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Spironolactone in Patients With Heart Failure, Preserved Ejection Fraction, and Worsening Renal Function

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ABSTRACT

BACKGROUND Treatment of heart failure with preserved ejection fraction (HFpEF) with spironolactone is associated with lower risk of heart failure hospitalization (HFH) but increased risk of worsening renal function (WRF). The prognostic implications of spironolactone-associated WRF in HFpEF patients are not well understood.

OBJECTIVES The purpose of this study was to investigate the association between WRF, spironolactone treatment, and clinical outcomes in patients with HFpEF.

METHODS In 1,767 patients randomized to spironolactone or placebo in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial)-Americas study, we examined the incidence of WRF (doubling of serum creatinine) by treatment assignment. Associations between incident WRF and subsequent risk for the primary study endpoint of cardiovascular (CV) death, HFH, or aborted cardiac arrest and key secondary outcomes, including CV death, HFH, and all-cause mortality according to treatment assignment, were examined in time-updated Cox proportional hazards models with an interaction term.

RESULTS WRF developed in 260 (14.7%) patients with higher rates in those assigned to spironolactone compared to placebo (17.8% vs. 11.6%; odds ratio: 1.66; 95% confidence interval: 1.27 to 2.17; $p < 0.001$). Regardless of treatment, incident WRF was associated with increased risk for the primary endpoint (hazard ratio: 2.04; 95% confidence interval: 1.52 to 2.72; $p < 0.001$) after multivariable adjustment. Although there was no statistical interaction between treatment assignment and WRF regarding the primary endpoint (interaction $p = 0.11$), spironolactone-associated WRF was associated with lower risk of CV death (interaction $p = 0.003$) and all-cause mortality (interaction $p = 0.001$) compared with placebo-associated WRF.

CONCLUSIONS Among HFpEF patients enrolled in TOPCAT-Americas, spironolactone increased risk of WRF compared with placebo. Rates of CV death were lower with spironolactone in both patients with and without WRF.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

WRF = worsening renal function

Worsening renal function (WRF) complicates medical treatment in approximately 25% of patients with chronic heart failure (HF), and is associated with a heightened risk of subsequent mortality, regardless of ejection fraction (1–5). In patients with heart failure and reduced ejection fraction (HFrEF), treatment with renin-angiotensin aldosterone system (RAAS) inhibitors, including mineralocorticoid receptor antagonists (MRAs), is associated with important reductions in HF hospitalization and mortality, but may increase the risk of WRF, perhaps due to alterations in intrarenal hemodynamics (6). Data from clinical trials of MRAs enrolling patients with HFrEF suggest that the prognostic implications of WRF associated with MRA treatment are less severe than WRF in placebo-treated patients and that clinical benefits of MRAs are maintained even among patients who experience WRF, leading some to classify this as pseudo-WRF (7).

Based on the reduction in HF hospitalizations and cardiovascular death seen during spironolactone treatment of HFpEF in the subset of patients from the Americas enrolled in the TOPCAT (Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial), MRAs are now encouraged for treatment of selected patients with HFpEF by consensus guidelines (8–13). However, more data are needed to inform the balance of safety and efficacy in spironolactone treatment of HFpEF. Using data from TOPCAT-Americas, we sought to explore the incidence of WRF and its prognostic implications in relation to spironolactone treatment in HFpEF.

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METHODS

PATIENT POPULATION. TOPCAT was a multinational, double-blind, randomized, placebo-controlled, parallel-group study that investigated the effects of the mineralocorticoid receptor antagonist (MRA) spironolactone versus placebo on clinical outcomes in patients with HFpEF. The rationale and design of the study have been previously published (11). In short, the trial included 3,445 patients >50 years of age with symptomatic HF and preserved ejection fraction (defined as a left ventricular ejection fraction ≥45%), who were followed for a mean of 3.3 years. Eligible patients had to have systolic blood pressure <140 mm Hg, serum potassium <5.0 mmol/l, and either a prior HF hospitalization within 12 months or elevated natriuretic peptide levels (B-type natriuretic peptide ≥100 pg/ml or N-terminal pro-B-type natriuretic peptide ≥360 pg/ml). Key exclusion criteria were severe renal dysfunction (defined as estimated glomerular function rate [eGFR] <30 ml/min/1.73 m^2 or serum creatinine ≥2.4 mg/dl), severe systemic illness with life expectancy of <3 years from randomization, and use of an aldosterone antagonist or potassium sparing diuretic agent within 14 days before randomization.

Due to previously reported differences in patient demographics, event rates, adherence to study medication, responses to treatment, and outcomes among TOPCAT subjects enrolled in Russia and the Republic of Georgia, we restricted our analyses to the subset of TOPCAT subjects enrolled in the Americas (United States, Canada, Argentina, Brazil; N = 1,767) (9,10,14).

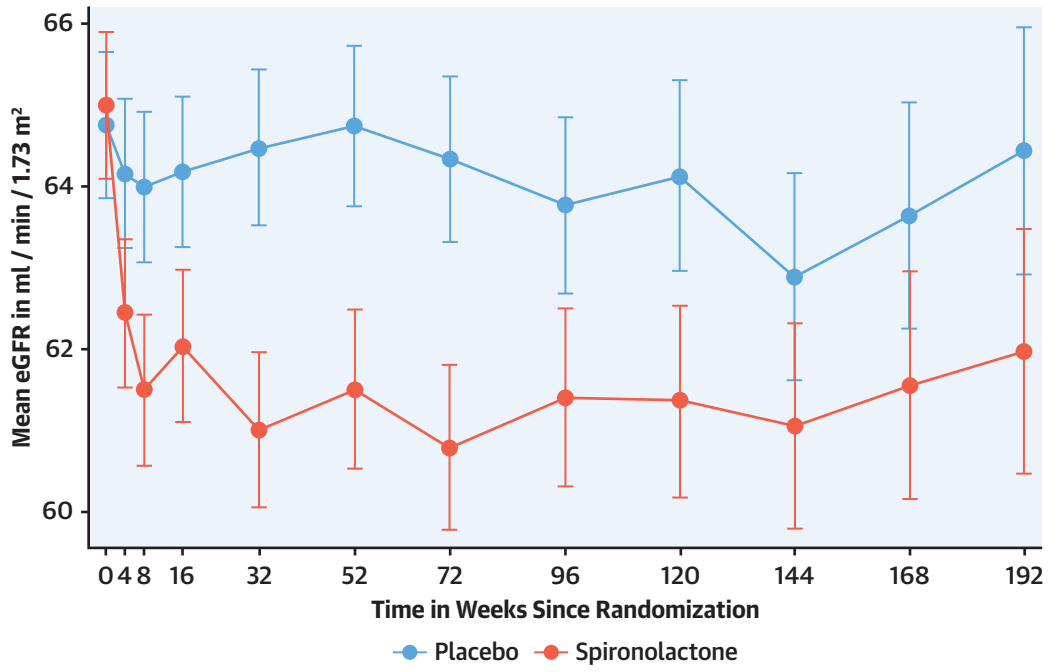
All patients provided informed consent. The protocol was approved by the Institutional Review Board at each of the participating centers prior to enrollment of the first patient. The study was overseen by the Institutional Review Board.

DEFINITION OF WORSENING RENAL FUNCTION. Per the study protocol, worsening renal function was defined as a serum creatinine value that increased to at least double the baseline value and was above an upper reference limit of 1.0 mg/dl for women and 1.2 mg/dl for men (11). Changes in eGFR from baseline to month 4 were also examined using the Chronic Kidney Disease Epidemiology Collaboration equation (15). As a sensitivity analysis, we also examined a more contemporary, eGFR-based definition of worsening renal function from the literature, defined as an absolute increase in creatinine of >0.3 mg/dl and a relative increase of creatinine of >25% or a relative decrease of eGFR of >25%, between baseline and month 4 (3,5,16,17).

MONITORING REGIMEN. Serum creatinine and serum potassium concentrations were recorded at baseline, at all scheduled study visits, and within 1 week of dose adjustment for all enrolled study subjects. Study drug instructions included a recommendation for down-titration for patients with serum potassium measurements ≥5.5 mmol/l and discontinuation for serum potassium ≥6.0 mmol/l or serum creatinine ≥3.0 mg/dl. If a potential nonstudy medication reason was identified for hyperkalemia or elevated creatinine, study drug could be restarted after consultation with the medical monitor (11).

STUDY OUTCOMES. The primary endpoint was the primary TOPCAT composite endpoint of cardiovascular death, aborted cardiac arrest, or hospitalization for the management of HF. Secondary study outcomes included cardiovascular death, all-cause

FIGURE 1 Mean eGFR (CKD-EPI) by Treatment



Change in mean estimated glomerular filtration rate (eGFR) over time in patients with heart failure with preserved ejection fraction treated with spironolactone and placebo. CKD-EPI = Chronic Kidney Disease Collaboration Epidemiology Equation.

mortality, HF hospitalization, stroke, myocardial infarction, and the composite endpoint of aborted cardiac arrest or sudden death. All clinical events were centrally adjudicated by an endpoints committee blinded to treatment group assignment.

STATISTICAL ANALYSIS. The population was divided into 4 groups according to the occurrence of WRF and treatment allocation at baseline. Baseline characteristics are presented by WRF categories as mean ± SD, median (interquartile range [IQR], or numbers and percentages as appropriate. The groups were compared using linear regression or Cuzick's nonparametric test for continuous variables and using chi-square tests for trend for categorical variables. To evaluate the relationship between worsening renal function and outcomes, crude and multivariable-adjusted Cox proportional hazard and Kaplan-Meier survival analyses were performed. Multivariable adjustment was done including demographics and variables that were found to differ significantly across baseline categories. Possible modification of the effect of WRF on clinical outcomes by treatment was examined in time-updated Cox models using an interaction term. Incidence rates pre- and post-WRF were estimated by censoring follow-up at the time of development of WRF and beginning follow-up at the time of development of WRF, respectively.

Landmark analyses for WRF according to the protocol definition, and sensitivity analyses using the eGFR-based definition, from baseline to month 4 were performed using Cox models. Estimates were presented as hazard ratios (HRs) or incidence rates (IRs) with 95% confidence intervals (CIs). Two-tailed p values <0.05 were considered statistically significant. Statistical analyses were performed using STATA Statistical Software version 15.0 (STATA Corp, College Station, Texas).

RESULTS

Among the total 1,767 patients with creatinine measurements available at baseline, median eGFR was 57.9 ml/min/1.73 m^2 (IQR: 45.1 to 73.6 ml/min/1.73 m^2), with corresponding median serum creatinine value of 1.1 mg/dl (IQR: 0.9 to 1.4 mg/dl). Overall, 260 (14.7%, 5.4 per 100 patient-years) experienced WRF by the primary study definition (doubling of serum creatinine from baseline) (Figure 1).

TABLE 1 Baseline Characteristics for Patients Who Did and Did Not Develop Worsening Renal Function During Follow-Up (N = 1,767)

	No WRF (n = 1,507 [85.3%])	WRF (n = 260 [14.7%])	p Value
Demographics			
Age, yrs	71.7 ± 9.7	70.8 ± 9.8	0.17
Female	742 (49.2)	140 (53.8)	0.17
White race	1,187 (78.8)	197 (75.8)	0.28
Body mass index, kg/m^2	33.7 ± 8.3	35.2 ± 9.2	0.007
Current smoker	97 (6.4)	20 (7.7)	0.46
LVEF, %	58.2 ± 7.8	58.2 ± 7.7	0.92
NYHA functional class III and IV	495 (33.0)	125 (48.1)	<0.001
Previous HFH	879 (58.4)	161 (61.9)	0.29
Systolic blood pressure, mm Hg	127 ± 16	130 ± 16	0.009
Heart rate, beats/min	69 ± 11	70 ± 11	0.23
QRS duration, ms	106 ± 32	105 ± 32	0.49
Biomarkers			
Creatinine, mg/dl	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.76
eGFR CKD-EPI, ml/min/1.73 m^2	60.6 ± 19.2	61.0 ± 20.4	0.75
Serum potassium, mmol/l	4.2 (3.9–4.5)	4.1 (3.8–4.4)	<0.001
Hemoglobin, g/dl	12.9 ± 1.7	12.3 ± 1.7	0.75
Medical therapy			
ACEi/ARB	1,175 (78.1)	220 (84.6)	0.017
Aspirin	862 (57.3)	165 (63.5)	0.06
Diuretic agents	1,329 (88.3)	244 (93.8)	0.008
Beta-blocker	1,165 (77.4)	222 (85.4)	0.004
Calcium-channel blocker	564 (37.5)	118 (45.4)	0.016

Values are mean ± SD, n (%), or median (interquartile range).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD-EPI = Chronic Kidney Disease Collaboration Epidemiology; HFH = heart failure hospitalization; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Patients who developed WRF had baseline characteristics similar to no WRF patients, except for having higher body mass index (BMI), more often New York Heart Association (NYHA) functional class III or IV HF, higher systolic blood pressure, and a greater prevalence of diabetes (**Table 1**, Supplemental Table 1). Other baseline differences in WRF versus no WRF patients included lower baseline serum potassium and more frequent treatment with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) or diuretic therapy (**Table 1**). In multivariable models, history of diabetes, current smoking, lower baseline hemoglobin, lower baseline potassium, beta-blocker treatment, and treatment with spironolactone were predictors of WRF (**Table 2**). In addition, ACEi/ARB treatment and lower baseline creatinine were associated with WRF in patients allocated to spironolactone, and higher NYHA functional class in patients allocated to placebo (**Table 2**).

TABLE 2 Multivariable Predictors at Baseline of Worsening Renal Function During Follow-Up

	HR (95% CI)	p Value
Creatinine (spironolactone arm)	0.52 (0.31–0.85)	0.01
Potassium (per 1 mEq/l)	0.61 (0.46–0.82)	0.001
Hemoglobin (per 1 g/dl)	0.83 (0.77–0.90)	<0.001
Beta-blocker	1.57 (1.11–2.21)	0.01
Current smoking	1.63 (1.03–2.57)	0.04
Spironolactone	1.71 (1.30–2.24)	<0.001
Diabetes	1.72 (1.33–2.23)	<0.001
ACEi/ARB (spironolactone arm)	1.91 (1.18–3.11)	0.009
NYHA functional class (placebo arm)	2.05 (1.45–2.91)	<0.001

CI = confidence interval; HR = hazard ratio; other abbreviations as in **Table 1**.

WRF AND OUTCOME. During a mean follow-up of 3.3 years, the primary outcome of CV death, aborted cardiac arrest, or HF hospitalization occurred in 522 (29.5%) patients. In time-updated analyses, incidence of the primary composite endpoint doubled after incident WRF (IR: 21.2; 95% CI: 16.3 to 27.6 per 100 patient-years vs. IR: 10.9; 95% CI: 9.9 to 11.9] per 100 patient-years). WRF was accordingly associated with an increased risk of the primary outcome (HR: 2.2; 95% CI: 1.7 to 3.0; $p < 0.001$).

Incidence of HF hospitalization after WRF occurrence was almost 2-fold higher when compared with patients without WRF development: IR: 15.2 (95% CI: 11.1 to 20.7) per 100 patient-years versus IR: 8.4 (95% CI: 7.6 to 9.3) per 100 patient-years. Incidence of CV death was nearly 3-fold higher in patients with versus without WRF development: IR: 12.1 (95% CI: 9.3 to 15.8) per 100 patient-years versus IR: 3.5 (95% CI: 3.0 to 4.1) per 100 patient-years. Similar associations were observed for other secondary outcomes (**Table 3**). In univariate time-updated analyses, WRF was consistently associated with CV death (HR: 3.1; 95% CI: 2.2 to 4.2; $p < 0.001$), HF hospitalization (HR: 2.2; 95% CI: 1.6 to 3.1; $p < 0.001$), all-cause mortality (HR: 2.9; 95% CI: 2.3 to 3.8; $p < 0.001$), and myocardial infarction (HR: 2.0; 95% CI: 1.1 to 3.7; $p = 0.02$) (**Table 4**). These associations remained consistent after adjusting for demographics, BMI, NYHA functional class, blood pressure, baseline potassium, history of diabetes, ACEi/ARB treatment, and diuretic requirement.

In sensitivity landmark analyses from baseline to month 4, using the same definition of WRF (doubling in serum creatinine), we found similar associations between WRF and the primary composite outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization (HR: 1.83; 95% CI: 1.08 to 3.13; $p = 0.026$), also after adjusting for potential confounders (Supplemental Table 2). WRF was also associated with the secondary outcomes of CV death, HF hospitalization, and all-cause mortality in this

landmark analysis (Supplemental Table 2). Similar associations were also noted in sensitivity analyses examining an alternate, eGFR-based definition of WRF and in time-updated models (Supplemental Tables 3 and 4).

SPIRONOLACTONE TREATMENT, WRF, AND OUTCOME. Patients randomized to spironolactone experienced WRF more frequently compared with patients receiving placebo (158 events [17.8% of patients] vs. 102 events [11.6% of patients]; OR: 1.66 (95% CI: 1.27 to 2.17; $p < 0.001$) (**Figure 2**). In sensitivity analyses accounting for the competing risk of death, these results were unchanged (Supplemental Figure 1). In total, 45 (17.3%) patients permanently discontinued study drug after development of WRF, with a higher percentage of discontinuations in the spironolactone group (20.9%) compared with the placebo group (11.8%) (Supplemental Table 5).

Prior to WRF, 74 (10.2%) patients on spironolactone treatment versus 96 (12.3%) patients receiving placebo experienced CV death (HR: 0.83; 95% CI: 0.61 to 1.12; $p = 0.22$), whereas following WRF, 22 (13.9%) versus 31 (30.4%) patients, respectively, experienced CV death (HR: 0.37; 95% CI: 0.22 to 0.64; $p < 0.001$) (**Central Illustration**). Patients developing WRF in the placebo group were at higher absolute risk of the primary endpoint than patients developing WRF in the spironolactone group: IR: 39.6 (95% CI: 25.5 to 61.3) per 100 patient-years versus IR: 16.7 (95% CI: 12.0 to 23.3) per 100 patient-years (**Central Illustration, Table 3**). Similar differences in absolute risk between the treatment arms were observed for the outcomes of HF hospitalization, CV death, and all-cause mortality (**Table 3, Figure 3**). Despite greater treatment differences post-WRF favoring spironolactone for both the primary composite endpoint and CV death in the Americas, there was no formal statistical treatment by region interaction observed (Supplemental Figure 2).

In Cox regression models, a statistically significant interaction was found between WRF and outcome by treatment allocation for the primary endpoint (interaction $p = 0.029$), CV death (interaction $p = 0.003$), and all-cause mortality (interaction $p = 0.001$), with lower risk for each endpoint associated with spironolactone-related WRF than placebo-related WRF (**Table 4**). After adjustment for age, sex, race, BMI, NYHA functional class, systolic blood pressure, baseline potassium, diabetes, ACEi/ARB treatment, and diuretic requirement, the strength of the interaction between treatment and WRF with regard to cardiovascular outcomes was attenuated (interaction $p = 0.113$), but remained statistically significant for CV death (interaction $p = 0.003$) and all-cause mortality (interaction $p = 0.001$) (**Table 4**).

TABLE 3 Incidence Rates for Cardiovascular Outcomes

Outcome	Incidence Rate per 100 Patient-Yrs Total population	Incidence Rate Per 100 Patient-Yrs Placebo	Incidence Rate Per 100 Patient-Yrs Spironolactone
Primary endpoint			
Prior to WRF	10.9 (9.9–11.9)	12.0 (10.6–13.6)	9.7 (8.5–11.2)
Post-WRF	21.2 (16.3–27.6)	39.6 (25.5–61.3)	16.7 (12.0–23.3)
Heart failure hospitalization			
Prior to WRF	8.4 (7.6–9.3)	9.3 (8.1–10.7)	7.4 (6.4–8.7)
Post-WRF	15.2 (11.1–20.7)	25.7 (15.2–43.4)	12.4 (8.5–18.3)
Cardiovascular death			
Prior to WRF	3.5 (3.0–4.1)	3.9 (3.2–4.7)	3.2 (2.5–4.0)
Post-WRF	12.1 (9.3–15.8)	21.4 (15.2–30.0)	7.3 (4.8–11.2)
All-cause mortality			
Prior to WRF	6.0 (5.3–6.7)	6.2 (5.3–7.3)	5.7 (4.8–6.7)
Post-WRF	15.1 (12.5–18.4)	22.3 (17.2–29.1)	10.9 (8.1–14.6)
Myocardial infarction			
Prior to WRF	1.7 (1.4–2.2)	1.8 (1.3–2.4)	1.7 (1.3–2.3)
Post-WRF	3.3 (1.9–5.7)	3.2 (1.2–8.5)	3.3 (1.7–6.4)
Stroke			
Prior to WRF	1.5 (1.2–1.9)	1.5 (1.1–2.1)	1.4 (1.0–2.0)
Post-WRF	1.9 (1.0–3.8)	2.3 (0.8–7.2)	1.7 (0.7–4.2)
Aborted cardiac arrest and sudden death			
Prior to WRF	1.4 (1.1–1.7)	1.5 (1.1–2.1)	1.2 (0.9–1.8)
Post-WRF	1.8 (1.0–3.2)	3.3 (1.7–6.6)	1.0 (0.4–2.6)

Incidence rates pre- and post-WRF were estimated by, respectively, censoring follow-up at the time of development of WRF and beginning follow-up at the time of development of WRF.

WRF = worsening renal function; other abbreviations as in Tables 1 and 2.

Sensitivity analyses that treated non-CV death as a competing risk for CV death and all-cause mortality as a competing risk for WRF produced qualitatively similar results (Supplemental Table 6, Supplemental Figure 3).

DISCUSSION

In this analysis of TOPCAT patients with HFpEF enrolled from the Americas, we found higher incidence of WRF in patients treated with spironolactone compared with placebo. Independent predictors of WRF were spironolactone treatment, diabetes, smoking, baseline treatment with beta-blocker, and ACEi/ARB treatment (only in spironolactone arm), lower baseline hemoglobin and potassium levels, lower baseline creatinine levels (only in spironolactone arm), and higher NYHA functional class (only in placebo arm). WRF during follow-up was associated with increased incidence of all-cause mortality, CV death, HF hospitalization, myocardial infarction, stroke, and sudden cardiac death. Compared with placebo, spironolactone treatment was associated with numerically lower rates of the

TABLE 4 Association Between Worsening Renal Function and Cardiovascular Outcomes in Time-Updated Analysis

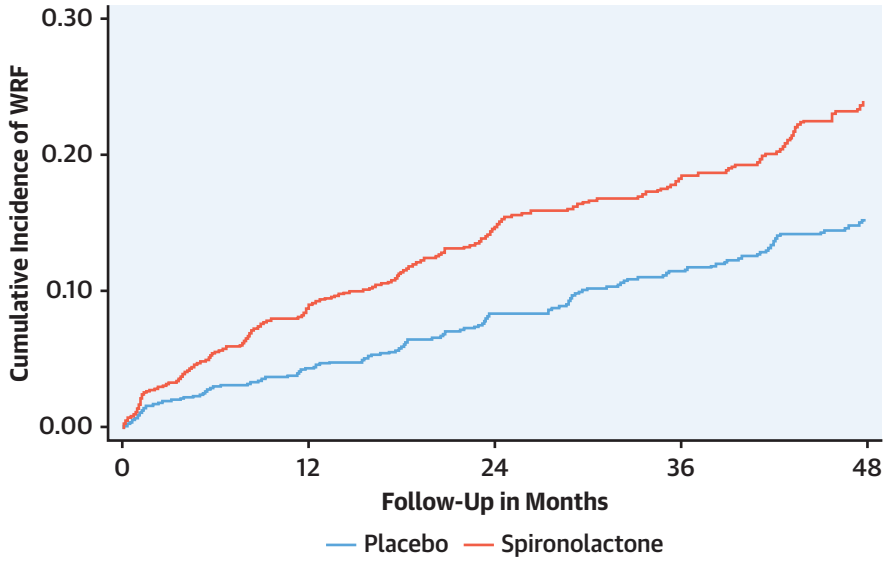
Outcome	Overall		Placebo Arm		Spironolactone Arm		Treatment Interaction
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	
Post-WRF—Univariate Model							
Primary endpoint	2.22 (1.67–2.96)	<0.001	3.79 (2.39–6.02)	<0.001	1.92 (1.33–2.77)	<0.001	**0.029**
HF hospitalization	2.22 (1.59–3.10)	<0.001	3.38 (1.95–5.86)	<0.001	2.00 (1.31–3.07)	0.001	0.154
CV death	3.06 (2.22–4.22)	<0.001	5.54 (3.63–8.46)	<0.001	1.91 (1.16–3.13)	0.011	**0.003**
Aborted cardiac arrest + sudden death	1.88 (0.98–3.62)	0.058	3.77 (1.64–8.68)	0.002	0.98 (0.34–2.83)	0.966	0.086
All-cause mortality	2.94 (2.30–3.76)	<0.001	4.86 (3.47–6.80)	<0.001	2.05 (1.43–2.94)	<0.001	**0.001**
Myocardial infarction	2.03 (1.12–3.69)	0.02	2.31 (0.81–6.52)	0.116	1.86 (0.89–3.90)	0.101	0.925
Stroke	1.34 (0.64–2.84)	0.441	1.74 (0.52–5.78)	0.369	1.12 (0.43–2.93)	0.818	0.748
Post-WRF—Multivariate Model*							
Primary endpoint	2.04 (1.52–2.73)	<0.001	3.17 (1.96–5.12)	<0.001	1.88 (1.28–2.75)	0.001	0.113
HF hospitalization	1.91 (1.36–2.69)	<0.001	2.72 (1.54–4.81)	0.001	1.79 (1.15–2.79)	0.010	0.347
CV death	3.17 (2.27–4.41)	<0.001	6.34 (4.05–9.90)	<0.001	2.07 (1.23–3.49)	0.006	**0.003**
Aborted cardiac arrest + sudden death	1.75 (0.90–3.41)	0.101	3.60 (1.49–8.68)	0.004	0.96 (0.32–2.91)	0.948	0.117
All-cause mortality	3.28 (2.54–4.24)	<0.001	5.98 (4.19–8.54)	<0.001	2.37 (1.61–3.48)	<0.001	**0.001**
Myocardial infarction	1.87 (1.02–3.46)	0.045	2.17 (0.74–6.36)	0.156	1.82 (0.84–3.95)	0.132	0.815
Stroke	1.33 (0.62–2.86)	0.468	1.79 (0.52–6.18)	0.361	1.08 (0.40–2.92)	0.885	0.728

*Adjusted for covariates age, sex, race, BMI, NYHA functional class, SBP, baseline potassium, diabetes, ACEi/ARB treatment, and diuretic therapy.
Abbreviations as in Tables 1 to 3.

primary composite endpoint, CV death, and all-cause mortality in those with and without WRF. Accordingly, these data support the concept that the benefits of spironolactone among patients with HFpEF enrolled in the TOPCAT study are preserved despite a higher incidence of WRF.

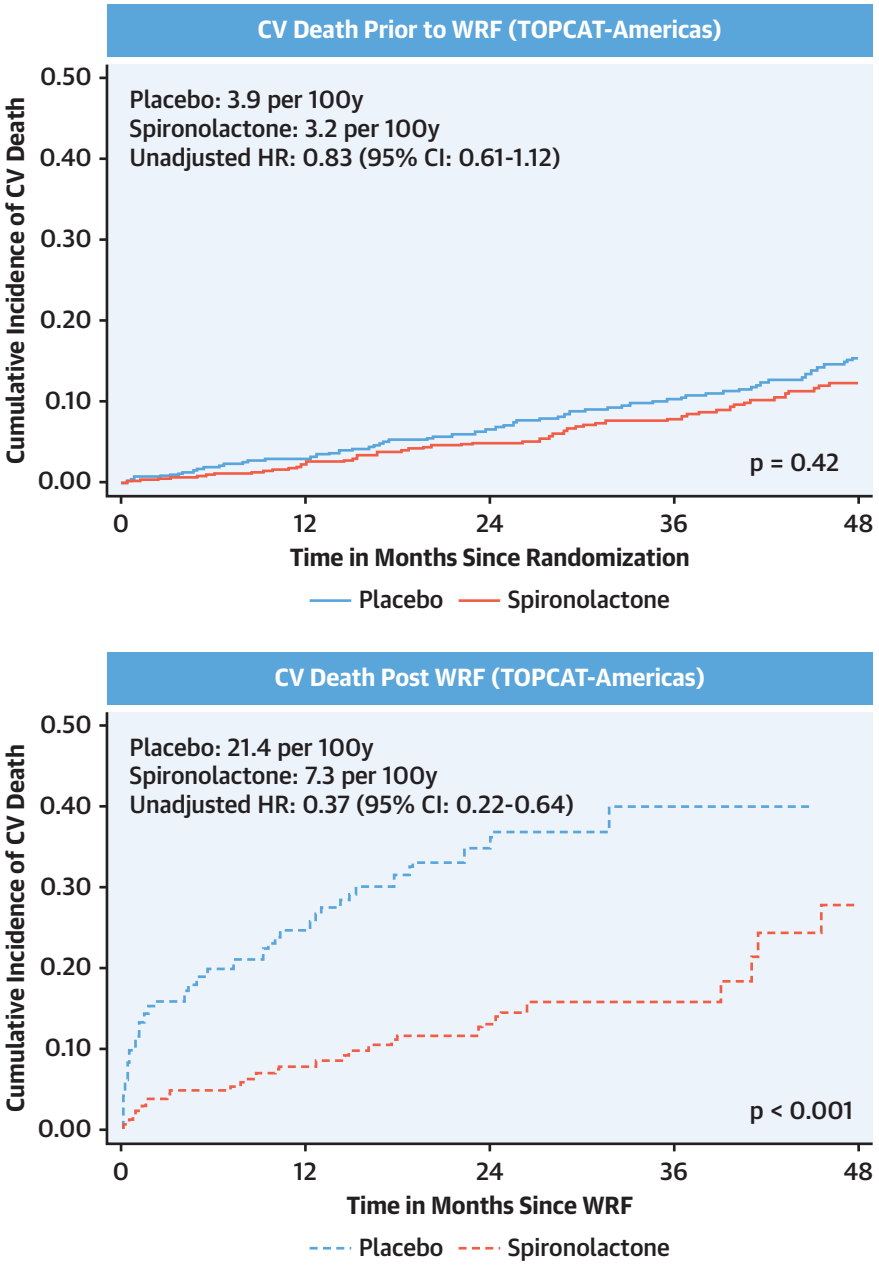
During the conduct of the TOPCAT trial, WRF as defined in the current analysis was a major challenge to the Data and Safety Monitoring Board, who ultimately decided it was not associated with a clinically significant safety risk (18). Few studies have examined the prognostic implications of WRF in HFpEF

FIGURE 2 Cumulative Probability of WRF by Treatment



Cumulative probability of worsening renal function (WRF) in patients with heart failure with preserved ejection fraction treated with spironolactone and placebo.

CENTRAL ILLUSTRATION **CV Death Prior to and Post-Worsening Renal Function**



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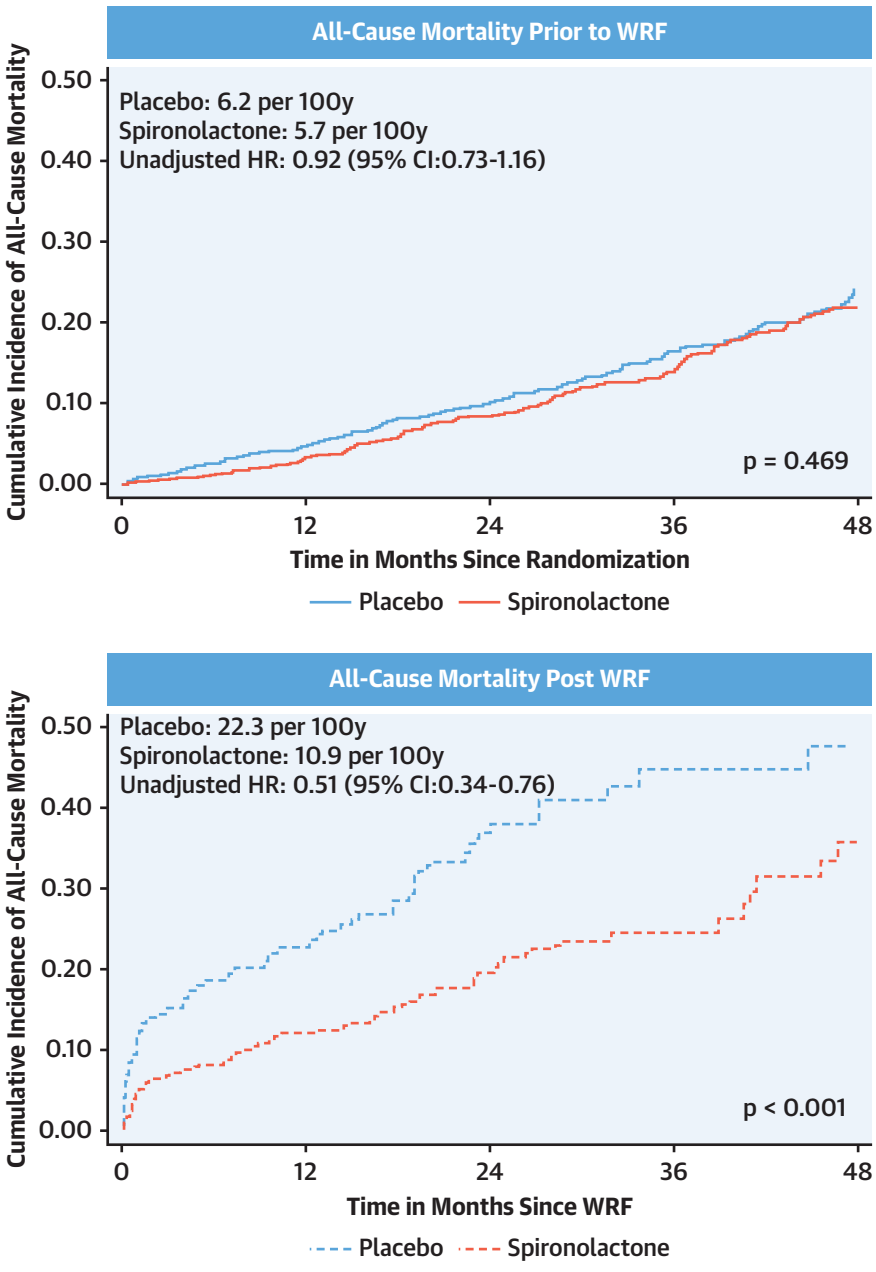
Cumulative incidence of cardiovascular (CV) death prior to and post-worsening renal function in patients with heart failure with preserved ejection fraction treated with spironolactone and placebo in the TOPCAT-Americas region. HR = hazard ratio; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial.

(4,5,19). In a recent meta-analysis, patients with HFpEF and RAAS inhibitor-induced WRF experienced increased mortality risk and no benefit from RAAS inhibition when compared with placebo (5). This was in contrast to patients with HFrEF, in whom the benefit of RAAS inhibitor treatment was maintained despite RAAS inhibitor-induced WRF. Furthermore, in the I-PRESERVE (Irbesartan in Patients with Heart

FIGURE 3 All-Cause Mortality Prior to and Post-WRF



Cumulative incidence of all-cause mortality prior to and post-worsening renal function (WRF) in patients with heart failure with preserved ejection fraction treated with spironolactone and placebo in the TOPCAT-Americas region. HR = hazard ratio; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial.

Failure and Preserved Ejection Fraction) trial of HFpEF, irbesartan-related WRF was associated with worse outcome compared with WRF in the placebo group (4).

In contrast to these data, our results regarding the effects of spironolactone in HFpEF are more in line with previously reported results in studies of HFrEF (2,5,17,20-24). Development of WRF during ACEi/ARB treatment in HFrEF was associated with risk of all-cause mortality, but to a lesser extent when compared with development of WRF in patients allocated to placebo (5,25). Analysis from the CHARM

(Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) program showed that although there was no formal interaction among candesartan treatment, WRF, and outcome in the total population, there was a trend toward worse outcome among patients with candesartan-related WRF compared with patients with WRF in the placebo arm (3). In the RALES (Randomized Aldactone Evaluation Study), treatment with spironolactone was associated with benefit regardless of WRF development during the titration period in patients with HFrEF (17). Our results extend these findings, suggesting a beneficial effect of spironolactone regardless of WRF development, to patients with HFpEF. These data support the concept that the benefits of spironolactone among patients with HFpEF are preserved despite a higher incidence of WRF. Accordingly, the clinical implications are that WRF should be expected in a significant proportion of HFpEF patients treated with spironolactone and that this should not per se lead to discontinuation of the treatment. Careful monitoring of renal function during treatment with spironolactone and interpretation of these measurements in context of the disease progression are of utmost importance for optimal patient care. As previously shown in this HFpEF patient population, careful laboratory surveillance of potassium is warranted as well (26).

RAAS activation in HF leads to glomerular efferent arteriolar vasoconstriction that increases glomerular filtration, and RAAS inhibitors counteract this effect (6). Thus, an initial decrease in eGFR by RAAS inhibition may be a marker of the baseline intensity of the RAAS activation and could therefore be seen as an expected response to therapy (4,5). This mechanism is a possible explanation to the favorable outcome associated with spironolactone-related WRF when compared with WRF in placebo-treated patients in this study. However, data on renal hemodynamics in patients with HFpEF and/or MRA treatment is lacking and should be further investigated, as it is thought that the pathophysiology of renal dysfunction in HFpEF is different from that in HFrEF (6,27,28).

It remains unclear why WRF may carry differential prognostic implications in spironolactone compared with placebo-treated patients with HFpEF. Although the precise pathophysiological mechanisms cannot be elucidated from this analysis, it is possible that changes in renal function may reflect different underlying pathophysiology in the 2 treatment groups. Among placebo-treated patients, WRF may be a marker of circulatory failure or cardiorenal disease progression, whereas for spironolactone-treated patients, WRF may merely reflect the impact of drug treatment on intrarenal hemodynamics and neurohumoral activation (29).

STUDY LIMITATIONS. As a post hoc and subgroup analysis of a clinical trial, results should be considered hypothesis-generating and not necessarily applicable to the general HFpEF population. We cannot rule out the chance of type 1 error given that the study was conducted in a subset of the population (Americas region only) and the use of multiple clinical endpoints. In TOPCAT, patients with an eGFR <30 ml/min/1.73 m^2 were excluded; inclusion of this group could have altered the results, as creatinine at baseline was a predictor of WRF in this analysis. Moreover, creatinine measurements were processed in local, not central laboratories. Finally, other definitions of WRF have been used in prior analyses, and our findings require replication in other studies to confirm our study results.

CONCLUSIONS

Despite increased incidence of WRF associated with spironolactone use in patients with HFpEF, the beneficial effects of spironolactone compared with placebo on cardiovascular mortality were more pronounced in those who developed WRF versus those that did not develop WRF. Future studies investigating epidemiology, pathophysiology, and treatment strategies related to renal dysfunction in HFpEF are warranted.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: In patients with HFpEF, spironolactone is associated with lower risks of cardiovascular and all-cause mortality even if renal function worsens.

TRANSLATIONAL OUTLOOK: Future investigation is needed to understand the epidemiology, pathophysiology, and optimum management of renal dysfunction in patients with HFpEF receiving spironolactone.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.