Visit-to-Visit Blood Pressure Variation is Associated with Outcomes in a U-shaped fashion in patients with Myocardial Infarction complicated with Systolic Dysfunction and/or Heart Failure: findings from the EPHESUS and OPTIMAAL trials

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Abstract

Background: Visit-to-visit office blood pressure variation (BPV) has prognostic implications independent from mean BP across several populations in the cardiovascular field. The association of BPV with outcomes in patients with myocardial infarction (MI) with systolic dysfunction and/or heart failure (HF) is yet to be determined.

Methods: Two independent cohorts were assessed: the EPHESUS and the OPTIMAAL trials with a total of >12,000 patients. The primary outcome was all-cause death. BPV was calculated as a coefficient of variation, i.e. the ratio of the standard-deviation to the mean BP along the post-baseline follow-up. Cox regression models were used to determine the associations between BPV and events.

Results: Compared to the middle and lower BPV tertiles, patients in the upper BPV tertile were older, more often female, hypertensive, diabetic, with peripheral artery disease, and had more frequent use of loop diuretics and ACEi/ARBs. They also had lower LVEF, hemoglobin, and eGFR (all $p<0.001$). BPV was independently associated with worse prognosis in a U-shaped manner. In the EPHESUS trial, both low and high BPV were associated with higher rates of death (and also CV death and the composite of CV death/CV hospitalization): adjusted HR (95%CI) for the outcome of death=1.99 (1.68-2.36) for high BPV and =1.60 (1.35-1.90) for low BPV. Similar results were observed in the OPTIMAAL trial population.

Conclusion: In two independent cohorts of MI patients with systolic dysfunction and/or HF, BPV was associated with worse prognosis in a U-shaped manner independently of the mean BP.

Key-words: visit to visit blood pressure variability; outcomes; myocardial infarction; heart failure.

Introduction

Visit-to-visit office blood pressure variability (BPV) has prognostic implications independent of mean blood pressure (BP) across several populations in the cardiovascular field[1-6]. High BPV may be related to one or more of autonomic dysfunction, arteriosclerosis, increased sympathetic tone, arterial stiffness, some blood pressure-lowering agents and treatment non-adherence[7-13].

Most studies have reported an association between high office systolic BPV and worse prognosis in the general population and in patients with hypertension[3]. However, in heart failure patients with reduced ejection fraction (HF-REF) the results have been inconsistent[4, 13]. For example, in subanalysis derived from the Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure trial (HEAAL), a high BPV was found to be associated with poorer cardiovascular (CV) outcomes[13]. On the other hand, in the Ivabradine and outcomes in chronic heart failure trial (SHIFT) was the low BPV that was associated with worse outcomes[4].

To the best of our knowledge, the association between office BPV and outcomes in patients with myocardial infarction (MI) complicated by left ventricular systolic dysfunction and/or HF setting have not been reported before and were therefore examined in the present study.

Methods

Study population

The derivation cohort was patients enrolled in the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[14, 15]. The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) was used for validation[16, 17]. Full details of the design and results of each trial are published[14, 17]. In short, both trials enrolled patients with left ventricular systolic dysfunction, HF or both between 12 h and 14 days after acute MI.

The studies were all conducted in accordance with the Declaration of Helsinki and approved by site ethics committees. All participants gave written informed consent to participate in the trials.

Outcomes

The primary outcome in both trials was all-cause death (with a coprimary endpoint of CV death or CV hospitalization in EPHESUS). We analyzed the association between BPV and the primary outcome of death in both EPHESUS and OPTIMAAL, exploring the association of BPV with CV death and CV hospitalization in the EPHESUS trial.

Visit-to-visit blood pressure variation

Blood pressure was measured in each trial at each visit after 5 min of rest in the seated position by a trained observer using an automated oscillometric monitor. Three measures were performed systematically and the mean of the 3 measures was calculated and inserted in the dataset. BPV was previously shown to be reproducible and applicable in clinical practice[18]. 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 with stable chronic cardiovascular disease[19]. Mean BP was calculated using measurements at each follow-up visit. BPV was calculated as a coefficient of variation, that is, the ratio of the standard deviation (SD) to the mean (CV=SD/mean*100%). Measurements from all follow-up visits were included. Altogether, a mean±SD of 7.7±2.7 visits (range, 2–14) were available in EPHESUS and 8.8±3.0 (range, 2-12) in OPTIMAAL.

Statistical methods

Continuous variables were expressed as mean±SD and categorical variables as frequencies and proportions. For comparison of means and proportions, one-way ANOVA test and chi-square test were used, respectively.

Factors associated with BPV (tertiles) were first identified using univariate followed by multivariable stepwise backward conditional multinomial logistic regression using the intermediate BPV category as reference. The covariates inserted in the models were identified among patient characteristics listed in Table 1 with a p-value <0.1. Linearity was assessed by plotting the β-estimates vs. mean by quintiles of the studied independent variable. Variables were then categorized in order to obtain log-linearity. Multinomial logistic regression data are presented as odds ratios (OR) and respective 95% confidence intervals (95%CI).

Cox proportional hazard regression models were used to model long-term survival as a function of the formulas both in univariable and multivariable analysis. 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 multivariable models, the adjustment covariates were chosen from demographic (age and gender), clinical/pharmacological (mean systolic blood pressure, heart rate, history of diabetes mellitus, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, left ventricular ejection fraction, diuretics, ACEi/ARB, and beta-blockers use, and also eplerenone allocation), and laboratory variables (hemoglobin, sodium, and estimated glomerular filtration rate calculated by the CKD-EPI equation[20]) that were previously found to be clinically relevant[21]. Additional adjustment in smoking status, alcohol consumption, mean heart rate and heart rate variability was also performed. These variables had a small proportion of missing values (<10%) and no multiple imputation was performed. We assessed interactions with the *Log* of time, age, sex, mean systolic blood pressure, heart rate, pulse pressure and eplerenone

allocation and none were significant (all p >0.10). The correlation between BPV, blood pressure SD, mean blood pressure and pulse pressure are presented in the results section. Whenever the correlation between two variables was >0.5 only one of them was inserted in the multivariable models due to colinearity issues.

The linearity assumption of the relationship between BPV and the log-hazard of outcome was assessed using restricted cubic splines with 3 knots equally spaced at the 10th, 50th and 90th percentiles according to the Harrell´s rule[22]. 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). **Supplemental Figure 1 & 2**.

A p-value <0.05 was considered as statistically significant.

All analysis was performed with the R® software. R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/.

Results

Baseline characteristics

The BPV tertiles were: ≤7.7 % (n=2180), 7.8-10.9 % (n=2163) and >10.9 % (n=2164). The absolute number of BP evaluations was similar across each tertile (n≈8). The mean systolic BP at baseline in each tertile was: 119.8 ± 14.5, 119.4 ± 16.0 and 118.2 ± 18.5 mmHg, respectively (p=0.004). For diastolic BP the respective values were 73.4 ± 10.0, 72.4 ± 10.4 and 70.6 ± 11.3 mmHg (<0.0001). Compared to those in the middle and lower BPV tertiles, patients in the upper BPV tertile in EPHESUS were older and more often female, but less often Caucasian. They more commonly had hypertension, diabetes, peripheral artery disease, and chronic obstructive pulmonary disease; they were more often treated with loop diuretics and ACEi/ARBs. Patients in the upper BPV tertile also had a lower mean left ventricular ejection fraction, hemoglobin, and estimated glomerular filtration rate (all p <0.001). Similar results were observed in the OPTIMAAL trial. **Table 1 & Supplemental Table 1**.

The integer (%) of BPV tertiles was also similar between the EPHESUS and OPTIMAAL trials (low ≤8% in EPHESUS vs. ≤9% in OPTIMAAL and high ≥11% for both). **Table 1 & Supplemental Table 1**.

Logistic regression analysis to determine the factors associated with BP variability

In the EPHESUS multivariable logistic regression analysis, lower BPV was independently and positively associated with Caucasian race (OR, 95%CI=1.37, 1.10-1.69) and pulse pressure <40 mmHg (OR, 95%CI=1.37, 1.17-1.61), and negatively associated with diabetes (OR, 95%CI=0.87, 0.76-0.99), peripheral vascular disease (OR, 95%CI=0.72, 0.60-0.88), SBP <120 mmHg (OR, 95%CI=0.84, 0.73-0.96) and use of ACEi/ARBs (OR,

95%CI=0.77, 0.65-0.91). On the other hand, higher BPV was independently and positively associated with age >70 years (OR, 95%CI=1.21, 1.05-1.39), SBP <120 mmHg (OR, 95%CI=1.24, 1.09-1.42), eGFR <60 ml/min/1.73m^2 (OR, 95%CI=1.19, 1.04-1.37) and use of ACEi/ARBs (OR, 95%CI=1.35, 1.12-1.63), and negatively associated with male gender (OR, 95%CI=0.80, 0.70-0.92) and pulse pressure <40 mmHg (OR, 95%CI=0.74, 0.62-0.87). The middle BPV tertile (i.e. intermediate BP variability) was used as the reference tertile. **Table 2**. In the OPTIMAAL trial data hypertension and estimated glomerular filtration rate <60 ml/min/1.73m^2 were also associated with high BPV. **Supplemental Table 2**.

Prognostic associations

BPV was independently associated with worse prognosis in a U-shaped manner. In EPHESUS, both low and high BPV were associated with higher event rates of death, CV death and the composite of CV death or CV hospitalization: adjusted HR (95% CI) for the outcome of death =1.99 (1.68-2.36) for low BPV and 1.60 (1.35-1.90) for high BPV. Similar results were observed for the other studied outcomes (CV death and CV death or CV hospitalization). Overlapping replication was found in the OPTIMAAL trial. **Table 3, Figure 1 & Supplemental Table 3**. A sensitivity analysis including patients with a minimum of 3 visits plus further adjustment on smoking status and alcohol consumption was also performed, providing overlapping results to those above described. **Supplemental Table 4**. Additional adjustment on the mean heart rate and its variability did not change the associations and no statistical interaction was present. **Supplemental Table 5**.

Data consistency

For simplification of the manuscript the data shown herein refer to systolic BPV, referred to as BPV throughout the text. The results for diastolic BPV were similar to those of systolic BPV. **Supplemental Figure 3**. Systolic and diastolic BPV were moderately correlated (Pearson correlation=0.51, p<0.0001).

The correlation between the SD and the coefficient of variation of both systolic and diastolic BPV was strong (Pearson correlation=0.97 for both) and provided overlapping results.

Systolic BPV was weakly correlated with mean SBP and mean pulse pressure (Pearson correlation <0.20). The prognostic associations of BPV were independent from the mean BP and pulse pressure.

Discussion

Among MI patients with systolic dysfunction and/or HF, those with low BPV differed substantially from those with high BPV with respect to their baseline characteristics. Despite these baseline differences, BPV was independently associated with worse prognosis in a U-shaped manner i.e. both low and high BPV were independently associated with higher event

rates compared to the rates observed in patients with intermediate BPV. These findings were replicated in two independent MI cohorts and provide novel information about BPV in this population.

The mean BPV (≈9%) observed in these MI patients with systolic dysfunction and/or HF was similar to that described for other high CV-risk populations such as heart failure with HF-REF, hypertension, stroke, coronary artery disease, and receiving hemodialysis[5, 13, 23, 24]. However, in these other populations a high BPV was consistently associated with worse prognosis. The only exception was in SHIFT, where in patients with HF-REF a low BPV was associated with higher event rates (compared to patients with intermediate and high BPV tertiles) with a significant statistical interaction between BPV and mean systolic BP whereby those at highest risk were in the subgroup with the lowest third of mean SBP and lowest third of BPV[4]. However, the mechanisms underpinning this association of low BPV with adverse outcomes in SHIFT are unknown[4]. One potential explanation might relate to the association between low BPV and low pulse pressure in EPHESUS (although not in OPTIMAAL). In patients with acute MI and/or HF-REF, low pulse pressure may reflect low stroke volume, and in these populations a lower pulse pressure is associated with worse outcomes[25-27]. Consequently, in EPHESUS, low BPV, might also reflect a lower stroke volume. However, this remains uncertain as the U-shaped association of V BPV was independent of the pulse pressure and no statistical interaction was observed.

The association of high BPV with higher morbidity and mortality reported in several patient-populations has been attributed to modifications on the factors influencing regional circulation and blood pressure[10-13]. In EPHESUS, high BPV was positively associated with older age, renal dysfunction, low systolic blood pressure, and higher use of ACEi/ARBs. In hypertensive populations, the use of ACEi/ARBs (and beta-blockers) was also found to be associated with increased BPV compared to calcium-channel blockers and non-loop diuretics[9]. Nonetheless, the clinical relevance of these findings is yet to be determined and warrants prospective assessment[9].

To the best of our knowledge, this is the first report of a U-shaped BPV association with outcomes in MI populations with systolic dysfunction and/or HF. The similar number of measures across the BPV spectrum plus the independence and replication of these results in two independent cohorts make these findings robust[24].

Currently there are multiple evidence-based life-saving therapies for patients with the characteristics of those described herein[28, 29]. Specifically targeting BPV in this population seems unlikely because one would have to avoid both low and high BPV simultaneously. However, further studies are warranted to understand the underlying mechanisms that link low BPV to increased morbidity and mortality rates.

Limitations

Several limitations in our study should be noticed. First, this is a post-hoc analysis of two randomized controlled trials, therefore the limitations inherent to observational studies are present in our report and no causality can be established. Second, the differences reported between BPV groups are likely due to between-group differences in patients` characteristics, rather than to on-treatment differences. Third, adherence to treatment along the trial is not reported in the dataset, however, in randomized trials patients' high motivation and close follow-up make overall adherence uncharacteristically high as compared to population-based studies. Fourth, these trials did not target hypertension, hence there was no predefined BP intervention at baseline which may have influenced BPV. Moreover, we also did not observe a treatment allocation interaction. Fifth, the EPHESUS and OPTIMAAL trials had different inclusion criteria. While EPHESUS required a LVEF≤40%, OPTIMAAL included patients with a LVEF≤35% or a left-ventricular end-diastolic dimension ≥65 mm and/or a new Q-wave anterior-wall acute myocardial infarction, or any reinfarction with previous pathological Q-waves in the anterior wall. These differences between the studies may account for the observed discrepancies in the factors associated with BPV. However, they reinforce the external validity of our results in complicated MI populations. Lastly, the mechanisms underlying BPV are not completely understood (especially for the association of low BPV with worse prognosis) and further studies are required. Specifically, high sympathetic activity could be associated with low BPV and portend adverse prognosis. However, we do not have sympathetic activity indexes available in the datasets.

Conclusion

In MI patients with systolic dysfunction and/or HF, BPV is associated with worse prognosis in a U-shaped fashion independently of the mean BP. Further studies are warranted to understand the underlying mechanisms related to BPV.

Conflicts of interest

The authors declare no conflicts of interest with regard to the present report.

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Table 1. EPHESUS: Population characteristics by blood pressure variability tertiles

Characteristics	N.	Global pop.	T1: ≤7.7 % (N=2180)	T2: 7.8-10.9 % (N=2163)	T3: >10.9 % (N=2164)	p-value
Age, years	6632	64.0 ± 11.5	62.5 ± 11.8	63.7 ± 11.1	65.5 ± 11.4	<0.0001
Male, n (%)	6632	4714 (71.1 %)	1617 (74.2 %)	1575 (72.8 %)	1434 (66.3 %)	<0.0001
Caucasian, n (%)	6632	5984 (90.2 %)	2009 (92.2 %)	1946 (90.0 %)	1923 (88.9 %)	0.0009
Hypertension, n (%)	6632	4007 (60.4 %)	1239 (56.8 %)	1317 (60.9 %)	1375 (63.5 %)	<0.0001
Diabetes, n (%)	6632	2142 (32.3 %)	626 (28.7 %)	717 (33.1 %)	757 (35.0 %)	<0.0001
AFib, n (%)	6632	874 (13.2 %)	259 (11.9 %)	301 (13.9 %)	284 (13.1 %)	0.13
PVD, n (%)	6632	823 (12.4 %)	216 (9.9 %)	292 (13.5 %)	298 (13.8 %)	<0.0001
COPD, n (%)	6632	625 (9.4 %)	187 (8.6 %)	189 (8.7 %)	233 (10.8 %)	0.022
Previous MI, n (%)	6632	1802 (27.2 %)	593 (27.2 %)	562 (26.0 %)	611 (28.2 %)	0.25
HF history, n (%)	6632	975 (14.7 %)	328 (15.0 %)	291 (13.5 %)	337 (15.6 %)	0.12
LVEF, %	6617	33.1 ± 6.1	33.5 ± 6.0	33.1 ± 6.0	32.8 ± 6.1	0.002
Hemoglobin, g/dL	6556	13.3 ± 1.7	13.4 ± 1.7	13.3 ± 1.7	13.2 ± 1.7	<0.0001
Sodium, mmol/L	6587	139.4 ± 4.4	139.7 ± 4.8	139.4 ± 4.1	139.3 ± 4.2	0.014
Potassium, mmol/L	6586	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	0.047
eGFR, ml/min/1.73m^2	6587	68.4 ± 20.9	69.8 ± 20.4	69.3 ± 21.0	66.2 ± 21.0	<0.0001
BMI, Kg/m^2	6611	27.4 ± 4.5	27.4 ± 4.5	27.4 ± 4.4	27.4 ± 4.7	0.81
SBP, mmHg	6630	119.1 ± 16.5	119.8 ± 14.5	119.4 ± 16.0	118.2 ± 18.5	0.004
DBP, mmHg	6630	72.1 ± 10.7	73.4 ± 10.0	72.4 ± 10.4	70.6 ± 11.3	<0.0001
Pulse pressure, mmHg	6630	48.9 ± 10.5	46.9 ± 9.3	48.8 ± 9.9	51.4 ± 11.3	<0.0001
Heart Rate, bpm	6628	74.7 ± 11.7	75.0 ± 11.3	74.6 ± 11.6	74.2 ± 12.1	0.078
Killip III/IV, n (%)	6507	1302 (19.8 %)	409 (18.9 %)	420 (19.6 %)	438 (20.4 %)	0.48
Loop diuretics, n (%)	6507	3661 (55.2 %)	1136 (52.1 %)	1152 (53.3 %)	1288 (59.5 %)	<0.0001
Thiazides, n (%)	6507	540 (8.1 %)	182 (8.3 %)	173 (8.0 %)	179 (8.3 %)	0.91
ACEi/ARBs, n (%)	6507	5751 (86.7 %)	1817 (83.3 %)	1883 (87.1 %)	1946 (89.9 %)	<0.0001
Beta-blockers, n (%)	6507	4961 (74.8 %)	1629 (74.7 %)	1614 (74.6 %)	1637 (75.6 %)	0.69
SBP variability coef., %	6507	9.8 ± 4.3	5.7 ± 1.7	9.3 ± 0.9	14.3 ± 3.8	<0.0001
N. SBP measures, n (%)	6632	7.7 ± 2.7	7.4 ± 2.7	8.3 ± 2.4	7.7 ± 2.6	<0.0001
Eplerenone allocation, n (%)	6632	3319 (50.0 %)	1117 (51.2 %)	1100 (50.9 %)	1043 (48.2 %)	0.093
Death, n (%)	6632	1032 (15.6 %)	360 (16.5 %)	220 (10.2 %)	366 (16.9 %)	<0.0001
CV death, n (%)	6632	890 (13.4 %)	321 (14.7 %)	186 (8.6 %)	299 (13.8 %)	<0.0001
CV death/CV hosp., n (%)	6632	1878 (28.3 %)	596 (27.3 %)	519 (24.0 %)	675 (31.2 %)	<0.0001

Legend: AFib, atrial fibrillation; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; HF, heart failure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CV, cardiovascular; T, tertiles.
T1, low SBP variability; T2, intermediate SBP variability; T3, high SBP variability.

Table 2. EPHESUS: Multinomial logistic regression to assess the factors associated with low and high blood pressure variability using intermediate variability as reference category

Variables	Low (≤7.7 %) vs. Intermediate (7.8-10.9 %)		High (>10.9 %) vs. Intermediate (7.8-10.9 %)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age >70 years	-	NS	1.205 (1.047-1.387)	0.010
Male gender (yes)	-	NS	0.803 (0.700-0.920)	0.002
Caucasian race (yes)	1.366 (1.103-1.692)	0.004	-	NS
Diabetes (yes)	0.865 (0.757-0.988)	0.033	-	NS
PVD (yes)	0.724 (0.598-0.878)	0.001	-	NS
SBP <120 mmHg	0.837 (0.732-0.956)	0.009	1.243 (1.087-1.420)	0.001
Pulse pressure <40 mmHg	1.373 (1.173-1.607)	<0.001	0.737 (0.622-0.874)	<0.001
eGFR <60 ml/min/1.73m^2	-	NS	1.191 (1.040-1.367)	0.012
ACEi/ARBs (yes)	0.769 (0.648-0.912)	0.003	1.350 (1.116-1.633)	0.002

Legend: PVD, peripheral vascular disease; SBP, systolic blood pressure at baseline; eGFR, estimated glomerular filtration rate at baseline; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers use at baseline.

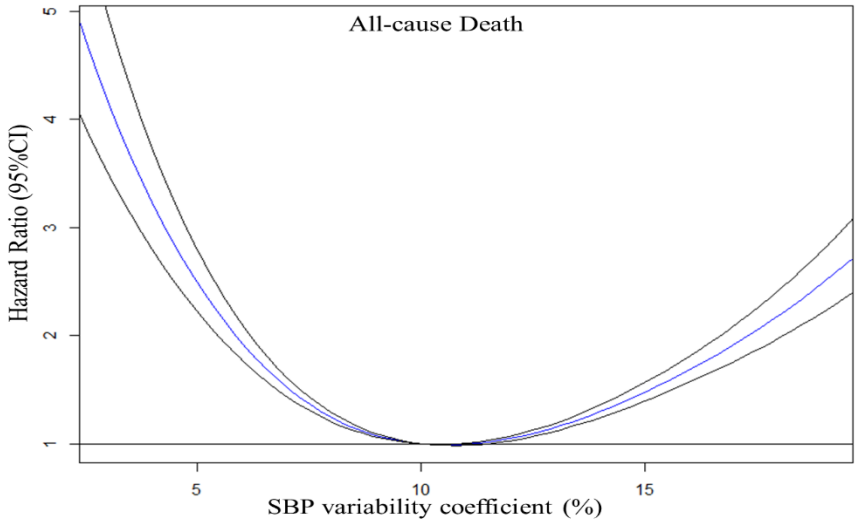
Low SBP variability: ≤7.7 %; Intermediate SBP variability: 7.8-10.9 %; High SBP variability: >10.9 %.

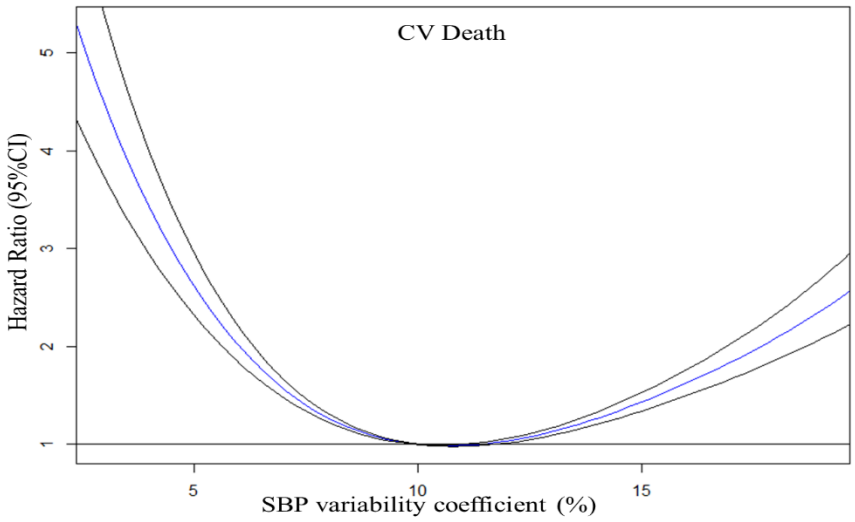
Table 3. EPHESUS: Prognostic associations of blood pressure variability

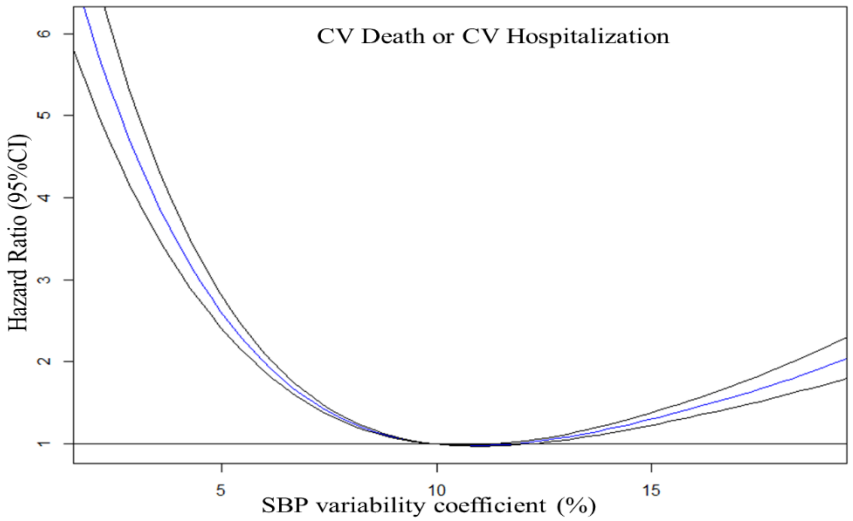
Outcome	SBP variability	Univariable: HR (95CI%)	p-value	Adjusted: HR (95CI%)*	p-value
Death	Low (≤7.7%)	1.781 (1.506-2.106)	<0.0001	1.989 (1.676-2.359)	<0.0001
	Intermediate (ref.)	1	-	1	-
	High (>10.9%)	1.745 (1.476-2.063)	<0.0001	1.602 (1.351-1.900)	<0.0001
CV death	Low (≤7.7%)	1.870 (1.561-2.241)	<0.0001	2.106 (1.751-2.532)	<0.0001
	Intermediate (ref.)	1	-	1	-
	High (>10.9%)	1.683 (1.401-2.021)	<0.0001	1.539 (1.276-1.855)	<0.0001
CV death/CV hosp.	Low (≤7.7%)	2.144 (1.894-2.427)	<0.0001	2.323 (2.048-2.634)	<0.0001
	Intermediate (ref.)	1	-	1	-
	High (>10.9%)	1.541 (1.353-1.754)	<0.0001	1.360 (1.192-1.552)	<0.0001

*model adjusted on age, sex, race, hypertension, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, left ventricular ejection fraction, hemoglobin, sodium, estimated glomerular filtration rate, systolic blood pressure, loop diuretics, ACEi/ARBs, beta-blockers, and eplerenone allocation.

Figure 1. “Spline” graphical representation of the prognostic implications of blood pressure variability







Legend: SBP, systolic blood pressure; CV, cardiovascular.

Model adjusted on age, sex, race, hypertension, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, left ventricular ejection fraction, hemoglobin, sodium, estimated glomerular filtration rate, systolic blood pressure, loop diuretics, ACEi/ARBs, beta-blockers, and eplerenone allocation.