Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

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Background**—**Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) patients with heart failure and preserved left ventricular ejection fraction assigned to spironolactone did not achieve a significant reduction in the primary composite outcome (time to cardiovascular death, aborted cardiac arrest, or hospitalization for management of heart failure) compared with patients receiving placebo. In a post hoc analysis, an ≈4-fold difference was identified in this composite event rate between the 1678 patients randomized from Russia and Georgia compared with the 1767 enrolled from the United States, Canada, Brazil, and Argentina (the Americas).

Methods and Results**—**To better understand this regional difference in clinical outcomes, demographic characteristics of these populations and their responses to spironolactone were explored. Patients from Russia/Georgia were younger, had less atrial fibrillation and diabetes mellitus, but were more likely to have had prior myocardial infarction or a hospitalization for heart failure. Russia/Georgia patients also had lower left ventricular ejection fraction and creatinine but higher diastolic blood pressure (all $P<0.001$). Hyperkalemia and doubling of creatinine were more likely and hypokalemia was less likely in patients receiving spironolactone in the Americas with no significant treatment effects in Russia/Georgia. All clinical event rates were markedly lower in Russia/Georgia, and there was no detectable impact of spironolactone on any outcomes. In contrast, in the Americas, the rates of the primary outcome, cardiovascular death, and hospitalization for heart failure were significantly reduced by spironolactone.

Conclusions**—**This post hoc analysis demonstrated greater potassium and creatinine changes and possible clinical benefits with spironolactone in patients with heart failure and preserved ejection fraction from the Americas.

Clinical Trial Registration**—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00094302.

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Key Words: heart failure ■ randomized controlled trials ■ spironolactone

Despite uniform inclusion and exclusion criteria, some variation in the patient population and background demographics is expected within multinational, randomized, clinical trials. Similarly, minor and occasionally even statistically significant differences (interactions) between treatment groups are found among different regions or countries within a multicenter trial.[1–7] These and other subgroup analyses are generally considered to be hypothesis generating, with the overall population results understood to be the most reliable.[1,8–13] The randomized, placebo-controlled Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial was conducted in 6 countries (United States, Russia, Georgia, Canada, Brazil, and Argentina). Overall, the group assigned to

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the active therapy with spironolactone did not achieve a significant reduction in the primary outcome, the composite of cardiovascular death, aborted cardiac arrest, or hospitalization for management of heart failure.[14]

In a post hoc analysis of this trial, an unusually large (≈4-fold) difference was identified in the placebo group primary event rate of the patients randomized from Russia and Georgia (Russia/Georgia) compared with those enrolled from the United States, Argentina, Brazil, and Canada (the Americas).[14] In an effort to better understand this regional heterogeneity, we describe the demographic, clinical, and laboratory characteristics of these populations; their prognosis; and their responses to spironolactone therapy.

Methods

Design and Study Population

TOPCAT was an international, randomized, double-blind, placebo-controlled trial sponsored by the National Heart, Lung, and Blood Institute. TOPCAT was conducted with the approval of local institutional review boards. The design and primary findings have been published.[14,15] Patients with symptomatic heart failure and a left ventricular ejection fraction ≥45% who provided written informed consent were eligible. Each patient had to have either a hospitalization within 12 months before randomization with heart failure as a major component of care or, if not, an elevated brain natriuretic peptide (BNP; BNP ≥100 pg/mL or N-terminal pro-BNP ≥360 pg/mL) within 60 days before randomization. Major exclusions were uncontrolled hypertension, serum potassium ≥5.0 mmol/L, creatinine ≥2.5 mg/dL, or estimated glomerular filtration rate <30 mL/min per 1.73 m^2 body surface area, recent acute events, and other severe comorbidities defined previously.[15]

Randomization and Study Drug

Consenting participants were randomly assigned to receive either spironolactone or matching placebo in a 1:1 ratio. Randomization was stratified according to qualification by hospitalization or natriuretic peptides. The starting dose was 15 mg spironolactone or placebo to be administered once daily, with a maximum dose of 3 tablets (45 mg). Potassium and creatinine levels were required within 1 week after each dose titration and at each scheduled study visit.[15] Adherence to study medication was ascertained by pill count.

Outcomes

The composite of death resulting from a cardiovascular cause, aborted cardiac arrest, or hospitalization for the management of heart failure was the primary outcome. Secondary outcomes included the individual components of the primary, as well as myocardial infarctions and strokes (each centrally adjudicated), all deaths, all hospitalizations, and cumulative hospitalizations for heart failure.

Hyperkalemia (potassium ≥5.5 mmol/L), hypokalemia (potassium <3.5 mmol/L), elevated serum creatinine (more than or equal to doubling to above the upper limit of normal), and serum creatinine ≥3.0 mg/dL were important safety measures, as were the number and types of reports of serious adverse events.

Statistical Analysis

All analyses reported in the primary TOPCAT article,[14] conducted in accordance with the initial TOPCAT statistical analysis plan, were repeated separately for the 2 regions, the Americas (United States, Canada, Brazil, and Argentina) and Russia/Georgia. Baseline characteristics were compared by use of the χ^2 and Wilcoxon rank-sum tests for binary and continuous variables, respectively. Continuous outcomes were assessed by use of linear regression models. Event-time outcomes were analyzed with Cox proportional hazards regression models. Hyperkalemia and hypokalemia were analyzed as binary variables with the use of logistic regression for adjusted models. All results pertaining to differences between treatment arms within region were conducted without adjustment for covariates. Comparisons of the occurrence of primary and secondary end points between regions were made with the use of placebo groups only and with the entire regional cohort. Comparisons of region-specific treatment effects were tested with treatment-region interaction terms. Rates of clinical outcomes by enrollment stratum within each region are reported and were compared.

Repeat postbaseline measures of systolic blood pressure, potassium, and creatinine obtained at months 1, 2, 4, 8, and 12 were analyzed by use of a generalized least-squares random-effects linear regression model. Changes in values of these measures from baseline to month 8 (after completion of dose titration) were assessed through the use of unadjusted and adjusted regression analyses, controlling for baseline values, enrollment stratum, and variables known to be associated with these changes in potassium.[16–19] Supportive analyses were repeated at 4 and 12 months and including only patients reported to be on treatment. Further sensitivity analysis was conducted including interaction terms between treatment and each model covariate. Values of $P<0.05$ were considered to be significant. All analyses were conducted with STATA 13.

Results

Populations and Study Drug Administration

From August 10, 2006, to January 31, 2012, 3445 participants were randomized. Participants were followed up for clinical and laboratory outcomes through their last semiannual visit, between January 1, 2013, and June 30, 2013, or until last contact. Of the 3445 patients enrolled, 1767 (51%) were randomized from the Americas (United States, 1151; Canada, 326; Brazil, 167; Argentina, 123), and 1678 participants (49%) were randomized from Russia (1066) and Georgia (612). This randomization was accomplished in 188 participating sites in the Americas and 45 sites in Russia/Georgia. In the Americas, 976 patients (55%) were enrolled in the stratum requiring a hospitalization for heart failure, and 791 patients (45%) were enrolled by elevated natriuretic peptides (BNP stratum). In Russia/Georgia, 1488 patients (89%) were enrolled in the hospitalization stratum and 190 patients (11%) by BNP stratum (Table 1). Within each region, the randomized treatment groups were well balanced (Table I in the online-only Data Supplement). However, between these regions, baseline characteristics were distinctly different for almost every variable (Table 1).

Mean follow-up was 3.3 years in each treatment group (interquartile range, 2.0–4.9 years). For the patients randomized in the Americas, the mean follow-up was 2.9 years; for those from Russia/Georgia, 3.7 years. Vital status at the end of study was unknown for 37 patients (2.1%) and 95 patients (5.7%) randomized in the Americas and in Russia/Georgia, respectively. At 8 months, in the Americas, the mean daily dose of study drug was 21.7 and 25.9 mg in the spironolactone and placebo groups, respectively; in Russia/Georgia, it was 28.4 and 29.5 mg in the spironolactone and placebo groups, respectively (P=0.001 for interaction; Table 2). At this time, a higher percentage of patients had discontinued study medication in the Americas (21.7%) than in Russia/Georgia (7.3%; $P<0.001$). Higher reported adherence in Russia/Georgia with less difference between placebo and active therapy dose was consistently reported during the study (Tables II and III in the online-only Data Supplement). Early permanent discontinuation as a result of breast tenderness or gynecomastia was more frequent in the spironolactone arm in both regions (2.1%

Table 1. Baseline Characteristics by Region*

	Americas (n=1767)	Russia/Georgia (n=1678)	*P* Value
Age, y	72 (64, 79)	66 (59, 71)	<0.001
Age ≥75 y, n (%)	720 (41)	228 (14)	<0.001
Female, n (%)	882 (50)	893 (53)	0.05
White race, n (%)	1384 (78)	1678 (100)	<0.001
Ejection fraction, %	58 (53, 64)	55 (50, 60)	<0.001
NYHA class, n (%)			
1	99 (6)	10 (1)	
2	1043 (59)	1151 (69)	
3	610 (35)	511 (30)	0.006†
4	10 (1)	5 (<1)	
Stratum, n (%)			
Hospitalization	976 (55)	1488 (89)	<0.001
BNP	791 (45)	190 (11)	
Current smoker, n (%)	117 (7)	243 (14)	<0.001
Systolic blood pressure, mm Hg	129 (118, 138)	130 (120, 140)	<0.001
Diastolic blood pressure, mm Hg	70 (62, 80)	80 (80, 85)	<0.001
Heart rate, bpm	68 (61, 76)	68 (62, 75)	0.49
Body mass index, kg/m^2	32.9 (28.0, 38.4)	29.4 (26.7, 33.2)	<0.001
Any cardiovascular disease history, n (%)	815 (46)	1208 (72)	<0.001
Atrial fibrillation, n (%)	743 (42)	471 (28)	<0.001
Diabetes mellitus, n (%)	788 (45)	330 (20)	<0.001
Insulin-treated	379 (21)	48 (3)	<0.001
Chronic kidney disease, n (%)	855 (48)	477 (28)	<0.001
Myocardial infarction, n (%)	359 (20)	534 (32)	<0.001
Percutaneous coronary intervention or coronary artery bypass graft surgery, n (%)	567 (32)	246 (15)	<0.001
Angina, n (%)	486 (28)	1127 (67)	<0.001
Dyslipidemia, n (%)	1250 (71)	823 (49)	<0.001
Chronic obstructive pulmonary disease, n (%)	291 (16)	112 (7)	<0.001
Stroke, n (%)	158 (9)	107 (6)	0.005
Sodium	140 (138, 142)	143 (140, 146)	<0.001
Potassium, mmol/L	4.2 (3.9, 4.5)	4.4 (4.1, 4.7)	<0.001
Creatinine, mg/dL	1.1 (0.9, 1.4)	1.0 (0.9, 1.1)	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	61 (49, 77)	69 (58, 81)	<0.001
BNP, pg/mL‡	234 (145, 391) (n=430)	376 (175, 702) (n=38)	0.016
NT-proBNP, pg/mL‡	900 (557, 1920) (n=257)	1045 (585, 1885) (n=143)	0.24
Hemoglobin, g/dL	12.8 (11.7, 14.0)	13.7 (12.6, 14.8)	<0.001
Medications, n (%)			
Diuretic	1573 (89)	1244 (74)	<0.001
Angiotensin-converting enzyme or angiotensin receptor blocker	1395 (79)	1505 (90)	<0.001
β-Blocker	1387 (79)	1289 (77)	0.23
Calcium channel blocker	682 (39)	612 (36)	0.19
Aspirin	1027 (58)	1223 (73)	<0.001
Statin	1148 (65)	657 (39)	<0.001
Long-acting nitrate	305 (17)	209 (12)	<0.001
Warfarin	592 (34)	195 (12)	<0.001

BNP indicates brain natriuretic peptide; and NYHA, New York Heart Association.
†Comparison of proportion of patients with NYHA class III/IV heart failure.
*Data reported as n (%) or median (quartiles 1, 3).
‡Among those enrolling via BNP stratum. The study-qualifying BNP or NT-proBNP values were reported in 868 of 981 patients enrolled in this stratum (88.5%); values were not collected for 113 patients (11.5%) who were enrolled before a change to the enrollment form was implemented in August 2007. BNP values were reported for 229 patients in the spironolactone group and 239 patients in the placebo group; NT-proBNP values were reported for 203 patients in the spironolactone group and 197 patients in the placebo group.

spironolactone versus 0.2% placebo in the Americas, 2.9% spironolactone versus 0.4% placebo in Russia/Georgia; $P<0.001$ for both), with no significant regional interaction ($P=0.87$).

Clinical Outcomes

A total of 522 patients (29.5%) in the Americas and 149 (8.9%) in Russia/Georgia had at least 1 confirmed primary outcome event (cardiovascular death, aborted cardiac arrest, or hospitalization for the management of heart failure), corresponding to incidence rates of 11.5 and 2.4 per 100 patient-years ($P<0.001$; Table IV in the online-only Data Supplement). Rates of death attributed to a cardiovascular cause and heart failure hospitalizations similarly differed by region ($P<0.001$ for both; Table IV in the online-only Data Supplement). In both regions combined, only 8 patients survived a resuscitated cardiac arrest, too few for meaningful analysis.

In the Americas, the primary event rate of 14.7 per 100 patient-years for those qualifying by hospitalization was higher than the 8.1 per 100 patient-years for those qualifying by natriuretic peptides (HR 1.78; 95% confidence interval [CI], 1.48–2.13; $P<0.001$). In Russia/Georgia, the primary event rate was 2.4 per 100 patient-years for both strata, each lower than the respective cohorts from the Americas ($P<0.001$). In the patients randomized from the Americas, regardless of treatment assignment, enrollment by the hospitalization stratum was also associated with higher rates of cardiovascular mortality (4.9 versus 3.5 per 100 patient-years), hospitalizations for heart failure (11.2 versus 6.2 per 100 patient-years), and all-cause death (8.0 versus 6.1 per 100 patient-years) compared with those enrolled on the basis of BNP (all $P<0.01$). In contrast, in Russia/Georgia, prerandomization heart failure hospitalization was not associated with an increased risk of the primary outcome, all-cause mortality, or cardiovascular death but was associated with increased risk for heart failure hospitalization because there were no adjudicated heart failure events within the BNP stratum of this region (Table 3).

The primary composite event rates for the spironolactone and placebo groups were 10.4 and 12.6 per 100 patient-years in the Americas and 2.5 and 2.3 per 100 patient-years in Russia/Georgia, respectively ($P<0.001$ for comparison of rates between regional placebo groups; Table 4). In the Americas, the hazard ratio for treatment with spironolactone was 0.82

Table 2. Reported Study Drug Use at Month 8 Visit

Month 8 Reported Daily Dose, mg	Americas, n (%)		Russia/Georgia, n (%)		P, Treatment-Region Interaction
	Spironolactone (n=866)	Placebo (n=846)	Spironolactone (n=823)	Placebo (n=830)	
0	212 (24.5)	160 (18.9)	59 (7.2)	61 (7.3)	
15	194 (22.4)	105 (12.4)	83 (10.1)	38 (4.6)	
30	319 (36.8)	386 (45.6)	570 (69.3)	597 (71.9)	
45	141 (16.3)	195 (23.0)	111 (13.5)	134 (16.1)	
Average dose, mg	21.7	25.9	28.4	29.5	0.001

(95% CI, 0.69–0.98), whereas in Russia/Georgia, it was 1.10 (95% CI, 0.79–1.51; Figure 1A). The interaction between treatment and region was not significant (*P*=0.12; Table 4).

The rates of cardiovascular death by treatment assignment were 3.6 and 4.9 per 100 patient-years in the spironolactone and placebo groups in the Americas and 2.0 and 1.6 per 100 patient-years in the spironolactone and placebo groups in Russia/Georgia (Table 4 and Figure 1B). In the Americas, the hazard ratio for treatment with spironolactone with respect to cardiovascular death was 0.74 (95% CI, 0.57–0.97), whereas in Russia/Georgia, it was 1.31 (95% CI, 0.91–1.90; *P*=0.012 for interaction; Table 4).

The rates for hospitalization for heart failure were 7.9 and 9.7 per 100 patient-years in the spironolactone and placebo groups in the Americas and 0.7 and 0.9 per 100 patient-years in the spironolactone and placebo groups in Russia/Georgia, respectively (Table 4). In the Americas, the hazard ratio for heart failure hospitalization with spironolactone treatment was 0.82 (95% CI, 0.67–0.99), whereas in Russia/Georgia, it was 0.76 (95% CI, 0.44–1.32; Figure 1C). Although the interaction between treatment and region was not significant (*P*=0.81), in the Americas, the treatment hazard ratio showed a significant decrease in the spironolactone group (Table 4). Cumulative hospitalizations (including recurrent hospitalizations) for heart failure occurred at rates of 15.3 and 1.1 per 100 patient-years for the patients randomized in the Americas and Russia/Georgia, respectively (*P*<0.001; Table IV in the online-only Data Supplement), with a reduced rate in those randomized to spironolactone in the Americas only (Table 4). Among the previously reported subgroups, 1 significant treatment interaction was detected in each region (Figures I and II in the online-only Data Supplement).

Deaths resulting from all causes occurred at rates of 7.1 and 2.1 per 100 patient-years and reports of hospitalizations for any diagnosis occurred at rates of 34.3 and 10.1 in those enrolled from the Americas and Russia/Georgia, respectively (*P*<0.001 for each; Table IV in the online-only Data Supplement). Within each region, there were no significant differences by treatment assignment for these major outcomes (Table 4).

Regardless of treatment assignment, reports of serious adverse events were more frequent in the cohort randomized in the Americas than in Russia/Georgia overall (64.2% and 33.1%, respectively), as well as in nearly all *Medical Dictionary for Regulatory Activities* categories (Table V in the online-only Data Supplement). Of the 15 categories, only renal/genitourinary was significantly higher in the spironolactone group, and this effect was not observed in Russia/Georgia (Table V in the online-only Data Supplement).

In the cohort enrolled in the Americas, hyperkalemia (potassium ≥5.5 mmol/L) was more frequent in the spironolactone group (25.2%) compared with the placebo group (8.9%; *P*<0.001). Conversely, hypokalemia (potassium <3.5 mmol/L) was less frequent in the spironolactone group (15.2%) than in the placebo group (26.2%; *P*<0.001). These effects of spironolactone were not observed in the Russia/Georgia patients (Table 4), and the differences in treatment effects between

Table 3. Summary of Trial Outcomes by Enrollment Stratum and Region

Outcome	Americas (n=1767) No. (%) With Event [Incidence Rate per 100 person-y]			Russia/Georgia (n=1678) No. (%) with Event [Incidence Rate per 100 person-y]		
	BNP (n=791)	Hospitalization (n=976)	Hospitalization vs BNP: HR (95% CI) *P* Value	BNP (n=190)	Hospitalization (n=1488)	Hospitalization vs BNP: HR (95% CI) *P* Value
Primary outcome	181 (22.9) [8.1]	341 (34.9) [14.7]	1.78 (1.48–2.13) <0.001	13 (6.8) [2.4]	136 (9.1) [2.4]	1.06 (0.60–1.89) 0.83
Cardiovascular mortality	86 (10.9) [3.5]	137 (14.0) [4.9]	1.43 (1.09–1.88) 0.009	13 (6.8) [2.4]	100 (6.7) [1.7]	0.70 (0.39–1.26) 0.24
Aborted cardiac arrest	2 (0.3) [0.1]	4 (0.4) [0.1]	N/A	0 (0.0) [0.00]	2 (0.1) [0.04]	N/A
Hospitalization for heart failure	138 (17.4) [6.2]	262 (26.8) [11.2]	1.76 (1.44–2.17) <0.001	0 (0.0) [0.0]	51 (3.4) [0.9]	N/A 0.015*
All-cause mortality	155 (19.6) [6.1]	230 (23.6) [8.0]	1.33 (1.09–1.64) 0.006	15 (7.9) [2.6]	126 (8.5) [2.1]	0.77 (0.45–1.32) 0.33

BNP indicates brain natriuretic peptide; CI, confidence interval; and HR, hazard ratio.
*Hazard ratio is undefined. *P* value is from log-rank test.

Table 4. Summary of Trial Outcomes by Treatment Arm and Region

	Americas (n=1767) No. (%) With Event [Incidence Rate per 100 patient-y]			Russia/Georgia (n=1678) No. (%) With Event [Incidence Rate per 100 patient-y]				
Outcome	Spironolactone (n=886)	Placebo (n=881)	HR (95% CI) *P* Value	Spironolactone (N=836)	Placebo (N=842)	HR (95% CI) *P* Value	*P*, Regional Difference*	*P*, Treatment-by-Region Interaction
Primary outcome	242 (27.3) [10.4]	280 (31.8) [12.6]	0.82 (0.69–0.98) 0.026	78 (9.3) [2.5]	71 (8.4) [2.3]	1.10 (0.79–1.51) 0.58	<0.001	0.12
Cardiovascular mortality	96 (10.8) [3.6]	127 (14.4) [4.9]	0.74 (0.57–0.97) 0.027	64 (7.7) [2.0]	49 (5.8) [1.6]	1.31 (0.91–1.90) 0.15	<0.001	0.01
Aborted cardiac arrest	2 (0.2) [0.08]	4 (0.5) [0.16]	N/A	1 (0.1) [0.03]	1 (0.1) [0.03]	N/A	N/A	N/A
Hospitalization for heart failure	184 (20.8) [7.9]	216 (24.5) [9.7]	0.82 (0.67–0.99) 0.042	22 (2.6) [0.72]	29 (3.4) [0.95]	0.76 (0.44–1.32) 0.327	<0.001	0.81
Recurrent heart failure	361 events [13.7]	438 events [17.0]	IRR=0.75 (0.58–0.96) 0.024	33 events [1.1]	37 events [1.2]	IRR=0.83 (0.42–1.62) 0.58	<0.001	0.59
All-cause mortality	178 (20.1) [6.5]	207 (23.5) [7.7]	0.83 (0.68–1.02) 0.08	74 (8.9) [2.3]	67 (8.0) [2.0]	1.12 (0.80–1.55) 0.51	<0.001	0.14
All-cause hospitalization	526 (59.4) [32.9]	535 (60.7) [35.8]	0.94 (0.83–1.05) 0.28	240 (28.7) [9.7]	257 (30.5) [10.4]	0.92 (0.77–1.10) 0.375	<0.001	0.94
Myocardial infarction	48 (5.4) [1.9]	46 (5.2) [1.8]	1.01 (0.68–1.52) 0.95	17 (2.0) [0.5]	18 (2.1) [0.6]	0.95 (0.49–1.84) 0.87	<0.001	0.86
Stroke	38 (4.3) [1.5]	39 (4.4) [1.6]	0.94 (0.60–1.47) 0.78	19 (2.3) [0.6]	21 (2.5) [0.7]	0.91 (0.49–1.69) 0.76	0.003	0.94
Doubling of creatinine†	158 (17.8) [6.8]	102 (11.6) [4.2]	1.60 (1.25–2.05) <0.001	17 (2.0) [0.6]	18 (2.1) [0.6]	0.95 (0.49–1.85) 0.89	<0.001	0.16
Creatinine ≥3.0 mg/dL	87 (9.8) [3.5]	80 (9.1) [3.2]	1.10 (0.81–1.49) 0.55	2 (0.2) [0.1]	4 (0.4) [0.2]	0.50 (0.09–2.75) 0.43	<0.001	0.38
Hyperkalemia‡ (potassium ≥5.5 mmol/L)	223 (25.2)	78 (8.9)	OR=3.46 (2.62–4.56) <0.001	99 (11.8)	79 (9.4)	OR=1.30 (0.95–1.77) 0.10	0.71	<0.001
Hypokalemia‡ (potassium <3.5 mmol/L)	135 (15.2)	231 (26.2)	OR=0.51 (0.40–0.64) <0.001	144 (17.2)	163 (19.4)	OR=0.87 (0.68–1.11) 0.26	<0.001	0.002

CI indicates confidence interval; HR, hazard ratio; IRR, incidence rate ratio [used for repeated events]; and OR, odds ratio.
*Comparison of regional event rates in placebo groups.
†Doubling of creatinine to above the upper limit of normal.
‡Any report of specified potassium value.

regions were significant (interaction P<0.001 and 0.002 for hyperkalemia and hypokalemia, respectively). In the cohort from the Americas, doubling of creatinine to a value beyond the upper limit of normal occurred more frequently in the spironolactone group (17.7%) than in the placebo group (11.6%; P<0.001). This alteration in creatinine occurred less frequently in the cohort randomized from Russia/Georgia, with no significant differences between treatment groups (Table 4).

At the 8-month visit, significant changes in potassium and creatinine were seen in both regions with spironolactone relative to placebo. However, these relative increases in potassium and creatinine were multifold greater in the patients from the Americas than in those from Russia/Georgia (P<0.001 for interaction; Table VI in the online-only Data Supplement). Significant decreases in systolic blood pressure associated with spironolactone were seen only in the Americas (P<0.001 for interaction). These differential results with spironolactone persisted in adjusted models including both main effect and interaction terms, were confirmed in sensitivity analyses conducted at the 4- and 12-month time points (Table VII in the online-only Data Supplement), and were

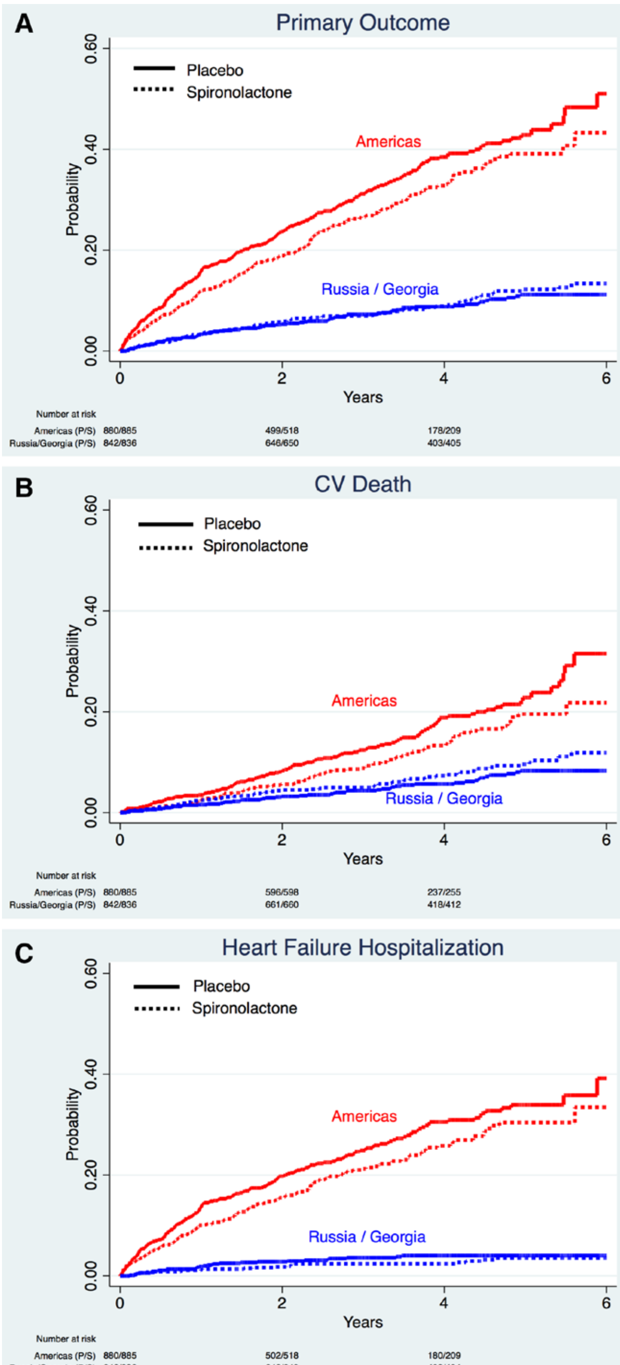

Figure 1. Kaplan-Meier plots of primary outcome and 2 major components. **A**, Time to primary outcome; **B**, time to cardiovascular (CV) death; and **C**, time to first confirmed hospitalization for heart failure.

amplified in additional sensitivity analysis restricted to patients reported to be on study medication at that visit (Table VIII in the online-only Data Supplement). All values obtained through the first year of follow-up are shown in Figure 2. The average magnitude of the systolic blood pressure reduction associated with spironolactone relative to placebo was greater in the Americas (4.2 mm Hg; $P<0.001$) than in Russia/Georgia (0.6 mm Hg: $P=0.10$; interaction $P<0.001$). Similarly, the average magnitude of the increase in potassium associated with spironolactone relative to placebo was greater in the Americas (0.26 mmol/L; $P<0.001$) than in Russia/Georgia (0.08 mmol/L; $P<0.001$; interaction $P<0.001$), and the average magnitude of the increase in creatinine associated with spironolactone relative to placebo was greater in the Americas (0.10 mg/dL; $P<0.001$) than in Russia/Georgia (0.02 mmol/L; $P=0.002$; interaction $P<0.001$). These 3 differences in magnitude of treatment response similarly persisted in adjusted models using these serial measurements.

Discussion

This post hoc analysis was based on the observation of an unusually large difference in the placebo event rates between the sites conducting TOPCAT in the 4 countries in the Americas compared with those in Russia and Georgia.[14] In addition to the marked differences in prognosis, this regional analysis revealed many additional important dissimilarities in patient characteristics; the potassium, creatinine, and blood pressure responses to spironolactone; and reports of adherence to study medications. Regional differences have complicated the interpretations of other randomized trials in cardiovascular medicine.[1–7,20–22] The prior observed pattern of fewer events in patients from Eastern Europe[2,5,7] may have been amplified in TOPCAT because Russia and Georgia contributed 49% of the total enrollment. However, the observed difference between regions in TOPCAT is striking in magnitude, exceeding that anticipated by variations in practice patterns; indeed, it is the marked difference in the placebo groups that distinguishes this from many previous reports of regional variation. This observed difference in population risk profiles obfuscates our ability to unite the results from these 2 disparate regions to draw conclusions about the results of the overall study.

The regional differences in almost every important baseline variable suggest that clinical diagnostic criteria were not uniformly interpreted or applied. Making the assessment that the dyspnea and fatigue of a patient with a preserved ejection fraction are attributed to heart failure rather than to the commonly associated comorbidities is notoriously difficult.[23–30] The additional protocol inclusion criterion in TOPCAT of either a prior hospitalization in which heart failure was a prominent feature or an elevated natriuretic peptide level was intended to both improve diagnostic certainty and to augment risk. The assumption that those with a prior hospitalization would have higher risk[31–35] was confirmed only for the patients randomized from the Americas, suggesting that the nonadjudicated qualifying hospitalization criterion enrolled different patient populations. However, multifold lower event rates were also observed in the patients qualifying by natriuretic peptides from Russia/Georgia. The event rates of those enrolled from the Americas were reflective of other clinical trial populations with symptomatic heart failure and preserved ejection fraction,[36,37] whereas the observed heart failure hospitalization rate of 1 per 100 patient-years in the placebo arm of the Russia/Georgia cohort is quite consistent with rates reported in hypertension trials such as the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Valsartan Antihypertensive Long-Term Use Evaluation (VALUE), and Losartan Intervention for Endpoint Reduction in Hypertension (LIFE), and it is 5-fold lower than the 2 prior heart failure with preserved ejection fraction trials, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity

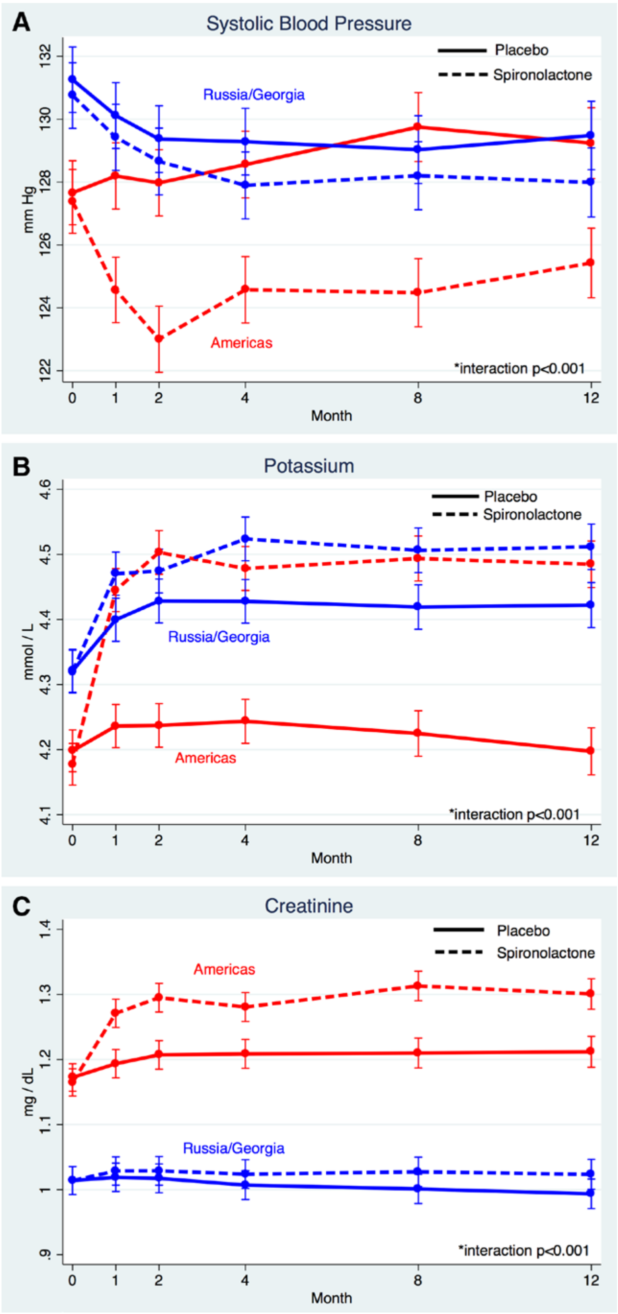

Figure 2. Longitudinal plots of blood pressure, potassium, and creatinine over the first 12 months of follow-up by treatment and region. **A**, Systolic blood pressure; **B**, potassium; and **C**, creatinine. *Magnitude of treatment effect differs by region for each variable (interaction *P*<0.001 for each, unadjusted and adjusted; see text).

(CHARM)-Preserved and Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE).[38] All-cause mortality provides a more unbiased assessment of disease severity than cardiovascular event rates. The death rate of the cohort from Russia/Georgia was more reflective of the general populations from their regions than of patients with heart failure,[39] whereas rates of death in the TOPCAT patients from the Americas were several-fold higher than age- and sex-matched estimates from US life tables (Table IX in the online-only Data Supplement).[40]

Our observation that the magnitude of the effects of spironolactone relative to placebo on blood pressure, potassium, and creatinine was substantially greater in the patients from the Americas is equally puzzling. In models adjusting for baseline factors known to influence potassium and creatinine responses to spironolactone (including age, estimated glomerular filtration rate, diabetes mellitus, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use), these important differences between geographic regions persisted.[16–19] These unexplained regional differences in the renal and electrolyte responses to spironolactone are an additional confounder of the TOPCAT results from the Russia/Georgia cohort. On the other hand, within each treatment group, the percentage of subjects discontinuing study treatment as a result of breast tenderness or gynecomastia was similar between the 2 regions.

There is a marked disparity in the number of randomized trial--based recommendations for patients with symptomatic heart failure according to ejection fraction because patients with reduced ejection fraction (generally <40%) have been the focus of most of the major randomized, controlled trials.[41,42] In sharp contrast, for those with preserved ejection fraction, there have been only 3 major randomized, placebo-controlled, clinical outcome trials, including TOPCAT, specifically addressing this large segment of the symptomatic heart failure population, and in each, the primary outcome was not found to be improved by the investigational therapy.[14,36,37] This lack of randomized, controlled, clinical trial evidence for effectiveness is reflected in the guidelines, which offer little direction for this substantial and expanding proportion of patients with heart failure, aside from empirical treatment of underlying comorbidities.[41–44] As a result, prognosis has been improving for those with reduced but not for those with preserved ejection fraction.[45,46]

This lack of evidence-based guidelines for treatment of heart failure with preserved ejection fraction continues to be perpetuated because diagnostic uncertainties, diverse and poorly understood mechanistic underpinnings, lack of animal models, and heterogeneous phenotypes with relatively greater contribution of comorbidities are some of the heightened challenges to garnering the extensive resources needed to conduct outcome trials in these patients.[21–28,47] In the absence of definitive data and with no new outcome trial results in the near term, physicians and patients faced with this serious medical condition must use the best available information to guide their therapeutic decisions. The overall neutral finding of TOPCAT with the observation of fewer hospitalizations for heart failure in the patients assigned to spironolactone would generally be considered the most reliable result of the trial. However, the marked regional differences in patient populations and responses to spironolactone in TOPCAT highly confound the interpretation of these overall findings. This post hoc regional analysis indicates that 2 distinctly different populations were enrolled and that only the cohort from the Americas shared the characteristics observed in other randomized trials and, importantly, with event rates as anticipated with the selection of patients with symptomatic heart failure with preserved ejection fraction. In contrast, the patients enrolled from Russia/Georgia did not manifest either the anticipated morbidity and mortality rates associated with symptomatic heart failure or most pharmacological responses to spironolactone. Although post hoc analyses of clinical trials are fraught with hazard, they may generate important incremental information.[48] Therefore, our findings in the TOPCAT patients randomized from the Americas of improved prognosis (lower rates of cardiovascular death and hospitalizations for heart failure) with the associated risks of hyperkalemia and increased creatinine with spironolactone should not be considered definitive. However, in the absence of stronger data, our findings may be informative to those currently faced with clinical decisions for patients with heart failure with preserved ejection fraction with anticipated risk profiles similar to those enrolled from the Americas.

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CLINICAL PERSPECTIVE

For the substantial proportion of patients with heart failure and preserved ejection fraction, no therapy has been shown to convincingly improve prognosis. In the randomized, placebo-controlled Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, allocation to spironolactone did not significantly reduce the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for the management of heart failure. In a post hoc analysis, an unusually large difference in event rates was observed, with those enrolled from Russia and Georgia experiencing lower event rates than anticipated for patients with symptomatic heart failure, and ≈4-fold lower rates compared with those enrolled from the Americas (United States, Canada, Brazil, and Argentina). In this analysis, we report the patient characteristics between these regions, their prognosis, and their responses to spironolactone therapy. We describe profound differences in baseline characteristics and greater changes in potassium, creatinine, and blood pressure with spironolactone in the patients randomized in the Americas, and in this group, in which the event rates were more consistent with symptomatic heart failure, the primary outcomes of cardiovascular death and hospitalization for heart failure were reduced in the spironolactone group. Although post hoc analyses are fraught with hazard, in the absence of more robust data for the treatment of patients with heart failure with preserved ejection fraction, our findings of greater risk for hyperkalemia, increased creatinine, and associated potential benefits on cardiovascular death and hospitalization for heart failure are worthy of consideration.

SUPPLEMENTAL MATERIAL

Table S1: Baseline characteristics by randomization arm within region

	Americas			Russia/Georgia		
	Spironolactone n=886	**Placebo n=881**	**p**	**Spironolactone n=836**	**Placebo n=842**	**p**
Age (years)	72.6 [64.2, 79.6]	72.1 [63.7, 78.7]	0.18	65.1 [59.1, 71.2]	65.9 [58.7, 71.6]	0.85
Age ≥ 75	379 (42.8%)	341 (38.7%)	0.08	116 (13.9%)	112 (13.3%)	0.73
Female	442 (49.9%)	440 (49.9%)	0.98	446 (53.3%)	447 (53.1%)	0.91
White Race	689 (77.8%)	695 (78.9%)	0.57	100%	100%	.
EF	59.0 [53.0, 64.0]	58.0 [51.5, 64.0]	0.35	55.0 [50.0, 60.0]	56.0 [51.0, 61.0]	0.14
NYHA Class						
1	51 (5.8%)	48 (5.5%)		5 (0.6%)	5 (0.6%)	
2	518 (58.5%)	525 (59.9%)		572 (68.4%)	579 (68.8%)	
3	312 (35.3%)	298 (34.0%)	0.65*	256 (30.6%)	255 (30.3%)	0.85*
4	4 (0.5%)	6 (0.7%)		3 (0.4%)	2 (0.2%)	
Stratum						
Hosp	500 (56.4%)	476 (54.0%)	0.31	732 (87.6%)	756 (89.8%)	0.15
BNP	386 (43.6%)	405 (46.0%)		104 (12.4%)	86 (10.2%)	
Current Smoker	59 (6.7%)	58 (6.6%)	0.95	117 (14.0%)	126 (15.0%)	0.57
SBP	128.0 [118.0, 138.0]	129.0 [118.0, 139.0]	0.73	130.0 [120.0, 140.0]	130.0 [124.0, 140.0]	0.44
DBP	71.0 [62.0, 80.0]	70.0 [62.0, 80.0]	0.42	80.0 [80.0, 85.0]	80.0 [80.0, 85.0]	0.70
Heart Rate	68.0 [60.0, 76.0]	68.0 [61.0, 76.0]	0.27	68.0 [62.0, 75.0]	68.0 [62.0, 75.0]	0.79
BMI	32.9 [28.0, 38.7]	32.8 [28.0, 38.2]	0.57	29.4 [26.5, 33.2]	29.6 [26.8, 33.1]	0.34
Any CVD History	392 (44.2%)	423 (48.1%)	0.10	597 (71.4%)	611 (72.7%)	0.57
Atrial fibrillation	375 (42.3%)	368 (41.9%)	0.85	236 (28.2%)	235 (27.9%)	0.90
Diabetes mellitus	391 (44.1%)	397 (45.2%)	0.66	174 (20.8%)	156 (18.5%)	0.24
DM: Insulin-treated	193 (21.8%)	186 (21.1%)	0.73	25 (3.0%)	23 (2.7%)	0.75
CKD	422 (47.6%)	433 (49.1%)	0.52	250 (29.9%)	227 (27.0%)	0.18
Myocardial infarction	169 (19.1%)	190 (21.6%)	0.18	275 (32.9%)	259 (30.8%)	0.36
PCI or CABG	277 (31.3%)	290 (32.9%)	0.46	126 (15.1%)	120 (14.3%)	0.63
Angina	225 (25.4%)	261 (29.7%)	0.04	558 (66.7%)	569 (67.7%)	0.69
Dyslipidemia	617 (69.6%)	633 (72.0%)	0.27	394 (47.1%)	429 (51.0%)	0.11
COPD	157 (17.7%)	134 (15.2%)	0.16	52 (6.2%)	60 (7.1%)	0.45
Stroke	69 (7.8%)	89 (10.1%)	0.09	59 (7.1%)	48 (5.7%)	0.26
Sodium	140 [138, 142]	140 [138, 142]	0.95	143 [140, 146]	143 [140, 146]	0.86
Potassium	4.2 [3.9, 4.5]	4.2 [3.9, 4.5]	0.48	4.4 [4.0, 4.7]	4.4 [4.1, 4.7]	0.96
Creatinine	1.1 [0.9, 1.4]	1.1 [0.9, 1.4]	0.48	1.0 [0.9, 1.1]	1.0 [0.9, 1.1]	0.89
eGFR	61.6 [48.8, 77.3]	60.7 [49.6, 75.8]	0.56	69.1 [58.2, 80.9]	68.9 [58.7, 81.4]	0.66

BNP (pg/ml)**	235 [149, 391] (N=206)	232 [142, 394] (N=224)	0.76	300 [175, 702] (N=23)	592 [129, 751] (N=15)	0.55
NT-proBNP (pg/ml)**	812 [517, 1462] (N=126)	1017 [632, 2276] (N=131)	0.005	1107 [563, 1754] (N=77)	1008 [622, 2056] (N=66)	0.64
Hemoglobin	12.9 [11.8, 14.0]	12.8 [11.7, 14.0]	0.91	13.6 [12.6, 14.8]	13.7 [12.8, 14.9]	0.25
Medications						
Diuretic	787 (88.8%)	786 (89.2%)	0.69	614 (73.4%)	630 (74.8%)	0.49
ACE-I or ARB	695 (78.4%)	700 (79.5%)	0.54	757 (90.6%)	748 (88.8%)	0.28
Beta-blocker	693 (78.2%)	694 (78.8%)	0.71	653 (78.1%)	636 (75.5%)	0.23
Calcium channel blocker	331 (37.4%)	351 (39.8%)	0.27	294 (35.2%)	318 (37.8%)	0.26
Aspirin	524 (59.1%)	503 (57.1%)	0.41	598 (71.5%)	625 (74.2%)	0.20
Statin	582 (65.7%)	566 (64.3%)	0.57	328 (39.2%)	329 (39.1%)	0.96
Long acting nitrate	152 (17.2%)	153 (17.4%)	0.89	110 (13.2%)	99 (11.8%)	0.39
Warfarin	301 (34.0%)	291 (33.0%)	0.70	102 (12.2%)	93 (11.1%)	0.47

* Comparison of proportion of patients with NYHA class III/IV

** Among those enrolling via BNP stratum. The study-qualifying BNP or NT-proBNP values were reported in 868 of 981 patients enrolled in this stratum (88.5%); values were not collected for 113 patients (11.5%) who were enrolled before a change to the enrollment form was implemented in August 2007. BNP values were reported for 229 patients in the spironolactone group and 239 patients in the placebo group; NT-proBNP values were reported for 203 patients in the spironolactone group and 197 patients in the placebo group.

Supplemental Table S2: Reported Study Drug Use at Months 4, 12, and 18

Month 4 reported dose	Americas		Russia/Georgia		
Daily Dose	Spiro N=877	Placebo N=865	Spiro N=831	Placebo N=837	Trt-Reg Interaction
• 0 mg	160 (18.2)	112 (12.9)	36 (4.3)	40 (4.8)	
• 15 mg	195 (22.2)	114 (13.2)	66 (7.9)	38 (4.5)	
• 30 mg	367 (41.8)	440 (50.9)	615 (74.0)	632 (75.5)	
• 45 mg	155 (17.7)	199 (23.0)	114 (13.7)	127 (15.2)	
• Average Dose	23.8 mg	27.6 mg	29.6 mg	30.2 mg	P<0.001
Month 12 reported dose	**Americas**		**Russia/Georgia**		
Daily Dose	**Spiro N=848**	**Placebo N=834**	**Spiro N=816**	**Placebo N=826**	**Trt-Reg Interaction**
• 0 mg	273 (32.2)	217 (26.0)	109 (13.4)	101 (12.2)	
• 15 mg	187 (22.1)	97 (11.6)	71 (8.7)	38 (4.6)	
• 30 mg	264 (31.1)	341 (40.9)	537 (65.8)	562 (68.0)	
• 45 mg	124 (14.6)	179 (21.5)	99 (12.1)	125 (15.1)	
• Average Dose	19.2 mg	23.7 mg	26.5 mg	27.9 mg	P=0.002
Month 18 reported dose	**Americas**		**Russia/Georgia**		
Daily Dose	**Spiro N=825**	**Placebo N=806**	**Spiro N=808**	**Placebo N=816**	**Trt-Reg Interaction**
• 0 mg	346 (41.9)	292 (36.2)	170 (21.0)	153 (18.8)	
• 15 mg	161 (19.5)	84 (10.4)	71(8.8)	45 (5.5)	
• 30 mg	225 (27.3)	276 (34.2)	482 (59.7)	505 (61.9)	
• 45 mg	93 (11.3)	154 (19.1)	85 (10.5)	113 (13.8)	
• Average Dose	16.2 mg	20.4 mg	24.0 mg	25.6 mg	P=0.017

Table S3: Timing and Occurrence of Treatment Discontinuation by Region and Treatment Arm

	N(%): Americas			N(%): Russia/Georgia				
	Spiro N=886	**Placebo N=881**	**P**	**Spiro N=836**	**Placebo N=842**	**P**	**Regional difference[1] (p)**	**Reg-Trt int (p)**
Any early permanent discontinuation of study drug	419 (47.3)	372 (42.2)	0.032	171 (20.4)	169 (20.1)	0.845	<0.001	0.24
Time from study entry to early permanent discontinuation								
• < 1 year	219 (24.7)	169 (19.2)		73(8.7)	63(7.5)			
• ≥ 1 year but < 2 years	93 (10.5)	81 (9.2)		47(5.6)	33(3.9)			
• ≥ 2 year but < 3 years	44 (5.0)	45 (5.1)		25(3.0)	36(4.3)			
• ≥ 3 years	63 (7.1)	77 (8.7)		26(3.1)	37(4.4)			
• No early permanent discontinuation	467 (52.7)	509 (57.8)		665(79.6)	673(79.9)			

[1] p-value for comparison of placebo groups; p<0.001 for comparison of spironolactone arms (Americas vs Russia/Georgia)

Table S4: Summary of Trial Outcomes by Region, Combining Treatment Arms

	Number (%) with Event, [Incidence rate per 100 patient-years]		Regional difference*	
	Americas (N=1,767)	**Russia / Georgia (N=1,678)**	Unadjusted (p)	Adjusted** (p)
Primary Outcome	522 (29.5%) [11.5]	149 (8.9%) [2.4]	<0.001	<0.001
CV Mortality	223 (12.6%) [4.3]	113 (6.7%) [1.8]	<0.001	<0.001
Aborted Cardiac Arrest	6 (0.3%) [0.12]	2 (0.1%) [0.03]	---	---
Hospitalization for Heart Failure	400 (22.6%) [8.8]	51 (3.0%) [0.8]	<0.001	<0.001
Recurrent HF	799 events [15.3]	70 events [1.1]	<0.001	<0.001
All-Cause Mortality	385 (21.8%) [7.1]	141 (8.4%) [2.1]	<0.001	<0.001
All-Cause Hospitalization	1061 (60.0%) [34.3]	497 (29.6%) [10.1]	<0.001	<0.001
Myocardial Infarction	94 (5.3%) 1.9 per 100 py	35 (2.1%) [0.6]	<0.001	0.001
Stroke	77 (4.4%) [1.5]	40 (2.4%) [0.6]	<0.001	0.09
Doubling of creatinine[1]	260 (14.7%) [5.4]	35 (2.1%) [0.6]	<0.001	<0.001
Creatinine ≥ 3.0 mg/dL	167 (9.5%) [3.3]	6 (0.4%) [0.1]	<0.001	<0.001
Hyperkalemia[2] (K≥5.5)	301 (17.0%)	178 (10.6%)	<0.001	0.005
Hypokalemia[2] (K<3.5)	366 (20.7%)	307 (18.3%)	0.07	0.64

*Comparison of regional event rates, combining treatment arms

**Adjusting for randomization strata, NYHA class, diabetic status, systolic blood pressure, potassium, creatinine, heart rate, age, race, sex, smoking status, atrial fibrillation, ACE/ARB usage, prior MI, prior stroke, and ejection fraction

Table S5: Reported Severe Adverse Events

PRIMARY CATEGORY[1]	Americas: Spironolactone N = 886 N	%	Americas: Placebo N = 881 N	%	Russia/Georgia: Spironolactone N = 836 N	%	Russia/Georgia: Placebo N = 842 N	%	Regional difference† (p)
Any Serious Adverse Event	560	63.2	575	65.3	275	32.9	280	33.2	<0.001
Auditory/Ocular	3	0.3	4	0.4	10	1.2	7	0.8	0.030
Cancer	38	4.3	31	3.5	15	1.8	19	2.3	0.001
Cardiovascular	363	41.0	365	41.4	215	25.7	201	23.9	<0.001
Endocrine and Metabolic	48	5.4	35	4.0	14	1.7	10	1.2	<0.001
Gastrointestinal	82	9.3	85	9.6	25	3.0	20	2.4	<0.001
Hematological	25	2.8	27	3.1	4	0.5	4	0.5	<0.001
Hepatobiliary/Pancreas	14	1.6	19	2.2	8	1.3	6	1.5	0.009
Infection	63	7.1	69	7.8	1	0.1	4	0.5	<0.001
Musculoskeletal/Skin	91	10.3	92	10.4	20	2.4	12	1.4	<0.001
Neurological/Psychiatric	65	7.3	80	9.1	31	3.7	22	2.6	<0.001
Pulmonary/Upper Respiratory	132	14.9	140	15.9	12	1.4	16	1.9	<0.001
Renal/Genitourinary	105	11.8	75	8.5*	11	1.3	14	1.7	<0.001
Sexual/Reproductive Function	2	0.2	2	0.2	4	0.5	5	0.6	0.14
Vascular (non-cardiac)	31	3.5	33	3.8	9	1	19	2.2	<0.001
Other	70	7.9	70	8.0	27	3.2	38	4.5	<0.001

† Comparison of regional frequencies, combining treatment groups
*p<0.05 for treatment difference, within region

Table S6: Changes in Systolic Blood Pressure, Potassium, and Creatinine at Month 8 from baseline by treatment and region

	Americas	Russia/Georgia	Differential treatment response by region (p)
SBP			
Baseline	127 ± 15	131±11	
Spiro (Month 8 change)	-2.8 (0.7)	-2.7 (0.5)	
Placebo (Month 8 change)	+2.1 (0.7)	-2.4 (0.5)	
Delta: Unadjusted	-4.9 (1.0) p <0.001	-0.2 (0.7) p=0.72	**<0.001**
*Delta: Adjusted**	-5.1 (0.9) p<0.001	-0.6 (0.6) p=0.29	**<0.001†**
Potassium			
Baseline	4.2 ± 0.4	4.3 ± 0.4	
Spiro (Month 8 change)	+0.31 (0.02)	+0.18 (0.02)	
Placebo (Month 8 change)	+0.02 (0.02)	+0.10 (0.02)	
Delta: Unadjusted	+0.30 (0.03) p<0.001	+0.09 (0.03) p=0.002	**<0.001**
*Delta: Adjusted**	+0.28 (0.02) p<0.001	+0.08 (0.02) p=0.001	**<0.001†**
Creatinine			
Baseline	1.2 ± 0.3	1.0 ± 0.2	
Spiro (Month 8 change)	+0.16 (0.01)	+0.01 (0.01)	
Placebo (Month 8 change)	+0.03 (0.01)	-0.01 (0.01)	
Delta: Unadjusted	+0.13 (0.02) p<0.001	+0.03 (0.01) p=0.003	**<0.001**
*Delta: Adjusted**	+0.12 (0.02) p<0.001	+0.03 (0.01) p=0.001	**<0.001†**

Data presented as mean ± sd or mean (se)

* Adjusted model adjusts for baseline value, age, baseline eGFR, history of diabetes, baseline use of ACE/ARB, and enrollment stratum

† p<0.001 after further inclusion of interactions between above covariates and treatment interaction terms

Table S7a: Changes in Systolic Blood Pressure, Potassium, and Creatinine at Month 4 from baseline by treatment and region

	Americas	Russia/Georgia	Differential treatment response by region (p)
SBP			
Baseline	127 ± 15	131±11	
Spiro (Month 4 change)	-2.6 (0.7)	-2.9 (0.4)	
Placebo (Month 4 change)	+0.8 (0.7)	-2.1 (0.4)	
Delta: Unadjusted	-3.4 (0.9) p <0.001	-0.8 (0.6) p =0.19	**0.021**
*Delta: Adjusted**	-3.7 (0.9) p <0.001	-1.2 (0.5) p =0.030	**0.010**
Potassium			
Baseline	4.2 ± 0.4	4.3 ± 0.4	
Spiro (Month 4 change)	+0.30 (0.02)	+0.21 (0.02)	
Placebo (Month 4 change)	+0.04 (0.02)	+0.11 (0.02)	
Delta: Unadjusted	+0.26 (0.03) p <0.001	+0.10 (0.03) p <0.001	**<0.001**
*Delta: Adjusted**	+0.25 (0.02) p <0.001	+0.09 (0.02) p <0.001	**<0.001**
Creatinine			
Baseline	1.2 ± 0.3	1.0 ± 0.2	
Spiro (Month 4 change)	+0.12 (0.01)	+0.01 (0.01)	
Placebo (Month 4 change)	+0.03 (0.01)	-0.01 (0.01)	
Delta: Unadjusted	+0.09 (0.01) p <0.001	+0.02 (0.01) p =0.045	**<0.001**
*Delta: Adjusted**	+0.09 (0.01) p <0.001	+0.02 (0.01) p =0.020	**<0.001**

Data presented as mean ± sd or mean (se)
* Adjusted model adjusts for baseline value, age, baseline eGFR, history of diabetes, baseline use of ACE/ARB, and enrollment stratum

Table S7b: Changes in Systolic Blood Pressure, Potassium, and Creatinine at Month 12 from baseline by treatment and region

	Americas	Russia/Georgia	Differential treatment response by region (p)
SBP			
Baseline	127 ± 15	131±11	
Spiro (Month 12 change)	-2.2 (0.7)	-2.9 (0.5)	
Placebo (Month 12 change)	+1.9 (0.7)	-2.1 (0.5)	
Delta: Unadjusted	-4.0 (1.0) p <0.001	-0.8 (0.7) p =0.22	**0.009**
*Delta: Adjusted**	-3.9 (0.9) p <0.001	-1.3 (0.6) p =0.026	**0.012**
Potassium			
Baseline	4.2 ± 0.4	4.3 ± 0.4	
Spiro (Month 12 change)	+0.31 (0.02)	+0.19 (0.02)	
Placebo (Month 12 change)	-0.00 (0.02)	+0.11 (0.02)	
Delta: Unadjusted	+0.31 (0.03) p <0.001	+0.08 (0.03) p =0.004	**<0.001**
*Delta: Adjusted**	+0.30 (0.02) p <0.001	+0.08 (0.03) p =0.001	**<0.001**
Creatinine			
Baseline	1.2 ± 0.3	1.0 ± 0.2	
Spiro (Month 12 change)	+0.16 (0.01)	+0.01 (0.01)	
Placebo (Month 12 change)	+0.04 (0.01)	-0.02 (0.01)	
Delta: Unadjusted	+0.12 (0.02) p <0.001	+0.03 (0.01) p =0.002	**<0.001**
*Delta: Adjusted**	+0.11 (0.02) p <0.001	+0.03 (0.01) p <0.001	**<0.001**

Data presented as mean ± sd or mean (se)
* Adjusted model adjusts for baseline value, age, baseline eGFR, history of diabetes, baseline use of ACE/ARB, and enrollment stratum

Table S8: Changes in Systolic Blood Pressure, Potassium, and Creatinine at Month 8 from baseline by treatment and region, of patients reported on study medication

Group	**Americas (Region 1)**	**Russia/Georgia (Region 2)**	**Differential treatment response by region (p)**
	SBP		
Baseline	127 ± 15	131±11	
Spiro (Month 8 change)	-3.6 (0.7)	-3.0 (0.5)	
Placebo (Month 8 change)	+2.1 (0.8)	-2.6 (0.5)	
Delta: Unadjusted	-5.7 (1.1) p<0.001	-0.4 (0.7) p=0.55	**<0.001**
*Delta: Adjusted**	-6.0 (0.9) p<0.001	-0.8 (0.6) p=0.15	**<0.001**
	Potassium		
Baseline	4.2 ± 0.4	4.3 ± 0.5	
Spiro (Month 8 change)	+0.34 (0.02)	+0.18 (0.02)	
Placebo (Month 8 change)	+0.01 (0.02)	+0.09 (0.02)	
Delta: Unadjusted	+0.33 (0.03) p<0.001	+0.10 (0.03) p=0.001	**<0.001**
*Delta: Adjusted**	+0.31 (0.02) p<0.001	+0.09 (0.02) p<0.001	**<0.001**
	Creatinine		
Baseline	1.2 ± 0.3	1.0 ± 0.2	
Spiro (Month 8 change)	+0.17 (0.01)	+0.01 (0.01)	
Placebo (Month 8 change)	+0.02 (0.01)	-0.01 (0.01)	
Delta: Unadjusted	+0.14 (0.02) p<0.001	+0.03 (0.01) p=0.005	**<0.001**
*Delta: Adjusted**	+0.14 (0.02) p<0.001	+0.03 (0.01) p=0.001	**<0.001**

Data presented as mean ± sd or mean (se)

*Adjusted for baseline value, enrollment stratum, age, diabetes, estimated glomerular filtration rate, use of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker

Table S9: Age- and gender-specific death rates observed in Russia, Georgia, and United States in general population and in TOPCAT trial

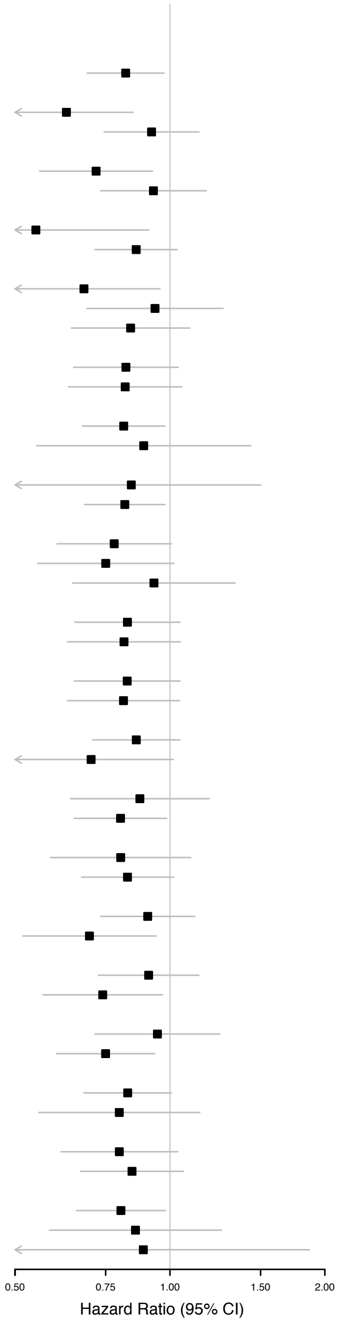
Source	Age	Death Rates: per 100 person-years Male	Female	Overall
Russia				
Life Tables	60-64	4.2	1.3	2.5
	65-69	5.3	1.9	3.1
TOPCAT	65 (mean)	3.6	1.9	2.7
Georgia				
Life Tables	60-64	1.9	0.9	1.3
	65-69	3.2	1.6	2.3
TOPCAT	65 (mean)	1.7	0.8	1.2
United States				
Life Tables	71-72	2.7	1.8	2.2
TOPCAT	71 (mean)	7.8	5.6	6.7

Supplemental Figure S1: Treatment effect by prespecified subgroups in the Americas

In TOPCAT, 22 subgroups (including the Americas vs. Russia/Georgia) were pre-specified and were reported on previously[14]. Two additional subgroups featured three or fewer primary events in the entire study, and were therefore omitted from region-specific analysis. In Figure S1 we display results pertaining to the primary outcome for the remaining 19 subgroups in the Americas. In Russia/Georgia, all enrolled patients were non-Hispanic white, eliminating the possibility of analyzing subgroups based on race or Hispanic status, and leaving 17 subgroups displayed in Figure S2. Only one significant interaction was found with respect to the primary outcome in each region. In patients enrolled from the Americas, the impact of spironolactone on the primary outcome was stronger for those enrolled based on BNP criteria compared to the hospitalization stratum (HR=0.63 [0.47-0.85]) vs HR=0.92 [0.75-1.14], p=0.046), though no significant interactions were found when analyzing heart failure or cardiovascular death separately in these patients. In Russia/Georgia, the impact of spironolactone was found to differ according to eGFR status (HR=1.91 [1.02-3.59] for those with eGFR< 60 vs HR=0.87 [0.59-1.28] for those with eGFR ≥ 60, interaction p=0.03).

Americas

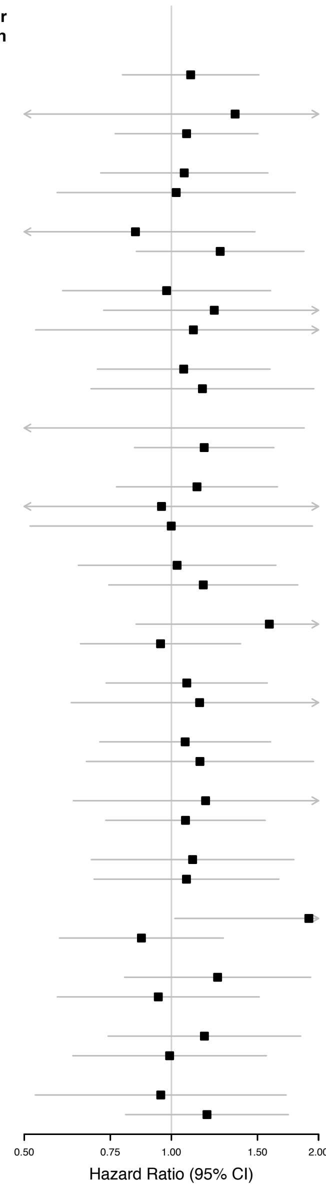
Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
All Patients	522/1761 (29.64)	0.82 (0.69–0.97)	
Randomization Stratum	.	.	
Not hospitalized for heart failure in the year prior to study enrollment	181/787 (23.0)	0.63 (0.47–0.85)	0.04
Hospitalized for heart failure during that time period	341/974 (35.0)	0.92 (0.74–1.14)	
Ejection fraction based on local reading	.	.	
Less than the median	247/787 (31.4)	0.72 (0.56–0.93)	0.15
At or above the median	275/974 (28.2)	0.93 (0.73–1.18)	
Ejection fraction based on local reading	.	.	
Less than 50%	63/197 (32.0)	0.55 (0.33–0.91)	0.12
Greater than or equal to 50%	459/1564 (29.4)	0.86 (0.72–1.03)	
Age	.	.	
50–64 years	137/491 (27.9)	0.68 (0.48–0.96)	0.39
65–74 years	166/552 (30.1)	0.94 (0.69–1.27)	
75 years or older	219/718 (30.5)	0.84 (0.64–1.09)	
Gender	.	.	
Male	281/879 (32.0)	0.82 (0.65–1.04)	0.98
Female	241/882 (27.3)	0.82 (0.64–1.05)	
Ethnicity	.	.	
Non−Hispanic	455/1444 (31.5)	0.81 (0.68–0.98)	0.74
Hispanic	67/317 (21.1)	0.89 (0.55–1.44)	
History of hypertension	.	.	
No	46/176 (26.1)	0.84 (0.47–1.50)	0.91
Yes	476/1585 (30.0)	0.82 (0.68–0.98)	
Diabetes mellitus	.	.	
No	237/974 (24.3)	0.78 (0.60–1.01)	0.64
Yes, Insulin−treated	168/379 (44.3)	0.75 (0.55–1.02)	
Yes, Non−insulin−treated	117/408 (28.7)	0.93 (0.65–1.34)	
New York Heart Association congestive heart failure class	.	.	
II	278/1139 (24.4)	0.83 (0.65–1.05)	0.91
III & IV	243/619 (39.3)	0.81 (0.63–1.05)	
Systolic blood pressure	.	.	
Less than the median	276/895 (30.8)	0.83 (0.65–1.05)	0.94
At or above the median	246/866 (28.4)	0.81 (0.63–1.04)	
Systolic blood pressure	.	.	
Less than 140 mm Hg	404/1358 (29.7)	0.86 (0.71–1.05)	0.32
Greater than or equal to 140 mm Hg	118/403 (29.3)	0.70 (0.49–1.01)	
Use of statins	.	.	
No	160/615 (26.0)	0.87 (0.64–1.19)	0.68
Yes	362/1146 (31.6)	0.80 (0.65–0.99)	
Pulse pressure		.	
Less than the median	158/570 (27.7)	0.80 (0.59–1.10)	0.88
At or above the median	364/1191 (30.6)	0.83 (0.67–1.02)	
Estimated GFR		.	
Less than the median	347/1030 (33.7)	0.91 (0.73–1.12)	0.15
At or above the median	175/731 (23.9)	0.70 (0.52–0.94)	
Estimated GFR		.	
Less than 60 ml/min/1.73m2	306/854 (35.8)	0.91 (0.73–1.14)	0.25
Greater than or equal to 60 ml/min/1.73m2	216/907 (23.8)	0.74 (0.57–0.97)	
BMI		.	
Less than the median	197/694 (28.4)	0.95 (0.71–1.25)	0.19
At or above the median	322/1060 (30.4)	0.75 (0.60–0.93)	
Prior Myocardial Infarction		.	
No	401/1403 (28.6)	0.83 (0.68–1.01)	0.92
Yes	121/358 (33.8)	0.80 (0.56–1.14)	
Heart Rate		.	
Less than the median	227/813 (27.9)	0.80 (0.61–1.03)	0.77
At or above the median	294/947 (31.0)	0.84 (0.67–1.06)	
Racial category		.	
White	390/1378 (28.3)	0.80 (0.66–0.98)	0.94
Black	104/302 (34.4)	0.86 (0.58–1.26)	
All Other	28/81 (34.6)	0.89 (0.42–1.87)	



Supplemental Figure S2: Treatment effect by prespecified subgroups in Russia/Georgia

Russia / Georgia

Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
All Patients	149/1676 (8.9)	1.10 (0.79–1.51)	
Randomization Stratum	.	.	
Not hospitalized for heart failure in the year prior to study enrollment	13/190 (6.8)	1.35 (0.44–4.13)	0.69
Hospitalized for heart failure during that time period	136/1486 (9.2)	1.07 (0.77–1.50)	
Ejection fraction based on local reading	.	.	
Less than the median	100/857 (11.7)	1.06 (0.72–1.58)	0.91
At or above the median	49/819 (6.0)	1.02 (0.58–1.79)	
Ejection fraction based on local reading	.	.	
Less than 50%	49/323 (15.2)	0.84 (0.48–1.48)	0.26
Greater than or equal to 50%	100/1353 (7.4)	1.26 (0.85–1.87)	
Age	.	.	
50–64 years	64/810 (7.9)	0.98 (0.60–1.60)	0.82
65–74 years	57/639 (8.9)	1.22 (0.73–2.06)	
75 years or older	28/227 (12.3)	1.11 (0.53–2.33)	
Gender	.	.	
Male	93/785 (11.8)	1.06 (0.71–1.59)	0.79
Female	56/891 (6.3)	1.16 (0.68–1.96)	
History of hypertension	.	.	
No	6/118 (5.1)	0.34 (0.06–1.87)	0.14
Yes	143/1558 (9.2)	1.17 (0.84–1.62)	
Diabetes mellitus	.	.	
No	107/1346 (7.9)	1.13 (0.77–1.65)	0.91
Yes, Insulin–treated	7/48 (14.6)	0.95 (0.21–4.30)	
Yes, Non–insulin–treated	35/282 (12.4)	1.00 (0.51–1.94)	
New York Heart Association congestive heart failure class	.	.	
II	71/1161 (6.1)	1.03 (0.65–1.64)	0.7
III & IV	78/515 (15.1)	1.16 (0.74–1.81)	
Systolic blood pressure	.	.	
Less than the median	41/552 (7.4)	1.59 (0.85–2.97)	0.16
At or above the median	108/1154 (9.4)	0.95 (0.65–1.39)	
Systolic blood pressure	.	.	
Less than 140 mm Hg	107/1208 (8.9)	1.08 (0.74–1.57)	0.86
Greater than or equal to 140 mm Hg	42/468 (9.0)	1.14 (0.62–2.09)	
Use of statins	.	.	
No	95/1020 (9.3)	1.07 (0.71–1.60)	0.84
Yes	54/656 (8.2)	1.14 (0.67–1.95)	
Pulse pressure	.	.	
Less than the median	40/547 (7.3)	1.17 (0.63–2.19)	0.79
At or above the median	109/1129 (9.7)	1.07 (0.73–1.56)	
Estimated GFR	.	.	
Less than the median	68/690 (9.9)	1.11 (0.69–1.78)	0.93
At or above the median	81/986 (8.2)	1.07 (0.69–1.66)	
Estimated GFR	.	.	
Less than 60 ml/min/1.73m2	45/476 (9.5)	1.91 (1.02–3.59)	0.03
Greater than or equal to 60 ml/min/1.73m2	104/1200 (8.7)	0.87 (0.59–1.28)	
BMI	.	.	
Less than the median	81/1019 (7.9)	1.24 (0.80–1.93)	0.4
At or above the median	68/657 (10.4)	0.94 (0.58–1.51)	
Prior Myocardial Infarction	.	.	
No	75/1142 (6.6)	1.17 (0.74–1.84)	0.61
Yes	74/534 (13.9)	0.99 (0.63–1.56)	
Heart Rate	.	.	
Less than the median	44/750 (5.9)	0.95 (0.53–1.72)	0.55
At or above the median	105/926 (11.3)	1.18 (0.81–1.74)	



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Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

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