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ORIGINAL RESEARCH ARTICLE

Blood pressure visit-to-visit variability and outcomes in patients with heart failure with preserved ejection fraction

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Abstract

Aims Previous studies report that blood pressure (BP) variability is associated with increased risk of adverse outcomes in patients diagnosed with cardiovascular disease. However, studies have not fully explored this association in patients with heart failure with preserved ejection fraction (HFpEF). This study sought to explore the association between visit-to-visit variability (VVV) of BP and clinical outcomes in patients with HFpEF.

Methods and results A total of 1988 patients (mean age of 67.73 ± 9.22, 51.7% female) from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial were included in this study. BP-VVV was determined by standard deviation (SD) of mean systolic BP (SBP-SD) from six measurements (baseline and months 1, 2, 4, 8, and 12) during the first 12 months after randomization. Mean on-treatment SBP during the first 12 months was 127.77 ± 10.42 mmHg, and the median of SBP-SD was 8.15 mmHg. A total of 192 (9.7%) patients met the primary outcome during the subsequent median follow-up of 35.16 months, including a composite of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest. Multiple Cox regression analysis showed that SBP-SD was independently associated with the increased risk of the primary outcome after adjusting for age, gender, method of BP measurement, treatment, renal function and common co-morbidities, and the mean SBP during the first 12 months [hazard ratio (HR) for fourth vs. first quartile, 1.63; 95% confidence interval (CI), 1.07–2.49; P = 0.024]. Analysis showed that SBP-SD as continuous variable was associated with a 23% increase in the risk of primary outcome (HR 1.23, 95% CI 1.06–1.43; P = 0.006).

Conclusions The findings of the current study show that high SBP-VVV in patients with HFpEF is associated with an increased risk of adverse outcomes independent of the mean on-treatment SBP.

Keywords TOPCAT trial; Heart failure with preserved ejection fraction; Blood pressure visit-to-visit variability; Outcome research

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) affects nearly half of patients diagnosed with HF. Incidence of all-cause mortality and HF readmission in patients with HFpEF is similar to that for patients with HF with reduced ejection fraction (HFrEF).[1,2] However, currently, no effective therapies are available for reducing adverse outcomes in HFpEF.[3–6] Treatment of HFpEF mainly focuses on optimizing co-morbidity management.[7] HFpEF patients show high incidence of hypertension; therefore, optimizing blood pressure (BP) management may reduce adverse events by improving haemodynamic status, diastolic dysfunction, abnormal ventricular arterial coupling, and left ventricular hypertrophy.[8] Recent studies report that on-treatment systolic BP (SBP) 120–129 mmHg is associated with a lower risk of clinical

outcomes in patients with HFpEF.[9] However, studies of the effect of on-treatment BP variability on clinical outcomes of HFpEF have not been explored.

Increased BP visit-to-visit variability (BP-VVV) is associated with a higher risk for cardiovascular events, including myocardial infarction (MI), stroke, and HF.[10–13] Moreover, BP-VVV is associated with high risk of cardiovascular and all-cause mortality in patients with hypertension,[14–20] atrial fibrillation (AF),[21] coronary heart disease,[22] and HFrEF[23–25] regardless of the mean follow-up BP level. Therefore, BP-VVV should be evaluated while optimizing HFpEF management. However, no studies have explored the relationship between BP-VVV and adverse outcomes in HFpEF.

Therefore, the aim of this study was to explore the association between BP-VVV and clinical outcomes in HFpEF patients. Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study was a multicentre randomized placebo-controlled trial of spironolactone in patients with HFpEF. Data from the TOPCAT trial comprise records of BP in almost every visit; therefore, it is suitable for investigating the relationship between BP-VVV and outcomes in a post hoc analysis.

Patients with HFpEF are mainly the elderly, with a high prevalence of co-morbidities such as hypertension and AF. This study hypothesized that higher BP-VVV is associated with worse outcomes in patients with HFpEF irrespective of the on-treatment BP based on findings on BP-VVV and outcomes from previous studies.

Methods

Study design and patients

This study conducted a post hoc analysis of the TOPCAT trial, a multicentre randomized placebo-controlled trial of spironolactone in patients with HFpEF[5] (ClinicalTrials.gov number NCT00094302). The trial was conducted by the National Heart, Lung, and Blood Institute. Patients attending 233 centres in six countries between 10 August 2006 and 31 January 2012 were included in this study. Key inclusion and exclusion criteria of the TOPCAT study were published in the study protocol.[26] In the trial, BP was determined at baseline and at every follow-up visit based on the protocol-defined schedule (at 1, 2, 4, 8, and 12 months and then after every 6 months after enrolment). For the current analyses, BP-VVV was determined during the first 12 months of the trial, and outcomes were analysed from the end of the first year to the end of the follow-up period. To exclude BP-VVV caused by different methods of measurement during follow-up, only patients who underwent the same methods of BP measurement from baseline to the first 12 months of follow-up were included. In addition, only HFpEF patients of white race and without peripheral artery disease (PAD) were included to exclude confounding factors caused by race and PAD.

Patients who experienced cardiovascular mortality, hospitalization for HF, or aborted cardiac arrest during the first 12 months of follow-up (n = 457; Supporting Information, *Figure S1*) were excluded as these events can affect BP-VVV. Patients who underwent different methods (manual or automated) of BP measurement during different visits were excluded (n = 173). In addition, patients with less than five BP measurements (n = 487) during the first 12 months, non-white race (n = 153), and those diagnosed with PAD (n = 187) were excluded (Supporting Information, *Figure S1*). The local ethics committees or institutional review boards approved the study before obtaining TOPCAT trial data from the National Heart, Lung, and Blood Institute.

Definitions of blood pressure visit-to-visit variability

During the first 12 months of the study, BP was determined during six visits (baseline and months 1, 2, 4, 8, and 12) by manual or automated devices following normal standard procedures. Notably, no specific procedures were recommended by the study protocol. BP-VVV was mainly determined by SBP and diastolic BP (DBP). Standard deviation (SD) of the mean of SBP and DBP for the six visits of every patient was calculated. If one measurement was missing during the first 12 months, SBP-SD or DBP-SD was calculated using other available data. Secondary assessment of BP-VVV was performed by the calculating coefficient of variation (CV) and the average real variability (ARV) of the mean BP between consecutive visits of patients for whom all six visits were reported.

Clinical outcomes

The primary study outcome was the composite outcomes of cardiovascular death, hospitalization for HF, or aborted cardiac arrest occurring after the first 12 months after randomization. Secondary outcomes included cardiovascular mortality, first HF hospitalization event, and all-cause mortality occurring more than 12 months after randomization. All events were discussed by an independent clinical endpoint committee.

Statistical analysis

Baseline characteristics were grouped based on SBP-SD and DBP-SD, and patients with or without the primary outcome. All continuous variables were presented as mean ± SD or

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median and interquartile range and were compared with one-way analysis of variance (ANOVA), Student's *t*-test, or Kruskal–Wallis one-way ANOVA based on the type of distribution of the data. Categorical variables were expressed as counts and percentages and were compared using χ^2 test. Kaplan–Meier curves for the primary outcome and the three secondary outcomes based on the SBP-SD or DBP-SD quartile were generated and compared using log-rank test. The relationship between SBP-SD or DBP-SD and the adjusted hazard ratios (HRs) of outcomes was presented using restricted cubic splines with four knots equally spaced at the 5th, 35th, 65th, and 95th percentiles.

Cox regression analysis was used to explore the relationship between SBP-SD or DBP-SD quartile and clinical outcomes. Proportional hazards assumption was assessed and verified. Univariate and multivariate-adjusted HRs and 95% confidence intervals (CIs) for each outcome were calculated with SBP-SD or DBP-SD modelled as a continuous variable (every 5 mmHg increase). Multivariate models were constructed after adjusting for age, gender, body mass index (BMI), hypertension, AF, diabetes mellitus (DM), prior myocardial infarction (MI), stroke, New York Heart Association (NYHA) class III/IV, estimated glomerular filtration rate (eGFR), ejection fraction (EF), method of BP measurement, randomization to spironolactone, number of visits, on-treatment SBP (for SBP) or on-treatment DBP (for DBP).

Subgroup analyses were performed based on age, gender, BMI, method of BP measurement, EF, randomized to spironolactone or placebo, with or without common co-morbidities (hypertension, DM, AF, prior MI) and different levels of on-treatment BP. Further, presence of interactions was assessed by adding interaction terms to the adjusted models.

Sensitivity analysis involved repeating analysis in patients with all six visits or eight visits in 24 months of follow-up using all SBP-VVV (SD, CV, and ARV) measurements as continuous variables. Clinical predictors of baseline characteristics associated with a high SBP-SD quartile were explored using logistic regression analysis.

Analyses were performed using R 3.6.1 (Vienna, Austria), and Free Stastics software versions 1.2. All analyses were two-sided. *P*-values < 0.05 were considered statistically significant.

Results

Baseline characteristics and outcomes

Out of the 3445 patients included in the TOPCAT trial, 1988 were included in the current study (Supporting Information, *Figure S1*). Mean number of visits of included patients was 5.98 ± 0.15. BP was measured manually (calibrated standard sphygmomanometer) in 87.1% of patients and by automated digital device in 12.9%. The mean age of included patients was 67.73 ± 9.22 years, 51.7% were female, 90.7% had a history of hypertension, 34% had a history of AF, and 49.2% were randomized to the spironolactone group (Supporting Information, *Table S1*). During the first 12 months of follow-up, average BP and percentage of antihypertensive treatment showed a significant decrease compared with the baseline level (Supporting Information, *Figure S2*). After a subsequent median of 35.16 months of follow-up, 192 (9.7%) patients met the primary outcome (composite endpoint of cardiovascular mortality and HF hospitalization or aborted cardiac arrest), including 124 (6.2%) patients with cardiovascular mortality, 98 (4.9%) with HF hospitalization, and 184 (9.3%) with all-cause mortality (Supporting Information, *Figure S1*).

Baseline characteristics and outcomes of patients in the SBP-SD quartile are presented in *Table 1*. Automated BP measurement, mean age, BMI, EF, on-treatment SBP, proportion of NYHA class III/IV, DM, AF, and high or low SBP category increased with increase in quartile (all $P_{\text{for trend}} < 0.01$, *Table 1*), whereas eGFR decreased with increase in quartile (all $P_{\text{for trend}} < 0.05$, *Table 1*). Similar baseline characteristics were observed for DBP-SD quartiles (Supporting Information, *Table S2*). Rates of HF hospitalization, cardiovascular mortality, and all-cause mortality gradually increased with increase in SD quartiles of SBP or DBP (all $P_{\text{for trend}} < 0.01$).

Baseline characteristics in patients with or without primary outcome are presented in *Table 2*. Patients with adverse events were mainly the elderly, those with higher SBP-SD and DBP-SD, those who frequently underwent automated BP measurement, NYHA class III/IV, DM, AF, a history of MI, stroke, but with lower EF, eGFR, baseline SBP, baseline and on-treatment DBP, and number of visits, and those who showed less frequency of female compared with those without events (all $P < 0.05$, *Table 2*). However, BMI, baseline heart rate, on-treatment SBP, and the proportions of female, randomized to spironolactone, history of hypertension, and current smoker were not significantly different between the two groups (all $P > 0.05$, *Table 2*).

Association between blood pressure visit-to-visit variability and clinical outcomes

Analysis using Kaplan–Meier curves showed that patients in the fourth quartile of SBP-SD were at higher risk for the primary and secondary outcomes (cardiovascular mortality, HF hospitalization, and all-cause mortality) compared with those in the first, second, to third quartiles (all log-rank $P < 0.01$; *Figure 1A–1D*, respectively). Similar findings were observed for the DBP-SD quartiles (all log-rank $P < 0.05$, Supporting Information, *Figure S3*).

Hazard ratios for the primary and secondary outcomes obtained from the univariate and multivariate Cox

Table 1 Baseline characteristics and outcomes by SBP-SD quartiles

SBP-SD (mmHg)	1st quartile (<5.47)	2nd quartile (5.47–8.14)	3rd quartile (8.15–11.50)	4th quartile (≥11.51)	*P*-value for trend
Number of patients	491	503	497	497	
Number of visits	5.97 ± 0.17	5.98 ± 0.13	5.98 ± 0.15	5.98 ± 0.15	0.732
Method of BP measurement, *n* (%)					<0.001
Manual	481 (98.0)	462 (91.8)	427 (85.9)	361 (72.6)	
Automated	10 (2.0)	41 (8.2)	70 (14.1)	136 (27.4)	
Age, years	66.13 ± 8.78	66.40 ± 9.08	68.61 ± 9.05	69.77 ± 9.48	<0.001
Female, *n* (%)	281 (57.2)	247 (49.1)	249 (50.1)	251 (50.9)	0.058
Randomization to spironolactone, *n* (%)	233 (47.5)	248 (49.3)	256 (51.5)	242 (48.7)	0.559
NYHA class III/IV, *n* (%)	133 (27.1)	120 (23.9)	153 (30.8)	171 (34.4)	0.001
Ejection fraction (%)	56.74 ± 6.96	55.95 ± 6.97	56.61 ± 7.25	57.80 ± 7.82	0.001
Co-morbidities, *n* (%)					
Hypertension	450 (91.6)	452 (89.9)	443 (89.1)	459 (92.4)	0.805
Diabetes mellitus	92 (18.7)	121 (24.1)	125 (25.2)	159 (32.0)	<0.001
Atrial fibrillation	127 (25.9)	140 (27.8)	191 (38.4)	217 (43.7)	<0.001
Prior MI	144 (29.3)	126 (25.0)	134 (27.0)	122 (24.5)	0.163
Stroke	30 (6.1)	28 (5.6)	26 (5.2)	32 (6.4)	0.887
Current smoker	45 (9.2)	80 (15.9)	55 (11.1)	34 (6.8)	0.054
Physical examination					
Body mass index, kg/m^2	30.29 ± 5.33	30.55 ± 5.55	31.25 ± 6.17	32.15 ± 6.90	<0.001
Baseline SBP, mmHg	129.23 ± 10.00	129.61 ± 11.36	129.31 ± 13.45	129.62 ± 15.28	0.946
Baseline heart rate, b.p.m.	69.02 ± 8.75	68.41 ± 9.46	68.24 ± 10.40	68.37 ± 10.77	0.613
On-treatment SBP, mmHg[a]	127.72 ± 8.49	126.87 ± 8.69	127.15 ± 10.63	129.34 ± 13.05	0.001
On-treatment SBP categories, *n* (%)					<0.001
Low (<110 mmHg)	13 (2.6)	15 (3.0)	27 (5.4)	30 (6.0)	
Middle (110–140 mmHg)	450 (91.6)	449 (89.3)	416 (83.7)	367 (73.8)	
High (>140 mmHg)	28 (5.7)	39 (7.8)	54 (10.9)	100 (20.1)	
Laboratory test					
eGFR, mL/min/1.73 m^2	71.88 ± 20.08	70.86 ± 19.24	66.92 ± 18.07	66.02 ± 18.05	<0.001
Primary outcome, *n* (%)	34 (6.9)	31 (6.2)	48 (9.7)	79 (15.9)	<0.001
Secondary outcome, *n* (%)					
Cardiovascular mortality	27 (5.5)	20 (4.0)	31 (6.2)	46 (9.3)	0.005
HF hospitalization	11 (2.2)	17 (3.4)	25 (5.0)	45 (9.1)	<0.001
All-cause mortality	35 (7.1)	34 (6.8)	42 (8.5)	73 (14.7)	<0.001

eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.
[a]Mean systolic blood pressure from visits of baseline up to 12 months.

regression models are presented in *Table 3*. After adjustment for confounding factors including age, gender, BMI, hypertension, AF, DM, prior MI, stroke, NYHA class III/IV, eGFR, EF, method of BP measurement, randomization to spironolactone, number of visits, and on-treatment SBP, patients in the fourth quartile of SBP-SD showed independently higher risk for the primary outcome (HR = 1.63, 95% CI = 1.07–2.49, *P* = 0.024). In addition, patients in the fourth quartile of SBP-SD showed significantly higher risk for HF hospitalization compared with those in other quartiles (HR = 2.44, 95% CI = 1.22–4.85, *P* = 0.011). SBP-SD as a continuous variable (per 5 mmHg increase) was associated with an independent higher risk for both primary outcomes and HF hospitalization (HR = 1.23, 95% CI = 1.06–1.43, *P* = 0.006, and HR = 1.35, 95% CI = 1.10–1.65, *P* = 0.004, respectively). However, SBP-SD as quartiles was not independently associated with the risk of cardiovascular mortality (*Table 3*). Although SBP-SD quartiles were not independently associated with all-cause mortality, SBP-SD as a continuous variable (per 5 mmHg increase) was associated with an independent higher risk for all-cause mortality (HR = 1.21, 95% CI = 1.03–1.41, *P* = 0.019).

Patients in the fourth quartile of DBP-SD showed significant independent association with increased risk for the primary outcome and HF hospitalization (HR = 1.87, 95% CI = 1.13–3.09, *P* = 0.015, and HR = 4.23, 95% CI = 1.65–10.8, *P* = 0.003, respectively, Supporting Information, *Table S3*). DBP-SD as a continuous variable was not significantly associated with the primary outcome (HR = 1.22, 95% CI = 0.97–1.52, *P* = 0.083); however, it was an independent risk factor for HF hospitalization (HR = 1.47, 95% CI = 1.10–1.97, *P* = 0.009). Meanwhile, DBP-SD (as quartiles or continuous variable) was not independently associated with the risk of cardiovascular and all-cause mortality (Supporting Information, *Table S3*).

Restricted cubic splines were used to present the relationship between SBP-SD and adjusted HRs for the primary and secondary outcomes (*Figure 2*). Higher SBP-SD was associated with a higher risk of primary outcome (*Figure 2A*), HF hospitalization (*Figure 2C*), and all-cause mortality (*Figure 2D*) but was not associated with cardiovascular mortality (*Figure 2B*). Moreover, spline curves showed that an SBP-SD > 10 mmHg was independently associated with a higher risk of a primary outcome, HF hospitalization, and

Table 2 Baseline characteristics in patient with and without the primary outcome

	Primary outcome	No primary outcome	*P*-value
Number of patients	192	1796	
Number of visits	5.95 ± 0.22	5.98 ± 0.14	0.004
Method of BP measurement, *n* (%)			0.008
Manual	155 (80.7)	1576 (87.8)	
Automated	37 (19.3)	220 (12.2)	
Age, years	71.76 ± 9.17	67.30 ± 9.12	<0.001
Female, *n* (%)	78 (40.6)	950 (52.9)	0.002
Randomization to spironolactone, *n* (%)	89 (46.4)	890 (49.6)	0.443
NYHA class III/IV, *n* (%)	83 (43.2)	494 (27.5)	<0.001
Ejection fraction (%)	55.62 ± 7.55	56.90 ± 7.25	0.021
Co-morbidities, *n* (%)			
Hypertension	177 (92.2)	1627 (90.6)	0.552
Diabetes mellitus	70 (36.5)	427 (23.8)	<0.001
Atrial fibrillation	98 (51.0)	577 (32.1)	<0.001
Prior MI	63 (32.8)	463 (25.8)	0.044
Stroke	20 (10.4)	96 (5.3)	0.007
Current smoker	17 (8.9)	197 (11.0)	0.438
Physical examination			
Body mass index, kg/m^2	31.58 ± 6.88	31.00 ± 5.96	0.208
Baseline heart rate, b.p.m.	68.84 ± 10.39	68.47 ± 9.82	0.627
Baseline SBP, mmHg	127.73 ± 13.93	129.63 ± 12.53	0.048
On-treatment SBP, mmHg[a]	127.41 ± 11.98	127.81 ± 10.24	0.613
SBP-SD, mmHg	10.15 (6.68, 13.63)	8.01 (5.31, 10.96)	<0.001
Baseline DBP, mmHg	73.22 ± 11.01	77.98 ± 9.46	<0.001
On-treatment DBP, mmHg[b]	73.15 ± 9.47	76.48 ± 7.45	<0.001
DBP-SD, mmHg	6.35 (4.98, 8.46)	5.24 (4.08, 7.53)	<0.001
Laboratory test			
eGFR, mL/min/1.73 m^2	63.06 ± 17.73	69.54 ± 19.06	<0.001

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.
[a]Mean systolic blood pressure from visits of baseline up to 12 months.
[b]Mean diastolic blood pressure from visits of baseline up to 12 months.

all-cause mortality but was not associated with cardiovascular mortality. However, our analysis did not show a definite relationship between DBP-SD and all outcomes (Supporting Information, *Figure S4*).

Interaction between on-treatment blood pressure categories and blood pressure variability

On-treatment SBP and DBP categories did not modify the association between SBP-SD or DBP-SD quartiles and the risk of primary outcome (both $P_{\text{for interaction}} > 0.05$, Supporting Information, *Tables S4* and *S5*). In addition, no interaction was observed between SBP-SD or DBP-SD as continuous variables and on-treatment SBP or DBP categories for the risk of primary outcome (both $P_{\text{for interaction}} > 0.05$, Supporting Information, *Figure S5*).

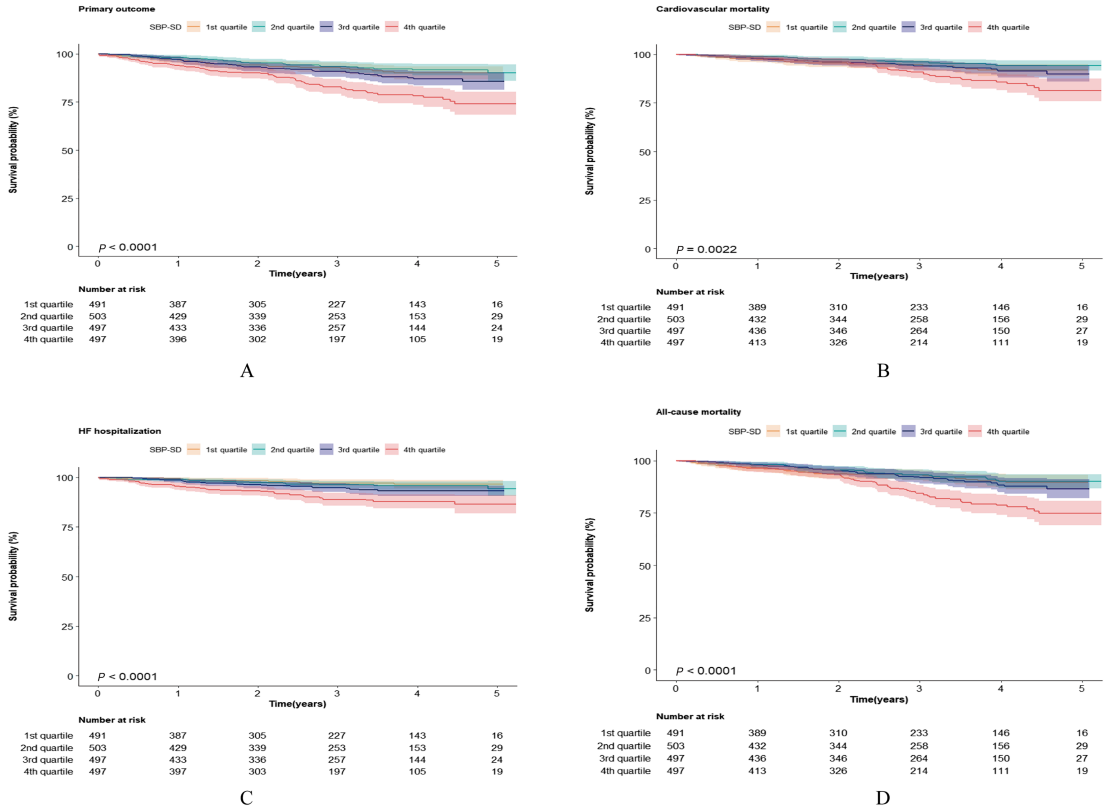
Subgroup analysis

Relationship between SBP-SD as a continuous variable (per 5 mmHg increase) and primary outcome in prespecified subgroups is presented in *Figure 3*. Subgroup analysis did not show significant interaction between SBP-SD and primary outcome (all $P_{\text{for interaction}} > 0.05$, *Figure 3*). Relationship between SBP-SD as continuous variable and all outcomes in patients with different levels of on-treatment SBP is presented in *Figure 4*. No interaction was observed between SBP-SD and the risk of primary and secondary outcomes for patients with low (<110 mmHg), middle (110–140 mmHg), or high (>140 mmHg) on-treatment SBP (all $P_{\text{for interaction}} > 0.05$, *Figure 4*).

Sensitivity analysis

Sensitivity analyses showed consistent findings when restricted to patients for whom all six visits were documented. The findings showed that a higher SBP-SD as a continuous variable was independently associated with a high risk of primary outcome, HF hospitalization, and all-cause mortality (all $P < 0.05$) but was not associated with cardiovascular mortality ($P = 0.277$). Analysis of CV or ARV as a continuous variable instead of SD showed that the two measurements of SBP-VVV were associated with high risk of primary outcome and secondary outcome, including HF hospitalization and all-cause mortality (all $P < 0.05$, Supporting Information, *Table S6*). Repeated

Figure 1 Kaplan–Meier curves for clinical outcomes. (A) Primary outcome; (B) cardiovascular mortality; (C) heart failure (HF) hospitalization; (D) all-cause mortality. Brown colour: first quartile; green colour: second quartile; blue colour; third quartile; red colour: fourth quartile. SBP-SD, standard deviation of systolic blood pressure.



analysis for patients with all eight visits during the first 24 months of follow-up showed that high SBP-VVV was associated with high risk of the primary outcome, HF hospitalization, and all-cause mortality (all $P < 0.05$, Supporting Information, *Table S7*).

Determinants of high systolic blood pressure visit-to-visit variability in heart failure with preserved ejection fraction

To explore the clinical predictors for high SBP-VVV in HFpEF, independent risk factors for higher SBP-SD (fourth quartile vs. first to third quartiles) from the baseline characteristics were analysed. Multivariate logistic regression analysis showed that BP measured by automated devices, older age, high BMI, high EF, and prevalence of AF were independently associated with prevalence of high SBP-SD during treatment (all $P < 0.05$, Supporting Information, *Table S8*).

Discussion

This study included 1988 patients with HFpEF from the TOPCAT trial. The findings of the study showed that high SBP-VVV, as assessed during six visits within 12 months, was associated with an increased risk of adverse outcomes, including HF hospitalization, all-cause mortality, and composite outcome of cardiovascular mortality and HF hospitalization. Consistent findings were observed after multivariate adjustments for potential confounding factors and were consistent with findings obtained from subgroup analysis. This is the first study that uses a large cohort of HFpEF patients to explore the association between SBP-VVV and risk of adverse outcomes independent of on-treatment SBP.

Previous studies report that SBP-VVV is associated with incidence of several cardiovascular diseases[10] including coronary heart disease,[17] stroke,[14,20,27] new-onset AF,[28] and HF[27] independent of absolute BP. In addition, increased SBP-VVV is an independent predictor of adverse outcomes including all-cause mortality and cardiovascular mortality in patients with established cardiovascular diseases (CVDs) such as

Table 3 Cox regression analysis for SBP-SD and clinical outcomes

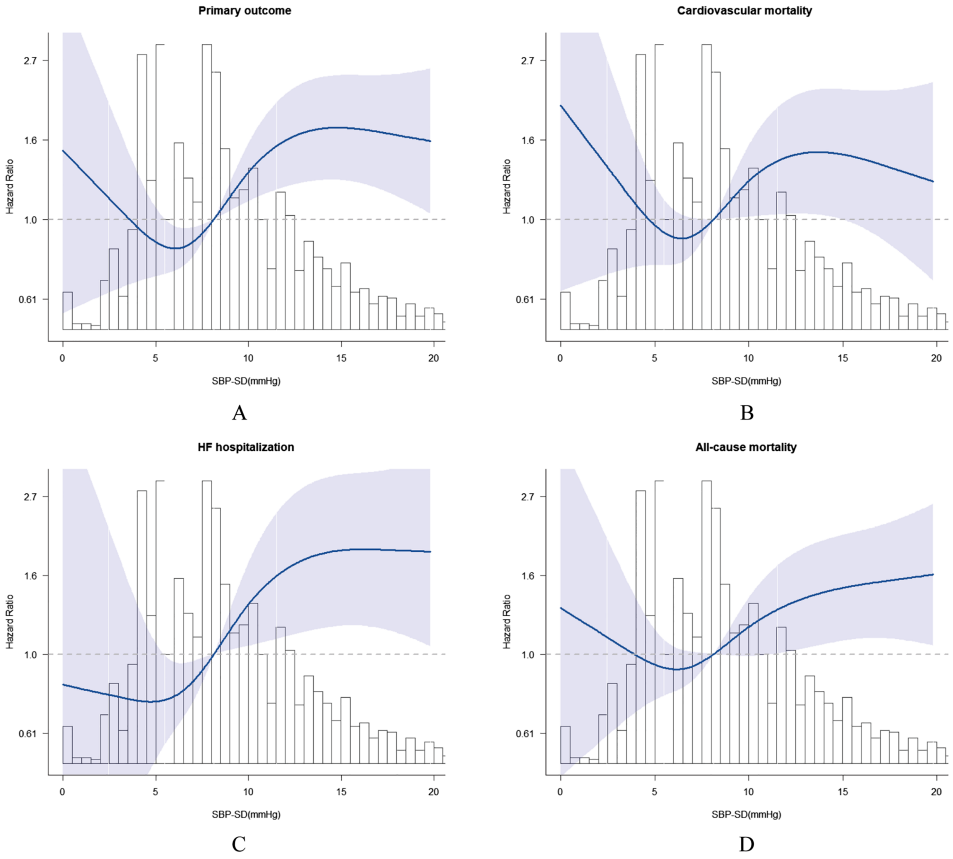
	Unadjusted		Adjusted[a]	
Outcome	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary outcome				
SD quartiles				
1st quartile	Ref.		Ref.	
2nd quartile	0.83 (0.51–1.36)	0.467	0.76 (0.47–1.24)	0.275
3rd quartile	1.28 (0.83–1.99)	0.266	0.96 (0.61–1.51)	0.869
4th quartile	2.4 (1.61–3.6)	<0.001	1.63 (1.07–2.49)	0.024
SD (per 5 mmHg)	1.45 (1.27–1.65)	<0.001	1.23 (1.06–1.43)	0.006
Cardiovascular mortality				
SD quartiles				
1st quartile	Ref.		Ref.	
2nd quartile	0.68 (0.38–1.21)	0.189	0.61 (0.34–1.09)	0.093
3rd quartile	1.04 (0.62–1.74)	0.889	0.78 (0.46–1.32)	0.35
4th quartile	1.73 (1.07–2.78)	0.024	1.21 (0.73–2.00)	0.465
SD (per 5 mmHg)	1.28 (1.07–1.53)	0.006	1.10 (0.90–1.34)	0.351
HF hospitalization				
SD quartiles				
1st quartile	Ref.		Ref.	
2nd quartile	1.42 (0.66–3.02)	0.369	1.25 (0.58–2.68)	0.566
3rd quartile	2.07 (1.02–4.2)	0.045	1.47 (0.71–3.04)	0.294
4th quartile	4.16 (2.15–8.05)	<0.001	2.44 (1.22–4.85)	0.011
SD (per 5 mmHg)	1.64 (1.38–1.95)	<0.001	1.35 (1.10–1.65)	0.004
All-cause mortality				
SD quartiles				
1st quartile	Ref.		Ref.	
2nd quartile	0.89 (0.55–1.43)	0.625	0.8 (0.50–1.29)	0.363
3rd quartile	1.08 (0.69–1.7)	0.727	0.8 (0.51–1.28)	0.356
4th quartile	2.1 (1.4–3.14)	<0.001	1.45 (0.95–2.23)	0.085
SD (per 5 mmHg)	1.39 (1.21–1.6)	<0.001	1.21 (1.03–1.41)	0.019

CI, confidential interval; HF, heart failure; HR, hazard ratio; SBP, systolic blood pressure; SD, standard deviation.
[a]Adjusted for age, gender, body mass index, hypertension, atrial fibrillation, diabetes mellitus, prior myocardial infarction, stroke, New York Heart Association class III/IV, estimated glomerular filtration rate, ejection fraction, method of blood pressure measurement, randomization to spironolactone, number of visits, and on-treatment SBP.

hypertension,[15,18,19] AF,[21] coronary heart disease,[22] and DM.[29,30] These findings show the significance of SBP-VVV in BP management in patients with established CVDs. In the current study, independent predictive value of SBP-VVV in HFpEF was explored based on the results in the common co-morbidities of HFpEF such as hypertension, AF, stable coronary disease, and DM. The predictive value of SBP-VVV on adverse outcomes in HFpEF may be attributed to SBP-VVV in patients with hypertension owing to the high prevalence of hypertension in the current study population. However, subgroup analysis did not show a significant interaction between hypertension and SBP-VVV on the primary outcome. Furthermore, prevalence of hypertension was not associated with high SBP-VVV, indicating that the prognostic value of high SBP-VVV on HFpEF was not attributed to hypertension. In addition, analysis showed no interaction between the prognostic value of SBP-VVV on outcomes and presence of other CVDs, implying that the independent association of SBP-VVV on adverse outcomes was not attributed to the prevalence of CVD as a co-morbidity of HFpEF.

The findings of the current study showed that high SBP-VVV was associated with an increased risk of the composite endpoints of cardiovascular mortality and HF hospitalization. Analysis of the separate outcomes showed that high SBP-VVV quartile was associated with an increased risk for HF hospitalization and all-cause mortality but not with cardiovascular mortality. A possible explanation is that cardiac haemodynamic status and other relevant changes may have been caused by high SBP-VVV. Takahari and Nagai recently reported that high SBP-VVV was correlated with a high level of N-terminal pro-B-type natriuretic peptide,[31] which may result in increased risk of HF hospitalization. Moreover, a nationwide population-based study reported that high SBP-VVV was associated with new-onset HF in a healthy population,[32] which may explain the adverse effects of high SBP-VVV on the risk of HF rehospitalization in patients with HFpEF. Previous systematic reviews and meta-analyses reported the harmful effects of high SBP-VVV on mortality in the general population or patients with established CVDs, which explains the high all-cause mortality.[11,12] Recent studies report that adverse effects of high SBP-VVV are associated with endothelial damage, coronary atheroma progression, coronary heart disease,[29,33] CVDs, and chronic kidney disease in patients with hypertension,[34,35] microvascular lesions in DM, and major bleeding in AF. These

Figure 2 Relationship between SBP-SD and risk of clinical outcomes presented by restricted cubic splines. (A) Primary outcome; (B) cardiovascular mortality; (C) heart failure (HF) hospitalization; (D) all-cause mortality. SBP-SD, standard deviation of systolic blood pressure during the first 12 months after randomization. Hazard ratio was adjusted for age, gender, body mass index, hypertension, atrial fibrillation, diabetes mellitus, prior myocardial infarction, stroke, New York Heart Association class III/IV, estimated glomerular filtration rate, ejection fraction, method of blood pressure measurement, randomization to spironolactone, number of visits, on-treatment SBP (for SBP), or on-treatment diastolic blood pressure (for diastolic blood pressure).



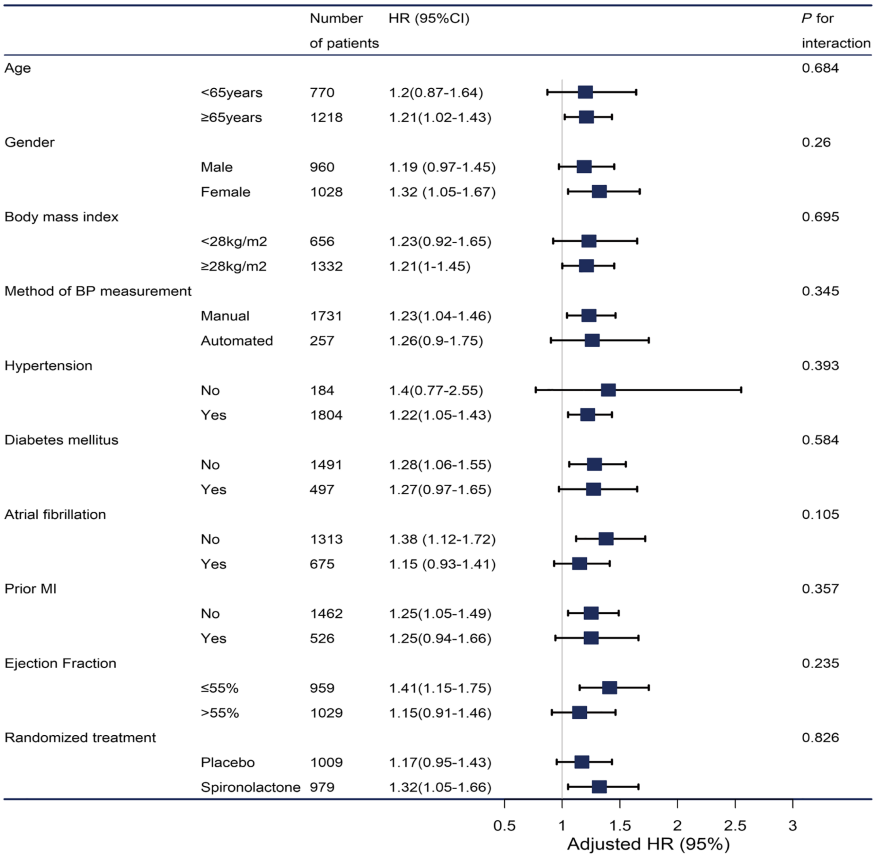
adverse effects of high SBP-VVV can increase risk of all-cause death.

The findings of the current study did not show an independent association between high SBP-VVV and increased risk of cardiovascular mortality in patients with HFpEF, which is consistent with findings reported by the VALUE trials on hypertension[18] and reports by AFFIRM study on AF.[21] This observation may be attributed to the fact that cardiovascular death accounts for about 60–70% of all-cause deaths, whereas non-cardiovascular death is an important competing risk in patients with HFpEF.[36] Effects of SBP-VVV on non-cardiovascular death may be higher compared with its role in cardiovascular mortality. In addition, other traditional risk factors for cardiovascular death may overshadow the role of SBP-VVV and patients who survive may tolerate high BP variability better.

The elderly and patients with high BMI, high EF, and high prevalence of AF showed high SBP-VVV compared with their counterparts. This finding is consistent with findings reported by the VALUE trial.[18] Moreover, patients who underwent determination of BP using automated devices showed higher SBP-VVV compared with those who underwent manual measurement. This finding is consistent with the results from the TROPHY trial.[37] This can be attributed to observer bias during manual measurement leading to a decrease in BP variability, whereas the error caused by automated devices would enhance SBP-VVV. However, analysis showed no interaction between methods of BP measurement and SBP-VVV on predicting risk of adverse outcomes, implying that the association between higher SBP-VVV and increased risk of adverse outcomes was consistent regardless of the method used for BP measurement.

Notably, analysis of DBP-SD as a continuous variable did not show significant association with an increased risk of the primary outcome. This finding was not consistent with findings reported for patients with hypertension[18] and stable coronary heart disease.[22] HFpEF is referred as an elderly disease and is associated with high prevalence of hypertension.

Figure 3 Risk of primary outcome for 5 mmHg increase in SBP-SD in different subgroups of patients. SBP-SD, standard deviation of systolic blood pressure during the first 12 months after randomization. Hazard ratio (HR) was adjusted for age, gender, body mass index, hypertension, atrial fibrillation, diabetes mellitus, prior myocardial infarction (MI), stroke, New York Heart Association class III/IV, estimated glomerular filtration rate, ejection fraction, method of blood pressure measurement, randomization to spironolactone, number of visits, on-treatment SBP (for SBP), or on-treatment diastolic blood pressure (for diastolic blood pressure). BP, blood pressure; CI, confidence interval.

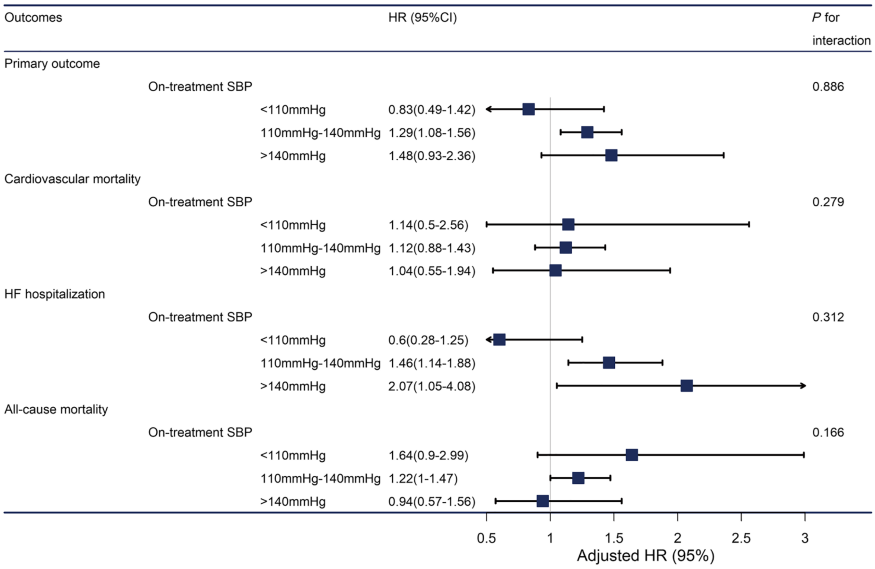


Elderly hypertensive patients often present with isolated systolic hypertension, implying that BP variability in elderly mainly focuses on SBP but not DBP. In addition, analysis of baseline characteristics showed that on-treatment DBP was lower in patients with primary outcome, whereas on-treatment SBP was not significantly different between the two groups. In the current study, on-treatment SBP and DBP were adjusted for SBP-SD or DBP-SD, respectively, during regression analysis. The negative effect of DBP-SD on primary outcome can be attributed to the confounding factor of on-treatment DBP.

Although all-cause mortality and HF readmission in HFpEF were similar to that in HFrEF, non-cardiovascular events were higher compared with those in HFrEF.[36] This can be attributed to the high rates of non-cardiovascular co-morbidities. Patients with HFpEF present with adverse events such as progressive right ventricular failure, pulmonary hypertension, end-stage renal disease, and multiorgan failure. Poor HF event caused by cardiogenetic shock and low output states are less frequently observed in HFpEF patients compared with HFrEF patients. Therapies that improve prognosis in HFrEF are not effective for HFpEF due to the complexity of the mechanism, concomitant disease, and poor outcomes in HFpEF syndrome.[38] Therefore, optimizing management of the co-morbidities in HFpEF is a potential approach for increasing efficacy of HFpEF therapies.

Optimizing BP management can reduce the risk of adverse outcomes due to the high prevalence and similar cardiac structure changes as hypertension (such as concentric hypertrophy or remodelling, left atrial enlargement, and dysfunction)[38,39] in patients with HFpEF. The findings of the current study show that higher SBP-VVV is associated with a higher risk of adverse outcomes irrespective of on-treatment SBP. This finding implies that reducing high BP variability in patients with HFpEF can be a novel approach for BP management in addition to achieving optimal on-treatment SBP. In clinical practice, BP variability is mainly affected by adherence to medication, intensity of BP-lowering treatment, and vascular autonomic function. Therefore, regular BP monitoring and effective adjustment

Figure 4 Risk of outcomes for 5 mmHg increase in SBP-SD in patients with different levels of on-treatment SBP. SBP-SD, standard deviation of systolic blood pressure during the first 12 months after randomization; On-treatment SBP, mean systolic blood pressure from visits of baseline up to 12 months. Hazard ratio (HR) was adjusted for age, gender, body mass index, hypertension, atrial fibrillation, diabetes mellitus, prior myocardial infarction, stroke, New York Heart Association class III/IV, estimated glomerular filtration rate, ejection fraction, method of blood pressure measurement, randomization to spironolactone, number of visits, or on-treatment SBP. CI, confidence interval; HF, heart failure.



of BP-lowering therapy during follow-up are important in management of HFpEF.

The strengths of the current study include use of a large sample size, sufficiently long follow-up period, and standard records of all available visits. This was a post hoc analysis of the TOPCAT trial, a prospective multicentre randomized controlled trial with high-quality baseline and follow-up data. To exclude the effects of adverse events on BP variability, patients who experienced events within the first 12 months were excluded. To ensure independent association of BP-VVV and outcomes, the study adjusted for several potential confounding factors including demographic data, prevalence of co-morbidities, on-treatment BP, and method of BP measurement. Further, subgroup analyses were conducted to explore possible interaction between SBP-VVV and patients of different ages, sex, co-morbidities, and on-treatment BP levels and effects of these factors on predicting the adverse outcomes. Analysis was repeated using other SBP-VVV measurements, including SBP-CV and ARV in patients with all visits, in the sensitivity analysis as the findings showed that SBP-SD was affected by on-treatment SBP and number of visits. The findings showed the robustness of the prognostic value of high SBP-VVV on the risk of adverse outcomes in patients with HFpEF.

This study had a few limitations. First, potential confounding factors were not completely excluded owing to the nature of observational studies. Second, although the different methods of BP measurement were adjusted for, and interaction between SBP-VVV and outcome was explored using subgroup analysis, effect of different BP measurement tools on SBP-VVV was not excluded. Third, no specific procedures were reported by the study protocol; therefore, details on BP measurement, such as the type of devices and validation for measurement accuracy, were not reported. Fourth, TOPCAT participants were slightly younger, showed high incidence of obesity, and had lower BP and better renal function compared with other HFpEF cohorts.[40] Due to the heterogeneous nature of HFpEF and lack of specific diagnostic criteria, the post hoc analysis of the TOPCAT trial may not be applicable to other HFpEF cohorts.

In conclusion, high SBP-VVV is associated with an increased risk of adverse outcomes independent of on-treatment SBP in patients with HFpEF. In addition to achieving high efficacy of HFpEF therapies, reducing SBP variability may help prevent adverse events in HFpEF patients.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics and outcomes of the total patients.
Table S2. Baseline characteristics and outcomes by DBP-SD quartiles.
Table S3. Cox regression analysis for DBP-SD and clinical outcomes.
Table S4. Interaction analysis between on-treatment SBP and SBP standard deviation for the primary outcome.
Table S5. Interaction analysis between on-treatment DBP and DBP standard deviation for the primary outcome.
Table S6. Risk of clinical outcomes for 5 mmHg increase in standard deviation, 5% increase in coefficient of variation, and 5 unit increase in average real variability of SBP-VVV in patients with all 6 visits (n = 1943).
Table S7. Risk of clinical outcomes for 5 mmHg increase in standard deviation, 5% increase in coefficient of variation, and 5 unit increase in average real variability of SBP-VVV in patients with all 8 visits during 24 months (n = 1493).
Table S8. Associations between baseline characteristics and SBP-SD (4th quartile vs. 1st to 3rd quartiles).
Figure S1. Flowchart patient inclusion criteria in this study.
Figure S2. Blood pressure and antihypertensive treatment at baseline and each visit during the first 12 month-follow up.
Figure S3. Kaplan Meier curves for clinical outcomes based on DBP-SD quartiles.
Figure S4. Relationship between DBP-SD and risk of clinical outcomes presented by restricted cubic splines.
Figure S5. Restricted cubic splines model for primary outcome according to on-treatment blood pressure.

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