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RESEARCH ARTICLE

Spironolactone dose in heart failure with preserved ejection fraction: findings from TOPCAT

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Aims Spironolactone up-titration may be limited by side effects that could be minimized at lower than target doses, but whether lower than target doses remain efficacious is unknown. In TOPCAT, spironolactone (or placebo) were started at 15 mg/day, and increased up to a maximum of 45 mg/day. The prognostic implications related to spironolactone dose are yet to be reported. We aimed to assess the average spironolactone/placebo doses provided during the trial, overall and within high-risk subgroups (e.g. elderly, renal dysfunction, high potassium); discontinuation rates; and the efficacy of lower than target doses in heart failure with preserved ejection fraction.

Methods and results Overall, 1767 patients from 'TOPCAT-Americas' were included. Linear, logistic and Cox regressions were applied. Patients randomized to spironolactone received lower doses than placebo: 22.5 (15.0–27.5) mg/day vs. 27.5 (17.5–27.5) mg/day ($P < 0.001$). Patients aged ≥75 years, with an estimated glomerular filtration rate ≤60 mL/min/1.73 m^2, and with potassium levels >4.5 mmol/L, received lower spironolactone doses (median ≈ 20 mg/day). This pattern of dose differences was not observed in patients taking placebo, where the between-subgroup placebo doses were similar (spironolactone–placebo by subgroup $P_{interaction} < 0.05$). Among patients taking spironolactone, 25.4% discontinued the drug during the first year, compared with 18.3% of the patients taking placebo ($P < 0.001$). Discontinuation rates in the aforementioned high-risk subgroups reached 30% during the first year. Spironolactone reduced the primary outcome of heart failure hospitalization/cardiovascular death without significant heterogeneity between the study subgroups ($P_{interaction} > 0.1$). Spironolactone discontinuation was associated with a two to fourfold higher risk of subsequent events.

Conclusion Spironolactone (but not placebo) was used at lower doses among the elderly, those with renal dysfunction and with higher potassium levels. The effect of spironolactone was homogeneous across these subgroups. In patients unable to tolerate target doses, a low-dose strategy should be preferred to stopping treatment.

Keywords Spironolactone • Heart failure with preserved ejection fraction • Mean dose • Discontinuation • Treatment effect

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Introduction

The updated American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure (HF) guidelines give spironolactone a class of recommendation IIb ('weak benefit') with a B-R ('moderate-quality randomized evidence') level of evidence for treating patients with HF and preserved ejection fraction (HFpEF) in the absence of contraindications.[1] This recommendation is based upon the results of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial that compared spironolactone with placebo in HFpEF, showing a small reduction in the primary composite outcome of cardiovascular death, aborted cardiac arrest, and HF hospitalization, not reaching statistical significance, but showing a reduction in HF hospitalizations.[2] Importantly, major geographical variations were found in TOPCAT, whereby patients randomized in Eastern Europe had low event rates, no spironolactone effect on blood pressure or potassium (K^+) levels, and low or non-detectable levels of spironolactone metabolites in the blood.[3–6] In a *post hoc* analysis with patients from 'the Americas', spironolactone effectively reduced the rate of the primary outcome and its individual components including cardiovascular death.[3]

In TOPCAT, spironolactone (or placebo) were started at a dose of 15 mg/day, and after 4 weeks, the dose should be increased to 30 mg/day if all safety parameters were acceptable. In the event that the subject continued to have ongoing HF symptoms, the investigator had the option to increase the dose up to 45 mg/day at 4 months.[2] In patients with HF with reduced ejection fraction (HFrEF) and based on findings from RALES (Randomized Aldactone Evaluation Study),[7] current guidelines recommend spironolactone doses of 25 mg/day, titrated and maintained at 50 mg/day whenever possible. The corresponding maintenance dose of eplerenone is 50 mg/day.[1,8] In the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, eplerenone dose was stratified according to renal function, where patients with an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 received up to 25 mg/day of eplerenone, whereas patients with higher eGFR received up to 50 mg/day.[9] This stratified analysis showed that the treatment effect was consistent regardless of the eGFR dose stratum, still more patients with impaired renal function experienced more side effects, such as hyperkalaemia, despite receiving lower eplerenone doses.[10]

After TOPCAT, guidelines do not provide specific dose recommendations for HFpEF; however, it may be assumed that the doses should be within the dose range used in TOPCAT, i.e. between 15 and 45 mg/day.[1] These doses are not currently commercialized and in TOPCAT some patient subgroups might have received low doses and/or have experienced more adverse events.

In this study, we sought to assess the spironolactone (and placebo) dose provided during the trial, overall and within subgroups of interest (e.g. elderly, female, those with renal impairment or higher baseline K^+ levels). Additionally, we aim to assess the discontinuation rates and treatment effects. The background hypothesis is that if patients in these subgroups of interest took lower spironolactone doses and, despite this, had similar treatment benefit, then one can hypothesize that the minimum tolerated dose is better than stopping treatment or force up-titration, which may increase side effects and drug discontinuation.

Methods

Study design and participants

The detailed methods of TOPCAT have been previously described.[2] In short, TOPCAT enrolled 3445 patients with symptomatic HF and a left ventricular ejection fraction (LVEF) ≥45% who were randomly assigned to spironolactone (15–45 mg/day) or matching placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF.[2] The median (pct_{25-75}) follow-up time was 2.9 (1.9–4.2) years.

TOPCAT was conducted in accordance with the Declaration of Helsinki and approved by all site ethics committees. All participants gave written informed consent to participate in the study.

In TOPCAT the patient subset who both had event rates compatible with HFpEF, had spironolactone side effects and adequate levels of spironolactone circulating metabolites were those from 'the Americas'; hence, consistently with previous reports, this analysis is limited to this subset ($n = 1767$).[3,4,11,12]

Subgroups of interest

The following subgroups were selected for dose comparison: sex was chosen because a recent observational report suggesting that women with HF could respond to lower doses of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and beta-blockers compared to men[13]; age, renal function, diabetes, and baseline K^+ levels were selected because these are identified 'high-risk' subgroups who may be prone to adverse events from mineralocorticoid receptor antagonist (MRA) therapy[14–16]; body mass index, blood pressure and ACEi/ARB treatment were also selected due to their potential influence on prognosis and MRA dose.[17–20]

Statistical analyses

Spironolactone and placebo doses were summarized with medians, means and the respective 25th–75th percentile range and standard deviations (SD). The average dose was obtained by computing the sum of the spironolactone doses for each patient at each study visit and dividing it by the number of study visits. For the between-group comparison of the doses, Mann–Whitney rank-sum tests were used. To assess if the differences of the doses were different across the subgroups of interest, we performed an interaction test from a linear regression model with the spironolactone or placebo dose as dependent variable and the subgroup plus an interaction term of treatment by subgroup as independent variables. We report the mean doses during the first year of follow-up for each patient as only about 10% of missing dose values were present during this time period; the doses during the entire follow-up are also presented in the supplementary material; however, the proportion of missing values greatly increased after the first follow-up year (online supplementary *Table S1*). The proportion of spironolactone or placebo discontinuation and the

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Table 1 Drug dose during 1-year follow-up

	Placebo dose (mg/day)		Spironolactone dose (mg/day)		$P_{interaction}$
	Median (pct_{25-75})	Mean ± SD	Median (pct_{25-75})	Mean ± SD	
Overall (n = 1767)	27.5 (17.5–27.5)	23.9 ± 8.6	22.5 (15.0–27.5)	21.1 ± 9.3	–
Placebo vs. spironolactone P-value	<0.001				
Sex					
Male (n = 885)	27.5 (17.5–27.5)	23.6 ± 8.7	22.5 (15.0–27.5)	21.4 ± 9.1	0.23
Female (n = 882)	27.5 (20.0–27.5)	24.2 ± 8.5	22.5 (15.0–27.5)	20.9 ± 9.5	
Male vs. female P-value	0.40		0.51		
Age					
<75 years (n = 1020)	27.5 (17.5–27.5)	24.0 ± 8.3	25.0 (15.0–27.5)	22.1 ± 9.0	0.016
≥75 years (n = 747)	27.5 (17.5–27.5)	23.8 ± 9.0	20.0 (15.0–27.5)	19.9 ± 9.6	
<75 vs. ≥75 years P-value	0.99		<0.001		
eGFR					
≤60 mL/min (n = 854)	27.5 (17.5–27.5)	23.3 ± 8.6	20.0 (12.5–27.5)	19.1 ± 9.1	0.002
>60 mL/min (n = 912)	27.5 (20.0–30.0)	24.5 ± 8.5	26.6 (15.0–27.5)	23.0 ± 9.2	
≤60 vs. >60 mL/min P-value	0.027		<0.001		
Diabetes					
No diabetes (n = 788)	27.5 (20.0–27.5)	24.1 ± 8.6	22.5 (15.0–27.5)	21.3 ± 9.3	0.81
Diabetes (n = 977)	27.0 (17.5–27.5)	23.7 ± 8.6	22.5 (15.0–27.5)	20.9 ± 9.5	
No diabetes vs. diabetes P-value	0.17		0.48		
Potassium					
≤4.5 mmol/L (n = 1389)	27.5 (17.5–27.5)	24.0 ± 8.7	24.0 (15.0–27.5)	21.7 ± 9.1	0.011
>4.5 mmol/L (n = 377)	27.5 (17.5–27.5)	23.6 ± 8.3	17.5 (12.5–27.5)	18.7 ± 10.0	
≤4.5 vs. >4.5 mmol/L P-value	0.60		0.001		
Body mass index					
≤30 kg/m^2 (n = 623)	27.5 (17.5–27.5)	23.1 ± 8.5	20.0 (15.0–27.5)	20.1 ± 9.1	0.52
>30 kg/m^2 (n = 1135)	27.5 (20.0–30.0)	24.4 ± 8.6	25.0 (15.0–27.5)	21.7 ± 9.4	
≤30 vs. >30 kg/m^2 P-value	0.039		0.004		
Systolic blood pressure					
≤120 mmHg (n = 615)	27.0 (16.3–27.5)	23.4 ± 8.8	22.5 (15.0–27.5)	21.1 ± 9.4	0.34
>120 mmHg (n = 1149)	27.5 (18.8–27.5)	24.2 ± 8.5	22.5 (15.0–27.5)	21.1 ± 9.3	
≤120 vs. >120 mmHg P-value	0.10		0.95		
ACEi/ARB treatment					
No ACEi/ARB (n = 381)	27.5 (17.5–27.5)	23.6 ± 8.6	22.5 (15.0–27.5)	21.3 ± 9.3	0.60
ACEi/ARB (n = 1385)	27.5 (18.8–27.5)	24.0 ± 8.6	22.5 (15.0–27.5)	21.1 ± 9.4	
No ACEi/ARB vs. ACEi/ARB P-value	0.74		0.81		

Values are given as median (25th–75th percentile) and mean ± SD.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; SD, standard deviation.
P-values are derived from a Mann–Whitney rank-sum test (with similar results from the Student's t-test); the interaction test is derived from a linear regression model.

studied side effects are reported with absolute numbers and proportions and compared using Chi-square tests. To assess if the differences in discontinuation and side effects found between the subgroups of interest were statistically significant, we performed an interaction test from a logistic regression model with discontinuation or side effect as dependent variable and the subgroup plus a treatment by subgroup interaction term as independent variables. Logistic regression models were used to assess the determinants of spironolactone up-titration during the first month. Cox proportional hazards models were used to explore the association between spironolactone treatment and the study primary outcome. The treatment effect estimates are presented with hazard ratios (HRs) and their respective 95% confidence interval (95% CI). To assess whether the treatment effect could vary by subgroup of interest, we performed interaction tests between the treatment and the subgroup of interest. Time-updated models were used to study the associations between spironolactone (or placebo) discontinuation and subsequent outcomes. Landmark analyses were performed to assess the association between spironolactone (or placebo) 4-week up-titration and subsequent outcomes. Statistical analyses were performed using the STATA/SE software, version 16.0 (Stata Corp, College Station, TX, USA).

Results

Spironolactone and placebo doses

As previously reported,[3] the median age was 72 (64–79) years, 41% were aged ≥75 years, 50% were female, the median body mass index (BMI) was 32 (28–38) kg/m^2, 45% had diabetes, 79% were treated with an ACEi/ARB, 48% had chronic kidney disease,

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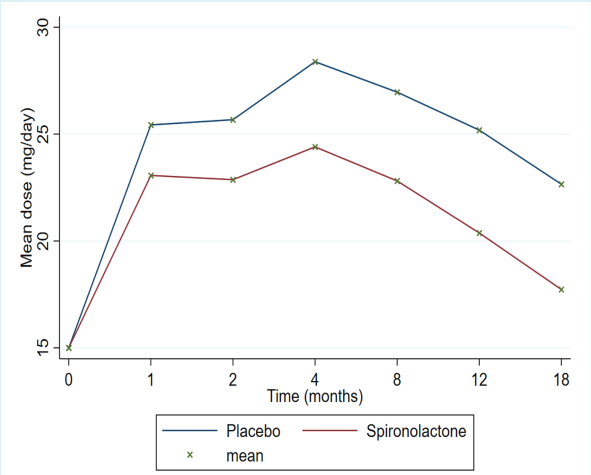

Figure 1 Profile plot of spironolactone vs. placebo dose throughout the follow-up. Representation of the spironolactone and placebo doses (in mg/day) over time.

the median eGFR was 61 (49–77) mL/min/1.73 m^2, the median K^+ was 4.2 (3.9–4.5) mmol/L, the median systolic blood pressure (SBP) was 129 (118–138) mmHg, and the median LVEF was 58 (53–64)%.

Patients randomized to spironolactone received lower doses than placebo. Overall, the median (pct_{25-75})/mean ± SD dose during 1-year follow-up was 27.5 (17.5–27.5)/23.9 ± 8.6 mg/day in the placebo group vs. 22.5 (15.0–27.5)/21.1 ± 9.3 mg/day in the spironolactone group ($P < 0.001$) (*Table 1, Figure 1* and online supplementary *Figure S1*).

In subgroups, women and men, diabetics and non-diabetics, those with a SBP below or above 120 mmHg, and those taking or not an ACEi/ARB received similar spironolactone and placebo doses (*Table 1*). Patients with a BMI ≤30 kg/m^2 received lower spironolactone doses than those with a BMI >30 kg/m^2; but without significant statistical heterogeneity vs. patients receiving a placebo ($P_{interaction} = 0.52$). Patients, aged ≥75 years, with an eGFR ≤60 mL/min/1.73 m^2, and those with a baseline K^+ >4.5 mmol/L, received lower spironolactone doses than patients aged <75 years, with an eGFR >60 mL/min/1.73 m^2, and with a K^+ ≤4.5 mmol/L, respectively; with significant heterogeneity vs. patients receiving placebo ($P_{interaction} < 0.05$).

In patients taking placebo, the between-subgroup placebo doses were similar and the dose difference pattern observed in patients taking spironolactone was not observed in those taking the corresponding placebo (*Table 1* and *Figure 2*).

Similar findings were observed during the first year at equally spaced time-points (4, 8 and 12 months) (online supplementary *Table S2*), and throughout the entire follow-up, where even lower doses were administered (online supplementary *Table S3*). (It should be noted that these findings including data from the entire follow-up period may be biased by a large proportion of missing values and drug discontinuation).

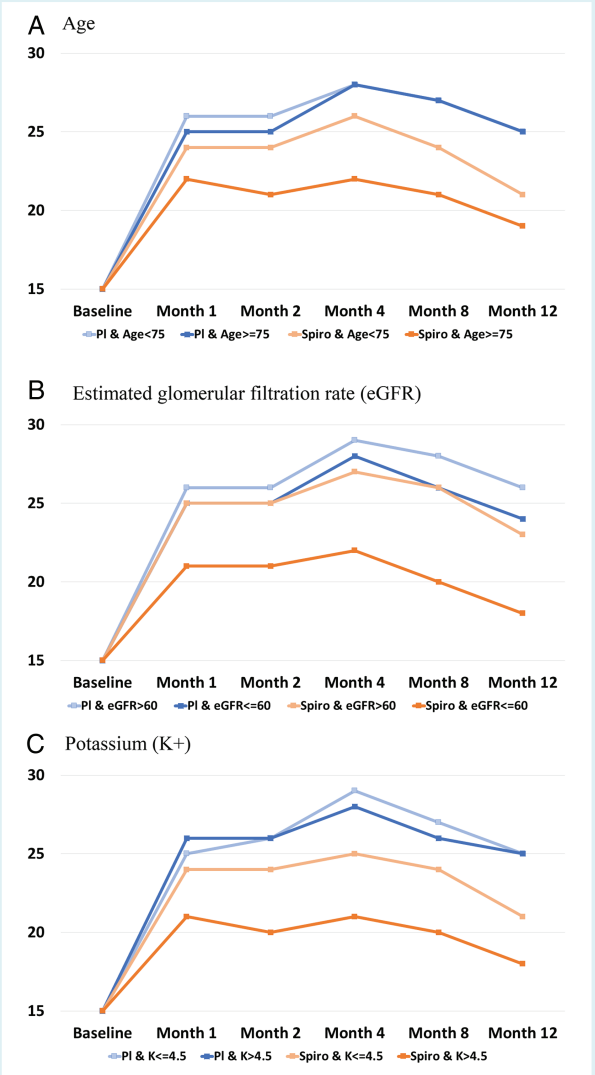

Figure 2 Spironolactone dose by subgroups over time. (*A*) Age. (*B*) Estimated glomerular filtration rate (eGFR). (*C*) Potassium (K^+). The y-axis represents the mean treatment dose in mg/day; the treatment by subgroup $P_{interaction}$ is <0.05 for all the represented subgroups (see also *Table 1*).

Spironolactone and placebo discontinuation

Among patients taking spironolactone, 25.4% discontinued the drug during the first year of the trial, compared with 18.3% of patients taking placebo ($P < 0.001$) (*Table 2*). Again, patients aged ≥75 years, and especially those with an eGFR ≤60 mL/min/1.73 m^2, and K^+ >4.5 mmol/L were more likely to permanently stop the drug, with discontinuation rates reaching 30% or more compared with 18% in the placebo group ($P_{interaction} < 0.05$ for eGFR and K^+) (*Table 2*).

The main reported discontinuation reasons were hyperkalaemia, worsening renal function (WRF) and off-label MRA use (online supplementary *Table S4*).

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Table 2 Drug discontinuation during 1-year follow-up

	Placebo discontinuation	Spironolactone discontinuation	$P_{interaction}$
Overall ($n = 1767$)	161 (18.3)	225 (25.4)	–
Placebo vs. spironolactone *P*-value	–	<0.001	
Sex			
Male ($n = 885$)	85 (19.3)	114 (25.7)	0.65
Female ($n = 882$)	76 (17.3)	111 (25.1)	
Male vs. female *P*-value	0.44	0.85	
Age			
<75 years ($n = 1020$)	96 (18.3)	114 (23.1)	0.25
≥75 years ($n = 747$)	65 (18.3)	111 (28.1)	
<75 vs. ≥75 years *P*-value	0.98	0.075	
eGFR			
≤60 mL/min ($n = 854$)	77 (17.8)	125 (29.6)	0.036
>60 mL/min ($n = 912$)	84 (18.9)	100 (21.6)	
≤60 vs. >60 mL/min *P*-value	0.72	0.006	
Diabetes			
No diabetes ($n = 788$)	84 (17.4)	118 (23.8)	0.82
Diabetes ($n = 977$)	77 (19.4)	107 (27.4)	
No diabetes vs. diabetes *P*-value	0.45	0.23	
Potassium			
≤4.5 mmol/L ($n = 1389$)	126 (18.6)	167 (23.5)	0.043
>4.5 mmol/L ($n = 377$)	35 (17.3)	58 (33.1)	
≤4.5 vs. >4.5 mmol/L *P*-value	0.69	0.009	
Body mass index			
≤30 kg/m^2 ($n = 623$)	59 (18.5)	82 (27.0)	0.59
>30 kg/m^2 ($n = 1135$)	102 (18.4)	141 (24.3)	
≤30 vs. >30 kg/m^2 *P*-value	0.97	0.39	
Systolic blood pressure			
≤120 mmHg ($n = 615$)	54 (17.1)	71 (23.8)	0.99
>120 mmHg ($n = 1149$)	107 (19.0)	153 (26.1)	
≤120 vs. >120 mmHg *P*-value	0.48	0.44	
ACEi/ARB treatment			
No ACEi/ARB ($n = 381$)	36 (19.5)	43 (21.9)	0.23
ACEi/ARB ($n = 1385$)	125 (18.0)	182 (26.4)	
No ACEi/ARB vs. ACEi/ARB *P*-value	0.65	0.21	

Values are given as numbers and proportions (%).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.
P-values are derived from a Chi^2 test; the interaction test is derived from a logistic regression.

Determinants of treatment up-titration at 4 weeks

During the first month, 531 (30.0%) of patients were not up-titrated to 30 mg/day. Patients without successful up-titration were more likely to be older, have lower eGFR, a BMI ≤30 kg/m^2, and a SBP ≤120 mmHg (online supplementary *Table S5*). Patients without successful up-titration did not experience higher event rate, nor the risk was modified by the randomized treatment allocation (spironolactone or placebo) (online supplementary *Table S6*).

Treatment effect

As previously reported,[3] spironolactone reduced the primary outcome of HF hospitalization or cardiovascular death without significant heterogeneity between the study subgroups ($P_{interaction} > 0.1$ for all) (online supplementary *Table S7*).

Side effects

Patients taking spironolactone experienced more often WRF and hyperkalaemia episodes during the follow-up. Diabetes was a risk factor for both WRF and hyperkalaemia. Females also had more WRF episodes; and patients with eGFR ≤60 mL/min/1.73 m^2, those with baseline K^+ >4.5 mmol/L, those taking ACEi/ARB and with SBP >120 mmHg also had more hyperkalaemia episodes (*Table 3*).

Time-updated outcomes after treatment discontinuation

Treatment discontinuation was associated with a two to fourfold higher risk of major cardiovascular events in adjusted models

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Table 3 Worsening renal function and hyperkalaemia occurrence at any time-point during the trial

	Placebo side effect	Spironolactone side effect	$P_{interaction}$
Overall ($n = 1767$)			–
Worsening renal function	289 (32.8)	389 (43.9)	
Placebo vs. spironolactone *P*-value	–	<0.001	
Hyperkalaemia	46 (5.2)	141 (15.9)	
Placebo vs. spironolactone *P*-value	–	<0.001	
Sex			
Worsening renal function			
Male ($n = 885$)	129 (29.3)	175 (39.4)	0.81
Female ($n = 882$)	160 (36.4)	214 (48.5)	
Male vs. female *P*-value	0.025	0.006	
Hyperkalaemia			
Male ($n = 885$)	22 (5.0)	73 (16.5)	0.63
Female ($n = 882$)	24 (5.5)	68 (15.4)	
Male vs. female *P*-value	0.76	0.66	
Age			
Worsening renal function			
<75 years ($n = 1020$)	179 (34.0)	217 (43.9)	0.48
≥75 years ($n = 747$)	110 (31.0)	172 (44.0)	
<75 vs. ≥75 years *P*-value	0.35	0.99	
Hyperkalaemia			
<75 years ($n = 1020$)	27 (5.2)	74 (15.0)	0.73
≥75 years ($n = 747$)	19 (5.4)	67 (17.2)	
<75 vs. ≥75 years *P*-value	0.90	0.38	
eGFR			
Worsening renal function			
≤60 mL/min ($n = 854$)	147 (34.0)	188 (44.7)	0.76
>60 mL/min ($n = 912$)	141 (31.5)	201 (43.3)	
≤60 vs. >60 mL/min *P*-value	0.42	0.69	
Hyperkalaemia			
≤60 mL/min ($n = 854$)	30 (6.9)	97 (23.0)	0.35
>60 mL/min ($n = 912$)	16 (3.6)	44 (9.5)	
≤60 vs. >60 mL/min *P*-value	0.026	<0.001	
Diabetes			
Worsening renal function			
No diabetes ($n = 788$)	141 (29.3)	198 (40.1)	0.98
Diabetes ($n = 977$)	147 (37.0)	191 (48.9)	
No diabetes vs. diabetes *P*-value	0.015	0.009	
Hyperkalaemia			
No diabetes ($n = 788$)	20 (4.2)	64 (13.0)	0.94
Diabetes ($n = 977$)	26 (6.6)	77 (20.0)	
No diabetes vs. diabetes *P*-value	0.12	0.006	
Potassium			
Worsening renal function			
≤4.5 mmol/L ($n = 1389$)	215 (31.7)	323 (45.5)	0.032
>4.5 mmol/L ($n = 377$)	73 (36.1)	66 (37.7)	
≤4.5 vs. >4.5 mmol/L *P*-value	0.24	0.063	
Hyperkalaemia			
≤4.5 mmol/L ($n = 1389$)	22 (3.3)	90 (12.7)	0.35
>4.5 mmol/L ($n = 377$)	24 (11.9)	51 (29.3)	
≤4.5 vs. >4.5 mmol/L *P*-value	<0.001	<0.001	
Body mass index			
Worsening renal function			
≤30 kg/m^2 ($n = 623$)	94 (29.5)	131 (43.2)	0.40
>30 kg/m^2 ($n = 1135$)	191 (34.4)	258 (44.5)	
≤30 vs. >30 kg/m^2 *P*-value	0.13	0.72	

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Table 3 (Continued)

	Placebo side effect	Spironolactone side effect	$P_{interaction}$
Hyperkalaemia			
≤30 kg/m^2 (n = 623)	13 (4.1)	51 (16.8)	0.25
>30 kg/m^2 (n = 1135)	32 (5.8)	90 (15.6)	
≤30 vs. >30 kg/m^2 *P*-value	0.28	0.65	
Systolic blood pressure			
Worsening renal function			
≤120 mmHg (n = 615)	88 (27.9)	117 (39.1)	0.80
>120 mmHg (n = 1149)	200 (35.5)	272 (46.5)	
≤120 vs. >120 mmHg *P*-value	0.020	0.037	
Hyperkalaemia			
≤120 mmHg (n = 615)	16 (5.1)	47 (15.7)	0.95
>120 mmHg (n = 1149)	30 (5.3)	94 (16.1)	
≤120 vs. >120 mmHg *P*-value	0.87	0.88	
ACEi/ARB treatment			
Worsening renal function			
No ACEi/ARB (n = 381)	61 (33.0)	77 (39.3)	0.28
ACEi/ARB (n = 1385)	227 (32.7)	312 (45.3)	
No ACEi/ARB vs. ACEi/ARB *P*-value	0.94	0.13	
Hyperkalaemia			
No ACEi/ARB (n = 381)	13 (7.1)	22 (11.2)	0.027
ACEi/ARB (n = 1385)	33 (4.8)	119 (17.3)	
No ACEi/ARB vs. ACEi/ARB *P*-value	0.21	0.040	

Values are given as numbers and proportions (%).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.
Worsening renal function defined as any eGFR drop >30% from the baseline value during the follow-up.
Hyperkalaemia defined as any potassium measurement >5.5 mmol/L during the follow-up.
P-values are derived from a Chi^2 test; the interaction test is derived from a logistic regression.

(*Table 4*). Compared with placebo, the risk was higher after spironolactone discontinuation, although the interaction test did not reach statistical significance. Primary outcome example: HR (95% CI) for placebo = 1.63 (1.22–2.18) and HR (95% CI) for spironolactone = 2.28 (1.72–3.02); $P_{interaction}$ = 0.13 (*Table 4*).

Discussion

The present study shows that spironolactone (but not placebo) was used at lower doses among the elderly, those with impaired renal function and with higher K^+ levels at baseline. Most of these patients received around 20 mg/day of spironolactone within the first year of follow-up, and around 15 mg/day if one considers the entire follow-up. These patients had more adverse events and discontinued the treatment more often. Nonetheless, the effect of spironolactone was homogeneous across these subgroups. These findings suggest that spironolactone doses <25 mg/day (around 15–20 mg/day) may be used in HFpEF, particularly in high-risk patients that may not tolerate higher doses. Keeping the patients on treatment (even with lower than recommended doses) seems preferable to stopping treatment, as the latter may increase the risk of subsequent events. It should also be highlighted that other subgroups such as men/women, diabetes/no-diabetes, ACEi/ARB treatment/no-ACEi/ARB treatment received similar spironolactone doses.

Differently from ACEi/ARBs and β-blockers in which randomized trials compared different doses of these drugs,[21–26] no trials have compared different MRA doses. So far, the best available evidence comes from the EMPHASIS-HF trial, where patients were stratified to different eplerenone or placebo doses according to renal function.[10] Despite receiving lower eplerenone or placebo doses, patients with impaired renal function experienced more side effects; however, the treatment effect was not modified by treatment dose/renal function ($P_{interaction}$ = 0.89). Hence, this stratified evidence strongly support the use of lower (≈25 mg/day) eplerenone doses in patients with HFrEF and impaired renal function. This way, the beneficial effect of treatment is preserved, while excessive dose-related side effects can be potentially avoided. Secondary non-stratified analyses of the TOPCAT trial suggest that elderly patients, those with impaired renal function and higher K^+ levels experience more adverse events and have higher rates of drug discontinuation without treatment effect heterogeneity between these subgroups.[11,27] The data depicted in the present report show that the spironolactone doses given to the elderly, to those with impaired renal function and with higher baseline K^+ are lower than the doses given to the younger, with better renal function and with lower K^+ levels. Importantly, the placebo doses were

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Table 4 Time-updated models to assess the risk of events after spironolactone or placebo discontinuation ($n = 1767$)

Outcome	No. (%) events before discontinuation (12 549 observations)	No. (%) events after discontinuation (4345 observations)	HR (95% CI)	*P*-value	$P_{interaction}$*
CV death or HFH ($n = 522$)	348 (2.9)	174 (5.1)	1.88 (1.55–2.29)	<0.001	0.13
CV death ($n = 223$)	106 (0.8)	117 (2.7)	2.76 (2.08–3.66)	<0.001	0.15
ACM ($n = 387$)	154 (1.2)	233 (5.4)	3.76 (3.02–4.67)	<0.001	0.32

ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio.
All models adjusted for age, sex, body mass index, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, estimated glomerular filtration rate, potassium, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
*P-value for interaction between drug discontinuation and spironolactone or placebo allocation.
HR (95%CI) for the placebo and spironolactone groups:
– CV death or HFH: HR (95% CI) 1.63 (1.22–2.18) and 2.28 (1.72–3.02) for placebo and spironolactone, respectively.
– CV death: HR (95% CI) 2.45 (1.69–3.56) and 3.60 (2.29–5.65) for placebo and spironolactone, respectively.
– ACM: HR (95% CI) 3.56 (2.64–4.77) and 4.38 (3.13–6.12) for placebo and spironolactone, respectively.

similar between these subgroups, strongly supporting the inability for titrating spironolactone to higher doses due to side effects and intolerance. During the first year of follow-up, the median dose among these high-risk subgroups was around 20 mg/day; and, importantly, treatment discontinuation rates reached nearly 30% for spironolactone vs. 18% for placebo in these subgroups. Discontinuation rates reaching 30% of the patients may seriously compromise the treatment effect that is aimed to improve medium to long-term outcomes, including repeat hospitalizations.[28] Furthermore, spironolactone discontinuation was associated with a subsequent high rate of adverse cardiovascular events. These findings support the continuation of spironolactone, even at lower doses (15–20 mg/day) if patients cannot tolerate higher doses. Furthermore, patients without successful up-titration during the 4-week optimization period did not experience higher event rates, nor the risk was modified by the randomized treatment allocation, supporting the notion that lower than target doses may also be effective. Strategies aimed at enabling an adequate drug maintenance and potential up-titration of renin–angiotensin–aldosterone system inhibitors, such as K^+ binders,[29] may be important to improve outcomes of HF patients; however, adequately powered outcome trials to assess the efficacy and safety of such a strategy are yet to be performed.[30] Furthermore, newer generation MRAs may be better tolerated than spironolactone.[31] However, these molecules also need to show that they are, at least, non-inferior to spironolactone. Despite these advances, it is likely that spironolactone will remain the most widely used MRA, mainly because it is affordable, widely available, and with a large and long clinical experience.[32] Still, MRAs are generally underused, even in populations who might experience great benefit.[33] With regard to dose adaptations, and until further evidence is available, it seems reasonable to adapt the spironolactone dose according to renal function and K^+ levels based on an algorithm that has been used in clinical trials (online supplementary *Table S8*). Notwithstanding, the data suggest that having lower spironolactone dose is better than stopping the drug, and efforts should be placed in order to keep patients on treatment.

Limitations

This is a post-hoc analysis of a randomized controlled trial, thus these findings are subject to the bias of observational studies, such as the impossibility of inferring causality. From the case repord forms we could not ascertain the exact reasons for study discontinuation in all patients; however, the provided reasons (e.g. renal dysfunction and hyperkalaemia) are expected and consistent with the previous reports. From these data, one cannot infer which spironolactone dose is more adequate; one can only say that many patients did not reach the target of dose of 45 mg/day, especially among those in the aforementioned high-risk subgroups that received less than half of the recommended dose. As the treatment effect was consistent in these subgroups, one may suppose that lower doses are probably as efficient and could avoid some side effects. Contrary to the EMPHASIS-HF trial (that had a pre-specified eplerenone dose stratification by renal function),[10] the TOPCAT trial assumed *a priori* that all patients should achieve similar spironolactone (or placebo) doses, hence the findings reported herein do not represent randomized evidence and should be regarded as hypothesis-generating. The association of spironolactone discontinuation with subsequent outcomes likely reflects the underlying patient risk rather than the direct treatment effect and, therefore, causality cannot be inferred. This study does not compare 'high vs. low' doses, instead it simply reports the 'average' doses. To ascertain the optimal spironolactone dose for patients with HFpEF (including the dose for high-risk subgroups), prospective, randomized and adequately powered studies will be required.

Conclusions

Spironolactone (but not placebo) was used at lower doses among the elderly, those with impaired renal function and higher K^+ levels at baseline. Most of these patients received around 20 mg/day of spironolactone within the first year of follow-up, which was less than half of the target dose. These patients had more adverse events and discontinued the treatment more often. Despite the lower treatment doses and higher discontinuation rates, the effect

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of spironolactone was homogeneous across these subgroups. These findings suggest that patients unable to tolerate target doses of spironolactone may benefit from lower doses that are possibly better tolerated while maintaining efficacy. A low-dose strategy should be preferred to stopping the treatment.

Supplementary Information

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

Table S1. Missing values on treatment doses.

Table S2. Drug dose during 1-year follow-up at equally spaced time-points (4, 8, and 12 months).

Table S3. Drug dose (mg) during the entire follow-up.

Table S4. Reported reasons for drug discontinuation.

Table S5. Factors associated with no spironolactone up-titration to 30 mg/day or more at day 30, i.e. the spironolactone dose achieved at 30 days was lower than 30 mg/day ($n = 531$).

Table S6. Landmark analysis of spironolactone (or placebo) achieved dose during the 4-week up-titration period ($n = 1656$).

Table S7. Subgroup analyses for the treatment effect (spironolactone vs. placebo) on the primary outcome of cardiovascular death or hospitalization for heart failure (total $n = 1767$).

Table S8. Dose adjustments after initiation of spironolactone treatment.

Figure S1. Histogram representation of the spironolactone vs. placebo dose throughout the follow-up.

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