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Association Between Annual Visit-to-Visit Blood Pressure Variability and Stroke in Postmenopausal Women

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Abstract—Accumulating evidence suggests that increased visit-to-visit variability (VVV) of blood pressure is associated with stroke. No study has examined the association between VVV of blood pressure and stroke in postmenopausal women, and scarce data exist as to whether this relation is independent of the temporal trend of blood pressure. We examined the association of VVV of blood pressure with stroke in 58 228 postmenopausal women enrolled in the Women's Health Initiative. Duplicate blood pressure readings, which were averaged, were taken at baseline and at each annual visit. VVV was defined as the SD for the participant's mean systolic blood pressure (SBP) across visits (SD) and about the participant's regression line with SBP regressed across visits (SDreg). Over a median follow-up of 5.4 years, 997 strokes occurred. In an adjusted model including mean SBP over time, the hazard ratios (95% CI) of stroke for higher quartiles of SD of SBP compared with the lowest quartile (referent) were 1.39 (1.03–1.89) for quartile 2, 1.52 (1.13–2.03) for quartile 3, and 1.72 (1.28–2.32) for quartile 4 (P trend $<$0.001). The relation was similar for SDreg of SBP quartiles in a model that additionally adjusted for the temporal trend in SBP (P trend $<$0.001). The associations did not differ by stroke type (ischemic versus hemorrhagic). There was a significant interaction between mean SBP and SDreg on stroke with the strongest association seen below 120 mm Hg. In postmenopausal women, greater VVV of SBP was associated with increased risk of stroke, particularly in the lowest range of mean SBP. **(*Hypertension*. 2012;60: 625-630.)** ● **Online Data Supplement**

Key Words: hypertension ■ blood pressure ■ stroke ■ postmenopause ■ women

In the United States, stroke is the fourth leading cause of death[1] and the leading cause of disability.[2] Women have lower age-adjusted stroke incidence than men.[2] However, because of the longer life expectancy in women, the lifetime risk of stroke is greater in women compared with men. Women also account for a large proportion of stroke deaths and disability after stroke.[2] A better understanding of the determinants of stroke in women has substantial implications in both the clinical and public health context.

Elevated blood pressure is a risk factor for stroke.[3] The prognostic value of blood pressure is based on the traditional method of obtaining auscultatory measurements in a clinic setting, typically averaged over several visits.[4] It is generally believed that readings obtained in this manner are limited by variability observed from one visit to the next.[5] However, there is accumulating evidence that increased visit-to-visit variability (VVV) of blood pressure is associated with a higher risk of stroke,[6] coronary heart disease,[7] and all-cause mortality,[8,9] associations that are independent of average blood pressure over time and other possible explanatory factors.

Studies reporting on VVV of blood pressure and prognosis have been relatively small[8,9] and included select patients who were already at high cardiovascular disease (CVD) risk.[6] Only one published study has specifically reported on stroke as an outcome.[6] This latter study included patients with previous transient ischemic attack, stroke, or multiple CVD risk factors.[6] Further, although individuals who have an increasing blood pressure over time may have a higher risk of stroke, scarce data exist as to whether the relation of VVV of

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From the Department of Medicine (D.S., J.D.N.), Columbia University Medical Center, New York, NY; Fred Hutchinson Cancer Research Center (A.K.A.), Seattle, WA; Department of Social and Preventive Medicine (M.J.L.), School of Public Health and Health Professions, University at Buffalo-State University of New York, Buffalo, NY; Department of Medicine (A.A.B.), University of Florida, Gainesville, FL; Department of Family and Preventive Medicine (M.A.), University of California San Diego, San Diego, CA; Division of Preventive Medicine (J.E.M.), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Epidemiology and Population Health (S.W.-S.), Albert Einstein College of Medicine, Bronx, NY.

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Correspondence to Daichi Shimbo, Columbia University Medical Center, 622 West 168th St, PH 9-310, New York, NY 10032. E-mail ds2231@columbia.edu

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blood pressure and stroke is independent of blood pressure increases over time.[6] Finally, no study has previously examined these relations in postmenopausal women, who are at increased risk for stroke. We determined whether VVV of blood pressure is associated with stroke and whether this relation is independent of the mean and temporal change in blood pressure over time, in a large well-characterized cohort of postmenopausal women with a wide range of CVD risk enrolled in the Women's Health Initiative (WHI).

Methods

Sample Population

WHI is a multicenter study of 161 808 postmenopausal women aged 50 to 79 years consisting of overlapping clinical trials and an observational study.[10] This analysis restricts the population to women enrolled in the clinical trial components (N=68 132) and excludes women who did not have blood pressure assessed at the baseline visit and ≥2 follow-up visits up to the year 3 visit, had experienced an incident stroke and/or mortality event before their year 3 visit, or did not have a year 3 visit or any subsequent follow-up, leaving a final sample size of 58 228. The online-only Data Supplement provides further details on the design of WHI and how the sample for the current analyses was selected. The protocol was approved by institutional review boards of the participating institutions; all of the trial participants provided written informed consent.

Blood Pressure and Heart Rate Measurement

Blood pressure and heart rate were measured at baseline and each annual study visit by certified staff with the use of standardized procedures and instruments. Appropriate cuff bladder size was determined at each visit based on arm circumference. Blood pressure was measured in the right arm with a mercury sphygmomanometer after the participant was seated and had rested for 5 minutes; 2 measures, taken 30 seconds apart, were recorded. The blood pressure at each visit was defined as the average of the 2 readings. Heart rate was measured manually once at each visit.

Outcome Ascertainment

Detailed definitions and methods for ascertaining and classifying outcomes have been published.[11] Briefly, fatal and nonfatal strokes were verified by review of medical charts by centrally trained physician adjudicators at each center. Stroke cases were centrally adjudicated at the WHI Clinical Coordinating Center. Stroke was defined as the rapid onset of a neurologic deficit lasting >24 hours, unless death supervened or a lesion compatible with acute stroke was evident on computed tomography or MRI scan. For this analysis, the primary outcome was defined as the occurrence of a fatal or nonfatal ischemic or hemorrhagic stroke. Ischemic stroke was defined as the occlusion of cerebral or pericerebral arteries with infarction not resulting from a procedure (cerebral thrombosis, cerebral embolism, or lacunar infarction). Hemorrhagic stroke was defined as subarachnoid hemorrhage, intracerebral hemorrhage, or other/unspecified intracranial hemorrhage not resulting from a procedure (nontraumatic epidural hemorrhage or subdural hemorrhage).

Statistical Analyses

VVV of blood pressure, the primary exposure, was defined as the SD about the participant's mean systolic blood pressure (SBP) across visits.[6,8,9] VVV of blood pressure was also defined as the SD about the participant's regression line (SDreg) with SBP regressed across visits. The estimation of SD assumes that a participant's blood pressure is constant over follow-up, and the estimation of SDreg assumes a linear temporal trend. The online-only Data Supplement provides further details on the definitions of SD and SDreg. Other measures of VVV, such as coefficient of variation and variation independent of the mean,[6,8,9] were not pursued, because these measures were highly correlated with SD (r=0.97 for the correlation between SD and coefficient of variation; r=0.90 for the correlation between SD and variation independent of the mean) and, therefore, likely represent the same underlying domain of blood pressure variability.

Baseline characteristics of participants were examined by SD of SBP quartiles. Tests for linear trend across quartiles were adjusted for age, race/ethnicity, and randomization assignment in the hormone therapy trial. Primary analyses used time-to-event methods based on the Cox regression model with time defined as the number of days from the third annual visit to the first postrandomization diagnosis of stroke. Stroke events were included through the protocol-specified termination date of March 31, 2005. The online-only Data Supplement provides details on how covariates were ascertained and defined. An initial model (model 1) provided hazard ratios for stroke associated with SD of SBP quartiles, with the lowest quartile serving as the referent, adjusting for age and race/ethnicity and allowing the hazard function to vary by 5-year age groups. Model 2 included covariates in model 1 plus the baseline status of diabetes mellitus, high cholesterol, smoking status, education level, previous hormone therapy use, physical activity level, body mass index, history of coronary heart disease, history of atrial fibrillation, left ventricular hypertrophy on 12-lead ECG, and additional stratification on history of stroke and hormone therapy trial assignment; mean SBP across visits (time-dependent variable); mean heart rate across visits (time-dependent variable); and antihypertensive medication use across visits (time-dependent variable). Antihypertensive medication use across visits was defined as never used (no antihypertensive medication use at baseline and all available follow-up visits), used at all visits (on antihypertensive medications at baseline and all available follow-up visits), newly started during follow-up (on no antihypertensive medications at baseline and on antihypertensive medications at one of the follow-up exams), and other (not in one of the above categories). To account for systematic changes in blood pressure, the final model (model 3) used SDreg of SBP as the exposure variable and included the covariates in model 2 plus a participant's linear change in SBP. All of the time-dependent variables, including SD and SDreg, were based on measures through year 3 and later updated at each subsequent visit, while a participant remained at risk. Models 1 to 3 were also fit with the corresponding exposure variable, SD or SDreg, modeled as a continuous variable.

Subgroup analyses tested interactions between SDreg of SBP and several baseline characteristics within the final Cox regression model. An additional analysis was performed in which mean diastolic blood pressure across visits was added to model 3. The relations across quartiles of SDreg of SBP remained unchanged. Similar findings were observed when SD of diastolic blood pressure was added to the multivariable model. Lastly, results did not change when mean pulse pressure across visits was added to model 3 instead of mean diastolic blood pressure across visits. We do not report further on these analyses, because the results do not alter the primary findings of the study.

All of the statistical tests were 2 sided, and P values <0.05 were considered to be statistically significant. Analyses were performed by SAS statistical software version 9.2 (SAS Inc, Cary, NC), and figures were constructed with R version 2.11.[12]

Results

Characteristics and Correlates of VVV of SBP

The means (SD) of the SD of SBP and of SBP across visits were 10.9 mm Hg (4.5 mm Hg) and 125.8 mm Hg (12.9 mm Hg), respectively. Higher quartiles of SD of SBP were associated with older age; higher body mass index; higher mean SBP, diastolic blood pressure, and pulse pressure; a small decrease in mean heart rate; randomization to the hormone therapy component; black race; not having successfully obtained a college degree or higher; antihypertensive medication use across visits; history of hypertension; statin,

Table. Hazard Ratios for Stroke by Quartiles of Visit-to-Visit Variability of Systolic Blood Pressure (Top Panel) and per Each 5-mm Hg Increase in Visit-to-Visit Variability of Systolic Blood Pressure (Bottom Panel)

		Visit-to-Visit Variability of Systolic Blood Pressure Modeled as Quartiles				
Characteristics		Q1	Q2	Q3	Q4	*P* Value for Trend
SD of systolic blood pressure, mm Hg		<6	6.0–8.9	9.0–12.9	≥13.0	. . .
Cases of stroke		150	212	260	375	. . .
Annualized %		0.20	0.26	0.32	0.49	. . .
Model		Hazard Ratio (95% CI)				*P* Value
Model 1†	1.00 (ref)	1.50 (1.11–2.03)	1.95 (1.46–2.60)	2.91 (2.19–3.86)		<0.001
Model 2‡	1.00 (ref)	1.39 (1.03–1.89)	1.52 (1.13–2.03)	1.72 (1.28–2.32)		<0.001
Model 3§	1.00 (ref)	1.08 (0.84–1.39)	1.26 (0.99–1.59)	1.46 (1.15–1.85)		<0.001
Visit-to-Visit Variability of Systolic Blood Pressure Modeled as a Continuous Variable (Per Each 5-mm Hg Increase)						
Model		Hazard Ratio (95% CI)				*P* Value
Model 1†		1.40 (1.32–1.49)				<0.001
Model 2‡		1.16 (1.08–1.24)				<0.001
Model 3§		1.12 (1.05–1.19)				<0.001

Data represent the SD from the mean in models 1 and 2 and the standard deviation (SDreg) from the least-squares regression line in model 3. Ref indicates referent; Q, quartile.

†Model 1 includes adjustment for age at baseline and race/ethnicity and stratified by 5-y age groups.

‡Model 2 includes adjustment for variables in model 1 plus baseline variables including diabetes mellitus, high cholesterol, smoking, education level, previous hormone therapy use, physical activity, body mass index, history of coronary heart disease, history of atrial fibrillation, left ventricular hypertrophy on 12-lead ECG, and additional stratification on history of stroke and hormone therapy trial assignment; mean systolic blood pressure (time-dependent variable); mean heart rate (time-dependent variable); and the use of antihypertensive medications (time-dependent variable).

§Model 3 includes adjustment for variables in model 2 and additionally the temporal trend (estimated slope from least-squares regression line) of systolic blood pressure (time dependent).

aspirin, and anticoagulation use; history of diabetes mellitus and high cholesterol; smoking status; the presence of left ventricular hypertrophy; history of coronary heart disease; history of stroke; history of atrial fibrillation; and lower physical activity (Table S1 in the online-only Data Supplement).

Relation Between VVV of SBP and Stroke

The mean (SD) number of visits that were used to estimate SD of SBP was 7.9 (1.8). Over a median (interquartile rate) follow-up of 5.4 years (1.7 years), a total (annualized rate) of 997 (0.32%) strokes occurred during 315 789 person-years of observation. Of the primary stroke events, 81.3% were ischemic and 18.7% were hemorrhagic. In an age-stratified model adjusted for age and race/ethnicity (model 1, top panel, Table), higher quartiles of the SD of SBP were significantly associated with an increasing risk of stroke. After further adjustment for CVD risk factors, prevalent CVD, mean SBP, mean heart rate, and antihypertensive medication use (model 2, top panel, Table), the relation between SD of SBP and stroke was attenuated, but the trend across quartiles remained significant. In a fully adjusted model that also accounted for linear change of SBP (model 3, top panel, Table), increasing quartiles of SDreg of SBP were significantly related to higher stroke risks. In this latter model, a steeper slope of SBP across visits was also associated with a higher risk of stroke ($P<0.05$). A similar pattern of results was observed when SD (models 1 and 2) or SDreg (model 3) of SBP was expressed as a continuous variable (bottom panel, Table). The hazard ratios (95% CIs) for each 5-mm Hg increase in SD of SBP did not differ by stroke type in model 2: 1.15 (95% CI, 1.07–1.25) for ischemic stroke and 1.18 (95% CI, 1.00–1.40) for hemorrhagic stroke (heterogeneity $P=0.78$). The hazard ratios (95% CIs) for each 5-mm Hg increase in SDreg of SBP also did not differ by stroke type in model 3, 1.12 (95% CI, 1.04–1.21) for ischemic stroke and 1.14 (95% CI, 0.97–1.34) for hemorrhagic stroke (heterogeneity $P=0.86$).

Subgroup Analyses

As Table S2 shows (see online-only Data Supplement), there was a significant interaction (interaction $P=0.005$) between mean SBP across visits and SDreg of SBP on stroke. The relation between SDreg of SBP and stroke became stronger with decreasing levels of mean SBP <140 mm Hg, particularly among individuals with mean SBP <120 mm Hg. In participants with mean SBP <120 mm Hg, the prevalence of episodic systolic hypertension (ie, having ≥1 visit with SBP >140 mm Hg) by quartiles of SDreg of SBP (<6, 6.0–8.9, 9.0–12.9, and ≥13.0 mm Hg) was 0.1%, 0.7%, 6.2%, and 39.6%, respectively. Participants with mean SBP <120 mm Hg and who were in the highest quartile of SDreg of SBP (≥13 mm Hg) had less than one third of their visits with SBP >140 mm Hg.

The hazard ratio for stroke was greater in younger than in older women (Table S2), although the interaction was borderline significant (interaction $P=0.05$). There was also a significant interaction of the number of visits used to estimate SDreg of SBP on the relationship between SDreg of SBP and stroke (Table S3 in the online-only Data Supplement).

Discussion

This study adds important information to the literature on VVV of blood pressure and stroke. Higher annual VVV of

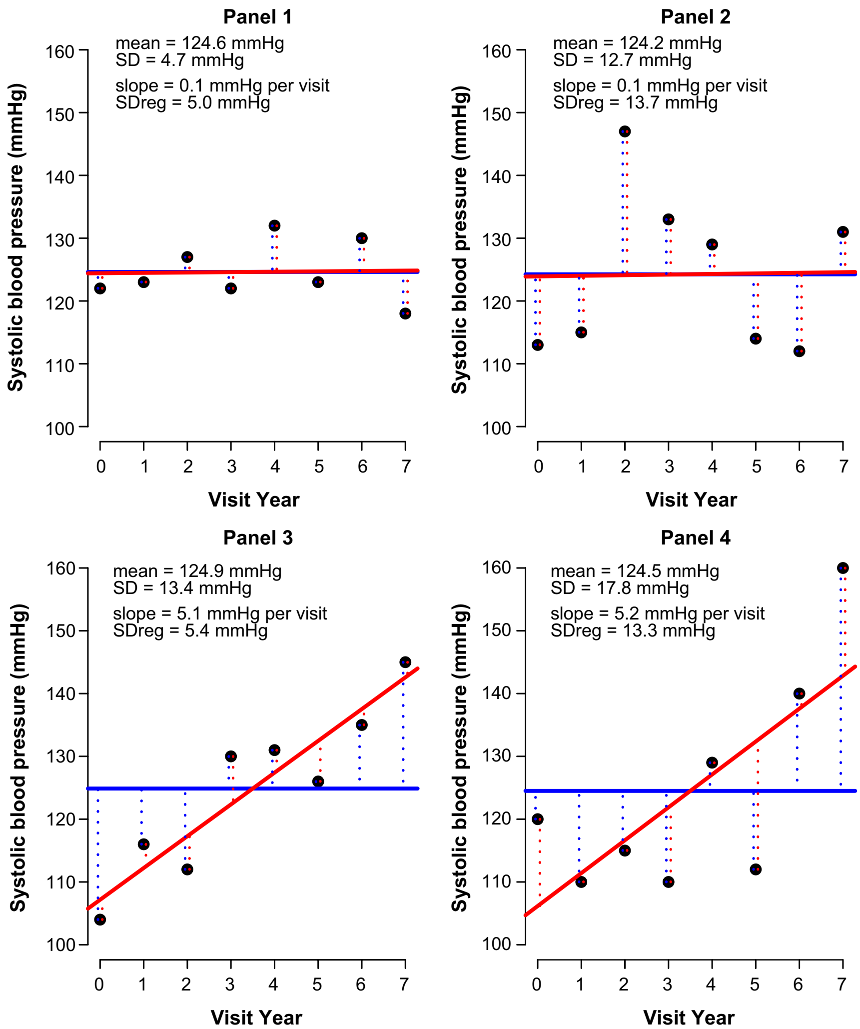

Figure. Representative patterns of visit-to-visit blood pressure variability. Plots illustrate systolic blood pressure (SBP) measures over follow-up of 4 different individuals (panels 1–4) with approximately the same mean SBP across visits. SDs from the mean and least-squares regression line are labeled "SD" and "SDreg," respectively. Slope of the regression line is labeled "slope." SBP at each visit is represented by black dots. SD is a measure of the VVV of SBP about the individual's mean (solid blue line), where the mean is assumed to be static. SDreg is a measure of the VVV of SBP about the individual's regression line (solid red line), where the mean (ie, regression line) is assumed to be a linear function of time. Conceptually, SD is the "average" of the deviations (lengths of dotted blue lines) about the mean (solid blue line), and SDreg is the average of the deviations (lengths of dotted red lines) about the regression line (solid red line). The 2 individuals in panels 3 and 4 (**bottom left** and **right panels**) have a larger temporal change in SBP across visits than the 2 individuals in panels 1 and 2 (**upper left** and **right panels**). The individual in panel 3 has a higher SD from the mean but a similar SDreg from the regression line compared with the individual in panel 1. A similar pattern is seen with the 2 individuals in panels 4 and 2. Furthermore, despite having similar mean SBP across visits, the individuals in panels 1 and 2 and, separately, the individuals in panels 3 and 4, have different SDs from the mean and also different SDregs from the regression line.

SBP was associated with an increased risk of stroke, independent of several possible explanatory factors, including age, race/ethnicity, CVD risk factors, prevalent CVD, randomization to hormone therapy, antihypertensive medication use, and mean SBP over time.

Rothwell et al[6] showed that higher VVV of SBP was associated with stroke in 4 cohorts that included >7000 patients who were already at high risk for stroke, including those with previous transient ischemic attack or minor stroke. Higher VVV of SBP was also associated with stroke in treated hypertensive patients who had ≥3 other CVD risk factors or prevalent CVD enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm.[6] Our study extends these findings by demonstrating that higher levels of annual VVV of SBP are independently associated with an increased risk of stroke in postmenopausal women representing a broad range of CVD risk.

VVV of blood pressure is commonly defined as SD of SBP.[6,8,9] Because SD of SBP represents the deviation of SBP from the mean, which is assumed to be static over time, then it is generally true that SD of SBP is higher with a greater linear increase in SBP over time compared with SBP that remains constant over time. Therefore, it is possible that the association between VVV of blood pressure and stroke may be explained by increasing blood pressure over time. However, in our study, SDreg of SBP and an increased temporal trend in SBP were independently associated with stroke, indicating that not only is an increase in blood pressure over time associated with stroke, but also VVV of blood pressure contributes to stroke in a manner that is independent of blood pressure trends. Rothwell et al[6] similarly reported that the relation between VVV of SBP and stroke was independent of the temporal trend in SBP. The Figure shows VVV and slopes of SBP in 4 representative individuals in our study who have approximately the same mean SBP. These examples are illustrative of how SD of SBP from the mean is partially determined by the temporal trend of SBP and that the SDreg of SBP from the regression line represents variability that is independent of the temporal trend of SBP. Although other studies have demonstrated a relation of VVV of blood pressure with total mortality,[8,9] cardiovascular mortality,[9] increased white matter hyperintensity volume in the brain,[13] and carotid intima-media thickness,[14] these studies did not examine whether the relations between VVV of blood pressure and these outcomes were independent of a temporal trend in blood pressure.

The relation between VVV of SBP and stroke was stronger in postmenopausal women with SBP in the lowest range (mean, <120 mm Hg). SBP was >140 mm Hg in a minority of visits in these participants. The VVV of SBP-stroke association was also possibly modified by younger age; the risk of stroke was stronger in the 50- to 59-year age category. Similar findings were reported in the study by Rothwell et al[6] in which the relation between VVV of SBP and stroke was stronger in participants who had mean SBP less than the median (≈143 mm Hg) and in those in the youngest tertile of age (<56 years). Therefore, VVV of blood pressure may be an important determinant of stroke, particularly in individuals who otherwise would be considered to be low risk based on their SBP and age.

As demonstrated by others,[6] the risk for stroke increased with the number of visits used to estimate VVV. The reproducibility of VVV of blood pressure may also increase with more measurements.[15,16] Therefore, for evaluating an individual's risk associated with VVV of blood pressure, clinicians should be wary in using only a few visits to estimate VVV. Future studies are needed to determine the minimum number of visits required to obtain reproducible and valid estimates of VVV. In addition, the optimal interval between visits (ie, days, months, or years) should also be determined.

The putative factors that explain the link between VVV of SBP and stroke are unclear. Arterial stiffness may play a role.[14] Subclinical atherosclerosis, increased wall stress, baroreceptor dysfunction, and endothelial dysfunction are other possible mechanisms.[6,8,17,18] However, it is unclear whether these factors are causes or consequences of VVV of SBP. Finally, the mechanisms into why lower SBP and younger age modified the relation between VVV of SBP and stroke in postmenopausal women needs to be clarified in future studies.

Finally, our study found that the relationship between VVV of SBP and stroke did not differ by stroke type (ie, ischemic versus hemorrhagic). In contrast, Rothwell et al[6] found that VVV of SBP was more predictive of ischemic than hemorrhagic strokes in treated hypertensive participants enrolled in Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm. The reasons for these divergent results are unclear. The different populations examined and the substantially smaller percentage of hemorrhagic versus ischemic strokes in either sample may be possible explanatory factors.

The sample was composed only women, whose age was restricted to 50 to 79 years. Thus, whether our results can be extended to men, elderly women, or younger premenopausal women remains to be determined. Furthermore, our analyses did not consider the various classes of antihypertensive medications that women may have been taking. Certain antihypertensive medication classes may have differential effects on VVV of SBP.[19,20] However, the relation of VVV of SBP with outcomes is also independent of antihypertensive medication class.[6,8] Lastly, it is possible that blood pressure readings were affected by measurement error in our study. However, because the presence of measurement error would have biased our results toward the null, it is likely that the association between VVV of SBP and stroke would be even stronger if measurement error were eliminated.

Major strengths of the study are the very large sample size, well-characterized cohort, and the large number of strokes that were available for analysis. This allowed for the consideration of several possible confounders in the relation between VVV of SBP and stroke and also the examination of this relation across various subgroups. An additional strength of the study was the careful and standardized assessment of blood pressure and cardiovascular risk factors in WHI and the central adjudication of all reported stroke events by study neurologists. Furthermore, the participants in WHI represent a broad ethnic, geographic, and socioeconomic sample of women in the United States. Finally, this is one of the few studies to examine whether the relation of VVV of blood pressure and stroke is independent of blood pressure increases over time.

Perspectives

The results from this large study of generally healthy postmenopausal women suggest that higher levels of annual VVV of SBP are independently associated with an increased risk of stroke. The increase in stroke risk is not explained by important factors, such as age, race/ethnicity, CVD risk factors, prevalent CVD, use of antihypertensive medications or hormone therapy, mean SBP over time, and the temporal trend of SBP. Notably, the association between VVV of SBP and stroke is stronger among women whose mean SBP is in the lowest range, which suggests a possible role for measures of VVV of blood pressure in refining office-based risk assessment. Future studies should identify the causal pathways that underlie the relation between VVV of SBP and stroke and investigate the mechanisms as to why the association between VVV and stroke is stronger in postmenopausal women with the lowest SBP.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study examines whether annual VVV of blood pressure is associated with stroke in postmenopausal women who have a wide range of CVD risk and whether this relation is independent of the temporal trend of blood pressure, which is a factor that contributes to VVV of blood pressure.
- The large sample size facilitates the examination of this relation across several subgroups.

What Is Relevant?

- The study examines whether VVV of blood pressure is independently associated with stroke, an important hypertension-related outcome.

Summary

In postmenopausal women, greater VVV of SBP was independently associated with increased risk of stroke. A stronger association was observed in those with mean SBP in the lowest range.

ONLINE SUPPLEMENT

ASSOCIATION BETWEEN ANNUAL VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY AND STROKE IN POSTMENOPAUSAL WOMEN: DATA FROM THE WOMEN'S HEALTH INITIATIVE

Short title: Blood Pressure Variability

Daichi Shimbo, MD[1]; Jonathan D. Newman, MD, MPH[1], Aaron K. Aragaki, MS[2]; Michael J. LaMonte, PhD[3]; Anthony A. Bavry, MD, MPH[4]; Matthew Allison, MD, MPH[5]; JoAnn E. Manson, MD, DrPH[6]; Sylvia Wassertheil-Smoller, PhD[7]

[1]Department of Medicine, Columbia University Medical Center, New York, NY

[2]Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Department of Social and Preventive Medicine, School of Public Health and Health Professions, University at Buffalo – SUNY, Buffalo, NY

[4]Department of Medicine, University of Florida, Gainesville, FL

[5]Department of Family and Preventive Medicine, University of California San Diego, San Diego, CA

[6]Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[7]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

Corresponding Author: Daichi Shimbo, MD; Columbia University Medical Center

622 West 168th Street, PH 9-310; New York, NY 10032; (212) 342-4490 Fax: (646) 304-7003

Email: ds2231@columbia.edu

Study Design

WHI is a multi-center study of 161,808 postmenopausal women aged 50 to 79 years consisting of overlapping clinical trials (CTs) and an observational study (OS).[1] Women were screened for participation in one or both of the trial components of the CT — dietary modification or hormone therapy. Women who were ineligible for, or unwilling to enroll in, these CT components were invited to enroll in the OS. The OS is a long-term prospective cohort study to identify and assess the impact of biological, lifestyle, biochemical, and genetic factors on the risk of heart disease, cancer, osteoporosis, and other major health events. CT participants were invited to join the calcium plus vitamin D (CaD) trial at their first or second annual follow-up visit, after initial randomization into the dietary modification and/or hormone therapy trials. The CT components examined multiple end points, including cardiovascular disease, cancer, and osteoporotic fractures. Women were excluded from the CTs for a variety of reasons including competing medical conditions, concerns about safety, and adherence or retention risks.[1] Blood pressure was measured at baseline and then annually in the CT components, but only at baseline and Year 3 in the OS. This analysis restricts the population to women enrolled in the CT components (N=68,132). Women were further excluded from the present analysis if they did not have blood pressure assessed at the baseline visit and at least two follow-up visits up to the Year 3 visit (N=6,641), had experienced an incident stroke and/or mortality event prior to their Year 3 visit (N=569), or their time to event could not be computed because they did not have a Year 3 visit or any subsequent follow-up (N=2,694), leaving a final sample size of 58,228.

Definitions of SD and SDreg

VVV of blood pressure, the primary exposure, was defined as the SD about the participant's mean SBP across visits, where the mean is assumed to be static. SD of SBP is computed by the following formula:

$$\mathrm{SD} = \sqrt{\sum_{i=1}^{n} \frac{(y_i - \bar{y})^2}{(n-1)}}$$

where n is the total number of visits (including baseline) of SBP for an individual, y_i is the SBP at each visit, and $\bar{y}$ is the mean of SBP across visits.

VVV of blood pressure was also defined as SDreg, the SD about the participant's regression line with SBP regressed across visits. SDreg of SBP is computed by the following formula:

$$\mathrm{SDreg} = \sqrt{\sum_{i=1}^{n} \frac{(y_i - (\hat{\beta}_0 + \hat{\beta}_1 * visit\ year))^2}{(n-2)}}$$

where n is the total number of visits (including baseline) of SBP for an individual, y_i is the SBP at each visit, visit year = (i - 1), $\hat{\beta}_0$ and $\hat{\beta}_1$ are the least squares estimates of the intercept and slope, and the mean (i.e., regression line) is assumed to be a linear function of time.

Conceptually, SD is the 'average' of the deviations about the mean (which is assumed to be static over time), and SDreg is the 'average' of the deviations about the regression line (which assumes a linear increase over time). Therefore in a participant whose BP does not change across visits, SD and SDreg are similar. In contrast, in a participant whose BP increases linearly over time, SD is higher than SDreg.

Covariates

At the baseline visit, CT participants provided data on demographics (age, gender, race/ethnicity), cardiovascular risk factors, prevalent cardiovascular disease, and medication use. Ethnicity was determined with the following categories: non-Hispanic white, African-American/black (non-Hispanic), Hispanic, Asian/Pacific Islander, American Indian/Alaska Native, or unknown (women who indicated "other" ethnicity or did not answer the question). Education was ascertained from a range of categories from no education to doctoral degree. Smoking was categorized as current, past, or never. Height and weight was measured, and body mass index was calculated as weight in kilograms divided by height in meters squared. Physical activity was assessed by asking about the frequency and duration of walking at various intensities and 3 other types of recreational activity classified by intensity (strenuous, moderate, or light). A 12-lead electrocardiogram was performed, and the presence of left ventricular hypertrophy was determined using Minnesota code criteria. Participants were asked to bring all of their medications to the baseline visit. The product or generic name, dosage, form, and strength of the medications were transcribed from the label into the study computer database and matched to the corresponding item in a pharmacy database: the Master Drug Data Base (Medi-Span). This database includes drug names (both brand and generic), national drug codes, and a therapeutic class code provided by the American Hospital Formulary Service for both prescription and over-the-counter products. Drugs from the following classes were considered to be antihypertensive agents: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, centrally acting antihypertensive agents, vasodilators, and combinations of these medications. The presence of high cholesterol was identified by the use of medications for high cholesterol. Diabetes was defined as a physician diagnosis plus the use of insulin or oral diabetes medication. As medication inventories were repeated at the first, third, sixth, and ninth annual visits, the use of antihypertensive agents was also determined at follow-up.

References

1. Design of the women's health initiative clinical trial and observational study. The women's health initiative study group. *Control Clin Trials*. 1998;19:61-109.

Table S1. Characteristics of the WHI Clinical Trial participants (n=58,228)* by Quartiles of Visit-to-Visit Variability† of Systolic Blood Pressure

	Quartiles of SD of Systolic Blood Pressure								
	Q1 <6 mm Hg		Q2 6-8.9 mm Hg		Q3 9-12.9 mm Hg		Q4 ≥13 mm Hg		
Participant Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**P trend‡**
Hormone therapy trial assignment									<0.001
CEE	937	6.5	1096	7.2	1241	8.1	1161	8.8	
CEE Placebo	1060	7.3	1135	7.5	1211	7.9	1143	8.7	
CEE+MPA	1785	12.4	1919	12.6	1985	12.9	1760	13.3	
CEE+MPA Placebo	1716	11.9	1837	12.1	1882	12.2	1646	12.5	
Not randomized (dietary modification trial participants only)	8933	61.9	9221	60.6	9066	58.9	7494	56.8	
Dietary modification trial assignment									0.38
Intervention	4200	29.1	4353	28.6	4343	28.2	3635	27.5	
Control	6364	44.1	6623	43.5	6612	43.0	5513	41.8	
Not randomized (hormone therapy trial participants only)	3867	26.8	4232	27.8	4430	28.8	4056	30.7	
Race/ethnicity									<0.001
White	12083	83.7	12703	83.5	12829	83.4	10605	80.3	
Black	1210	8.4	1317	8.7	1433	9.3	1535	11.6	
Hispanic	558	3.9	607	4.0	524	3.4	487	3.7	
American Indian	54	0.4	60	0.4	69	0.4	50	0.4	

Asian/Pacific Islander	352	2.4	343	2.3	325	2.1	337	2.6	
Unknown	174	1.2	178	1.2	205	1.3	190	1.4	
Education level									<0.001
0-8 years	178	1.2	202	1.3	230	1.5	222	1.7	
Some high school	433	3.0	463	3.1	610	4.0	596	4.5	
High school diploma/GED	2516	17.5	2831	18.7	2809	18.4	2550	19.4	
School after high school	5539	38.6	5891	39.0	5972	39.1	5351	40.8	
College degree or higher	5678	39.6	5732	37.9	5653	37.0	4405	33.6	
Antihypertensive medication use§									<0.001
Never used	10040	69.6	9785	64.3	8563	55.7	4915	37.2	
Used at all visits	2438	16.9	3082	20.3	3796	24.7	4651	35.2	
Newly started during follow-up	886	6.1	1215	8.0	1738	11.3	2165	16.4	
Other	1067	7.4	1126	7.4	1288	8.4	1473	11.2	
History of hypertension‖	3763	28.6	5040	36.6	6974	49.0	8940	70.9	<0.001
HMG-CoA reductase inhibitor use	855	5.9	929	6.1	995	6.5	1043	7.9	0.02
Aspirin use	2492	17.3	2814	18.5	2933	19.1	2868	21.7	<0.001
Anticoagulation use	48	0.3	65	0.4	81	0.5	96	0.7	<0.001
History of high cholesterol	1393	10.8	1599	11.9	1676	12.3	1829	15.4	<0.001
Diabetes mellitus	463	3.2	559	3.7	700	4.6	823	6.2	<0.001
Smoking status									<0.001
Never	7573	53.0	7723	51.3	7926	52.1	6749	51.7	
Past	5701	39.9	6254	41.6	6159	40.5	5321	40.8	

Current	1022	7.1	1063	7.1	1141	7.5	978	7.5	
Left ventricular hypertrophy on 12-lead ECG	555	3.9	630	4.2	821	5.5	1088	8.4	<0.001
History of CHD	647	4.5	764	5.1	878	5.8	1053	8.1	<0.001
History of stroke	101	0.7	109	0.7	164	1.1	195	1.5	<0.001
History of atrial fibrillation	452	3.2	503	3.4	612	4.0	612	4.7	<0.001
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age at screening, years	61.4	6.7	62.1	6.8	63.0	6.9	64.7	7.0	<0.001
Body mass index, kg/m^2	28.4	5.7	28.6	5.7	28.9	5.9	29.2	5.9	<0.001
Total energy expenditure from recreational physical activity, MET-hours/week	11.2	12.8	10.7	12.4	10.7	12.6	10.4	12.4	<0.001
Mean systolic blood pressure,§ mm Hg	120.6	13.1	123.3	13.0	127.2	13.2	134.6	13.8	<0.001
Mean diastolic blood pressure,§ mm Hg	72.8	7.2	73.6	7.2	74.7	7.3	76.4	7.6	<0.001
Mean pulse pressure,§ mm Hg	47.8	10.3	49.7	10.6	52.6	11.2	58.2	12.3	<0.001
Mean heart rate,§ beats/minute	69.8	7.1	69.7	7.2	69.7	7.3	69.3	7.6	<0.001

*Includes participants in the CT components with a baseline blood pressure measurement and at least two follow-up measures at Years 1, 2 or 3, and had time to event data available after Year 3.

†Represents the standard deviation (SD) from the mean calculated from systolic blood pressure from baseline to Year 3 visits.

‡Adjusted for age, race/ethnicity, and randomization assignment in the hormone therapy trial.

§Includes data collected at baseline and Years 1, 2 and 3.

||Defined by a self-reported history of treated hypertension, baseline systolic blood pressure ≥ 140 mmHg, or baseline diastolic blood pressure ≥ 90 mmHg.

Table S2. Hazard Ratios for Stroke Per Each 5 mm Hg Increase in SDreg* of Systolic Blood Pressure in Selected Subgroups

Subgroup	HR (95% CI)	P value†
Main effect	1.12 (1.05 - 1.19)	<0.001
Age, years		0.05
50-59	1.25 (1.10 - 1.42)	
60-69	1.15 (1.07 - 1.23)	
70-79	1.05 (0.96 - 1.15)	
Race/ethnicity		0.84
White	1.12 (1.04 - 1.20)	
Black	1.06 (0.91 - 1.23)	
Hispanic	1.27 (0.86 -1.87)	
American Indian	1.10 (0.62 - 1.94)	
Asian/Pacific Islander	1.30 (0.89 - 1.90)	
Unknown	1.34 (0.84 - 2.12)	
Body mass index, kg/m^2		0.35
< 25	1.09 (0.97 - 1.23)	
25 - <30	1.08 (0.98 -1.20)	
≥ 30	1.16 (1.06 - 1.28)	
Smoking		0.30
Never	1.14 (1.05 - 1.24)	
Past	1.12 (1.01 - 1.23)	
Current	0.97 (0.80 - 1.18)	
Diabetes		0.57
No	1.11 (1.03 - 1.19)	
Yes	1.16 (0.99 - 1.36)	
Left ventricular hypertrophy on 12-lead ECG		0.07
No	1.14 (1.07 - 1.22)	
Yes	0.97 (0.82 - 1.15)	
History of atrial fibrillation		0.29
No	1.13 (1.05 - 1.20)	
Yes	0.99 (0.79 - 1.25)	
History of CHD		0.52
No	1.12 (1.05 - 1.21)	
Yes	1.06 (0.91 - 1.25)	
History of stroke		0.60
No	1.11 (1.04 - 1.19)	
Yes	1.22 (0.88 - 1.69)	

Mean systolic blood pressure, mm Hg		0.005
< 120	1.43 (1.16 - 1.76)	
120-129	1.23 (1.06 - 1.42)	
130-139	1.15 (1.02 - 1.30)	
≥ 140	1.05 (0.96 - 1.15)	
Antihypertensive medication use		0.34
Never used	1.21 (1.06 - 1.37)	
Used at all visits	1.06 (0.97 - 1.16)	
Newly started during follow-up	1.12 (0.98 - 1.28)	
Other	1.22 (1.03 - 1.44)	
HMG-CoA reductase inhibitor use		0.74
No	1.12 (1.05 - 1.20)	
Yes	1.08 (0.88 - 1.32)	
Aspirin use		0.66
No	1.11 (1.03 - 1.19)	
Yes	1.14 (1.02 - 1.28)	
Anticoagulation use		0.33
No	1.12 (1.05 - 1.19)	
Yes	0.93 (0.65 - 1.33)	
Hormone therapy trial assignment		0.85
Intervention groups	1.09 (0.97 - 1.23)	
Control groups	1.08 (0.94 - 1.23)	
Not randomized (dietary modification trial participants only)	1.15 (1.05 - 1.25)	
Dietary modification trial assignment		0.52
Intervention group	1.09 (0.96 - 1.23)	
Control group	1.14 (1.04 - 1.26)	
Not randomized (hormone therapy trial participants only)	1.09 (0.99 - 1.21)	

*Adjusted for covariates in Model 3 (covariates are listed in the footnote in Table 1).
†P value corresponds to test of interaction. This corresponds to a k-1 degree of freedom (df) test for categorical variables (k=number of categories), a 1-df test of trend for age and body mass index, and a 1-df test between intervention and control groups of the WHI clinical trials.

Table S3. Hazard Ratios for Stroke Per Each 5 mm Hg Increase in Visit-to-Visit Variability of Systolic Blood Pressure* by Number of Visits Used to Estimate Visit-to-Visit Variability of Systolic Blood Pressure

Number of visits used to estimate visit-to-visit variability of systolic blood pressure	HR (95% CI)	P trend
3 to 4	1.02 (0.91 - 1.14)	0.02
5	1.14 (1.00 - 1.30)	
6	1.19 (1.04 - 1.35)	
7	1.04 (0.87 - 1.23)	
8	1.35 (1.12 - 1.63)	
9	1.25 (0.94 - 1.66)	
10 to 11	1.44 (0.85 - 2.45)	

*SDreg in Model 3 (covariates are listed in the footnote in Table 1).

WHI Administrative Information

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

For a list of all the investigators who have contributed to WHI science, please visit:
https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf