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Visit-to-Visit Blood Pressure Variation and Outcomes in Heart Failure with Reduced Ejection Fraction: findings from the EMPHASIS-HF trial

Short title: Blood pressure variability in heart failure

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Abstract

Background: Visit-to-visit office blood pressure variability (BPV) has been associated with morbidity and mortality outcomes in several cardiovascular conditions. The aim of this study was to evaluate the association between BPV and outcomes in patients with heart failure and reduced ejection fraction (HFrEF) and the effect of eplerenone on BPV.

Methods and Results: We evaluated the associations between BPV, calculated as systolic blood pressure coefficient of variation ($SBP-CoV=SD/mean*100\%$), and the primary composite endpoint of cardiovascular mortality or HF hospitalization, and its components, in 2549 patients from the EMPHASIS-HF trial. Lower SBP-CoV was independently associated with a higher risk of all the studied outcomes, while higher as well as lower SBP-CoV were associated with a higher risk of cardiovascular death. After a median follow-up period of 21 months the risk of the composite outcome of cardiovascular death or HF hospitalization was almost double in the lower SBP-CoV tertile as compared to the intermediate tertile (adjusted HR: 2.01, 95%CI [1.62-2.51], $p<0.001$). The relationship between SBP-CoV and outcomes was not modified by eplerenone (p -value for interaction=0.48). An interaction was detected between mean SBP and SBP-CoV for the primary outcome ($p=0.048$) and for HF hospitalization ($p=0.018$). The effect modification was slight, but lower SBP-CoV was associated with worse outcomes in patients with both low and high SBP, while this interaction was less clear for patients with SBP in the "normal" range.

Conclusions: In our patients with HFrEF and mild symptoms, both a lower and higher SBP-CoV were associated with worse outcomes. SBP-CoV did not modify the benefit of eplerenone. Further studies are warranted to clarify the role of BPV in HF.

Keywords: heart failure; visit-to-visit blood pressure variability; prognosis; systolic blood pressure.

ClinicalTrials.gov identifier: NCT00232180

Introduction

Visit-to-visit office blood pressure variability (BPV) has been associated with several cardiovascular events (e.g. stroke, myocardial infarction, and cardiovascular mortality) [1-5], independently of other cardiovascular risk factors. Both low and high BPV have also been associated with worse outcomes depending on the context and population (general population, chronic kidney disease, hypertension, diabetes, high risk population, heart failure, etc.) [6-12]. BPV can be influenced by several factors such as medication adherence, class of antihypertensive medication, intensity of blood pressure (BP) treatment, autonomic dysfunction and patient age [13-15].

In a secondary analysis of the high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HF) trial (HEAAL), a high BPV was found to be associated with poorer cardiovascular outcomes [9]. Conversely, in the ivabradine and outcomes in chronic heart failure trial (SHIFT), low BPV was associated with worse outcomes [16]. Finally, in a recent analysis of patients with myocardial infarction and left ventricular dysfunction, heart failure or other high-risk features, there was a U-shaped relationship between BPV and outcomes, with an excess of mortality in both the high and the low BPV tertiles [7].

In order to characterize the relationship between visit-to-visit BPV and outcomes further in HFrEF, and to determine whether eplerenone might modulate the effects of BPV on prognosis, we analysed BPV in patients enrolled in the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms trial (EMPHASIS-HF).

Methods

Study population

The primary objectives, the protocol and the outcomes of the EMPHASIS-HF have been previously described in detail [17]. In brief, EMPHASIS-HF was a randomized, double-blind, placebo-controlled outcomes trial in patients with chronic systolic heart failure and mild symptoms. The study was conducted in accordance with the Declaration of Helsinki and approved by site ethics committees. All participants gave written informed consent to participate in the trial.

Outcomes

The primary outcome in this trial was a composite of death from cardiovascular causes or a first hospitalization for heart failure. We analysed the effect of systolic blood pressure coefficient of variation (SBP-CoV) on the primary outcome, as well as the effect of SBP-CoV on the two components of this composite. We also examined whether the effect of eplerenone on these outcomes was modified by SBP-CoV.

Visit-to-visit blood pressure variation

Blood pressure was measured at each visit after 5 min of rest in the seated position by a trained observer using a validated oscillometric semi-automated blood pressure machine with the appropriate cuff size. During the site assessment visits, each site was confirmed to keep a certificate of calibration every 3-6 months and these were monitored during site visits. The clinic visits were timed to coincide with trough measurements. Three blood pressure measures were performed systematically and the average of these measures was recorded in the study dataset. Time interval between office visits was: screening, baseline, week 1, week 4, every three months for the first year and thereafter, every 4 months for the entire duration of the trial. Mean BP (systolic and diastolic) was calculated as the average of all post-baseline BP values up to and including first event or last BP measurement, whichever comes first. Only subjects with at least two visits and therefore two averaged (average of three measurements) systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were included in the analysis. Standard deviation (SD) was calculated for HF hospitalization, CV death, and HF hospitalization/CV death events separately and included the same measurements as for mean BP. BPV was calculated as SBP coefficient of variation, that is, the ratio of the SD to the mean ($SBP-CoV = SD/mean * 100\%$). The correlation between mean SBP and SBP SD was modest. There was almost no correlation between mean SBP and SBP coefficient of variation (SBP-CoV), and therefore, SBP-CoV was chosen for further analysis instead of SD being less dependent on the mean.

Statistical methods

Categorical data are presented as percentages, normally distributed continuous data as mean \pm SD, and non-normally distributed variables as median and interquartile range (IQR). Differences in means and

proportions amongst SBP-CoV tertiles were analysed with one-way ANOVA tests and chi-square test, respectively.

Univariate and multivariate Cox proportional hazard regression models were used to model time-to-event for primary and secondary outcomes. Multivariate models include the following selected covariates: treatment, gender, age, diabetes, haemoglobin, estimated glomerular filtration rate, systolic blood pressure, myocardial infarction, body mass index and heart rate. Proportional hazards assumptions for dependent variables were visually assessed by plotting the $\log[-\log(S(t))]$ function as a function of survival time (t), where S(t) represents the survival function. In the multivariate models, the adjustment covariates were chosen from demographic, clinical/pharmacological, and laboratory variables that were previously found to be clinically and prognostically relevant [18], with additional adjustment for treatment allocation (epplerenone or placebo). Estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19]. We assessed the prespecified SBP-CoV tertile by treatment interactions as well as SBP-CoV tertile by 3 SBP-category interactions in univariate and multivariate Cox models. The linearity assumption of the relationship between SBP-CoV and the log-hazard of outcome was assessed using restricted cubic splines with five knots equally spaced at the 0th, 25th, 50th, 75th and 100th percentiles according to the Harrell's rule [20]. The Wald test associated with the nonlinear component was statistically significant, and a nonlinear relationship was assumed regarding all the studied outcomes (p-value for linearity <0.001). A p-value less than 0.05 was considered as statistically significant. No adjustment for multiplicity of testing was performed providing this is a hypothesis-generating study. All analysis was performed with the SAS software (SAS Institute Inc., Cary, NC, USA).

Results

Demographics and Clinical Characteristics

Patients were divided into SBP-CoV tertiles as follows: tertile 1 (T1) $\leq 6.0\%$ (n=851), tertile 2 (T2) 6.1 – 9.0% (n=790), and tertile 3 (T3) $>9.0\%$ (n=908). There was a significant trend to a higher number of blood pressure measurements from the lower to the upper tertile (p<0.001 for trend). The baseline characteristics of the three groups were similar except for the frequency of an ischemic etiology and higher body mass index (BMI), in T1 compared to T2 and T3. Overall, the mean number of blood pressure measures available was

6.4±3.2. The mean SBP at baseline was similar across tertiles (124.5±15.2 vs 125.1±17.0 vs 123.5±17.9 for lower, middle and upper tertiles, respectively; p=0.15), whereas DBP was lowest in the upper tertile of SBP-CoV (75.6±9.7 vs 75.2±10.0 vs 73.8±10.9 T1, T2 and T3, respectively; p<0.001) (**Table 1**).

We also explored clinical outcomes dividing patients in SBP-CoV quintiles (quintile 1 (Q1) ≤4.5%, n=493; quintile 2 (Q2) 4.5 – 6.6%, n=500; quintile 3 (Q3) 6.7 – 8.5%, n=489; quintile 4 (Q4) 8.6 – 11%, n=502; and quintile 5 (Q5) >11%, n=476) and in tertiles of DBP coefficient of variation (DBP-CoV; tertile 1 (T1) ≤7.1%, n=826; tertile 2 (T2) 7.2 – 11.5%, n=824; and tertile 3 (T3) >11.5%, n=810).

Clinical Outcomes

SBP-CoV was independently associated with worse outcomes. In particular, lower SBP-CoV was associated with a higher rate of the composite of cardiovascular (CV) death or HF hospitalization (HFH) (adjusted HR (T1 vs T2) 2.01, 95%CI [1.62-2.51]) and HFH (adjusted HR (T1 vs T2) 1.78, 95%CI [1.36-2.32]) (**Table 2 & Fig. 1**). Both low and high SBP-CoV were associated with CV death: adjusted HR T1 vs T2 2.48 (95%CI 1.81-3.39) and adjusted HR T3 vs T2 1.68 (1.24-2.29) (**Table 2**). These results were consistent also exploring SBP variability SD (CV death and HFH adjusted HR (T1 vs T2) 2.43, 95%CI [1.97-3.01]; HFH adjusted HR (T1 vs T2) 2.25, 95%CI [1.75-2.90]; CV death adjusted HR T1 vs T2 2.43 (95%CI 1.83-3.24) and adjusted HR T3 vs T2 1.46 (1.09-1.95) (see **Table, Supplemental Digital Content 1**, that illustrates clinical outcomes in systolic blood pressure variability SD tertiles). To better depict the trend of the risk we also evaluated clinical outcomes in SBP-CoV quintiles. We showed an increase of risk for the composite of CV death or HFH (adjusted HR (Q1 vs Q3) 2.80, 95%CI [2.13-3.69]; adjusted HR (Q5 vs Q3) 1.49, 95%CI [1.12-1.99]) and CV death (adjusted HR (Q1 vs Q3) 3.33, 95%CI [2.40-4.81]; adjusted HR (Q5 vs Q3) 1.82, 95%CI [1.25-2.66]) in the lower and higher quintile, meanwhile only the lower quintile of SBP-CoV was associated with HFH (adjusted HR (Q1 vs Q3) 2.42, 95%CI [1.73-3.37]) (see **Table, Supplemental Digital Content 2**, that illustrates clinical outcomes in systolic blood pressure coefficient of variation quintiles). Finally, we determined the effect of DBP-CoV on outcomes. Lower DBP-CoV, but not higher, was associated with a higher rate of all studied outcomes (CV death and HFH adjusted HR (T1 vs T2) 1.51, 95%CI [1.23-1.86]; CV death adjusted HR (T1 vs T2) 1.43, 95%CI [1.08-1.89]; HFH adjusted HR (T1 vs T2) 1.55, 95%CI [1.20-2.01]) (see **Table, Supplemental Digital Content 3**, that illustrates clinical

outcomes in diastolic blood pressure coefficient of variation tertiles). Models adjusted for confounding factors and for randomized treatment gave similar findings (**Table 2** & see **Table, Supplemental Digital Content 4**, that illustrates the prognostic associations of systolic blood pressure coefficient of variation adjusted for confounding factors).

Univariate and multivariate sensitivity analyses that included patients with a minimum of three BP measures gave consistent findings (see **Table, Supplemental Digital Content 5**, that illustrates the prognostic associations of systolic blood pressure coefficient of variation in patients with 3 or more blood pressure measurements).

The relationship between SBP-CoV and outcomes was not modified by eplerenone (p value for interaction=0.482) or hypertensive status (p value for interaction=0.484) (see **Table, Supplemental Digital Content 6**, that illustrates the interaction of systolic blood pressure coefficient of variation against other factors). The effect of eplerenone was consistent across all SBP-CoV tertiles (**Table 2**).

SBP-CoV and mean SBP interaction

SBP modified the relationship between SBP-CoV and the primary outcome (p for interaction = 0.049) and, particularly, HF hospitalization (p for interaction = 0.018) (**Fig. 2** & see **Table, Supplemental Digital Content 6**, that illustrates the interaction of systolic blood pressure coefficient of variation against other factors). The worse outcomes associated with both low and high SBP-CoV were accentuated in people with a low (<110 mmHg) and high (>140 mmHg) mean SBP, compared to an SBP between 110 and 140 mmHg (“intermediate”) (see **Table, Supplemental Digital Content 7**, that illustrates the prognostic associations between tertiles of mean systolic blood pressure and systolic blood pressure coefficient of variation).

Discussion

In HFrEF patients in EMPHASIS-HF, low SBP-CoV was associated with worse outcomes, whereas high SBP-CoV was associated with higher rate of cardiovascular death only. It also seemed that low and high SBP-CoV had stronger prognostic implications in the context of low and high SBP, with less of an “effect” of SBP-CoV when the SBP was within the range of 110 to 140 mmHg. SBP-CoV did not modify the favourable impact of eplerenone on outcomes.

Our findings differ from many prior investigations of SBP-CoV in other disease states where the majority of the studies reported a higher risk of adverse outcomes with higher rather than lower SBP-CoV [1]. Focusing specifically on HF, Rossignol and colleagues [9] also showed that higher visit-to-visit systolic BPV was associated with worse outcomes in the 3834 patients with HFrEF in HEAAL. On the other hand, in 6505 HFrEF patients in SHIFT [16], lower SBP-CoV was associated with higher event rates, in keeping in with the present findings in EMPHASIS-HF.

Although explanations have been suggested for an association between high SBP-CoV and worse outcomes [15], the potential mechanisms underlying the association between low SBP-CoV and poor outcomes are still debated. In HFrEF low SBP-CoV may be related to classical factors involved in BP control as reduced cardiac output and myocardial contractile reserve, but also to intrinsic factors such as a blunted baroreflex sensibility [21], impaired autonomic nervous system integrity [22] and altered circadian hormonal secretion [23]. Collectively, the dysregulation of these pathways may identify sicker patients at higher risk of adverse events.

In the EMPHASIS-HF [17] eplerenone significantly reduced the risk of the primary outcome (composite of death from cardiovascular causes or HF hospitalization) by 37%. Although the mechanisms through which mineralocorticoid receptor antagonists are thought to provide cardiovascular protection, such as reduction in cardiac fibrosis and neurohormonal activation [24,25], might also affect BPV, we found that eplerenone did not affect SBP-CoV and that effect of eplerenone was consistent across SBP-CoV tertiles.

Similarly, in the SHIFT trial [16], a statistical interaction was found between mean SBP and SBP-CoV with regards to the primary outcome and HF hospitalization. While the effect modification was slight, low SBP-CoV was more likely to be associated with adverse outcomes in patients with both low and high SBP, while the SBP within the "normal" range showed less relevance, consistent with our findings. This "interaction" may be potentially attributable to two linked mechanisms: on the one hand, hypertension is a well-known risk factor for worse cardiovascular outcomes in most populations whereas, on the other, pump failure and poor contractile reserve may lead to a low SBP in the setting of left ventricular systolic dysfunction. This U-shaped relationship appeared to influence mainly HF hospitalizations that may be more susceptible to variations in blood pressure. In the EPHEBUS trial [26] patients were enrolled early after myocardial infarction (3 to 14 days after the index event) and SBP-CoV was also associated with outcomes

in a U-shaped manner, but without interaction with SBP. The different settings and populations may explain these slightly different findings.

As with SBP-CoV, patients in the lowest third of DBP-CoV had the highest risk [1]. Noteworthy, a previous study conducted in a large HFrEF population showed that patients in the lower tertile of DBP-CoV had the worse outcome [16], confirming our findings. This association is likely driven by similar pathophysiological mechanisms as above discussed for SBP-CoV.

Limitations

Some limitations of the present analysis should be acknowledged. Firstly, our analysis was *post-hoc* and exploratory. However, data were derived from a large randomized controlled trial, providing sufficient statistical power for reliable analysis of the relationships between SBP-CoV and risk. Second, our results were obtained in patients with HFrEF and mild symptoms and generalization to other patients with HF is not possible. Third, the mechanisms underlying the relationship between SBP-CoV and outcomes (especially for the association between low SBP-CoV and worse outcomes) are not completely understood and further studies are required. Fourth, a threshold systolic blood pressure value was used to determine entry into the trial, which may have influenced SBP-CoV of some extent [27]. Fifth, because of the multicentric design of the study that encompassed end-points not primarily focused on blood pressure measurement, different devices for blood pressure measurement were used. Notwithstanding, all BP measurements were made using validated semi-automated blood pressure machines with calibration records monitored during every clinical research monitoring visit. Moreover, having different devices reduces the probability of a systematic error to occur, reinforcing the validity of our associations i.e. they were not affected by random fluctuations in the measurements. Finally, these findings are hypothesis generating only, as interactions tests are statistically weak and these tests were not adjusted for multiplicity.

Conclusion

In our cohort of HFrEF patients with mild symptoms both a low and high SBP-CoV and low DBP-CoV were associated with worse outcomes. SBP-CoV did not modify the effect of eplerenone and eplerenone did not modify SBP-CoV. Further studies are warranted to clarify the role of BPV in HF.

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Legends for illustrations

FIGURE 1. “Spline” graphical representation of the prognostic implications of systolic blood pressure coefficient of variation (SBP-CoV). Blue line: hazard ratio; dashed lines: 95% confidence interval.

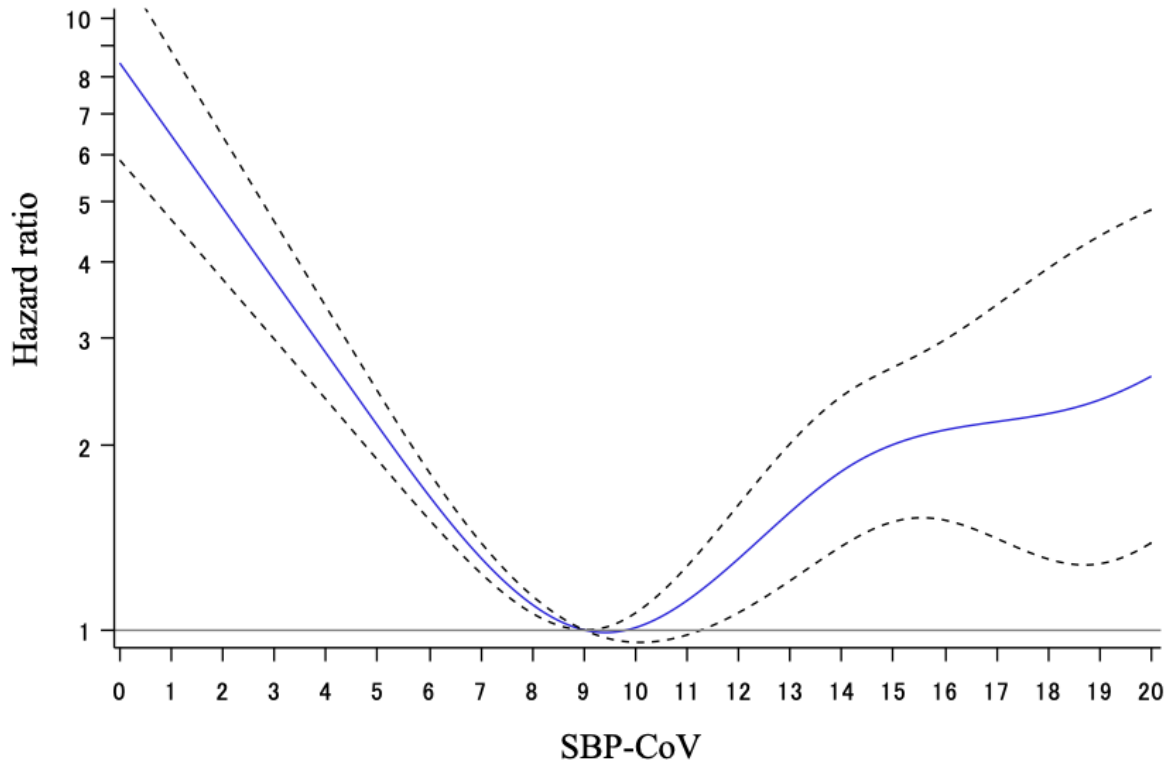
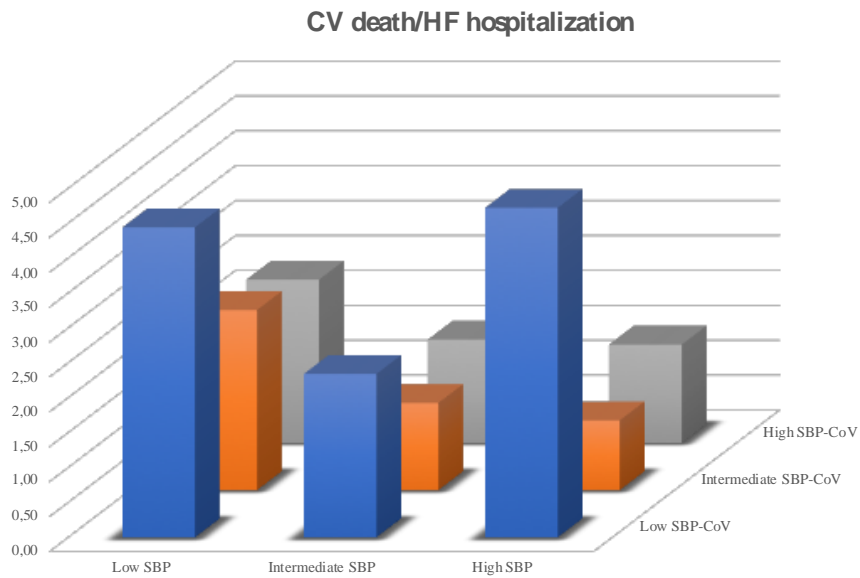
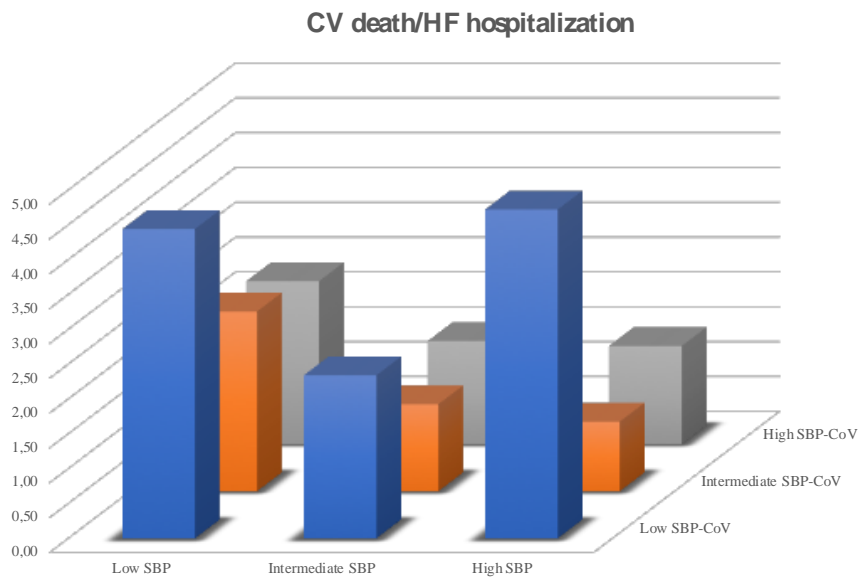


FIGURE 2. Interaction between mean systolic blood pressure (SBP) and systolic blood pressure coefficient of variation (SBP-CoV) for (A) the primary endpoint of cardiovascular death or heart failure hospitalization, (B) heart failure (HF) hospitalization, and (C) cardiovascular (CV) mortality.

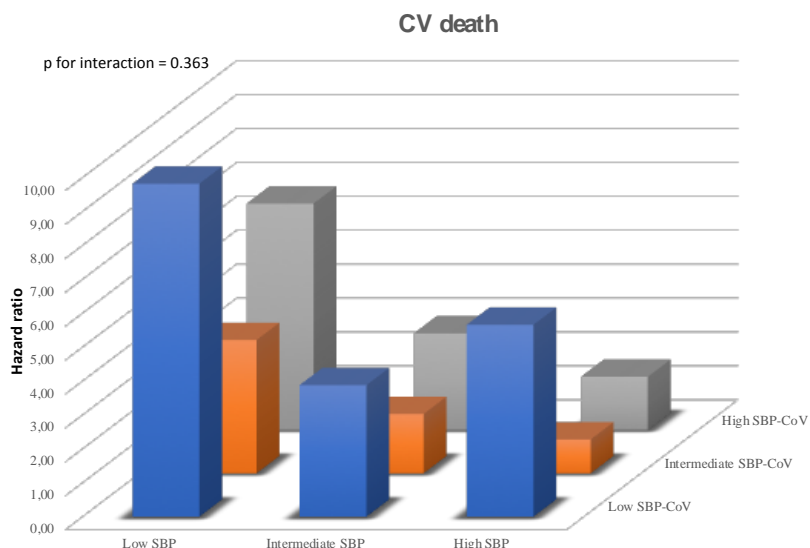
A



B



C



List of Supplemental Digital Content

Supplemental Digital Content 1. Table that illustrates clinical outcomes in systolic blood pressure variability SD tertiles. docx

Supplemental Digital Content 2. Table that illustrates clinical outcomes in systolic blood pressure coefficient of variation quintiles. docx

Supplemental Digital Content 3. Table that illustrates clinical outcomes in diastolic blood pressure coefficient of variation tertiles. docx

Supplemental Digital Content 4. Table that illustrates the prognostic associations of systolic blood pressure coefficient of variation adjusted for confounding factors. docx

Supplemental Digital Content 5. Table that illustrates the prognostic associations of systolic blood pressure coefficient of variation in patients with 3 or more blood pressure measurements. docx

Supplemental Digital Content 6. Table that illustrates the interaction of systolic blood pressure coefficient of variation against other factors. docx

Supplemental Digital Content 7. Table that illustrates the prognostic associations between tertiles of mean systolic blood pressure and systolic blood pressure coefficient of variation. docx

TABLE 1. Population characteristics by systolic blood pressure coefficient of variation tertiles

Characteristics	Global population (N=2.549)	T1: $\leq 6.0\%$ (N=851)	T2: 6.1-9.0% (N=790)	T3: $>9.0\%$ (N=908)	p-value
Age, years	68.6 \pm 7.6	68.4 \pm 7.8	68.5 \pm 7.5	69.0 \pm 7.6	0.170
Male, n (%)	1988 (78)	662 (77.8)	619 (78.4)	707 (77.9)	0.956
Hypertension, n (%)	1697 (66.6)	586 (68.9)	523 (66.2)	588 (64.8)	0.183
Diabetes, n (%)	778 (30.5)	265 (31.1)	231 (29.2)	282 (31.1)	0.642
AFib, n (%)	792 (31.1)	269 (31.6)	263 (33.3)	260 (28.6)	0.108
PVD, n (%)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0.574
COPD, n (%)	355 (13.9)	124 (14.6)	99 (12.5)	132 (14.5)	0.394
Smoker, n (%)	260 (10.2)	82 (9.6)	85 (10.8)	93 (10.2)	0.578
Previous MI, n (%)	1275 (50.0)	470 (55.2)	400 (50.6)	405 (44.6)	<0.001
Ischemic HF, n (%)	1752 (68.8)	642 (75.5)	550 (69.6)	560 (61.8)	<0.001
Hemoglobin, g/dL	13.8 \pm 1.6	13.8 \pm 1.6	13.9 \pm 1.5	13.8 \pm 1.5	0.063
BMI, Kg/m ²	27.6 \pm 4.8	27.8 \pm 4.8	27.7 \pm 4.8	27.3 \pm 4.9	0.048
SBP, mmHg	124.3 \pm 16.8	124.5 \pm 15.2	125.1 \pm 17.0	123.5 \pm 17.9	0.153
DBP, mmHg	74.8 \pm 10.2	75.6 \pm 9.7	75.2 \pm 10.0	73.8 \pm 10.9	<0.001
Heart rate, bpm	73.3 \pm 15.5	73.0 \pm 15.2	73.3 \pm 15.3	73.5 \pm 15.9	0.778
Thiazides, n (%)	267 (10.5)	103 (12.1)	71 (9.0)	93 (10.2)	0.115
SBP variability coef., %	7.9 \pm 4.1	3.8 \pm 1.7	7.4 \pm 0.8	12.2 \pm 3.0	<0.001
SBP measures, n	6.4 \pm 3.2	5.4 \pm 3.1	6.9 \pm 3.0	6.8 \pm 3.1	<0.001
Eplerenone allocation, n (%)	1284 (50.4)	413 (48.5)	399 (50.5)	472 (52.0)	0.350

List of abbreviations: AFib, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; T, tertiles.

T1, low SBP variability; T2, intermediate SBP variability; T3, high SBP variability.

TABLE 2. Prognostic associations of systolic blood pressure coefficient of variation (SBP-CoV)

Outcome	SBP-CoV tertiles	Unadjusted HR (95CI%)	p-value	Adjusted HR (95CI%)*	p-value	Adjusted HR (95CI%)†	p-value
CV death/HF hosp.‡	Low ($\leq 6.0\%$)	1.98 (1.60;2.46)	<0.001	2.01 (1.62;2.51)	<0.001	1.97 (1.58;2.44)	<0.001
	Intermediate (ref.)	1	-	1	-	1	-
	High ($>9.0\%$)	1.22 (0.98;1.53)	0.077	1.13 (0.90;1.42)	0.283	1.21 (0.97;1.52)	0.090
CV death§	Low ($\leq 6.0\%$)	2.29 (1.69;3.11)	<0.001	2.48 (1.81;3.39)	<0.001	2.03 (1.42;2.90)	<0.001
	Intermediate (ref.)	1	-	1	-	1	-
	High ($>9.0\%$)	1.71 (1.27;2.31)	<0.001	1.68 (1.24;2.29)	<0.001	2.27 (1.67;3.08)	<0.001
HF hosp.#	Low ($\leq 6.0\%$)	1.76 (1.36;2.29)	<0.001	1.78 (1.36;2.32)	<0.001	1.75 (1.35;2.27)	<0.001
	Intermediate (ref.)	1	-	1	-	1	-
	High ($>9.0\%$)	1.13 (0.87;1.48)	0.364	1.04 (0.79;1.36)	0.793	1.12 (0.86;1.46)	0.404

List of abbreviations: CV, cardiovascular; HF, heart failure.

*model adjusted on: gender, age, diabetes, hemoglobin, estimated glomerular filtration rate, systolic blood pressure, myocardial infarction, body mass index, heart rate and HF medications.

†model adjusted on gender, age, diabetes, hemoglobin, estimated glomerular filtration rate, systolic blood pressure,

myocardial infarction, body mass index, heart rate, HF medications and treatment arm.

p-value for interaction of SBP-CoV tertiles by treatment: ‡unadjusted = 0.482; adjusted = 0.340; §unadjusted = 0.645; adjusted = 0.854; #unadjusted = 0.085; adjusted = 0.103