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CLINICAL RESEARCH
Hypertension

Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks

Maria H. Mehlum[1,2], Knut Liestøl[3], Sverre E. Kjeldsen[2,4,5], Stevo Julius[5], Tsushung A. Hua[6], Peter M. Rothwell[7], Giuseppe Mancia[8], Gianfranco Parati[9,10], Michael A. Weber[11], and Eivind Berge[4]*

[1]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway; [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [3]Department of Informatics, University of Oslo, Oslo, Norway; [4]Department of Cardiology, Oslo University Hospital, Oslo, Norway; [5]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA; [6]Unit of Biostatistics and Pharmacometrics, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [7]Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, John Radcliffe Hospital, University of Oxford, Oxford, UK; [8]University of Milano-Bicocca, Milan, and Policlinico di Monza, Monza, Italy; [9]Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, IRCCS, Istituto Auxologico Italiano, Milan, Italy; [10]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; and [11]Department of Cardiovascular Medicine, State University of New York, Downstate College of Medicine, NY, USA

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Aims Blood pressure variability is associated with increased risk of cardiovascular events, particularly in high-risk patients. We assessed if variability was associated with increased risk of cardiovascular events and death in hypertensive patients at different risk levels.

Methods and results The Valsartan Antihypertensive Long-term Use Evaluation trial was a randomized controlled trial of valsartan vs. amlodipine in patients with hypertension and different risks of cardiovascular events, followed for a mean of 4.2 years. We calculated standard deviation (SD) of mean systolic blood pressure from visits from 6 months onward in patients with ≥3 visits and no events during the first 6 months. We compared the risk of cardiovascular events in the highest and lowest quintile of visit-to-visit blood pressure variability, using Cox regression. For analysis of death, variability was analysed as a continuous variable. Of 13 803 patients included, 1557 (11.3%) had a cardiovascular event and 1089 (7.9%) died. Patients in the highest quintile of SD had an increased risk of cardiovascular events [hazard ratio (HR) 2.1, 95% confidence interval (95% CI) 1.7–2.4; $P < 0.0001$], and a 5 mmHg increase in SD of systolic blood pressure was associated with a 10% increase in the risk of death (HR 1.10, 95% CI 1.04–1.17; $P = 0.002$). Associations were stronger among younger patients and patients with lower systolic blood pressure, and similar between patients with different baseline risks, except for higher risk of death among patients with established cardiovascular disease.

Conclusion Higher visit-to-visit systolic blood pressure variability is associated with increased risk of cardiovascular events in patients with hypertension, irrespective of baseline risk of cardiovascular events. Associations were stronger in younger patients and in those with lower mean systolic blood pressure.

Keywords Blood pressure variability • Cardiovascular events • Stroke • Hypertension

Introduction

Guidelines for treatment of hypertension focus on 'usual blood pressure', defined as the mean of office blood pressure readings over several visits. It is the level of this mean blood pressure that is thought to account for the risk of cardiovascular events attributable to blood pressure, and that is used to decide if antihypertensive therapy is indicated, while occasional high blood pressures have not been taken as

* Corresponding author. Tel: +47 22119100, Fax: +47 22119181, Email: eivind.berge@medisin.uio.no

an indication for treatment.[1,2] Although variation in blood pressure is physiological,[3] a growing number of publications from clinical and observational studies have indicated that increased variability contribute to the risk of cardiovascular events[4–12] and death,[5,7,13–15] independently of mean blood pressure. The risk is mainly attributable to the variability of the mean blood pressures from different visits (visit-to-visit variability) and to a lesser extent to the variability of individual blood pressures during visits (within-visit variability).[4,16,17]

Most studies have concluded that the association between blood pressure variability and risk of cardiovascular events is higher among patients with high baseline risk.[4,6,7,11,14,18,19] In the present analysis, we aimed to assess if the risk associated with increased blood pressure variability is similar among patients at different levels of baseline risk of cardiovascular events, and whether the association is modified by any other factor, using data from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.

Methods

The VALUE trial was a multinational randomized controlled, double-masked trial of valsartan vs. amlodipine in 15 245 patients with hypertension and at least one additional risk factor for cardiovascular events. Patients were randomly assigned to amlodipine 5 or 10 mg or valsartan 80 or 160 mg from Visit 1 onwards. In addition, patients could receive hydrochlorothiazide (or loop diuretics in case of impaired renal function) or other blood pressure lowering drugs (except angiotensin receptor blockers and calcium antagonists), if needed to reach the target blood pressure of less than 140/90 mmHg. The methods of the VALUE trial have been reported previously.[20] The trial was conducted in accordance with the Declaration of Helsinki. All patients gave informed, written consent, and the trial protocol was approved by ethics committees in all participating countries.[20]

Visits took place monthly during the first 6 months, and every 6 months thereafter, up to a maximum of 72 months (17 visits). Blood pressure was measured three times during each visit, with the patient in the sitting position, after 5 min of rest. Blood pressure was measured using a calibrated standard sphygmomanometer or a validated digital device, and mean blood pressure was calculated as the mean of all three readings. For the present analysis, we selected patients who did not have a cardiovascular event during the first 6 months and who had a minimum of three visits from Visit 6 onwards (target population). The reason for excluding patients who had a cardiovascular event during the first 6 months was to avoid the potential impact of blood pressure change on early events during the dose titration period. We also defined a per-protocol population as patients who had three or more per-protocol visits. A per-protocol visit was defined as a visit where there had been no pause in allocated treatment during the 30 days before the visit. We used the Joint ESC Guidelines for classifying risk.[21] Patients were defined as having moderate risk if they had no previous cardiovascular disease (which was the level of risk for over two-thirds of patients in this group) and very high risk if they had one or more cardiovascular diseases at baseline (myocardial infarction, stroke/transient ischaemic attack (TIA), peripheral arterial disease, or left ventricular hypertrophy).

For the calculation of blood pressure variability, we excluded blood pressures taken before 6 months, in order to avoid confounding from changes in blood pressure or in the dose of blood pressure lowering drugs that took place during this early phase.[4,6,20] We used blood pressure measurements from all visits from 6 to 60 months in the main analysis (since very few patients had visits after 60 months), irrespective of whether the patient was taking allocated treatment. The precision of measured blood pressure variability is dependent on the number of blood pressure measurements.[8,22] Our main analysis therefore included measurements after events, since variability has been shown to remain unchanged after an event.[6,19] As the primary measure of visit-to-visit blood pressure variability we used the standard deviation (SD) of the mean blood pressure from all visits. We also calculated the coefficient of variation (CV) and the average real variability (ARV) of the mean blood pressure between consecutive visits. Within-visit blood pressure variability was defined as the SD of the three blood pressures from each visit, averaged across all visits. As previous analyses have shown that within-visit variability is of lesser importance for risk of cardiovascular events than visit-to-visit variability,[4,16,17] we have focused on visit-to-visit variability in this report.

The primary effect variable for the present analysis was the time to the first composite cardiovascular endpoint of cardiac event or stroke. Cardiac events were defined as sudden cardiac death, fatal myocardial infarction, death during or after percutaneous coronary intervention or coronary bypass surgery, death due to heart failure, death associated with recent myocardial infarction on autopsy, heart failure requiring hospital management, non-fatal myocardial infarction, or emergency procedures to prevent myocardial infarction. Stroke was defined as fatal or non-fatal ischaemic stroke, haemorrhagic stroke, or unclassified stroke. Secondary effect variables were the components of the primary cardiovascular endpoint. Death was classified as all-cause death, cardiovascular death (from cardiac events or stroke), and non-cardiovascular death (e.g. from malignancy).

Statistical analysis

The main analysis was done in the target population of patients who did not have a cardiovascular event during the first 6 months, and who had a minimum of three visits from Visit 6 onwards. Continuous and categorical variables were compared using the Student's *t*-tests and χ^2 tests, respectively. Cardiovascular endpoints were analysed by time to first event, using Cox regression models. The assumption of proportional hazards was tested using log minus log plots for each variable in the model. To account for possible non-linear effects of blood pressure variability, systolic visit-to-visit blood pressure variability was divided into quintiles and entered into the main Cox model as a categorical variable, using the lowest quintile of blood pressure variability as the reference category. Other variables in the model were determined by backward elimination, and we used a *P*-value of <0.05 to decide if a variable should be included in the model. The final, main model included the following variables: age, sex, allocated treatment, diabetes mellitus, atrial fibrillation, creatinine, heart rate, left ventricular hypertrophy, smoking status, history of myocardial infarction, history of stroke/TIA, history of peripheral arterial disease, and mean systolic blood pressure during treatment. We repeated the main analysis for diastolic blood pressure.

We performed a sensitivity analysis restricted to patients in the per-protocol population and a propensity score analysis matching patients in the highest quintile of visit-to-visit variability with patients from the three lowest quintiles of variability. To eliminate the possibility that the predictive value of blood pressure variability was influenced by measurements taken after an event, we also performed an analysis restricted to patients who had no cardiovascular events during the first 24 months and tested whether variability from 4 to 24 months was predictive of cardiovascular events after this point. In addition, we performed a matched case–control analysis, comparing blood pressure variability before the event in each case with variability from same number of visits in controls. We repeated the analysis excluding patients with atrial fibrillation, and, to account for any confounding from low drug adherence, we performed a separate analysis

Table 1 Baseline characteristics of all patients and of patients in the lowest and highest quintiles of standard deviation of visit-to-visit systolic blood pressure variability

	All patients (*N* = 13 803)	Quintile 1 (<5.83 mmHg) (*n* = 2761)	Quintile 5 (>13.66 mmHg) (*n* = 2760)	*P*-value
Female gender	5864 (42.5%)	1217 (44.1%)	1324 (48.0%)	0.003
Age (years)	67.1 (8.1)	66.5 (8.0)	68.7 (8.3)	<0.0001
Treatment				
Amlodipine	6931 (50.2%)	1589 (57.6%)	1055 (38.2%)	<0.0001
Valsartan	6872 (49.8%)	1172 (42.4%)	1705 (61.8%)	<0.0001
Number of visits (mean)				
Target population	8.7 (1.7)	8.5 (1.9)	8.4 (1.9)	0.02
Per protocol population	8.4 (1.9)	8.2 (2.1)	8.1 (2.1)	0.02
Ethnicity				
Caucasian	12364 (89.6%)	2499 (90.5%)	2448 (88.7%)	0.02
Black	542 (3.9%)	69 (2.5%)	173 (6.3%)	<0.0001
Asian	495 (3.6%)	129 (4.7%)	59 (2.1%)	<0.0001
Other	402 (2.9%)	64 (2.3%)	80 (2.9%)	0.2
Systolic blood pressure (mmHg)	154.6 (19.0)	153.2 (16.9)	160.1 (20.6)	<0.0001
Heart rate, beats/min	72.3 (10.7)	72.4 (9.9)	72.5 (11.2)	0.9
Creatinine (μmol/L)	100.5 (23.1)	98.5 (22.0)	103.5 (27.3)	<0.0001
Diabetes mellitus	4655 (33.7%)	918 (33.2%)	1008 (36.5%)	0.01
Atrial fibrillation	332 (2.4%)	72 (2.6%)	76 (2.8%)	0.7
Smoking	3328 (24.1%)	809 (29.3%)	620 (22.5%)	<0.0001
Body mass index (kg/m^2)	28.6 (5.0)	28.3 (4.7)	28.6 (5.3)	0.008
Left ventricular hypertrophy	2458 (17.8%)	448 (16.2%)	643 (23.3%)	<0.0001
History of myocardial infarction	6301 (45.6%)	1152 (41.7%)	1213 (43.9%)	0.09
History of peripheral arterial disease	1898 (13.8%)	373 (13.5%)	461 (16.7%)	0.001
History of stroke/TIA	2699 (19.6%)	483 (17.5%)	598 (21.7%)	<0.0001
Systolic blood pressure during treatment, mean (mmHg)[a]	139.0 (11.1)	135.1 (7.0)	146.5 (13.6)	<0.0001
SD, mean (mmHg)	10.0 (5.1)	4.1 (1.3)	17.9 (4.2)	<0.0001
CV, mean (%)	7.1 (3.4)	3.0 (1.0)	12.3 (2.7)	<0.0001
ARV, mean	10.2 (19.0)	4.2 (1.7)	19.9 (6.3)	<0.0001

Data are numbers (%) or means (SD).
ARV, average real variability; CV, coefficient of variation; SD, standard deviation; TIA, transient ischaemic attack.
[a]Mean systolic blood pressure from Visit 6 up to Visit 15.

adjusting for the number of capsules returned during the study period. We also performed a sensitivity analysis using the model that was used in the main analysis of the VALUE trial (age, history of myocardial infarction, and left ventricular hypertrophy), and we adjusted for maximum blood pressure during the treatment period. Finally, we repeated the analysis using the other measures of blood pressure variability (CV and ARV) and using blood pressure variability as a continuous variable.

Subgroup analyses were performed of patients defined by baseline risk of cardiovascular disease, and by age, sex, allocated treatment, mean systolic blood pressure at baseline and at 6 months, diabetes mellitus, atrial fibrillation, smoking status, and history of cardiovascular diseases. We separately analysed subgroups defined by mean systolic blood pressure during treatment, and we assessed if there was interactions by adding interaction terms in the adjusted models. Finally, we identified clinical factors associated with increased blood pressure variability, using logistic regression analysis. All analyses were performed with the SPSS software (SPSS Statistics, Chicago, IL, USA), version 22.0.

Results

Of the 15 245 patients included in the VALUE trial, 13 803 represented the target population and were included in the analysis (see Supplementary material online, *Figure S1*). *Table 1* summarizes the baseline characteristics of the target population. Mean age was 67.1 years, most patients were of Caucasian origin (89.6%), 45.6% had coronary artery disease, and 19.6% had a history of stroke or TIA. The mean number of visits was 8.7, and the mean visit-to-visit SD was 10.0 (see Supplementary material online, *Figure S2*). Patients with the highest variability were more often treated with valsartan and generally had more cardiovascular disease and more risk factors (*Table 1*). The number of visits and the number of per-protocol visits were similar in the two groups. *Table 1* also shows blood pressure variability in the same groups. Mean visit-to-visit SD of systolic blood pressure was 4.1 mmHg in the lowest quintile and 17.9 mmHg in the highest quintile. Mean within-visit SD was 1.7 mmHg in the lowest

Table 2 Risk of cardiovascular events (non-fatal or fatal) for the highest vs. lowest quintile of standard deviation of visit-to-visit systolic blood pressure

	Number of patients (%) (*N* = 13 803)	Adjusted hazard ratio[a]	95% CI	*P*-value
Cardiovascular event	1557 (11.3)	2.1	1.7–2.4	<0.0001
Cardiac event	1190 (8.6)	2.3	1.9–2.8	<0.0001
Myocardial infarction	503 (3.6)	3.2	2.3–4.3	<0.0001
Congestive heart failure	489 (3.5)	3.1	2.2–4.3	<0.0001
Other[b]	198 (1.4)	0.5	0.3–0.8	0.002
Stroke	444 (3.2)	1.5	1.1–2.1	0.008
Ischaemic stroke	359 (2.6)	1.9	1.3–2.7	<0.0001
Haemorrhagic stroke	42 (0.3)	0.6	0.3–1.5	0.3
Unclassified stroke	43 (0.3)	0.6	0.2–1.7	0.4

Bottom quintile is reference quintile.
[a]Adjustment for age, sex, allocated treatment, diabetes mellitus, atrial fibrillation, creatinine, heart rate, left ventricular hypertrophy, smoking status, history of myocardial infarction, history of stroke/TIA, history of peripheral arterial disease, and mean systolic blood pressure during the treatment period.
[b]Procedures to prevent myocardial infarction, death during coronary bypass surgery or percutaneous vascular interventions, or sudden cardiac death.

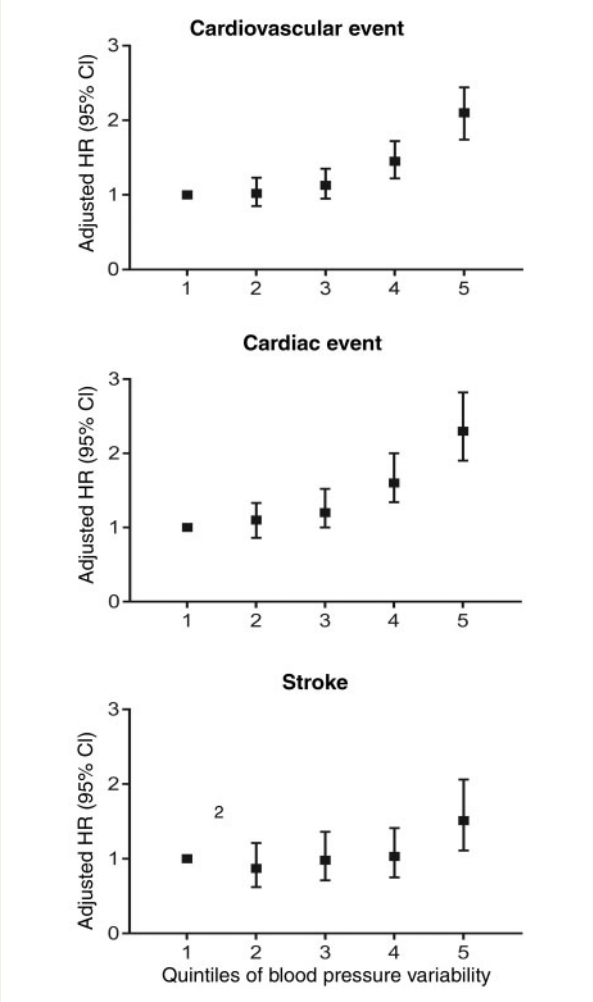

Figure 1 Risk of cardiovascular event, cardiac event, and stroke in different quintiles of standard deviation of visit-to-visit systolic blood pressure, relative to the lowest quintile (reference group). HR: hazard ratio.

quintile and 7.4 mmHg in the highest quintile of within-visit variability. Supplementary material online, *Table S1* presents baseline characteristics in the individual quintiles of visit-to-visit SD of systolic blood pressure.

Visit-to-visit blood pressure variability and cardiovascular events

The mean duration of follow-up was 4.0 years (SD 0.8 years). Among the 13 803 patients included, 1557 patients (11.3%) had a cardiovascular event, of whom 1190 (8.6%) had a cardiac event and 444 (3.2%) had a stroke (*Table 2*). Seventy-seven patients had both a cardiac event and a stroke (0.6%).

Estimated visit-to-visit SD of systolic blood pressure was increased by only 0.7 mmHg after a first cardiac event and 0.8 mmHg after a first stroke, confirming earlier studies that have shown that the estimation of blood pressure variability may be based on all measurements,[19] irrespective of whether the patient had a cardiovascular event during follow-up. Compared to patients with the lowest variability, those in the highest quintile of SD had an increased risk of a cardiovascular event (HR 2.1, 95% CI 1.7–2.4; $P < 0.0001$, *Table 2*, *Figure 1*). The risks of cardiac events and stroke were both increased (HR 2.3, 95% CI 1.9–2.8; $P < 0.0001$ and HR 1.5, 95% CI 1.1–2.1; $P = 0.008$, respectively, *Table 2*, *Figure 1*), as were the risks of myocardial infarction (HR 3.2, 95% CI 2.3–4.3; $P < 0.0001$), congestive heart failure (HR 3.1, 95% CI 2.2–4.3; $P < 0.0001$), and ischaemic stroke (HR 1.9, 95% CI 1.3–2.7; $P < 0.0001$), but not haemorrhagic stroke (HR 0.6, 95% CI 0.3–1.5; $P = 0.3$, *Table 2*). Supplementary material online, *Table S2* shows the risk for the individual quintiles of visit-to-visit SD of systolic blood pressure.

Sensitivity analyses showed that the results were the same in the analysis of the per-protocol population (see Supplementary material online, *Table S3*) and in the propensity score analysis (see Supplementary material online, *Table S4*), except that the association was not statistically significant for stroke in the per-protocol population. The analysis restricted to patients who did not have an event before 24 months showed that blood pressure variability from 4 to

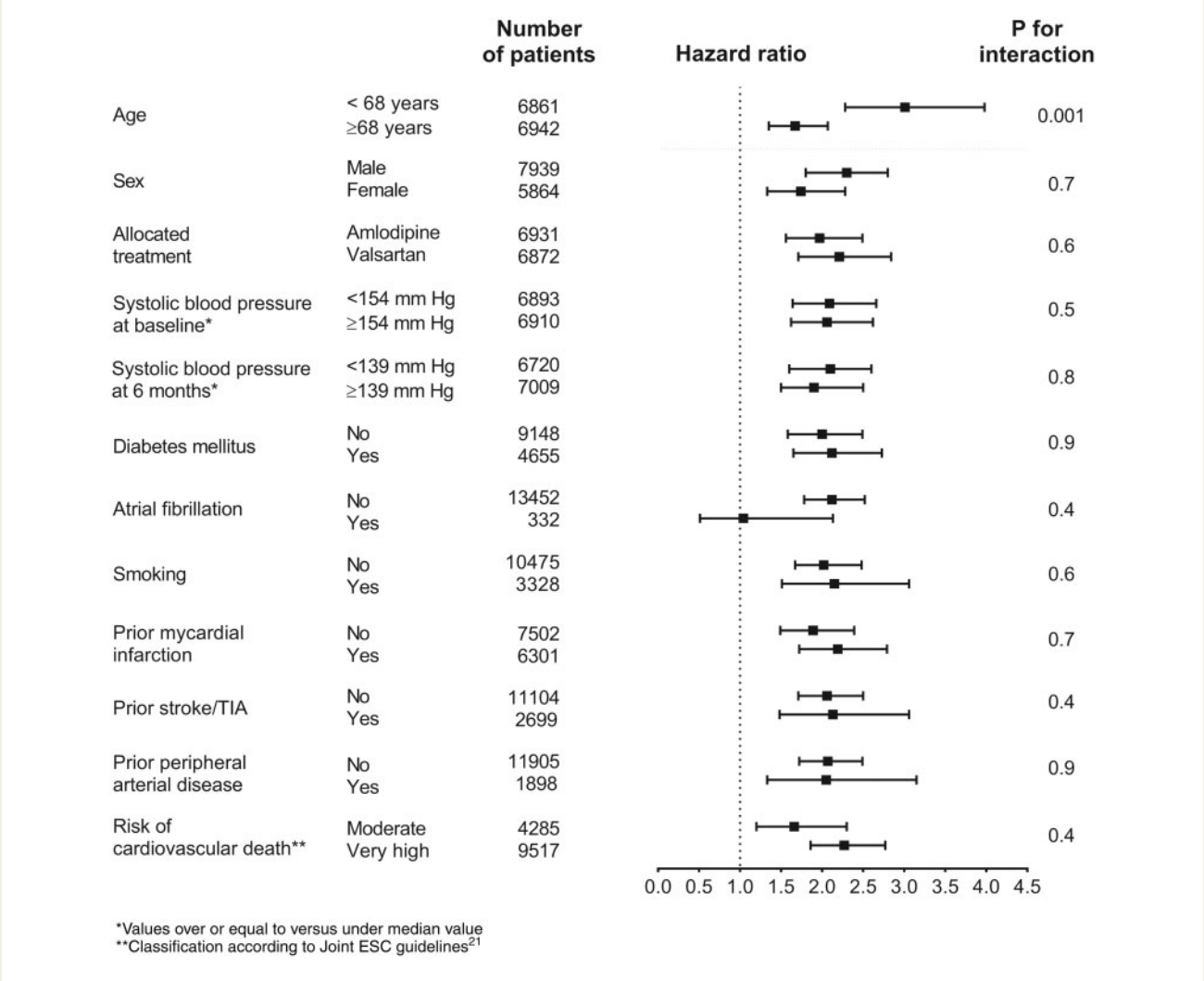

Figure 2 Risk of cardiovascular event for the highest vs. lowest quintile of standard deviation of visit-to-visit systolic blood pressure in different subgroups of patients.

24 months predicted cardiovascular events after this point (HR 1.5, 95% CI 1.2–1.9; $P < 0.0001$), but not stroke (see Supplementary material online, *Table S5*). The case–control analysis also showed that blood pressure variability was higher among cases than among matched controls (mean difference in SD 1.25 mmHg, 95% CI 0.87–1.63; $P < 0.0001$, see Supplementary material online, *Table S6*). Sensitivity analyses also showed that the results were similar when excluding patients with atrial fibrillation, when adjusting for adherence to allocated treatment, using the model that was used in the primary VALUE trial report, adjusting for maximal systolic blood pressure during the treatment period, using CV or ARV as measures of variability, or when analysing blood pressure variability as a continuous variable (see Supplementary material online, *Tables S7–S12*).

Subgroup analyses showed that the association between visit-to-visit blood pressure variability and cardiovascular events was similar in patients at moderate and very high risk (*Figure 2*). Subgroup analyses also showed that blood pressure variability was associated with a significantly higher risk in patients with age below median age (68 years) than in older patients (P for interaction = 0.001, *Figure 2*). The association was similar in the two treatment groups (*Figure 2* and Supplementary material online, *Table S13*), and there was no effect modification for any of the other factors.

We performed a separate subgroup analysis of patients defined by mean systolic blood pressure during the treatment period, comparing patients with values above or equal to median value and patients with values below the median value (137.8 mmHg). The association between blood pressure variability and risk of a cardiovascular event was significant both among patients with higher or lower blood pressure ($P < 0.0001$) but was stronger among patients with lower blood pressure during the treatment period (P for interaction < 0.0001, *Figure 3*). The same was found for cardiac events (P for interaction <0.0001), but for stroke the association was not significant among those with higher blood pressure ($P = 0.4$, *Figure 3*), and there was no significant interaction (P for interaction = 0.1).

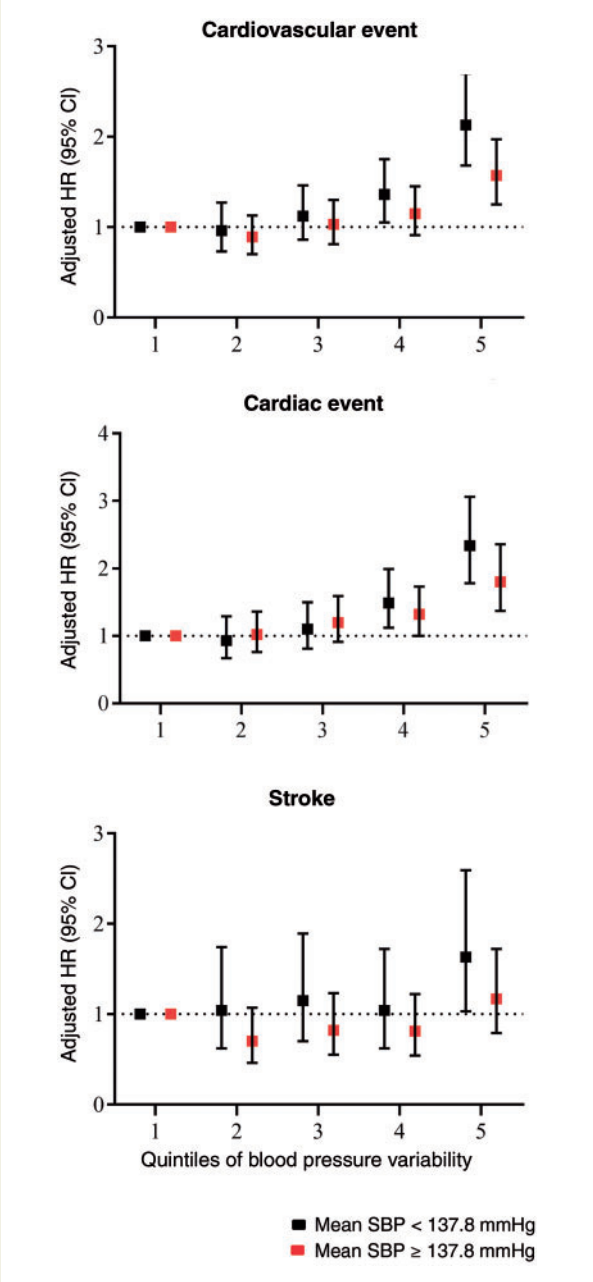

Figure 3 Risk of cardiovascular event, cardiac event, and stroke among patients with mean systolic blood pressure during treatment equal to or above median (red) and below the median value (black) by quintiles of standard deviation of visit-to-visit systolic blood pressure. The lowest quintile is reference group. HR: hazard ratio.

Finally, we found that a number of clinical factors were associated with increased blood pressure variability, including allocation to valsartan, higher systolic blood pressure, black ethnicity, and higher age (see Supplementary material online, *Table S14*).

We repeated the analysis for diastolic blood pressure and found that visit-to-visit variability remained significantly associated with cardiovascular events (see Supplementary material online, *Table S15*).

Visit-to-visit blood pressure variability and death

For the analysis of death, we analysed variability as a continuous variable, since patients who died had fewer visits (mean 5.8 visits, SD 1.9 visits) than other patients (mean 9.0 visits, SD 1.4 visits), which meant that the comparison of the highest and the lowest quintiles became less precise.[8,22] There was a significantly increased risk of death (HR 1.10, 95% CI 1.04–1.17; $P = 0.002$), equivalent to a 10% increase in risk for 5 mmHg increase in SD of visit-to-visit systolic blood pressure (*Table 3*). For cardiovascular and non-cardiovascular death, the HR was 0.93 (95% CI 0.84–1.03; $P = 0.1$) and 1.23 (95% CI 1.14–1.33; $P < 0.0001$), respectively.

The results were similar in sensitivity analyses of the per-protocol population, the subset of patients who did not have any cardiovascular event before 24 months, and when using CV or ARV as measures of blood pressure variability (see Supplementary material online, *Tables S16–S18*).

Subgroup analyses again showed that the association was stronger for younger patients (P for interaction = 0.02, *Figure 4*). There was also a stronger association for those at very high risk, defined as having established cardiovascular disease (P for interaction = 0.04).

For diastolic blood pressure, for a 5 mmHg increase in the SD of visit-to-visit systolic blood pressure, the HR for death was 1.09 (95% CI 0.97–1.23) while the HR for cardiovascular and non-cardiovascular death was 0.97 (95% CI 0.80–1.17) and 1.20 (95% CI 1.03–1.39), respectively.

Within-visit blood pressure variability

Within-visit variability of systolic blood pressure was small compared to visit-to-visit-variability (4.1 mmHg vs. 10.0 mmHg), which meant that the separation of variability into quintiles gave very little difference between the quintiles. We therefore analysed within-visit variability as a continuous variable and found that within-visit systolic blood pressure variability was associated with an increased risk of a cardiovascular event (HR 1.15, 95% CI 1.03–1.29; $P = 0.01$, *Table 4*), equivalent to a 15% increase in risk for a 5 mmHg increase in SD. There was no significant association with the risk of death (*Table 4*).

Table 3 Risk of death for 5 mmHg increase in standard deviation of visit-to-visit systolic blood pressure

	Number of patients (%) (N = 13 803)	Adjusted hazard ratio[a]	95% CI	P-value
Deaths of all causes	1089 (7.9)	1.10	1.04–1.17	0.002
Cardiovascular deaths	430 (3.1)	0.93	0.84–1.03	0.1
Non-cardiovascular deaths	659 (4.8)	1.23	1.14–1.33	<0.0001

[a]Adjustment for age, sex, allocated treatment, diabetes mellitus, atrial fibrillation, creatinine, heart rate, left ventricular hypertrophy, smoking status, history of myocardial infarction, history of stroke/TIA, history of peripheral arterial disease, and mean systolic blood pressure during the treatment period.

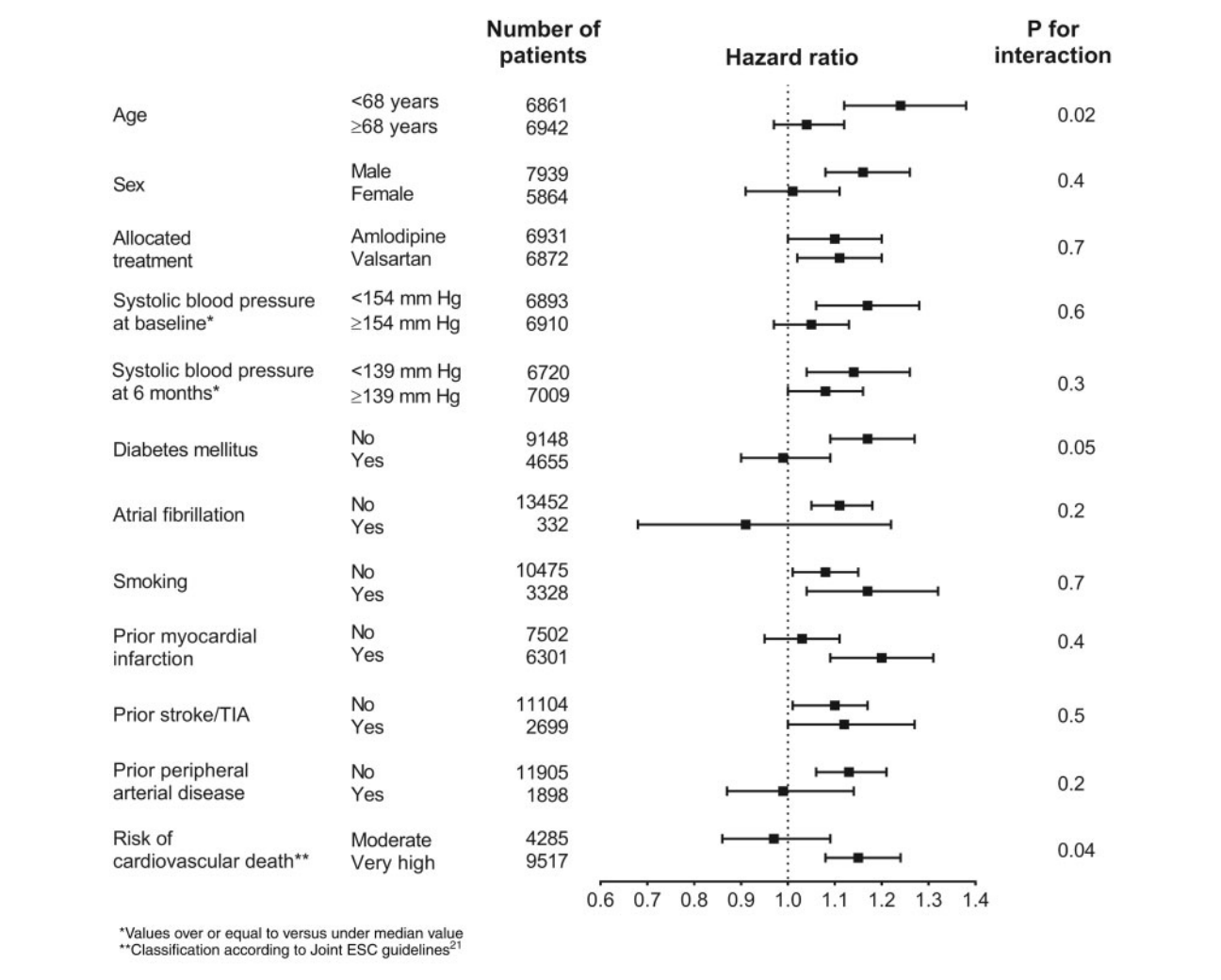

Figure 4 Risk of death for 5 mmHg increase in standard deviation of visit-to-visit systolic blood pressure in different subgroups of patients.

Table 4 Risk of cardiovascular events (non-fatal or fatal) and death for 5 mmHg increase in standard deviation of within-visit systolic blood pressure

	Number of patients (%) (*N* = 13 803)	Adjusted hazard ratio[a]	95% CI	*P*-value
Cardiovascular event	1557 (11.3)	1.15	1.03–1.29	0.01
Cardiac event	1190 (8.6)	1.16	1.02–1.32	0.02
Myocardial infarction	503 (3.6)	1.12	0.92–1.38	0.3
Congestive heart failure	489 (3.5)	1.15	0.94–1.40	0.2
Other[b]	198 (1.4)	1.21	0.90–1.64	0.2
Stroke	444 (3.2)	1.04	0.84–1.29	0.7
Ischaemic stroke	359 (2.6)	1.05	0.83–1.33	0.7
Haemorrhagic stroke	42 (0.3)	0.98	0.48–1.99	1.0
Unclassified stroke	43 (0.3)	0.92	0.44–1.89	0.8
Death of all causes	1089 (7.9)	1.00	0.87–1.16	0.9
Cardiovascular death	430 (3.1)	1.08	0.87–1.33	0.5
Non-cardiovascular death	659 (4.8)	0.94	0.78–1.13	0.5

[a]Adjustment for age, sex, allocated treatment, diabetes mellitus, atrial fibrillation, creatinine, heart rate, left ventricular hypertrophy, smoking status, history of myocardial infarction, history of stroke/TIA, history of peripheral arterial disease, and mean systolic blood pressure during the treatment period.
[b]Procedures to prevent myocardial infarction, death during coronary bypass surgery or percutaneous vascular interventions, or sudden cardiac death.

Discussion

In this analysis of data from the large VALUE trial we found that visit-to-visit systolic blood pressure variability was associated with an increased risk of cardiovascular events and death, and that the associations were similar for patients at different levels of risk. The associations were independent of allocated treatment, mean blood pressure during follow-up and other factors, and were robust in a number of sensitivity analyses, indicating that blood pressure variability is important not only in high-risk patients.[5,18,19,23,24] The increase in risk associated with blood pressure variability was numerically higher in high-risk patients, particularly the increase in risk of death, which might suggest that, in high-risk patients, other risk factors add to the effect of blood pressure variability.

We also found that younger patients were particularly susceptible to the impact of blood pressure variability, despite a higher blood pressure variability and higher absolute risk among older patients. Similar interactions with age have been found in other studies.[4,8] One possible explanation is that younger patients, often with lower blood pressure and fewer risk factors, are more sensitive to blood pressure variability, and that, with higher age, other risk factors overshadow the negative influence of blood pressure variability.[4] Another possible explanation is the so called 'healthy survivor effect': Individuals with high blood pressure variability who survive to an older age are likely to tolerate the effect of blood pressure variability better than other patients and will therefore have a lower risk of cardiovascular events than younger people.[25]

Similar to the findings of a stronger association between blood pressure variability and risk in younger people, we found that the increase in risk was steeper among patients with a lower systolic blood pressure during follow-up.[4,8] Again, one interpretation is that patients with lower blood pressure are more vulnerable to blood pressure variability[1] and that, with higher blood pressure, the contribution of variability is less pronounced.[4,26]

Importantly, we found a clear association between visit-to-visit blood pressure variability and each of the two components of the primary effect variable for this analysis, cardiac events and stroke,[4–6] although the associations were stronger for cardiac events. The Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT BPLA) trial showed similar-sized associations for both endpoints.[4] One possible explanation for the stronger effect on cardiac events in our analysis may be that almost half of the patients had a history of myocardial infarction, compared to no patients in the ASCOT BPLA trial.[4] The numbers of patients and endpoints were also lower in our analysis, and blood pressure variability was smaller (mean 10.0 vs. 12.2 mmHg), which makes it more difficult to discriminate high from low risk of events. Alternatively, blood pressure variability has indeed a stronger effect on cardiac events than on stroke, as suggested by some other studies.[14,15]

We also found an association between visit-to-visit blood pressure variability and risk of death,[5,10,13–15] although the association was weaker than for total cardiovascular events, probably due to fewer visit in the analysis of death. For the analysis of cardiovascular death, the number of events was even lower, and the follow-up period was shorter than in other studies,[6,7,13] which may explain the absence of an association for this event. Other explanations may be that, in patients who die from cardiovascular causes other risk factors overshadow the effects of blood pressure variability,[4] and that those who survive have better tolerance towards blood pressure variability, as discussed earlier. Finally, we found that the effect of diastolic visit-to-visit blood pressure variability was smaller than that of systolic variability,[4] as was the effect of within-visit blood pressure variability compared to that of visit-to-visit variability.[4,16]

The strengths of this study include the large number of patients, followed with regular visits for a long period of time, with standardised procedures for blood pressure measurements at all visits, and close to complete information on baseline risk factors, blood pressure readings, and clinical events. We adjusted in the analyses for a number of key prognostic variables, including compliance with allocated treatment[5] and mean blood pressure during follow-up[27] and excluded blood pressure readings during the first 6 months, when dose titration took place and blood pressure was unstable, to avoid confounding from these factors. Another strength is the many sensitivity analyses, including analysis of a per-protocol population, a propensity score analysis, the analysis restricted to patients with no events before 24 months, and the matched case–control analysis, which indicate robustness of the association between blood pressure variability and risk of cardiovascular events and death.

The main limitation is the analysis of observational data, which means that there is a possibility of confounding from other factors than blood pressure variability, for example, mean blood pressure. However, we adjusted for mean blood pressure during follow-up, both in the multivariable analysis using SD as the measure of variability, and in the sensitivity analyses using CV, and we performed separate subgroup analyses of patients with high and low blood pressure and found consistent results. Another possible confounding factor is patients' adherence to allocated treatment. However, the number of per-protocol visits was the similar in patients with high and low blood pressure variability, and associations remained the same when adjusting for adherence to allocated treatment or when analysing associations in the target population vs. the per-protocol population.[4,5,28,29] One can also question the method of including blood pressure readings after events in our main analysis of risk of future events, as has also been done by others.[4,6,19] However, we additionally performed a sensitivity analysis restricted to patients with no events during the first 24 months, and a matched case–control analysis, which gave similar results. Finally, as blood pressure could be measured using either calibrated standard sphygmomanometer or a validated digital device, blood pressure variability could potentially have been influenced by the method of blood pressure measurement.[30] However, the association between blood pressure variability and risk of cardiovascular events have been found for both methods of measurement,[4,6,8,14] and so the method of blood pressure measurement may not be a true confounder in this analysis.

Visit-to-visit variability in blood pressure can be difficult to measure in clinical practice but can be assessed using graphical charts showing blood pressures at clinical visits. Clinical suspicion of increased variability should be raised by the presence of traditional risk factors, as shown here as well as in previous studies[6,8,11,15,24] and high within-visit variability or ambulatory blood pressure variability should raise awareness of the possibility of high visit-to-visit variability and poor quality of blood pressure control.

In conclusion, all patients with hypertension receiving blood pressure lowering treatment should be monitored carefully to achieve consistency of control, irrespective of baseline risk, particularly younger patients or those with a low mean systolic blood pressure.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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