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Visit-to-Visit Blood Pressure Variability and Progression of White Matter Hyperintensities Among Older People With Hypertension

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A B S T R A C T

Objectives: Visit-to-visit blood pressure (BP) variability is a risk factor for cardiovascular disease and cognitive decline. Our aim was to assess the association between visit-to-visit BP variability and progression of white matter hyperintensities (WMH).
Design: Post-hoc analysis in the magnetic resonance imaging substudy of the randomized controlled trial prevention of dementia by intensive vascular care.
Setting and participants: Community-dwelling people age 70–78 years with hypertension.
Methods: Participants had 3 to 5 twice yearly BP measurements and 2 magnetic resonance imaging scans at 3 and 6 years follow-up. We used linear regression adjusted for age, sex, WMH at scan 1, (change in) total brain volume, and cardiovascular risk factors.
Results: Among the 122 participants, there was a modest association between visit-to-visit systolic BP variability and WMH progression [beta = 0.03 mL/y per point increase in variability, 95% confidence interval (CI) 0.00–0.05, $P = .058$]. Additional adjustment for slope in systolic BP reduced the associated P value to .043. Visit-to-visit diastolic BP variability was not associated with WMH progression (beta = 0.01 mL/y, 95% CI −0.02 to 0.03, $P = .68$). Visit-to-visit pulse pressure variability was associated with WMH progression (beta 0.03 mL/y, 95% CI 0.01–0.05, $P < .01$).
Conclusions: Higher visit-to-visit systolic BP and pulse pressure variability is associated with more progression of WMH among people age 70–78 years with hypertension.
Implications: Interventions to reduce visit-to-visit BP variability may be most effective in people with low WMH burden.

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Visit-to-visit blood pressure (BP) variability is an independent risk factor for cardiovascular disease (CVD).[1] The nature of this relation is not yet fully understood, but proposed mechanisms are through arterial stiffness, endothelial dysfunction, or subclinical inflammation.[1] Several studies have linked visit-to-visit BP variability to an increased risk of cognitive decline and potentially also dementia.[2] One hypothesized mechanism for this association is through progression of cerebral small vessel disease, which is characterized by neuroimaging markers such as white matter hyperintensities (WMH), microbleeds, and lacunes.[3] Our aim was to assess the association between visit-to-visit BP variability and progression of WMH.

Methods

This is a post-hoc analysis from the prevention of dementia by intensive vascular care (preDIVA) magnetic resonance imaging (MRI) substudy, described previously.[4] In brief, the preDIVA randomized controlled trial compared incident dementia among community-dwelling people age 70 to 78 years, randomized to either 6 to 8 years of intensive vascular care or usual care. A subgroup of preDIVA participants with a systolic BP ≥140 mm Hg at baseline underwent

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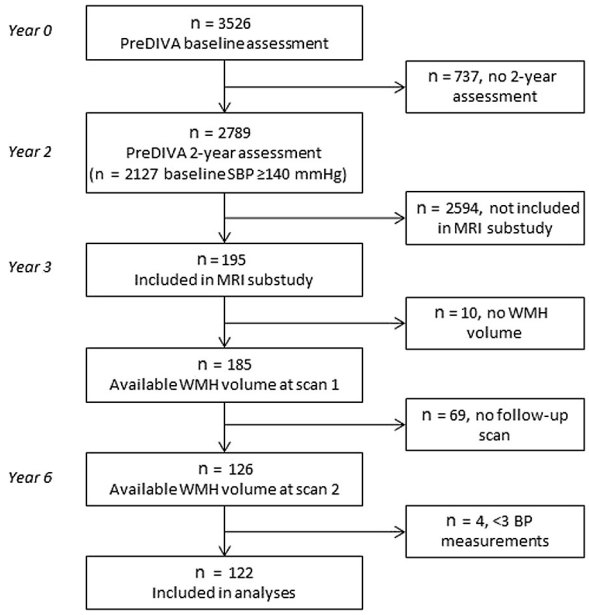

Fig. 1. Flowchart.

MRI. Ethical approval was obtained from the local institutional review board and informed consent was obtained.

At baseline and after 2, 4, 6, and 7 to 8 years, BP was recorded as the mean of 2 measurements, in sitting position, using a standard protocol with an automated monitor. Sociodemographics, medical history, medication use, body mass index, and cholesterol were also obtained. At 3 and 6 years follow-up, an MRI scan was done. MRI included 3D 3T T1-weighted ($1.1 \times 1.1 \times 1.2$ mm^3) and fluid-attenuated inversion recovery (FLAIR; $1.1 \times 1.1 \times 1.2$ mm^3) sequences.[4] WMH was automatically segmented from FLAIR sequences[5] and total brain volume (TBV) was derived from Statistical Parametric Mapping 12 (Wellcome Trust Centre for Neuroimagin at University College London).[6]

Visit-to-visit BP variability was defined as the systolic coefficient of variation (CV) over all available visits (ie, the standard deviation divided by the mean systolic BP multiplied by 100). Being the result of dividing 2 BP values, the CV is unit less. Participants were included if they had 2 MRI scans with WMH volume available and at least 3 BP measurements, deemed the minimum to calculate variability. WMH progression was normally distributed. The association between visit-to-visit BP variability and WMH progression (volume at scan 2 minus scan 1) was analyzed using linear regression. Model 1 was unadjusted, model 2 adjusted for TBV at scan 1, change in TBV during follow-up, WMH volume at scan 1, sex and age, and model 3 additionally for diabetes mellitus, history of stroke, obesity, total cholesterol, and smoking. Results are presented for model 3, unless stated otherwise. In sensitivity analyses, we additionally adjusted for trend in systolic BP, operationalized as the slope of BP over all available visits, and randomization group. Other sensitivity analyses were done using CV of diastolic BP and of pulse pressure (that is, the difference between systolic and diastolic BP), systolic and diastolic BP at baseline, slope in systolic BP, and age. Subgroup analyses stratified for antihypertensive medication use, systolic BP at baseline (divided at the median), history of CVD, and WMH volume at scan 1 (divided at the median). All analyses were performed using R studio v 3.4.3 (RStudio, Inc., Boston, MA).

Results

Of the 195 participants in the preDIVA MRI substudy, 122 were included (Figure 1). Baseline characteristics of the included and excluded participants were comparable (Table 1). Mean age of the included participants was 73.8 [standard deviation (SD) 2.5] years and 58 (47.5%) were male. Mean systolic BP at baseline was 161.1 (SD 15.1) mm Hg, and during follow-up mean CV of systolic BP was 8.7 (SD 4.3). CV was based on 4 BP measurements in 89.3% of participants (n = 109). Scan 1 took place 41 [interquartile range (IQR) 38–43] months after preDIVA baseline assessment and scan 2 after 74 (IQR 72–77) months. Median WMH volume was 6.1 mL (IQR 3.5–11.1) at scan 1 and 8.0 mL (IQR 4.4–13.6) at scan 2, with a progression of 0.53 mL/y (IQR 0.15–1.05).

One point increase in CV of systolic BP was significantly associated with 0.043 mL/y [95% confidence interval (CI) 0.015–0.072, $P = .003$] WMH progression in model 1 (unadjusted). The association was also significant in model 2 (beta = 0.027 mL/y, 95% CI 0.001–0.054, $P = .042$), when adjusted for TBV at scan 1, change in TBV during follow-up, WMH volume at scan 1, sex, and age. Additional adjustment for diabetes mellitus, history of stroke, obesity, total cholesterol, and smoking (model 3) reduced significance (beta = 0.026 mL/y, 95% CI −0.001 to 0.053, $P = .058$; Table 2). With additional adjustment for slope in systolic BP, the association between variability and WMH progression was also significant in model 3 (beta = 0.027 mL/y, 95% CI 0.001–0.054, $P = .043$). Adjusting model 3 for randomization group did not influence the association (beta = 0.026 mL/y, 95%CI −0.001 to 0.053, $P = .0564$). CV based on diastolic BP was not associated with WMH progression (beta = 0.006 mL/y, 95% CI −0.022 to 0.034, $P = .679$), nor when adjusting for slope in diastolic BP. CV based on pulse pressure was associated with WMH progression (beta 0.027 mL/y, 95% CI 0.009–0.046, $P = .004$), also when adjusted for slope in pulse pressure. Diastolic BP at baseline (beta 0.014 mL/y, 95% CI 0.002–0.026, $P = .023$) and slope in systolic BP (beta 0.025 mL/y, 95%

Table 1
Baseline Characteristics

Baseline Characteristics	Excluded Participants (n = 73)	Included Participants (n = 122)	*P* Value
Age (y)	74.1 (SD 2.5)	73.8 (SD 2.5)	.41
Men	34 (46.6%)	58 (47.5%)	1.00
Systolic BP (mm Hg)	161.7 (SD 16.3)	161.2 (SD 15.1)	.82
Diastolic BP (mm Hg)	85.0 (SD 11.0)	84.6 (SD 9.4)	.80
Antihypertensive medication	32 (43.8%)	49 (40.2%)	.66
Body mass index (kg/m^2)	27.4 (SD 3.9)	26.3 (SD 3.5)	.05
Total cholesterol (mmol/L)	5.6 (SD 1.2)	5.5 (SD 1.2)	.54
Current smokers	6 (8.2%)	10 (8.2%)	1.00
Diabetes mellitus	7 (9.6%)	11 (9.0%)	1.00
History of stroke/TIA	5 (6.8%)	8 (6.6%)	1.00
History of CVD (other than stroke/TIA)	17 (23.3%)	22 (18.0%)	.47
TBV (mL)	931.7 [892.8–1019.4]	959.7 [910.0–1038.4]	.51
WMH volume (mL)	7.3 [3.8–11.2]	6.1 [3.5–11.1]	.60

TIA, transient ischemic attack.
Data are presented as mean (SD), median [IQR], or number (percentage).

Table 2
Associations With WMH Progression

Independent Variable	Beta (95% CI)	*P* Value
Systolic BP variability	0.026 (−0.001 to 0.053)	.058
Diastolic BP variability	0.006 (−0.022 to 0.034)	.679
Pulse-pressure variability	0.027 (0.009-0.046)	.004
Systolic BP at baseline	0.007 (−0.001 to 0.014)	.082
Diastolic BP at baseline	0.014 (0.002–0.0262)	.023
Slope in systolic BP	0.025 (0.004–0.046)	.021
Age	−0.002 (−0.051 to 0.048)	.941

Data are presented for model 3; adjusted for TBV at scan 1, change in TBV during follow-up, WMH volume at scan 1, sex, age (except for the analyses on age), diabetes mellitus, history of stroke, obesity, total cholesterol, and smoking.

CI 0.004–0.046, $P = .021$) were significantly associated with WMH progression, but systolic BP at baseline and age were not (Table 2).

Subgroup analyses showed a stronger association of systolic BP variability and WMH progression among participants without antihypertensive medication at baseline (beta = 0.03 mL/y, 95% CI 0.00–0.06, $P = .031$), without a history of CVD (beta = 0.04 mL/y, 95% CI 0.00–0.07, $P = .028$), and participants with a low WMH volume (<6.14 mL) at scan 1 (beta = 0.03 mL/y, 95% CI 0.01–0.05, $P = .005$), although the P for interaction of all subgroup analyses was not statistically significant (Supplementary Table S1).

Discussion

Higher visit-to-visit systolic BP and pulse pressure variability was associated with more progression of WMH among community-dwelling people age 70 to 78 years with hypertension. Although strength of the association was slightly attenuated after full adjustment, the effect size remained similar. Diastolic BP variability was not associated with WMH progression.

Our results concur with previous reports on the association between systolic BP variability with WMH.[7,8] Previous research has focused on WMH volume at 1 point in time, whereas our study assessed the progression of WMH volume over time. WMH progression has been suggested as a mediator in the association between BP variability and cognition/dementia.[3] In the overall preDIVA population, including 2305 participants during an average of 6.4 years of follow-up, we did not find an association between visit-to-visit BP variability and dementia.[9] This discrepancy might be explained by the often mixed pathology of dementia in older people, whereby an association with the vascular component alone does not automatically translate to an association with dementia.[10] Another explanation might be that follow-up was too short to establish an association with dementia.

A high WMH load at the first scan is a strong predictor for WMH progression.[11] Interestingly, we found that the association between visit-to-visit BP variability and WMH progression was strongest in participants with lower WMH volumes at scan 1. Although the interaction was not significant and a causal relation is not established, this could indicate that the effect of variability is mainly on the development of new WMH lesions, rather than progression of existing ones. This suggests that interventions to reduce BP variability should target people with a low WMH burden.

A strength of our study is the systematic approach to both the BP measurements and automatic segmentation of WMH volumes on serial 3T MRI. By adjusting for WMH volume at scan 1, we eliminated the effect of the strongest predictor of WMH progression. The CV as a unit automatically accounts for the differences in mean BP between participants. A limitation is the long interval between BP measurements and the limited number of available measurements. This also leaves us unable to adjust for the level of BP control in detail. Selective drop-out of participants with higher morbidity might have influenced our results because 35% of participants did not have a second scan. However, based on characteristics at baseline, selective drop-out was not a major concern. Another limitation is the randomized design of preDIVA, although the intervention did not significantly reduce WMH progression and additional adjustment for randomization group did not change the results.[4] We assessed people age 70 to 78 years with hypertension at baseline, potentially prohibiting generalizability.

Conclusions and Implications

High visit-to-visit systolic BP and pulse pressure variability is associated with more progression of WMH volume. Interventions to reduce variability may be most effective in people with low WMH burden.

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Appendix

Supplementary Table S1
Subgroup Analyses

Subgroup	N	Beta (95% CI)	*P* Value	*P* for Interaction
Antihypertensive medication	49	0.01 (−0.04 to 0.07)	.639	.46
No antihypertensive medication	73	0.03 (0.00−0.06)	.031	
Low systolic BP (<158 mm Hg)	60	0.01 (−0.03 to 0.05)	.505	.71
High systolic BP (≥158 mm Hg)	62	0.03 (−0.01 to 0.07)	.142	
History of CVD	29	0.01 (−0.07 to 0.05)	.822	.12
No history of CVD	89	0.04 (0.00−0.07)	.028	
Low WMH volume at scan 1 (<6.14 mL)	61	0.03 (0.01−0.05)	.005	.71
High WMH volume at scan 1 (≥6.14 mL)	61	0.03 (−0.02 to 0.08)	.236	

Based on model 3, adjusted for TBV at baseline, change in TBV during follow-up, WMH volume at baseline, sex, age, diabetes mellitus, history of stroke (except for the subgroup analysis on history of CVD), obesity, total cholesterol, and smoking.