Cognitive Decline and Blood Pressure

Systolic Blood Pressure Variation and Mean Heart Rate Is Associated With Cognitive Dysfunction in Patients With High Cardiovascular Risk

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Abstract—Elevated systolic blood pressure (SBP) correlates to cognitive decline and incident dementia. The effects of heart rate (HR), visit to visit HR variation, and visit to visit SBP variation are less well established. Patients without preexisting cognitive dysfunction (N=24,593) were evaluated according to mean SBP, SBP visit to visit variation (coefficient of variation [standard deviation/mean×100%], CV), mean HR, and visit to visit HR variation (HR-CV) in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. Cognitive function was assessed with mini mental state examination. Cognitive dysfunction (fall in mini mental state examination ≤24 points), important cognitive decline (drop of ≥25 points), and cognitive deterioration (drop of >1 point per year or decline to <24 points) were assessed. SBP and HR were measured over 10.7±2.2 (mean±SD) visits. Mean SBP, mean HR, and SBP-CV were associated with cognitive decline, dysfunction, and deterioration (all P<0.01, unadjusted). After adjustment, only SBP-CV (P=0.0030) and mean HR (P=0.0008) remained predictors for cognitive dysfunction (odds ratios [95% confidence intervals], 1.32 [1.10–1.58] for 5th versus 1st quintile of SBP-CV and 1.40 [1.18–1.66] for 5th versus 1st quintile of mean HR). Similar effects were observed for cognitive decline and deterioration. SBP-CV and mean HR showed additive effects. In conclusion, SBP-CV and mean HR are independent predictors of cognitive decline and cognitive dysfunction in patients at high CV risk.

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Key Words: heart rate  hypertension  myocardial infarction  stroke

Cardiovascular risk factors, particularly elevated systolic blood pressure (SBP), have been linked to cognitive dysfunction and cognitive decline in cardiovascular disease potential involving mechanisms, such as endothelial dysfunction, microemboli, and oxidative stress, promoting cerebral atherosclerosis. The visit to visit variation of blood pressure has been suggested to be linked to stroke and to cognitive decline. Recently, elevated resting heart rates (HR) were found to be related to cardiovascular outcomes in hypertension, coronary artery disease, and heart failure and to induce endothelial dysfunction, antiangiogenic mechanisms in hypercholesterolemia after vascular occlusions, and to enhance stroke size in experimental models. In patients after a first stroke, elevated HR >76 bpm was associated with cardiovascular mortality and with a more pronounced cognitive decline after a second stroke. Although the effects of noncontrolled SBP on cognitive decline have been studied, limited or no such information is available for SBP visit to visit variation, mean HR, and HR...
visit to visit variation. In this article, we analyze the relationship between mean on-treatment SBP, SBP-variation, mean on-treatment HR, and HR-variation and cognitive decline (≥25 points reduction in the mini mental state examination [MMSE]) and cognitive dysfunction defined as a score of ≤24 points indicative of clinically relevant cognitive impairment. Cognitive deterioration was defined as reduction of ≥1 point per year or decline to ≤24 points). The latter end point is sensitive to the absolute level of MMSE and to changes over time although accounting for different durations of follow-up. We used the pooled data set of the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND). 17,18

Methods

Studied Patients

The primary objective and protocol of the ONTARGET and TRANSCEND trials have been described in detail previously. 17,18 In brief, patients age ≥55 years without symptomatic heart failure at entry and with a history of coronary artery disease, peripheral artery disease, prior TIA or stroke or diabetes mellitus complicated by organ damage were eligible for inclusion in the studies. In ONTARGET patients known to be tolerant to ACE inhibitors were randomly assigned to ramipril 10 mg kd, telmisartan 80 mg qd, or the combination thereof (double-dummy design), whereas in TRANSCEND patients intolerant to ACE inhibitors were randomized to telmisartan 80 mg qd or matching placebo. Study medication was given on top of preexisting treatment used by the treating physicians and investigators. The other medications were given according to best clinical practice in the individual study centers. Investigators were advised to maintain preexisting blood pressure medications targeting blood pressures of <130/80 mm Hg for patients with chronic kidney disease and 140/90 mm Hg in the other individuals. Patients with on-treatment blood pressure >160/100 mm Hg at entry were not eligible. 17,18 Visits were scheduled at 6 weeks and 6 months after randomization and every 6 months thereafter. In ONTARGET, 25,620 patients from 733 centers in 40 countries were randomized, whereas in TRANSCEND, 5926 patients from a subset of 630 centers were randomized. The median follow-up period in both studies was 56 months. The protocol procedures and main results of ONTARGET and TRANSCEND have been published previously 17,18 showing comparable outcomes in the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure (time to first event) in the 3 active treatment arms of ONTARGET and a lower event rate in the telmisartan group of TRANSCEND which, however, was not significant.

The primary objective of this analysis was to evaluate the association of in-trial mean SBP, visit to visit SBP variation, mean HR, and visit to visit HR variation with cognitive decline and incident cognitive dysfunction in high risk cardiovascular patients. At each visit in both studies, resting blood pressure and HR were measured in duplicate in sitting position after 3 minutes of rest using an automated validated device (Omron, model HEM 757; Omron corporation, Kyoto, Japan). In-trial blood pressure and HR were averaged using mean measurements at each individual visit. Visit to visit variation of BP and HR was calculated as coefficient of variation (CV), that is, the ratio of standard deviation (SD) and mean (CV=SD/ mean×100%). Measurements from all visits (including baseline values) before the final MMSE were included, and ≥3 visits with data were required for inclusion in the analysis. The studies were approved by the local ethics committees in accordance with the Declaration of Helsinki.

Cognitive function was evaluated in all patients by MMSE. The score ranges from 0 to 30 with lower scores indicative of greater degree of cognitive impairment. MMSE was done at baseline, after 2 years and at the penultimate visit (usually between 3 and 5 years). The majority of patients were evaluated at 3 to 5.5 years (88.5%), and in only 11.5% of patients, the 2-year MMSE was the last evaluation. In line with a previous report, 19 cognitive dysfunction was defined as MMSE ≤24 points at the last available visit (2 years or penultimate), and cognitive decline was defined as ≥25 points decrease of MMSE. The MMSE and its changes are related to future dementia, although its accuracy in the diagnosis of dementia is weak. 19,20 It has been widely used to determine cognitive changes over time and is a feasible instrument in large clinical trials. 21,22 Sensitivity analyses pointed out that changes between 3 and 4 points decline might reliably reflect a significant cognitive decline. 21,22 To overcome these uncertainties, we present a ≥25 point MMSE decline as indication for a significant cognitive decline. Similar results were obtained when a cutoff of 2 points was evaluated. To account for different follow-up periods, in the combined outcome of cognitive deterioration, a decline in ≥1 MMSE points per year or a reduction to ≤24 points was also evaluated.

The different treatment arms of ONTARGET and TRANSCEND did not show any differences in cognitive function at baseline. 24 To explore the role of mean SBP, SBP-CV, mean HR, and HR-CV on cognitive function, data of enrolled patients without cognitive dysfunction at baseline (MMSE ≥24 points) and ≥1 available follow-up score was included in this analysis.

31,546 patients were enrolled in ONTARGET or TRANSCEND. In 4166 patients, there was preexisting significant cognitive dysfunction (MMSE ≤24) or no MMSE score at baseline was available. In further 2646 patients, no follow-up MMSE was available; in an additional 42 patients, <3 visits were available for the calculation of SBP/HR mean and variation, and in further 99 patients, data for important covariates (those to be used in model building) were missing. Thus, 24593 patients remained in the present analysis (Figure 1). On average, SBP and HR measurements were available from 10.7±2.2 visits (range 3–13) over an observation period of 53.1±11.5 months.

Statistical Analysis

Patients were subdivided in quintiles based on their mean SBP, SBP-CV, mean HR, and HR-CV, allowing cohort statistical evaluations with adequate group sizes. Baseline characteristics were presented for quintiles, continuous data as mean±standard deviations, and categorical data as percentages. Quintiles were tested for differences using ANOVA for continuous data and the χ2 test for categorical data. For each of the 4 parameters (SBP mean, SBP-CV, HR mean, and HR-CV), rates of cognitive dysfunction, decline, and deterioration were determined by quintiles.
and tested for differences using the \( \chi^2 \) test. In addition, we developed a multivariate logistic regression model that included all 4 parameters of interest and the MMSE value at baseline and, in addition, all potential predictors of cognitive dysfunction, decline, and deterioration, particularly those displayed in Table. A stepwise selection procedure with \( P \) limits of 0.25 for entry into the model and 0.15 for stay in the model was applied; it was further checked whether the resulting optimal model was

<table>
<thead>
<tr>
<th>Variable</th>
<th>A: Cognitive Dysfunction</th>
<th>B: Cognitive Decline</th>
<th>C: Cognitive Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE at baseline, per score unit</td>
<td>0.65 (0.63–0.67)</td>
<td>1.07 (1.03–1.11)</td>
<td>0.75 (0.73–0.77)</td>
</tr>
<tr>
<td>DBP CV quintiles</td>
<td></td>
<td></td>
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<tr>
<td>2 vs 1</td>
<td>0.84 (0.71–1.00)</td>
<td>0.80 (0.65–0.98)</td>
<td>0.81 (0.69–0.94)</td>
</tr>
<tr>
<td>3 vs 1</td>
<td>0.81 (0.68–0.97)</td>
<td>0.83 (0.68–1.02)</td>
<td>0.74 (0.64–0.87)</td>
</tr>
<tr>
<td>4 vs 1</td>
<td>0.89 (0.75–1.06)</td>
<td>0.89 (0.72–1.09)</td>
<td>0.83 (0.71–0.97)</td>
</tr>
<tr>
<td>5 vs 1</td>
<td>0.96 (0.81–1.15)</td>
<td>0.97 (0.79–1.20)</td>
<td>0.86 (0.73–1.01)</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.05 (1.04–1.06)</td>
<td>1.06 (1.05–1.07)</td>
<td>1.06 (1.04–1.062)</td>
</tr>
<tr>
<td>BMI, per unit</td>
<td>0.99 (0.98–1.00)</td>
<td></td>
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<tr>
<td>eGFR, per 10 U</td>
<td></td>
<td>0.97 (0.93–1.00)</td>
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</tr>
<tr>
<td>Female vs Male</td>
<td>1.15 (1.03–1.29)</td>
<td>1.09 (0.98–1.20)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
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<tr>
<td>Asian vs White</td>
<td>0.93 (0.80–1.08)</td>
<td>0.83 (0.70–1.00)</td>
<td>0.92 (0.80–1.05)</td>
</tr>
<tr>
<td>Black vs White</td>
<td>1.39 (1.02–1.88)</td>
<td>1.80 (1.27–2.54)</td>
<td>1.41 (1.07–1.86)</td>
</tr>
<tr>
<td>Other vs White</td>
<td>1.16 (0.99–1.36)</td>
<td>1.24 (1.02–1.50)</td>
<td>1.16 (1.00–1.34)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everyday vs mainly sedentary</td>
<td>0.87 (0.76–0.99)</td>
<td>0.83 (0.70–1.00)</td>
<td>0.87 (0.74–0.94)</td>
</tr>
<tr>
<td>5–6 times/week vs mainly sedentary</td>
<td>0.89 (0.71–1.11)</td>
<td>0.81 (0.66–0.98)</td>
<td>0.81 (0.66–0.98)</td>
</tr>
<tr>
<td>2–4 times/week vs mainly sedentary</td>
<td>1.02 (0.88–1.18)</td>
<td>0.95 (0.84–1.09)</td>
<td>0.95 (0.84–1.09)</td>
</tr>
<tr>
<td>≤ Once/week vs mainly sedentary</td>
<td>0.89 (0.74–1.07)</td>
<td>0.86 (0.73–1.01)</td>
<td>0.86 (0.73–1.01)</td>
</tr>
<tr>
<td>Formal education</td>
<td></td>
<td></td>
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<tr>
<td>College/University vs ≤ 8 y</td>
<td>0.42 (0.35–0.50)</td>
<td>0.42 (0.34–0.50)</td>
<td>0.46 (0.40–0.54)</td>
</tr>
<tr>
<td>Trade/Technical vs ≤ 8 y</td>
<td>0.56 (0.48–0.66)</td>
<td>0.59 (0.49–0.70)</td>
<td>0.57 (0.50–0.66)</td>
</tr>
<tr>
<td>9–12 yr vs ≤ 8 y</td>
<td>0.61 (0.54–0.69)</td>
<td>0.58 (0.50–0.67)</td>
<td>0.64 (0.58–0.72)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.81 (0.72–0.91)</td>
<td>0.74 (0.65–0.85)</td>
<td>0.78 (0.70–0.86)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.09 (0.97–1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td>1.22 (1.08–1.38)</td>
<td>1.25 (1.09–1.45)</td>
<td>1.20 (1.07–1.34)</td>
</tr>
<tr>
<td>New stroke</td>
<td>2.43 (1.96–3.00)</td>
<td>2.66 (2.11–3.35)</td>
<td>2.21 (1.82–2.70)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>1.29 (1.10–1.50)</td>
<td>1.35 (1.12–1.61)</td>
<td>1.28 (1.11–1.47)</td>
</tr>
<tr>
<td>New diabetes mellitus</td>
<td>1.17 (0.96–1.44)</td>
<td></td>
<td></td>
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<tr>
<td>Doubling of creatinine</td>
<td>1.41 (1.01–1.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>0.85 (0.76–0.95)</td>
<td>0.90 (0.79–1.04)</td>
<td>0.86 (0.77–0.95)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>0.84 (0.74–0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.09 (0.98–1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>1.12 (1.00–1.25)</td>
<td>1.20 (1.05–1.37)</td>
<td>1.13 (1.02–1.25)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.92 (0.82–1.02)</td>
<td>0.90 (0.79–1.02)</td>
<td>0.92 (0.83–1.01)</td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td>0.87 (0.74–1.02)</td>
<td>0.86 (0.71–1.05)</td>
<td>0.88 (0.76–1.02)</td>
</tr>
<tr>
<td>c-Statistic of complete model</td>
<td>0.784</td>
<td>0.709</td>
<td>0.739</td>
</tr>
<tr>
<td>c-Statistic of model without BP/HR indices</td>
<td>0.781</td>
<td>0.700</td>
<td>0.734</td>
</tr>
<tr>
<td>Likelihood ratio test</td>
<td>( P=0.0001 )</td>
<td>( P=0.0002 )</td>
<td>( P&lt;0.0001 )</td>
</tr>
</tbody>
</table>

Predictors resulting from multivariate logistic regression model selection (global \( P \) value given for predictors with >2 categories).

ASA indicates aspirin; BMI, body mass index; BP, blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MMSE, mini mental status examination; and OR, odds ratio.
minimal in terms of Akaike’s Information Criterion. The likelihood ratio test was used to check whether the addition of BP and HR parameters (as described above) significantly improve the predictive quality of the models; c-statistics are given as well. The association between SBP-CV and mean HR as continuous variables and cognitive outcomes was also analyzed nonparametrically with restricted cubic splines, allowing for potentially nonlinear relationship. Additionally, as a sensitivity analysis, decline in MMSE was modeled as a continuous variable (reported in the online-only Data Supplement). Results are presented as odds ratios (OR) with 95% confidence intervals. All analyses were done using SAS version 9.2 (SAS Institute, NC).

**Results**

**Correlation of Means, Standard Deviations, and CVs**

The correlation between mean SBP and SBP SD was modest ($r=0.28$), as was the correlation between mean HR and HR SD ($r=0.31$). There was almost no correlation between mean SBP and SBP coefficient of variation (CV; $r<0.01$) and between mean H and HR-CV ($r=0.05$), and therefore, CV was chosen for further analysis instead of SD being less dependent on the mean. There was almost no correlation between mean SBP and mean HR ($r=0.01$), whereas the correlation between SBP-CV and HR-CV was small ($r=0.15$).

**Demographics and Clinical Characteristics**

Demographic data and clinical characteristics are presented for mean SBP, SBP-CV quintiles mean HR, and HR-CV quintiles (Table S1 in the online-only Data Supplement). Table S1 also contains a column for those 6953 patients who could not be included in the analysis. Because of the big sample size, most of the variables and characteristics were significantly different between quintiles, but the relevance of these (partly small) differences is unsure. As expected, there were some differences with cardiovascular medication, for example beta blockers were used more often at low HR. There were also some differences between the patients included in this analysis and the remaining patients of ONTARGET and TRANSCEND. Some of these differences were as a result of the selection of patients with MMSE >24 at study entry; excluding patients with preexisting cognitive dysfunction mainly affected patients with older age, less advanced formal education, less physical activity, black ethnicity, and worse kidney function. In line with the higher age of the excluded patients, means of SBP/HR and CVs were also slightly higher.

**Proportions of Cognitive Dysfunction, Decline, and Deterioration by SBP Mean and CV**

Cognitive dysfunction was observed in 1857 patients (7.6%) and cognitive decline in 1176 patients (4.8%); 1017 patients (4.1%) fulfilled the criteria for both end points. Regarding mean SBP (Figure 2A, left), incident cognitive dysfunction increased from 6.0% in the lowest to 9.4% in the highest quintile ($P<0.0001$). Cognitive decline (middle) ranged from 4.0% in the lowest to 5.7% in the highest quintile ($P=0.0012$). For the quintiles of SBP-CV (Figure 2B), cognitive dysfunction rates increased from 6.3% in the lowest to 10.2% in the highest quintile ($P<0.0001$). Cognitive decline rates ranged from 4.1% in the lowest to 6.4% in the highest quintile ($P<0.0001$; Figure 2B). Similar results were obtained for cognitive deterioration (right; 7.4%–11.2% for mean SBP [$P<0.0001$] and 7.8%–12.1% for SBP-CV [$P<0.0001$], respectively).

**Proportions of Cognitive Dysfunction, Decline, and Deterioration by HR Mean and CV**

Regarding mean HR, incident cognitive dysfunction (Figure 2C, left) increased from 5.6% in the lowest to 9.1% in the highest quintile ($P<0.0001$). Cognitive decline (Figure 2C, middle) ranged from 3.4% in the lowest to 5.6% in the highest quintile ($P<0.0001$), with similar results for cognitive deterioration (6.8%–11.0%, right). For the quintiles of HR-CV (Figure 2D), cognitive dysfunction rates (left) ranged from 6.9% in the second (ie, lowest rate) to 8.5% in the highest quintile ($P=0.027$). Cognitive decline (middle) rates were evaluated from 4.0% to 5.4% in the fifth quintile of HR-CV ($P=0.0098$; Figure 2D). Cognitive deterioration showed similar results (right).

**Multivariate Model With Adjustment for Confounders**

With respect to the incidence of cognitive dysfunction, SBP-CV ($P=0.0030$) and mean HR ($P<0.0008$) remained to be significant predictors after adjusting. The confounders, such as MMSE, at baseline, DBP-CV, age, body mass index, estimated glomerular filtration rate, sex, ethnicity, physical activity, formal education, alcohol consumption, history of stroke and new stroke during study conduct, history of diabetes mellitus, and new diabetes mellitus during study conduct, as well as concomitant medication with aspirin, beta blockers, diuretics, nitrates, statins, and hypoglycemics are given in Table. Compared with the lowest SBP-CV quintile (reference), the OR for having cognitive dysfunction was 1.32 (95% CI, 1.10–1.58; $P=0.0029$) in the highest quintile (Figure 3A, left). When comparing the highest mean HR quintile to the lowest, the OR was 1.40 (1.18–1.66; $P<0.0001$; Figure 3B, left). Among the other predictive variables, baseline MMSE (0.65 [0.63–0.67] per unit), age (1.05 [1.04–1.06] per year), formal education (eg, college/university versus <8 years education 0.42 [0.35–0.49]), and incident stroke during the studies (2.42 [1.96–3.00]) and history of previous stroke before entry into the studies (1.22 [1.08–1.38]) had the strongest associations with cognitive dysfunction. The ORs for all confounders that remained in the model after the selection procedure are presented in Table, A.

Mean HR ($P=0.0002$; Figure 3B) also was an independent predictor for cognitive dysfunction (left), decline (middle), and deterioration (right) after adjusting for the other parameters and all confounders. For mean HR, the upper 3 quintiles had significantly higher odds compared with the referent quintile, but with no apparent differences among these 3 quintiles were seen. Patients with higher MMSE baseline values had a greater chance for decline (OR, 1.07 [1.03–1.11] per unit). The ORs for all other factors in the model are presented in Table, B. Similar results were obtained for cognitive deterioration (Table, C; Figure 3, right). The nonlinear relationship between SBP-CV as a continuous variable and the risk of cognitive outcomes (as a result of modeling with cubic splines) is shown in Figure 4A. A similar nonlinear relationship was observed with mean HR as shown in Figure 4B.
Figure 2. Cognitive dysfunction (left), cognitive decline (middle), and cognitive deterioration (right) according to mean systolic blood pressure (A), systolic blood pressure coefficient of variation (CV; B), mean heart rate (C), and heart rate coefficient of variation (D).

Interaction With Stroke

No apparent heterogeneity in the effects of SBP-CV and mean HR on cognitive dysfunction, decline, and deterioration was seen in patients with or without previous stroke (before or during the studies [P values for test on interaction 0.61 for SBP-CV, 0.35 for mean HR on cognitive dysfunction, 0.76 for SBP-CV, 0.097 for mean HR for cognitive decline, and 0.62 for SBP-CV, 0.29 for mean HR for cognitive deterioration]).
Thus, the effects of high SBP variation and high mean HR apply similarly to patients with and without stroke.

Interaction With Atrial Fibrillation
No apparent heterogeneity in the effects of SBP-CV and mean HR on cognitive dysfunction and decline was seen in patients with or without atrial fibrillation (before or during the studies \( P \) values for test on interaction 0.40 for SBP-CV, 0.43 for mean HR on cognitive dysfunction, 0.31 for SBP-CV, 0.11 for mean HR for cognitive decline). Thus, the effects of high SBP variation and high mean HR apply similarly to patients with and without atrial fibrillation. Only for the association between mean HR and cognitive deterioration, there is some indication \( (P=0.042) \) for a heterogeneous effect; the detrimental effect of higher mean HR seems to be confined to patients without atrial fibrillation.

Interaction With Ethnicity
No heterogeneity in the effects of SBP-CV and mean HR was seen in patients with different ethnicities on cognitive dysfunction \( (P=0.91) \) and cognitive decline \( (P=0.44) \) and cognitive deterioration \( (P=0.99) \). However, the effect of mean HR on cognitive decline and deterioration seems to be differential between ethnicities \( (P=0.025 \) for decline, \( P=0.022 \) for deterioration); the detrimental effect of high mean HR is evident only in whites and Asians, whereas no effect is seen in blacks and patients of other ethnic origin.

Interaction of Blood Pressure Variation and Mean HR on Cognitive Function
To test whether there is any interaction between SBP-CV and mean HR, the respective interaction term was added to the multivariate model, which resulted from the model selection process described above. It turned out that no apparent interaction was present \( (P=0.55) \) for new cognitive dysfunction, \( P=0.11 \) for cognitive decline, \( P=0.70 \) for cognitive deterioration). The additivity in the detrimental effect of high SBP-CV and high mean HR is shown in Figure 5, which shows ORs for combination of quintiles with the combination of first quintiles as reference for cognitive dysfunction (A), decline (B), and deterioration (C). Patients in the highest quintiles for each parameter show an OR of 1.85 (1.44–2.38) for cognitive dysfunction; for cognitive decline, the maximum OR is seen in
the combined fifth SBP-CV and fourth HR mean quintile (2.03 [1.50–2.75]). The detailed results are given in Table S2A–2C.

**Sensitivity Analyses**

When the analyses described above are run in the subset of patients with ≥3 visits subsequent the 6 week visit (n=24,365), the results are essentially the same. This has been done to reflect the possibility that SBP variation might be induced by BP reduction in the beginning of the trials. Further, in a linear model with (continuous) reduction in MMSE per year as dependent variable and the same variables, which were included in the logistic regression models described above,

**Additive Effects of SBP (CV) and mean HR**

**Figure 4.** Development of cognitive dysfunction (left), cognitive decline (middle), and cognitive deterioration (right) according to systolic blood pressure coefficient of variation (SBP-CV; A) and mean heart rate (B) as continuous variables. Odds ratios calculated based on logistic regression with restricted cubic splines (SBP-CV reference, 6%; mean heart rate reference, 60 bpm; gray area is 95% confidence band).

**Figure 5.** Additive effects of systolic blood pressure variation (SBP-CV) and mean heart rate (HR mean) on cognitive dysfunction (A), cognitive decline (B), and cognitive deterioration (C).
as independent variables, the significant effect of SBP-CV \((P<0.0001)\) and mean HR \((P=0.0018)\) as well as the effects of the main predictors (baseline MMSE, age, education, and stroke) was confirmed (cf. Table S3). We also explored whether our results were dependent on the definition of cut-offs, for example, 25 points for MMSE at study end and 1 point for yearly reduction. Figure S1 shows that the upper quintiles of SBP-CV and mean HR show consistently higher cumulative percentages of patients being <27 at final MMSE (Figure S1A and 1C) and also higher cumulative percentages of patients with yearly reductions in MMSE independent of its magnitude (Figure S1B and 1D). Thus, the effects demonstrated are not dependent on the specific choices of cut-offs, and similar effects would have been shown if cut-offs were different.

Discussion

Cardiovascular risk factors are the driving force in the development of cognitive dysfunction, including Alzheimer’s disease, leading to increased prevalence of dementia in the aging population. Herein, we report that SBP-CV and mean HR are related independently to cognitive decline as judged from the MMSE score by a decline ≥5 points, incident cognitive dysfunction defined as clinically relevant cognitive dysfunction to the MMSE score ≤24, and cognitive deterioration as drop in MMSE by ≥1 point per year or decline to ≤24 points).

The present analysis investigated the association of SBP and HR on incident cognitive dysfunction, cognitive decline, and cognitive deterioration. Many studies were conducted to identify the association of cardiovascular risk with SBP or HR by using a single measurement of SBP or HR. However, over time, SBP or HR as risk markers may vary and can place patients into different risk groups. Time varying statistical analyses have been used to analyze outcomes by Kaplan–Meier analyses for the shift of patients from one to another risk group, an approach which was used to study the effects of SBP on clinical outcomes in the ONTARGET trial. Herein, we have used multiple readings of HR and SBP for a given patient and averaged values when the number of visits exceeded 2 and determined mean SBP and mean HR over 10.7±2.2 visits. There was no or only a modest association of mean SBP and mean HR with the variation parameter, indicating that mean and CV are independent of each other. The data were collected over multiple visits and thereby giving a better integration of the total load of hemodynamic risk markers.

Blood Pressure Mean and Blood Pressure Variability

SBP was associated with cognitive dysfunction, cognitive decline, and cognitive deterioration, but after adjusting for confounders, the effect was not independent of traditional cardiovascular risk factors. The blood pressure hypothesis has been questioned before because variation, stability, and episodic signs of hypertension may be of greater importance in producing cardiovascular outcomes. Accordingly, visit to visit variation of SBP was shown to predict the occurrence of stroke in hypertensive individuals, as well as all-cause mortality in the general population and was associated with microbleeds and white matter lesions in patients after an ischemic stroke. Although associations of blood pressure with cognitive decline are convincing, secondary analyses of cardiovascular trials aiming to investigate cognitive decline after blood pressure lowering have been inconsistent. The Syst-Eur trial included 2418 patients and was terminated prematurely as a result of significant differences in the incidence of stroke, leading to a short follow-up of only 2 years. Dementia incidence was reduced and there was no significant change of MMSE, but there was a decline in the control group with decreasing diastolic blood pressure. In patients with prior stroke or transitory ischemic attack, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed in 6105 randomized patients (with 48% being hypertensive) after follow-up of 3.5 years a relative risk reduction by 19% of incident dementia or cognitive decline defined as a MMSE reduction of ≥23 points, but only in patients with a recurrent stroke. In contrast, Systolic Hypertension in the Elderly Program, the unblinded Medical Research Council’s Trial on Hypertension in Older Adults, Hypertension in the Very Elderly Trial, and Study on Cognition and Prognosis in the Elderly showed trends but no significant effects of hypertensive therapies on cognitive function. Also treatment with RAS-inhibitors and non-RAS inhibitors showed no difference in patients after stroke (Prevention Regimen for Effectively Avoiding Second Strokes [PROFESS]) or in high risk patients of ONTARGET and TRANSCEND. Interestingly, the association of SBP variation to stroke or cerebral lesions has not been investigated in cardiovascular intervention trials in high risk patients, except in one study on 201 elderly hypertensive individuals in Japan. Because observational studies never prove causality and, in addition, drugs might act differently on SBP variation, intervention trials in high risk patients ought to prospectively investigate pharmacological interventions on SBP variation and outcomes. In a study on low risk hypertensives, in-trial mean BP was more predictive than SBP-CV. It is open to speculation whether variation of blood pressure over time is caused by instable blood pressure regulation adding to the risk of plaque instability.

Heart Rate

In addition to blood pressure, HR has been identified to be associated with cardiovascular outcomes in patients with hypertension, myocardial infarction, and heart failure. Reduction of clinical events by HR reduction with the If-channel inhibitor ivabradine, qualifying HR as a modifiable risk factor and not only as a risk marker, has only been shown in heart failure. In experimental animals after psychosocial stress, pharmacological HR reduction reduces stroke size. In patients after stroke, cognitive decline was accelerated in patients with a HR >67 bpm and was, furthermore, associated with mortality, including cardiovascular mortality, but not recurrent stroke rates. These findings suggest that stroke quality, for example, reduction in stroke size rather than a reduction of second strokes, might occur at low HR. Thus, the findings in the PRoFESS trial on patients after a previous stroke can be extended to patients without prior strokes because there was no significant interaction of HR risk relationship in patients with or without stroke in this analysis. Therefore, high HR may be a new risk marker of cognitive dysfunction and incident dementia in high risk patients with prevalent cardiovascular disease. It is tempting to speculate whether HR reduction by pharmacological interventions might reduce risk and delay cognitive dysfunction because in animals with...
atherosclerosis, HR reduction has a strong protective effects on plaque formation,\textsuperscript{57,58} promotes collateral growth,\textsuperscript{49} protects endothelial function, and prevents erectile dysfunction,\textsuperscript{50} an association which was also observed in humans.\textsuperscript{51} Therefore, HR reduction should be tested in individuals with high risk for cognitive decline, for example after a stroke. Variation of HR was not shown to be of predictive value for cognitive decline or function, and this might be as a result of variability in office conditions where HR is taken.

**Autonomic Regulation in Cognitive Impairment**

Changes of HR and blood pressure relation have been observed in patients with dementia. In patients with Alzheimer’s dementia, a higher HR was observed compared with controls.\textsuperscript{52–54} Baroreflex function is impaired in Alzheimer dementia,\textsuperscript{52} which might contribute to hypotensive syndromes\textsuperscript{55} and enhanced postural blood pressure drops with subsequently impaired cortical perfusion.\textsuperscript{53} Therefore, autonomic regulation resulting in higher blood pressure variation, greater HR, and its variability caused by central autonomic dysregulation might be mechanisms contributing to these findings.

**Limitations and Strengths**

This analysis is a retrospective exploratory analysis of randomized trials with neutral outcomes. Therefore, the allocation of individuals was not subject to randomization. However, this is the largest database in patients with high cardiovascular risk and long follow-up with an average of >10 visits. Furthermore, this is the first study investigating the association of variation of SBP over time with mean HR on incident cognitive decline and incident cognitive dysfunction. The strength is the availability of these measurements in >10 visits, providing a good integration of HRs over the whole study period. This analysis is confined to patients in sinus rhythm because atrial fibrillation per se is associated with cognitive dysfunction in this cohort.\textsuperscript{55} Moreover, in ONTARGET and TRANSCEND, blood pressure was rather well controlled, and the results could have been different in patients with uncontrolled or even resistant hypertension. However, TRANSCEND and ONTARGET are trials on high risk patients on contemporary treatments for cardiovascular protection, in whom, on top of proven treatments, SBP-CV and mean HR show significant associations with cognitive function and incident impairment of cognition.

**Conclusion**

This study demonstrates that long-term SBP variations and mean HR levels are associated with the development of cognitive dysfunction, decline, and deterioration in high risk patients with atherosclerosis or after stroke or high-risk diabetes mellitus.

**Perspectives**

The secondary analysis of ONTARGET investigated the SBP variation and HR on new onset of cognitive decline, dysfunction, and deterioration in a large population of patients at high cardiovascular risk. HR and blood pressure variation may be considered markers of cognitive dysfunction in this patient population. HR and blood pressure variation might be important to judge the future risk of cognitive dysfunction. It should be incorporated in the clinical judgment of these patients. The study shows that SBP and mean HR are associated with cognitive dysfunction, with both parameters acting synergistically on this pathology. They should be incorporated in the work up of cardiovascular high risk patients. Studies on HR reduction and smoothening of SBP profiles are warranted.

**Sources of Funding**

Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) were funded by Boehringer Ingelheim, Germany. All authors received scientific support from Boehringer Ingelheim. M. Böhm and U. Laufs are supported by the Deutsche Forschungsgesellschaft (KFO 196).

**Disclosures**

H. Schumacher is an employee of Boehringer Ingelheim, Germany. The other authors report no conflict.

**References**


**Novelty and Significance**

**What Is New?**
- The secondary analysis of Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial investigated the systolic blood pressure variation and heart rate on new onset of cognitive decline, dysfunction, and deterioration in a large population of patients at high cardiovascular risk.
- Heart rate and blood pressure variation may be considered as markers of cognitive dysfunction in this patient population.

**What Is Relevant?**
- Heart rate and blood pressure variation might be important to judge the future risk of cognitive dysfunction. It should be incorporated in the clinical judgment of these patients.

**Summary**

The study shows that systolic blood pressure and mean heart rate are associated with cognitive dysfunction, with both parameters acting synergistically on this pathology. They should be incorporated in the work up of cardiovascular high risk patients. Studies on heart rate reduction and smoothening of systolic blood pressure profiles are warranted.
Systolic Blood Pressure Variation and Mean Heart Rate Is Associated With Cognitive Dysfunction in Patients With High Cardiovascular Risk

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Systolic blood pressure variation and mean heart rate is associated with cognitive dysfunction in patients with high cardiovascular risk

ONLINE SUPPLEMENT

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Running Title: Blood pressure, heart rate and cognitive decline
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### Table S2a
Additive effects of SBP CV and HR mean on cognitive dysfunction (MMSE>=24), odds ratios with 95% CIs

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<th>4th</th>
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Test on SBP-CV by HR mean interaction: p=0.55

### Table S2b
Additive effects of SBP CV and HR mean on cognitive decline (reduction in MMSE>=5), odds ratios with 95% CIs

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Test on SBP-CV by HR mean interaction: p=0.11

### Table S2c
Additive effects of SBP CV and HR mean on cognitive impairment/decline, odds ratios with 95% CIs

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Test on SBP-CV by HR mean interaction: p=0.70
Sensitivity analysis in a linear model for predictors for reduction of MMSE per year; variables from logistic regression model selection (cf. Table 1) with p<0.15 presented (global p-value given for predictors with more than 2 categories)

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<th>Variables</th>
<th>Estimate</th>
<th>95% CI</th>
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<td>SBP CV quintiles</td>
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<tr>
<td>2 vs 1</td>
<td>0.007</td>
<td>(-0.017 - 0.032)</td>
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<tr>
<td>3 vs 1</td>
<td>0.006</td>
<td>(-0.019 - 0.031)</td>
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<td>4 vs 1</td>
<td>0.031</td>
<td>(0.005 - 0.057)</td>
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<td>5 vs 1</td>
<td>0.062</td>
<td>(0.034 - 0.090)</td>
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<tr>
<td>Mean HR quintiles</td>
<td>p=0.0018</td>
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<tr>
<td>2 vs 1</td>
<td>-0.008</td>
<td>(-0.032 - 0.016)</td>
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<td>3 vs 1</td>
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<td>4 vs 1</td>
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<td>5 vs 1</td>
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<td>MMSE at baseline, per score unit</td>
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<td></td>
<td>0.123</td>
<td>(0.118 - 0.129)</td>
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<td>p=0.022</td>
<td></td>
</tr>
<tr>
<td>2 vs 1</td>
<td>-0.030</td>
<td>(-0.054 - 0.005)</td>
</tr>
<tr>
<td>3 vs 1</td>
<td>-0.040</td>
<td>(-0.065 - 0.014)</td>
</tr>
<tr>
<td>4 vs 1</td>
<td>-0.020</td>
<td>(-0.047 - 0.006)</td>
</tr>
<tr>
<td>5 vs 1</td>
<td>-0.014</td>
<td>(-0.042 - 0.014)</td>
</tr>
<tr>
<td>Age, per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.012</td>
<td>(0.011 - 0.013)</td>
</tr>
<tr>
<td>Female vs Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>(-0.003 - 0.034)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Asian vs White</td>
<td>-0.020</td>
<td>(-0.043 - 0.003)</td>
</tr>
<tr>
<td>Black vs White</td>
<td>0.154</td>
<td>(0.096 - 0.211)</td>
</tr>
<tr>
<td>Other vs White</td>
<td>0.045</td>
<td>(0.017 - 0.074)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Everyday vs Mainly sedentary</td>
<td>-0.064</td>
<td>(-0.086 - 0.043)</td>
</tr>
<tr>
<td>5-6 times/week vs Mainly sedentary</td>
<td>-0.050</td>
<td>(-0.082 - 0.018)</td>
</tr>
<tr>
<td>2-4 times/week vs Mainly sedentary</td>
<td>-0.046</td>
<td>(-0.069 - 0.022)</td>
</tr>
<tr>
<td>≤ Once/week vs Mainly sedentary</td>
<td>-0.036</td>
<td>(-0.065 - 0.008)</td>
</tr>
<tr>
<td>Formal education</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>College/University vs ≤ 8 years</td>
<td>-0.168</td>
<td>(-0.191 - 0.146)</td>
</tr>
<tr>
<td>Trade/Technical vs ≤ 8 years</td>
<td>-0.124</td>
<td>(-0.147 - 0.101)</td>
</tr>
<tr>
<td>9-12 years vs ≤ 8 years</td>
<td>-0.100</td>
<td>(-0.120 - 0.080)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>-0.031</td>
<td>(-0.048 - 0.014)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>0.045</td>
<td>(0.024 - 0.065)</td>
</tr>
<tr>
<td>New stroke</td>
<td>0.294</td>
<td>(0.249 - 0.340)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.050</td>
<td>(0.024 - 0.074)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>0.018</td>
<td>(0.001 - 0.035)</td>
</tr>
<tr>
<td>Statins</td>
<td>-0.016</td>
<td>(-0.033 - 0.001)</td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td>-0.022</td>
<td>(-0.050 - 0.005)</td>
</tr>
</tbody>
</table>
**figure S1**

Cumulative percentage of patients below cut-off levels for

(A) final MMSE by SBP-CV quintiles,

(B) yearly MMSE change by SBP-CV quintiles,

(C) final MMSE by HR mean quintiles,

(D) yearly MMSE change by HR mean quintiles
figure S1

Cumulative percentage of patients below MMSE at time of last follow-up (A, C) and below change in MMSE per year (B, D) by SBP-CV quintiles (A, B) and mean HR quintiles (C, D). It is shown that the highest quintiles consistently show highest percentages across all values on the abscissa (x-axis). This indicates that the detrimental effect of high SBP-CV and mean HR is independent of the choice of cut-off levels (MMSE at last follow-up of 25, yearly reduction of 1 point).
睡眠和血压（摘要）

生理性过度觉醒相关失眠与高血压相关

Insomnia With Physiological Hyperarousal Is Associated With Hypertension

Yun Li, Alexandros N. Vgontzas, Julio Fernandez-Mendoza, Edward O. Bixler, Yuanfeng Sun, Junyong Zhou, Rong Ren, Tao Li, Xiangdong Tang

既往研究提示客观睡眠时间缩短的失眠者具有更高的高血压患病风险，并推测其潜在的机制在于生理性过度觉醒。在本研究中，我们采用睡眠觉醒标准测试法，即多次睡眠潜伏期试验（Multiple Sleep Latency Test, MSLT）来测试生理性过度觉醒相关失眠是否与高血压风险增加有关。本研究纳入了219例慢性失眠患者及96名正常人，慢性失眠的标准诊断为失眠症状持续≥6个月。所有受试者都采用实验导睡眠图来进行标准的MSLT，并监测一夜。我们把超过MSLT平均中位数值（即>14分钟），及MSLT平均值75%分位数（即>17分钟）定义为过度觉醒。并用血压测量或专科医师的诊断来定义高血压。在控制了年龄、性别、体重指数、呼吸暂停-低通气指数、糖尿病、吸烟、饮酒及应用咖啡因等因素后，我们发现失眠并MSLT>14分钟的受试者患高血压的几率增加300%（OR=3.27，95%可信区间：1.2-8.96），而较而言，失眠并MSLT>17分钟的受试者患高血压的几率甚至高达400%（OR=4.33，95%可信区间：1.48-12.68）。综上所述，生理性过度觉醒相关失眠与高血压风险有显著相关性。另外，MSLT值增高可能是评估生理性过度觉醒及慢性失眠生物学严重程度的一个可靠的指标。（Hypertension. 2015;65:644-650.）

认知功能下降和血压（摘要）

收缩压变异和平均心率与高危心血管患者的认知功能障碍有关

Systolic Blood Pressure Variation and Mean Heart Rate Is Associated With Cognitive Dysfunction in Patients With High Cardiovascular Risk

Michael Böhm, Helmut Schumacher, Darryl Leong, Giuseppe Mancia, Thomas Unger, Roland Schmieder, Florian Custodis, Hans-Christoph Diedner, Ulrich Laufs, Eva Lonn, Karen Sliwa, Koon Teo, Robert Fagard, Josep Redon, Peter Sleight, Craig Anderson, Martin O’Donnell, Salim Yusuf

收缩压升高与认知功能减退以及痴呆事件的发生有关，但心率、每次随访中心率变异及收缩压的变异对其影响尚不明确。在“正在进行单独使用替米沙坦和联合应用雷米普利的全球终点试验（Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial）”以及“使用替米沙坦治疗的血管紧张素转换酶不耐受患者的心脑血管疾病随机评估研究（Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease）”中，24,593例来自不存在认知功能障碍的患者，评估了平均收缩压、收缩压的变异(标准差/均数×100%，变异系数)、平均心率、心率的变异(变异系数)、并使用简易智能量表来评估认知功能。按照认知功能障碍(在简易智能量表中下降≥24分)，重要认知能力下降(下降≥5分)，以及认知能力恶化(每年下降≥1分或低至24分以下)来评估，收缩压和心率的测量次数超过10.7±2.2（平均值±标准差）。平均收缩压、平均心率以及收缩压的变化与认知功能下降、认知功能障碍、认知功能退化有关（所有P<0.01，未校正）。经过校正后，只有收缩压的变异系数(P=0.0030)和平均心率(P=0.0008)是认知功能障碍的危险因子(收缩压的变异系数第5分位数比第一分位数的OR值为1.32，95%可信区间为1.10-1.58；平均心率第5分位数比第一分位数的OR值为1.40，95%可信区间为1.18-1.66)。对认知能力下降和认知能力退化可观察到类似的影响。收缩压变异和平均心率表现出相互的效应。总之，在高危心血管风险的患者中收缩压变异和平均心率是认知功能下降和认知功能障碍的独立预测因素。（Hypertension. 2015;65:651-661.）