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

Qi Zhang1, Bingyang Zhou1, Yu Ma1, Yuecheng Hu1, Ximing Li1,2,3* and Hongliang Cong1,2,3*

1Department of Cardiology, Tianjin Chest Hospital, #261 Taierzhuangnan Road, Jinnan District, Tianjin, China; 2Tianjin Medical University, Tianjin, China and 3Chest Hospital, Tianjin University, Tianjin, China

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

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 HFrEF. However, studies of the effect of on-treatment BP variability on clinical outcomes of HFrEF 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. Moreover, BP-VVV is associated with high risk of cardiovascular and all-cause mortality in patients with hypertension, atrial fibrillation (AF), coronary heart disease, and HFrEF regardless of the mean follow-up BP level. Therefore, BP-VVV should be evaluated while optimizing HFrEF management. However, no studies have explored the relationship between BP-VVV and adverse outcomes in HFrEF.

Therefore, the aim of this study was to explore the association between BP-VVV and clinical outcomes in HFrEF 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 HFrEF. 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 HFrEF 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 HFrEF 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 HFrEF (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. 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 HFrEF 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 S2). 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
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 χ² 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 S2). 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<0.01, Table 1), whereas eGFR decreased with increase in quartile (all P<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<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–ID, 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

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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

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**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 (%) | Manual | 481 (98.0) | 462 (91.8) | 427 (85.9) | 361 (72.6) | <0.001 |
| 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 |
| Physical examination |                 |                          |                          |                      |                 |
| Body mass index, kg/m² | 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 | 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) | 0.054 |
| Middle (110–140 mmHg) | 450 (91.6) | 449 (89.3) | 416 (83.7) | 367 (73.8) | 0.001 |
| High (>140 mmHg) | 28 (5.7) | 39 (7.8) | 54 (10.9) | 100 (20.1) | 0.001 |
| Laboratory test | eGFR, mL/min/1.73 m² | 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.

*Mean systolic 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 $P_{	ext{for interaction}} > 0.05$, 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 $P_{	ext{for interaction}} > 0.05$, 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 $P_{	ext{for interaction}} > 0.05$, 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 $P_{	ext{for interaction}} > 0.05$, 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 ($P = 0.277$). 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

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

|                        | Primary outcome | No primary outcome | P-value |
|------------------------|----------------|--------------------|---------|
| Number of patients     | 192            | 1796               | 0.004   |
| Number of visits       | 5.95 ± 0.22    | 5.98 ± 0.14        | 0.008   |
| Method of BP measurement, n (%) |                |                    |         |
| 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 (%) |            |                     | 0.443   |
| NYHA class III/IV, n (%) | 89 (46.4)   | 890 (49.6)         |         |
| Ejection fraction (%)  | 83 (43.2)      | 494 (27.5)         | <0.001  |
| Co-morbidity, n (%)    | 55.62 ± 7.55   | 56.90 ± 7.25       | 0.021   |
| Physical examination   |                |                    |         |
| Body mass index, kg/m² | 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 | 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 | 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 m²   | 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.

<sup>a</sup>Mean systolic blood pressure from visits of baseline up to 12 months.

<sup>b</sup>Mean diastolic blood pressure from visits of baseline up to 12 months.
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 including coronary heart disease, stroke, new-onset AF, and HfPEF 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...
The prevalence of CVD as a co-morbidity of HFpEF.

SBP-VVV on adverse outcomes was not attributed to the other CVDs, implying that the independent association of prognostic value of SBP-VVV on outcomes and presence of hypertension was not attributed to hypertension. Furthermore, prevalence of hypertension was not associated with high SBP-VVV, indicating that the prognostic value of hypertension, AF, stable coronary disease, and DM. 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.

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

| Outcome               | Unadjusted HR (95% CI) | P-value | Adjusted a HR (95% CI) | P-value |
|-----------------------|------------------------|---------|------------------------|---------|
| Primary outcome SD quartiles | Ref.                  |         | Ref.                   |         |
| 1st quartile          | 0.83 (0.51–1.36)       | 0.467   | 0.76 (0.47–1.24)       | 0.275   |
| 2nd quartile          | 1.28 (0.83–1.99)       | 0.266   | 0.96 (0.61–1.51)       | 0.869   |
| 3rd quartile          | 2.41 (1.61–3.6)        | <0.001  | 1.63 (1.07–2.49)       | 0.024   |
| 4th quartile          | 1.45 (1.27–1.65)       | <0.001  | 1.23 (1.06–1.43)       | 0.006   |
| Cardiovascular mortality SD quartiles | Ref.                  |         | Ref.                   |         |
| 1st quartile          | 0.68 (0.38–1.21)       | 0.189   | 0.61 (0.34–1.09)       | 0.093   |
| 2nd quartile          | 1.04 (0.62–1.74)       | 0.889   | 0.78 (0.46–1.32)       | 0.35    |
| 3rd quartile          | 1.73 (1.07–2.78)       | 0.024   | 1.21 (0.73–2.00)       | 0.465   |
| 4th quartile          | 1.28 (1.07–1.53)       | 0.006   | 1.10 (0.90–1.34)       | 0.351   |
| HF hospitalization SD quartiles | Ref.                  |         | Ref.                   |         |
| 1st quartile          | 1.42 (0.66–3.02)       | 0.369   | 1.25 (0.58–2.68)       | 0.566   |
| 2nd quartile          | 2.07 (1.02–4.2)        | 0.045   | 1.47 (0.71–3.04)       | 0.294   |
| 3rd quartile          | 4.16 (2.15–8.05)       | <0.001  | 2.44 (1.22–4.85)       | 0.011   |
| 4th quartile          | 1.64 (1.38–1.95)       | <0.001  | 1.35 (1.10–1.65)       | 0.004   |
| All-cause mortality SD quartiles | Ref.                  |         | Ref.                   |         |
| 1st quartile          | 0.89 (0.55–1.43)       | 0.625   | 0.8 (0.50–1.29)        | 0.363   |
| 2nd quartile          | 1.08 (0.69–1.7)        | 0.727   | 0.8 (0.51–1.28)        | 0.356   |
| 3rd quartile          | 2.1 (1.4–3.14)         | <0.001  | 1.45 (0.95–2.23)       | 0.085   |
| 4th quartile          | 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.

aAdjusted 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.

hypothesis,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 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.
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\textsuperscript{18} and reports by AFFIRM study on AF.\textsuperscript{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.\textsuperscript{16} 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{18} and stable coronary heart disease.\textsuperscript{22} HFpEF is referred as an elderly disease and is associated with high prevalence of hypertension.
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 HFrEF were similar to that in HFrEF, non-cardiovascular events were higher compared with those in HFrEF. 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 cardiogenic 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. 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) 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

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**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.

|                          | Number of patients | HR (95% CI) | P for interaction |
|--------------------------|--------------------|-------------|-------------------|
| **Age**                  |                    |             |                   |
| <65 years                | 770                | 1.2 (0.87-1.64) | 0.684             |
| ≥65 years                | 1218               | 1.21 (1.02-1.43) |                   |
| **Gender**               |                    |             |                   |
| Male                     | 960                | 1.19 (0.97-1.45) | 0.26              |
| Female                   | 1028               | 1.32 (1.05-1.67) |                   |
| **Body mass index**      |                    |             |                   |
| <28 kg/m²                | 656                | 1.23 (0.92-1.65) | 0.695             |
| ≥28 kg/m²                | 1332               | 1.21 (1-1.45)   |                   |
| **Method of BP measurement** |                |             |                   |
| Manual                   | 1731               | 1.23 (1.04-1.46) | 0.345             |
| Automated                | 257                | 1.26 (0.9-1.75)  |                   |
| **Hypertension**         |                    |             |                   |
| No                       | 184                | 1.4 (0.77-2.55)  | 0.393             |
| Yes                      | 1804               | 1.22 (1.05-1.43) |                   |
| **Diabetes mellitus**    |                    |             |                   |
| No                       | 1491               | 1.28 (1.08-1.55) | 0.584             |
| Yes                      | 497                | 1.27 (0.97-1.65) |                   |
| **Atrial fibrillation**  |                    |             |                   |
| No                       | 1313               | 1.38 (1.12-1.72) | 0.105             |
| Yes                      | 675                | 1.15 (0.93-1.41) |                   |
| **Prior MI**             |                    |             |                   |
| No                       | 1462               | 1.26 (1.05-1.49) | 0.357             |
| Yes                      | 526                | 1.25 (0.94-1.66) |                   |
| **Ejection Fraction**    |                    |             |                   |
| ≤55%                     | 959                | 1.41 (1.15-1.75) | 0.235             |
| >55%                     | 1029               | 1.15 (0.91-1.46) |                   |
| **Randomized treatment** |                    |             |                   |
| Placebo                  | 1009               | 1.17 (0.95-1.43) | 0.826             |
| Spironolactone           | 979                | 1.32 (1.05-1.66) |                   |

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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. 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.

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