressure greater than five years have a greater risk of stroke than patients with a small baseline SBPV.

Acknowledgments

We acknowledge The First Affiliated Hospital of Nanchang University, The Affiliated Hospital of Jiujiang University and The Second Affiliated Hospital of Nanchang University for support in preparation of this report. We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

REFERENCES

1 Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 2012,380(9859):2095-2128

2 Shimbo D, Newman JD, Aragaki AK, *et al*. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. Hypertension, 2012,60(3):625-630

3 Gunewardene HO. The stroke in high arterial pressure: A study of 150 cases. Br Med J, 1932,1(3708):180-182

4 Hemphill JC, Greenberg SM, Anderson CS, *et al*. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Stroke, 2015,46(7):2032-2060

5 Pringle E, Phillips C, Thijs L, *et al*. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J Hypertens, 2003,21(12):2251-2257

6 Rothwell PM, Howard SC, Dolan E, *et al*. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet, 2010,375(9718):895-905

7 Yokota K, Sakurada T, Koitabashi K, *et al*. Association Between Residual Kidney Function and Visit-to-Visit Blood Pressure Variability in Peritoneal Dialysis Patients. Adv Perit Dial, 2015,31:49-53

8 Nagai M, Hoshide S, Nishikawa M, *et al*. Visit-to-visit

blood pressure variability in the elderly: associations with cognitive impairment and carotid artery remodeling. Atherosclerosis, 2014,233(1):19-26
9 Gondo K, Miura S, Suematsu Y, *et al*. Association Between Visit-to-Visit Variability in Blood Pressure and Cardiovascular Events in Hypertensive Patients After Successful Percutaneous Coronary Intervention. J Clin Med Res, 2015,7(7):545-550
10 Patel A, Macmahon S, Chalmers J, *et al*. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med, 2008,358(24):2560-2572
11 Tully P J, Debette S, Dartigues J F, *et al*. Antihypertensive Drug Use, Blood Pressure Variability, and Incident Stroke Risk in Older Adults: Three-City Cohort Study. Stroke, 2016,47(5):1194-1200
12 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA, 2000,283(15):2008-2012
13 Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011([http://www.cochrane-handbook.org]).
14 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg, 2010,8(5): 336-341
15 Wells G, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Http://Www.Ohri.Ca/Programs/Clinical_Epidemiology/Oxford.Asp.(http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
16 Yinon L, Chen Y, Parvez F, *et al*. A prospective study of variability in systolic blood pressure and mortality in a rural Bangladeshi population cohort. Prev Med, 2013,57(6):807-812
17 Mcmullan CJ, Lambers Heerspink HJ, *et al*. Visit-to-Visit Variability in Blood Pressure and Kidney and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Nephropathy: A Post Hoc Analysis From the RENAAL Study and the Irbesartan Diabetic Nephropathy Trial. Am J Kidney Dis, 2014,64(5):714-722
18 Lau KK, Wong YK, Chan YH, *et al*. Visit-to-visit blood pressure variability as a prognostic marker in patients with cardiovascular and cerebrovascular diseases--relationships and comparisons with vascular markers of atherosclerosis. Atherosclerosis, 2014,235(1):230-235
19 Gao S, Hendrie HC, Wang C, *et al*. Redefined Blood Pressure Variability Measure and Its Association With Mortality in Elderly Primary Care Patients. Hypertension, 2014,64(1):45-52
20 Muntner P, Whittle J, Lynch AI, *et al*. Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality: A Cohort Study. Ann Intern Med, 2015,163(5):329-338
21 Men X, Sun W, Fan F, *et al*. China Stroke Primary Prevention Trial: Visit-to-Visit Systolic Blood Pressure Variability Is an Independent Predictor of Primary Stroke in Hypertensive Patients. J Am Heart Assoc, 2017,6(3):e4350
22 Chang TI, Tabada GH, Yang J, *et al*. Visit-to-visit variability of blood pressure and death, end-stage renal disease, and cardiovascular events in patients with chronic kidney disease. J Hypertens, 2016,34(2):244-252
23 Dai H, Lu Y, Song L, *et al*. Visit-to-visit Variability of Blood Pressure and Risk of Stroke: Results of the Kailuan Cohort Study. Sci Rep, 2017,7(1):285-286
24 Poortvliet RK, Ford I, Lloyd SM, *et al*. Blood pressure variability and cardiovascular risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One, 2012,7(12):e52438
25 Schutte R, Thijs L, Liu YP, *et al*. Within-subject blood pressure level--not variability--predicts fatal and nonfatal outcomes in a general population. Hypertension, 2012,60(5):1138-1147
26 Hata J, Arima H, Rothwell PM, *et al*. Effects of Visit-to-Visit Variability in Systolic Blood Pressure on Macrovascular and Microvascular Complications in Patients With Type 2 Diabetes Mellitus: The ADVANCE Trial. Circulation, 2013,128(12):1325-1334
27 Suchy-Dicey AM, Wallace ER, Mitchell SV, *et al*. Blood pressure variability and the risk of all-cause mortality, incident myocardial infarction, and incident stroke in the cardiovascular health study. Am J Hypertens, 2013,26(10):1210-1217
28 Wang J, Shi X, Ma C, *et al*. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease. J Hypertens, 2017,35(1):10-17
29 Ko Y, Park JH, Yang MH, *et al*. The significance of blood pressure variability for the development of hemorrhagic transformation in acute ischemic stroke. Stroke, 2010,41(11):2512-2518
30 Sheng YC, Wang K, Xu L, *et al*. A cyclic fluctuation model for 24-h ambulatory blood pressure monitoring in Chinese patients with mild to moderate hypertension. Acta Pharmacol Sin, 2013,8(34):1043-1051

(Received Dec. 1, 2018; revised July 20, 2019)