Systolic blood pressure and cardiovascular outcomes in heart failure with preserved ejection fraction: an analysis of the TOPCAT trial

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Aims	Recent guidelines have advocated for stricter systolic blood pressure (SBP) control in heart failure with preserved ejection fraction (HFpEF), though data regarding the optimal SBP in HFpEF are sparse.
Methods and results	We analysed participants from the Americas from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study with available baseline and 8-week visit SBP data ($n = 1645$). We related baseline SBP to several efficacy and safety outcomes. To determine whether blood pressure lowering was responsible for the potential beneficial effects of spironolactone observed in the Americas, we assessed the randomized treatment adjusting for baseline and change in 8-week SBP. The average age was 71.7 ± 9.7 years, 50% were women, and 79% were White. Patients in the lowest baseline SBP quartile were less often female, more often White, had lower body mass index, lower baseline diastolic blood pressure and pulse pressure, and more often had atrial fibrillation. After multivariable adjustment, there was no relationship observed between baseline SBP quartiles and any outcome. Spironolactone reduced SBP by 4.4 ± 0.6 mmHg compared with placebo (and consistently across baseline SBP quartiles). There was minimal change in the treatment effect for all outcomes after adjusting for baseline SBP and 8-week change in SBP.
Conclusion	No relationship was observed between baseline SBP quartiles and outcomes in TOPCAT. The anti-hypertensive effects of spironolactone did not account for the potential benefit in cardiovascular outcomes in the Americas.
Keywords	Heart failure with preserved ejection fraction • Heart failure hospitalization • Spironolactone • Blood pressure

Introduction

Thus far, no interventions have been shown to reduce mortality in patients with heart failure with preserved ejection fraction (HFpEF), and therefore treatment has mainly focused on management of co-morbidities.[1–3] Though expert opinion suggests management of systemic hypertension remains a cornerstone of therapy, and reduction of systolic blood pressure (SBP) has reduced cardiovascular events in the general population, there is a paucity of evidence to suggest the same effect in HFpEF. For

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example, while there are several clinical trials of blood pressure (BP) lowering therapies in HFpEF,[1,2,4] a dedicated trial of BP targets powered for cardiovascular events in HFpEF has not been performed. The relationship of SBP to cardiovascular events, likewise, has not been studied in stable HFpEF outpatients.[5] The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive vs. standard BP control improved cardiovascular outcomes, including incident heart failure (HF), but this trial excluded patients with HF.[6] Despite limited data, an SBP goal of <130 mmHg was recently recommended for HFpEF patients.[7]

Hypertension is a very common co-morbidity in HFpEF, and the extent to which SBP control may influence clinical outcomes remains unclear. Control of BP in patients with HFpEF may reduce cardiovascular events by several mechanisms including improving haemodynamics, diastolic function, ventricular–arterial coupling, and left ventricular (LV) hypertrophy.[8] In the Americas, spironolactone reduced the primary and several secondary endpoints in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study.[9,10] Whether these effects were mediated through SBP reduction is unknown.

In this study, we first assessed the prognostic role of SBP in patients with HFpEF enrolled in the Americas in TOPCAT. Subsequently, we studied whether BP lowering effect of spironolactone was responsible for the potential beneficial effects observed in adverse cardiovascular event reduction in the Americas.

Methods

TOPCAT study design and objectives

The design of the TOPCAT study has been described in detail previously.[10] Briefly, TOPCAT was a multi-centre, international, randomized, double blinded, placebo-controlled trial of spironolactone in adults with HFpEF recruited from over 270 clinical sites. The trial was funded by the National Heart, Lung, and Blood Institute as a contract with the Brigham and Women's Hospital (Clinical Coordinating Center) and the New England Research Institute (Data Coordinating Center). Enrollment began in August 2006 and ended in January 2012, and the primary results of the trial were published in April 2014[11] (mean follow-up was 3.5 years). The primary aim of the TOPCAT study was to determine whether treatment with spironolactone, compared with placebo, could produce a clinically meaningful reduction in the composite outcome of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization in adults with symptomatic HF and documented LV ejection fraction (LVEF) ≥45%. All study participants provided written informed consent.

Inclusion criteria for TOPCAT were as follows: age ≥ 50 years; diagnosis of HF based on at least one HF symptom at the time of study screening and at least one HF sign within the 12 months prior to screening; LVEF ≥45% (per local reading); at least one HF hospitalization in the 12 months prior to study screening or B-type natriuretic peptide (BNP) > 100 pg/mL or N-terminal pro-BNP > 360 pg/mL (in the absence of an alternative explanation for elevated natriuretic peptide level) within the 60 days prior to screening; serum potassium <5.0 mmol/L prior to randomization.[10] In addition, SBP was required to be controlled (<140 mmHg or 140–160 mmHg if the patient was taking at least three anti-hypertensive medications to control BP). There were multiple exclusion criteria for TOPCAT, as detailed previously.[10] Examples of exclusion criteria include severe systemic illness with a

life expectancy of less than 3 years, severe chronic kidney disease, a history of significant hyperkalaemia, known intolerance to aldosterone antagonists, and recent myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention.

For the present study, we excluded: (i) patients from Russia and Georgia ($n = 1678$), given the significant regional differences previously described,[9] and (ii) missing SBP at baseline or the 8-week visit ($n = 122$). All hospitalizations were adjudicated by a clinical endpoint committee at Brigham and Women's Hospital, blinded to study-drug assignments, according to pre-specified criteria.[10] The primary endpoint of the study was the time to death from cardiovascular causes, aborted cardiac arrest, or HF hospitalization. Secondary endpoints included cardiovascular mortality, HF hospitalization, and recurrent HF hospitalization. Safety outcomes included hyperkalaemia (any serum potassium >5.5 mEq/L), hypokalaemia (any serum potassium ≤3.5 mEq/L), and doubling of serum creatinine.

Statistical analysis

Baseline characteristics grouped by quartiles of baseline SBP were described using means ± standard deviation and medians and interquartile ranges or percentages as appropriate for the levels of measurement and distributions of the variables. We used quartiles of SBP rather than clinical cut-offs in order to avoid digit preference for BP readings ending in '0'. The SBP quartiles were compared using analysis of variance (ANOVA) for continuous variables and chi-squared tests (or Fisher's exact test when appropriate) for categorical variables.

The association between SBP quartiles and the efficacy and safety outcomes were assessed using crude and multivariable adjusted Cox regression. In a complementary analysis using restricted cubic splines, we examined the association between SBP and all outcomes. Four knots placed at the 5th, 35th, 65th, and 95th percentiles were used for all efficacy outcomes, while the safety outcomes were analysed linearly. For recurrent HF hospitalization, we used negative binomial regression. Covariates were chosen based upon a combination of clinical relevance and previous prognostic implication in TOPCAT.[12] Multivariable models adjusted for New York Heart Association class, diabetes status, creatinine, heart rate, age, sex, race, smoking status, atrial fibrillation, peripheral arterial disease, ejection fraction, number of anti-hypertensive medications, and assignment to spironolactone vs. placebo.

We next determined the placebo-adjusted change in BP from baseline to the 8-week visit (the time at which maximal BP change occurred in the trial, as shown in *Figure 1*). Subsequent analyses were landmarked starting from the 8-week visit. To assess whether the treatment effect was independent of baseline SBP, an interaction term between treatment and continuous SBP was tested. Finally, to assess whether the change in SBP accounted for the beneficial effects of spironolactone, seen in the Americas, we generated Cox models assessing the relationship between treatment assignment and outcomes adjusting for baseline SBP and change in SBP between baseline and the 8-week visit. Analyses were performed using STATA version 12, and a two-sided *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 lists the baseline characteristics of the study population, stratified by quartiles of SBP. Of the initial study population of
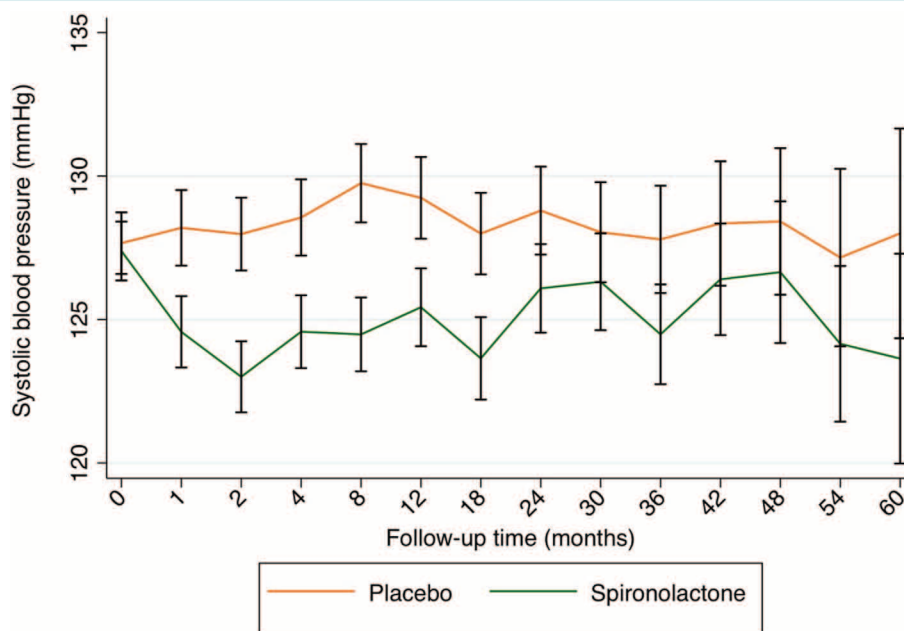
Figure 1 Average systolic blood pressure during follow-up by treatment arm. Average systolic blood pressure decreased to a maximum at the 8-week (2-month) visit in the spironolactone arm. Bars represent standard deviation.

1767 participants in the Americas, 1645 participants met the inclusion criteria for the present analysis. The mean baseline BP was $126 \pm 15/71 \pm 11$ mmHg. The average age was 71.7 ± 9.7 years, 50% were women, and 79% were White. Participants in the lowest quartile (SBP < 118 mmHg) were less often female, more often White, had lower body mass index, lower baseline diastolic BP and pulse pressure, less frequently had hypertension and diabetes mellitus, and more often had atrial fibrillation ($P < 0.05$ for all comparisons). These participants also used less BP lowering therapy and more often had evidence of LV hypertrophy on electrocardiogram ($P < 0.001$).

Table 2 shows event rates and crude and multivariable adjusted hazard ratios for all outcomes, stratified by SBP quartiles (quartile 1 designated as the referent quartile). There was no relationship between SBP quartile and any outcome after multivariable adjustment. *Figure 2* shows event rates for both safety and efficacy outcomes by SBP quartile, stratified by randomization group, and demonstrates consistent effects of spironolactone across SBP quartiles. In a complementary analysis, supplementary material online, *Figure S1* and *Figure S2* show the relationship between SBP and several efficacy and safety outcomes after multivariable adjustment. The relationship between the efficacy outlines was non-linear ($P < 0.05$ for non-linearity), whereas the relationship was linear for the safety endpoints ($P > 0.05$ for non-linearity). A J-shaped relationship was observed between SBP as a continuous variable and the primary outcome and cardiovascular death ($P < 0.05$ for overall relationship). The nadir risk appeared to occur around a SBP of 135 mmHg with the risk increasing below and above that cutoff. There was no relationship between SBP and any of the safety outcomes, though there was a trend toward an

increased risk of doubling of serum creatinine with higher SBP ($P = 0.056$)

In the overall population, spironolactone significantly reduced SBP soon after start of the therapy (*Figure 1*) compared to placebo. By the 8-week visit, SBP was -4.4 ± 0.6 mmHg mmHg lower than the placebo group (*Table 3*). SBP remained lower in the spironolactone compared to the placebo group by roughly the same amount through the 60-month duration of the study (*Figure 1*). Interestingly, as seen in *Table 3*, spironolactone had a similar BP lowering effect in the four SBP baseline quartiles (P for interaction = 0.30).

To determine whether the potential beneficial effects of spironolactone were mediated by BP reduction, we performed Cox regression (or negative binomial regression for recurrent HF hospitalization) adjusting for SBP and change in BP by the 8-week visit. As shown in *Table 4*, adjustment had little effect on the hazard ratios (or incidence rate ratio) for the composite endpoint, cardiovascular mortality, HF hospitalization, and recurrent HF hospitalization. There were no significant interactions between treatment group and baseline SBP or change in SBP (from baseline to 8-week visit) for any of the four efficacy outcomes (P for interaction >0.05 for all analyses).

Discussion

In an analysis of the TOPCAT trial restricted to the Americas, there was no relationship between SBP quartiles and efficacy outcomes after multivariable adjustment. Additionally, the beneficial effects of spironolactone in the Americas were independent of baseline SBP, and the BP reduction by spironolactone accounted for only a small proportion of the beneficial effects observed in the trial. Our

Table 1 Baseline clinical characteristics by systolic blood pressure quartile

	SBP < 118 mmHg n = 403	118 ≤ SBP < 128 mmHg n = 373	128 ≤ SBP < 138 mmHg n = 403	SBP ≥ 138 mmHg n = 466	*P-value*
SBP (mmHg)	107 ± 7	122 ± 3	132 ± 3	146 ± 7	
DBP (mmHg)	64 ± 9	70 ± 10	74 ± 10	77 ± 11	<0.001
Pulse pressure (mmHg)	43 ± 9	52 ± 9	58 ± 10	68 ± 13	<0.001
Randomization to spironolactone, n (%)	202 (50.1)	191 (51.2)	207 (51.4)	225 (48.3)	0.79
Age, years	71 ± 10	72 ± 9	72 ± 9	71 ± 10	0.41
Female, n (%)	186 (46.2)	173 (46.4)	192 (47.6)	271 (58.2)	<0.001
White race, n (%)	335 (83.1)	307 (82.3)	328 (81.4)	332 (71.2)	<0.001
NYHA class III or IV, n (%)	143 (35.6)	135 (36.3)	125 (31.0)	159 (34.1)	0.41
Enrolment through HF hospitalization stratum, n (%)	225 (55.8)	200 (53.6)	208 (51.6)	266 (57.1)	0.39
Physical characteristics					
Body mass index (kg/m^2)	32.8 ± 8.6	33.6 ± 8.6	34.0 ± 7.7	34.7 ± 8.1	0.008
Heart rate (b.p.m.)	69 ± 11	70 ± 11	69 ± 11	68 ± 12	0.2
Co-morbidities, n (%)					
Hypertension	336 (83.4)	320 (85.8)	370 (92.0)	450 (96.6)	<0.001
Atrial fibrillation	199 (49.4)	184 (49.3)	175 (43.5)	146 (31.3)	<0.001
Diabetes mellitus	165 (40.9)	161 (43.2)	171 (42.5)	235 (50.4)	0.022
Myocardial infarction	90 (22.3)	74 (19.8)	82 (20.4)	95 (20.4)	0.83
COPD	74 (18.4)	51 (13.7)	57 (14.2)	88 (18.9)	0.08
Asthma	46 (11.4)	49 (13.1)	35 (8.7)	50 (10.7)	0.26
Stroke	36 (8.9)	26 (7.0)	36 (9.0)	49 (10.5)	0.36
Peripheral arterial disease	52 (12.9)	43 (11.5)	43 (10.7)	59 (12.7)	0.75
Current smoker	23 (5.7)	27 (7.2)	23 (5.7)	28 (6.0)	0.79
Medication, n (%)					
ACEI and/or ARB	309 (76.7)	279 (75.0)	307 (76.2)	404 (86.7)	<0.001
Beta-blocker	328 (81.4)	309 (83.1)	302 (74.9)	356 (76.4)	0.012
Calcium channel blocker	117 (29.0)	125 (33.6)	155 (38.5)	237 (50.9)	<0.001
Diuretic	355 (88.1)	330 (88.7)	348 (86.4)	430 (92.3)	0.039
Other anti-hypertensive medication	54 (13.4)	49 (13.2)	60 (14.9)	106 (22.7)	<0.001
Anti-hypertensive medications, n	3.2 ± 1.2	3.1 ± 1.2	3.1 ± 1.2	3.6 ± 1.2	<0.001
Laboratory testing					
Estimated glomerular filtration rate (mL/min/1.73 m^2)	60 ± 21	60 ± 20	60 ± 19	61 ± 20	0.68
Haemoglobin (mg/dL)	12.8 ± 1.7	13.0 ± 1.7	13.0 ± 1.7	12.8 ± 1.6	0.11
ECG and imaging data					
Ejection fraction (%)	58 ± 8	58 ± 8	58 ± 8	59 ± 8	0.05
ECG left ventricular hypertrophy, n (%)	27 (8.6)	24 (8.1)	47 (15.8)	56 (16.6)	<0.001
ECG atrial fibrillation, n (%)	132 (42.0)	114 (38.3)	105 (35.2)	74 (22.0)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; NYHA, New York Heart Association; SBP, systolic blood pressure.

analysis questions the prognostic value of SBP, as well as the utility of SBP lowering, in HFpEF.

Our results are similar to findings observed in HF with reduced ejection fraction (HFrEF). Vasodilators, except for hydralazine and nitrates, consistently reduce SBP across the baseline SBP range.[13–15] Patients with the lowest baseline SBP assigned to hydralazine/nitrates showed a less significant decrease in SBP, which may be related to accompanied improved forward flow. In addition, similar to these studies, the beneficial effects of the therapies tested were independent of baseline SBP or change in SBP.

The J-shaped relationship observed in this analysis of HFpEF patients has been observed in several other high-risk patient populations, including those with coronary artery disease and diabetes as well as previous stroke.[16,17] Additionally, in a *post hoc* analysis of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

Table 2 Event rates and crude and adjusted hazard ratios for efficacy and safety outcomes by systolic blood pressure quartile

	SBP < 118 mmHg n = 403	118 ≤ SBP < 128 mmHg n = 373	128 ≤ SBP < 138 mmHg n = 403	SBP ≥ 138 mmHg n = 466
Composite endpoint				
Event rate (per 100 person-years)	13.0 (10.9, 15.4)	11.0 (9.1, 13.3)	9.6 (8.0, 11.6)	10.3 (8.6, 12.2)
Crude model HR (95% CI)	Ref.	0.86 (0.66, 1.11)	0.75 (0.58, 0.96)	0.80 (0.62, 1.02)
Multivariable adjusted model HR (95% CI)	Ref.	0.91 (0.70, 1.17)	0.84 (0.65, 1.07)	0.83 (0.65, 1.07)
Cardiovascular mortality				
Event rate (per 100 person years)	5.0 (3.8, 6.4)	4.7 (3.6, 6.1)	3.4 (2.6, 4.6)	3.3 (2.5, 4.4)
Crude model HR (95% CI)	Ref.	0.94 (0.65, 1.37)	0.69 (0.46, 1.01)	0.67 (0.45, 0.98)
Multivariable adjusted model HR (95% CI)	Ref.	0.95 (0.65, 1.39)	0.75 (0.51, 1.12)	0.71 (0.48, 1.06)
HF hospitalization				
Event rate (per 100 person years)	9.8 (8.1, 12.0)	7.9 (6.3, 9.9)	7.4 (6.0, 9.2)	8.7 (7.2, 10.5)
Crude model HR (95% CI)	Ref.	0.81 (0.60, 1.09)	0.77 (0.58, 1.03)	0.88 (0.67, 1.16)
Multivariable adjusted model HR (95% CI)	Ref.	0.86 (0.64, 1.16)	0.88 (0.66, 1.18)	0.93 (0.70, 1.23)
Recurrent HF hospitalization				
Event rate (per 100 person years)	16.1 (14.0, 18.5)	14.6 (12.5, 17.0)	13.4 (11.6, 15.6)	15.2 (13.3, 17.4)
Crude model HR (95% CI)	Ref.	0.92 (0.63, 1.34)	0.84 (0.58, 1.23)	0.91 (0.63, 1.30)
Multivariable adjusted model HR (95% CI)	Ref.	0.81 (0.57, 1.16)	0.88 (0.62, 1.26)	0.83 (0.59, 1.18)
Hyperkalaemia				
Event rate (per 100 person years)	6.8 (5.4, 8.6)	6.3 (4.9, 8.1)	5.9 (4.7, 7.5)	5.8 (4.6, 7.3)
Crude model HR (95% CI)	Ref.	0.92 (0.65, 1.30)	0.90 (0.64, 1.26)	0.87 (0.62, 1.20)
Multivariable adjusted model HR (95% CI)	Ref.	0.90 (0.64, 1.28)	0.91 (0.65, 1.28)	0.86 (0.61, 1.21)
Hypokalaemia				
Event rate (per 100 person years)	6.4 (5.1, 8.2)	7.4 (5.9, 9.4)	6.5 (5.2, 8.2)	6.8 (5.5, 8.4)
Crude model HR (95% CI)	Ref.	1.15 (0.82, 1.61)	1.05 (0.75, 1.46)	1.08 (0.78, 1.48)
Multivariable adjusted model HR (95% CI)	Ref.	1.18 (0.84, 1.64)	1.10 (0.79, 1.54)	1.09 (0.78, 1.52)
Doubling of creatinine				
Event rate (per 100 person years)	4.9 (3.8, 6.4)	5.6 (4.4, 7.3)	3.9 (2.9, 5.2)	7.0 (5.7, 8.6)
Crude model HR (95% CI)	Ref.	1.15 (0.79, 1.67)	0.80 (0.54, 1.18)	1.42 (1.01, 1.99)
Multivariable adjusted model HR (95% CI)	Ref.	1.19 (0.82, 1.72)	0.86 (0.58, 1.28)	1.29 (0.91, 1.83)

CI, confidence interval; HF, heart failure; HR, hazard ratio; SBP, systolic blood pressure.

(PARADIGM-HF) trial, a randomized trial of patients with HFrEF, the relationship between SBP and several outcomes was also noted to be J-shaped.[18] It is difficult to know, however, whether the relationship is truly causal or confounded. For instance, low SBP in HFpEF may signify a sicker patient population. In addition, a low SBP may reflect low stroke volume from atrial fibrillation or perhaps a small LV cavity due to significant hypertrophy. Consistent with this notion, the lowest quartile SBP group had a higher frequency of atrial fibrillation and demonstrated lower pulse pressure, a surrogate of stroke volume.

As a result of the SPRINT trial, professional society guidelines have recently recommended an SBP goal of <130 mmHg, a deviation from the previously defined SBP goal of <140 mmHg.[7] Notably, however, the SPRINT trial excluded patients with prevalent HF. While our primary analysis did not show significant relationships between SBP quartiles and adverse events, a complementary analysis using restricted cubic splines showed that a baseline SBP of approximately 135 mmHg represented the lowest risk for adverse events. While it is impossible to suggest 135 mmHg as the goal of therapy given the non-randomized nature of this analysis, our results raise the question of the optimal SBP goal in HFpEF.

Reducing SBP to <130 mmHg would likely require a significant increase in the use of anti-hypertensive therapy, which increases the risks associated with the anti-hypertensive therapy itself as well as polypharmacy. Therefore, a randomized trial of achieved SBP targets in HFpEF may be warranted.

We found that spironolactone modestly reduced BP in HFpEF. Interestingly, the amount of SBP reduction was less than that observed in Aldo-DHF, another study of spironolactone in HFpEF [placebo-adjusted reduction 8 (95% confidence interval 5–11) mmHg].[19] This may be related to the differences in exclusion criteria. For instance, Aldo-DHF did not have similarly strict inclusion criteria for SBP as in TOPCAT, and therefore some patients may have had more significant hyperaldosteronism that was responsive to mineralocorticoid inhibition. The magnitude of BP reduction is similar to perindopril in HFpEF,[4] but less potent than angiotensin receptor neprilysn inhibition.[20] Furthermore, the SBP reduction in TOPCAT accounted for only a very small proportion of the adverse event reduction. The potential benefits of spironolactone in HFpEF are therefore multifactorial and go beyond reducing SBP. As an extension of this principle, in the echocardiographic substudy of TOPCAT, spironolactone did not
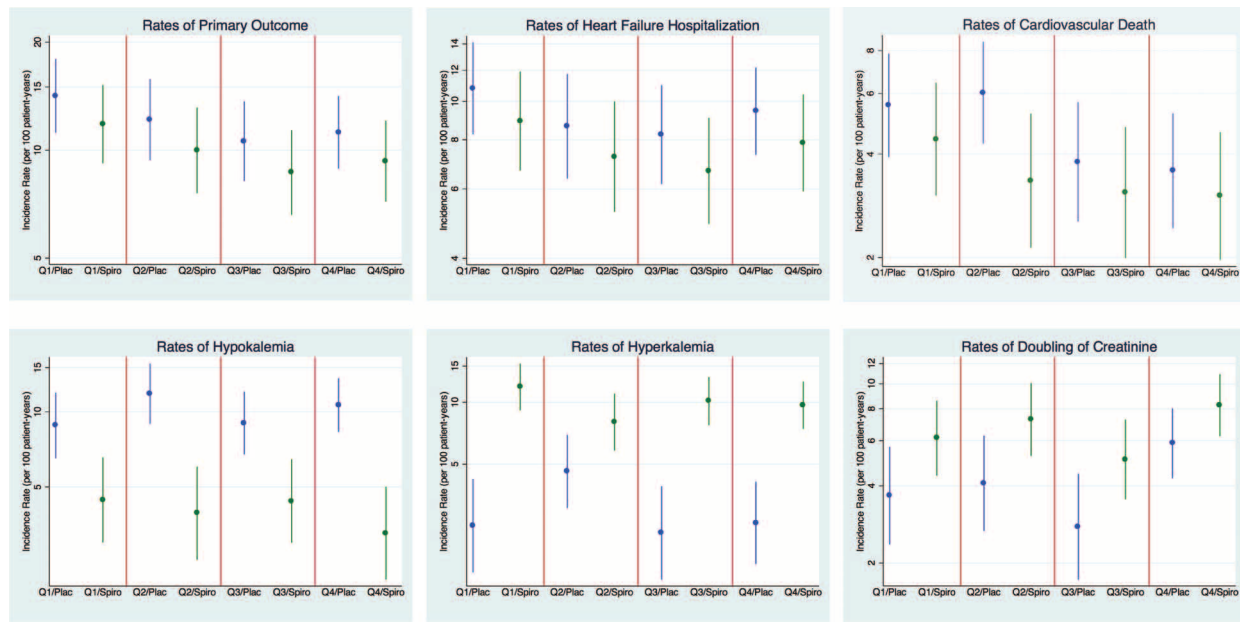
Figure 2 Event rates by systolic blood pressure quartile. Event rates are displayed for safety and efficacy outcomes by systolic blood pressure quartile and stratified by assignment to spironolactone or placebo. Spironolactone demonstrated a consistent effect across the systolic blood pressure quartiles.

Table 3 Placebo-adjusted change in systolic blood pressure at the 8-week visit by treatment arm

Baseline SBP group	Treatment effect of spironolactone vs. placebo	
	Change in SBP (95% CI)	P-value
All patients	−4.4 (−6.2, −2.7)	<0.0001
SBP < 118 mmHg	−3.1 (−6.4, 0.2)	0.068
118 mmHg ≤ SBP < 128 mmHg	−6.2 (−9.3, −3.2)	0.0001
128 mmHg ≤ SBP < 138 mmHg	−4.1 (−7.1, −1.0)	0.001
SBP ≥ 138 mmHg	−5.2 (−8.6, −1.8)	0.003

CI, confidence interval; SBP, systolic blood pressure.

significantly decrease LV mass index,[21] which may partially underpin why SBP reduction in TOPCAT by spironolactone did not relate to improved outcomes. Spironolactone, in other studies, decreased myocardial fibrosis, improved endothelial function and vascular compliance, and even reduced oxidative stress in the failing heart.[10] Accordingly, co-morbidities have been suggested to induce a pro-inflammatory state in HFpEF, which induces reactive oxygen species from coronary microvascular endothelial cells. These events, in turn, limit nitric oxide bioavailability and decrease protein kinase G activity, accelerating LV remodelling and increasing collagen production, which worsens diastolic function.[22] Thus, alternative biologic mechanisms may explain the potential beneficial effects of spironolactone and why SBP control may not be the primary driver of events in HFpEF.

Though hypertension is common in HFpEF and may drive a significant number of the pathophysiological disturbances, reducing BP when already reasonably controlled (SBP was <140 mmHg

in the vast majority of patients by trial design) may not afford additional benefit. Our results are concordant with a study of angiotensin receptor neprilysin inhibition in HFpEF using surrogate endpoints, whereby improvement in several functional, laboratory, and echocardiographic parameters was also independent of change in SBP.[20]

There are some limitations of the study. We used in office BP measures, while ambulatory BP monitoring may provide a more accurate assessment of the true treatment effect of spironolactone. In addition, because BP was well controlled in the trial, as an entry criterion, our results cannot be extrapolated to HFpEF patients with poorly controlled BP. Finally, we may have been underpowered to detect relationships between SBP and some of the less frequent efficacy or safety outcomes. Our analysis was restricted to the Americas due to regional variation, but the majority of the events occurred in the Americas.[9] Therefore, limitation of the cohort to the Americas likely resulted in only a small loss of statistical power.

Table 4 Effect of change in systolic blood pressure on the efficacy of spironolactone in reducing outcomes

Efficacy outcomes	Unadjusted hazard ratio, spironolactone vs. placebo (95% CI)	P-value	Multivariable adjusted hazard spironolactone vs. placebo (95% CI)[a]	P-value
Composite endpoint	0.82 (0.68, 0.99)	0.043	0.85 (0.70, 1.02)	0.08
Cardiovascular mortality	0.74 (0.56, 0.98)	0.037	0.73 (0.55, 0.96)	0.025
HF hospitalization	0.82 (0.66, 1.02)	0.07	0.85 (0.68, 1.06)	0.14
Recurrent HF hospitalization[b]	0.73 (0.56, 0.96)	0.022	0.76 (0.58, 0.99)	0.044

CI, confidence interval; HF, heart failure.
Analyses were landmarked from the 8-week visit.
[a]Adjusted for baseline systolic blood pressure and change in systolic blood pressure at the 8-week visit.
[b]Presented as incidence rate ratio (95% CI).

In summary, in patients with HFpEF, we did not observe significant relationships between SBP quartiles and the vast majority of the efficacy and safety outcomes. In addition, spironolactone consistently reduced SBP across baseline SBP quartiles, and BP reduction explained only a small proportion of the effect of spironolactone on several cardiovascular outcomes. The potential benefits of spironolactone in HFpEF may thus be mediated by other mechanisms. Future clinical trials of SBP targets in HFpEF may be warranted.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Relationship between systolic blood pressure and efficacy outcomes in TOPCAT.

Figure S2. Relationship between systolic blood pressure and safety outcomes in TOPCAT.

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