

Night-time diastolic blood pressure variability relates to stroke recurrence in patients who had ischaemic stroke with small artery occlusion

Tingting Wang ¹, Jie Xu ^{1,2}, Anxin Wang ^{1,2}, Ying Liu,¹ Xingquan Zhao,^{1,2} Yongjun Wang,^{1,2} Yilong Wang^{1,2}

To cite: Wang T, Xu J, Wang A, *et al.* Night-time diastolic blood pressure variability relates to stroke recurrence in patients who had ischaemic stroke with small artery occlusion. *Stroke & Vascular Neurology* 2022;**7**:e000718. doi:10.1136/svn-2020-000718

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/svn-2020-000718>).

Received 17 November 2020
Accepted 10 August 2021
Published Online First
30 November 2021



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

²China National Clinical Research Center for Neurological Diseases, Beijing, China

Correspondence to

Dr Yilong Wang;
yilongwang528@163.com

ABSTRACT

Background and purpose The association between blood pressure variability (BPV) and stroke recurrence among patients who had ischaemic stroke (IS) remains unclear. This study aimed to investigate the association between BPV and stroke recurrence in patients who had IS of large artery atherosclerosis (LAA) subtype and small artery occlusion (SAO) subtype.

Methods Data from the BOSS (Blood Pressure and Clinical Outcome in Transient Ischemic Attack or Ischemic Stroke) study were examined. IS subtypes were diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment criteria. BPV was performed by 24-hour ambulatory blood pressure monitoring and defined through SD of blood pressure. The primary outcome was stroke recurrence within 90 days after discharge. Multivariable Cox regression model was used to assess the association between BPV and stroke recurrence in patients who had IS of LAA subtype and SAO subtype.

Results A total of 1390 patients who had IS from the BOSS study were included in the present study. Multivariable analysis suggests that 24-hour systolic BPV (SBPV) and night-time diastolic BPV (DBPV) were significantly associated with stroke recurrence among all patients who had IS (HR, 2.50, 95% CI 1.07 to 5.84; HR, 1.85, 95% CI 1.07 to 3.21, respectively). Night-time SBPV and night-time DBPV were significantly associated with stroke recurrence in patients with SAO subtype (HR, 2.77, 95% CI 1.07 to 7.15; HR, 3.60, 95% CI 1.39 to 9.29, respectively). However, in the adjusted model, only night-time DBPV remained significant in patients with SAO subtype (HR, 3.87, 95% CI 1.40 to 10.71). Similar results were not found in patients who had IS of LAA subtype.

Conclusions High night-time DBPV was associated with increased risk of stroke recurrence among patients who had IS of SAO subtype. The results of this study have implications for the secondary prevention management and future research of patients who had IS of SAO subtype. The association between BPV and stroke recurrence in patients who had IS of LAA subtype and SAO subtype should be investigated in larger, population-based studies.

INTRODUCTION

Large artery atherosclerosis (LAA) and small artery occlusion (SAO) are the main aetiological subtypes of ischaemic stroke (IS)

according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.¹ The incidence rate and recurrence rate of stroke are both high in the two subtypes,² but much higher in the LAA subtype.³ Hypertension is an independent risk factor for incidence of stroke and possibly a potential risk factor for recurrence of stroke among patients who had IS. Previous studies showed that high blood pressure (BP) was associated with stroke recurrence in patients with SAO subtype rather than LAA subtype or other subtypes,⁴ and suggested that the high BP might have different effects on the pathogenesis of large artery and small artery diseases.

Most studies used mean BP as the index factor to predict the incidence or recurrence rate of stroke.⁵ However, BP shows noticeable fluctuation over the short and long term, and mean BP may not be able to reflect the stability of BP.⁶ Although blood pressure variability (BPV) was historically viewed as a phenomenon that could affect the accuracy of mean BP, it has been increasingly recognised as a potential risk factor for future strokes and coronary events in recent decades, the predictive capacity of which showed even better than the mean BP.^{7–15}

The aim of the present study was to investigate the association between BPV and stroke recurrence in patients who had IS of LAA subtype and SAO subtype. We hope to find the different effects of BPV on stroke recurrence in patients with LAA subtype and SAO subtype and to provide implications for targeted management of BP for patients who had IS with large artery and small artery diseases.

METHODS

Study population

The BOSS (Blood Pressure and Clinical Outcome in Transient Ischemic Attack or

Ischemic Stroke) study was a hospital-based, prospective cohort study designed to assess the association between BP parameters and clinical outcomes of IS and transient ischaemic attack (TIA). It was conducted in 61 mainly tertiary urban hospitals from 16 provinces and 4 municipalities evenly distributed across the mainland of China. A total of 2608 patients who had IS and patients with TIA (≥ 18 years) were enrolled consecutively in this registry within 7 days after index events. The methods and the main results have been published previously.¹⁶ The present study was a post-hoc analysis of the BOSS study. In the current study, we included participants in the BOSS study who were diagnosed with IS according to the WHO criteria¹⁷ and were successfully classified as LAA subtype or SAO subtype according to the TOAST criteria.¹

Written informed consent was obtained from all patients or their legal proxies before participation.

Ambulatory blood pressure monitoring and BPV

A 24-hour ambulatory blood pressure monitoring (ABPM) was performed within 3–14 days after the index events. Measurements were taken every 15 min during the day (06:00–21:59) and every 30 min at night (22:00–05:59). Patients could take normal daily activities during daytime and go to bed and wake up at the prescribed time. BP recorded readings exceeding 75% of the expected measurements were considered for analysis according to the European Society of Hypertension guideline.¹⁸

Daytime BPV and night-time BPV were calculated through SD of the daytime and night-time periods. The 24-hour BPV was identified by weighted 24-hour SD (w24hSD) according to the following formula^{19,20}:

$$w24hSD = \frac{\text{daytime SD} \times 16 + \text{nighttime SD} \times 8}{24}$$

where 16 and 8 were the number of hours included in the daytime and night-time subperiods, respectively.

Classification of stroke subtypes

All patients diagnosed with IS were further classified according to the TOAST criteria.² The specific standards and methods of classification were performed as described previously.^{4,21} Subtype classification was based on the patient's clinical features and was combined with at least one diagnostic test, including brain imaging examination (CT or MRI), imaging of intracranial arteries (magnetic resonance angiography) and extracranial arteries (carotid ultrasonography or CT angiography), as well as laboratory tests for the diagnosis of prethrombotic state. All patients' clinical features and results of diagnostic tests were reviewed by at least two trained neurologists from each participating hospital, who finally made the decision on the subtype classification.

Covariables

Clinical information was collected by trained investigators or research coordinators at enrolment and follow-up visits. Risk factors for stroke such as medical history (including IS, TIA, myocardial infarction, congestive heart failure, known atrial fibrillation or flutter, hypertension, diabetes

mellitus and dyslipidaemia) and lifestyle (including smoking and drinking) were recorded on admission. The presence of IS, TIA, myocardial infarction and congestive heart failure was defined as a medical chart-confirmed history. The presence of hypertension, diabetes mellitus and dyslipidaemia was defined as self-reported disease history or a patient who was on antihypertensive, antidiabetic or lipid-lowering medication. Atrial fibrillation or flutter was defined as a reported history of atrial fibrillation or flutter, or diagnosed by the in-hospital ECG. Current smoker was defined as those who reported smoking at the index of the event. Former smoker was defined as those who quit smoking within 1 year. Moderate or heavy drinking was defined as consuming at least two standard alcoholic beverages per day. The severity of stroke was assessed using National Institutes of Health Stroke Scale score on admission. Secondary prevention medications (including antiplatelet, antihypertensive, antidiabetic and lipid-lowering treatments) were recorded during hospitalisation.

Clinical outcome

The primary outcome of this study was stroke recurrence within 90 days after discharge. Stroke recurrence was defined as a new stroke (including IS and haemorrhagic stroke) after the index event.²² The new clinical manifestations were not due to oedema, haemorrhagic transformation or other intracranial complications. The new symptoms should last more than 24 hours and there was evidence of a new stroke on MRI or CT brain imaging. At 90-day follow-up after discharge, patients were asked whether they had experienced hospital readmission due to the new symptoms. Hospitals admitting patients with recurrent stroke were connected to verify the diagnosis.

Statistical analysis

In this study, the SD of BP was considered a categorical variable and the optimal cut-off value was identified through 90-day receiver operating curve analysis.⁹ High BPV (HBPV) was defined as those whose SD of BP was higher than the optimal cut-off values. Patients enrolled in this study were divided into two groups according to the status of HBPV (with and without HBPV). Each group was then stratified by TOAST subtypes. For descriptive analysis, categorical variables were described by frequencies and percentages, and continuous variables were described by mean with SD. For baseline characteristics, χ^2 test was used for categorical variables and Kruskal-Wallis test was used for continuous variables to compare the differences between patients with LAA subtype and SAO subtype. χ^2 test and multivariable Cox regression model were used to investigate the association between BPV and risk of stroke recurrence, stratified by LAA subtype and SAO subtype. The Cox model was adjusted for potential confounders including age, gender, severity of stroke, history of TIA, lifestyle (including smoking and drinking) and corresponding average BP. These confounders were significant in the univariate analysis between confounders and

recurrent stroke events (online supplemental file), or were potential confounders of stroke recurrence according to previous studies.²³ The proportional hazards assumption was assessed by testing the interaction between BPV and time. Unadjusted and adjusted HRs with 95% CIs were both reported. A two-tailed probability value of <0.05 was considered significant in the univariate and multivariable analyses. Analyses of this study used SAS V.9.4.

RESULTS

Baseline characteristics

Of 2608 patients enrolled in the BOSS study, 840 who recorded less than 75% of the expected measurements of ABPM were excluded. Another 378 patients were also excluded, including 290 patients diagnosed with TIA, 18 patients who had IS who failed to be classified by TOAST subtypes and 70 patients classified as cardiogenic embolism subtype or others. Finally, a total of 1390 patients who had IS were included in the present analysis, including 860 patients with LAA subtype and 530 patients with SAO subtype. The mean number of ABPM was 71.1 ± 9.9 for 24 hours, 55.3 ± 10.5 for daytime and 15.8 ± 5.7 for night-time. The baseline characteristics of the included patients are presented in table 1 according to TOAST subtypes. Patients with SAO subtype were a little younger than those with LAA subtype. Besides, the rate of hypertension was higher in patients with LAA subtype than those with SAO subtype.

Association between BPV and stroke recurrence in patients who had IS of LAA subtype and SAO subtype

The optimal cut-off values calculated through SD were used to separate patients with and without HBPV. For systolic BP, the optimal cut-off values for 24 hours, night-time and daytime were 12.5 mm Hg, 14.5 mm Hg and 16.5 mm Hg. For diastolic BP, the corresponding values were 14.0 mm Hg, 11.5 mm Hg and 7.5 mm Hg. The rate of stroke recurrence in all patients was 3.8%, in patients with LAA subtype was 4.1% and in patients with SAO subtype was 3.4%.

Table 2 shows the results of the univariate analysis on the association between BPV and stroke recurrence in patients who had IS of LAA subtype and SAO subtype. For all patients, the rates of stroke recurrence were different between patients with and without high 24-hour systolic BPV (SBPV) and night-time diastolic BPV (DBPV) ($p=0.02$ and $p=0.02$, respectively). After stratification by TOAST subtypes, the rates of stroke recurrence in patients with high night-time SBPV and night-time DBPV were significantly higher than those without corresponding HBPV in SAO subtype ($p=0.02$ and $p=0.002$, respectively). Similar results were not found in patients with LAA subtype.

At the same time, we used multivariable Cox regression model to investigate the association between BPV and stroke recurrence in patients with LAA subtype and SAO subtype, in which BPV was entered as a dichotomous variable. For all patients, the high 24-hour SBPV and high

night-time DBPV showed significant trends of association with increased risk of stroke recurrence (HR, 2.50, 95% CI 1.07 to 5.84, $p=0.03$; HR, 1.85, 95% CI 1.07 to 3.21, $p=0.03$, respectively). However, after stratification by TOAST subtypes, the association between BPV and stroke recurrence was only found during night-time, and the association was only found in patients with SAO subtype (for SBPV: HR, 2.77, 95% CI 1.07 to 7.15, $p=0.04$; for DBPV: HR, 3.60, 95% CI 1.39 to 9.29, $p=0.008$). After adjusting for potential confounders, including age, gender, severity of stroke, history of TIA, lifestyle (including smoking and drinking) and corresponding average BP, only in patients with SAO subtype was BPV associated with stroke recurrence and only night-time DBPV remained associated with stroke recurrence (HR, 3.87, 95% CI 1.40 to 10.71, $p=0.01$). The above data suggest that when DBPV was high at night (SD of night-time DBP >11.5 mm Hg), the risk of stroke recurrence might increase by 287% in patients with SAO subtype. However, similar results were not found in patients with LAA subtype. Unadjusted and adjusted HRs with 95% CIs are listed in table 3. Figure 1 shows the Kaplan-Meier curves of the association between night-time BPV and risk of stroke recurrence among patients who had IS of SAO subtype and LAA subtype.

DISCUSSION

In the present study, we found that 24-hour SBPV and night-time DBPV were associated with stroke recurrence in all patients who had IS. Night-time SBPV and night-time DBPV were associated with stroke recurrence in patients who had IS of SAO subtype. However, after adjusting for several traditional risk factors and potential confounders, only night-time DBPV was found to be associated with stroke recurrence in patients who had IS of SAO subtype. The results of this study suggest that high night-time DBPV assessed through 24-hour ABPM might be a predictor of a recurrent stroke in patients who had IS of SAO subtype.

Comparison with other studies

Several prospective studies including populations and patients with hypertension or diabetes have searched for the association between BPV and stroke outcomes but reported inconsistent results.^{24–29} The post-hoc analysis of the Syst-Eur (Systolic hypertension in Europe) trial found that only increased night-time SBPV was an independent risk factor for stroke incidence in an elderly population with hypertension.²⁴ However, the results of the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study found that the rate of cerebrovascular events was higher in patients with hypertension with increased SBPV or DBPV during daytime or night-time than in those with low BPV.²⁵ However, a meta-analysis of individual data from the IDACO (International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome) study, which included >8000 people randomly recruited from 11 populations and covered on average

Table 1 Baseline characteristics of patients with different TOAST subtypes

Variate	All N=1390	LAA n=860	SAO n=530	P value
Age, years	62.5±10.5	63.0±10.2	61.7±11.0	0.0102
Male, n (%)	960 (69.1)	606 (70.5)	354 (66.8)	0.1522
BMI, kg/m ²	24.9±3.6	24.9±3.9	25.0±2.9	0.1199
24-hour heart rate, bpm	70.4±9.5	70.4±9.4	70.6±9.6	0.5566
24-hour average BP				
SBP, mm Hg	143.0±17.8	143.3±17.7	142.5±18.0	0.4809
DBP, mm Hg	84.8±13.2	84.5±13.0	85.3±13.5	0.2896
Daytime average BP				
SBP, mm Hg	144.2±17.9	144.5±17.8	143.8±18.0	0.4904
DBP, mm Hg	85.8±13.6	85.5±13.5	86.4±13.9	0.1887
Night-time average BP				
SBP, mm Hg	138.7±20.2	139.1±20.1	138.0±20.2	0.4591
DBP, mm Hg	81.2±13.5	81.1±13.3	81.3±13.8	0.9586
NIHSS score on admission, n (%)				< 0.0001
≤4	1053 (75.8)	607 (70.6)	446 (84.2)	
5–15	327 (23.5)	245 (28.5)	82 (15.5)	
>15	10 (0.7)	8 (0.9)	2 (0.4)	
Medical history, n (%)				
Ischaemic stroke	327 (23.5)	206 (24.0)	121 (22.8)	0.6490
Transient ischaemic attack	29 (2.1)	22 (2.6)	7 (1.3)	0.2930
Myocardial infarction	31 (2.2)	23 (2.7)	8 (1.5)	0.1911
Congestive heart failure	9 (0.7)	6 (0.7)	3 (0.6)	0.5154
Known atrial fibrillation or flutter	17 (1.2)	11 (1.3)	6 (1.1)	0.6843
Hypertension	985 (70.9)	620 (72.2)	365 (68.9)	0.0480
Diabetes mellitus	317 (22.9)	213 (24.8)	104 (19.7)	0.0890
Dyslipidaemia	135 (9.7)	93 (10.8)	42 (7.9)	0.1868
Current or former smoker	620 (44.6)	387 (45.0)	233 (44.0)	0.7390
Moderate or heavy drinking	532 (38.3)	329 (38.3)	203 (38.3)	1.0000
Secondary prevention, n (%)				
Antiplatelet	266 (19.2)	163 (19.0)	103 (19.4)	0.8142
Antihypertensive	762 (54.9)	479 (55.8)	283 (53.4)	0.1994
Lipid-lowering	140 (10.1)	83 (9.7)	57 (10.8)	0.7850
Antidiabetic	265 (19.1)	175 (20.4)	90 (17.0)	0.0577

Data shown as mean±SD or frequency (percentage).

P values are related to the comparison between LAA subtype and SAO subtype.

BMI, body mass index; BP, blood pressure; bpm, beats per minute; DBP, diastolic blood pressure; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SAO, small artery occlusion; SBP, systolic blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

11 years of follow-up, suggested that 24-hour SBPV and 24-hour DBPV were associated with a fatal or non-fatal stroke; similar results were not found for daytime or night-time BPV.²⁸ These studies included different subjects with or without treatment and there were various BPV devices used, which limited the interpretation of the results. In addition, in these studies, no results were provided for risk of stroke recurrence in patients who had IS. To assess the association between BPV and risk of stroke recurrence, we used 24-hour ABPM to measure BPV in patients who had IS and finally found that high night-time DBPV

was associated with increased risk of stroke recurrence among patients who had IS of SAO subtype, which might be a novel finding. The results of the study suggested that night-time DBPV might play an important role in the prognosis of small artery diseases.

Potential mechanisms

Several possible reasons had been presented in previous studies to explain why BPV during night was more predictive than daytime BPV; for example, nocturnal monitoring could exclude the external interference and avoid

Table 2 Comparison of stroke recurrence rates in patients who had IS with and without HBPV, stratified by TOAST subtypes

BP items	BP SD (mm Hg)	All		LAA		SAO	
		Patients with events/total patients, n/N (%)	P value	Patients with events/total patients, n/N (%)	P value	Patients with events/total patients, n/N (%)	P value
24 hours	SBP SD \geq 12.5	47/1047 (4.5)	0.02	31/647 (4.8)	0.06	16/400 (4.0)	0.18
	SBP SD <12.5	6/343 (1.8)		4/213 (1.9)		2/130 (1.5)	
	DBP SD \geq 14.0	16/294 (5.4)	0.10	9/167 (5.4)	0.34	7 (5.5)	0.13
	DBP SD <14.0	37/1096 (3.4)		26/693 (3.8)		11 (2.7)	
Night-time	SBP SD \geq 14.5	23/451 (5.1)	0.08	12/264 (4.6)	0.64	11/187 (5.9)	0.02
	SBP SD <14.5	30/939 (3.2)		23/596 (3.9)		7/343 (2.0)	
	DBP SD \geq 11.5	21/361 (5.8)	0.02	10/207 (4.8)	0.52	11/154 (7.1)	0.002
	DBP SD <11.5	32/1029 (3.1)		25/653 (3.8)		7/376 (1.9)	
Daytime	SBP SD \geq 16.5	24/461 (5.2)	0.06	16/282 (5.7)	0.10	8/179 (4.5)	0.33
	SBP SD <16.5	29/929 (3.1)		19/578 (3.3)		10/351 (2.9)	
	DBP SD \geq 7.5	50/1198 (4.2)	0.08	33/734 (4.5)	0.13	17/464 (3.7)	0.37
	DBP SD <7.5	3/192 (1.6)		2/126 (1.6)		1/66 (1.5)	

P values are related to the comparison of patients with and without HBPV.

BP, blood pressure; DBP, diastolic blood pressure; HBPV, high blood pressure variability; IS, ischaemic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; SBP, systolic blood pressure; ; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Table 3 Association between BPV and stroke recurrence in patients who had IS, stratified by TOAST subtypes

Time	BP SD (mm Hg)	Stroke subtypes	Unadjusted HR (95% CI)	Unadjusted P value	Adjusted HR (95% CI)	Adjusted P value
24 hours	SBP SD \geq 12.5	All	2.50 (1.07 to 5.84)	0.03	1.88 (0.78 to 4.55)	0.16
		LAA	2.65 (0.93 to 7.50)	0.07	2.27 (0.76 to 6.78)	0.14
		SAO	2.29 (0.53 to 9.99)	0.27	1.51 (0.32 to 7.12)	0.60
	DBP SD \geq 14.0	All	1.65 (0.892 to 2.96)	0.10	1.41 (0.74 to 2.68)	0.30
		LAA	1.48 (0.69 to 3.17)	0.31	1.04 (0.45 to 2.42)	0.93
		SAO	2.08 (0.81 to 5.37)	0.13	2.05 (0.70 to 6.03)	0.19
Night-time	SBP SD \geq 14.5	All	1.64 (0.95 to 2.83)	0.07	1.37 (0.78 to 2.42)	0.27
		LAA	1.28 (0.63 to 2.57)	0.50	1.08 (0.52 to 2.26)	0.84
		SAO	2.77 (1.07 to 7.15)	0.04	1.95 (0.70 to 5.44)	0.20
	DBP SD \geq 11.5	All	1.85 (1.07 to 3.21)	0.03	1.70 (0.95 to 3.05)	0.07
		LAA	1.33 (0.64 to 2.77)	0.45	1.04 (0.48 to 2.25)	0.93
		SAO	3.60 (1.39 to 9.29)	0.008	3.87 (1.40 to 10.71)	0.01
Daytime	SBP SD \geq 16.5	All	1.67 (0.97 to 2.87)	0.06	1.53 (0.87 to 2.70)	0.14
		LAA	1.72 (0.88 to 3.34)	0.11	1.66 (0.83 to 3.32)	0.15
		SAO	1.56 (0.61 to 3.96)	0.35	0.98 (0.33 to 2.84)	0.96
	DBP SD \geq 7.5	All	2.75 (0.86 to 8.83)	0.09	2.50 (0.76 to 8.23)	0.13
		LAA	3.02 (0.72 to 12.58)	0.13	3.03 (0.70 to 13.20)	0.14
		SAO	2.54 (0.34 to 19.15)	0.37	2.26 (0.29 to 17.80)	0.44

P values are related to the comparison of patients with and without HBPV.

BP, blood pressure; BPV, blood pressure variability; DBP, diastolic blood pressure; HBPV, high blood pressure variability; IS, ischaemic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; SBP, systolic blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

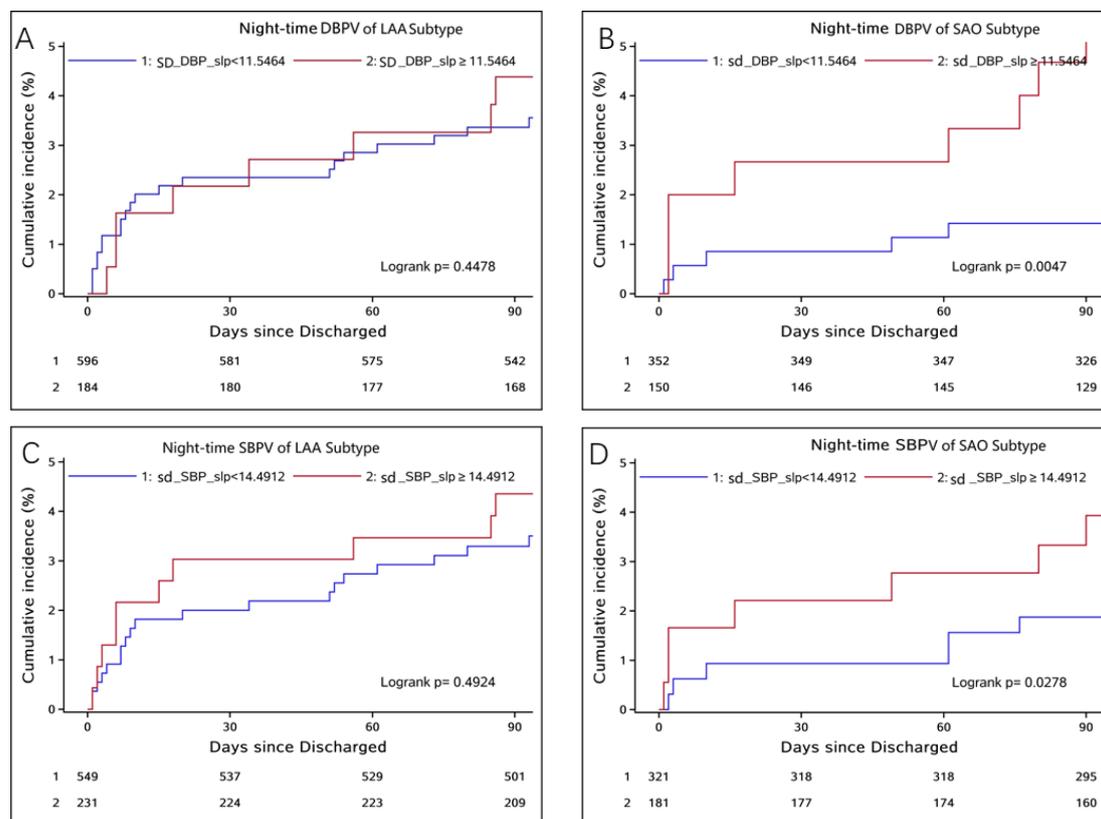


Figure 1 Relations between night-time BPV and risk of stroke recurrence among patients who had IS of SAO subtype and LAA subtype. (A) High night-time DBPV of LAA subtype was not related to increased risk of stroke recurrence. (B) High night-time DBPV of SAO subtype was significantly related to increased risk of stroke recurrence. (C) High night-time SBPV of LAA subtype was not related to increased risk of stroke recurrence. (D) High night-time SBPV of SAO subtype was significantly related to increased risk of stroke recurrence before adjusting for corresponding confounders and potential risk factors. BPV, blood pressure variability; DBP, diastolic blood pressure; DBPV, diastolic blood pressure variability; IS, ischaemic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; SBP, systolic blood pressure; SBPV, systolic blood pressure variability.

the persistent hyperactivity of sympathetic nerve system. The underlying mechanisms whereby BPV is related to stroke recurrence in SAO subtype are largely unknown. Reasonable explanations can only be speculated. HBPV represents increased fluctuation of blood flow, which could dampen smooth blood flow to small arteries, resulting in less perfusion of the arterioles.^{30–31} At the same time, increased BPV could inhibit nitric oxide production, which might impair endothelial function and damage the blood–brain barrier as well as the ‘neurovascular unit’.^{32–33} For small vessels which had already been damaged, the above potential mechanisms could further destroy their structure and function, which could result in the dysfunction of autoregulation of cerebral blood flow and thereby increase the risk of a recurrent stroke.³⁴ For example, when BP is below the lower threshold of cerebral blood flow autoregulation, hypotension would happen and result in IS. Inversely, when BP exceeds the upper threshold, hypertension would lead to haemorrhagic stroke. Heart is perfused during diastole. Meanwhile, high DBPV might influence the ventricular end diastolic volume, which could lead to extreme cerebral perfusion, especially in patients with destroyed autoregulation of cerebral blood flow.

Strengths and limitations

To our knowledge, this is the first study to investigate the association between BPV and stroke recurrence in patients who had IS of different TOAST subtypes. We found that high night-time DBPV was associated with increased risk of stroke recurrence in patients who had IS of SAO subtype. Moreover, we collected detailed clinical features at enrolment so that we could realise to account for several potential confounders. However, there were several limitations to our study. First, the sample size was relatively small in each TOAST subtype, which was responsible for the lower statistical power in this study. Second, the ABPM devices were not unified among all participating hospitals. Although internal monitoring, duration, qualified recording numbers and other parameters required were the same, the quality of monitoring was not guaranteed, which might have influenced the analysis of data. Third, we used SD to calculate BPV in our study. Other metrics used to calculate BPV, such as average real variability or successive variation, were also demonstrated to be effective in predicting the outcomes. However, these measures were complicated and the correlation coefficients were more than 0.83.³⁵ In contrast, SD is easier to obtain and more practical and we believe it

will have greater value in clinical application. Fourth, although we have accounted for the most important potential confounders in our study, we could not exclude unknown and residual confounding factors cannot be completely excluded as explanations for the results.

CONCLUSIONS

High night-time DBPV calculated through 24-hour ABPM was associated with increased risk of stroke recurrence among patients who had IS of SAO subtype. This association was independent of average night-time DBP. The results of this study suggest that, compared with SBPV, night-time DBPV might play a more important role in the prognosis of small artery diseases. The secondary prevention of patients who had IS of SAO subtype might pay more attention to the management of night-time DBPV. The association between BPV and stroke recurrence in patients who had IS with large artery and small artery diseases should be investigated in larger, population-based studies.

Contributors TW: study concept and design, analysis and interpretation of data, drafting of the manuscript. JX: analysis and interpretation of data, drafting of the manuscript. AW: analysis and interpretation of data. YL: revision of the manuscript. XZ: study concept and design, study supervision. YoW: study concept and design, obtaining funding, study supervision. YiW: study concept and design, study supervision, analysis and interpretation of data, clinical revision of the manuscript for intellectual content.

Funding The study was funded by grants from the National Key R&D Program of China (no. 2018YFC1312400, 2018YFC1312402), the Ministry of Science and Technology of the Beijing Outstanding Young Scientist Program (BJJWZYJH01201910025030), the National Natural Science Foundation of China (no. 81825007), the 'Thirteenth-Five' Key Development and Research Plan by the Ministry of Science and Technology of the People's Republic of China (no. 2017YFC1307900), and Supporting-Top Youth Team by Beijing Municipal Science and Technology Commission (no. 2016000021223TD03).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the central institutional review boards of Beijing Tiantan Hospital. Written informed consent was obtained from all patients or their legal proxies before participation. The ethics approval number was KYSB2017-084-01.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The corresponding author is responsible for the data in this study. Anyone wishing to access the data has to obtain the consent of the corresponding author.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Tingting Wang <http://orcid.org/0000-0002-3809-2209>

Jie Xu <http://orcid.org/0000-0002-8320-218X>

Anxin Wang <http://orcid.org/0000-0003-4351-2877>

REFERENCES

- Adams HP, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. TOAST. trial of ORG 10172 in acute stroke treatment. *Stroke* 1993;24:35–41.
- Hart RG, Diener H-C, Coultts SB, *et al*. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429–38.
- Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology* 2004;62:569–73.
- Wang Y, Xu J, Zhao X, *et al*. Association of hypertension with stroke recurrence depends on ischemic stroke subtype. *Stroke* 2013;44:1232–7.
- Lewington S, Clarke R, Qizilbash N, *et al*. Age-Specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.
- Grassi G, Bombelli M, Brambilla G, *et al*. Total cardiovascular risk, blood pressure variability and adrenergic overdrive in hypertension: evidence, mechanisms and clinical implications. *Curr Hypertens Rep* 2012;14:333–8.
- Rothwell PM, Howard SC, Dolan E, *et al*. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375:895–905.
- Webb AJS, Mazucco S, Li L, *et al*. Prognostic significance of blood pressure variability on beat-to-beat monitoring after transient ischemic attack and stroke. *Stroke* 2018;49:62–7.
- Palatini P, Saladini F, Mos L, *et al*. Short-Term blood pressure variability outweighs average 24-h blood pressure in the prediction of cardiovascular events in hypertension of the young. *J Hypertens* 2019;37:1419–26.
- Arashi H, Ogawa H, Yamaguchi J-I, *et al*. Impact of visit-to-visit variability and systolic blood pressure control on subsequent outcomes in hypertensive patients with coronary artery disease (from the HIJ-CREATE substudy). *Am J Cardiol* 2015;116:236–42.
- Stevens SL, Wood S, Koshiaris C, *et al*. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016;354:i4098.
- 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;163:329–38.
- Geeganage C, Tracy M, England T, *et al*. Relationship between baseline blood pressure parameters (including mean pressure, pulse pressure, and variability) and early outcome after stroke: data from the Tinzaparin in acute ischaemic stroke trial (TAIST). *Stroke* 2011;42:491–3.
- Kim BJ, Kwon SU, Wajsbrodt D, *et al*. Relationship of inter-individual blood pressure variability and the risk for recurrent stroke. *J Am Heart Assoc* 2018;7:e009480.
- Filomena J, Riba-Llena I, Vinyoles E, *et al*. Short-Term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension* 2015;66:634–40.
- Xu J, Liu Y, Tao Y, *et al*. The design, rationale, and baseline characteristics of a nationwide cohort registry in China: blood pressure and clinical outcome in TIA or ischemic stroke. *Patient Prefer Adherence* 2016;10:2419–27.
- Stroke-1989. recommendations on stroke prevention, diagnosis, and therapy. *Report of the WHO task force on stroke and other cerebrovascular disorders*. *Stroke* 1989;20:1407–31.
- Parati G, Stergiou G, O'Brien E, *et al*. European Society of hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014;32:1359–66.
- Bilo G, Giglio A, Styczkiewicz K, *et al*. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 2007;25:2058–66.
- Palatini P, Reboldi G, Beilin LJ, *et al*. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the ambulatory blood Pressure-International study. *Hypertension* 2014;64:487–93.
- Amarenco P, Lavallée PC, Labreuche J, *et al*. One-Year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med* 2016;374:1533–42.
- Hicks KA, Tchong JE, Bozkurt B, *et al*. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American heart association Task force on clinical data standards (writing Committee to develop cardiovascular endpoints data standards). *J Am Coll Cardiol* 2015;66:403–69.
- Flach C, Muruet W, Wolfe CDA, *et al*. Risk and secondary prevention of stroke recurrence: a population-base cohort study. *Stroke* 2020;51:2435–44.
- 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;21:2251–7.



- 25 Verdecchia P, Angeli F, Gattobigio R, *et al.* Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am J Hypertens* 2007;20:154–61.
- 26 Ozawa M, Tamura K, Okano Y, *et al.* Identification of an increased short-term blood pressure variability on ambulatory blood pressure monitoring as a coronary risk factor in diabetic hypertensives. *Clin Exp Hypertens* 2009;31:259–70.
- 27 Eguchi K, Ishikawa J, Hoshida S, *et al.* 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.
- 28 Hansen TW, Thijs L, Li Y, *et al.* Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 2010;55:1049–57.
- 29 Nakanishi K, Jin Z, Homma S, *et al.* Night-Time systolic blood pressure and subclinical cerebrovascular disease: the cardiovascular abnormalities and brain lesions (CABL) study. *Eur Heart J Cardiovasc Imaging* 2019;20:765–71.
- 30 Russell RW. How does blood-pressure cause stroke? *Lancet* 1975;2:1283–5.
- 31 Mitchell GF, van Buchem MA, Sigurdsson S, *et al.* Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 2011;134:3398–407.
- 32 Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 2006;7:41–53.
- 33 Iadecola C, Duering M, Hachinski V, *et al.* Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2019;73:3326–44.
- 34 Strandgaard S, Olesen J, Skinhoj E, *et al.* Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* 1973;1:507–10.
- 35 Vidal-Petiot E, Ford I, Greenlaw N, *et al.* Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016;388:2142–52.

Supplement

Table S1 Baseline Characteristics Among Patients with or without Recurrent Stroke Events

Variate	ALL (N=1390)	Stroke (N=53)	None stroke (N=1337)	P value
Age, years	62.5±10.5	64.1±10.4	62.4±10.5	0.22
Male, No. (%)	960 (69.1)	38 (71.7)	922 (69.0)	0.67
BMI, kg/m²	24.9±3.6	25.4±3.3	24.9±3.6	0.20
24h-heart rate, bpm	70.4±9.5	72.4±11.6	70.4±9.4	0.28
24-hour average BP				
SBP, mmHg	143.0±17.8	150.7±16.6	142.7±17.8	0.002
DBP, mmHg	84.8±13.2	87.9±13.4	84.6±13.1	0.07
Daytime average BP				
SBP, mmHg	144.2±17.9	151.3±16.4	143.9±19.9	0.004
DBP, mmHg	85.8±13.6	88.5±13.5	88.5±13.5	0.13
Night-time average BP				
SBP, mmHg	138.7±20.2	148.6±20.3	138.3±20.1	0.001
DBP, mmHg	81.2±13.5	86.1±14.6	81.0±13.4	0.02
NIHSS score at admission,				0.002
No. (%)				
≤4	1053 (75.8)	30 (56.6)	1023 (76.5)	
5-15	327 (23.5)	23 (43.4)	304 (22.7)	
> 15	10 (0.7)	0	10 (0.75)	
Medical history, No. (%)				
Ischemic stroke	327 (23.5)	16 (30.2)	311 (23.3)	0.24
Transient ischemic attack	29 (2.1)	1 (1.9)	28 (2.1)	0.01
Myocardial infarction	31 (2.2)	1 (1.9)	30 (2.2)	0.87
Hypertension	985 (70.9)	44 (83.0)	941 (70.4)	0.13
Diabetes mellitus	317 (22.9)	19 (35.9)	298 (22.3)	0.06
Dyslipidemia	135 (9.7)	9 (17.0)	126 (9.5)	0.07

Current or former smoker	620 (44.6)	20 (37.7)	600 (44.9)	0.31
Moderate or heavy drinking	532 (38.3)	16 (30.2)	516 (38.6)	0.22

Data shown as mean \pm SD or frequency (percentage).

Abbreviations: LAA, large-artery atherosclerosis; SAO, small-artery occlusion; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale.

The P values are related to comparison between patients with recurrent stroke events and patients without recurrent stroke events.

Supplement

Table S1 Baseline Characteristics Among Patients with or without Recurrent Stroke Events

Variate	ALL (N=1390)	Stroke (N=53)	None stroke (N=1337)	P value
Age, years	62.5±10.5	64.1±10.4	62.4±10.5	0.22
Male, No. (%)	960 (69.1)	38 (71.7)	922 (69.0)	0.67
BMI, kg/m²	24.9±3.6	25.4±3.3	24.9±3.6	0.20
24h-heart rate, bpm	70.4±9.5	72.4±11.6	70.4±9.4	0.28
24-hour average BP				
SBP, mmHg	143.0±17.8	150.7±16.6	142.7±17.8	0.002
DBP, mmHg	84.8±13.2	87.9±13.4	84.6±13.1	0.07
Daytime average BP				
SBP, mmHg	144.2±17.9	151.3±16.4	143.9±19.9	0.004
DBP, mmHg	85.8±13.6	88.5±13.5	88.5±13.5	0.13
Night-time average BP				
SBP, mmHg	138.7±20.2	148.6±20.3	138.3±20.1	0.001
DBP, mmHg	81.2±13.5	86.1±14.6	81.0±13.4	0.02
NIHSS score at admission,				0.002
No. (%)				
≤4	1053 (75.8)	30 (56.6)	1023 (76.5)	
5-15	327 (23.5)	23 (43.4)	304 (22.7)	
> 15	10 (0.7)	0	10 (0.75)	
Medical history, No. (%)				
Ischemic stroke	327 (23.5)	16 (30.2)	311 (23.3)	0.24
Transient ischemic attack	29 (2.1)	1 (1.9)	28 (2.1)	0.01
Myocardial infarction	31 (2.2)	1 (1.9)	30 (2.2)	0.87
Hypertension	985 (70.9)	44 (83.0)	941 (70.4)	0.13
Diabetes mellitus	317 (22.9)	19 (35.9)	298 (22.3)	0.06
Dyslipidemia	135 (9.7)	9 (17.0)	126 (9.5)	0.07

Current or former smoker	620 (44.6)	20 (37.7)	600 (44.9)	0.31
Moderate or heavy drinking	532 (38.3)	16 (30.2)	516 (38.6)	0.22

Data shown as mean \pm SD or frequency (percentage).

Abbreviations: LAA, large-artery atherosclerosis; SAO, small-artery occlusion; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale.

The P values are related to comparison between patients with recurrent stroke events and patients without recurrent stroke events.