ORIGINAL RESEARCH

China Stroke Primary Prevention Trial: Visit-to-Visit Systolic Blood Pressure Variability Is an Independent Predictor of Primary Stroke in Hypertensive Patients

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***Background*—**The optimal range of blood pressure variability remains unclear. We aimed to stratify the degree of risk of stroke based on visit-to-visit systolic blood pressure (SBP) variability in a large Chinese hypertensive population in 32 communities.

***Methods and Results*—**We retrospectively analyzed the data of 20 702 hypertensive patients from the China Stroke Primary Prevention Trial. The participants were randomized into 2 treatment groups to receive either enalapril or enalapril plus folic acid. Their blood pressures were measured every 3 months. The outcome was the first stroke. Three parameters of SBP variability were calculated: standard deviation, coefficient of variation, and average real variability. The records of first 4, 6, 8, 10 and 12 visits at which SBP was measured were used to calculate SBP variability and to predict subsequent stroke risk in adjusted Cox regression models. After median follow-up of 4.5 years, 597 patients had experienced stroke. Visit-to-visit SBP variability was an independent predictor of subsequent stroke (eg, the hazard ratio for the highest quintile of average real variability [22.67–61.07 mm Hg] over 6 visits was 1.55, 95% CI 1.07–2.25, P=0.021), independent of mean SBP over the follow-up period. Its value was more predictive when more blood pressure records were used.

***Conclusions*—**Visit-to-visit SBP variability is an independent predictor of primary stroke in Chinese hypertensive patients. This predictive value depends on the number of blood pressure measurements used to calculate variability but is independent of mean SBP.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00794885. **(*J Am Heart Assoc*. 2017;6: e004350. DOI: 10.1161/JAHA.116.004350.)**

Key Words: hypertension • stroke • systolic blood pressure variability

Stroke is the leading cause of death in China and the second leading cause of death in the world.[1] Almost 77% of strokes are first attacks; therefore, primary prevention is of great importance.[2] Hypertension is the most treatable and prevalent risk factor for stroke.[3,4] It affects >1 billion people around the world.[5] In China, ≈200 million people suffer from hypertension.[6] The diagnosis and treatment of hypertension focus on comparisons to the normal blood pressure (BP) range,[7–9] which is calculated by the average BP during a defined period, according to all major clinical guidelines.[10–12]

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Accompanying Tables S1 through S13 and Figure S1 are available at http://jaha.ahajournals.org/content/6/3/e004350/DC1/embed/inline-supplementary-material-1.pdf

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Recently, debate has ensued regarding the optimal BP level. Although visit-to-visit systolic BP variability (SBPV) has proven to be a strong predictor of stroke, independent of mean systolic BP (SBP),[13] it is still often dismissed or considered a random phenomenon.[14] Visit-to-visit BP variability (BPV) represents episodic hypertension, which is usually untreated because the patient's BP may be within the normal range during the requisite repeated readings.[8,9] In the Oxford vascular study, 87% of the 150 patients had an average SBP >160 mm Hg during the previous 10 years, but 69% had an SBP <130 mm Hg on at least 2 visits.[15]

Several prior studies have focused on the relationship between visit-to-visit BPV and stroke primary prevention, but the optimal stable range of BPV is still unclear, as are the numbers of BP measurements and the intervals between visits that are used to calculate BPV. We studied a large cohort of hypertensive patients from 32 communities in Jiangsu and Anhui provinces from the China Stroke Primary Prevention Trial (CSPPT) and analyzed the different predictive values of visit-to-visit SBPV across different numbers of visits regarding stroke.

Methods

Study Population and Data Source

All patients in this study were participants in the CSPPT; the design and methods of the CSPPT have been described elsewhere.[16] In brief, the CSPPT was a large, long-term, multicommunity, controlled, randomized, double-blind study. Half of the participants received enalapril and folic acid and half received enalapril alone to evaluate the effect of folic acid on lowering BP and blood homocysteine levels in reducing the risk of stroke and other cardiovascular events in Chinese hypertensive patients. In total, 20 702 hypertensive patients were screened and enrolled from May 2008 to May 2009. Hypertension was defined as SBP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg at the screening visit and recruitment visit or, alternatively, currently under hypertension treatment. All participants were aged 45 to 75 years without any history of stroke, myocardial infarction, heart failure, coronary revascularization, congenital heart disease, and secondary hypertension. Details of inclusion and exclusion criteria have been described previously.[16] Written informed consent was obtained from each patient, and the protocol was approved by the ethics committees of the relevant institutional review boards.

Follow-up and Outcomes

After a 3-week run-in treatment, participants were followed up every 3 months. BP, study outcome events, and other details were recorded on each visit.

Stroke was the primary outcome, and it was defined (1) as rapidly developed clinical signs of focal or global deficits of cerebral function with symptoms lasting for ≥24 hours unless interrupted by surgery or death or (2) as a demonstrated lesion on brain computed tomography or magnetic resonance imaging scan 24 hours to 3 months after the attack that is consistent with clinical signs and with no apparent causes other than vascular origin. If no brain computed tomography or magnetic resonance imaging scan was available, stroke was still diagnosed in the presence of the specific symptoms and signs of focal disturbance of cerebral function.

The stroke was further divided into ischemic, hemorrhagic, or undetermined stroke based on the following criteria. Ischemic stroke was defined as an acute episode of focal cerebral function deficit caused by an infarction of the central nervous system. Hemorrhage may be a consequence. In this situation, the stroke was still an ischemic stroke with hemorrhagic transformation but was not a hemorrhagic stroke. Hemorrhagic stroke was defined as an acute episode of focal or global cerebral function deficit caused by intraparenchymal, intraventricular hemorrhage; however, subarachnoid hemorrhage was not an end point event of this study. Undetermined stroke was defined as a stroke with no imaging data available to categorize ischemic or hemorrhagic stroke.

Because patients with stroke histories were excluded, the first attack of symptomatic stroke during the follow-up period was regarded as the first attack. Any stroke after the first stroke was regarded as a recurrent stroke, which was not the primary end point of this study.

The end point working group consisted of 2 neurologists, who collected relevant medical information and made preliminary assessments of the suspected end point events. Every case reported as a stroke event by both neurologists was further reviewed by the end point adjudication committee, which consisted of 3 neurologists. The end point adjudication committee was blinded to treatment and the resultant diagnosis. The data of each suspected case was reviewed by one of the neurologists on the end point adjudication committee to determine whether or not the case met the stroke definition criteria. When a case was questionable, all end point adjudication committee neurologists reviewed the data and could request additional data to resolve the disagreement. For such case, a final assessment was made by the committee chairman.

BP Measurement

BP was measured manually by a trained researcher using a standard mercury sphygmomanometer. Participants did not smoke or drink coffee in the 30 minutes prior to the measurement and took their regular medications as usual.

After resting 5 minutes in a seated position, BP was measured 3 times. The average of at least 2 valid readings in each follow-up visit was recorded and used for further analyses.

Basic Information

Sex, age, alcohol consumption, and cigarette smoking were recorded using questionnaires. Participants' height and weight were also measured at the recruitment visit. Body mass index (BMI) was calculated as weight in kilograms by height in square meters (kg/m^2).

Laboratory Tests

The laboratory test results were from the baseline data collected at the recruitment visit, including fasting plasma glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and blood homocysteine and creatinine.

Visit-to-Visit SBPV Parameters

In this study, 3 parameters of BPV were calculated: the first for standard deviation (SD) of SBP (SBPV-SD), the second for coefficient variation (CV) of SBP (SBPV-CV), and the third for average real variability (ARV) of SBP (SBPV-ARV).

Statistical Analysis

SBPV quintiles were used to describe patient characteristics. Continuous data assumed to have normal distribution were described as mean±SD. Continuous data not assumed to have normal distribution were presented as median values (25th and 75th percentiles). Categorical variables are described as frequencies or percentages. Continuous data in different groups were compared by ANOVA or independent *t* tests, and categorical variables were compared by chi-square tests. Variability of visit-to-visit SBP was quantified using 3 sets of analyses: Standard deviation:

$$(\mathrm{SD} = \sqrt{\frac{1}{N}\sum_{k=1}^{N}(\mathrm{BP_k} - \overline{\mathrm{BP}})^2})$$

Coefficient of variation:

$$(\mathrm{CV} = \frac{\sqrt{\frac{1}{N}\sum_{k=1}^{N}(\mathrm{BP_k} - \overline{\mathrm{BP}})^2}}{\overline{\mathrm{BP}}})$$

Average real variability:

$$(\mathrm{ARV} = \frac{1}{N-1}\sum_{k=1}^{N-1}|\mathrm{BP_{k+1}} - \mathrm{BP_k}|)$$

The first-visit BP (or baseline BP) was excluded. The other visits with valid BP readings were used for further analyses. The first 4, 6, 8, 10, and 12 visits at which BP was measured in patients who did not have stroke during the respective between-visit periods were used to calculate BPV. Patients who had a stroke between visits or who did not have at least the respective number of visits at which BP was measured were excluded. The association between patient characteristics and visit-to-visit BPV was assessed by linear regression. Multivariate Cox proportional hazard regression models were used to test the predictive power of subsequent, ischemic, and hemorrhagic stroke after the respective number of follow-up visits. BPV parameters were further divided by quintiles to test the dose-response relationship between BPV and stroke risk. Hazard ratios (HRs) and corresponding 95% CIs were calculated in relation to the lowest quintile (referent). Trend tests were computed by modeling BPV quintiles and medians as continuous variables. In the primary Cox regression analysis, we adjusted for mean SBP over the respective number of visits, age, sex, study center, randomized treatment group (enalapril–folic acid or enalapril), and other baseline risk factors (baseline SBP, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, homocysteine, creatinine, smoking status, alcohol consumption, and BMI). Further subgroup analyses were conducted for sex, age >60 and <60 years, baseline BMI >25 and <25, and mean SBP >140 and <140 mm Hg over the respective number of visits. A value of $P<0.05$ was considered statistically significant for all analyses. All statistical analyses were performed using Empower Stats software (R)(www.empowerstats.com, X&Y Solutions, Inc. Boston, MA) and R software, version 3.2.0(http://www.R-project.org/).

Results

Patient Characteristics

In this study, 20 702 patients were from 32 communities in China, with a mean of 14.6 follow-up visits, ranging from 1 to 22 visits, and a median follow-up time of 4.5 years. The sample size for the total number of visits is available in Table S1. The number of included and excluded patients at respective visits is shown in Table S2. The flow of inclusion and exclusion procedures is shown in Figure 1. Patients characteristics can be found in Table 1.

We also examined whether there was a significant difference in baseline SBP, mean SBP, and visit-to-visit SBPV over the respective visits between participants receiving enalapril only and enalapril plus folic acid, and the results were insignificant (Table S3). Consequently, the data from the 2 treatment groups were combined. In the subsequent analyses, however, the data were adjusted for randomized

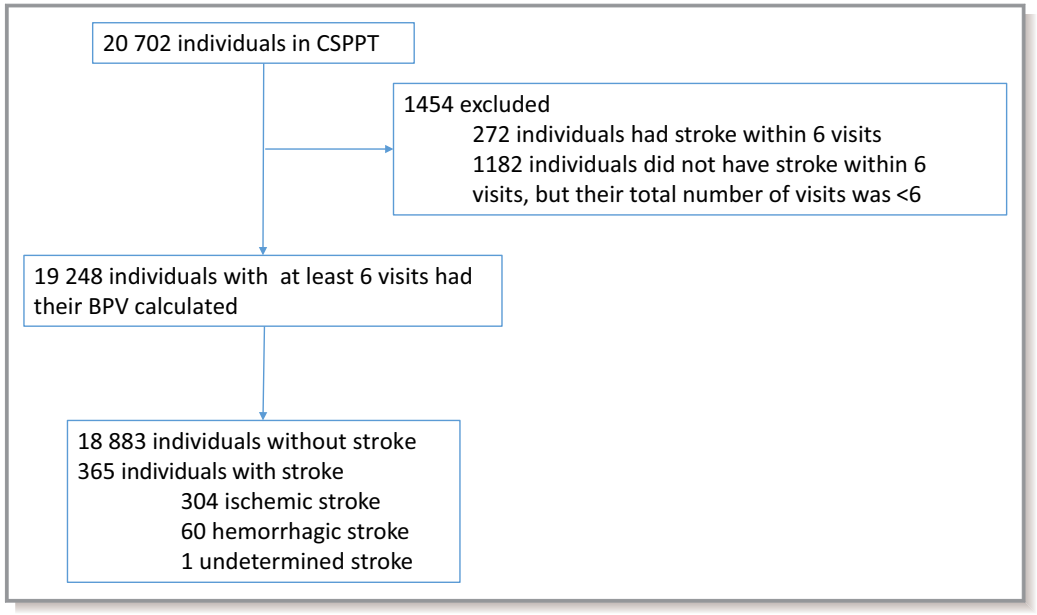

Figure 1. Flow of participants in the analysis of BPV over 6 visits. BPV indicates blood pressure variability; CSPPT, China Stroke Primary Prevention Trial.

treatment group to avoid the effect of drugs on stroke outcomes. Reproducibility of variability was moderate (intra-class correlation coefficient for SBPV-SD was 0.21, 95% CI 0.19–0.22, visit 1—N/2 versus visit N/2—N, in which N is the total number of visit times).

Association Between Visit-to-Visit SBPV and Mean SBP

Higher quintiles of BPV over respective visits were associated with higher mean SBP during respective follow-up periods and higher baseline SBP. There was only a weak correlation among the 3 measures of visit-to-visit SBPV and average SBP during the follow-up period (eg, when n=6, $r<0.4$, [SD 0.33, CV 0.10, ARV 0.29]). The results are shown in Tables S4 through S6.

Association Between Visit-to-Visit SBPV and Stroke

After adjustment for mean SBP over 4, 6, and 8 visits, age, sex, center, randomized treatment group (enalapril–folic acid or enalapril), and other baseline risk factors (baseline SBP, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, homocysteine, creatinine, smoking status, alcohol consumption, and BMI), the 3 variables for SBPV (SD, CV, and ARV) over 4, 6, and 8 visits were independent predictors of subsequent stroke (eg, CV over 8 visits: HR 1.05, 95% CI 1.01–1.09, $P<0.01$) (Table S7). However, when SBPV was calculated over >8 visits, SD and CV failed to show significant associations with the risk of subsequent stroke in the multivariate regression model. ARV failed to show a significant association with the risk of subsequent stroke when it was calculated over >10 visits.

When we further divided stroke into ischemic stroke and hemorrhagic stroke, SBPV over 4, 6, 8, 10, and 12 visits was an independent predictor of subsequent ischemic stroke (eg, CV over 8 visits: HR 1.06, 95% CI 1.01–1.10, $P<0.01$). SBPV-ARV, however, failed to show predictive value over >10 visits. SBPV had no association with hemorrhagic stroke in the multivariate regression models (Tables S8 and S9).

For comparison, we also analyzed the value of mean SBP over respective visits to predict subsequent, ischemic, and hemorrhagic stroke in the multivariate Cox regression model (adjusting for sex, age, study center, and baseline risk factors for stroke) (Tables S7 through S9). The results showed that mean SBP was an independent predictor of stroke, ischemic stroke, and hemorrhagic stroke, even if the number of visits used to calculate the mean SBP varied.

Predictive Value of Different Visit-to-Visit SBPV Levels for Stroke

When divided into quintiles, higher SBPV quintiles over 4, 6, and 8 visits, respectively, had higher risks of subsequent stroke (eg, for 6 visits, see Figure 2 and Table S10; for 8 visits, see Figure S1 and Table S11). As the number of visits increased, the predictive value of the highest quintiles of SBPV was even greater (Table 2). Similar trends were found in the relationship of SBPV quintiles and subsequent ischemic stroke (Table S12).

Table 1. Baseline Characteristics of Quintiles of Standard Deviation of SBP Over 6 Visits

	Q1	Q2	Q3	Q4	Q5
Quintile range, mm Hg	1.24–9.90	9.90–12.74	12.74–15.46	15.46–19.15	19.15–43.55
Patients, n	3679	3907	3894	3935	3833
Male, n (%)	1580 (42.9)	1556 (39.8)	1564 (40.2)	1558 (39.6)	1572 (41.0)
Age, y, mean (SD)	58.8 (7.5)	59.2 (7.4)	59.9 (7.5)	60.6 (7.4)	61.7 (7.4)
BMI, mean (SD)	25.1 (3.6)	25.1 (3.6)	25.1 (3.6)	24.9 (3.7)	24.7 (3.8)
Fasting plasma glucose, mmol/L, mean (SD)	5.8 (1.6)	5.8 (1.7)	5.8 (1.8)	5.8 (1.7)	5.8 (1.7)
TG, mmol/L, mean (SD)	1.7 (0.9)	1.7 (1.0)	1.7 (1.8)	1.6 (0.9)	1.6 (0.9)
TC, mmol/L, mean (SD)	5.5 (1.2)	5.5 (1.2)	5.5 (1.2)	5.5 (1.2)	5.5 (1.2)
HDL, mmol/L, mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)
Homocysteine, μmol/L, mean (IQR)	12.4 (10.3–15.2)	12.3 (10.3–15.1)	12.5 (10.4–15.4)	12.5 (10.5–15.6)	12.8 (10.8–16.0)
Creatinine, mg/dL, mean (SD)	65.8 (16.6)	65.2 (16.5)	65.6 (17.9)	65.7 (17.9)	66.7 (18.4)
Baseline SBP, mm Hg, mean (SD)	160.5 (17.2)	163.2 (18.7)	165.8 (19.3)	169.2 (20.0)	175.9 (22.6)
Baseline DBP, mm Hg, mean (SD)	92.9 (10.9)	93.2 (11.4)	94.0 (12.0)	94.3 (12.0)	95.8 (13.0)
Smoking status, n (%)					
Never	2572 (69.9)	2753 (70.5)	2682 (68.9)	2771 (70.5)	2531 (66.1)
Former	314 (8.5)	271 (6.9)	303 (7.8)	282 (7.2)	286 (7.5)
Current	792 (21.5)	881 (22.6)	908 (23.3)	880 (22.4)	1014 (26.5)
Alcohol consumption, n (%)					
Never	2554 (69.5)	2702 (69.2)	2698 (69.3)	2781 (70.7)	2575 (67.2)
Former	263 (7.2)	290 (7.4)	279 (7.2)	256 (6.5)	275 (7.2)
Current	860 (23.4)	913 (23.4)	915 (23.5)	896 (22.8)	980 (25.6)
Treatment group					
Enalapril	1826 (49.6)	1973 (50.5)	1930 (49.6)	1949 (49.5)	1904 (49.7)
Enalapril–folic acid	1853 (50.4)	1934 (49.5)	1964 (50.4)	1986 (50.5)	1929 (50.3)

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; IQR, interquartile range; Q1 to Q5, each quintile of standard deviation over 6 visits; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

For example, when BPV was calculated over 6 visits, in the unadjusted Cox regression analyses, the HR of subsequent stroke increased when the SBPV levels increased; the HR for stroke was 2.38 (95% CI 1.70–3.35) for the highest versus the lowest quintiles of SBPV-SD (19.15–43.55 versus 1.24–9.90 mm Hg), 1.77 (95% CI 1.28–2.44) for the highest versus the lowest quintile of SBPV-CV (13.32–28.64% versus 1.05–7.08%), and 2.29 (95% CI 1.62–3.24) for the highest versus the lowest quintile of SBPV-ARV (22.67–61.07 versus 0.80–10.00 mm Hg). The adjusted model (adjusted for sex, age, baseline risk factors, mean SBP, and number of visits) showed that the dose-effect relationships among the 3 SBPV variables and subsequent stroke risk were still more significant in the highest quintiles after controlling for clinical data and mean SBP (6 visits: highest quintile of SD versus the lowest: HR 1.49, 95% CI 1.03–2.17, P=0.03; highest quintile of CV versus the lowest: HR 1.42, 95% CI 1.01–2.01, P=0.04; highest quintile of ARV versus the lowest: HR 1.55, 95% CI 1.07–2.25, P=0.02). Over 6 visits, the P value for trend was 0.0175 for the SBPV-SD quintiles, 0.0065 for SBPV-CV, and 0.0047 for SBPV-ARV.

Different Predictive Values of Visit-to-Visit SBPV for Stroke by Stratification

When we further stratified the population by sex, there was no significant difference in visit-to-visit SBPV between male and female participants in our study (eg, BPV over 6 visits: SD, P=0.083; CV, P=0.140; ARV, P=0.093) (Table S13). Visit-to-visit SBPV-SD, however, was more predictive for stroke in female than male participants after multivariate Cox regression analysis when calculated over number of visits; for example, adjusted HR for SBPV-SD over 6 visits was 1.04 (95% CI 1.01–1.06) in female participants. Visit-to-visit SBPV-CV and SBPV-ARV showed the same predictive value for stroke in female participants (eg, 6 visits: adjusted HR for CV

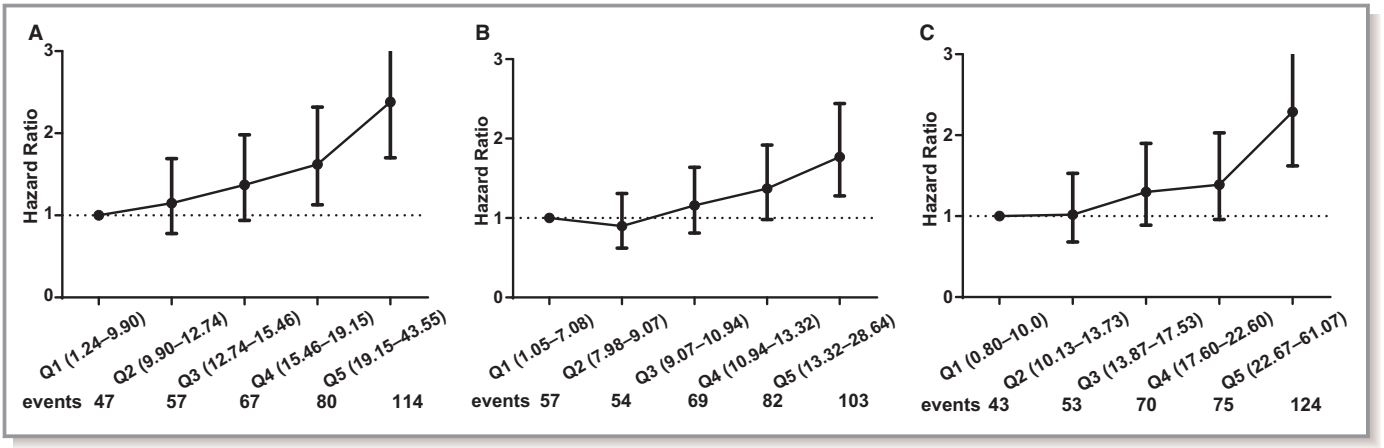

Figure 2. Hazard ratios for risk of subsequent stroke by quintiles of visit-to-visit systolic blood pressure standard deviation, coefficient of variation and average real variability over 6 visits, with the first quintile (Q1) as the reference. The hazard ratios (95% CI) for risks of subsequent stroke in a crude model by quintiles of visit-to-visit systolic blood pressure variability parameters over the first 6 visits. A, Standard deviation. B, Coefficient of variation. C, Average real variability. The first quintile of each parameter is the reference category. Numbers of subsequent stroke events by quintiles are given in Table S10; Q1 to Q5, each quintile of the same parameters.

1.06, 95% CI 1.02–1.10; adjusted HR for ARV 1.04, 95% CI 1.01–1.06) (Table 3).

The 3 parameters of visit-to-visit SBPV were higher in older patients (aged ≥60 years, all $P<0.001$) (Table S13). In a multivariate Cox regression model for stroke after stratification by age (after adjustment for mean SBP and baseline risk factors), visit-to-visit SBPV was a stronger predictor in older patients (aged ≥60 years). In patients >60 years, for example, when SBPV was calculated over 6 visits, adjusted HR for CV was 1.06 (95% CI 1.02–1.10) (Table 3).

Patients with lower BMI levels (<25) were associated with higher visit-to-visit SBPV (all $P<0.001$) (Table S13). The association of visit-to-visit SBPV with subsequent stroke was stronger in patients with higher BMI. In an adjusted Cox regression model for subsequent stroke (after adjustment for mean SBP and all baseline risk factors), for patients with higher BMI, HR for CV over 6 visits was 1.07 (95% CI 1.03–1.12) (Table 3).

Higher mean SBP (≥140 mm Hg) was associated with higher visit-to-visit SBPV (all $P<0.001$) (Table S13), and the

Table 2. HRs of Visit-to-Visit SBPV (Top Versus Bottom Quintile) and Mean SBP for the Risk of Subsequent Stroke, Calculated by Increasing Numbers of Visits

Number of visits	HR for Mean SBP	HR for SBP Variability		
	HR (95% CI) *P* Value	HR (95% CI) *P* Value		
		SD	CV	ARV
4	1.02 (1.01–1.03)	1.33 (0.98–1.80)	1.47 (1.09–1.98)	1.44 (1.05–1.99)
	<0.0001	0.068	0.012	0.026
6	1.03 (1.02–1.03)	1.49 (1.03–2.17)	1.42 (1.01–2.01)	1.55 (1.07–2.25)
	<0.0001	0.035	0.045	0.021
8	1.03 (1.02–1.04)	1.59 (1.03–2.46)	1.49 (1.00–2.21)	1.78 (1.11–2.86)
	<0.0001	0.038	0.051	0.017
10	1.05 (1.03–1.06)	1.41 (0.84–2.37)	1.40 (0.87–2.24)	1.60 (0.88–2.92)
	<0.0001	0.19	0.16	0.12
12	1.05 (1.03–1.07)	0.91 (0.51–1.63)	1.06 (0.63–1.76)	1.66 (0.77–3.59)
	<0.0001	0.76	0.83	0.19

Each row shows the hazard ratio of visit-to-visit SBPV for subsequent stroke. The data are from patients who did not have a stroke during the first number of visits and had at least a respective number of visits. The model was adjusted for age, sex, center, treatment group, baseline stroke risk factors (baseline SBP, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, homocysteine, creatinine, smoking status, alcohol consumption, and body mass index), and mean SBP over the period of respective visits. Number of visits ranged from 4 (1 year) to 12 (4 years). ARV indicates average real variability; CV, coefficient of variation; HR, hazard ratio; SBP, systolic blood pressure; SBPV, systolic blood pressure variability; SD, standard deviation.

Table 3. Stratified Analysis of Multivariate HRs of Visit-to-Visit SBP Variability Over 6 Visits for Subsequent Stroke

	Events n (%)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	*P* Value‡
SD				
Male	158 (2.0)	1.05 (1.03–1.08)§	1.03 (1.00–1.05)	0.29
Female	207 (1.8)	1.06 (1.04–1.09)§	1.04 (1.01–1.06)§	
Aged <60 years	138 (1.4)	1.06 (1.03–1.09)§	1.02 (0.99–1.05)	0.24
Aged ≥60 years	227 (2.3)	1.06 (1.04–1.08)§	1.04 (1.02–1.06)§	
BMI <25	177 (1.7)	1.05 (1.03–1.08)§	1.02 (0.99–1.04)	0.11
BMI ≥25	188 (2.0)	1.07 (1.04–1.09)§	1.05 (1.02–1.08)§	
Mean SBP <140 mm Hg	105 (1.2)	1.04 (1.00–1.08)‖	1.04 (1.00–1.08)	0.91
Mean SBP ≥140 mm Hg	260 (2.5)	1.05 (1.03–1.07)§	1.03 (1.01–1.05)§	
CV				
Male	158 (2.0)	1.05 (1.01–1.10)§	1.04 (0.99–1.08)	0.37
Female	207 (1.8)	1.17 (1.03–1.11)§	1.06 (1.02–1.10)§	
Aged <60 years	138 (1.4)	1.06 (1.01–1.10)‖	1.03 (0.98–1.07)	0.23
Aged ≥60 years	227 (2.3)	1.07 (1.03–1.10)§	1.06 (1.02–1.10)§	
BMI <25	177 (1.7)	1.05 (1.01–1.09)‖	1.03 (0.99–1.07)	0.11
BMI ≥25	188 (2.0)	1.08 (1.04–1.13)§	1.07 (1.03–1.12)§	
Mean SBP <140 mm Hg	105 (1.2)	1.05 (1.00–1.10)	1.05 (0.99–1.10)	0.94
Mean SBP ≥140 mm Hg	260 (2.5)	1.03 (1.01–1.05)§	1.05 (1.01–1.08)§	
ARV				
Male	158 (2.0)	1.04 (1.02–1.06)§	1.02 (1.00–1.05)	0.21
Female	207 (1.8)	1.04 (1.03–1.06)§	1.04 (1.01–1.06)§	
Aged <60 years	138 (1.4)	1.04 (1.01–1.06)§	1.01 (0.99–1.03)	0.09
Aged ≥60 years	227 (2.3)	1.04 (1.03–1.06)§	1.03 (1.01–1.05)§	
BMI <25	177 (1.7)	1.04 (1.02–1.05)§	1.01 (1.00–1.03)	0.17
BMI ≥25	188 (2.0)	1.04 (1.03–1.06)§	1.03 (1.01–1.05)§	
Mean SBP <140 mm Hg	105 (1.2)	1.03 (1.00–1.06)	1.03 (1.00–1.05)	0.94
Mean SBP ≥140 mm Hg	260 (2.5)	1.03 (1.02–1.05)§	1.02 (1.01–1.04)§	

Blood pressure variability was calculated over the first 6 visits for patients who had a stroke during the course of the 6 visits, and patients who did not have at least 6 visits were excluded. ARV indicates average real variability; BMI, body mass index; CV, coefficient of variation; HR, hazard ratio; SBP, systolic blood pressure; SD, standard deviation.

*Model 1 was adjusted for age, sex, and center;

†Model 2 was adjusted for age, sex, center, treatment group, baseline stroke risk factors (baseline systolic blood pressure, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, homocysteine, creatinine, smoking status, alcohol consumption, and BMI), and mean systolic blood pressure over the period of visits.

‡*P* value indicates interaction *P* value between subgroups.

§$P<0.01$.

‖$P<0.05$.

predictive value of visit-to-visit SBPV was greater in the group with higher mean SBP (≥140 mm Hg). After adjustment for baseline clinical data and mean SBP over the follow-up period, SBPV was a stronger predictor of subsequent stroke in the group with higher mean SBP. For patients with higher mean SBP, the adjusted HR for SBPV-CV over 6 visits was 1.05 (95% CI 1.01–1.08) (Table 3).

The interaction *P* value in each stratification noted in the results failed to show significant values.

Discussion

The data confirm that visit-to-visit variability of SBP remains a predictor of stroke in Chinese hypertensive patients, although all participants were using antihypertension therapy. Higher SBPV presents an even stronger predictive value for stroke. Based on the condition that visit-to-visit BP was measured every 3 months, more visits (range 4–8 visits) brought SBPV more significant predictive value for subsequent stroke.

In present major guidelines for hypertension, average BP is the recommended crucial component in the management of cardiovascular disease.[8,9] Nevertheless, because BP measurements often fluctuate from one visit to another, average BP can sometimes fail to accurately reflect a patient's real-world BP or out-of-office BP. This kind of BP fluctuation is known as *visit-to-visit* BP variability. Formerly, visit-to-visit BP variability was regarded as "noise," and using the average BP of ≥2 visits was recommended to reduce this noise.[17] More evidence has shown that this variability in visit-to-visit BP is not an accidental phenomenon; it is reproducible and, furthermore, has an independent association with cardiovascular outcomes.[18] A meta-analysis of 13 prospective studies stated that the combined BPV-SD HR among 60 096 individuals for stroke was 1.02 after adjustment for mean SBP and age,[19] suggesting that visit-to-visit BP variability is a new marker worth studying for its effectiveness in predicting stroke.

Moreover, several studies have been published to prove relationships between visit-to-visit BPV and markers of vascular dysfunction, such as increased arterial stiffness, atherosclerosis,[20] the activity of the sympathetic nerves,[21] the effect of different antihypertensive drugs,[22] and patients' adherence to treatment of hypertension.[23]

Average BP plays a crucial part in stroke, and this result was shown in our study (HR 1.03 for mean SBP over 8 visits). Average BP of more visits was an even better predictor of stroke. What cannot be overlooked is the role of visit-to-visit SBPV on stroke.

In this study, we focused on the visit-to-visit SBPV but not diastolic BPV because existing results show more evidence supporting the association between SBPV and future cardiovascular events than that of diastolic BPV.[13]

We stratified the power of SBPV to access the association with 2 stroke subtypes: ischemic and hemorrhagic stroke. A previous study from this research group showed that visit-to-visit BPV significantly accelerated the progress of cerebral microbleeds rather than the progress of cerebral white matter lesions during follow-up of 1.5 years.[24] Considering the higher risk of hemorrhagic stroke in Chinese patients,[1] it is necessary to analyze the association between SBPV and subtypes of stroke in China. Overall, 18.8% of stroke patients and 0.57% of all participants in our study had hemorrhagic stroke; these proportions are higher than existing data in this field (eg, 0.4% of all participants in the ASCOT-PBLA study).[13] Although the absolute number of hemorrhagic stroke patients was only 120, and visit-to visit SBPV failed to show a significant association with hemorrhagic stroke, it might still be meaningful. Moreover, mean SBP showed predictive value for hemorrhagic stroke. These findings demonstrate the potentially different mechanisms of visit-to-visit SBPV and mean SBP in predicting hemorrhagic stroke. Visit-to-visit SBPV and mean SBP are both independent predictors of ischemic stroke.

The difference in visit-to-visit SBPV between female and male participants was not significant in our study; however, SBPV was a more predictive marker for subsequent stroke in female than male participants. Moreover, 85% of the women in our study were postmenopausal (n=12 205). Perhaps the loss of the protective effect of the β-adrenergic receptor in vasodilation together with decreased estrogen levels since menopause[25] lead to susceptibility to stroke for postmenopausal women with higher visit-to-visit SBPV.

It is well accepted that age is a major cause of arterial stiffness, and BP has a positive association with age.[26] In our results, the effect of visit-to-visit SBPV on stroke was also greater in older patients because older patients had higher SBPV. This conclusion was not in line with prior studies.[13]

Several studies have found an inverse relationship between BMI and BPV.[27,28] Our analysis revealed a similar result. In addition, the predictive value of visit-to-visit SBPV was more significant in patients with higher BMI (BMI ≥25).

We found that visit-to-visit SBPV was most predictive in patients with uncontrolled mean SBP levels (≥140 mm Hg), which reminded us of the potentially equal value of both mean SBP and visit-to-visit SBPV in clinical practice.

We must mention that the *P* value for interaction in each stratification failed to show a significant value, which means these stratification results may be less persuasive and may be affected by the sample size in each stratification.

There is still no consensus on the best way to define visit-to-visit BPV. Several metrics have been used to calculate BPV in the literature, namely, SD, CV, ARV, and variation independent of the mean, among which SD and CV are widely used. In a meta-analysis of 77 299 patients,[29] BPV-SD turned out to be a better predictor of stroke than other indices, independent of mean SBP, but Rothwell proposed that variation independent of the mean and ARV were superior for predicting cardiovascular outcomes.[13,22] In this study, we used SD, CV, and ARV over the same numbers of BP measurements (or numbers of visits) to calculate visit-to-visit BPV and to predict subsequent stroke. When calculated over the same respective visits, BPV-ARV seemed to be slightly more sensitive in the highest quintile than the other 2 variables for predicting subsequent stroke (Table 3). It is probable that SD, CV, and ARV reflect different determinants. SD and CV put emphasis on the extreme values, whereas ARV gives more weight to the consecutive changes that may have more value for predicting subsequent stroke.

In the existing studies to date, indices, number of visits, and visit-to-visit time intervals have been inconsistent. In the Trial of Preventing Hypertension study, BPV-SD tended to increase when there were more measurement times during the follow-up period and longer visit-to-visit time intervals

(lower density of measurement).[30] And there is still no standard definition in the assessment of visit-to-visit BPV. According to our finding, when more measurement times were used to calculate BPV (4, 6, and 8 visits, respectively), its predictive value for subsequent stroke increased. The precise estimation of BPV increases the predictive value of subsequent stroke. Because the purpose of CSPPT was based on antihypertension drugs with or without folic acid to prevent stroke in hypertensive patients, the BP readings were reliable, and the time intervals between visits were the same (3 months), which made the estimation of BPV reasonably accurate. When the number of visits was >10, BPV seemed to lose its predictive value for subsequent stroke. Perhaps the subsequent follow-up period after 10 visits was not long enough to provide a sufficient sample of stroke events, thus the results of analyses were not precise enough for this reason.

Patients' emotional states and BP measurement circumference may also influence visit-to-visit BPV, but these factors are difficult to adjust for.

In clinical practice, episodic hypertension should not be dismissed or considered to be a random phenomenon and left untreated. Our finding suggests that visit-to-visit SBPV is an independent predictor of stroke. Furthermore, patient BP may be within the normal range on several requisite visits, but such patients may still have hypertension. In this situation, doctors should emphasize visit-to-visit BPV rather than just a single normal BP reading at 1 visit. Our finding also suggests that in female, older, higher BMI populations and those with uncontrolled mean BP, we should pay extra attention to patients' visit-to-visit SBPV levels.

Visit-to-visit BPV is easy to calculate and needs no additional devices or costs. We propose that long-term management for reduction of visit-to-visit SBPV results in improved stroke outcomes. Generally, we should choose antihypertensive drugs, which could reduce both mean BP and visit-to-visit BPV at the same time. Calcium channel blockers were proven to be more effective in reducing visit-to-visit BPV, whereas beta blockers and angiotensin receptor blockers were found to increase visit-to-visit BPV.[22] Moreover, according to the latest research, after adjustment for mean BP and visit-to-visit BPV, beta blockers and angiotensin receptor blockers increased stroke risks in older patients.[31] This means that an underlying relationship exists among visit-to-visit BPV and stroke, but whether it is a causal link and how antihypertensive drugs affect this relationship remain uncertain. Consequently, how to manage visit-to-visit BPV is still unclear.

Our study has some potential shortcomings. First, the participants took other kinds of antihypertensive agents (except enalapril) at the same time to control their BP under prescription, but we had no data on the use of other antihypertensive drugs during the follow-up period, thus we were not able to analyze the effect of different antihypertensive drugs on visit-to-visit BPV. Second, the CSPPT is a randomized controlled trial and has inclusion and exclusion criteria; it was not designed to study the association between visit-to-visit BPV and stroke. Moreover, our study is a secondary post hoc analysis, which naturally is a source of bias, and the findings may be chance observations. Third, we used the same number of visits to calculate BPV and to predict subsequent stroke; the overall mean follow-up period from the first visit was 4.5 years, which limits the results' accuracy to some extent when more visits were used.

Conclusion

In Chinese hypertensive patients, visit-to-visit SBPV was a strong predictor of stroke, especially ischemic stroke, independent of mean SBP over the follow-up period. In addition, higher visit-to-visit SBPV was associated with higher risk of stroke. This value was more predictive when more visits were used to calculate SBPV.

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Disclosures

None.

References

1. Rafael L, Mohsen N, Kyle F, Stephen L, Kenji S, Victor A, Jerry A, Timothy A, Rakesh A, Ahn SY. 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;380:2163–2196.
2. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.
3. Charles W, Cathie S, Martin D, Joanna W, Peter S. Stroke. *Lancet*. 2003;362:1211–1224.
4. Lawes CMM, Hoorn SV, Rodgers A; For the International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet*. 2008;371:1513–1518.
5. WHO document. A global brief on hypertension. 2015. Available at http://www.who.int/cardiovascular_disease/publication/global_brief_hypertension/. Accessed December 23, 2016.
6. Liu LS. 2010 Chinese guidelines for the management of hypertension. *Chin J Hypertens*. 2011;39:579–615.
7. Chobanian A; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.
8. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens*. 2005;23:697–701.
9. Parati G, Stergiou GS, Asmar R, Bilo G, De LP, Imai Y, Kario K, Lurbe E, Manolis A, Mengden T. European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *J Hypertens*. 2008;26:1505–1530.
10. Leenen FH. Blood pressure lowering, not vascular mechanism of action, is the primary determinant of clinical outcome. *Can J Cardiol*. 2004;20(suppl B):77B–82B.
11. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008;336:1121–1123.
12. Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. *Lancet*. 2008;371:2219–2221.
13. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905.
14. Tom M. When measurements are misleading: modelling the effects of blood pressure misclassification in the English population. *BMJ*. 2004;328:933.
15. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363:1925–1933.
16. Yong H, Jianping L, Xianhui Q, Yining H, Xiaobin W, Gottesman RF, Genfu T, Binyan W, Dafang C, Mingli H. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in china: the CSPPT randomized clinical trial. *JAMA*. 2015;313:1325–1335.
17. Bruce A, Brian MC, Stephen D, Barbara D, Laura H, Marc J, Larry M, Albert R, Julia S, Elaine U. Recommendations for blood pressure measurement in human and experimental animals; part 1: blood pressure measurement in humans. *Hypertension*. 2006;48:e3.
18. Paul M, Cara J, Levitan EB, Elizabeth H, Daichi S, Webber LS, Suzanne O, Richard R, Marie KW. Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care. *J Hypertens*. 2011;29:2332–2338.
19. Diaz KM, Tanner RM, Louise F, Levitan EB, Kristi R, Daichi S, Paul M. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. *Hypertension*. 2014;64:965–982.
20. Lau KK, Wong YK, Chan YH, Teo KC, Chan KH, Li LSW, Cheung RTF, Siu CW, Shu LH, Tse HF. 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;235:230–235.
21. Paolo P, Stevo J. The role of cardiac autonomic function in hypertension and cardiovascular disease. *Curr Hypertens Rep*. 2009;11:199–205.
22. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS. Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*. 2010;9:469–480.
23. Krakoff LR. Fluctuation: does blood pressure variability matter? *Circulation*. 2012;126:525–527.
24. Wenhong L, Ran L, Wei S, Qing P, Weiwei Z, En X, Yan C, Meiping D, Yansheng L, Zhen H. Different impacts of blood pressure variability on the progression of cerebral microbleeds and white matter lesions. *Stroke*. 2012;43:2916–2922.
25. Briant LJB, Charkoudian N, Hart EC. Sympathetic regulation of blood pressure in normotension and hypertension: when sex matters. *Exp Physiol*. 2015;101:219–229.
26. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation*. 1983;68:50–58.
27. Okada H, Fukui M, Tanaka M, Matsumoto S, Mineoka Y, Nakanishi N, Asano M, Yamazaki M, Hasegawa G, Nakamura N. Visit-to-visit blood pressure variability is a novel risk factor for the development and progression of diabetic nephropathy in patients with type 2 diabetes. *Diabetes Care*. 2013;36:1908–1912.
28. Kei A, Masahiro K, Rudolph S, Lutgarde T, Miki H, Michihiro S, Azusa H, Taku O, Ryusuke I, Hirohito M. Home blood pressure variability as cardiovascular risk factor in the population of Ohasama. *Hypertension*. 2012;61:61–69.
29. Chenhui T, Yuxi S, Neng D, Dachun X, Wei C, Jiguang W, Athanase P, Van Sloten TT, Jacques B, Safar ME. Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients. *J Clin Hypertens*. 2015;17:107–115 (109).
30. Levitan EB, Niko K, Suzanne O, Stevo J, Paul M. Blood pressure measurement device, number and timing of visits, and intra-individual visit-to-visit variability of blood pressure. *J Clin Hypertens*. 2012;14:744–750.
31. Tully PJ, Debette S, Dartigues J-F, Helmer C, Artero S, Tzourio C. Antihypertensive drug use, blood pressure variability, and incident stroke risk in older adults. *Stroke*. 2016;47:1194–1200.

SUPPLEMENTAL MATERIAL

Table S1. Sample size of the total times of visits.

n	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
	20701	20514	20233	19932	19612	19248	18796	18355	17826
n	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
	17292	16668	15962	15144	14149	12886	11124	9067	6206
n	**19**	**20**	**21**	**22**					
	3454	1447	456	43					

“n” was the total times of visits.

Table S2. Sample size, number of events and excluded number in first n times of visits

Times of visits (n)	Sample size N	Subsequent stroke events N (%)	Excluded number N	
			Patients who had stroke within n times of follow-up	Non-stroke patients with less than n times of visits
4	19932	464(2.3)	173	597
6	19248	365(1.9)	272	1182
8	18355	268(1.5)	369	1978
10	17292	183(1.1)	454	2956
12	15962	109(0.7)	528	4212

Table S3. Baseline systolic blood pressure, mean systolic blood pressure and visit-to-visit systolic blood pressure variability differences between different treatment groups

	Enalapril group	Enalapril-folic acid acid group	P value
4 visits			
N	9952	9980	
Baseline SBP, mean(SD), mm Hg	167.0(20.4)	166.9(20.3)	0.704
Mean SBP, mean(SD), mm Hg	143.0(13.2)	142.8(13.2)	0.212
SD, mean(SD), mm Hg	14.2(6.8)	14.3(6.7)	0.398
CV, mean(SD), %	9.9(4.5)	10.0(4.5)	0.220
ARV, mean(SD), mm Hg	16.9(9.1)	17.1(9.1)	0.146
6 visits			
N	9582	9666	
Baseline SBP, mean(SD), mm Hg	167.0(20.4)	167.0(20.3)	0.987
Mean SBP, mean(SD), mm Hg	142.1(12.3)	142.0(12.2)	0.525
SD, mean(SD), mm	14.8(5.6)	14.8(5.6)	0.826

Hg			
CV, mean(SD), %	10.4(3.7)	10.4(3.7)	0.987
ARV, mean(SD), mm Hg	17.2(7.5)	17.2(7.5)	0.842
8 visits			
N	9133	9222	
Baseline SBP, mean(SD), mm Hg	167.1(20.4)	167.2(20.3)	0.668
Mean SBP, mean(SD), mm Hg	141.2(11.6)	141.2(11.6)	0.976
SD, mean(SD), mm Hg	15.0(5.0)	15.0(5.0)	0.822
CV, mean(SD), %	10.6(3.3)	10.6(3.3)	0.750
ARV, mean(SD), mm Hg	17.0(6.5)	17.1(6.6)	0.722
10 visits			
N	8645	8647	
Baseline SBP, mean(SD), mm Hg	167.1(20.3)	167.4(20.4)	0.346
Mean SBP, mean(SD), mm Hg	140.3(11.1)	140.3(11.1)	0.917
SD, mean(SD), mm	15.0(4.6)	15.0(4.6)	0.720

Hg			
CV, mean(SD), %	10.6(3.1)	10.7(3.0)	0.724
ARV, mean(SD), mm	16.8(5.9)	16.8(5.9)	0.642
Hg			

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; SBP, systolic blood pressure.

Table S4. Association between standard deviation of visit-to-visit blood pressure variability by quintiles and age, baseline systolic blood pressure, mean systolic blood pressure over n times of follow-up period (n=4, 6, 8, 10)

	SD					P
4 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	59.0(7.6)	59.4(7.5)	59.8(7.4)	60.5(7.5)	61.2(7.4)	<0.001
Baseline SBP	161.8(17.7)	164.5(19.1)	165.5(19.8)	168.7(20.3)	173.9(22.4)	<0.001
Mean SBP	139.1(12.1)	141.0(12.3)	142.0(12.5)	143.7(12.9)	148.5(14.1)	<0.001
6 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.8(7.5)	59.2(7.4)	59.9(7.5)	60.6(7.4)	61.7(7.4)	<0.001
Baseline SBP	160.5(17.2)	163.2(18.7)	165.8(19.3)	169.2(20.0)	175.9(22.6)	<0.001
Mean SBP	137.5(10.8)	139.8(11.3)	140.2(11.2)	143.2(11.8)	148.7(13.1)	<0.001
8 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.4(7.4)	59.3(7.4)	60.1(7.4)	61.0(7.4)	61.7(7.3)	<0.001
Baseline	159.6(16.9	163.3(18.1	166.0(18.9	169.5(19.9	176.8(23.1	<0.001

SBP	)	)	)	)	)	
Mean SBP	136.4(10.1)	138.8(10.3)	140.0(10.6)	142.7(10.9)	147.8(12.6)	<0.001
10 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.3(7.3)	59.5(7.4)	60.0(7.4)	61.2(7.4)	61.9(7.3)	<0.001
Baseline SBP	159.1(16.8)	163.2(17.6)	166.3(19.0)	169.7(19.6)	177.5(23.2)	<0.001
Mean SBP	135.3(9.3)	137.7(9.9)	139.3(10.1)	141.9(10.3)	147.0(12.0)	<0.001

SBP indicates systolic blood pressure; SD, standard deviation; Q1-Q5, quintiles of standard deviation over n visits (n=4, 6, 8, 10).

Table S5. Association between coefficient of variation of visit-to-visit blood pressure variability by quintiles and age, baseline systolic blood pressure, mean systolic blood pressure over n times of follow-up period (n=4, 6, 8, 10)

	CV					P
4 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	59.4(7.6)	59.4(7.5)	60.0(7.5)	60.1(7.5)	61.1(7.3)	<0.001
Baseline SBP	164.0(18.5)	165.1(19.5)	166.6(20.4)	167.7(20.5)	171.1(21.9)	<0.001
Mean SBP	141.8(12.9)	142.1(13.0)	143.3(12.9)	142.7(13.1)	144.4(14.0)	<0.001
6 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	59.0(7.6)	59.5(7.5)	59.8(7.4)	60.4(7.5)	61.4(7.4)	<0.001
Baseline SBP	162.5(18.1)	164.8(19.3)	166.6(20.2)	168.3(20.3)	172.3(22.2)	<0.001
Mean SBP	140.5(11.7)	141.5(11.9)	141.6(12.0)	142.4(12.4)	144.1(13.0)	<0.001
8 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.7(7.5)	59.5(7.4)	60.0(7.4)	60.8(7.5)	61.4(7.3)	<0.001
Baseline	162.0(17.8	164.5(18.8	166.8(20.0	168.8(20.5	173.1(22.5	<0.001

SBP	)	)	)	)	)	
Mean SBP	139.8(11.3)	140.1(10.8)	141.0(11.5)	141.8(11.8)	143.2(12.2)	<0.001
10 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.8(7.4)	59.5(7.4)	60.1(7.4)	60.9(7.4)	61.6(7.3)	<0.001
Baseline SBP	161.8(17.5)	164.6(18.9)	166.6(19.4)	169.1(20.6)	173.8(22.7)	<0.001
Mean SBP	138.6(10.4)	139.3(10.6)	140.1(10.8)	140.9(11.3)	142.5(11.8)	<0.001

SBP indicates systolic blood pressure; CV, coefficient of variation; SD, standard deviation;

Q1-Q5, coefficient of variation over n visits (n=4, 6, 8, 10).

Table S6. Association between average real variability of visit-to-visit blood pressure variability by quintiles and age, baseline systolic blood pressure, mean systolic blood pressure over n times of follow-up period (n=4, 6, 8, 10)

	ARV					P
4 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	59.2(7.6)	59.5(7.6)	59.8(7.4)	60.3(7.4)	61.2(7.5)	<0.001
Baseline SBP	162.4(18.1)	164.7(18.9)	165.8(19.8)	168.0(20.5)	173.0(22.4)	<0.001
Mean SBP	139.4(12.3)	140.7(12.3)	142.1(12.7)	143.7(12.6)	147.9(14.3)	<0.001
6 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.9(7.5)	59.3(7.5)	59.8(7.4)	60.4(7.5)	61.5(7.4)	<0.001
Baseline SBP	160.9(17.8)	164.2(18.7)	165.5(19.5)	168.8(20.3)	174.0(22.3)	<0.001
Mean SBP	137.8(11.0)	139.8(11.4)	141.2(11.6)	143.1(11.8)	147.3(13.1)	<0.001
8 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.6(7.5)	59.2(7.4)	60.0(7.5)	60.7(7.5)	61.5(7.3)	<0.001
Baseline	160.5(17.4	163.2(18.4	165.8(19.0	169.3(20.2	174.3(22.6	<0.001

SBP	)	)	)	)	)	
Mean SBP	136.7(10.2)	138.7(10.6)	140.3(10.7)	142.2(11.2)	146.3(12.5)	<0.001
10 visits						
	Q1	Q2	Q3	Q4	Q5	
Age	58.6(7.5)	59.2(7.4)	60.0(7.4)	60.6(7.4)	61.8(7.3)	<0.001
Baseline SBP	160.2(17.6)	163.0(18.9)	165.6(18.9)	169.1(20.2)	174.7(22.5)	<0.001
Mean SBP	135.4(9.4)	137.9(9.9)	139.1(10.2)	141.2(10.5)	142.5(11.9)	<0.001

SBP indicates systolic blood pressure; ARV, average real variability; SD, standard deviation;

Q1-Q5, coefficient of variation over n visits (n=4, 6, 8, 10).

Table S7. Multivariate hazard ratios of visit-to-visit systolic blood pressure variability and mean systolic blood pressure for subsequent stroke.

4 visits(N=19932)				
	Events N(%)	Crude HR(95% CI)	Model 1* HR(95% CI)	Model 2† HR(95% CI)
SD	464(2.3)	1.04(1.03,1.05)§	1.04(1.02,1.05)§	1.02(1.01,1.03)§
CV	464(2.3)	1.04(1.02,1.06)§	1.04(1.02,1.06)§	1.03(1.01,1.05)§
ARV	464(2.3)	1.03(1.02,1.04)§	1.02(1.02,1.03)§	1.01(1.00,1.02)‖
		Crude HR(95% CI)	Model 1* HR(95% CI)	Model 3‡ HR(95% CI)
Mean SBP	464(2.3)	1.03(1.03,1.04)§	1.03(1.02,1.03)§	1.02(1.01,1.03)§
6 visits(N=19248)				
	Events N(%)	Crude HR(95% CI)	Model 1* HR(95% CI)	Model 2† HR(95% CI)
SD	365(1.9)	1.06(1.05,1.08)§	1.06(1.04,1.08)§	1.03(1.01,1.05)§
CV	365(1.9)	1.07(1.04,1.10)§	1.06(1.04,1.09)§	1.05(1.02,1.08)§
ARV	365(1.9)	1.04(1.03,1.06)§	1.04(1.03,1.05)§	1.02(1.01,1.04)‖
		Crude HR(95% CI)	Model 1* HR(95% CI)	Model 3‡ HR(95% CI)
Mean SBP	365(1.9)	1.04(1.03,1.04)§	1.03(1.03,1.04)§	1.03(1.02,1.03)§
8 visits(N=18355)				
	Events	Crude	Model 1*	Model 2†

	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	268(1.5)	1.07(1.05,1.10)§	1.07(1.05,1.09)§	1.03(1.01,1.06)§
CV	268(1.5)	1.08(1.04,1.11)§	1.07(1.03,1.11)§	1.05(1.01,1.09)§
ARV	268(1.5)	1.06(1.04,1.07)§	1.05(1.04,1.07)§	1.03(1.01,1.05)‖
		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	268(1.5)	1.04(1.03,1.05)§	1.04(1.03,1.05)§	1.03(1.02,1.04)§
10 visits(N=17292)				
	Events	Crude	Model 1*	Model 2†
	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	183(1.1)	1.08(1.05,1.11)§	1.07(1.04,1.10)§	1.03(1.00,1.06)
CV	183(1.1)	1.08(1.03,1.13)§	1.07(1.02,1.12)§	1.04(0.99,1.09)
ARV	183(1.1)	1.06(1.04,1.09)§	1.06(1.03,1.08)§	1.03(1.01,1.06)‖
		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	183(1.1)	1.05(1.04,1.06)§	1.05(1.03,1.06)§	1.04(1.02,1.05)§
12 visits(N=15962)				
	Events	Crude	Model 1*	Model 2†
	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	109(0.7)	1.09(1.05,1.13)§	1.09(1.05,1.13)§	1.03(0.99,1.08)
CV	109(0.7)	1.09(1.02,1.15)§	1.07(1.01,1.14)‖	1.05(0.98,1.12)
ARV	109(0.7)	1.07(1.04,1.10)§	1.06(1.03,1.09)§	1.03(0.99,1.06)

		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	109(0.7)	1.06(1.04,1.07)§	1.05(1.04,1.07)§	1.05(1.03,1.07)§

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval;

*Model 1 was adjusted for age, sex and center;

†Model 2 was adjusted for age, sex, center, treatment group, 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), and mean systolic blood pressure over the period of n visits.

‡Model 3was adjusted for age, sex, center, treatment group, 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);

§P<0.01; ||P<0.05.

Table S8. Multivariate hazard ratios of visit-to-visit systolic blood pressure variability and mean systolic blood pressure for subsequent ischemic stroke.

4 visits(N=19932)				
	Events N(%)	Crude HR(95% CI)	Model 1* HR(95% CI)	Model 2† HR(95% CI)
SD	379(1.9)	1.04(1.03,1.06)§	1.04(1.02,1.05)§	1.02(1.01,1.04)§
CV	379(1.9)	1.05(1.03,1.07)§	1.04(1.02,1.06)§	1.03(1.01,1.06)§
ARV	379(1.9)	1.03(1.02,1.04)§	1.03(1.02,1.04)§	1.02(1.00,1.03)§
		Crude HR(95% CI)	Model 1* HR(95% CI)	Model 3‡ HR(95% CI)
Mean SBP	379(1.9)	1.03(1.02,1.04)§	1.03(1.02,1.03)§	1.02(1.01,1.02)§
6 visits(N=19248)				
	Events N(%)	Crude HR(95% CI)	Model 1* HR(95% CI)	Model 2† HR(95% CI)
SD	304(1.6)	1.07(1.05,1.09)§	1.06(1.04,1.08)§	1.04(1.02,1.06)§
CV	304(1.6)	1.08(1.05,1.11)§	1.07(1.04,1.10)§	1.06(1.02,1.09)§
ARV	304(1.6)	1.05(1.04,1.06)§	1.04(1.03,1.06)§	1.03(1.01,1.04)§
		Crude HR(95% CI)	Model 1* HR(95% CI)	Model 3‡ HR(95% CI)
Mean SBP	304(1.6)	1.04(1.03,1.05)§	1.03(1.03,1.04)§	1.02(1.01,1.03)§
8 visits(N=18355)				
	Events	Crude	Model 1*	Model 2†

	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	224(1.2)	1.08(1.05,1.10)§	1.07(1.05,1.10)§	1.04(1.01,1.07)§
CV	224(1.2)	1.09(1.05,1.13)§	1.08(1.04,1.12)§	1.06(1.01,1.10)§
ARV	224(1.2)	1.06(1.04,1.08)§	1.06(1.04,1.07)§	1.03(1.01,1.05)§
		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	224(1.2)	1.04(1.03,1.05)§	1.04(1.03,1.05)§	1.03(1.02,1.04)§
10 visits(N=17292)				
	Events	Crude	Model 1*	Model 2†
	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	153(0.9)	1.10(1.07,1.13)§	1.09(1.06,1.12)§	1.04(1.01,1.08)‖
CV	153(0.9)	1.10(1.05,1.16)§	1.10(1.04,1.15)§	1.06(1.01,1.12)‖
ARV	153(0.9)	1.07(1.05,1.10)§	1.07(1.04,1.09)§	1.04(1.01,1.07)§
		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	153(0.9)	1.05(1.04,1.06)§	1.05(1.03,1.06)§	1.04(1.02,1.05)§
12 visits(N=15962)				
	Events	Crude	Model 1*	Model 2†
	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	90(0.6)	1.11(1.07,1.16)§	1.11(1.06,1.15)§	1.06(1.01,1.11)‖
CV	90(0.6)	1.12(1.06,1.20)§	1.11(1.04,1.19)§	1.08(1.01,1.16)‖
ARV	90(0.6)	1.08(1.04,1.11)§	1.07(1.03,1.10)§	1.03(1.00,1.07)

		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	90(0.6)	1.06(1.04,1.07)§	1.05(1.03,1.07)§	1.04(1.02,1.06)§

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval;

*Model 1 was adjusted for age, sex and center;

†Model 2 was adjusted for age, sex, center, treatment group, 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), and mean systolic blood pressure over the period of n visits.

‡Model 3was adjusted for age, sex, center, treatment group, 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);

§P<0.01; ||P<0.05.

Table S9. Multivariate hazard ratios of visit-to-visit systolic blood pressure variability and mean systolic blood pressure for subsequent hemorrhagic stroke.

4 visits(N=19932)				
	Events N(%)	Crude HR(95% CI)	Model 1* HR(95% CI)	Model 2† HR(95% CI)
SD	84(0.4)	1.03(1.00,1.06)	1.03(1.00,1.06)	1.01(0.98,1.04)
CV	84(0.4)	1.02(0.97,1.07)	1.02(0.97,1.07)	1.01(0.96,1.06)
ARV	84(0.4)	1.01(0.99,1.04)	1.02(0.99,1.04)	1.00(0.96,1.06)
		Crude HR(95% CI)	Model 1* HR(95% CI)	Model 3‡ HR(95% CI)
Mean SBP	84(0.4)	1.03(1.02,1.05)§	1.04(1.02,1.05)§	1.04(1.02,1.05)§
6 visits(N=19248)				
	Events N(%)	Crude HR(95% CI)	Model 1* HR(95% CI)	Model 2† HR(95% CI)
SD	60(0.3)	1.04(0.99,1.08)	1.04(1.00,1.09)	1.01(0.96,1.05)
CV	60(0.3)	1.02(0.96,1.09)	1.03(0.96,1.10)	1.01(0.95,1.08)
ARV	60(0.3)	1.02(0.99,1.06)	1.03(0.99,1.06)	1.01(0.95,1.08)
		Crude HR(95% CI)	Model 1* HR(95% CI)	Model 3‡ HR(95% CI)
Mean SBP	60(0.3)	1.04(1.02,1.06)§	1.04(1.02,1.06)§	1.04(1.02,1.06)§
8 visits(N=18355)				
	Events	Crude	Model 1*	Model 2†

	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	44(0.2)	1.04(0.99,1.10)	1.04(0.98,1.10)	1.01(0.95,1.07)
CV	44(0.2)	1.03(0.95,1.13)	1.03(0.94,1.12)	1.01(0.9f31.11)
ARV	44(0.2)	1.04(1.00,1.08)	1.04(1.00,1.08)	1.02(0.98,1.06)
		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	44(0.2)	1.04(1.02,1.06)§	1.04(1.02,1.06)§	1.04(1.02,1.07)§
10 visits(N=17292)				
	Events	Crude	Model 1*	Model 2†
	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	30(0.2)	0.98(0.91,1.06)	0.98(0.90,1.06)	0.95(0.87,1.04)
CV	30(0.2)	0.94(0.83,1.06)	0.94(0.83,1.06)	0.93(0.82,1.06)
ARV	30(0.2)	1.00(0.94,1.07)	1.00(0.94,1.07)	0.98(0.92,1.05)
		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	30(0.2)	1.04(1.01,1.07)‖	1.04(1.01,1.07)‖	1.04(1.01,1.08)‖
12 visits(N=15962)				
	Events	Crude	Model 1*	Model 2†
	N(%)	HR(95% CI)	HR(95% CI)	HR(95% CI)
SD	19(0.1)	0.97(0.97,1.08)	0.97(0.87,1.08)	0.91(0.81,1.03)
CV	19(0.1)	0.88(0.74,1.05)	0.88(0.74,1.05)	0.88(0.74,1.05)
ARV	19(0.1)	1.03(0.95,1.11)	1.03(0.95,1.11)	0.99(0.91,1.08)

		Crude	Model 1*	Model 3‡
		HR(95% CI)	HR(95% CI)	HR(95% CI)
Mean SBP	19(0.1)	1.06(1.02,1.09)§	1.06(1.03,1.10)§	1.08(1.03,1.12)§

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval;

*Model 1 was adjusted for age, sex and center;

†Model 2 was adjusted for age, sex, center, treatment group, 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), and mean systolic blood pressure over the period of n visits.

‡Model 3was adjusted for age, sex, center, treatment group, 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);

§P<0.01; ||P<0.05.

Table S10. The modifying effect of visit-to-visit systolic blood pressure variability over 6 times of visits on subsequent stroke.

	Events N(%)	Crude Model* HR(95% CI)	Model 1† HR(95% CI)	Model 2‡ HR(95% CI)	P value‡	P for trend
SD (Quartiles, mm Hg)						
Q1	47(1.3)	1	1	1		0.0175
Q2	57(1.5)	1.15(0.78,1.69)	1.13(0.77,1.66)	1.13(0.76,1.68)	0.56	
Q3	67(1.7)	1.37(0.94,1.98)	1.30(0.89,1.89)	1.25(0.85,1.84)	0.26	
Q4	80(2.0)	1.62(1.13,2.32)§	1.50(1.05,2.15)‖	1.36(0.94,1.99)	0.10	
Q5	114(3.0)	2.38(1.70,3.35)§	2.13(1.51,3.00)§	1.49(1.03,2.17)‖	0.03	
CV (Quartiles, %)						
Q1	57(1.5)	1	1	1		0.0065
Q2	54(1.4)	0.90(0.62,1.31)	0.88(0.61,1.28)	0.93(0.64,1.36)	0.72	
Q3	69(1.8)	1.16(0.81,1.64)	1.11(0.78,1.58)	1.14(0.79,1.64)	0.48	
Q4	82(2.1)	1.37(0.98,1.92)	1.28(0.92,1.80)	1.30(0.91,1.84)	0.14	
Q5	103(2.7)	1.77(1.28,2.44)§	1.60(1.15,2.21)§	1.42(1.01,2.01)‖	0.04	
ARV (Quartiles, mm Hg)						
Q1	43(1.3)	1	1	1		0.0047
Q2	53(1.4)	1.02(0.68,1.53)	1.00(0.67,1.50)	0.98(0.65,1.48)	0.92	
Q3	70(1.7)	1.30(0.89,1.90)	1.24(0.85,1.81)	1.17(0.79,1.73)	0.43	
Q4	75(1.9)	1.39(0.96,2.03)	1.31(0.90,1.91)	1.18(0.80,1.74)	0.41	
Q5	124(3.0)	2.29(1.62,3.24)§	2.07(1.46,2.94)§	1.55(1.07,2.25)‖	0.02	

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; HR, hazard ratio; CI, confidence interval;

SD Q1-Q5 indicates each quintiles of SD (1.24-9.90, 9.90-12.74, 12.74-15.46, 15.46-19.15, 19.15-43.55 mm Hg);

CV Q1-Q5, each quintiles of CV (1.05-7.08, 7.08-9.07, 9.07-10.94, 10.94-13.32, 13.32-28.64 %);

ARV Q1-Q5, each quintiles of ARV (0.80-10.00, 10.13-13.73, 13.87-17.53, 17.60-22.60, 22.67-61.07 mm Hg);

*Crude model was unadjusted.

†Model 1 was adjusted for age, sex and center;

‡Model 2 was adjusted for age, sex, center, treatment group, 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), and mean systolic blood pressure over the period of 6 visits

§$P<0.01$; ||$P<0.05$.

Table S11. The modifying effect of visit-to-visit systolic blood pressure variability over 8 times of visits on subsequent stroke.

	Events N(%)	Crude Model* HR(95% CI)	Model 1† HR(95% CI)	Model 2‡ HR(95% CI)	P value‡	P for trend
SD (quintiles, mm Hg)						
Q1	34(1.0)	1	1	1		0.047
Q2	42(1.1)	1.14(0.73,1.80)	1.11(0.70,1.74)	1.08(0.68,1.73)	0.74	
Q3	50(1.3)	1.37(0.88,2.11)	1.30(0.84,2.01)	1.26(0.80,1.97)	0.32	
Q4	50(1.3)	1.35(0.88,2.09)	1.25(0.81,1.94)	1.07(0.68,1.70)	0.76	
Q5	92(2.5)	2.63(1.77,3.90)§	2.38(1.60,3.54)§	1.59(1.03,2.46)‖	0.03	
CV (quintiles, %)						
Q1	42(1.2)	1	1	1		0.041
Q2	39(1.0)	0.85(0.55,1.31)	0.83(0.54,1.28)	0.86(0.55,1.35)	0.52	
Q3	53(1.4)	1.15(0.77,1.73)	1.10(0.74,1.65)	1.14(0.75,1.72)	0.54	
Q4	53(1.4)	1.15(0.77,1.73)	1.08(0.72,1.61)	1.02(0.67,1.55)	0.93	
Q5	81(2.2)	1.83(1.26,2.65)§	1.69(1.16,2.45)§	1.49(1.00,2.21)	0.05	
ARV (quintiles, mm Hg)						
Q1	24(0.9)	1	1	1		0.0022
Q2	46(1.2)	1.36(0.83,2.23)	1.33(0.81,2.18)	1.21(0.73,2.01)	0.46	
Q3	37(1.0)	1.08(0.65,1.81)	1.03(0.62,1.72)	0.95(0.56,1.60)	0.83	
Q4	62(1.6)	1.77(1.11,2.84)‖	1.66(1.03,2.66)‖	1.42(0.87,2.31)	0.16	
Q5	99(2.4)	2.77(1.78,4.33)§	2.54(1.62,3.98)§	1.78(1.11,2.86)‖	0.02	

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; HR, hazard ratio; CI, confidence interval;

SD Q1-Q5 indicates each quintiles of SD (2.0-10.5, 10.5-13.1, 13.1-15.6, 15.6-18.9, 18.9-47.8 mmHg)

CV Q1-Q5, each quintiles of CV (1.5-7.6, 7.6-9.4, 9.4-11.1, 11.1-13.2, 13.2-29.0 %)

ARV Q1-Q5, each quintiles of ARV (1.7-10.4, 10.5-13.9, 14.0-17.2, 17.2-21.5, 21.5-56.0 mmHg)

*Crude model was unadjusted.

†Model 1 was adjusted for age, sex and center;

‡Model 2 was adjusted for age, sex, center, treatment group, 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), and mean systolic blood pressure over the period of 6 visits

§$P<0.01$; ||$P<0.05$.

Table S12. The modifying effect of visit-to-visit systolic blood pressure variability over 6 times of visits on subsequent ischemic stroke.

	Events N(%)	Crude Model* HR(95% CI)	Model 1† HR(95% CI)	Model 2‡ HR(95% CI)	P value‡	P for trend
SD (quintiles, mm Hg)						
Q1	39(1.1)	1	1	1		0.022
Q2	47(1.2)	1.14(0.75,1.75)	1.11(0.73,1.70)	1.09(0.71,1.69)	0.69	
Q3	55(1.4)	1.35(0.90,2.03)	1.26(0.84,1.90)	1.20(0.78,1.83)	0.40	
Q4	64(1.6)	1.56(1.04,2.32)‖	1.41(0.95,2.11)	1.28(0.84,1.93)	0.24	
Q5	99(2.6)	2.49(1.72,3.61)§	2.15(1.48,3.12)§	1.53(1.02,2.30)‖	0.04	
CV (quintiles, %)						
Q1	48(1.3)	1	1	1		0.0075
Q2	43(1.1)	0.86(0.57,1.29)	0.82(0.55,1.24)	0.86(0.57,1.31)	0.48	
Q3	54(14)	1.07(0.73,1.58)	1.02(0.69,1.50)	1.03(0.69,1.53)	0.89	
Q4	71(1.8)	1.40(0.97,2.03)	1.29(0.90,1.87)	1.30(0.89,1.90)	0.17	
Q5	88(2.3)	1.79(1.26,2.55)§	1.57(1.10,2.24)‖	1.41(0.97,2.05)	0.07	
ARV (quintiles, mm Hg)						
Q1	36(1.1)	1	1	1		0.0091
Q2	45(1.2)	1.04(0.67,1.61)	1.01(0.65,1.57)	0.97(0.62,1.52)	0.89	
Q3	56(1.4)	1.24(0.81,1.88)	1.17(0.77,1.77)	1.08(0.70,1.67)	0.72	
Q4	60(1.5)	1.33(0.88,2.01)	1.22(0.81,1.85)	1.08(0.71,1.66)	0.71	
Q5	107(2.6)	2.36(1.62,3.44)§	2.07(1.42,3.03)§	1.56(1.04,2.34)‖	0.03	

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; HR, hazard ratio; CI, confidence interval;

SD Q1-Q5 indicates each quintiles of SD (1.24-9.90, 9.90-12.74, 12.74-15.46, 15.46-19.15, 19.15-43.55 mm Hg);

CV Q1-Q5, each quintiles of CV (1.05-7.08, 7.08-9.07, 9.07-10.94, 10.94-13.32, 13.32-28.64 %);

ARV Q1-Q5, each quintiles of ARV (0.80-10.00, 10.13-13.73, 13.87-17.53, 17.60-22.60, 22.67-61.07 mm Hg);

*Crude model was unadjusted.

†Model 1 was adjusted for age, sex and center;

‡Model 2 was adjusted for age, sex, center, treatment group, 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), and mean systolic blood pressure over the period of 6 visits

§$P<0.01$; ||$P<0.05$.

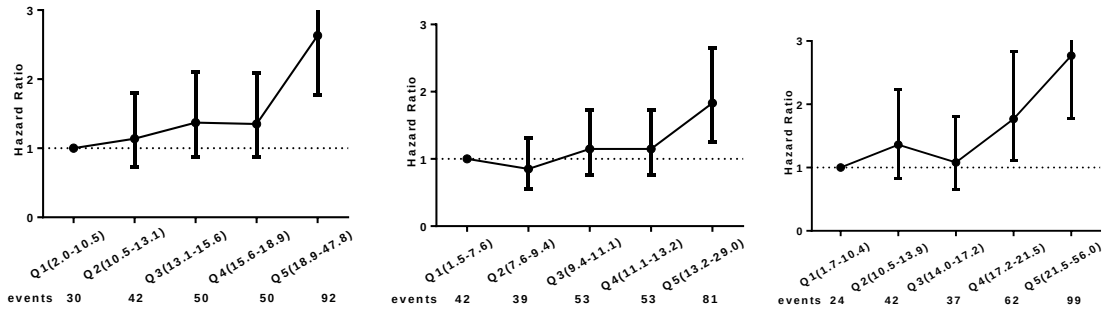
Table S13. Stratified comparisons of visit-to-visit systolic blood pressure variability over 6 visits.

	Males (N=7830) Mean(SD)	Females (N=11418) Mean(SD)	P value
SBPV-SD, mm Hg	14.7(5.7)	14.8(5.5)	0.083
SBPV-CV,%	10.3(3.8)	10.4(3.7)	0.140
SBPV-ARV, mm Hg	17.1(7.6)	17.3(7.5)	0.093
	Age<60years (N=9670) Mean(SD)	Age≥60years (N=9578) Mean(SD)	
SBPV-SD, mm Hg	14.2(5.4)	15.4(5.7)	<0.001
SBPV-CV,%	10.1(3.6)	10.7(3.8)	<0.001
SBPV-ARV, mm Hg	16.4(7.2)	18.0(7.8)	<0.001
	BMI<25kg/m2 (N=10197) Mean(SD)	BMI>25 kg/m2 (N=9043) Mean(SD)	
SBPV-SD, mm Hg	14.9(5.7)	14.6(5.5)	<0.001
SBPV-CV,%	10.5(3.8)	10.2(3.6)	<0.001
SBPV-ARV,	17.5(7.7)	16.9(7.3)	<0.001

mm Hg			
	Mean SBP<140mm Hg(N=8921) Mean(SD)	Mean SBP>140mm Hg(N=10327) Mean(SD)	
SBPV-SD, mm Hg	13.2(4.8)	16.1(5.9)	<0.001
SBPV-CV,%	10.0(3.6)	10.7(3.8)	<0.001
SBPV-ARV, mm Hg	15.4(6.5)	18.8(8.0)	<0.001

SD indicates standard deviation; CV, coefficient of variation; ARV, average real variability; SBPV, systolic blood pressure variability; SBP, systolic blood pressure.

Figure S1. Hazard ratios for risk of subsequent stroke by quintiles of visit-to-visit blood pressure variability over 8 visits (SD, CV and ARV).



The hazard ratios (95% CI) for risks of subsequent stroke in crude model, by quintiles of visit-to-visit systolic blood pressure variability parameters over the first eight visits (standard deviation, coefficient of variation and average real variability respectively by order). The first quintiles of each parameter is the reference category. Numbers of subsequent stroke events by quintiles are given in Table S11; Q1-Q5, each quintile of the same parameters.