Chapter 4

Blood pressure lowering medication, visit-to-visit blood pressure variability and cognitive function in old age

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Abstract

Background Visit-to-visit blood pressure variability is associated with cognitive impairment. We assessed to what extent the association between blood pressure variability and cognitive impairment is mediated by the association of blood pressure lowering mediation with both blood pressure variability and cognition.

Methods We studied 5,606 participants from the PROspective Study of Pravastatin in the Elderly at Risk. Blood pressure was measured every three months during 3.2 years; blood pressure variability was defined as the standard deviation of blood pressure measurements during follow up. Cognitive function was assessed at baseline and during follow-up using the Stroop test, Letter-Digit Coding test, immediate and delayed Picture-Word Learning tests. Multivariate regression models were used with and without adjustments for blood pressure lowering medication to calculate the percentage to which blood pressure lowering medication mediated the association between blood pressure variability and cognition.

Results Participants taking calcium-antagonists had a higher score in baseline Letter-Digit Coding test (mean difference (95% confidence interval (CI) 0.45 (0.06; 0.88). Participants taking beta-blockers had a steeper decline in Stroop test (additional change per year (95% CI) 0.40 (0.09; 0.70) and Letter-Digit Coding test (0.08 (-0.15; -0.02)). Furthermore, a steeper decline in Stroop test was found in participants taking RAS-inhibitors (0.50 (0.16; 0.85). Systolic blood pressure variability was higher in participants taking beta-blockers and RAS-inhibitors (mean difference in systolic blood pressure variability in mmHg (95% CI) 0.75 (0.45; 1.04) and 1.37 (1.04; 1.71) respectively). Participants taking diuretics, calcium antagonists and RAS-inhibitors had a higher diastolic blood pressure variability (mean difference in diastolic BP variability in mmHg (95% CI) 0.27 (0.04; 0.49), 0.37 (0.12; 0.62) and 0.65 (0.37; 0.93) SD, respectively). Beta estimates remained essentially the same when we adjusted for blood pressure lowering medication in the association of blood pressure variability with cognitive function.

Conclusion The association between blood pressure variability and cognitive impairment was not mediated by blood pressure lowering medication.

Introduction

Visit-to-visit blood pressure variability independent of average blood pressure is associated with higher cardiovascular risk in older adults. Several observational studies have shown that higher levels of blood pressure variability are related with increased risk of stroke, coronary events, heart failure hospitalization and cardiovascular and all-cause mortality. (1-5) Furthermore, blood pressure variability has been associated with white matter hyperintensities, intima media thickness and carotid artery atherosclerosis in older adults. (6-8) Recent evidence has shown that older subjects with higher levels of blood pressure variability have worse cognitive function.(9-11) Again, these findings were independent of average blood pressure.

Besides average blood pressure, reducing the variability of blood pressure might therefore be of importance. Blood pressure lowering medication may have class-specific effects on blood pressure variability, but evidence on the association of blood pressure lowering medication with blood pressure variability is limited. A recent meta-analysis of clinical trials showed that compared with other drugs, systolic blood pressure variability was reduced the most in subjects using calcium-channel blockers and non-loop diuretics; systolic blood pressure variability was higher in subjects using angiotensin-converting enzyme (ACE) inhibitors and beta-blockers.(12) Besides the effects on blood pressure variability, blood pressure lowering medication, especially calcium channel blockers, also seem to have class-specific effects in decreasing the risk of dementia.(13-16) Therefore, we hypothesized that the association between blood pressure variability and cognitive impairment might partially be caused by different effects of blood pressure lowering medication on both blood pressure variability and cognitive function.

We have previously described the association between blood pressure variability and cognitive function within this study population. Now, we evaluated whether the association between blood pressure variability and cognitive function could be mediated by blood pressure lowering medication.(9) We used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a multicenter trial including 5,804 participants with a mean age of 75 years, who all had repeated measurements of blood pressure and different domains of cognitive function over a mean follow-up period of 3.2 years.

Methods

Study design

Data in this study were obtained from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER): a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin treatment to prevent vascular events in elderly men and women with pre-existing cardiovascular disease or risk factors thereof.(17) Primary outcome of this trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years. PROSPER included 5,804 individuals aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands.(17) In the present study we included 5,606 participants for whom data on blood pressure lowering medication and blood pressure variability were available. The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent.

Blood pressure lowering medication

Information about use and type of blood pressure lowering medication was self-recorded at baseline. A research nurse reported change in blood pressure lowering medication during every three-monthly study visit. Dosage of blood pressure lowering medication was unknown. For the present study, we only investigated participants who used one or more of the following classes of blood pressure lowering medication: diuretics, beta-blockers, calcium antagonists and renin-angiotensin system (RAS)-inhibitors (including angiotensin-converting-enzyme and angiotensin-receptor antagonists).

Blood pressure measurements

Blood pressure was measured at baseline and every three months during a mean 3.2 year follow-up period. Blood pressure was measured in sitting position using a fully automatic electronic sphygmomanometer (Omron M4®). All measurements were performed in the same clinical setting. Average blood pressure was calculated for each participant as the mean value of all blood pressure measurements during follow-up. Blood pressure variability was defined as the standard deviation of all blood pressure measurements during follow-up for each participant.

Cognitive function

The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function at baseline; a cutoff score of 24 points or more (out of 30) was used as an inclusion criterion to exclude subjects with poor cognitive function at baseline.(18) Cognitive function was tested at baseline, after 9, 18, 30 months and at the end of the study by a cognitive test battery consisting of four different tests.(18) For the current study, we used data on cognitive function assessed at the end of follow-up; to ensure that the determinant (blood pressure variability during follow-up) preceded the outcome variable (cognitive function). The time point of the measurement at the end of the study varied between 36 months and 48 months. The Stroop-Colour-Word-Test was used to test selective attention and reaction time of the participants. The participants were asked to read a color name which was displayed in a color different from the color it actually names. The outcome parameter was total number of seconds to complete the test; a higher score therefore indicates worse performance. General cognitive speed was tested by the Letter-Digit Coding Test. The participants had to match certain digits with letters according to a provided key. The outcome variable was the total number of correct entries in 60 seconds, and therefore higher scores represent better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory performance. Fifteen pictures were presented at the participants, and they were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the test to measure their delayed recall. The outcome parameter is the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests and the procedures has been published previously.(18)

Statistical analyses

In the present study, we compared participants using the specific class of blood pressure lowering medication with participants not using this specific medication class. Baseline characteristics of the study participants are reported as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. We used an independent t-test (for continuous variables) and a Chi-square test (for categorical variables) to assess whether there was a difference in baseline characteristics between participants using a specific medication class compared to participants not using this medication class.

We first investigated the association between blood pressure lowering medication and blood pressure variability by multivariate linear regression models. Independent variables were blood pressure lowering medication class; systolic and blood pressure variability were

the dependent variables. Second, we assessed the association between blood pressure lowering medication and cognitive function at baseline and cognitive decline during follow-up. For the baseline associations, we used multivariate linear regression models, with class of blood pressure lowering medication as an independent variable and cognitive tests as dependent variables. Furthermore, for the association of blood pressure lowering medication with cognitive decline over time,. linear mixed models were used, which included class of blood pressure lowering medication, time (in years) and the interaction term between class of blood pressure lowering medication and time. We performed our analyses according to two different models. In a minimally adjusted model, we adjusted our analyses for age, sex and country. In the final model (fully adjusted model), we additionally adjusted our analyses for the following potential confounders: study treatment, cardiovascular diseases and risk factors (history of vascular disease, history of hypertension, history of diabetes mellitus, smoking status, cholesterol levels, body mass index), estimated glomerular filtration rate (eGFR), number of blood pressure lowering medications, and average blood pressure during follow-up. Concerning the association between blood pressure lowering medication and blood pressure variability, we additionally adjusted for use of other blood pressure lowering medications. Furthermore, the analyses between blood pressure lowering medication and cognition were adjusted for education (defined as age left school).

In a third statistical analysis, we determined whether blood pressure lowering medication mediated the association of blood pressure variability and cognitive function. For this, we added class of blood pressure lowering medication to the model which examined the association between blood pressure variability and cognitive function. Each class of blood pressure lowering medication was first included separately in the analysis; however we also included combinations of blood pressure lowering medication and all blood pressure lowering medication. We did not incorporate interaction between blood pressure lowering medication and blood pressure variability in the model. Finally, we calculated the percentage of the association explained by blood pressure lowering medication.(19) We defined a percentage of 10% or greater as evidence of potential medication. To account for change in blood pressure lowering medication during follow-up, we performed an additional sensitivity analysis in which we excluded all participants who changed their blood pressure lowering medication during follow-up.

All analyses were performed using SPSS (version 20.0.0, SPSS Inc., Chicago, IL).

Results

Out of the 5,804 participants of PROSPER, we excluded 198 participants who had only one or two blood pressure measurements during follow-up. This resulted in a final study sample of 5,606 participants.

Table 1 shows the baseline characteristics in different classes of blood pressure lowering medication. Participants taking RAS-inhibitors had the lowest age and participants taking loop diuretics had the highest age at baseline. Prevalence of vascular diseases and risk factors varied among the groups, most probably reflecting differences in indications for which blood pressure lowering medication was prescribed. Systolic blood pressure was lowest

Table 1. Baseline characteristics in different classes of blood pressure lowering medication

	Blood pressure lowering medication			
	Diuretics	Beta-blockers	Calcium antagonists	RAS-inhibitors
	N=2266	N=1451	N=1406	N=1032
Demographics				
Age (years)	75.63 (3.41)**	75.29 (3.37)	75.41 (3.28)	75.35 (3.35)
Female, n (%)	1457 (64.3%)**	792 (54.6%)*	684 (48.6%)*	565 (54.7%)*
Country, n (%)				
The Netherlands	326 (15.4%)**	321 (22.1%)*	224 (15.9%)**	286 (27.7%)**
Ireland	932 (41.4%)**	538 (37.1%)*	428 (30.4%)**	467 (45.3%)**
Scotland	1008 (44.5%)**	592 (40.8%)*	754 (53.6%)*	279 (27.0%)**
Education (age left school)	15.12 (1.96)	15.15 (2.09)	15.04 (1.92)*	15.28 (2.24)*
Total number of medications	4.29 (2.26)**	4.21 (2.11)**	4.81 (2.29)**	4.47 (2.29)**
Total number of BP measurements during follow-up	11.24 (2.83)	11.38 (2.64)	11.22 (2.87)	11.16 (2.74)
Vascular risk factors				
History of hypertension, n (%)	1998 (88.2%)**	1192 (82.2%)**	1069 (76.0%)**	952 (92.2%)**
History of diabetes mellitus, n (%)	174 (7.7%)**	120 (8.3%)**	138 (9.8%)	173 (16.8%)**
History of stroke or TIA, n (%)	234 (10.3%)	137 (9.4%)*	170 (12.1%)	133 (12.9%)*
History of MI, n (%)	253 (11.2%)**	232 (16.0%)*	267 (19.0%)**	173 (16.8%)*
History of vascular disease, n (%)	880 (38.8%)**	710 (48.9%)**	853 (60.7%)**	443 (42.9%)
Current smoker, n (%)	339 (15.0%)**	182 (12.5%)**	216 (15.4%)**	136 (13.2%)**
Body mass index (kg/m^2)	27.82 (4.43)**	27.31 (4.02)**	27.19 (4.13)**	27.67 (4.37)**
Total cholesterol (mmol/L)	5.78 (0.91)**	5.72 (0.89)	5.67 (0.89)	5.68 (0.91)
Blood pressure				
Systolic blood pressure (mmHg)	154.97 (21.24)*	155.52 (23.33)	153.83 (21.71)**	158.77 (23.52)**
Diastolic blood pressure (mmHg)	84.28 (11.41)*	83.69 (0.30)	82.40 (11.47)**	85.53 (12.33)**
Estimated glomerular filtration rate (ml/min/1.73m^2)	56.86 (14.06)**	58.69 (15.23)**	58.00 (13.44)**	59.19 (14.19)*

Data are presented as mean (standard deviation) unless stated otherwise. Abbreviations: n, number; BP, blood pressure; TIA, transient ischemic attack; MI, myocardial infarction. **p<0.001 *p<0.05 representing the differences in characteristics between participants taking a specific blood pressure lowering medication class, and participants not taking this specific class.

Table 2. Association between blood pressure variability and blood pressure lowering medication

	Systolic BPV				Diastolic BPV			
	Minimally adjusted		Fully adjusted		Minimally adjusted		Fully adjusted	
	Unstd. Beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value
Diuretics	-0.15 (-0.42; 0.12)	0.281	-0.52 (-0.84; -0.21)	0.001	0.27 (0.04; 0.49)	0.020	0.23 (-0.04; 0.50)	0.089
Beta-blockers	0.75 (0.45; 1.04)	<0.001	0.59 (0.28; 0.91)	<0.001	-0.08 (-0.32; 0.17)	0.530	-0.09 (-0.36; 0.18)	0.530
Calcium antagonists	0.15 (-0.15; 0.45)	0.327	-0.05 (-0.38; 0.28)	0.778	0.37 (0.12; 0.62)	0.004	0.38 (0.10; 0.67)	0.008
RAS-inhibitors	1.37 (1.04; 1.71)	<0.001	0.98 (0.62; 1.35)	<0.001	0.65 (0.37; 0.93)	<0.001	0.53 (0.21; 0.84)	0.001

Abbreviations: BPV, blood pressure variability; Unstd., unstandardized; CI, confidence interval. Data represent difference in blood pressure variability (BPV) when compared to participants not taking the class of blood pressure lowering medication as unstandardized beta (95% confidence interval). Minimally adjusted: adjusted for age, sex, country. Fully adjusted: minimally adjustments + use of other blood pressure lowering medication, treatment (pravastatin/placebo), body mass index, ldl, hdl, triglycerides, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, average blood pressure during follow-up, eGFR, number of medications.

Table 3. Association of blood pressure lowering medication with cognitive function and decline

		Stroop		Letter-Digit Coding test		PLTi		PLTd	
		Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value
Diuretics	Baseline	0.47 (-1.06; 1.99)	0.547	-0.06 (-0.47; 0.36)	0.790	0.03 (-0.09; 0.14)	0.661	0.06 (-0.10; 0.22)	0.431
	Annual change	0.04 (-0.23; 0.32)	0.767	0.04 (-0.02; 0.10)	0.147	0.00 (-0.03; 0.02)	0.744	0.00 (-0.04; 0.03)	0.953
Beta-blockers	Baseline	-1.09 (-2.62; 0.45)	0.165	0.27 (-0.15; 0.69)	0.204	0.04 (-0.08; 0.15)	0.530	0.05 (-0.11; 0.21)	0.547
	Annual change	0.40 (0.09; 0.70)	0.009	-0.08 (-0.15; -0.02)	0.013	-0.02 (-0.05; 0.01)	0.160	-0.02 (-0.06; 0.02)	0.231
Calcium antagonists	Baseline	-0.43 (-2.02; 1.16)	0.596	0.45 (0.06; 0.88)	0.042	0.05 (-0.07; 0.16)	0.425	0.09 (-0.07; 0.26)	0.272
	Annual change	0.20 (-0.11; 0.51)	0.211	0.00 (-0.06; 0.07)	0.977	-0.02 (-0.04; 0.01)	0.219	-0.02 (-0.06; 0.02)	0.375
RAS-inhibitors	Baseline	1.36 (-0.43; 3.14)	0.136	-0.02 (-0.51; 0.47)	0.935	-0.05 (-0.18; 0.08)	0.443	-0.02 (-0.20; 0.17)	0.857
	Annual change	0.50 (0.16; 0.85)	0.004	0.06 (-0.01; 0.14)	0.090	-0.01 (-0.04; 0.02)	0.439	0.00 (-0.04; 0.05)	0.872

Abbreviations: LDCT, letter-digit coding test; PLTi, picture-learning test, immediate; PLTd, picture-learning test, delayed; Unstd., unstandardized; CI, confidence interval. Data represent mean (95% confidence interval) of each baseline cognitive test score. For the longitudinal analyses, estimates represent the additional change in each cognitive function test per year in the different blood pressure lowering medication groups. Adjustments were made for age, sex, country, education, systolic and diastolic blood pressure at baseline, body mass index, ldl, hdl, triglycerides, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, eGFR, number of medications, and where appropriate for test version and treatment code.

in participants taking loop diuretics and highest in participants taking RAS-inhibitors. Participants taking calcium antagonists had the lowest mean diastolic blood pressure and participants taking RAS-inhibitors had the highest mean diastolic blood pressure.

The association between blood pressure lowering medication and visit-to-visit blood pressure variability is shown in table 2. Participants taking beta-blockers and RAS-inhibitors had a higher variability in systolic blood pressure (mean difference in systolic blood pressure variability when compared to participants not taking this medication class in mmHg (95% CI) 0.75 (0.45; 1.04) and 1.37 (1.04; 1.71) respectively). Results remained significant when further adjusting for use of other blood pressure lowering medication, number of blood pressure lowering medications, average systolic blood pressure during follow-up and cardiovascular diseases and risk factors. Participants taking diuretics, calcium antagonists and RAS-inhibitors had a higher diastolic blood pressure variability (mean difference in diastolic blood pressure variability when compared to participants not taking this medication class in mmHg 0.27 (0.04; 0.49), 0.37 (0.12; 0.62) and 0.65 (0.37; 0.93) SD, respectively). Results remained materially the same when further adjusting for use of other blood pressure lowering medication, number of blood pressure lowering medications, average diastolic blood pressure during follow-up and cardiovascular diseases and risk factors.

Table 3 shows the association of blood pressure lowering medication with cognitive function and decline. At baseline, there were no differences in Stroop test, Letter-Digit Coding test, and immediate and delayed Picture-Word Learning tests between participants taking diuretics, beta-blockers and RAS-inhibitors when compared to participants taking not this medication class. Participants taking calcium-antagonists had a higher score in Letter-Digit Coding test at baseline (mean difference (95% CI) 0.45 (0.06; 0.88). Participants taking beta-blockers had a steeper decline in Stroop test (additional change in seconds per year (95% CI) 0.40 (0.09; 0.70) and in Letter-Digit Coding test (additional change in digits coded per year (95% CI) -0.08 (-0.15; -0.02). Furthermore, participants taking RAS-inhibitors had a worse performance in Stroop test during follow-up (additional change in seconds per year (95% CI) 0.50 (0.16; 0.85). No differences in cognitive decline were found between participants using diuretics and calcium antagonists when compared to participants not using these medication classes.

Furthermore, we investigated whether the association between blood pressure variability and cognition was mediated by blood pressure lowering medication (table 4). When we additionally adjusted for each different class of blood pressure lowering medication, beta

Table 4. Association between blood pressure variability and cognitive function mediated through different combinations of blood pressure lowering medication

Difference in cognitive test score	Stroop test		Letter-Digit Coding test		Picture-Word Learning test, immediate		Picture Word Learning test, delayed	
	Unstd. beta (95% CI)	Mediated (%)	Unstd. beta (95% CI)	Mediated (%)	Unstd. Beta (95% CI)	Mediated (%)	Unstd. beta (95% CI)	Mediated (%)
Systolic BPV	0.47 (0.31; 0.64)	--	-0.09 (-0.13; -0.06)	--	-0.02 (-0.03; -0.01)	--	-0.02 (-0.04; -0.01)	--
+ all BPLM	0.49 (0.32; 0.66)	3.8%	-0.10 (-0.13; -0.06)	1.1%	-0.02 (-0.03; -0.01)	0.0%	-0.02 (-0.04; -0.01)	0.0%
+ diuretics	0.48 (0.31; 0.65)	1.7%	-0.09 (-0.13; -0.06)	0.0%	-0.02 (-0.03; -0.01)	0.0%	-0.02 (-0.04; -0.01)	0.0%
+ beta-blockers	0.48 (0.31; 0.65)	1.5%	-0.10 (-0.14; -0.06)	2.1%	-0.02 (-0.03; -0.01)	0.0%	-0.03 (-0.04; -0.01)	0.1%
+ calcium antagonists	0.47 (0.30; 0.64)	0.3%	-0.09 (-0.13; -0.06)	1.1%	-0.02 (-0.03; -0.01)	4.8%	-0.02 (-0.04; -0.01)	0.0%
+ RAS-inhibitors	0.48 (0.31; 0.65)	1.3%	-0.09 (-0.13; -0.06)	1.1%	-0.02 (-0.03; -0.01)	0.0%	-0.03 (-0.04; -0.01)	0.1%
Diastolic BPV	0.34 (0.15; 0.53)	--	-0.06 (-0.10; 0.01)	--	-0.02 (-0.03; 0.00)	--	-0.02 (-0.04; 0.00)	--
+ all BPLM	0.35 (0.15; 0.54)	2.1%	-0.06 (-0.11; 0.02)	1.7%	-0.02 (-0.03; 0.00)	5.9%	-0.02 (-0.04; 0.00)	5.9%
+ diuretics	0.34 (0.15; 0.53)	0.3%	-0.06 (-0.10; 0.01)	0.0%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	0.0%
+ beta-blockers	0.34 (0.15; 0.53)	0.9%	-0.06 (-0.10; 0.01)	1.7%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	5.9%
+ calcium antagonists	0.34 (0.15; 0.54)	1.5%	-0.06 (-0.10; 0.01)	3.4%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	0.0%
+ RAS-inhibitors	0.34 (0.15; 0.53)	0.6%	-0.06 (-0.10; 0.02)	1.7%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	0.0%

Abbreviations: BPV, blood pressure variability; Unstd., unstandardized; CI, confidence interval. Data represent change of cognitive function with each 1 mmHg increase in blood pressure variability as unstandardized beta (95% confidence interval). Adjusted for age, sex, country, treatment (pravastatin/placebo), body mass index, education, ldl, hdl, triglycerides, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, average blood pressure during follow-up, eGFR, number of medications.

estimates for cognitive function did not essentially change. Furthermore, when we adjusted for all blood pressure lowering medication, beta estimates also remained essentially the same.

An additional sensitivity analysis in which we excluded all participants (n=2,766) who changed their blood pressure lowering medication during follow-up, revealed materially the same results (supplemental tables 1, 2 and 3; available on request).

Discussion

In this prospective cohort study including 5,606 men and women with a mean age of 75 years, we showed that blood pressure lowering medication, including diuretics, beta-blockers, calcium-channel blockers and RAS inhibitors, did not mediate the association between high levels of blood pressure variability and cognitive impairment.

The last few years, visit-to-visit blood pressure variability has received increasing attention, especially in the association with cardiovascular diseases and cognitive impairment. The association between blood pressure lowering medication and visit-to-visit blood pressure variability has previously been investigated by Rothwell and colleagues.(4) They hypothesized that class-specific differences of antihypertensive medication in preventing stroke might be due to their different effects on visit-to-visit blood pressure variability.(5) In their systematic review and meta-analysis, they showed that inter-individual systolic blood pressure variability was reduced the most by calcium-antagonists and non-loop diuretic drugs, and increased by ACE-inhibitors, angiotensin-2-receptor blockers and beta-blockers.(12) Besides the association with lower systolic blood pressure variability, these findings are in line with our results, in which we also showed higher systolic blood pressure variability in participants taking beta-blockers and RAS-inhibitors.

The underlying mechanism by which blood pressure lowering medication is associated with blood pressure variability, has not been fully understood. Although most blood pressure lowering medications have an effect on reducing blood pressure variability, there is evidence that the most effective are those acting on the arterial baroreflex and calcium channel.(20) Furthermore, previous studies showed that calcium antagonists and diuretics have arterial effects, including reduction of arterial stiffness and vasoconstriction, by which blood pressure variability is also reduced.(21, 22) Cumulative evidence from animal studies shows that higher levels of blood pressure variability produce lesions of arterial endothelial

cells, activation of the renin-angiotensin system, and inflammation.(20) Subsequently, this may lead to impaired cerebral microvasculature and hemodynamics, with comprised cerebral flow and eventually, impaired cerebral function. Future studies are needed to identify underlying mechanisms of the effects of blood pressure lowering medication on blood pressure variability.

Although this study provides evidence for an association between classes of blood pressure lowering medication and higher blood pressure variability, we found no proof that blood pressure lowering medication mediates the previously demonstrated relation of blood pressure variability with cognitive impairment. A possible explanation for this might be that the magnitude of effect of blood pressure lowering medication on blood pressure variability was relatively low, and only accounts for a small proportion of all variability. A second explanation might be that blood pressure lowering medication itself did not associate with cognitive function, which strengthens the finding that blood pressure variability, independent of blood pressure lowering medication, is associated with cognitive impairment.

One important issue that merits further discussion is the principle of confounding by indication, in which allocation of treatment may reflect a decision influenced by patient characteristics and prognostic factors.(23) Indeed, we found that characteristics of the study participants differed across classes of blood pressure lowering medication in the population under study, of which the high prevalence of diabetes mellitus in participants taking RAS-inhibitors is an example. In addition, besides blood pressure lowering medication, many other factors influence blood pressure variability, such as incident diseases, inflammation pathways and baroreceptor regulation.(3, 24) Although adjusting for possible confounders like histories of cardiovascular diseases and risk factors did not essentially change our results, our findings could still have been affected by unknown or unmeasured factors. Furthermore, another limitation could be that the combination of several drugs of one participant may be modifying the associations of blood pressure lowering medication with both blood pressure variability and cognitive function. However, when we adjusted our analyses for number of blood pressure lowering medications, our results did not materially change. Strength of our study is the large sample of participants taking blood pressure lowering medication, who all had repeated measures of blood pressure over a mean follow-up period of 3.2 years. Furthermore, the prospective nature of this study allowed us to study our research question in a clinical setting, rather than a trial context.
In conclusion, we found that use of beta-blockers and RAS-inhibitors was associated with higher levels of blood pressure variability. Furthermore, blood pressure lowering medica-

tion did not mediate the association between high levels of blood pressure variability and cognitive impairment.

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