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Visit-to-visit variability of blood pressure and cardiovascular outcomes in patients with stable coronary heart disease. Insights from the STABILITY trial

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Aims To study the relation between visit-to-visit variability of blood pressure (BP) and cardiovascular risk in patients with stable coronary heart disease.

Methods and results In 15 828 patients from the STABILITY trial (darapladib vs. placebo in patients with established coronary heart disease), BP variability was assessed by the standard deviation (SD) of systolic BP, the SD of diastolic BP, maximum BP, and minimum BP, from 5 measurements (baseline and months 1, 3, 6, and 12) during the first year after randomisation. Mean (SD) average BP during the first year of study was 131.0 (13.7) mmHg over 78.3 (8.3) mmHg. Mean (SD) of the visit-to-visit SD was 9.8 (4.8) mmHg for systolic and 6.3 (3.0) mmHg for diastolic BP. During the subsequent median follow-up of 2.6 years, 1010 patients met the primary endpoint, a composite of time to cardiovascular death, myocardial infarction, or stroke. In Cox regression models adjusted for average BP during first year of study, baseline vascular disease, treatment, renal function and cardiovascular risk factors, the primary endpoint was associated with SD of systolic BP (hazard ratio for highest vs. lowest tertile, 1.30, 95% CI 1.10–1.53, $P = 0.007$), and with SD of diastolic BP (hazard ratio for highest vs. lowest tertile, 1.38, 95% CI 1.18–1.62, $P < 0.001$). Peaks and troughs in BP were also independently associated with adverse events.

Conclusion In patients with stable coronary heart disease, higher visit-to-visit variabilities of both systolic and diastolic BP are strong predictors of increased risk of cardiovascular events, independently of mean BP.

Keywords STABILITY trial • Visit-to-visit variability of blood pressure • Coronary heart disease

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Introduction

Blood pressure (BP) variability is usually merely considered as an obstacle to accurate measurement of average BP level, itself a well-established cardiovascular risk factor.[1–3] However, recent studies have shown that an elevated BP variability, as assessed by visit-to-visit variability, independently of mean BP level (and to a lesser extent the highest SBP for a given mean BP), was also a risk factor for cardiovascular events. This was first demonstrated in 2010 by Rothwell *et al.*[4] in patients with a previous transient ischaemic attack from several cohorts and in patients with treated hypertension from the ASCOT-BPLA trial. It was recently confirmed in patients from the ADVANCE[5] and ALLHAT[6] trials, as well as in the very large cohort of US veterans[7] and in a meta-analysis.[8] However, the risk associated with BP variability in a population of patients with coronary heart disease (CHD) has never been evaluated. Furthermore, the risk associated with the lowest diastolic BP for a given mean BP or in other terms whether episodic drops in diastolic BP might trigger cardiovascular events, has never been investigated but is of particular interest in a population with established CHD, especially in the light of current debate regarding the optimal BP targets, following the SPRINT and HOPE-3 trials.[9–11]

Using data from the STABILITY randomized controlled trial, which compared darapladib vs. placebo in 15 828 patients with established CHD, we investigated whether visit-to-visit BP variability and highest or lowest systolic or diastolic BP, for a given mean BP, were associated with subsequent cardiovascular events in CHD patients.

Methods

Study design and patients

The present study is a secondary analysis of the STABILITY trial, a multicentre, double-blind, randomized clinical trial which compared darapladib to placebo in 15 828 patients with established CHD (ClinicalTrials.gov number NCT00799903). Patients were included between December 2008 and April 2010, in a total of 663 centres in 39 countries. A detailed description of the trial and its main results has been published elsewhere.[12] Patients were eligible for enrolment if they had CHD, as documented by at least one of the following: previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG), or multivessel CHD. In addition, at least one of the following additional predictors of cardiovascular risk was required: an age of 60 years or older, diabetes requiring pharmacotherapy, a high-density lipoprotein cholesterol level of less than 40 mg per deciliter (1.03 mmol/L), status as a smoker of five or more cigarettes per day at study entry or within 3 months before screening, moderate renal dysfunction, or polyvascular arterial disease. The study found no difference in cardiovascular outcomes between the two treatment arms, which were therefore lumped together in the present analysis.

BP variability was assessed during the first year of the study and outcomes were analysed from the end of the first year to the end of the follow-up period. Patients who experienced cardiovascular events (MI, stroke, any coronary revascularization procedure, hospitalization for unstable angina) or died during the first year ($n = 973$, Supplementary material online, *Table S1*) were excluded since events could impact BP variability. Patients with <1-year follow-up ($n = 274$), or <3 BP measurements ($n = 787$) during the first 12 months were also excluded (Supplementary material online, *Figure S1*). Local ethics committees or institutional review boards have approved the study prior to recruitment and all patients gave written informed consent.

Assessment of BP variability

During the first year of the study, diastolic and systolic BP were measured at 5 visits (baseline, month 1, month 3, month 6, and month 12) after 5 min of rest in the seated position by a trained observer, using an automated oscillometric OMRON® monitor which calculated the mean of three BP measurements. Visit-to visit-variability was assessed from the standard deviation (SD) of BP across these 5 visits. If up to two measures during the first year were missing, SD was calculated using the available measurements. Secondary measures of variability included average real variability (ARV),[13] and maximum and minimum BP. ARV was calculated in patients with all 5 visits reported, as the mean absolute difference in BP between each visit and the subsequent one, from the first to the fourth visit. Maximum and minimum BP were defined as highest and lowest BP values across the 5 visits. All parameters were evaluated for both systolic and diastolic BP.

Outcomes

The primary outcome was the composite of cardiovascular mortality, non-fatal MI or non-fatal stroke (Major Adverse Cardiovascular Event, MACE) occurring beyond the first 12 months following randomization. The secondary outcomes were cardiovascular mortality, MI (fatal or not), stroke (fatal or not), all-cause mortality, hospitalization for heart failure (HF) and the composite endpoint of total coronary events (TCE, a composite of CHD mortality, MI, hospitalization for unstable angina, or any coronary revascularization procedure), occurring after the first 12 months after randomization. Outcomes were analysed using time to events methods. For patients with multiple events, the time to the first applicable event after 12 months was considered in each analysis. All events were adjudicated by an independent committee.

Statistical analysis

The characteristics of the patients included in the present analysis were analysed for the total population, and by tertiles of SD of systolic and diastolic BP. Continuous variables were summarized with the median, 25th, and 75th percentiles, or mean and SD, as appropriate. Categorical variables were summarized as frequencies and percentages. Trend tests were used to compare patient characteristics across tertiles of SD of BP.

Cox proportional hazards models, both unadjusted and adjusted, were used to calculate the hazard ratio (HR) associated with each outcome by tertile of SD of BP. Similar analyses were performed by tertiles of ARV, by tertiles of maximum BP and by tertiles of minimum BP. The lowest tertile was used as the reference except for minimum BP for which the highest tertile was the reference. Separate models were generated for systolic BP and for diastolic BP.

Unadjusted and multivariable-adjusted HRs for each outcome were also calculated with SD of systolic and diastolic BP modelled as a continuous variable, and the HRs and 95% CI reported per 5 mmHg variation for each parameter. Modelling assumptions were confirmed. The proportional hazards assumption was assessed and verified.

Covariates used for multivariable-adjustment were selected a priori as potential confounders and included treatment allocation, average systolic (or diastolic, as appropriate) BP over the first 12 months of the study, age, sex, race, region of enrolment, diabetes, body mass index, smoking status, prior MI, prior PCI or CABG, or multivessel CHD, polyvascular disease, family history of premature CHD, baseline glomerular filtration rate (GFR) estimated from the Modification of Diet in Renal Disease (MDRD) equation, use of beta-blockers, use of statins, use of aspirin, use of renin–angiotensin system inhibitors, baseline low-density and high-density

Table 1 Baseline characteristics of the patients for total population and by tertiles of SD of systolic BP

Parameter	Total population $n = 13\,794$	SD of systolic blood pressure categories 1st tertile (<7.16 mmHg) $n = 4553$	2nd tertile (7.16–10.95 mmHg) $n = 4549$	3rd tertile (≥10.95 mmHg) $n = 4692$	*P*-value for trend
Age (years)	65.0 (59.0–71.0)	63.0 (57.0–70.0)	64.0 (59.0–70.0)	66.0 (60.0–72.0)	<0.001
Female	2540 (18.4%)	685 (15.0%)	790 (17.4%)	1065 (22.7%)	<0.001
Body mass index-kg/m^2	28.3 (25.5–31.7)	28.2 (25.5–31.6)	28.4 (25.7–31.8)	28.3 (25.5–31.6)	0.98
Diabetes	5317 (38.5%)	1664 (36.5%)	1720 (37.8%)	1933 (41.2%)	<0.001
Race					
White	10 806 (78.3%)	3596 (79.0%)	3575 (78.6%)	3635 (77.5%)	0.28
Black	300 (2.2%)	101 (2.2%)	86 (1.9%)	113 (2.4%)	
Asian/Pacific	2393 (17.3%)	774 (17.0%)	778 (17.1%)	841 (17.9%)	
Other	295 (2.1%)	82 (1.8%)	110 (2.4%)	103 (2.2%)	
Smoking status					
Current	2472 (17.9%)	932 (20.5%)	788 (17.3%)	752 (16.0%)	<0.001
Former	7028 (50.9%)	2273 (49.9%)	2382 (52.4%)	2373 (50.6%)	
Never	4293 (31.1%)	1348 (29.6%)	1378 (30.3%)	1567 (33.4%)	
Hypertension	10 716 (77.7%)	3272 (71.9%)	3531 (77.6%)	3913 (83.4%)	<0.001
Average systolic BP (mmHg)	130.6 (121.8–140.0)	128.2 (119.2–137.0)	129.6 (121.4–139.2)	134.2 (125.0–143.4)	<0.001
Average diastolic BP (mmHg)	78.4 (72.8–83.8)	78.0 (72.6–83.0)	78.4 (72.8–83.6)	79.0 (73.2–84.8)	<0.001
Average pulse pressure (mmHg)	51.8 (45.0–59.4)	49.8 (43.4–57.0)	51.0 (44.6–58.8)	54.8 (47.6–62.4)	<0.001
Polyvascular disease	1994 (14.5%)	566 (12.4%)	647 (14.2%)	781 (16.6%)	<0.001
CHD qualifying diagnosis					
Prior myocardial Infarction	8198 (59.4%)	2795 (61.4%)	2727 (59.9%)	2676 (57.0%)	<0.001
Prior PCI	6880 (49.9%)	2265 (49.7%)	2281 (50.1%)	2334 (49.7%)	0.99
Prior CABG	4547 (33.0%)	1426 (31.3%)	1506 (33.1%)	1615 (34.4%)	0.001
Multivessel CHD	2062 (14.9%)	632 (13.9%)	663 (14.6%)	767 (16.3%)	<0.001
Prior stroke	814 (5.9%)	217 (4.8%)	259 (5.7%)	338 (7.2%)	<0.001
Medication at baseline					
Aspirin	12 790 (92.7%)	4248 (93.3%)	4219 (92.7%)	4323 (92.1%)	0.03
Statins	13 439 (97.4%)	4454 (97.8%)	4418 (97.1%)	4567 (97.3%)	0.14
Beta-blockers	10 917 (79.1%)	3554 (78.1%)	3565 (78.4%)	3798 (80.9%)	<0.001
RAS blockers	10 664 (77.3%)	3411 (74.9%)	3472 (76.3%)	3781 (80.6%)	<0.001
Calcium channel blockers	3793 (27.5%)	1121 (24.6%)	1275 (28.0%)	1397 (29.8%)	<0.001
Diuretics	4825 (35.0%)	1450 (31.8%)	1546 (34.0%)	1829 (39.0%)	<0.001
HbA1C (%)	7.1 (6.4–8.1)	7.1 (6.4–8.1)	7.1 (6.4–8.1)	7.2 (6.5–8.2)	
eGFR (mmol/L)	78.0 (66.0–90.0)	78.0 (66.0–90.0)	78.0 (66.0–90.0)	72.0 (60.0–84.0)	<0.001
Total cholesterol (mmol/L)	4.1 (3.5–4.7)	4.1 (3.5–4.7)	4.1 (3.5–4.8)	4.1 (3.5–4.7)	0.92
Lp-PLA2 (μmol/min/L)	171.9 (142.8–203.5)	174.2 (144.9–206.4)	172.0 (142.8–203.1)	169.7 (140.6–201.4)	<0.001

Data are median (25th–75th percentile) or number (%). Some percentages do not add up to 100 because of rounding.
SD, standard deviation; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; eGFR, estimated glomerular filtration rate; RAS blockers, renin–angiotensin system blockers; Lp-PLA2, lipoprotein-associated phospholipase A2 activity.

lipoprotein cholesterol levels, and lipoprotein-associated phospholipase A2 activity. The unadjusted models included randomized treatment and average systolic or diastolic BP as appropriate.

The adjusted cumulative rate of first MACE event after 12 months post-randomization was calculated from the fitted Cox regression model using the product-limit estimator of the survivor function and the direct adjusted method.[14]

The interaction of sex, diabetes, hypertension, and baseline systolic BP (<120 mmHg, 120 to 140 mmHg, and >140 mmHg) with BP variability as assessed by tertiles of SD of BP were evaluated for both for systolic and diastolic BP in adjusted Cox regression models.

All statistical analyses were performed using SAS 9.4 (SAS institute). *P*-values <0.05 were considered statistically significant. No adjustments were made for multiple comparisons and the results of all outcome analyses performed have been reported.

Results

Study population

13 794 patients were included in this study. Baseline characteristics of the patients are given in *Table 1*. Median age was 65 years, 81.6%

were male, 78.3% were white, and 77.7% had a past or present history of hypertension. Mean ± SD of the average systolic BP over the first 12 months of the study was 131.0 ± 13.7 mmHg and mean of the average diastolic BP was 78.3 ± 8.3 mmHg. Mean SD of systolic BP of the first 12 months of the study was 9.8 ± 4.8 mmHg and mean SD of diastolic BP was 6.3 ± 3.0 mmHg. Patients randomized to darapladib vs. placebo had similar average systolic and diastolic BP and mean SD of systolic and diastolic BP over the first year of the study. Participants in a higher tertile of SD of systolic BP were older, more likely to be female, to have diabetes, hypertension, and polyvascular disease, less likely to be current smokers, and had a lower GFR (*Table 1*). Baseline characteristics of the patients by tertiles of SD of diastolic BP are given in Supplementary material online, *Table S2*. Participants in a higher tertile of SD of diastolic BP were more likely to be female, to have diabetes, hypertension, and polyvascular disease and have a lower GFR.

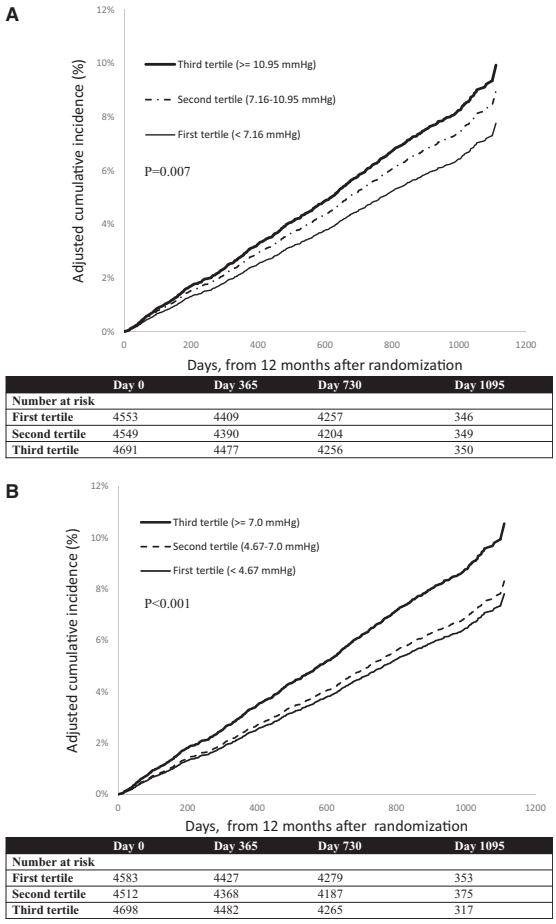
SD of systolic BP

During a median follow-up of 2.6 years after the BP variability assessment period, 1010 patients experienced at least one MACE, the first event being cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke in 410, 423, and 177 patients, respectively. The cumulative incidence of MACE was higher as BP variability increased, both for systolic and diastolic BP (*Figure 1*).

In Cox regression models adjusted for mean BP during first year of study, treatment allocation, baseline vascular disease, renal function, and cardiovascular risk factors, patients with higher SD of systolic BP had a higher risk of MACE (adjusted HR for highest vs. lowest tertile 1.30; 95% CI 1.10–1.53 and for middle vs. lowest tertile, 1.17, 95% CI 0.99–1.38, *P* for trend = 0.007), as well as a higher risk of MI and TCE (*Summarizing illustration* and Supplementary material online, *Table S3*). The multivariable adjusted HRs of primary and secondary outcomes with SD considered as a continuous variable are shown in *Table 2*. SD of systolic BP was associated with the risk of MACE (adjusted HR per 5 mmHg increase in SD, 1.14; 95% CI 1.07–1.21, $P < 0.001$), cardiovascular mortality (adjusted HR 1.15; 95% CI 1.05–1.27, $P = 0.003$), MI (adjusted HR 1.20; 95% CI 1.10–1.32, $P < 0.001$), all-cause mortality (adjusted HR 1.12; 95% CI 1.04–1.20, $P = 0.004$), and TCE (adjusted HR 1.11; 95% CI 1.05–1.17, $P < 0.001$). In contrast, neither the risk of stroke nor the risk of hospitalization for heart failure was associated with SD of systolic BP (Supplementary material online, *Table S3* and *Table 2*).

SD of diastolic BP

Likewise, diastolic BP variability was associated with a higher risk of MACE (adjusted HR for highest vs. lowest tertile 1.38; 95% CI 1.18–1.62, and for middle vs. lowest tertile, 1.07; 95% CI, 0.90–1.27, *P* for trend <0.001), cardiovascular mortality, MI, all-cause mortality, and TCE (*Summarizing illustration* and Supplementary material online, *Table S4*). When analysed as a continuous variable (*Table 2*), SD of diastolic BP was also significantly associated with MACE (HR per 5 mmHg increase 1.28; 95% CI 1.15–1.41, $P < 0.001$), cardiovascular mortality (adjusted HR 1.32; 95% CI 1.13–1.53, $P < 0.001$), MI (adjusted HR 1.28; 95% CI 1.09–1.49, $P = 0.002$), all-cause mortality (adjusted HR 1.26; 95% CI 1.12–1.42, $P < 0.001$), and TCE (adjusted HR 1.18; 95% CI 1.08–1.29, $P < 0.001$). A higher variability in diastolic BP was not significantly associated with the risks of stroke or hospitalization for heart failure (Supplementary material online, *Table S4* and *Table 2*).



Number at risk	Day 0	Day 365	Day 730	Day 1095
First tertile	4553	4409	4257	346
Second tertile	4549	4390	4204	349
Third tertile	4691	4477	4256	350

Number at risk	Day 0	Day 365	Day 730	Day 1095
First tertile	4583	4427	4279	353
Second tertile	4512	4368	4187	375
Third tertile	4698	4482	4265	317

Figure 1 Adjusted cumulative incidence for the primary composite outcome MACE, by tertile of SD of systolic BP (panel *A*) and by tertile of SD of diastolic BP (panel *B*). Adjusted cumulative incidence of the primary outcome is indicated by tertiles of SD of systolic BP (panel *A*) and by tertiles of SD of diastolic BP (panel *B*), as function of time after 12 months post-randomization, in days. Analyses were adjusted for treatment allocation, average systolic (panel *A*), or diastolic (panel *B*) BP over the first 12 months of the study, age, sex, race, region of enrolment, diabetes, body mass index, smoking status, prior myocardial infarction, prior percutaneous coronary intervention or coronary-artery bypass grafting, or multivessel coronary heart disease, polyvascular disease, family history of premature coronary heart disease, baseline glomerular filtration rate, use of beta-blockers, use of statins, use of aspirin, use of renin–angiotensin system inhibitors, baseline low-density and high-density lipoprotein cholesterol levels, and lipoprotein-associated phospholipase A2 activity. The number of patients at risk for each group at time intervals is indicated below each plot. MACE, major adverse cardiac event; BP, blood pressure.

Table 2 Effects of 5-mmHg increments in SD, ARV, and maximum BP and 5-mmHg decrement in minimum BP, for systolic and diastolic BP, on primary and secondary outcomes

		Systolic BP			Diastolic BP	
Outcome	**Model**		**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
MACE						
SD	Unadjusted		1.18 (1.02–1.05)	<0.001	1.32 (1.04–1.08)	<0.001
SD	Adjusted		1.14 (1.07–1.21)	<0.001	1.28 (1.15–1.41)	<0.001
ARV	Adjusted		1.10 (1.05–1.16)	<0.001	1.20 (1.11–1.30)	<0.001
Maximum BP	Adjusted		1.10 (1.05–1.15)	<0.001	1.17 (1.09–1.26)	<0.001
Minimum BP	Adjusted		1.07 (1.02–1.12)	0.007	1.15 (1.23–1.06)	<0.001
Cardiovascular mortality						
SD	Unadjusted		1.22 (1.02–1.06)	<0.001	1.45 (1.05–1.11)	<0.001
SD	Adjusted		1.15 (1.05–1.27)	0.004	1.32 (1.13–1.53)	<0.001
ARV	Adjusted		1.11 (1.02–1.20)	0.01	1.30 (1.15–1.46)	<0.001
Maximum BP	Adjusted		1.12 (1.05–1.20)	<0.001	1.18 (1.06–1.31)	0.002
Minimum BP[a]	Adjusted	<120 mmHg	1.12 (1.03–1.22)	0.04	1.22 (1.09–1.36)	<0.001
		≥120 mmHg	1.03 (0.94–1.13)			
Myocardial infarction						
SD	Unadjusted		1.23 (1.02–1.06)	<0.001	1.28 (1.02–1.08)	<0.001
SD	Adjusted		1.20 (1.10–1.32)	<0.001	1.28 (1.09–1.49)	0.003
ARV	Adjusted		1.15 (1.07–1.24)	<0.001	1.11 (0.98–1.26)	0.09
Maximum BP	Adjusted		1.14 (1.07–1.22)	<0.001	1.19 (1.07–1.32)	0.002
Minimum BP	Adjusted		1.10 (1.03–1.18)	0.007	1.14 (1.02–1.28)	0.02
Stroke						
SD	Unadjusted		1.10 (0.99–1.05)	0.19	1.09 (0.97–1.06)	0.48
SD	Adjusted		1.05 (0.90–1.21)	0.57	1.06 (0.84–1.35)	0.63
ARV	Adjusted		1.03 (0.91–1.16)	0.63	1.07 (0.89–1.30)	0.47
Maximum BP	Adjusted		1.07 (0.96–1.18)	0.22	1.08 (0.91–1.27)	0.40
Minimum BP	Adjusted		0.99 (0.89–1.11)	0.90	1.00 (0.84–1.19)	0.99
All-cause mortality						
SD	Unadjusted		1.17 (1.02–1.05)	<0.001	1.34 (1.04–1.09)	<0.001
SD	Adjusted		1.12 (1.04–1.20)	0.005	1.26 (1.12–1.42)	<0.001
ARV	Adjusted		1.05 (0.99–1.12)	0.13	1.22 (1.11–1.34)	<0.001
Maximum BP	Adjusted		1.10 (1.04–1.16)	<0.001	1.17 (1.08–1.27)	<0.001
Minimum BP[a]	Adjusted	<120 mmHg	1.14 (1.06–1.22)	<0.001	1.15 (1.06–1.26)	0.001
	Adjusted	≥120 mmHg	0.96 (0.90–1.03)			
Hospitalization for HF						
SD	Unadjusted		1.07 (0.99–1.04)	0.33	1.31 (1.01–1.10)	0.02
SD	Adjusted		0.97 (0.83–1.14)	0.73	1.17 (0.92–1.48)	0.22
ARV	Adjusted		1.00 (0.89–1.13)	>0.99	1.02 (0.84–1.24)	0.86
Maximum BP[a]	Adjusted	<140 mmHg	0.84 (0.71–0.98)	0.02	1.06 (0.89–1.25)	0.54
	Adjusted	≥140 mmHg	1.04 (0.93–1.16)			
Minimum BP[a]	Adjusted	<120 mmHg	1.10 (0.95–1.26)	0.07	1.18 (0.99–1.40)	0.06
		≥120 mmHg	0.90 (0.78–1.04)			
TCE						
SD	Unadjusted		1.13 (1.01–1.03)	<0.001	1.20 (1.02–1.06)	<0.001
SD	Adjusted		1.11 (1.05–1.17)	<0.001	1.18 (1.08–1.29)	<0.001
ARV	Adjusted		1.09 (1.04–1.14)	<0.001	1.09 (1.02–1.17)	0.02
Maximum BP	Adjusted		1.08 (1.04–1.12)	<0.001	1.13 (1.06–1.20)	<0.001
Minimum BP	Adjusted		1.05 (1.01–1.10)	0.01	1.08 (1.01–1.15)	0.03

HRs are given for a 5-mmHg increase in the variable for SD, ARV and maximum BP, and for a 5-mmHg decrease in the variable for minimum BP.
BP, blood pressure; ARV, average real variability; MACE, Major Adverse Cardiovascular Event (composite of cardiovascular mortality, non-fatal myocardial infarction or non-fatal stroke); HF, heart failure; TCE, total coronary events (composite of coronary heart disease mortality, myocardial infarction, hospitalization for unstable angina, or any coronary revascularization procedure).
[a]To test the linearity assumption, each measurement and its association with the outcome of interest was plotted for visual inspection and compared with restricted cubic spline models. All SD, ARV and most minimum and maximum BP measurements were found to be linearly related to outcome. A linear spline transformation with the inflection point at 120 mmHg was used for minimum systolic BP, for all-cause mortality, cardiovascular mortality and hospitalization for heart failure. A similar transformation was used for maximum systolic BP, for hospitalization for heart failure, with the inflection point at 140 mmHg. Measurements greater than 80 mmHg were set to 80 mmHg when assessing the relationship between minimum diastolic BP and all-cause mortality or CV death.

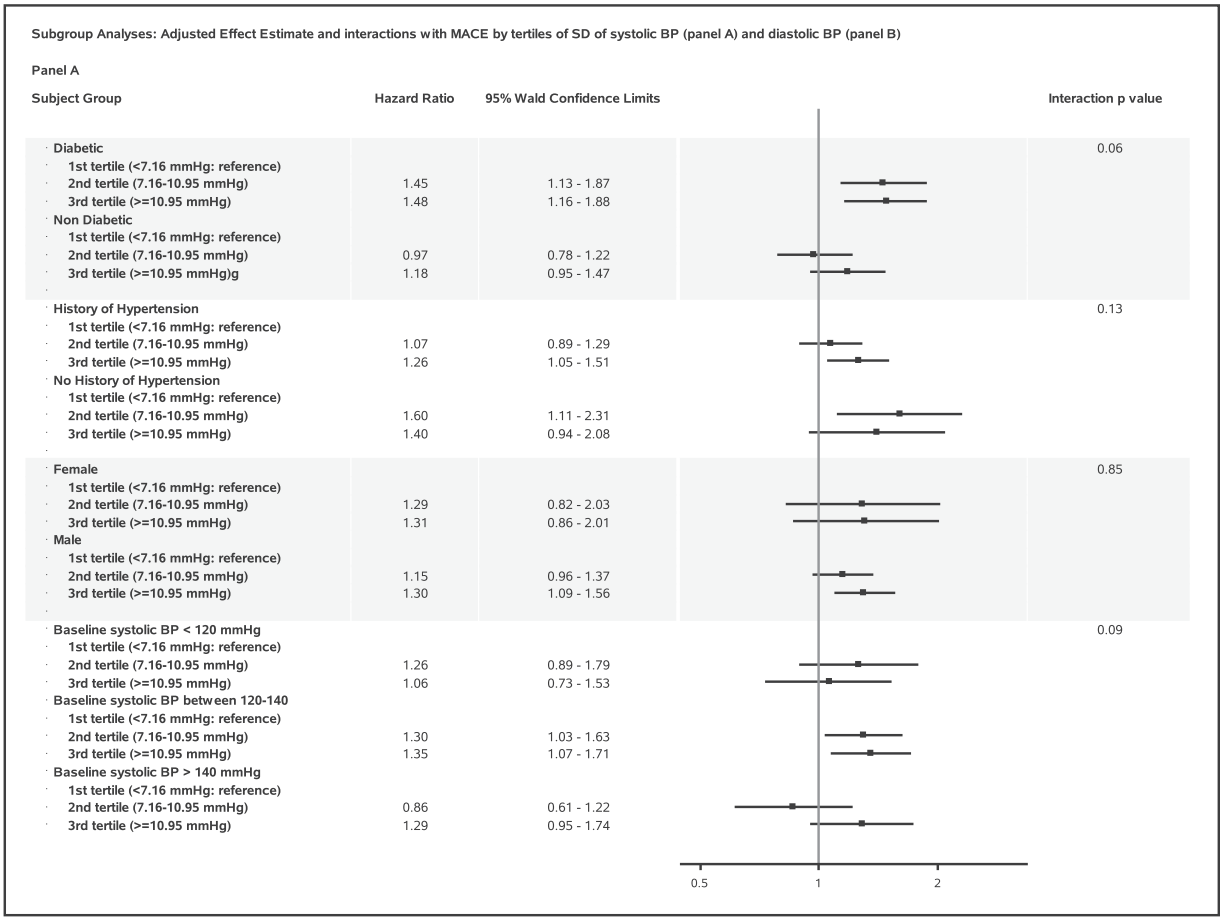


Figure 2 Subgroup analyses: adjusted effect estimate and interactions with MACE by tertiles of SD of systolic BP (panel *A*) and diastolic BP (panel *B*). The interaction of diabetes, history of hypertension, sex, and baseline systolic BP (<120 mmHg, 120 to 140 mmHg, and >140 mmHg) with BP variability as assessed by tertiles of SD of BP were evaluated for both for systolic (panel *A*) and diastolic (panel *B*) BP in adjusted Cox regression models. Adjusted hazard ratios are indicated for each subgroup by tertiles, the first tertile being used as a reference (see legend of *Figure 1* for covariates). MACE, major adverse cardiac event; BP, blood pressure.

Similar results were found when variability of BP was assessed by average real variability (*Summarizing illustration and Table 2*, Supplementary material online, *Tables S3* and *S4*).

Maximum and minimum BP

Higher maximum systolic and diastolic BP were both associated with an increased risk of MACE (*Summarizing illustration*), MI, all-cause mortality, and TCE (Supplementary material online, *Tables S3* and *S4*). Higher maximum systolic BP was also associated with increased risk of CV mortality. Minimum systolic BP was not significantly associated with outcomes when analysed by tertiles (*Summarizing illustration* and Supplementary material online, *Table S4*), but lower values of minimal systolic BP, at least below the threshold of 120 mmHg, were associated with an increased risk of MACE, cardiovascular mortality, myocardial infarction, all-cause mortality, and TCE, when analysed as a continuous variable with linear spline transformations in case of non-linearity (*Table 2*).

In this population of patients with stable CHD, lower values of minimum diastolic BP were markedly associated with increased risk of adverse events, with adjusted HRs (95%CI) for lowest vs. highest tertiles of 1.48 (1.14–1.92) for MACE (*Summarizing illustration*), 1.68 (1.16–2.45) for cardiovascular mortality, 1.57 (1.07–2.32) for MI, and 1.45 (1.08–1.94) for all-cause mortality (Supplementary material online, *Table S4*), and similar findings in the continuous analysis (*Table 2*).

Interaction analyses

The associations between SD of systolic and diastolic BP and outcomes were consistent across subgroups defined by sex, diabetes, hypertension, and baseline BP. *P*-values for interaction between SD of systolic BP and MACE were 0.85, 0.06, 0.13, and 0.09 for sex,

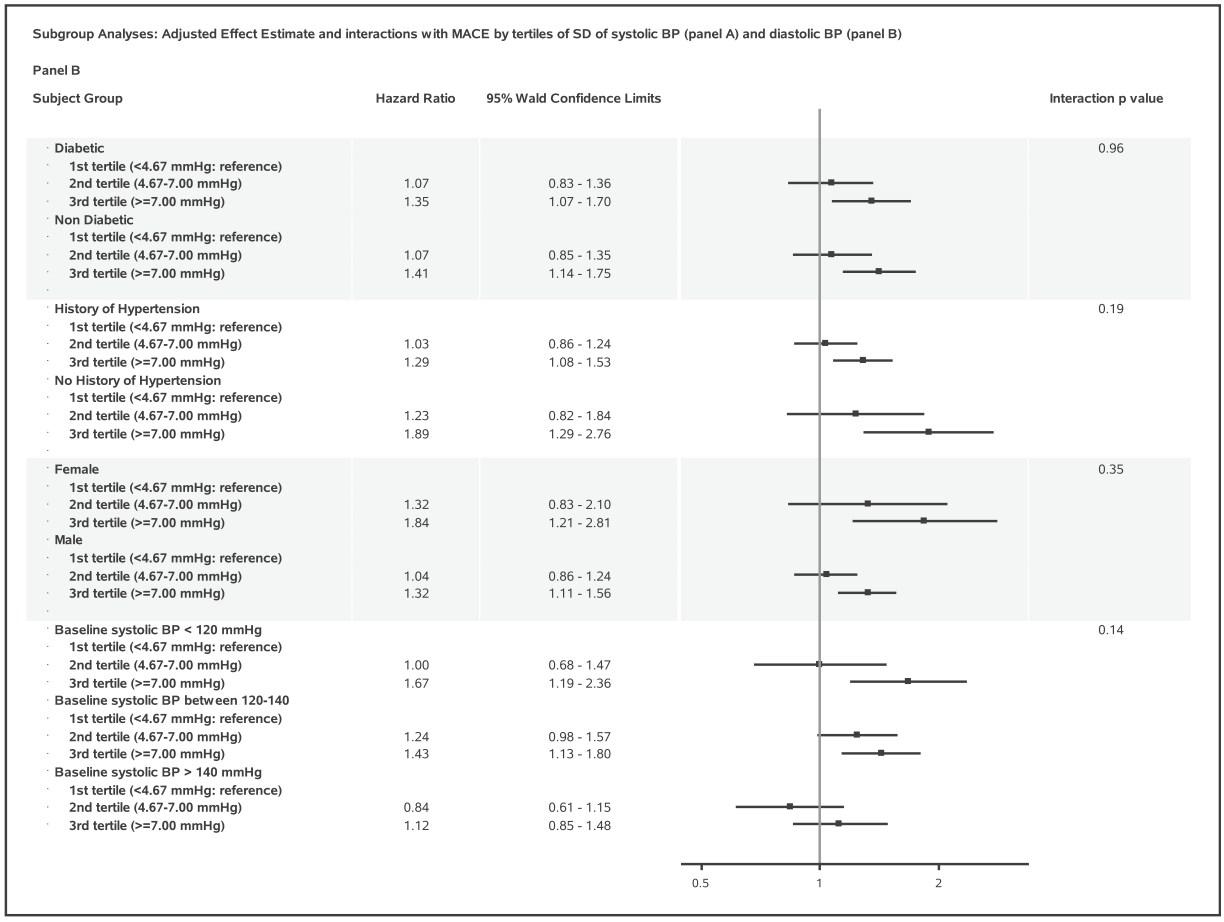


Figure 2 *Continued.*

diabetes, hypertension, and baseline systolic BP, respectively. *P*-values for interaction between SD of diastolic BP and MACE were 0.35, 0.96, 0.19, and 0.14 for sex, diabetes, hypertension, and baseline systolic BP, respectively. Forest plots of HRs of MACE for each tertile of SD of systolic and diastolic BP by subgroup are given in *Figure 2*.

Discussion

In this study conducted in 13 794 stable CHD patients from the STABILITY trial, we showed that higher visit-to visit variabilities of systolic and diastolic BP, measured across five measurements within 1 year, were strongly associated with an increased risk of subsequent adverse cardiovascular events, including MACE and mortality. This finding persisted after multiple adjustments for potential confounders and was consistent across subgroups analyses. This first study of visit-to-visit variability conducted in a large cohort of patients with CHD, combined with previous evidence obtained in other populations,[4–6,8,15] confirms that variability of BP is associated with an increased risk for cardiovascular events, even after adjusting multiple covariates including mean BP.

Small studies had previously suggested an association between variability of BP and cardiovascular events. Lau *et al.*[16] showed in 274 patients with CHD that a Mediterranean diet was associated with a lower visit-to-visit variability and a reduced risk of cardiovascular events, and Cay *et al.*[17] found that a higher variability on ambulatory BP measurement was associated with a higher rate of restenosis after percutaneous coronary intervention in 100 normotensive patients. To our knowledge, this is the first large study on the association between BP variability and cardiovascular outcome in stable CHD patients. Apart from the large number of patients, our study has several other strengths. STABILITY was not a hypertension trial, hence there was no predefined BP intervention at baseline which may have influenced BP variability, and changes in antihypertensive medications over time were minimal. In addition, because patients in this study were participating in a randomized controlled trial, the assessment of risk factors was accurate, outcomes were adjudicated, and there was high-quality follow-up.

In the study conducted by Rothwell *et al.*[4] in patients with previous transient ischaemic attack and in patients from the ASCOT-BPLA trial, visit-to-visit variability of systolic BP was associated with both stroke and CHD. Since these seminal studies, reports regarding the

A

metric of variability	model	Tertile of systolic BP variability measure 1st tertile n=4553	2nd tertile n=4549	3rd tertile n=4692	p-value
SD	unadjusted	1.00 (reference)	1.15 (0.98 -1.35)	1.39 (1.19-1.62)	<0.001
SD	adjusted	1.00 (reference)	1.17 (0.99-1.38)	1.30 (1.10-1.53)	0.007
ARV	adjusted	1.00 (reference)	1.06 (0.89-1.26)	1.28 (1.08-1.51)	0.009
maximum BP	adjusted	1.00 (reference)	0.95 (0.78-1.16)	1.22 (0.93-1.59)	0.04
minimum BP	adjusted	1.12 (0.87-1.45)	1.00 (0.83-1.21)	1.00 (reference)	0.47

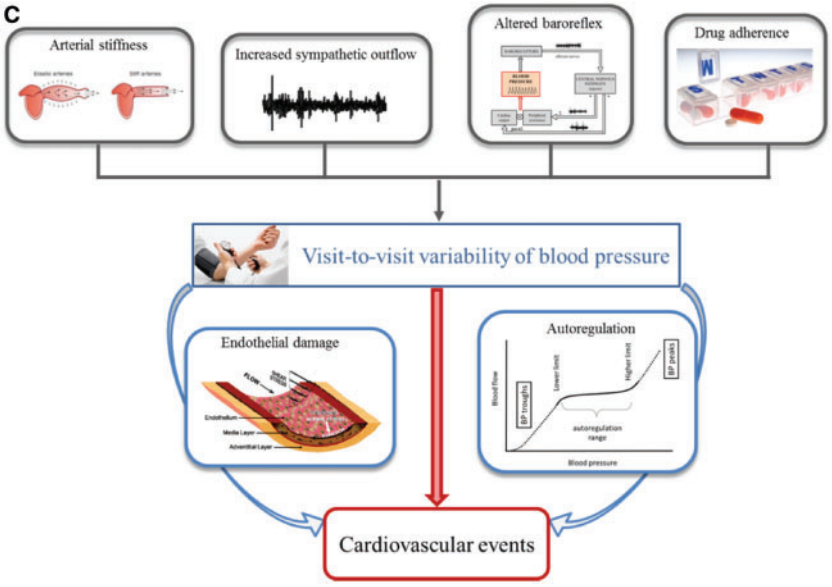
Values of tertiles for the different variability metrics are as follows:
SD: 1st tertile (<7.16 mmHg) - 2nd tertile [7.16-10.95 mmHg[- 3rd tertile (≥10.95 mmHg)
ARV: 1st tertile (<7.70 mmHg) - 2nd tertile [7.70-12.70 mmHg[- 3rd tertile (≥12.70 mmHg)
maximum BP: 1st tertile (<136 mmHg) - 2nd tertile [136-149 mmHg[- 3rd tertile (≥149 mmHg)
minimum BP: 1st tertile (<113 mmHg) - 2nd tertile [113-125 mmHg{ - 3rd tertile (≥125 mmHg)

B

metric of variability	model	Tertile of diastolic BP variability measure 1st tertile n=4583	2nd tertile n=4512	3rd tertile n=4699	p-value
SD	unadjusted	1.00 (reference)	1.08 (092 -1.27)	1.44 (1.24-1.68)	<0.001
SD	adjusted	1.00 (reference)	1.07 (0.90-1.27)	1.38 (1.18-1.62)	<0.001
ARV	adjusted	1.00 (reference)	1.10 (0.93-1.30)	1.42 (1.19-1.68)	<0.001
maximum BP	adjusted	1.00 (reference)	1.20 (0.99-1.46)	1.51 (1.17-1.94)	0.006
minimum BP	adjusted	1.48 (1.14-1.92)	1.16 (0.96-1.41)	1.00 (reference)	0.008

Values of tertiles for the different variability metrics are as follows:
SD: 1st tertile (<4.67 mmHg) - 2nd tertile [4.67-7.00 mmHg[- 3rd tertile (≥7.00 mmHg)
ARV: 1st tertile (<5.00 mmHg) - 2nd tertile [5.00-8.30 mmHg[- 3rd tertile (≥8.30 mmHg)
maximum BP: 1st tertile (<82 mmHg) - 2nd tertile [82-90 mmHg[- 3rd tertile (≥90 mmHg)
minimum BP: 1st tertile (<67 mmHg) - 2nd tertile [67-75 mmHg[- 3rd tertile (≥75 mmHg)

C



Summarizing Illustration

association between BP variability and stroke have yielded inconsistent results. Studies conducted in 8811 patients ≥55 years with diabetes (69% with a history of hypertension) from the ADVANCE trial[5] and 4819 elderly patients (70–82 years) from the PROSPER study[18] found no association between BP variability and stroke. In 33 357 hypertensive adults from the trial ALLHAT, the link depended on the treatment arm,[6] whereas in the study conducted in nearly 29 00 000 US veterans (63% with hypertension) by Gosmanova *et al.*,[7] SD of systolic BP was significantly associated with stroke. The lack of association between BP variability and stroke in our study likely reflects the markedly lower number of stroke than cardiac events in our population, and/or a stronger association between BP

variability and stroke in patients with previous transient ischaemic attack than in patients with CHD (in our population, 5.9% of the patients a history of stroke at baseline).

Studies on the associations between diastolic BP variability and cardiovascular outcome have yielded conflicting results which may depend on patients' comorbidities.[4,15,18] Importantly, in our population of stable CHD patients, associations between variability of BP and cardiovascular outcomes were observed not only for systolic but also for diastolic BP, in agreement with the key role of diastolic BP in myocardial perfusion. In this regard, the role of low nadir diastolic BP measurements has probably been overlooked in studies of BP variability so far. Our results show that in CHD patients, minimum diastolic BP is markedly associated with cardiovascular outcomes, including mortality. The heart is perfused during diastole, and in CHD patients both impaired autoregulation and coronary stenosis may explain that troughs in diastolic BP are associated with a poor cardiovascular prognosis, even after adjustment for mean diastolic BP. These results are in line with our recent findings of a marked increase in adverse cardiovascular outcomes for diastolic BP values below 70 mmHg in patients with CHD.[11]

Mechanisms underlying increased variability in BP are complex and only partially elucidated.[19,20] BP variability is a marker of arterial stiffness,[21,22] and we indeed found that it was related to factors correlated with arterial stiffness, such as age, diabetes and polyvascular disease. Other pathophysiological explanations for increased BP variability include altered baroreflex sensitivity and autonomic dysfunction,[23,24] sleep disorders,[25] and seasonal changes in outdoor temperature.[26] Drug classes of antihypertensive drugs also have differential influence on BP variability.[27–29] Irregular drug adherence is another explanation for increased variability.[30,31] These could all be factors explaining the link between BP variability and the increased risk of cardiovascular events. In addition, animal data have shown that variations in BP induce direct end-organ damage and endothelial dysfunction independently of mean BP level.[32,33] Finally, peaks in BP have been shown to be associated with adverse outcome[4,5] and we confirm this finding, but we also show that nadirs of BP, in particular diastolic BP, which accompany a greater variability may have deleterious effects *per se*, as explained above and as illustrated in the *Summarizing illustration*.

Our study has several limitations. First, adherence to treatment was not measured in our patients but has been shown to contribute to BP variability.[31,34] In addition, as patients with an event within the first year of the study were excluded to avoid any confounding effect of events on variability assessment, the most severe patients were excluded from this analysis. Furthermore, left ventricular ejection fraction was not measured at baseline and therefore not taken into account in the multivariable adjustment. The main limitations are those of post-hoc observational studies; even though the associations between systolic and diastolic BP variability and outcome were strong and persisted after multiple adjustments; our findings do not establish a causal link between variability and outcome.

In conclusion, variabilities of systolic and diastolic BP are associated with adverse events in patients with stable CHD. Whether reducing variability reduces cardiovascular risk remains unknown, but our results may explain differential effects of BP lowering drugs, beyond BP reduction,[27] and call for more attention to changes in BP variability beyond mean BP level in cardiovascular trials and to consistency of BP control during follow-up of hypertensive patients.

Summarizing illustration: Visit-to-visit variability of blood pressure and cardiovascular events.

Visit-to visit variability of blood pressure (VVV-BP), assessed by standard deviation (SD), average real variability (ARV), maximum and minimum blood pressure (BP) over the first year of the study, is strongly associated with subsequent cardiovascular events. This association remains significant after multiple adjustments for confounding factors.

(*Panel A*) Hazard ratios (95%CI) for primary outcome by tertiles of SD, ARV, maximum and minimum of systolic BP. (*Panel B*) Hazard ratios (95%CI) for primary outcome by tertiles of SD, ARV, maximum and minimum of diastolic BP. (*Panel C*) Arterial stiffness, increased sympathetic activity, altered baroreflex and irregular drug adherence are factors known to increase VVV-BP variability, also associated with increased cardiovascular events. In addition, VVV-BP, by inducing direct endothelial damage and by overcoming autoregulation capacities of target organs (through nadirs and/or peaks of BP), may be directly responsible for cardiovascular events. Further dedicated studies are still needed to demonstrate whether reducing VVV-BP improves cardiovascular outcome, independently of variations in mean BP.

Supplementary material

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

Authors' contribution

E.V-P., A.S., K.C., P.G.S. conceived and designed the research; A.S., K.C. performed statistical analysis; E.V-P., A.S., K.C., P.G.S. analysed and interpreted the data; E.V-P., A.S. designed tables and figures; E.V.-P. drafted the manuscript: All authors made critical revision of the manuscript for important intellectual content; A.S., D.A., P.E.A., C.P.C., M.R.C., C.H., J.L.L-S., R.A.H.S., L.W., H.D.W., P.G.S. acquired the data; L.W., H.D.W. handled funding and supervision of the STABILITY trial.

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