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

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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:

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

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:

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

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).

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