ORIGINAL RESEARCH

Effect of Visit-to-Visit Variation of Heart Rate and Systolic Blood Pressure on Outcomes in Chronic Systolic Heart Failure: Results From the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT) Trial

Michael Böhm, MD; Michele Robertson, BSc; Jeffrey Borer, MD; Ian Ford, PhD; Michel Komajda, MD; Felix Mahfoud, MD; Sebastian Ewen, MD; Karl Swedberg, MD; Luigi Tavazzi, MD

***Background*—**Elevated resting heart rate (HR) and low systolic blood pressure (SBP) are related to poor outcomes in heart failure (HF). The association between visit-to-visit variation in SBP and HR and risk in HF is unknown.

***Methods and Results*—**In Systolic Heart Failure Treatment with the I_f inhibitor ivabradine Trial (SHIFT) patients, we evaluated relationships between mean HR, mean SBP, and visit-to-visit variations (coefficient of variation [CV]=SD/mean×100%) in SBP and HR (SBP-CV and HR-CV, respectively) and primary composite endpoint (cardiovascular mortality or HF hospitalization), its components, all-cause mortality, and all-cause hospitalization. High HR and low SBP were closely associated with risk for primary endpoint, all-cause mortality, and HF hospitalization. The highest number of primary endpoint events occurred in the highest HR tertile (38.8% vs 16.4% lowest tertile; $P<0.001$). For HR-CV, patients at highest risk were those in the lowest tertile. Patients in the lowest thirds of mean SBP and SBP-CV had the highest risk. The combination of high HR and low HR-CV had an additive deleterious effect on risk, as did that of low SBP and low SBP-CV. Ivabradine reduced mean HR and increased HR-CV, and increased SBP and SBP-CV slightly.

***Conclusions*—**Beyond high HR and low SBP, low HR-CV and low SBP-CV are predictors of cardiovascular outcomes with additive effects on risk in HF, but with an unknown effect size. Beyond HR reduction, ivabradine increases HR-CV. Low visit-to-visit variation of HR and SBP might signal risk of cardiovascular outcomes in systolic HF.

***Clinical Trial Registration*—**URL: http://www.isrctn.com/. Unique identifier: ISRCTN70429960. **(*J Am Heart Assoc*. 2016;5: e002160 doi: 10.1161/JAHA.115.002160)**

Key Words: blood pressure • heart failure • heart rate–blood pressure variation

In patients with chronic heart failure (HF), low (<120 mm Hg) systolic blood pressure (SBP)[1–3] and elevated (>70 bpm) heart rate (HR)[4,5] are associated with poor outcome. In patients with hypertension, it has been shown that high visit-to-visit blood pressure variation predicts cardiovascular risk,[6] which is independent of other cardiovascular risk factors, including SBP at baseline.[7] Increased variation of SBP might be partially related to abnormal autonomic function[8,9] or arterial stiffness[9] and is associated with carotid atherosclerosis,[10] silent cerebral injury, stroke,[11] and cognitive decline.[12] The mechanisms and the potential value for outcome prediction of visit-to-visit HR variation (HR-CV) are not known. It is also currently unknown whether visit-to-visit variation of SBP (SBP-CV) is associated with outcomes

From the Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany (M.B., F.M., S.E.); Robertson Center for Biostatistics, University of Glasgow, United Kingdom (M.R., I.F.); Division of Cardiovascular Medicine and the Howard Gilman Institute for Heart Valve Disease and the Schiavone Institute for Cardiovascular Translational Research, State University of New York Downstate Medical Center, New York, NY (J.B.); Institute of Cardiometabolism and Nutrition (ICAN), Pierre et Marie Curie Paris VI University, La Pitié-Salpétrière Hospital, Paris, France (M.K.); Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden (K.S.); Maria Cecilia Hospital, GVM Care and Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy (L.T.).

Correspondence to: Michael Böhm, MD, Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Str. 1, DE 66424 Homburg/Saar, Germany. E-mail: michael.boehm@uks.eu

Received July 7, 2015; accepted November 7, 2015.

in HF, where patients usually present with low blood pressure.[1–3] In the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), it has been shown that in patients with systolic HF (ejection fraction ≤35%) and HR ≥70 beats per minute (bpm)[13] or ≥75 bpm,[14] selective HR reduction with ivabradine reduced cardiovascular death or HF hospitalization. This analysis aimed to rigorously characterize the association of SBP and diastolic blood pressure (DBP) and their visit-to-visit variation (CV [coefficient of variation]) as well as HR and HR-CV with cardiovascular outcomes in the SHIFT trial.

Methods

Studied Patients and Procedures

The primary objectives, the protocol and the outcomes of SHIFT have been previously described in detail.[3,13–15] In brief, SHIFT was a randomized, double-blind, placebo-controlled outcomes trial in patients with sinus rhythm and chronic moderate-to-severe HF. Patients had left ventricular systolic dysfunction with an ejection fraction ≤35% and an HR ≥70 bpm in sinus rhythm. In total, 6505 patients in 37 countries (677 medical centers) were randomly assigned to either placebo or ivabradine 5 mg BID, which could be uptitrated to 7.5 mg BID or downtitrated to 2.5 mg BID depending on tolerability and HR. HR was measured by a 12-lead electrocardiogram on 2 consecutive visits before randomization, at baseline, and at every follow-up visit in the study. The primary endpoint was the composite of cardiovascular death or hospitalization for HF. Secondary endpoints included the individual components of the primary endpoint, HF death, all-cause hospitalization, and all-cause death. All outcomes were adjudicated by an endpoint validation committee according to predefined criteria.[13,15] Blood pressure was measured at every visit preferably on the same arm after at least 5 minutes of rest with patients in a seated position. The study was reviewed by an institutional review board, and all patients gave written consent.

Visit-to-visit variation of systolic and diastolic blood pressure (SBP-CV and DBP-CV) has previously shown to be reproducible and applicable in clinical practice.[16] The average of several measurements over time has been shown to provide more-precise information on the risk for cardiovascular events in a population of patients after myocardial infarction (MI) or stroke.[17] Mean BP and mean HR were calculated using measurements at each postbaseline visit. Visit-to-visit variation of BP and HR were calculated as a CV, that is, the ratio of SD to the mean (CV=SD/mean×100%). Measurements from all postbaseline visits were included. Altogether, 7±2.4 visits (range, 2–12) were available for the whole group (placebo: 6.8±2.5; range, 2–12; ivabradine: 7.1±2.2; range, 2–12). Data were analyzed for all visits and in a sensitivity analysis for patients with a minimum of 3 visits.

Statistical Analysis

Descriptive statistics are presented as mean±SD for continuous variables and as numbers and percentages for categorical variables. Distributions of patients according to mean HR, HR-CV, mean SBP, and SBP-CV were divided into thirds, allowing statistical evaluations of the cohort with adequate group sizes. Statistics in the thirds were tested for differences using ANOVA for continuous data and chi-square for categorical data. Variation in risk across the thirds of means and CVs was tested in a Cox proportional hazard model adjusted for beta-blocker use, New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), ischemic heart failure, age, estimated glomerular filtration rate (eGFR), body mass index, and history of diabetes and, where applicable, adjusted for baseline HR, baseline SBP, mean HR, mean SBP, and mean DBP. Adjusted hazard ratios were calculated with reference to the lowest risk group or the middle risk group, as appropriate. Pearson correlations were calculated for the mean, CV, and SDs of the HR, SBP, and DBP. Differences in mean values of parameters between the ivabradine and placebo values were tested using 2-sample *t* tests. Differences in median values of these parameters were compared using a Kruskal–Wallis test. SAS software (version 9.2; SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Correlation of Mean SDs and CVs

CV was chosen as a measure of variation because it is more independent of the mean than SD. The correlation between HR-CV and HR mean was not significant (r=0.017; P=0.35) in the placebo population. It was slightly more pronounced, but still weak (r=0.108; P<0.0001), in patients treated with ivabradine. In contrast, the association of mean HR to SD of HR was r=0.27 (P<0.0001) in patients on placebo and r=0.36 (P<0.0001) in patients on ivabradine. Similar results were obtained with blood pressure: mean SBP was related to SD of SBP with placebo (r=0.27; P<0.0001) and with ivabradine (r=0.32; P<0.0001). The association was weaker for SBP-CV with placebo (r=0.05; P=0.0123) and with ivabradine (r=0.10; P<0.0001). Therefore, CV was chosen for the analysis instead of SD, because it was less dependent on the mean. There was a weak correlation between mean SBP and mean HR (−0.054; P=0.0034) with placebo, but none with ivabradine (r=0.014; P=0.45), whereas the correlation between SBP-CV and HR-CV was moderate with placebo (r=0.09; P<0.0001) and ivabradine (r=0.11; P<0.0001).

Demographics and Clinical Characteristics

Demographic data and clinical characteristics are presented for in-trial mean HR and in-trial mean SBP in patients assigned either to placebo or ivabradine (Tables 1 through 4). Table 1 shows baseline characteristics of placebo patients according to thirds of mean HR. There were some statistical differences, some of which might be relevant. Elderly people tend to have lower HR, whereas patients with lower left ventricular function and current smokers have higher HR. There were differences according to use of beta-blocker, with patients on beta-blockers and, in particular, those on higher doses having lower HR. Similar results were observed in the ivabradine population (Table 2). Table 3 summarizes baseline characteristics according to thirds of mean SBP. Patients with low SBP appear to be younger and also have lower DBP. Higher beta-blocker dose was more frequently observed in patients with higher SBP. Similar results were obtained in the ivabradine group (Table 4). Analyses were done on group sizes of between 961 and 988. We report on the data of all visits available. When patients with 1, 3, or more visits were evaluated in a sensitivity analysis, similar results were obtained (not shown).

Clinical Outcomes According to HR and HR-CV

Figure 1 shows the association of the primary endpoint (cardiovascular death or heart failure hospitalization; Figure 1A), HF hospitalization (Figure 1B), and all-cause mortality (Figure 1C) with mean HR in patients on placebo (left) and in patients on ivabradine (right). There was a clear association between increased cardiovascular outcomes and higher mean HR in both the placebo group (left) and the ivabradine group (right). This was true not only for the primary endpoint and HF hospitalization, but also for all-cause mortality. The associations were similar in the ivabradine group (right panels), which had lower mean HR as a whole (data not shown), for these 3 endpoints.

Slightly different results were observed with HR-CV. The middle third had the lowest nominal risk (Figure 2), with a significant increase of risk in the third with the lowest HR-CV. For the primary endpoint, the lowest third of HR-CV was associated with the highest risk on placebo (Figure 2A, left). This effect was attenuated with ivabradine (Figure 2A, right). Similar results were obtained for HF hospitalization (Figure 2B) and all-cause mortality (Figure 2C).

Figure 3 summarizes adjusted hazard ratios for HF outcomes according to mean HR and HR-CV. There was a step-wise increase in the risk for the primary endpoint, cardiovascular mortality, HF hospitalization, all-cause mortality, and all-cause hospitalization with increased HR in the placebo group (Figure 3A) and the ivabradine group (data not shown). For HR-CV, the middle tertiles of the placebo group (Figure 3B) and ivabradine group (data not shown) had the lowest risk. Furthermore, HR-CV, at all stages, appeared to be higher in the ivabradine group than in the placebo group (data not shown).

Interaction of HR and HR-CV

In order to test whether there was an interaction between mean HR and HR-CV on risk of HF outcomes, outcomes were analyzed according to thirds of HR and HR-CV. The risk for the primary endpoint (Figure 4A), cardiovascular mortality (Figure 4B), and HF hospitalization (Figure 4C) was greatest in patients with the lowest third of HR-CV and highest third of mean HR; risk was lowest patients in the middle third of HR-CV and with the lowest mean HR. These associations were more pronounced in patients on placebo (left) than in those on ivabradine (right), where risk was generally lower. Importantly, the HR-CV values did not differ in the different tertiles of mean HR. The values were on placebo: HR mean tertile 1: HR-CV, 0.093; tertile 2: HR-CV, 0.095; and tertile 3: HR-CV, 0.099; and on ivabradine: HR mean tertile 1: HR-CV, 0.102; tertile 2: HR-CV, 0.115; and tertile 3: HR-CV, 0.118, respectively.

Clinical Outcomes According to SBP and SBP-CV

Figure 5 summarizes the association between third of mean SBP and risk of the primary endpoint (Figure 5A), HF hospitalization (Figure 5B) and all-cause mortality (Figure 5C) in the placebo (left) and ivabradine (right) groups. The lowest third of SBP (ie, <117 mm Hg) was predictive of the highest outcome rates, whereas risk appeared broadly similar for patients in the middle and upper thirds. For patients on placebo (left) and ivabradine (right), log-rank P was <0.001. Figure 6 summarizes the effect of SBP-CV on the risk of heart failure outcomes. Interestingly, the lowest third of SBP-CV was predictive for the greatest risk of the primary outcome (Figure 6A), HF hospitalization (Figure 6B) and all-cause mortality (Figure 6C) in the placebo group (left) and ivabradine group (right). For all associations, log-rank P<0.001, except for all-cause mortality with placebo (P=0.004). Figure 7 summarizes adjusted hazard ratios for HF outcomes according to mean SBP and SBP-CV. The third with the lowest SBP-CV had the lowest risk, and this was used as the reference hazard ratio (HR=1.0). The associations were similar for placebo (Figure 7B) and ivabradine (not shown). As with mean HR and HR-CV, there was an interaction between SBP and SBP-CV (Figure 8). Patients with the highest risk for primary endpoint (Figure 8A), cardiovascular mortality (Figure 8B), and HF hospitalization (Figure 8C) whether on placebo (left) or ivabradine (right) were those in the group with the lowest third of mean SBP and lowest third of SBP-CV. Again, as with mean HR and HR-CV, SBP-CV values were

Table 1. Placebo Population: Baseline Characteristics by In-Trial HR Mean Tertiles

	Heart Rate			
	≤70 bpm (N=978)	>70 and ≤78.7 bpm (N=988)	>78.7 bpm (N=964)	*P* Value
Age (y), mean (SD)	61.8 (10.6)	60.3 (11.2)	58.4 (12.2)	<0.001
Male (%)	747 (76.4)	757 (76.6)	752 (78.0)	0.655
Caucasian vs non-Caucasian (%)	880 (90.0)	862 (87.2)	837 (86.8)	0.066
Current smokers (%)	123 (12.6)	173 (17.5)	213 (22.1)	<0.001
Body mass index (kg/m^2), mean (SD)	27.7 (4.4)	27.9 (5.0)	28.1 (5.5)	0.144
Resting heart rate (bpm), mean (SD)	75.0 (5.2)	77.7 (6.9)	87.2 (10.9)	<0.001
Systolic blood pressure (mm Hg), mean (SD)	121.7 (15.5)	121.1 (15.5)	120.7 (16.3)	0.328
Diastolic blood pressure (mm Hg), mean (SD)	75.3 (8.9)	75.3 (9.5)	76.1 (9.7)	0.088
LVEF (%), mean (SD)	29.7 (4.8)	28.9 (5.4)	28.3 (5.2)	<0.001
eGFR (mL/min per 1.73 m^2), mean (SD)	73.5 (22.4)	75.7 (23.0)	76.9 (23.1)	0.004
Serum creatinine (μmol/L), mean (SD)	97.2 (25.6)	96.0 (27.6)	94.9 (24.5)	0.149
Haemoglobin (g/L), mean (SD)	140.8 (14.5)	141.8 (14.6)	143.9 (15.6)	<0.001
NYHA Class III/IV vs Class II (%)	458 (46.8)	478 (48.4)	556 (57.7)	<0.001
Ischemic heart failure (%)	718 (73.4)	655 (66.3)	591 (61.3)	<0.001
History of MI (%)	611 (62.5)	546 (55.3)	475 (49.3)	<0.001
History of hypertension (%)	669 (68.4)	633 (64.1)	605 (62.8)	0.024
History of diabetes (%)	258 (26.4)	311 (31.5)	333 (34.5)	<0.001
History of stroke (%)	82 (8.4)	93 (9.4)	87 (9.0)	0.722
History of COPD (%)	68 (7.0)	86 (8.7)	165 (17.1)	<0.001
Coronary artery disease (%)	768 (78.5)	701 (71.0)	642 (66.6)	<0.001
Beta-blocker at randomization (%)	916 (93.7)	908 (91.9)	807 (83.7)	<0.001
Beta-blocker dose: no BB (%)	62 (6.5)	80 (8.2)	157 (16.4)	<0.001
Beta-blocker dose: <25% (%)	122 (12.7)	123 (12.7)	136 (14.2)	
Beta-blocker dose: 25%; 50% (%)	260 (27.1)	263 (27.1)	229 (24.0)	
Beta-blocker dose: 50%; 100% (%)	273 (28.5)	261 (26.9)	237 (24.8)	
Beta-blocker dose: ≥100% (%)	241 (25.2)	244 (25.1)	196 (20.5)	
Selective beta-blocker at randomization (%)	546 (55.8)	510 (51.6)	417 (43.3)	<0.001
Beta-2 agonists at randomization (%)	10 (1.0)	23 (2.3)	54 (5.6)	<0.001
Drugs for obstructive airway disease at randomization (%)	43 (4.4)	73 (7.4)	142 (14.7)	<0.001
Adrenergics, inhalants at randomization (%)	23 (2.4)	46 (4.7)	86 (8.9)	<0.001
Adrenergics and other drugs for obstructive airway disease at randomization (%)	15 (1.5)	29 (2.9)	46 (4.8)	<0.001
ACE inhibitor at randomization (%)	784 (80.2)	783 (79.3)	722 (74.9)	0.011
Diuretic at randomization (%)	785 (80.3)	802 (81.2)	820 (85.1)	0.014
ARB at randomization (%)	128 (13.1)	147 (14.9)	147 (15.2)	0.348
Calcium-channel blocker at randomization (%)	79 (8.1)	87 (8.8)	64 (6.6)	0.195
Antialdosterone at randomization (%)	548 (56.0)	576 (58.3)	617 (64.0)	0.001
Device (%)	28 (2.9)	48 (4.9)	42 (4.4)	0.065

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Table 2. Ivabradine Population: Baseline Characteristics by In-Trial HR Mean Tertiles

	Heart Rate			
	≤60.4 bpm (N=965)	>60.4 and ≤68.6 bpm (N=966)	>68.6 bpm (N=961)	*P* Value
Age (y), mean (SD)	62.1 (10.6)	61.3 (11.3)	59.0 (11.6)	<0.001
Male (%)	695 (72.0)	751 (77.7)	741 (77.1)	0.006
Caucasian vs non-Caucasian (%)	870 (90.2)	854 (88.4%)	833 (86.7)	0.059
Current smokers (%)	122 (12.6)	164 (17.0)	209 (21.7)	<0.001
Body mass index (kg/m^2), mean (SD)	27.9 (4.6)	28.1 (5.1)	28.1 (5.6)	0.623
Resting heart rate (bpm), mean (SD)	75.5 (6.0)	78.2 (7.5)	85.3 (11.0)	<0.001
Systolic blood pressure (mm Hg), mean (SD)	121.7 (15.4)	121.9 (15.8)	122.0 (17.0)	0.906
Diastolic blood pressure (mm Hg), mean (SD)	75.1 (9.3)	75.5 (9.7)	76.6 (9.9)	0.003
LVEF (%), mean (SD)	29.4 (5.0)	29.1 (5.1)	28.4 (5.4)	<0.001
eGFR (mL/min per 1.73 m^2), mean (SD)	72.8 (21.7)	75.1 (23.0)	76.8 (23.7)	<0.001
Serum creatinine (μmol/L), mean (SD)	97.0 (26.2)	95.8 (25.6)	95.5 (27.3)	0.438
Hemoglobin (g/L), mean (SD)	140.0 (14.2)	141.4 (14.9)	142.4 (15.3)	0.002
NYHA Class III/IV vs Class II (%)	450 (46.6)	479 (49.6)	531 (55.3)	<0.001
Ischemic heart failure (%)	694 (71.9)	671 (69.5)	600 (62.4)	<0.001
History of MI (%)	575 (59.6)	558 (57.8)	478 (49.7)	<0.001
History of hypertension (%)	666 (69.0)	641 (66.4)	615 (64.0)	0.066
History of diabetes (%)	234 (24.2)	282 (29.2)	349 (36.3)	<0.001
History of stroke (%)	68 (7.0)	63 (6.5)	58 (6.0)	0.668
History of COPD (%)	66 (6.8)	121 (12.5)	122 (12.7)	<0.001
Coronary artery disease (%)	729 (75.5)	713 (73.8)	660 (68.7)	0.002
Beta-blocker at randomization (%)	903 (93.6)	876 (90.7)	817 (85.0)	<0.001
Beta-blocker dose: no BB (%)	62 (6.6)	90 (9.4)	144 (15.3)	<0.001
Beta-blocker dose: <25% (%)	130 (13.7)	138 (14.4)	156 (16.5)	
Beta-blocker dose: 25%; 50% (%)	229 (24.2)	235 (24.6)	236 (25.0)	
Beta-blocker dose: 50%; 100% (%)	285 (30.1)	256 (26.8)	213 (22.6)	
Beta-blocker dose: ≥100% (%)	240 (25.4)	238 (24.9)	194 (20.6)	
Selective beta-blocker at randomization (%)	478 (49.5)	463 (47.9)	467 (48.6)	0.778
Beta-2 agonists at randomization (%)	9 (0.9)	22 (2.3)	28 (2.9)	0.007
Drugs for obstructive airway disease at randomization (%)	55 (5.7)	78 (8.1)	113 (11.8)	<0.001
Adrenergics, inhalants at randomization (%)	31 (3.2)	42 (4.3)	61 (6.3)	0.004
Adrenergics and other drugs for obstructive airway disease at randomization (%)	23 (2.4)	24 (2.5)	42 (4.4)	0.018
ACE inhibitor at randomization (%)	769 (79.7)	794 (82.2)	740 (77.0)	0.018
Diuretic at randomization (%)	795 (82.4)	793 (82.1)	835 (86.9)	0.006
ARB at randomization (%)	159 (16.5)	116 (12.0)	123 (12.8)	0.010
Calcium-channel blocker at randomization (%)	96 (9.9)	80 (8.3)	75 (7.8)	0.214
Antialdosterone at randomization (%)	561 (58.1)	615 (63.7)	600 (62.4)	0.032
Device (%)	27 (2.8)	32 (3.3)	30 (3.1)	0.803

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Table 3. Placebo Population: Baseline Characteristics by In-Trial Systolic Blood Pressure Mean Tertiles

	SBP			
	≤117 mm Hg (N=984)	>117 and ≤128.7 mm Hg (N=974)	>128.7 mm Hg (N=977)	*P* Value
Age (y), mean (SD)	58.1 (12.3)	60.5 (11.0)	61.9 (10.8)	<0.001
Male (%)	764 (77.6)	766 (78.6)	730 (74.7)	0.101
Caucasian vs non-Caucasian (%)	805 (81.8)	872 (89.5)	907 (92.8)	<0.001
Current smokers (%)	168 (17.1)	179 (18.4)	163 (16.7)	0.586
Body mass index (kg/m^2), mean (SD)	26.5 (4.7)	27.8 (4.6)	29.4 (5.2)	<0.001
Resting heart rate (bpm), mean (SD)	80.9 (10.7)	79.6 (9.0)	79.2 (8.8)	<0.001
Systolic blood pressure (mm Hg), mean (SD)	108.8 (11.9)	121.3 (11.2)	133.6 (13.0)	<0.001
Diastolic blood pressure (mm Hg), mean (SD)	70.1 (8.4)	76.0 (8.0)	80.7 (8.5)	<0.001
LVEF (%), mean (SD)	27.6 (5.4)	29.2 (5.2)	30.1 (4.5)	<0.001
eGFR (mL/min per 1.73 m^2), mean (SD)	76.8 (25.1)	75.3 (21.9)	73.9 (21.4)	0.024
Serum creatinine (μmol/L), mean (SD)	95.7 (25.4)	96.1 (25.9)	96.4 (26.5)	0.847
Hemoglobin (g/L), mean (SD)	140.9 (14.9)	141.7 (14.4)	143.9 (15.4)	<0.001
NYHA Class III/IV vs Class II (%)	529 (53.8)	494 (50.7)	473 (48.5)	0.063
Ischemic heart failure (%)	602 (61.2)	675 (69.3)	690 (70.6)	<0.001
History of MI (%)	529 (53.8)	567 (58.2)	538 (55.1)	0.125
History of hypertension (%)	430 (43.7)	657 (67.5)	824 (84.3)	<0.001
History of diabetes (%)	236 (24.0)	315 (32.3)	352 (36.0)	<0.001
History of stroke (%)	81 (8.2)	94 (9.7)	88 (9.0)	0.545
History of COPD (%)	107 (10.9)	104 (10.7)	109 (11.2)	0.943
Coronary artery disease (%)	638 (64.8)	719 (73.8)	757 (77.5)	<0.001
Beta-blocker at randomization (%)	872 (88.6)	873 (89.6)	890 (91.1)	0.191
Beta-blocker dose: no BB (%)	112 (11.5)	101 (10.5)	87 (9.1)	<0.001
Beta-blocker dose: <25% (%)	171 (17.5)	120 (12.5)	90 (9.4)	
Beta-blocker dose: 25%; 50% (%)	282 (28.9)	233 (24.3)	238 (24.9)	
Beta-blocker dose: 50%; 100% (%)	239 (24.5)	261 (27.2)	273 (28.6)	
Beta-blocker dose: ≥100% (%)	171 (17.5)	245 (25.5)	266 (27.9)	
Selective beta-blocker at randomization (%)	431 (43.8)	492 (50.5)	552 (56.5)	<0.001
Beta-2 agonists at randomization (%)	27 (2.7)	29 (3.0)	31 (3.2)	0.854
Drugs for obstructive airway disease at randomization (%)	89 (9.0)	83 (8.5)	86 (8.8)	0.920
Adrenergics, inhalants at randomization (%)	53 (5.4)	53 (5.4)	49 (5.0)	0.900
Adrenergics and other drugs for obstructive airway disease at rand (%)	33 (3.4)	32 (3.3)	25 (2.6)	0.528
ACE inhibitor at randomization (%)	736 (74.8)	764 (78.4)	793 (81.2)	0.003
Diuretic at randomization (%)	831 (84.5)	781 (80.2)	799 (81.8)	0.045
ARB at randomization (%)	142 (14.4)	137 (14.1)	143 (14.6)	0.936
Calcium-channel blocker at randomization (%)	30 (3.0)	59 (6.1)	141 (14.4)	<0.001
Antialdosterone at randomization (%)	703 (71.4)	607 (62.3)	434 (44.4)	<0.001
Device (%)	71 (7.2)	28 (2.9)	19 (1.9)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Table 4. Ivabradine Population: Baseline Characteristics by In-Trial Systolic Blood Pressure Mean Tertiles

	SBP			
	≤119.2 mm Hg (N=971)	>119.2 and ≤130.6 mm Hg (N=964)	>130.6 mm Hg (N=967)	*P* Value
Age (y), mean (SD)	58.4 (11.9)	61.7 (10.9)	62.4 (10.5)	<0.001
Male (%)	753 (77.5)	743 (77.1)	700 (72.4)	0.014
Caucasian vs non-Caucasian (%)	795 (81.9)	868 (90.0)	903 (93.4)	<0.001
Current smokers (%)	166 (17.1)	157 (16.3)	174 (18.0)	0.609
Body mass index (kg/m^2), mean (SD)	26.6 (4.8)	28.1 (4.9)	29.5 (5.2)	<0.001
Resting heart rate (bpm), mean (SD)	79.9 (9.5)	79.3 (9.3)	79.8 (9.3)	0.271
Systolic blood pressure (mm Hg), mean (SD)	108.8 (11.9)	122.2 (11.0)	134.6 (13.3)	<0.001
Diastolic blood pressure (mm Hg), mean (SD)	70.1 (8.6)	76.1 (7.9)	81.0 (9.1)	<0.001
LVEF (%), mean (SD)	28.0 (5.5)	29.1 (5.1)	29.8 (4.7)	<0.001
eGFR (mL/min per 1.73 m^2), mean (SD)	76.0 (23.7)	75.2 (22.5)	73.5 (22.3)	0.060
Serum creatinine (μmol/L), mean (SD)	96.6 (26.8)	95.4 (25.0)	96.5 (27.3)	0.534
Hemoglobin (g/L), mean (SD)	140.3 (14.9)	141.1 (14.4)	142.6 (15.1)	0.003
NYHA Class III/IV vs Class II (%)	495 (51.0)	484 (50.3)	486 (50.3)	0.935
Ischemic heart failure (%)	618 (63.6)	684 (71.0)	669 (69.2)	0.002
History of MI (%)	543 (55.9)	565 (58.6)	508 (52.5)	0.027
History of hypertension (%)	468 (48.2)	652 (67.6)	806 (83.4)	<0.001
History of diabetes (%)	230 (23.7)	282 (29.3)	354 (36.6)	<0.001
History of stroke (%)	65 (6.7)	51 (5.3)	73 (7.5)	0.127
History of COPD (%)	98 (10.1)	93 (9.6)	121 (12.5)	0.091
Coronary artery disease (%)	665 (68.5)	722 (74.9)	722 (74.7)	0.002
Beta-blocker at randomization (%)	865 (89.1)	874 (90.7)	866 (89.6)	0.500
Beta-blocker dose: no BB (%)	106 (11.0)	90 (9.4)	101 (10.8)	<0.001
Beta-blocker dose: <25% (%)	188 (19.5)	133 (14.0)	104 (11.1)	
Beta-blocker dose: 25%; 50% (%)	250 (26.0)	234 (24.6)	218 (23.2)	
Beta-blocker dose: 50%; 100% (%)	247 (25.6)	242 (25.4)	266 (28.3)	
Beta-blocker dose: ≥100% (%)	172 (17.9)	254 (26.7)	250 (26.6)	
Selective beta-blocker at randomization (%)	409 (42.1)	483 (50.1)	520 (53.8)	<0.001
Beta-2 agonists at randomization (%)	15 (1.5)	23 (2.4)	21 (2.2)	0.395
Drugs for obstructive airway disease at randomization (%)	74 (7.6)	69 (7.2)	105 (10.9)	0.007
Adrenergics, inhalants at randomization (%)	38 (3.9)	44 (4.6)	53 (5.5)	0.258
Adrenergics and other drugs for obstructive airway disease at randomization (%)	25 (2.6)	26 (2.7)	39 (4.0)	0.122
ACE inhibitor at randomization (%)	758 (78.1)	776 (80.5)	778 (80.5)	0.313
Diuretic at randomization (%)	837 (86.2)	783 (81.2)	811 (83.9)	0.012
ARB at randomization (%)	122 (12.6)	125 (13.0)	152 (15.7)	0.090
Calcium-channel blocker at randomization (%)	28 (2.9)	82 (8.5)	142 (14.7)	<0.001
Antialdosterone at randomization (%)	700 (72.1)	580 (60.2)	503 (52.0)	<0.001
Device (%)	52 (5.4)	24 (2.5)	13 (1.3)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure.

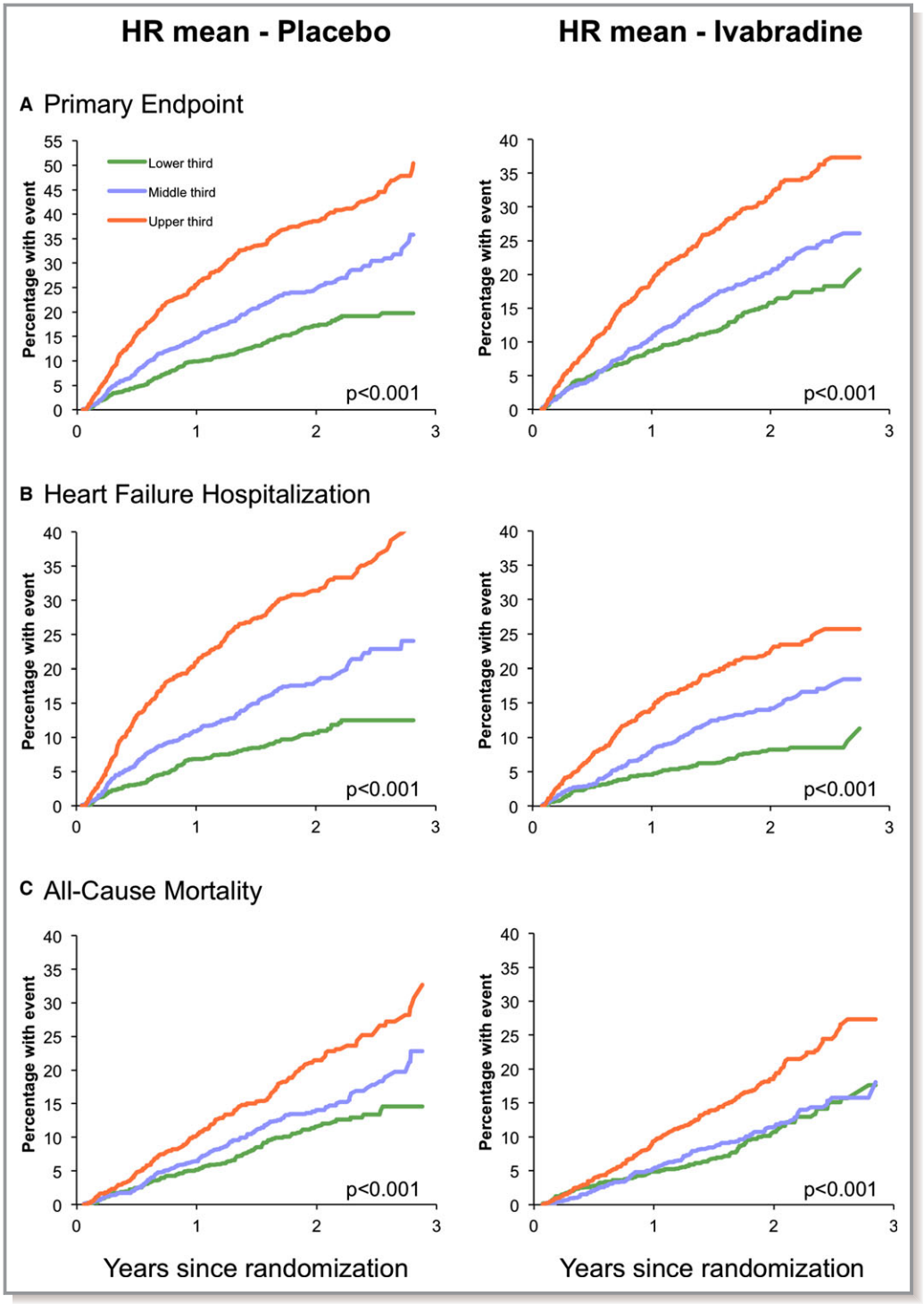

Figure 1. Kaplan–Meier event curves for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), heart failure hospitalization (B), and all-cause mortality (C) in placebo (left) and ivabradine (right) patients according to thirds of mean rate (heart rate mean) tertiles. Cox regression *P* values are given. HR CV indicates coefficient of heart rate variation.

similar in the mean SBP tertiles (placebo: SBP mean tertile 1: SBP-CV, 0.074; tertile 2: SBP-CV, 0.072; and tertile 3: SBP-CV, 0.073; ivabradine: SBP mean tertile 1: SBP-CV, 0.075; tertile 2: SBP-CV, 0.073; tertile 3: SBP-CV, 0.078).

Clinical Outcome According to DBP and DBP-CV

We also determined the effect of mean DBP and DBP-CV on the risk of HF outcomes. As with SBP, patients with the

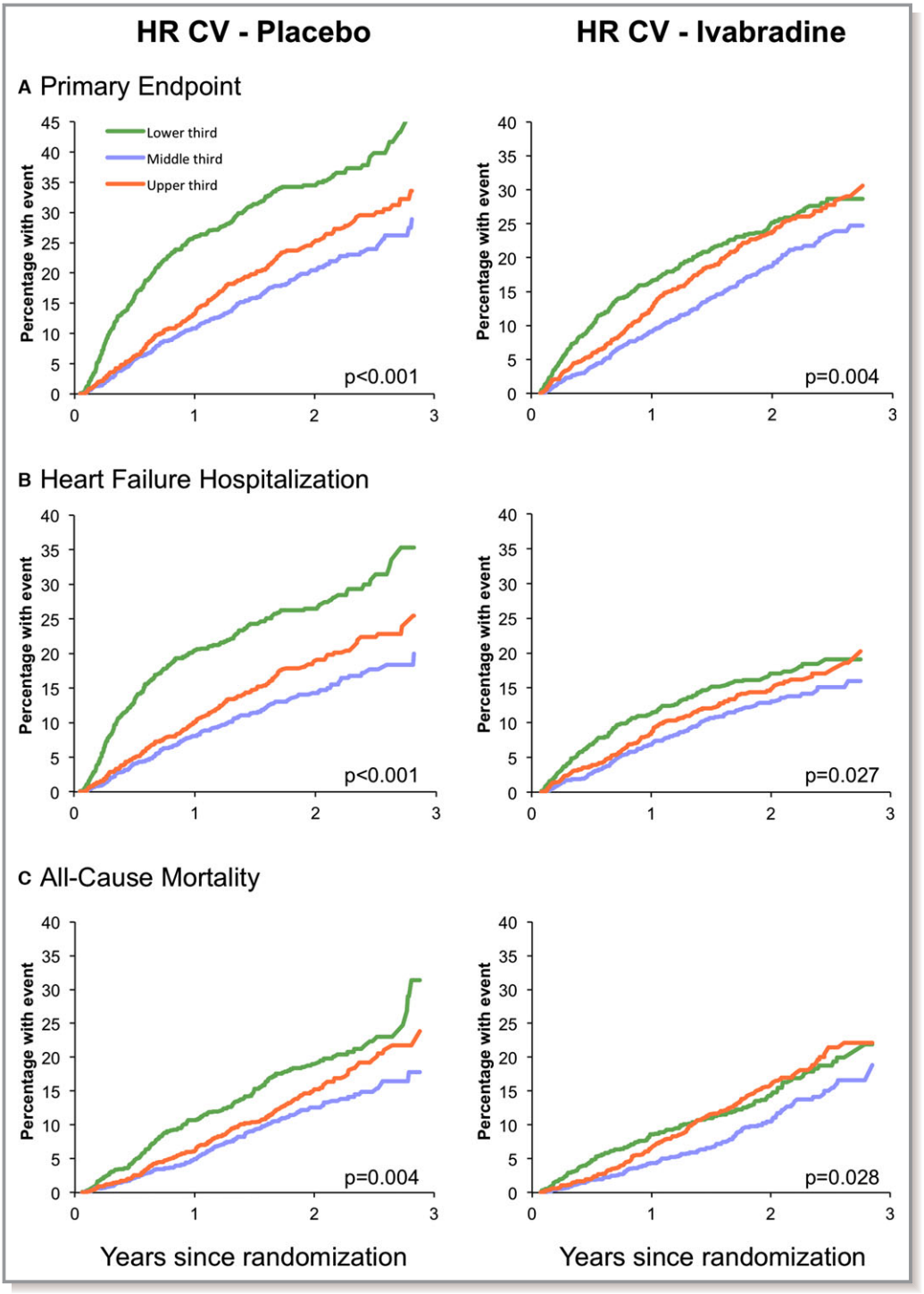

Figure 2. Kaplan–Meier event curves for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), heart failure hospitalization (B), and all-cause mortality (C) in placebo (left) and ivabradine (right) patients according to thirds of coefficient of heart rate variation (HR CV). Cox regression *P* values are given.

lowest third of DBP had the highest risk (Figure 9), whether they were taking placebo (left) or ivabradine (right). Patients with the lowest third of DBP-CV also had the highest risk (Figure 10). Adjusted hazard ratios for HF outcomes according to mean DBP and DBP-CV are summarized in Figure 11. Interaction between mean DBP and DBP-CV was similar to that between mean SBP and SBP-CV (Figure 12).

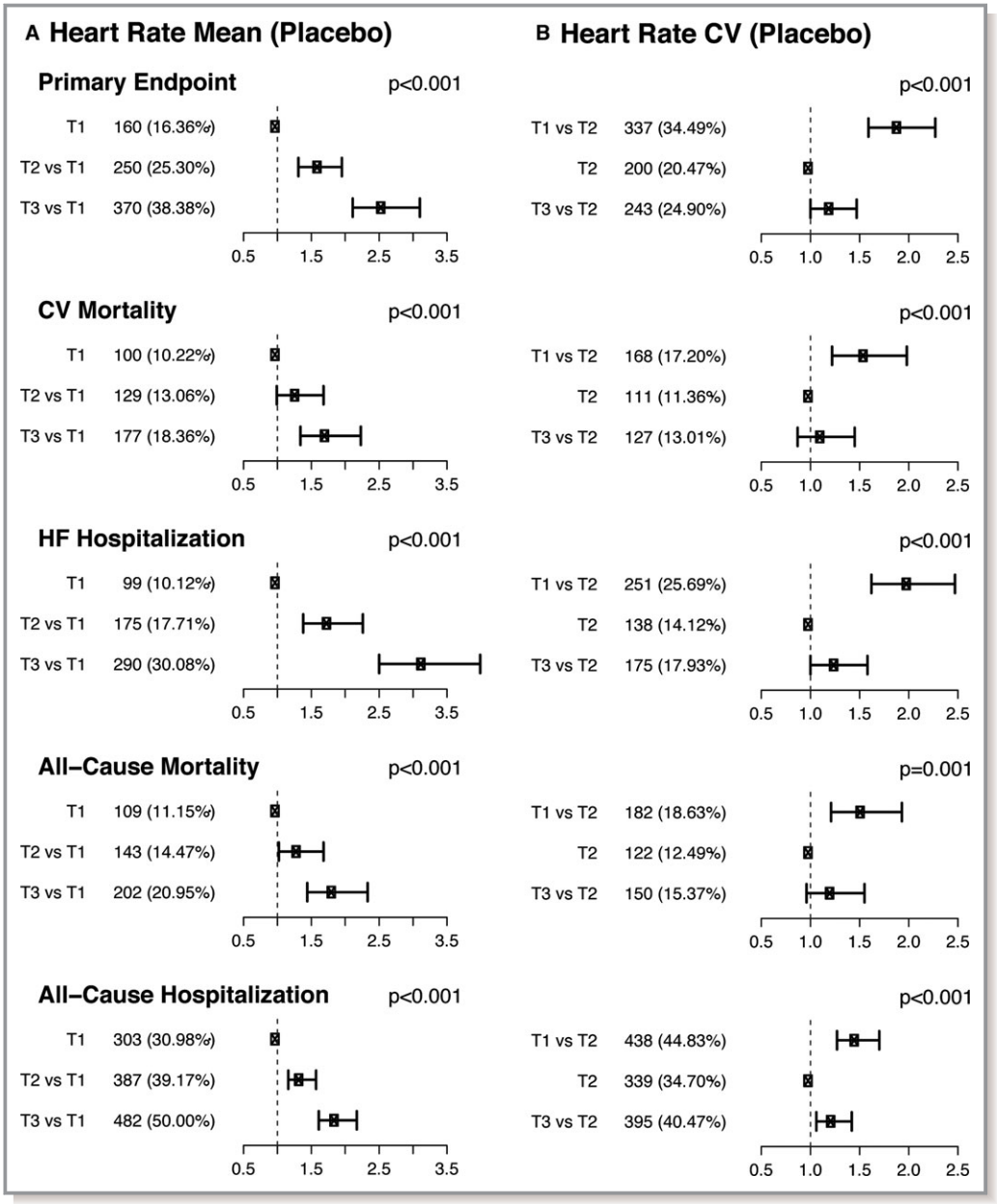

Figure 3. Adjusted hazard ratios show the association in placebo patients between thirds of heart rate (A, HR mean, left) and heart rate coefficient of variation (B, HR CV, right) and the primary endpoint (cardiovascular death or hospitalization for heart failure), cardiovascular mortality (CV mortality), heart failure hospitalization (HF hospitalization), all-cause mortality, and all-cause hospitalization.

Effect of Ivabradine on HR-CV and SBP-CV

Whereas the effect of ivabradine on outcome reduction is known to be related to reduction in HR,[5,13] its effects on HR-CV and SBP-CV were unknown. We tested the difference between placebo- and ivabradine-treated patients according to median or mean values of HR, SBP, DBP, HR-CV, SBP-CV, and DBP-CV (Table 5). Mean HR values were significantly reduced by ivabradine compared to placebo. Whereas mean SBP increased slightly with ivabradine, no significant differences were detected in mean DBP. Interestingly, treatment with ivabradine increased HR-CV and led to small absolute increases in SBP-CV and DBP-CV.

Discussion

In this analysis, we have shown that the individual visit-to-visit variations in HR and SBP together with mean HR and mean SBP were associated with cardiovascular outcomes in a population of patients with systolic HF on contemporary

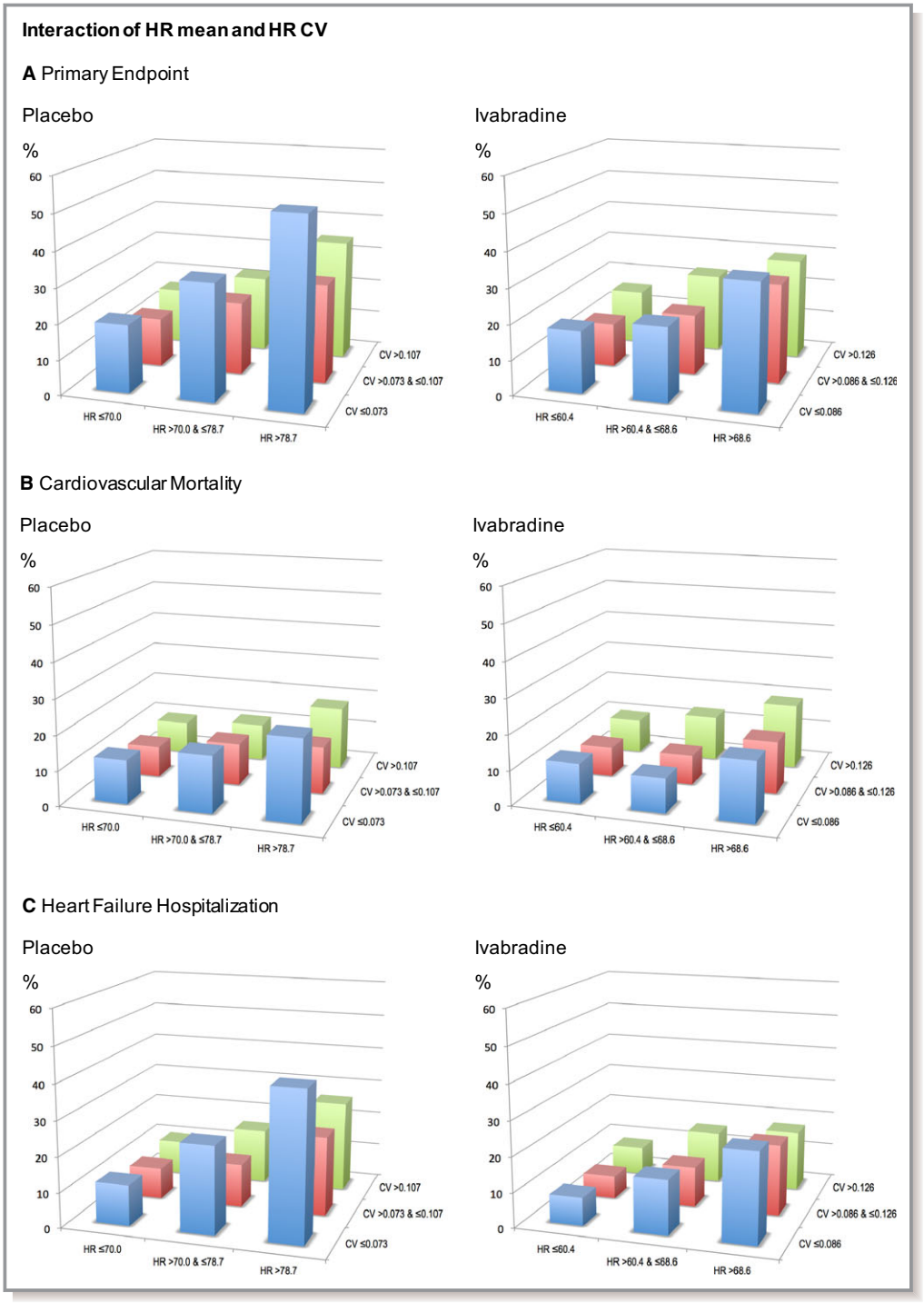

Figure 4. Interaction between mean heart rate (HR mean) and heart rate coefficient of variation (HR CV) for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), cardiovascular mortality (B), and heart failure hospitalization (C) in placebo (left) and ivabradine (right) patients.

treatments. A high HR and a low SBP were associated with the primary composite endpoint of the SHIFT trial, cardiovascular mortality or HF hospitalization, as well as its individual components, all-cause mortality, and all-cause hospitalization. Patients with the lowest third of HR-CV had the highest risk of outcomes. The effects of mean HR and HR-CV on risk were additive. Low mean SBP and low SBP-CV were also related to poor outcomes. Interestingly, in addition to its HR-reducing effect, ivabradine restored HR-CV and slightly increased SBP-CV.

Previous studies have shown that high resting HR[4,5] and low SBP[1–3] are associated with increased cardiovascular

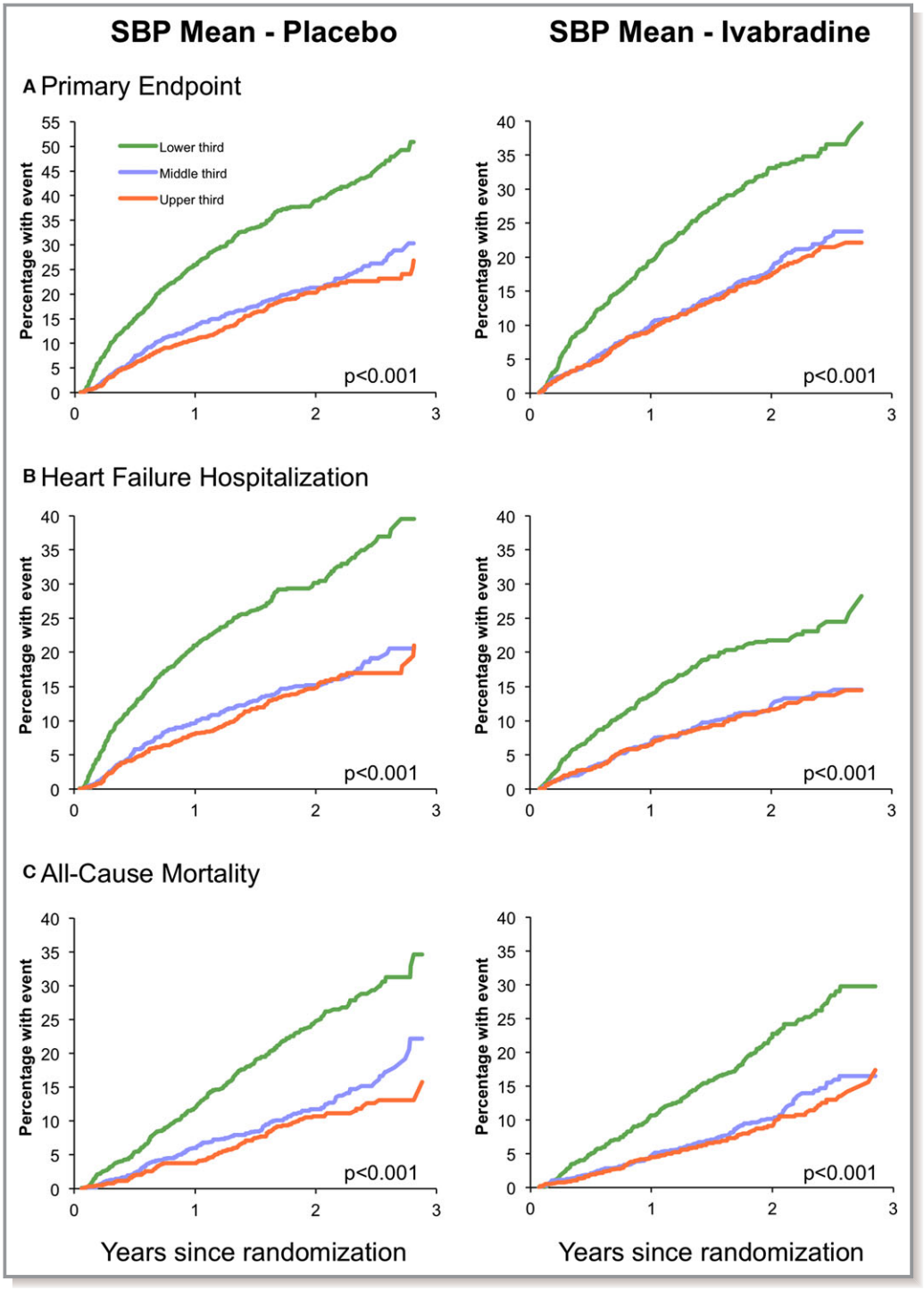

Figure 5. Kaplan–Meier event curves for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), heart failure hospitalization (B), and all-cause mortality (C) in placebo (left) and ivabradine (right) patients according to thirds of mean systolic blood pressure (SBP mean).

mortality and early rehospitalization for worsening HF. These studies are mainly based on a single measurement of HR and SBP. By using the mean of multiple measurements, our findings agree with these previous studies, showing that risk of the primary endpoint of SHIFT was related to tertiles of baseline HR. After HR was reduced by ivabradine, there was a reduction in HF death, HF hospitalization, and a nonsignificant reduction of cardiovascular death in the overall SHIFT population.[14,15] We also showed that the association of HR to risk was sustained when HR remained high, despite treatment with ivabradine. This is in line with the finding that in patients with low HR on ivabradine, there was a strong risk

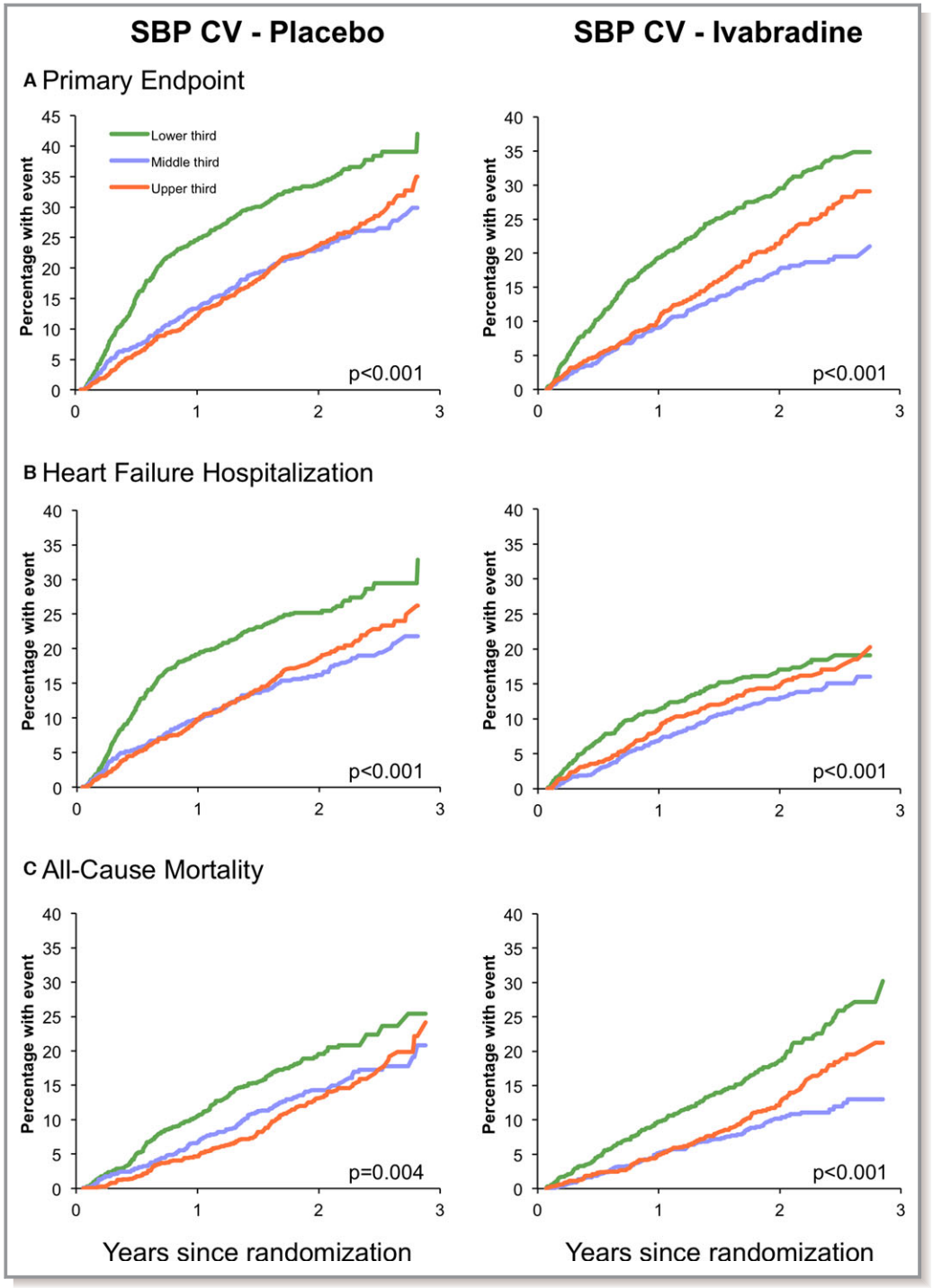

Figure 6. Kaplan–Meier event curves for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), heart failure hospitalization (B), and all-cause mortality (C) in placebo (left) and ivabradine (right) patients according to thirds of coefficient of variation of systolic blood pressure (SBP CV). Cox regression *P* values are given.

reduction, whereas there was a high residual risk in patients whose HR did not decline on treatment.[5] Adjusting risk by the number of heart beats reduced neutralized risk reduction by ivabradine in SHIFT.[5] The novelty of this report is that low visit-to-visit variation of SBP and HR are also associated with risk in this population, who usually present with low or normal SBP,[1–3] but high HR.[4,5]

Here, we investigated the mean HR and SBP values over all visits during the observation periods. It has been shown that in patients at higher cardiovascular risk, mean SBP and HR

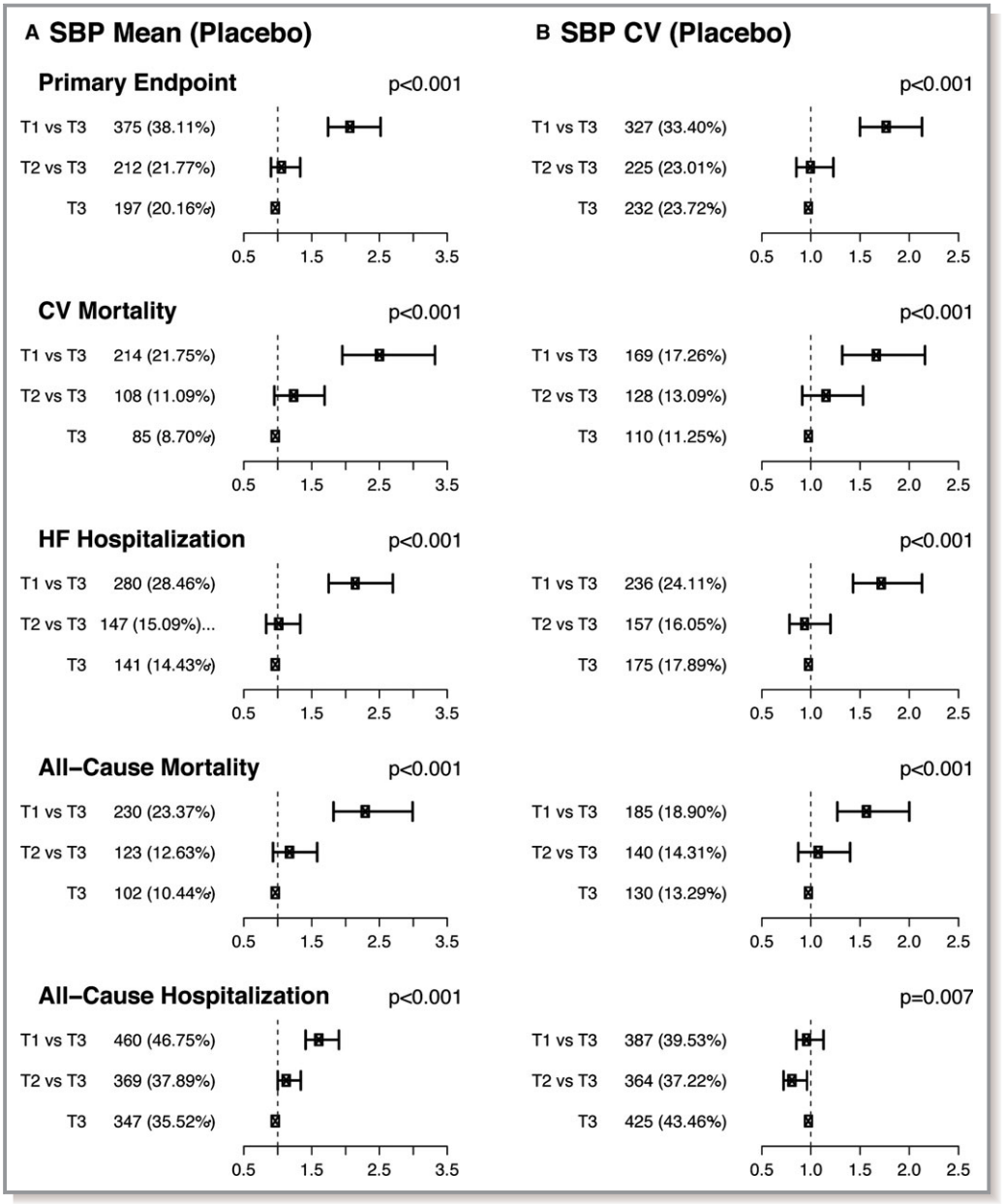

Figure 7. Adjusted hazard ratios show the association in placebo patients between thirds of systolic blood pressure (A, SBP mean, left) and systolic blood pressure coefficient of variation (B, SBP CV, right) and the primary endpoint (cardiovascular death or hospitalization for heart failure), cardiovascular mortality (CV mortality), heart failure hospitalization (HF hospitalization), all-cause mortality, and all-cause hospitalization.

measured at several visits long term is more predictive of outcomes than HR and SBP measured just at baseline.[17] In hypertensive individuals, in addition to long-term mean SBP, variation of SBP is predictive of, and also independently associated with, risk.[8,9] Mechanistically, it was suggested that this variation is associated with episodic peaks and, thus high variance of SBP might be important in the short run for triggering of vascular events.[18] In the HF population of SHIFT, patients with the lowest SBP variation had the highest subsequent risk. Patients with low SBP and low SBP-CV were at the highest risk, providing evidence that HF patients with persistently low BP have the highest risk. Again, this is opposite to what is observed in hypertension. Interestingly, here, we show that not only low SBP-CV, but also low HR-CV is associated with outcome. Patients in the middle third of HR-CV nominally had the lowest risk. Risk was particularly high in HF patients with low HR-CV and high mean HR. Clinically, it is important for physicians to note that patients presenting constantly with high HR and low SBP at several visits over time are at a particularly high risk of death or hospitalization.

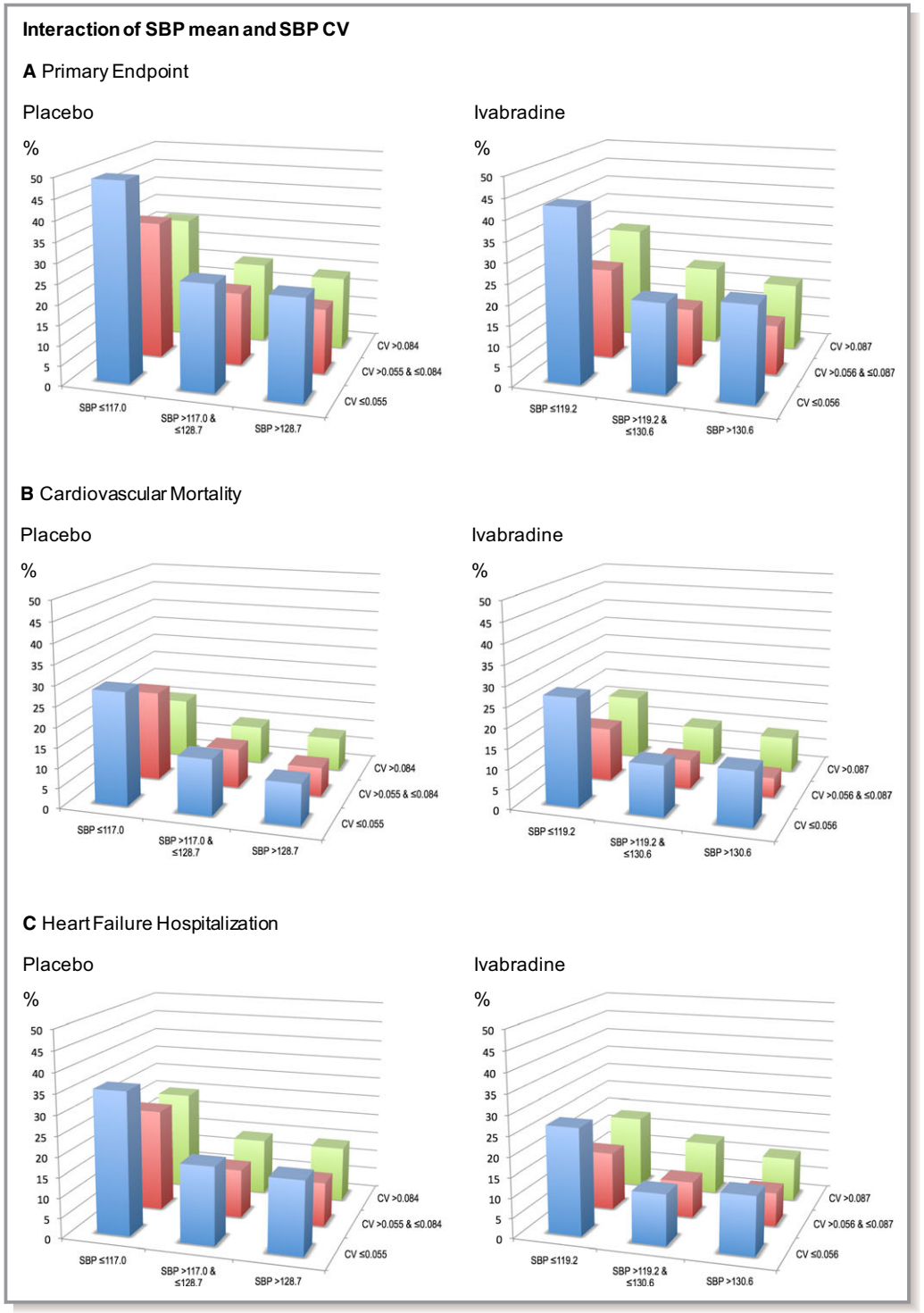

Figure 8. Interaction between mean systolic blood pressure (SBP mean) and systolic blood pressure coefficient of variation (SBP CV) for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), cardiovascular mortality (B), and heart failure hospitalization (C) in placebo (left) and ivabradine (right) patients.

Associations of mean SBP and SBP-CV with risk are opposite in HF and hypertension ("inverse epidemiology"). Similar patterns were also observed for DBP, which is also associated with risk in hypertensive individuals.[19]

Mechanistically, high intraindividual variation of blood pressure was suggested to be related to nonadherence to treatment with antihypertensive drugs.[20] However, unlike in hypertension trials,[21–23] here, low SBP variation was associ-

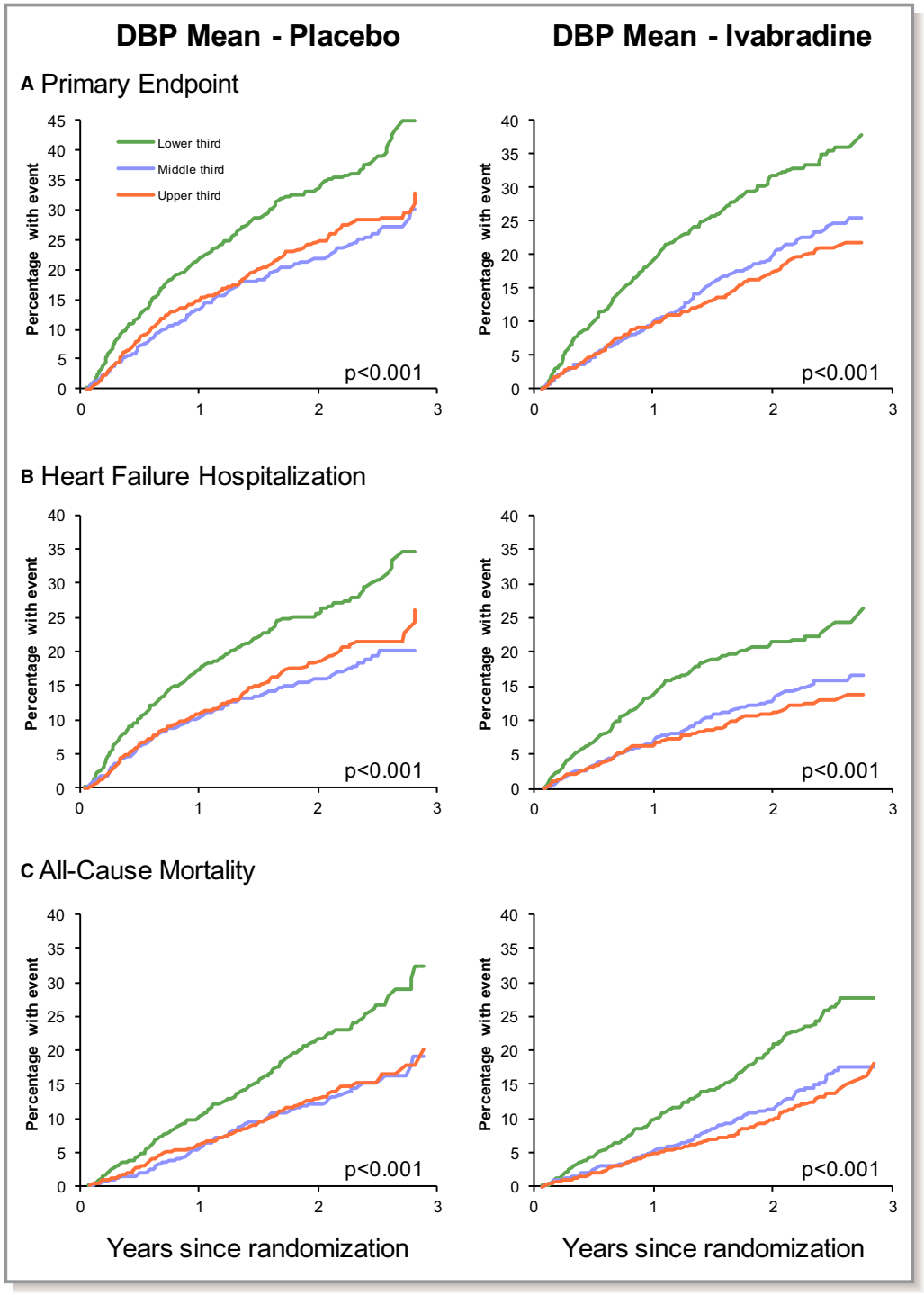

Figure 9. Kaplan–Meier event curves for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), heart failure hospitalization (B), and all-cause mortality (C) in placebo (left) and ivabradine (right) patients according to third of mean diastolic blood pressure (DBP). Cox regression *P* values are given.

ated with increased risk. This indicates that, as with mean SBP, the SBP-CV risk relation in HF is opposite to that in hypertension. Nonadherence to the study medication, ivabradine, and to placebo amounted to 21% and 19%, respectively. However, we did not capture adherence to accompanying HF cotreatment, all affecting at least blood pressure. Thus, we cannot say whether adherence changes to those drugs contribute to this finding. Because the association occurs on ivabradine and on placebo, nonadherence does not likely play a role. Thus, eventually, autonomic dysfunction related to

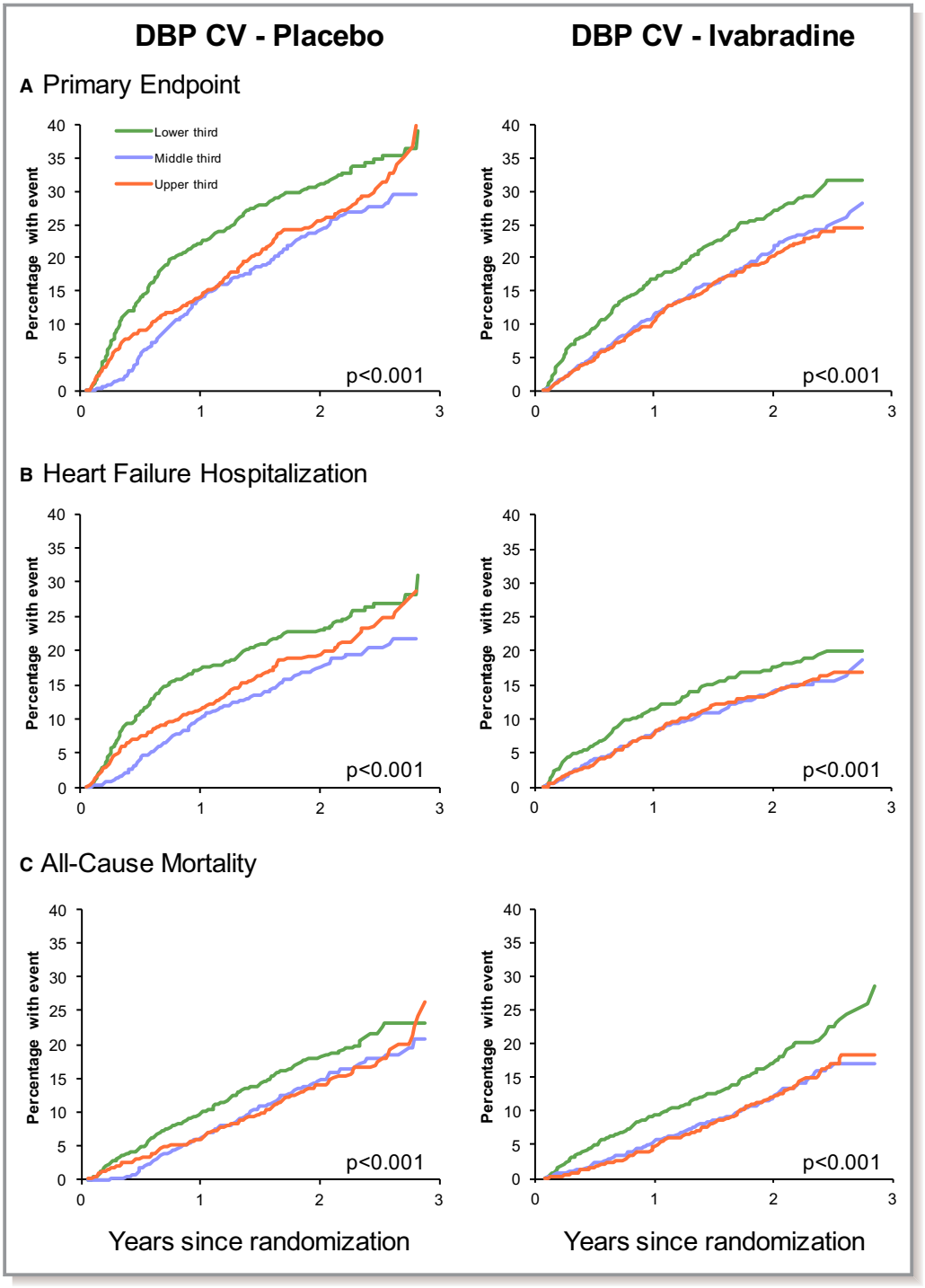

Figure 10. Kaplan–Meier event curves for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), heart failure hospitalization (B), and all-cause mortality (C) in placebo (left) and ivabradine (right) patients according to third of diastolic blood pressure coefficient of variation (DBP CV). Cox regression *P* values are given.

persistent high HR or severely impaired cardiac output associated with low SBP resulting in a small variation might also play a role in higher event rates. Beyond hypertension, the effect of visit-to-visit variation of BP was shown to be predictive in subjects with diabetes, which might also be influenced by the degree of autonomic dysfunction.[24] Interestingly, the association between SBP as well as SBP-CV to risk was not, or minimally, changed by ivabradine. In contrast, ivabradine increased HR-CV. It has previously been shown that several antihypertensive drugs differentially affect

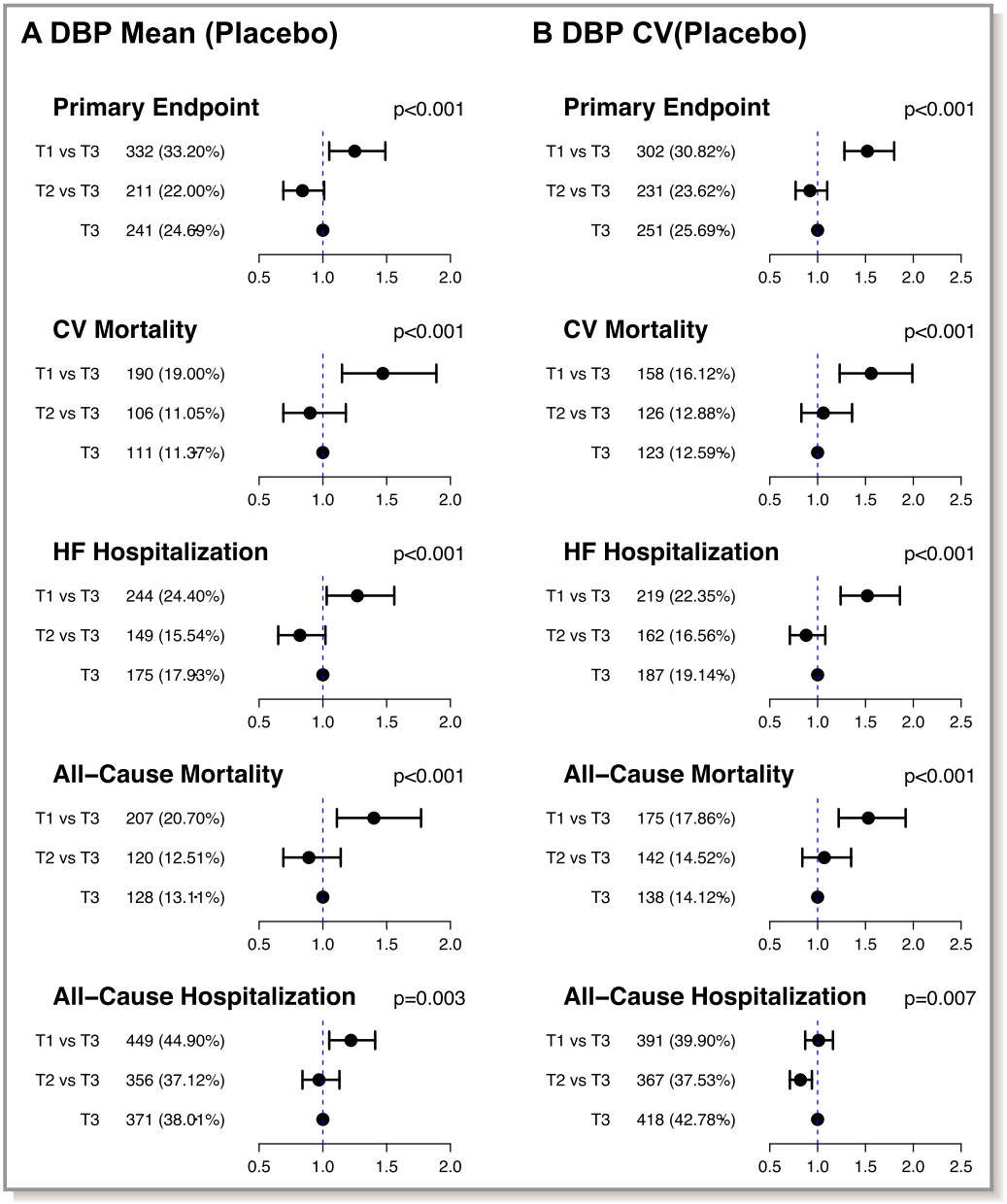

Figure 11. Association in placebo patients between thirds of diastolic blood pressure (A, DBP mean, left) and diastolic blood pressure coefficient of variation (B, DBP CV, right) and the primary endpoint (cardiovascular death or hospitalization for heart failure), cardiovascular mortality (CV mortality), heart failure hospitalization (HF hospitalization), all-cause mortality, and all-cause hospitalization.

SBP-CV, which has been shown to be related to their effects of reducing stroke.[22] In SHIFT,[14,15] the effect of ivabradine is attributed to HR reduction, given that risk reduction is neutralized when the effects were adjusted for the reduction of HR by ivabradine.[5] Here, we have documented that HR-CV was increased by ivabradine. Therefore, in patients with low HR-CV, restoration of HR variation by ivabradine might add another contributing mechanism, or at least indicator, for the risk-reducing effect of the I_f inhibitor beyond HR reduction itself. However, this analysis is hypothesis generating because we cannot say how much this finding could contribute to risk reduction by ivabradine. It could also be the consequence of improvement of HF with a reduction of neuroendocrine dysfunction after HR reduction by ivabradine.

Limitations

Some limitations of the present analysis should be acknowledged. This was a post-hoc exploratory analysis. Individuals were not subjected to randomization. Nevertheless, the large

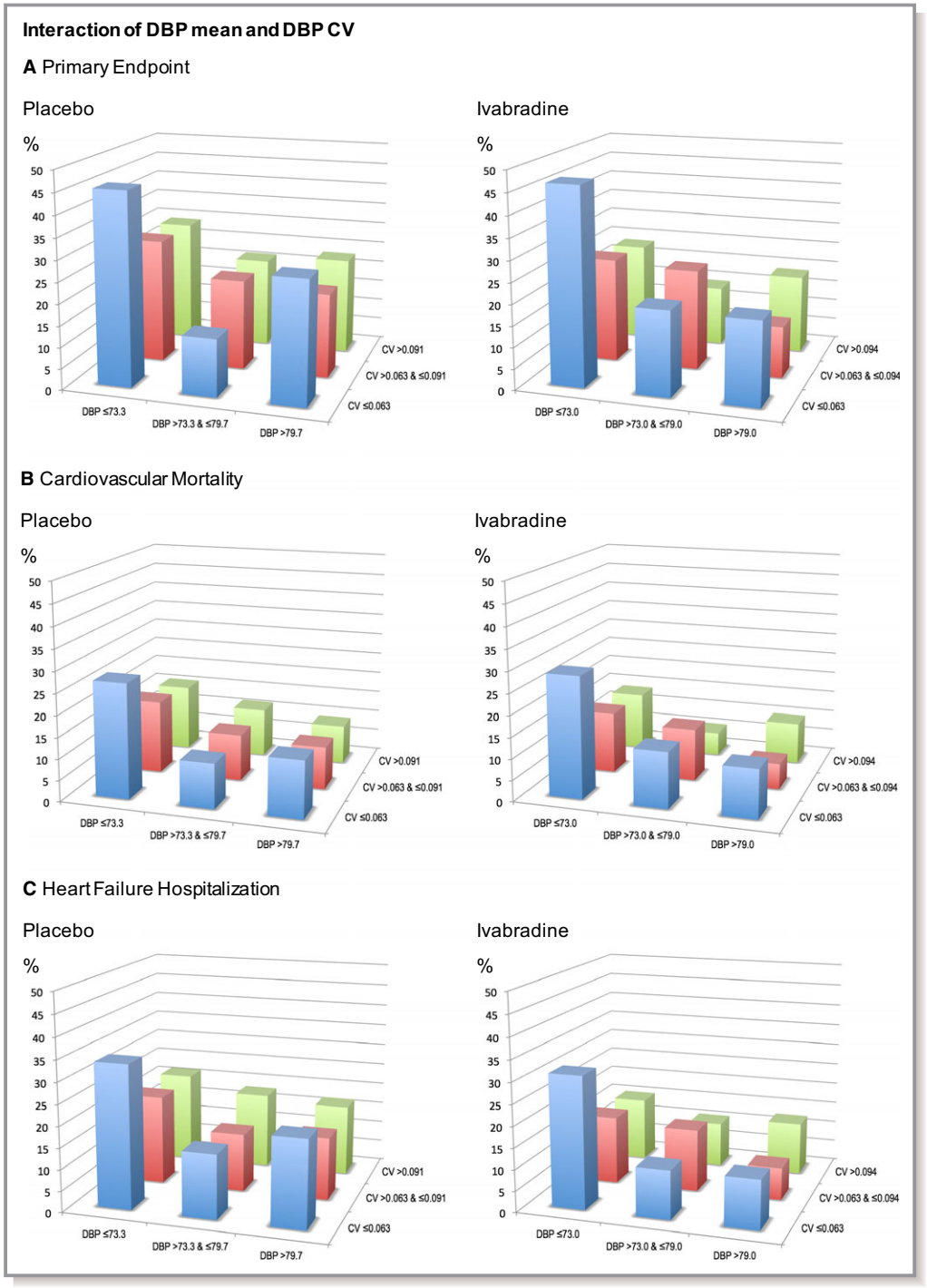

Figure 12. Interaction between mean heart rate (HR mean) and heart rate coefficient of variation (HR CV) for the primary endpoint (cardiovascular death or heart failure hospitalization) (A), cardiovascular mortality (B), and heart failure hospitalization (C) in placebo (left) and on ivabradine (right) patients.

study population and the rigorous capture of HR and SBP data provide the statistical power to allow reliable analysis of the relationships to risk. In addition, these findings might have clinical importance because they show physicians that low SBP variation and low HR variation over a series of visits might provide important clinical information on future outcomes in HF patients. It has to be emphasized that these data apply to HF with systolic dysfunction, whereas in the HF population with preserved ejection fraction, no data are available.

Table 5. Effect of Ivabradine on Values (Mean Values and Their Variations in Heart Rate, Systolic Blood Pressure, and Diastolic Blood Pressure

	Placebo (Mean)	Ivabradine (Mean)	*P* Value*
Heart rate	75.4	65.7	<0.0001
Systolic blood pressure	122.6	125.0	<0.0001
Diastolic blood pressure	76.2	75.8	0.0619
Heart rate CV	0.095	0.112	<0.0001
Systolic blood pressure CV	0.073	0.075	0.0072
Diastolic blood pressure CV	0.079	0.081	0.0640

CV indicates coefficient of variation.
**t* test was used to compare differences between mean values.

Conclusions

The results of this post-hoc analysis in an HF population with systolic dysfunction treated with recommended drugs according to contemporary guidelines have shown that beyond HR and SBP, variations in these clinical parameters over time are predictive of risk. Physicians should therefore note that patients with low variation of HR and SBP might be at particular risk and require adjustment of treatment and careful follow-up. In HF, inverse epidemiology occurs: High SBP-CV is associated with higher risk in hypertension,[6–11] but lower risk in systolic HF. Finally, ivabradine restored HR variation, which could be a marker for, or even contribute to, risk reduction beyond HR reduction.

Sources of Funding

SHIFT was funded by Servier, France.

Disclosures

All authors received scientific support from Servier, France.

References

1. Gheorghiade M, Vaduganathan M, Ambrosy A, Böhm M, Campia U, Cleland JG, Fedele F, Fonarow GC, Maggioni AP, Mebazaa A, Mehra M, Metra M, Nodari S, Pang PS, Ponikowski P, Sabbah HN, Komajda M, Butler J. Current management and future directions for the treatment of patients hospitalized for heart failure with low blood pressure. *Heart Fail Rev*. 2013;18:107–122.
2. Ambrosy AP, Vaduganathan M, Mentz RJ, Greene SJ, Subacius H, Konstam MA, Maggioni AP, Swedberg K, Gheorghiade M. Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. *Am Heart J*. 2013;165:216–225.
3. Komajda M, Böhm M, Borer JS, Ford I, Robertson M, Manolis AJ, Tavazzi L, Swedberg K. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. *Eur J Heart Fail*. 2014;16:810–816.
4. Logeart D, Gueffet JP, Rouzet F, Pousset F, Chavelas C, Solal AC, Jondeau G. Heart rate per se impacts cardiac function in patients with systolic heart failure and pacing: a pilot study. *Eur J Heart Fail*. 2009;11:53–57.
5. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010;376:886–894.
6. Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, Inoue R, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension*. 2008;52:1045–1050.
7. Pierdomenico SD, Di NM, Esposito AL, Di MR, Ballone E, Lapenna D, Cuccurullo F. Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens*. 2009;22:842–847.
8. Hata Y, Kimura Y, Muratani H, Fukiyama K, Kawano Y, Ashida T, Yokouchi M, Imai Y, Ozawa T, Fujii J, Omae T. Office blood pressure variability as a predictor of brain infarction in elderly hypertensive patients. *Hypertens Res*. 2000;23:553–560.
9. Hsieh YT, Tu ST, Cho TJ, Chang SJ, Chen JF, Hsieh MC. Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: a 5.5-year prospective analysis. *Eur J Clin Invest*. 2012;42:245–253.
10. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation*. 2012;126:569–578.
11. Nagai M, Kario K. Visit-to-visit blood pressure variability, silent cerebral injury, and risk of stroke. *Am J Hypertens*. 2013;26:1369–1376.
12. Matsumoto A, Satoh M, Kikuya M, Ohkubo T, Hirano M, Inoue R, Hashimoto T, Hara A, Hirose T, Obara T, Metoki H, Asayama K, Hosokawa A, Totsune K, Hoshi H, Hosokawa T, Sato H, Imai Y. Day-to-day variability in home blood pressure is associated with cognitive decline: the Ohasama study. *Hypertension*. 2014;63:1333–1338.
13. Swedberg K, Komajda M, Böhm M, Borer J, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled trial. *Lancet*. 2010;376:875–885.
14. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol*. 2013;102:11–22.
15. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). *Eur J Heart Fail*. 2010;12:75–81.
16. Muntner P, Joyce C, Levitan EB, Holt E, Shimbo D, Webber LS, Oparil S, Re R, Krousel-Wood M. Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care. *J Hypertens*. 2011;29:2332–2338.
17. Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, Yusuf S, Böhm M. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. *Clin Res Cardiol*. 2014;103:149–159.
18. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948.
19. Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, Muntner P. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. *Hypertension*. 2014;64:965–982.
20. Muntner P, Levitan EB, Joyce C, Holt E, Mann D, Oparil S, Krousel-Wood M. Association between antihypertensive medication adherence and visit-to-visit variability of blood pressure. *J Clin Hypertens (Greenwich)*. 2013;15:112–117.
21. Krakoff LR. Fluctuation: does blood pressure variability matter? *Circulation*. 2012;126:525–527.
22. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905.
23. Hata J, Arima H, Rothwell PM, Woodward M, Zoungas S, Anderson C, Patel A, Neal B, Glasziou P, Hamet P, Mancia G, Poulter N, Williams B, MacMahon S, Chalmers J. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. *Circulation*. 2013;128:1325–1334.
24. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010;375:906–915.

Effect of Visit–to–Visit Variation of Heart Rate and Systolic Blood Pressure on Outcomes in Chronic Systolic Heart Failure: Results From the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT) Trial

Michael Böhm, Michele Robertson, Jeffrey Borer, Ian Ford, Michel Komajda, Felix Mahfoud, Sebastian Ewen, Karl Swedberg and Luigi Tavazzi

J Am Heart Assoc. 2016;5:e002160; originally published February 12, 2016;
doi: 10.1161/JAHA.115.002160
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980