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Visit-to-visit blood pressure variation and outcomes in heart failure with reduced ejection fraction: findings from the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms trial

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Background: Visit-to-visit office blood pressure (BP) 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 and the effect of eplerenone on BPV.

Methods and results: We evaluated the associations between BPV, calculated as SBP coefficient of variation ($SBP-CoV = SD/mean \times 100\%$), and the primary composite endpoint of cardiovascular mortality or heart failure hospitalization (HFH), and its components, in 2549 patients from the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms 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 HFH was almost double in the lower SBP-CoV tertile as compared with the intermediate tertile [adjusted hazard ratio: 2.01, 95% confidence interval (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 HFH ($P = 0.018$). 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.

Conclusion: In our patients with heart failure and reduced ejection fraction 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 heart failure.

ClinicalTrials.gov identifier: NCT00232180.

Keywords: heart failure, prognosis, SBP, visit-to-visit blood pressure variability

Abbreviations: BP, blood pressure; BPV, visit-to-visit office blood pressure variability; CoV, coefficient of variation; HFH, heart failure hospitalization; HFREF, heart failure with reduced ejection fraction

INTRODUCTION

Visit-to-visit office blood pressure (BP) variability (BPV) has been associated with several cardiovascular events [e.g. stroke, myocardial infarction (MI) 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 BP treatment, autonomic dysfunction and patient age [13–15].

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In a secondary analysis of the high-dose vs. low-dose losartan on clinical outcomes in patients with heart failure 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 MI and left ventricular (LV) 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].

To further characterize the association between visit-to-visit BPV and outcomes in heart failure with reduced ejection fraction (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 SBP 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

BP was measured at each visit after 5 min of rest in the seated position by a trained observer using a validated oscillometric semiautomated BP 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 BP 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 3 months for the first year and thereafter, every 4 months for the entire duration of the trial. Mean BP (SBP and DBP) was calculated as the average of all postbaseline BP values up to and including first event or last BP measurement, whichever comes first. Only patients with at least two visits and therefore two averaged (average of three measurements) SBP and DBP values were included in the analysis. SD was calculated for heart failure hospitalization (HFH),

cardiovascular death, and HFH/cardiovascular death events separately and included the same measurements as for mean BP. BPV was calculated as SBP-CoV, that is, the ratio of the SD to the mean ($\text{SBP-CoV} = \text{SD}/\text{mean} \times 100\%$). The correlation between mean SBP and SBP SD was modest. There was almost no correlation between mean SBP and 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. 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, sex, age, diabetes, haemoglobin, estimated glomerular filtration rate, SBP, MI, BMI 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 (eplerenone or placebo). Estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation [19]. We assessed the prespecified SBP-CoV tertile by treatment interactions as well as SBP-CoV tertile by three 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, North Carolina, USA).

RESULTS

Demographics and clinical characteristics

Patients were divided into SBP-CoV tertiles as follows: tertile 1 (T1) of 6.0% or less ($n = 851$), tertile 2 (T2) 6.1–9.0% ($n = 790$) and tertile 3 (T3) more than 9.0% ($n = 908$). There was a significant trend to a higher number of BP 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 cause and higher BMI, in T1 compared with T2 and T3. Overall, the mean number of BP measures available was

TABLE 1. Population characteristics by SBP coefficient of variation tertiles

Characteristics	Global population, N = 2,549	T1: ≤6.0%, N = 851	T2: 6.1–9.0%, N = 790	T3: >9.0%, N = 908	P value
Age (years)	68.6 ± 7.6	68.4 ± 7.8	68.5 ± 7.5	69.0 ± 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
Haemoglobin (g/dl)	13.8 ± 1.6	13.8 ± 1.6	13.9 ± 1.5	13.8 ± 1.5	0.063
BMI (kg/m ²)	27.6 ± 4.8	27.8 ± 4.8	27.7 ± 4.8	27.3 ± 4.9	0.048
SBP (mmHg)	124.3 ± 16.8	124.5 ± 15.2	125.1 ± 17.0	123.5 ± 17.9	0.153
DBP (mmHg)	74.8 ± 10.2	75.6 ± 9.7	75.2 ± 10.0	73.8 ± 10.9	<0.001
Heart rate (bpm)	73.3 ± 15.5	73.0 ± 15.2	73.3 ± 15.3	73.5 ± 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 ± 4.1	3.8 ± 1.7	7.4 ± 0.8	12.2 ± 3.0	<0.001
SBP measures, n	6.4 ± 3.2	5.4 ± 3.1	6.9 ± 3.0	6.8 ± 3.1	<0.001
Eplerenone allocation, n (%)	1284 (50.4)	413 (48.5)	399 (50.5)	472 (52.0)	0.350

AFib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; T, tertiles; T1, low SBP variability; T2, intermediate SBP variability; T3, high SBP variability.

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 death or HFH [adjusted hazard ratio (HR) (T1 vs. T2) 2.01, 95% confidence

interval (CI) (1.62–2.51)] and HFH [adjusted HR (T1 vs. T2) 1.78, 95% CI (1.36–2.32)] (Table 2 and Fig. 1). Both low and high SBP-CoV were associated with cardiovascular 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 [cardiovascular 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); cardiovascular 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) (refer to Table, Supplemental Digital Content 1, <http://links.lww.com/HJH/B155>, that illustrates clinical outcomes in SBP 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 cardiovascular 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 cardiovascular death [adjusted HR (Q1 vs. Q3) 3.33, 95% CI (2.40–4.81) adjusted HR (Q5 vs. Q3)

TABLE 2. Prognostic associations of SBP coefficient of variation

Outcome	SBP-CoV tertiles	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI) ^a	P value	Adjusted HR (95% CI) ^b	P value
CV death/HF hosp. ^c	Low (≤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 ^d	Low (≤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. ^e	Low (≤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

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SBP-CoV, SBP coefficient of variation.

^aModel adjusted on sex, age, diabetes, haemoglobin, estimated glomerular filtration rate, SBP, myocardial infarction, BMI, heart rate and HF medications.

^bModel adjusted on sex, age, diabetes, haemoglobin, estimated glomerular filtration rate, SBP, myocardial infarction, BMI, heart rate, HF medications and treatment arm. P value for interaction of SBP-CoV tertiles by treatment.

^cUnadjusted = 0.482; adjusted = 0.340.

^dUnadjusted = 0.645; adjusted = 0.854.

^eUnadjusted = 0.085; adjusted = 0.103.

FIGURE 1 'Spline' graphical representation of the prognostic implications of SBP coefficient of variation. Grey line: hazard ratio; dashed lines: 95% confidence interval.

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)] (refer to Table, Supplemental Digital Content 2, <http://links.lww.com/HJH/B155>, that illustrates clinical outcomes in SBP-CoV 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 [cardiovascular death and HFH adjusted HR (T1 vs. T2) 1.51, 95% CI (1.23–1.86); cardiovascular 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)] (refer to Table, Supplemental Digital Content 3, <http://links.lww.com/HJH/B155>, that illustrates clinical outcomes in DBP-CoV tertiles). Models adjusted for confounding factors and for randomized treatment gave similar findings (Table 2 and refer to Table, Supplemental Digital Content 4, <http://links.lww.com/HJH/B155>, that illustrates the prognostic associations of SBP-CoV adjusted for confounding factors).

Univariate and multivariate sensitivity analyses that included patients with a minimum of three BP measures gave consistent findings (refer to Table, Supplemental Digital Content 5, <http://links.lww.com/HJH/B155>, that illustrates the prognostic associations of SBP-CoV in patients with three or more BP 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) (refer to Table, Supplemental Digital Content 6, <http://links.lww.com/HJH/B155>, that illustrates the interaction of SBP-CoV against other factors). The effect of eplerenone was consistent across all SBP-CoV tertiles (Table 2).

SBP coefficient of variation and mean SBP interaction

SBP modified the relationship between SBP-CoV and the primary outcome (P for interaction = 0.049) and, particularly,

HFH (P for interaction = 0.018) (Fig. 2 and refer to Table, Supplemental Digital Content 6, <http://links.lww.com/HJH/B155>, that illustrates the interaction of SBP-CoV 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 with an SBP between 110 and 140 mmHg (intermediate) (refer to Table, Supplemental Digital Content 7, <http://links.lww.com/HJH/B155>, that illustrates the prognostic associations between tertiles of mean SBP and SBP-CoV).

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 110–140 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 heart failure, Rossignol *et al.* [9] also showed that higher visit-to-visit 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

FIGURE 2 Interaction between mean SBP and SBP coefficient of variation for (a) the primary endpoint of cardiovascular death or heart failure hospitalization, (b) heart failure hospitalization and (c) cardiovascular mortality.

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 HFH) 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 regard to the primary outcome and HFH. Although 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 LV systolic dysfunction. This U-shaped relationship appeared to influence mainly HFHs that may be more

susceptible to variations in BP. In the EPHEsus trial [26] patients were enrolled early after MI (3–14 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. First, 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 heart failure 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 SBP 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 BP measurement, different devices for BP measurement were used. Notwithstanding, all BP measurements were made using validated semiautomated BP 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, because 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.

In conclusion, 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 heart failure.

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Conflicts of interest

K.S. has received honoraria (modest) from AstraZeneca, Novartis, Pfizer and Servier. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

REFERENCES

1. Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, *et al.* 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.
2. Kronish IM, Lynch AI, Oparil S, Whittle J, Davis BR, Simpson LM, *et al.* The association between antihypertensive medication nonadherence and visit-to-visit variability of blood pressure: findings from the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 2016; 68:39–45.
3. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension* 2011; 57:160–166.
4. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT, *et al.* Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study. *Ann Intern Med* 2015; 163:329–338.
5. Shimbo D, Newman JD, Aragaki AK, LaMonte MJ, Bavry AA, Allison M, *et al.* Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertension* 2012; 60:625–630.
6. Chang TI, Reboussin DM, Chertow GM, Cheung AK, Cushman WC, Kostis WJ, *et al.* Visit-to-visit office blood pressure variability and cardiovascular outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension* 2017; 70:751–758.
7. Ferreira JP, Duarte K, Pitt B, Dickstein K, McMurray JJV, Zannad F, *et al.* 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 EPHE-SUS and OPTIMAAL trials. *J Hypertens* 2018; 36:1736–1742.
8. Rossignol P, Cridlig J, Leher P, Kessler M, Zannad F. Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL. *Hypertension* 2012; 60:339–346.
9. Rossignol P, Girerd N, Gregory D, Massaro J, Konstam MA, Zannad F. Increased visit-to-visit blood pressure variability is associated with worse cardiovascular outcomes in low ejection fraction heart failure patients: insights from the HEAAL study. *Int J Cardiol* 2015; 187:183–189.
10. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010; 375:938–948.
11. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; 375:895–905.
12. Vidal-Petiot E, Stebbins A, Chiswell K, Ardissino D, Aylward PE, Cannon CP, *et al.* Visit-to-visit variability of blood pressure and cardiovascular outcomes in patients with stable coronary heart disease. Insights from the STABILITY trial. *Eur Heart J* 2017; 38:2813–2822.
13. Hong K, Muntner P, Kronish I, Shilane D, Chang TI. Medication adherence and visit-to-visit variability of systolic blood pressure in African Americans with chronic kidney disease in the AASK trial. *J Hum Hypertens* 2016; 30:73–78.
14. Kostis JB, Sedjro JE, Cabrera J, Cosgrove NM, Pantazopoulos JS, Kostis WJ, *et al.* Visit-to-visit blood pressure variability and cardiovascular death in the Systolic Hypertension in the Elderly Program. *J Clin Hypertens (Greenwich)* 2014; 16:34–40.
15. Mancia G. Visit-to-visit blood pressure variability: an insight into the mechanisms. *Hypertension* 2016; 68:32–33.
16. Bohm M, Robertson M, Borer J, Ford I, Komajda M, Mahfoud F, *et al.* 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 α 1 Inhibitor Ivabradine Trial (SHIFT) trial. *J Am Heart Assoc* 2016; 5:e002160.
17. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364:11–21.
18. Collier TJ, Pocock SJ, McMurray JJ, Zannad F, Krum H, van Veldhuisen DJ, *et al.* The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. *Eur Heart J* 2013; 34:2823–2829.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604–612.
20. Harrell F. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. New York: Springer; 2001.
21. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. *Am J Physiol Regul Integr Comp Physiol* 2002; 283:R815–R826.
22. Grassi G, Bombelli M, Seravalle G, Dell'Oro R, Quarti-Trevano F. Diurnal blood pressure variation and sympathetic activity. *Hypertens Res* 2010; 33:381–385.
23. Giles TD, Roffidal L, Quiroz A, Sander G, Tresznewsky O. Circadian variation in blood pressure and heart rate in nonhypertensive congestive heart failure. *J Cardiovasc Pharmacol* 1996; 28:733–740.
24. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, *et al.* Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol* 2001; 37:1228–1233.
25. Brown NJ. Eplerenone: cardiovascular protection. *Circulation* 2003; 107:2512–2518.
26. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348:1309–1321.
27. Musini VM, Wright JM. Factors affecting blood pressure variability: lessons learned from two systematic reviews of randomized controlled trials. *PLoS One* 2009; 4:e5673.