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Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial

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Background—Heart failure (HF) with preserved ejection fraction patients have equally impaired health-related quality of life (HRQL) compared with those with HF with reduced ejection fraction, but limited studies have evaluated the impact of therapies on changes in HRQL.

Methods and Results—Patients ≥50 years of age, with symptomatic HF and left ventricular ejection fraction ≥45%, were enrolled in Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) and randomized to spironolactone or placebo. Patients completed the Kansas City Cardiomyopathy Questionnaire (KCCQ), which was the primary HRQL instrument, and EQ5D visual analog scale at baseline, 4 months, 12 months, and annually thereafter. McMaster Overall Treatment Evaluation was assessed at 4 and 12 months to assess global change scores. Change scores (+SD) were calculated to determine between-group differences, and multivariable repeated-measures models were created to identify other factors associated with change scores. Paired KCCQ data were available for 91.7% of 3445 TOPCAT patients. By 4 months, the mean change in KCCQ was 7.7±16 and mean change in EQ5D visual analog scale was 4.7±16. Adjusted mean changes in KCCQ for the spironolactone group were significantly better than those for the placebo group at 4-month (1.54 better; P=0.002), 12-month (1.35 better; P=0.02), and 36-month (1.86 better; P=0.02) visits. No between-group differences in EQ5D visual analog scale change scores or McMaster Overall Treatment Evaluation were noted. Older age, obesity, current smoking, New York Heart Association class III/IV, and comorbid illnesses were associated with declines in KCCQ scores. Use of spironolactone was an independent predictor of improved KCCQ scores.

Conclusions—In symptomatic HF with preserved ejection fraction patients, use of spironolactone was associated with an improvement in HF-specific HRQL. Several modifiable risk factors were associated with HRQL deterioration.

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

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Key Words: clinical trial ■ heart failure ■ predictors ■ preserved ejection fraction ■ quality of life

Half of the entire heart failure (HF) population have HF with preserved ejection fraction (HF-PEF), with over-representation among elderly, women, and minority populations.[1,2] Patients with HF-PEF have equally impaired health status compared with those with HF with reduced ejection fraction (HF-REF) because of similarly impaired functional capacity, signs and symptoms of HF, and depression.[3,4] Health-related quality of life (HRQL) is a component of health status and will be used in this article for simplicity. However, no therapy has been proven to improve survival and hospitalizations in large clinical trials of HF-PEF patients,[5–7] and few trials have evaluated the impact of treatments on HRQL in this understudied population.[8–10]

See Clinical Perspective

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The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT)[6] was conducted in 6 countries and enrolled a large number of symptomatic HF-PEF patients to test whether spironolactone improved outcomes compared with placebo. The trial demonstrated a reduction in HF hospitalizations, but no improvement in the primary combined end point of cardiovascular mortality, HF hospitalizations, or aborted cardiac arrest. A key prespecified secondary outcome measure was the impact of spironolactone on changes in HRQL.[11] The primary objective of this article is to provide the detailed analysis of the effect of spironolactone on short- (4 and 12 months) and long-term (>12 months) changes in HRQL. A secondary objective is to determine the factors associated with changes in HRQL.

Methods

The design, patient characteristics, and primary outcome for TOPCAT have been previously published.[6,11,12] Briefly, TOPCAT study was a multicenter, international, randomized, double-blind, placebo-controlled trial of spironolactone versus placebo in subjects with symptomatic HF-PEF enrolled in United States, Russia, Republic of Georgia, Canada, Brazil, and Argentina. Participants were enrolled from August 2006 until January 2012. The subjects enrolled in the study were ≥50 years of age, with left ventricular ejection fraction ≥45% and either a hospitalization primarily for the treatment of HF within the year before randomization (hospitalization stratum) or an elevated natriuretic peptide level within 60 days before randomization (natriuretic peptide stratum). Key exclusion criteria included life expectancy<3 years, uncontrolled hypertension, constrictive pericarditis, known infiltrative or hypertrophic cardiomyopathy, history of serious or unprovoked hyperkalemia, and estimated glomerular filtration rate <30 mL/min per 1.73 m^2. TOPCAT was conducted with the approval of local institutional review boards.

Assessment of Quality of Life

Three self-administered questionnaires were used to assess different aspects of HRQL: the Kansas City Cardiomyopathy Questionnaire (KCCQ)[13] for assessing HF-specific HRQL related to HF, the EQ5D Visual analog scale (EQ5D-VAS)[14] for assessing generic HRQL to measure non–HF related perceptions, and the McMaster Overall Treatment Evaluation (McMaster OTE) for assessing the individual patient's perception of overall changes in HRQL since the beginning of therapy to help quantify change scores.[15] The primary HRQL outcome measure is the KCCQ overall summary score with supportive analyses of the other 2 instruments. The KCCQ is a HF-specific 23-item self-administered questionnaire developed to evaluate HF patients' HRQL, symptoms, and function. Domains include physical limitation, symptoms (frequency, severity, and change over time), quality of life, social limitations, and self-efficacy. Each response is given an ordinal value, and scale scores are transformed into a 0 to 100 range, with higher scores indicating better HRQL. KCCQ has been validated in HF populations, including in HF-PEF,[16] and is responsive to important changes in health state.[17,18] A clinically meaningful difference in KCCQ score is established as 5 points.[18] The EQ5D-VAS has 5 items for utility assessment and a single VAS for generic HRQL.[14] The 5-item utility portion of the EQ-5D was not administered to minimize burden to the subjects because cost-effectiveness analysis were not required. Only the single VAS component was used, which is a vertical scale from 0 to 100, with 0 representing the worst possible HRQL and 100 representing the best possible HRQL. The EQ5D-VAS has been used in multiple populations, including HF,[19,20] and a clinically meaningful difference in EQ5D-VAS score is established as 5 points.[21] The McMaster Overall Treatment Evaluation[15] is a self-administered 3-item instrument that measures the patient's perception of changes in their HRQL since start of therapy. The first question asks if there has been a change in their health since treatment began. The subject responds with a check in 1 of 3 boxes: better, no change, or worse. If either better or worse was checked, then the second question asks the subject to rate how much better (worse) their condition has changed ranging from a very great deal better (worse) to almost the same, hardly better (worse) at all. The scores obtained on a Likert scale ranged across 15 points from +7 to −7, with a score of 0 for subjects who stated no change on question 1. Question 3 asked "how important is this change (better/worse) to you?" on a 7-point scale. These 3 instruments collectively provide an overall assessment of the impact of therapy on patients' HRQL.

The KCCQ and EQ5D-VAS (with appropriate validated translations in all languages) were given to all participants enrolled in the study. The KCCQ and EQ5D-VAS were administered at baseline, 4 months, 12 months, and then annually until final study visit. The McMaster OTE was administered at 4 months and 12 months only for subjects in the United States, Canada, and Argentina to ensure valid translations of this instrument.

Statistical Analysis

The prespecified primary HRQL outcome measure was the KCCQ overall summary score. The outcomes were predefined as changes in KCCQ and EQ5D-VAS, and change scores were computed from baseline to each study visit occurring at months 4, 12, 24, 36, 48, and 60 with primary focus on the first 12 months with unadjusted change scores created. For each outcome, a backward selection method was used to select the baseline covariates, which were significantly associated with change in outcome at each time point to identify factors that influence the change scores in addition to randomization. Randomized treatment group, randomization stratum, and the baseline value of the outcome measure were forced into all covariate-adjusted models. Candidate variables were prespecified. Otherwise, nonsignificant variables were not included in final model. Mean changes at each time point were compared across the 2 randomized treatment groups using analysis of covariance, adjusting for baseline outcome value, stratum, and all baseline covariates significant for that outcome at ≥1 visit. The impacts of therapy on changes in KCCQ and EQ5D-VAS scores over time were examined using a repeated-measure analysis of covariance (using all follow-up time points). A Bonferonni correction was applied to both analysis of covariance models given multiple testing as a conservative estimate (P<0.0083 corrected). Time was treated as a categorical variable (months 4, 12, 24, 36, 48, and 60), and the interaction term of treatment and time was tested to examine whether treatment group effect on change in each outcome differed depending on the time point.

The repeated-measures models were also repeated separately for subjects in each of the 2 regions (Americas and Eastern Europe) given the significant differences in patient characteristics and clinical outcomes in the primary article.[6] The impact of randomization on change scores was calculated for patients who permanently discontinued study drug and those who did not discontinue study drug. The proportion of subjects in each treatment arm reporting improvement, no change, or decline on the McMaster OTE was calculated. Statistical analyses were performed at the TOPCAT Data Coordinating Center at New England Research Institutes (Watertown, MA) with SAS Version 9.3 statistical software (SAS Institute) and R Version 3.0.2 software (R Foundation for Statistical Computing, http://www.r-project.org/) and verified at the Brigham and Women's Hospital. A P<0.05 was considered statistically significant.

Results

The distributions of KCCQ and EQ5D-VAS scores at each follow-up visit are presented in Table 1. Of the 3445 patients enrolled in TOPCAT, paired baseline and follow-up KCCQ data were available for 3158 (91.7%) at 4 months and 2902 (84.2%) at 12 months. Paired EQ5D-VAS data were available for 3149 (91.4%) at 4 months and 2886 (83.8%) at 12 months. At 24 months, ≈69% completed KCCQ and EQ5D-VAS scores with decreasing responses for subsequent months (Table 1). The mean KCCQ score was 54.8±21 at

Table 1. Means and Frequencies of KCCQ and EQ5D-VAS Scores at Each Visit

	Baseline (N=3400)		Month 4 (N=3190)		Month 12 (N=2951)		Month 24 (N=2408)		Month 36 (N=1792)		Month 48 (N=1267)		Month 60 (N=809)	
	N	Mean±SD or N(%)	N	Mean±SD or N(%)	N	Mean±SD or N(%)	N	Mean±SD or N(%)	N	Mean±SD or N(%)	N	Mean±SD or N(%)	N	Mean±SD or N(%)
KCCQ score	3400	54.8±19.6	3176	62.8±19.6	2922	63.8±20.1	2379	64.7±19.6	1776	65.2±19.2	1258	65.7±19.0	808	66.2±18.8
Change in KCCQ score		N/A	3158	7.7±15.9	2902	8.2±18.0	2364	8.9±18.5	1762	9.4±19.2	1250	9.9±19.3	807	11.1±20.2
KCCQ Categories														
0–25		219 (6.4%)		83 (2.6%)		93 (3.2%)		75 (3.2%)		52 (2.9%)		39 (3.1%)		23 (2.8%)
26–50		1260 (37.1%)		787 (24.8%)		639 (21.9%)		471 (19.8%)		324 (18.2%)		211 (16.8%)		123 (15.2%)
51–75		1281 (37.7%)		1416 (44.6%)		1282 (43.9%)		1065 (44.8%)		810 (45.6%)		572 (45.5%)		379 (46.9%)
76–100		640 (18.8%)		890 (28.0%)		908 (31.1%)		768 (32.3%)		590 (33.2%)		436 (34.7%)		283 (35.0%)
EQ5D score	3395	60.3±17.3	3172	65.3±16.5	2912	65.9±16.5	2374	66.6±16.2	1773	67.4±15.6	1257	67.7±15.7	805	68.4±15.7
Change in EQ5D score		N/A	3149	4.7±16.2	2886	5.0±17.2	2355	5.7±17.9	1756	7.0±17.8	1247	7.8±17.9	803	8.6±18.1)
EQ5D-VAS categories														
0–25		100 (2.9%)		51 (1.6%)		43 (1.5%)		35 (1.5%)		21 (1.2%)		19 (1.5%)		7 (0.9%)
26–50		1134 (33.4%)		707 (22.3%)		650 (22.3%)		499 (21.0%)		336 (19.0%)		228 (18.1%)		145 (18.0%)
51–75		1582 (46.6%)		1629 (51.4%)		1452 (49.9%)		1154 (48.6%)		866 (48.8%)		604 (48.1%)		361 (44.8%)
76–100		579 (17.1%)		785 (24.7%)		767 (26.3%)		686 (28.9%)		550 (31.0%)		406 (32.3%)		292 (36.3%)

COPD indicates chronic obstructive lung disease; CV, cardiovascular; EQ5D-VAS, EQ5D visual analog scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; and NYHA, New York Heart Association.

baseline and increased to 62.8±20 by 4 months and 63.8±20 by 12 months. The mean EQ5D-VAS score was 60.3±17 at baseline and increased to 65.3±16 by 4 months and 65.9±17 by 12 months.

Quality of Life Outcomes

The unadjusted and adjusted mean change (±standard error) in KCCQ scores from baseline at each visit are presented by treatment group in Figure 1A and 1B. The unadjusted mean change improved in both spironolactone and placebo groups during follow-up. The adjusted mean change in KCCQ was significantly higher in the spironolactone group than in the placebo group at month 4 (P=0.002) and month 12 (P=0.02), with less consistent differences beyond 12 months. Randomization to spironolactone was also associated with improved KCCQ clinical scores and KCCQ symptom scores at 4 months compared with placebo; however, these differences did not persist beyond 4 months (Figure I in the Data Supplement). There were no significant treatment group differences in the other KCCQ domains (social interference, physical scores, quality of life) during follow-up. The unadjusted and adjusted mean changes (±standard error) in EQ5D-VAS are presented in Figure 2. There was no significant difference in mean change in EQ5D-VAS between spironolactone and placebo groups at any visit in either the unadjusted or the adjusted analyses. There were no significant differences in the McMaster OTE perception of change scores at 4 months and 12 months in patients randomized to spironolactone versus placebo (Figure 3).

When evaluating patients on study drug, there were significant improvements in KCCQ for spironolactone versus placebo at 4 and 12 months with persistence through 48 months (Figure IIA in the Data Supplement). No differences were seen in EQ5D-VAS change scores between the groups (Figure IIB in the Data Supplement).

Predictors of Longitudinal Changes in KCCQ and EQ5D-VAS

In the multivariable repeated-measures model, randomization to spironolactone was associated with a 1.36 point additional increase in KCCQ scores compared with the change for subjects randomized to placebo, adjusting for all other variables (Table 2). Additional predictors of improvements in KCCQ scores include hospitalization stratum, living in the Americas (as opposed to Russia/Georgia), and taking other cardiovascular medications. The percentage of meals eaten at home was also associated with changes in KCCQ but the effects were not linear. Predictors of declines in KCCQ scores include New York Heart Association (NYHA) Class III/IV functional class, older age, higher baseline KCCQ score, obesity, current smoking, use of a hypoglycemic medicine, history of chronic obstructive lung disease, bone fractures, hypertension, and thyroid disease. There was a general upward trend in KCCQ changes over time, although the overall test for time was not statistically significant (P=0.055). The difference in mean EQ5D-VAS change between treatment groups was 0.467 points, which was not statistically significant (P=0.223), and the difference in change in EQ5D-VAS over

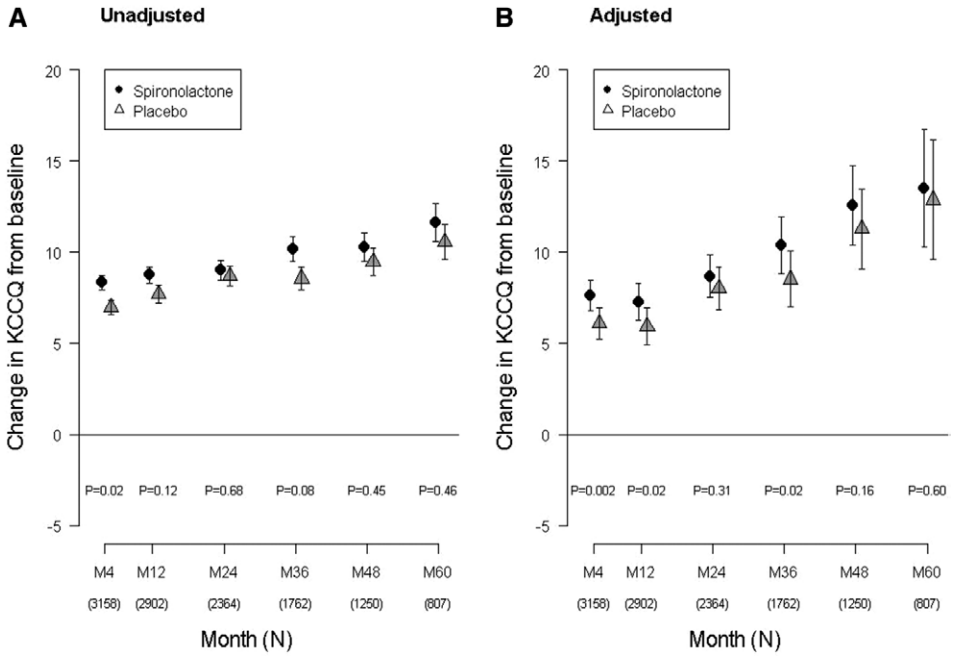

Figure 1. Unadjusted (**A**) and adjusted (**B**) mean (SE) of change in Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline at each visit by treatment group.

time was significant (P<0.001), indicating that the average change in EQ5D-VAS was increasing over time (Table 3). Several predictive variables for KCCQ scores were consistent predictors for the EQ5D-VAS change scores, including living in the Americas with improved scores and obesity, chronic obstructive lung disease, bone fracture, thyroid disease, NYHA Class III/IV, and use of a hypoglycemic agent with a decline in EQ5D-VAS. Compared with non-Hispanic White patients, Black and Hispanic patients noted improvements in EQ5D-VAS over time, but not in KCCQ scores. The presence of chronic kidney disease and atrial fibrillation were associated with declines in EQ5D-VAS, but not in KCCQ scores.

Regional Differences in Quality of Life Responses

Given the regional differences between patient characteristics and outcomes between those randomized in the Americas versus Russia/Georgia, all key analyses were repeated in both regions separately. Patients in the Americas (Table I in the

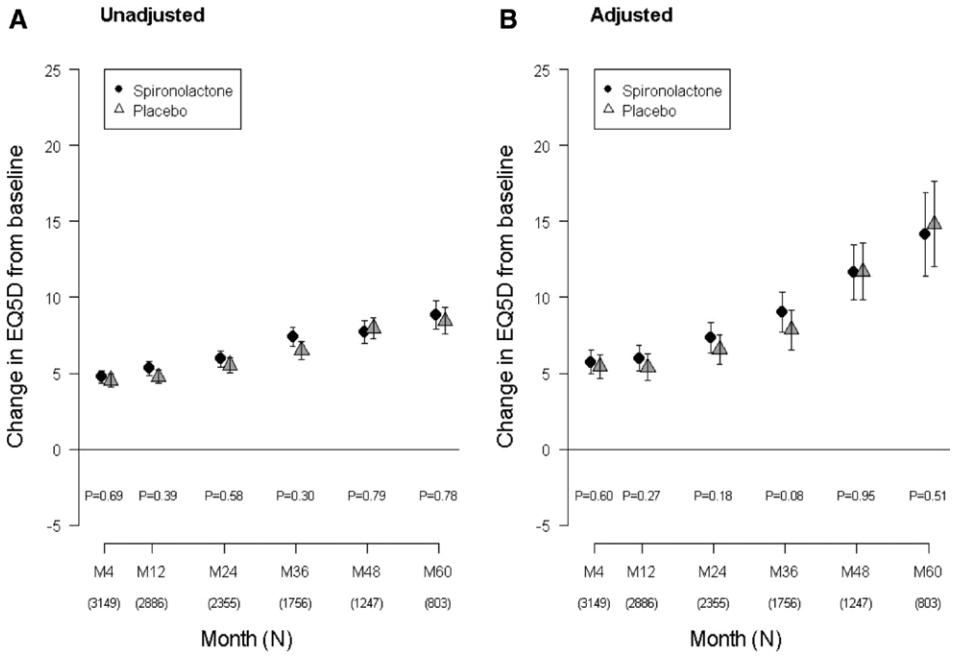

Figure 2. Unadjusted (**A**) and adjusted (**B**) mean (SE) of change in EQ5D visual analog scale (EQ5D-VAS) from baseline at each visit by treatment group.

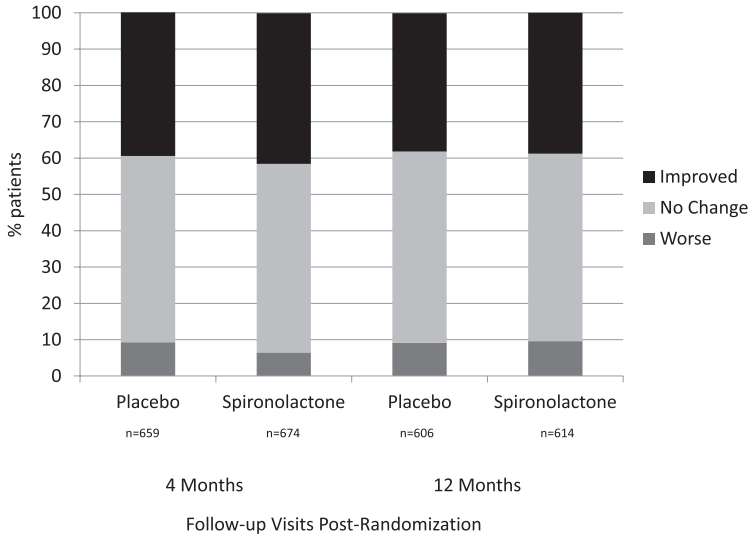

Figure 3. Impact of spironolactone vs placebo on patient's perception of change using McMaster Overall Treatment Evaluation.

Data Supplement) started with a better overall HRQL and had a smaller improvement over time than patients in Russia/Georgia (Table II in the Data Supplement). Patients randomized to spironolactone in the Americas noted a 2.079±0.74 greater improvement in KCCQ compared with placebo patients (P=0.005). In contrast, subjects randomized to spironolactone in Russia/Georgia noted a 0.654±0.50 greater improvement in KCCQ compared to placebo patients (P=0.192). However, the interaction term of region and treatment group was not significant (P for interaction=0.130). Additional regional similarities and differences are detailed in Figure IIIA and IIIB in the Data Supplement. The multivariable models did not change dramatically for either KCCQ (Tables III and IV in the Data Supplement) or EQ5D-VAS (Tables V and VI in the Data Supplement).

Discussion

The management goals of HF-PEF patients continue to improve survival, reduce morbidity and hospitalizations, attenuate disease progression, and improve HRQL and exercise capacity. Patient's preferences for the priority of these goals are highly individualized.[22] Despite the importance of HRQL in HF-PEF, limited data exist on the impact of therapies on this important patient-reported outcome.[23,24] The primary HRQL analysis of TOPCAT demonstrated that spironolactone use was associated with a statistically significant improvement in HRQL using the HF-specific KCCQ driven by improvements in symptoms and clinical scores domains. However, there was not an improvement in generic HRQL based on EQ5D-VAS or in the McMaster OTE, suggesting that non–HF related HRQL was not influenced. In a multivariable model that adjusted for baseline HRQL and factors associated with HRQL, use of spironolactone remained statistically associated with improvements in HRQL using repeated measures extending to 60 months.

Improving HRQL in patients with medical therapy has historically been difficult given the various factors associated with change scores, insensitivities of the instruments to measure small (but important) differences, and lack of complete data during longer follow-up periods in part because of competing risks of death. Use of spironolactone was associated with a short-term and long-term difference in KCCQ scores. The generic HRQL (measured by EQ5D-VAS) improved in both groups without a between-treatment difference. As in other publications of TOPCAT with disparate outcomes in the Americas and Russia/Georgia,[6,25] there were regional differences in HRQL responses with significant improvements in the Americas. After adjusting for baseline characteristics, randomized treatment group, and baseline HRQL values, mean changes in KCCQ and EQ5D were significantly better for patients from the Americas than for those from Russia/Georgia. However, the patient characteristics and other predictors of change scores were similar in the 2 regions.

Several studies have evaluated therapies on HRQL in HF-PEF. The Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study randomized 422 patients with HF-PEF to spironolactone or placebo, and there was no difference in Minnesota Living with Heart Failure (MLHF) scores by 12 months.[8] The Irbesartan in Heart Failure with Preserved Ejection Fraction study (I-PRESERVE) demonstrated no impact of irbesartan on changes in MLHF scores compared with placebo, although both groups noted clinically meaningful changes.[5] The Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial demonstrated no differences in change of HRQL using the MLHF questionnaire with median improvements of 8 points in both sildenafil and placebo groups.[9] Patients receiving candesartan in CHARM-Preserved noted an improvement in overall perception of change in their HRQL compared with placebo, but impact on MLHF scores has not been reported.[26] There is more experience with KCCQ in HF-REF populations. Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial (SHIFT) assessed HRQL in HF-REF and demonstrated a similar magnitude of improvement in KCCQ scores over 12 months with a 2.4 point between-group difference between ivabradine and placebo.[27] Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) enrolled 1699 patients with NYHA Class I/II HF and demonstrated improvement in KCCQ of 1.3 points

Table 2. Repeated Measures Model for Changes in KCCQ

Model Covariates	Changes in KCCQ Estimates (SE)	*P* Value*
Randomization to spironolactone (vs placebo)	1.36 (0.44)	0.002
Visit month		0.055†
12 (vs 4)	0.53 (0.28)	0.057
24 (vs 4)	0.79 (0.33)	0.017
36 (vs 4)	0.79 (0.38)	0.038
48 (vs 4)	1.18 (0.43)	0.006
60 (vs 4)	1.46 (0.51)	0.004
Baseline KCCQ score (per 1 point increase)	−0.42 (0.01)	<0.001
Hospitalization stratum	1.44 (0.55)	0.009
Americas‡ (vs Russia/Georgia)	2.14 (0.78)	0.006
Age, y	−0.08 (0.03)	0.002
Race/ethnicity		0.640†
Black, non-Hispanic (vs White, non-Hispanic)	1.00 (0.98)	0.308
Hispanic (vs White, non-Hispanic)	0.30 (0.91)	0.742
Other/missing (vs White, non-Hispanic)	−1.37 (1.94)	0.481
Obesity	−1.73 (0.48)	<0.001
Smoking Status		0.022†
Current (vs never)	−1.82 (0.79)	0.022
Former (vs never)	0.44 (0.51)	0.390
Atrial fibrillation	−1.07 (0.61)	0.077
Angina pectoris	−1.17 (0.78)	0.134
Asthma	−1.59 (0.96)	0.100
Coronary artery disease	−0.71 (0.84)	0.401
Myocardial infarction	0.13 (0.60)	0.832
COPD	−2.33 (0.73)	0.002
Bone fracture	−1.83 (0.73)	0.012
Hypertension	−2.17 (0.81)	0.007
Pacemaker	−0.77 (0.90)	0.394
Stroke	−1.24 (0.85)	0.144
Thyroid disease	−1.40 (0.63)	0.025
Calcium-channel blocker	0.57 (0.46)	0.219
Aspirin	−0.49 (0.52)	0.349
Statins	−0.53 (0.50)	0.291
Warfarin	0.05 (0.71)	0.948
Hypoglycemic agent	−1.56 (0.56)	0.005
Other CV medication§	1.20 (0.49)	0.014
Cooking salt score	0.00 (0.07)	0.996
Meals at home, %		0.012†
Almost all (vs None)	1.06 (1.08)	0.326
75% (vs None)	1.02 (1.19)	0.391
50% (vs None)	0.00 (1.32)	0.998
25% (vs None)	5.01 (1.62)	0.002
Living situation		0.092†
Currently living with spouse/sig other (vs living alone)	1.05 (0.57)	0.066
Currently living with someone other than spouse (vs living alone)	−0.16 (0.87)	0.856
NYHA functional class III/IV (vs I/II)	−2.13 (0.51)	<0.001

The baseline KCCQ score was 54.8. COPD indicates chronic obstructive lung disease; CV, cardiovascular; KCCQ, Kansas City Cardiomyopathy Questionnaire; and NYHA, New York Heart Association.

*All *P* values provided are from *t* tests with exception of those denoted with † from Type 3 F-Test. Models contain all covariates that were statistically significant across the 6 time points.

‡Americas represent subjects enrolled in United States, Canada, Brazil, or Argentina.

§CV medications other than aspirin, calcium-channel blocker, hypoglycemic agent, long-acting nitrate, statin, warfarin, diuretic, angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), beta-blocker.

better than defibrillator alone and 2 points better in cohort with left bundle branch block.[28] The Placement of Aortic Transcatheter Valve (PARTNERS) trial evaluated transcutaneous aortic valve replacement versus surgical aortic valve replacement and demonstrated significant improvements in KCCQ at 1 month with a 5.5 point difference, but there were no differences at 6 or 12 months.[29] The addition of surgical ventricular restoration to bypass surgery did not result in significant difference between KCCQ change scores in comparison to bypass alone in The Surgical Treatment for Ischemic Heart Failure (STICH).[30] Finally, the magnitude of change and between-group differences in TOPCAT was similar to the magnitude seen with cardiac rehabilitation in the Heart failure: a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial (5.2 versus 3.3 point change score in comparison with usual care).[31] Thus, the noted improvements in HRQL with spironolactone in HF-PEF deserve closer evaluation.

Understanding factors that influence future HRQL can be important for medical decision making about therapies and goals of care, especially as some patients will prefer HRQL as the more important outcome.[32–34] We identified several factors that are associated with declining KCCQ scores during follow-up, including older age, obesity, active smoking, need for hypoglycemic agents, NYHA Class III or IV functional capacity, and comorbid illnesses beyond HF. Some of these same factors influenced baseline HRQL as well.[35] Interestingly, despite female sex influencing baseline HRQL,[35] this did not influence longitudinal change in HRQL and did not make it into the final model. Older age and diabetes mellitus are 2 factors that influenced future declines in HRQL in HF-REF.[36] A study enrolling 111 HF-REF and HF-PEF patients referred to cardiac rehabilitation demonstrated that higher BMI and worse NYHA class at baseline were associated with worse HRQL over a mean of 2.8 years.[37] Smokers had a nonsignificant trend toward worse HRQL. The presence of chronic obstructive lung disease, thyroid disease, and hypertension may increase anxiety or directly impact symptom burdens with some overlap with HF symptoms and could lead to decrements in HRQL. The presence of some of these comorbid illnesses may impact

Table 3. Repeated Measures Model for Changes in EQ5D-VAS

	Changes in EQ5D-VAS	
Model Covariates	Estimates (SE)	*P* Value*
Randomization to spironolactone (vs placebo)	0.47 (0.38)	0.223
Visit month		<0.001†
12 (vs 4)	0.35 (0.27)	0.200
24 (vs 4)	0.78 (0.33)	0.018
36 (vs 4)	1.51 (0.36)	<0.001
48 (vs 4)	2.04 (0.42)	<0.001
60 (vs 4)	2.35 (0.48)	<0.001
Baseline EQ5D-VAS score (per 1 point increase)	−0.59 (0.01)	<0.001
Hospitalization stratum	−0.03 (0.48)	0.956
Americas‡ vs Russia/Georgia	1.69 (0.67)	0.012
Age, y	−0.05 (0.02)	0.051
Race/ethnicity		<0.001†
Black, non-Hispanic (vs White, non-Hispanic)	2.61 (0.86)	0.003
Hispanic (vs White, non-Hispanic)	3.37 (0.80)	<0.001
Other/missing (vs White, non-Hispanic)	−0.32 (1.71)	0.851
Obesity	−1.52 (0.42)	<0.001
Atrial fibrillation	−1.06 (0.53)	0.043
Angina pectoris	−0.63 (0.71)	0.371
Coronary artery bypass grafting	−0.06 (0.66)	0.928
Coronary artery disease	−0.80 (0.80)	0.316
Chronic kidney disease	−1.18 (0.42)	0.005
COPD	−1.76 (0.63)	0.005
Diabetes mellitus	1.93 (0.87)	0.026
Bone fracture	−2.05 (0.64)	0.001
Hypertension	−1.22 (0.70)	0.082
Implantable cardioverter defibrillator	0.64 (1.73)	0.711
Myocardial infarction	0.35 (0.52)	0.503
Stroke	−0.81 (0.74)	0.276
Thyroid disease	−1.29 (0.55)	0.018
PCI	−0.84 (0.64)	0.190
Hypoglycemic agent	−3.15 (0.92)	<0.001
Warfarin	−0.11 (0.62)	0.855
Long-acting nitrate	−1.36 (0.57)	0.017
Aspirin	0.45 (0.45)	0.324
Other CV medication§	−0.38 (0.43)	0.372
Cooking salt score	0.21 (0.06)	<0.001
Meals at home, %		0.006†
Almost all (vs none)	0.07 (0.95)	0.940
75% (vs none)	1.23 (1.05)	0.242
50% (vs none)	−1.48 (1.16)	0.203
25% (vs none)	2.39 (1.43)	0.094
NYHA functional class III/IV (vs I/II)	−2.69 (0.44)	<0.001

The baseline EQ5D-VAS score was 60.3. COPD indicates chronic obstructive lung disease; CV, cardiovascular; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

*All *P* values provided are from *t* tests with exception of those denoted with † from Type 3 F-Test. Models contain all covariates that were statistically significant across the 6 time points.

‡Americas represent subjects enrolled in United States, Canada, Brazil, or Argentina.

§CV medications other than aspirin, calcium-channel blocker, hypoglycemic agent, long-acting nitrate, statin, warfarin, diuretic, angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), beta blocker.

the degree to which a HF-specific intervention can improve a patient's HRQL, and this complex interaction should be further elucidated in future research. Interim cardiovascular events were not included in the model, and this may provide a link between excess comorbid illnesses and more severe HF with decrements in HRQL.[20] In contrast, few factors improved KCCQ scores longitudinally. Randomization to spironolactone independently improved KCCQ even after adjusting for all important factors. Nevertheless, given the equal impairment in HRQL between HF-PEF and HF-REF patients,[3] confirmation of the factors that influence declines in HRQL is important, especially because some of these factors are modifiable.

There are several limitations to this analysis. First, there was a dramatic decline in the completion of the HRQL instruments beyond 12- and 24-month visits, which creates a healthy cohort effect that may have caused the overall mean HRQL scores to improve over time. Moreover, nonfatal events may influence these HRQL perceptions. Focus on change scores should be within a short time frame as the primary efficacy end point for HRQL (eg, 6–8 months) to avoid competing risks of death, attrition, and comorbid illnesses. The large sample size with 3 distinct measures of HRQL may identify statistically significant differences that may not be perceivable by patients. However, the a priori determination of KCCQ as the primary HRQL measure reduces this concern. Populations in clinical trials tend to be healthier than the community-based cohorts, and HRQL responses to spironolactone may be different in patients who were not eligible for enrollment in TOPCAT. Finally, close follow-up and frequent visits may have influenced HRQL beyond the therapy, which may be the reason for over 50% of subjects having a clinically meaningful change score in the KCCQ in the placebo arm. Nevertheless, this is one of the largest studies in HF-PEF assessing HRQL.

In conclusion, stable, symptomatic patients with HF-PEF who receive spironolactone note an improvement in HF-specific HRQL compared with patients receiving placebo by 4 months, and this difference is seen ≤36 months. The beneficial effects are independent of multiple factors that influence patient change scores. Given the relatively small magnitude of change scores, further research is required to better delineate the potential role of this therapy to improve HRQL, an important target of novel interventions in this undertreated population.

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CLINICAL PERSPECTIVE

This study reports the primary quality of life longitudinal outcomes for the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT), one of the largest trials conducted on patients with heart failure with preserved ejection fraction. Given the equally impaired quality of life in this population compared with heart failure with reduced ejection fraction, strategies to improve these outcomes are paramount. The relative complete ascertainment of quality of life data allowed for rigorous assessments of longitudinal impact of therapy. Patients who were randomized to spironolactone noted improved quality of life using the Kansas City Cardiomyopathy Questionnaire in comparison to patients receiving placebo. These differences were noted by 4 months and persisted to 36 months. No differences were seen with generic measures of quality of life (EQ-5D and McMaster Overall Treatment Evaluation). Independent predictors of declines in quality of life included older age, obesity, current smoking, comorbid illnesses, and advanced New York Heart Association class III/IV. Some of these reversible factors may be novel targets for improving quality of life in this patient population. Moreover, clinicians may consider more careful evaluation of their patients' quality of life when they have these high-risk features because more intensive and focused management may attenuate this progressive decline and may help in shared decision making about goals of care. Overall, these results suggest a modest, but statistically significant, improvement in quality of life with the use of spironolactone in heart failure with preserved ejection fraction patients.