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CLINICAL RESEARCH

Associations Between Depressive Symptoms and HFpEF-Related Outcomes

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ABSTRACT

OBJECTIVES This study analyzed changes in depressive symptoms in patients with heart failure and preserved ejection fraction (HFpEF) who were enrolled in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial.

BACKGROUND There are limited longitudinal data for depressive symptoms in patients with HFpEF.

METHODS In patients enrolled in the United States and Canada (n = 1,431), depressive symptoms were measured using Patient Health Questionnaire-9 (PHQ-9). Clinically meaningful changes in PHQ-9 scores were defined as worse (≥3-point increase) or better (≥3-point decrease). Multivariate models were used to identify predictors of change in depressive symptoms. Cox proportional hazard models were used to determine the impact of symptom changes from baseline on subsequent incident cardiovascular events.

RESULTS At 12 months, 19% of patients experienced clinically worsening depressive symptoms, 31% better, and 49% unchanged. Independent predictors of clinically meaningful improvement in depressive symptoms included higher baseline PHQ-9 scores, male sex, lack of chronic obstructive pulmonary disease, and randomization to spironolactone. After data were adjusted for cardiovascular comorbidities, higher baseline PHQ-9 was associated with all-cause mortality (hazard ratio [HR]: 1.09; 95% confidence interval [CI]: 1.02 to 1.16; p = 0.011), whereas worsening depressive symptoms at 12 months were associated with cardiovascular death (HR: 2.47; 95% CI: 1.32 to 4.63; p = 0.005) and all-cause mortality (HR: 1.82; 95% CI: 1.13 to 2.93; p = 0.014). Randomization to spironolactone was associated with modest but statistically significant reduction in depressive symptoms over the course of the trial (p = 0.014).

CONCLUSIONS Higher baseline depressive symptoms and worsening depressive symptoms were associated with all-cause mortality. Randomization to spironolactone was associated with modest reduction in depressive symptoms. (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function [TOPCAT]; NCT00094302) (J Am Coll Cardiol HF 2020;8:1009–20) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HRQL = health-related quality of life

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-OS = KCCQ-overall score

PHQ-9 = Patient Health Questionnaire-9

Up to 40% of patients with heart failure (HF), in the United States have comorbid depression (1), a rate nearly 3 times greater than the general population (2). Depressed patients with HF experience worse cardiovascular (CV) outcomes (1) and health-related quality of life (HRQL) (3,4) than their nondepressed counterparts (1), but no drug therapy trial to date has shown improved depressive symptoms in patients with HF (5–7). Few large prospective studies have examined depressive symptoms in HF with preserved ejection fraction (HFpEF) (8,9), yet patients with HFpEF have equally impaired CV outcomes (9,10), HRQL (11), and higher rates of clinical depression (9) than those with HF with reduced ejection fraction (HFrEF). Predictors of change in depressive symptoms over time have not been comprehensively studied, and the prognostic significance of changes in depressive symptoms over time in patients with HFpEF remains unknown.

Overall, the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial showed no improvement in the spironolactone group in the primary composite endpoint of CV mortality, HF hospitalizations, and aborted cardiac arrest. However, significant regional differences among the Americas (United States, Canada, Brazil, and Argentina) and in Russia/Georgia have been reported, and in the Americas, there was a significant improvement in the primary composite outcome in the spironolactone arm (12). Additionally, the study showed improvements in HF-specific HRQL for spironolactone relative to that in placebo at follow-up of 12 and 36 months (13). The present study aimed to, first, identify the variates associated with changes in depressive symptoms between baseline and 12 months, second, to examine the impact of spironolactone on the change in depressive symptom, and third, to determine the association between depressive symptoms and subsequent clinical outcomes.

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METHODS

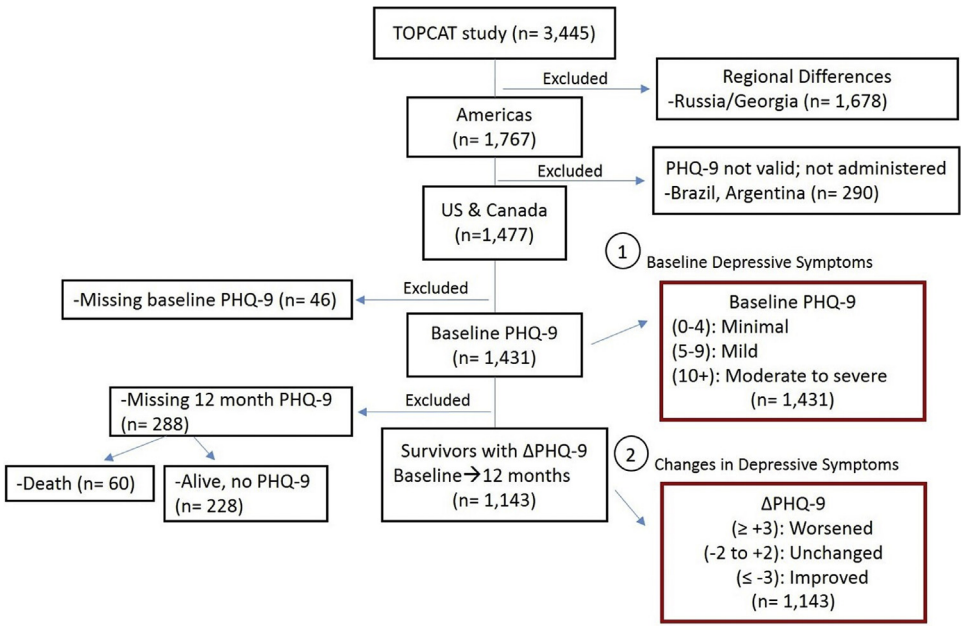
STUDY POPULATION. As described previously (8,13,14), TOPCAT was a multinational, randomized, double-blinded, placebo-controlled trial which randomized symptomatic patients with HFpEF to spironolactone or placebo. Patients were recruited between August 2006 and January 2012. Participants were ≥50 years of age with LVEF ≥45% and were enrolled either through documented HF hospitalization within the previous 12 months before randomization or an elevated natriuretic peptide level within 60 days before randomization. The present study included only patients enrolled in the United States and Canada because validated translations of the Patient Health Questionnaire-9 (PHQ-9) were not available in the other countries. The study was approved by the institutional review board at each participating site, and all patients provided written informed consent.

DEPRESSIVE SYMPTOMS. Depressive symptoms were assessed using the PHQ-9 instrument, a 9-item self-reported questionnaire that asks about depressive symptoms experienced by the patient in the previous 2 weeks (15). Each item assesses a depressive symptom and is rated on an ordinal scale from "0" (not at all) to "3" (nearly every day) for a total summary score ranging from 0 to 27. PHQ-9 scores were organized into categories of severity, from 0 to 4 (minimal), 5 to 9 (mild), 10 to 14 (moderate), 15 to 19 (moderately severe), and 20 to 27 (severe) (15). Clinical depression was defined as a rating ≥10. PHQ-9 has been readily used and validated in patients with HF (7,16,17). For primary analysis, clinically meaningful changes in PHQ-9 scores were defined as worse (≥3-point increase) or better (≥3-point decrease). For sensitivity analysis, 2 other criteria were used to define clinically meaningful changes, an increase or decrease ≥5 points (18) and a post-treatment score <10 and 50% improvement in PHQ-9 (15,19).

HEALTH-RELATED QUALITY OF LIFE. HF-specific HRQL was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) (20). The KCCQ is a validated, 23-item patient-reported instrument designed to assess HRQL in HF patients with reduced and preserved EF (21). Responses are transformed to overall summary scores within a range of 0 to 100 (higher scores represent better HRQL).

CLINICAL OUTCOMES. The primary endpoint was a composite of time to death from CV causes, aborted cardiac arrest, or HF hospitalization, according to previously described prespecified criteria (12). Individual components of the composite outcome, including all-cause mortality, CV death, HF hospitalization, and aborted cardiac arrest, were used as secondary CV outcomes. All events were adjudicated by a blinded clinical endpoint committee at Brigham and Women's Hospital.

FIGURE 1 Flow Diagram of Patients Included for Depressive Symptoms Assessment



A total of 1,477 patients were enrolled in the United States and Canada and were offered the PHQ-9 assessment at baseline. A completion rate of 97% was achieved at baseline (n = 1,431), and 80% of them had paired data at 12 months (n = 1,143). PHQ-9 = Patient Health Questionnaire-9; TOPCAT = Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function.

STATISTICAL ANALYSIS. Flow diagram was constructed to show the populations included in the analyses (Figure 1). PHQ-9 score and KCCQ-overall score (OS) were prespecified outcome measurements for depressive symptoms and HRQL, respectively. Baseline characteristics of patients were divided into baseline PHQ-9 categories. Continuous characteristics were summarized using mean ± SD or median (interquartile range) as appropriate. Categorical characteristics were summarized using frequencies and percentages. Linear regression and chi square tests for trend were used to assess for trends within baseline characteristics across the categories. A 2-tailed Student's *t*-test and a chi square test were used to assess associations between 2 categories. Similar descriptive statistics were used to compare baseline characteristics of patients who did and did not complete PHQ-9 at baseline, to describe characteristics of patients who did and did not complete PHQ-9 at 12 months and to describe baseline characteristics stratified by categorical changes in depressive symptoms (≥3-point changes) from baseline to 12 months.

A histogram was used to show the distribution of change scores calculated between baseline and 12 months. To identify predictors of changes in depressive symptoms, backwards ($p < 0.05$) multivariate stepwise regression modeling was performed. The multivariate stepwise regression model included all baseline characteristics displayed in Table 1. In the first model, the change in depressive symptoms (PHQ-9) was considered a continuous variable, thus stepwise multivariate linear regression was used. In the second model, a ≥3-point improvement in depressive symptoms (≥3-point decrease in PHQ-9) was considered a categorical variable and multivariate logistic regression was used.

Mean PHQ-9 scores were compared between the treatment groups at prespecified follow-up time at 12 months using the Student's *t*-test. Further comparison adjustments for baseline PHQ-9 were performed using multivariate linear regression. The associations between spironolactone and placebo in the PHQ-9 score were also measured through the 48-month visit using longitudinal analysis adjusted for respective baseline values. Cox proportional hazards models were used to assess the associations of baseline and changes in depressive symptoms on the subsequent primary composite outcome, CV death, HF hospitalization, aborted cardiac arrest, all-cause

TABLE 1 Baseline Characteristics Stratified by PHQ-9 Categories

	PHQ-9 Category 0–4 Minimal Depressive Symptoms (n = 632)	PHQ-9 Category 5–9 Mild Depressive Symptoms (n = 417)	PHQ-9 Category ≥10 At Least Moderate Depressive Symptoms (n = 382)	p Trend
PHQ-9	1.9 ± 1.4	6.8 ± 1.4	14.4 ± 3.8	NA
KCCQ-overall score	72.3 ± 18.7	54.8 ± 19.8	38.4 ± 18.5	<0.001
Age	73.2 ± 9.3	72.6 ± 9.8	68.0 ± 10.0	<0.001
Men	356 (56)	207 (50)	182 (48)	0.005
Race category				0.003
White	507 (80)	334 (80)	275 (72)	
Black	104 (16)	68 (16)	83 (22)	
Other	21 (3)	15 (4)	24 (6)	
Medical history				
Hypertension	561 (89)	379 (91)	351 (92)	0.09
Atrial fibrillation	303 (48)	190 (46)	154 (40)	0.02
Angina	167 (26)	127 (30)	139 (36)	<0.001
Myocardial infarction	142 (22)	92 (22)	83 (22)	0.78
PCI	154 (24)	89 (21)	78 (20)	0.13
CABG	140 (22)	86 (21)	85 (22)	0.96
Stroke	50 (8)	49 (12)	37 (10)	0.24
ICD	21 (3)	13 (3)	8 (2)	0.28
Pacemaker	96 (15)	73 (18)	56 (15)	0.95
Diabetes	251 (40)	212 (51)	216 (57)	<0.001
COPD	95 (15)	79 (19)	88 (23)	0.001
Asthma	57 (9)	62 (15)	59 (15)	0.001
Chronic kidney disease	295 (47)	220 (53)	188 (49)	0.31
Body mass index	33.0 ± 7.9	34.1 ± 8.7	36.7 ± 9.4	<0.001
NYHA functional class (III/IV)	181 (29)	180 (43)	178 (47)	<0.001
LVEF, %	57.5 ± 7.7	57.9 ± 7.6	58.1 ± 7.2	0.19
Potassium, mg/dl	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	0.003
eGFR, ml/min/1.73 m^2	61.9 (50.6, 75.3)	58.4 (47.1, 74.1)	60.6 (48.8, 79.2)	0.83
Hemoglobin, g/dl	13.0 ± 1.6	12.6 ± 1.7	12.5 ± 1.6	<0.001
Current smoker	36 (6)	27 (6)	33 (9)	0.08
Alcohol drinks/week				<0.001
0	429 (68)	305 (73)	297 (78)	
1–10	181 (29)	101 (24)	79 (21)	
>10	22 (3)	11 (3)	4 (1)	
Activity (AHA definition)				<0.001
Poor	414 (66)	310 (75)	310 (82)	
Intermediate	105 (17)	66 (16)	43 (11)	
Ideal	110 (17)	39 (9)	24 (6)	
Currently living alone	190 (30)	149 (36)	102 (27)	0.46
Currently living with spouse	373 (59)	214 (51)	225 (59)	0.69
Medical treatment				
Diuretic	557 (88)	373 (89)	353 (92)	0.034
ACE inhibitor	299 (47)	191 (46)	210 (55)	0.033
ARB	188 (30)	143 (34)	122 (32)	0.36
β-blocker	508 (80)	342 (82)	310 (81)	0.7
Hypoglycemic agent	228 (36)	190 (46)	207 (54)	<0.001
Aspirin	379 (60)	248 (59)	225 (59)	0.74
Warfarin	252 (40)	159 (38)	119 (31)	0.007
Antidepressants	69 (11)	75 (18)	87 (23)	<0.001

Values are mean ± SD, n (%), or median (25th, 75th percentiles).

ACE = angiotensin angiotensin-converting enzymes; AHA = American Heart Association; ARB = aldosterone receptor blocker; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NA = not applicable; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PHQ-9 indicates Patient Health Questionnaire-9.

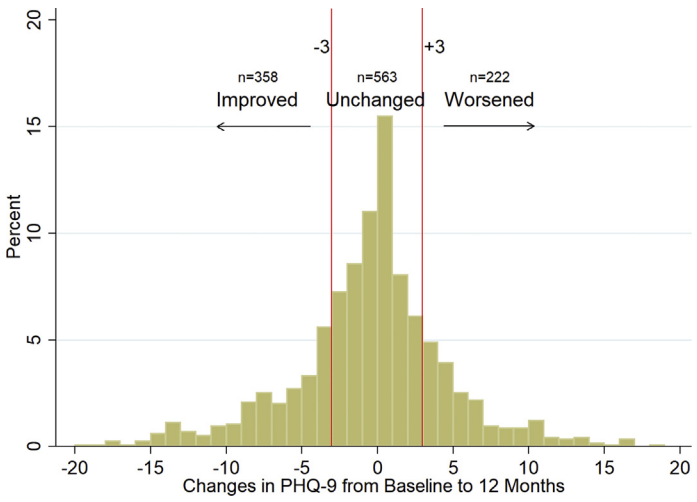
mortality, and permanent discontinuation of drug therapy. On-treatment analysis was also performed to assess the effect of drug discontinuation. Logistic regression was used to test whether baseline depression modified the odds of having clinically meaningful improvement in KCCQ score over 12 months, defined by a change of ≥5 points, and whether there was a treatment interaction in depression status. Statistical analyses were performed using StataCorp SE14 software (College Station, Texas). Two-tailed p value of <0.05 was used for significance.

RESULTS

CLINICAL PROFILES AND BASELINE DEPRESSIVE SYMPTOMS. A total of 1,477 patients were enrolled in the United States and Canada and were offered PHQ-9 assessment at baseline. A completion rate of 97% was achieved at baseline (n = 1,431), and 80% of them had paired data at 12 months (n = 1,143). Baseline characteristics were similar between PHQ-9 completers and noncompleters, except mean LVEF was slightly higher in the noncompleters (61 ± 8% vs. 58 ± 8%, respectively; p = 0.012) (Supplemental Table 1). At baseline, 27% of patients reported moderate-to-severe depressive symptoms, 44% reported minimal symptoms, and 29% reported mild symptoms (**Table 1**). Patients with more depressive symptoms at baseline were younger, more likely to be female and nonwhite, had worse mean KCCQ-OS, higher mean body mass indexes, were more likely to be in New York Heart Association (NYHA) functional class III/IV, were less likely to drink alcohol and less likely to achieve ideal physical activity level. They also had a higher prevalence of comorbidities including angina, diabetes, chronic obstructive pulmonary disease (COPD), and asthma. Patients with greater baseline depressive symptoms were more likely to be taking diuretics, angiotensin- converting enzyme inhibitors, hypoglycemic agents, and antidepressants.

CHANGES IN DEPRESSIVE SYMPTOMS. In patients with paired data at 12 months, the mean PHQ-9 score was 6.4 ± 5.5 at baseline with a mean change of −1.0 ± 5.2 points over 12 months. Compared to those with paired PHQ-9 score at 12 months, patients who were missing the 12-month PHQ-9 score had higher baseline PHQ-9 scores, lower baseline KCCQ-OS, higher prevalence of baseline COPD, higher baseline prevalence for NYHA functional class III/IV, and lower LVEF (Supplemental Table 2). Use of the clinically significant 3-point change threshold showed 31% of patients had improved depressive symptoms, 19% had worsened, and 49% had unchanged symptoms (**Figure 2**). Patients whose depressive symptoms improved (PHQ-9 ≥3-point decrease) over 12 months had higher baseline mean PHQ-9 scores and lower baseline mean KCCQ-OS and were less likely to be white than those who had worse or unchanged depressive symptoms (**Table 2**). Patients who improved their depressive symptoms were also more likely randomized to spironolactone.

FIGURE 2 Distribution of Changes in Depressive Symptoms Between Baseline and 12 Months



Use of the clinically significant 3-point change threshold in PHQ-9 demonstrated 31% of patients had reduced depressive symptoms, 19% worsened, and 49% were unchanged. PHQ-9 = Patient Health Questionnaire-9.

PREDICTORS OF CHANGES IN DEPRESSIVE SYMPTOMS. In stepwise multivariate linear regression model that excluded KCCQ and medications, independent predictors of continuous improvement in depressive symptoms (decreasing PHQ-9) had higher baseline PHQ-9 cores, NYHA functional class I/II, and lack of COPD (**Table 3**). When baseline KCCQ-OS and medications were added to the stepwise model, higher KCCQ-OS and lack of use of antidepressants predicted improvement in depressive symptoms, whereas COPD and NYHA functional class were no longer significant predictors.

Regarding clinically meaningful improvement in depressive symptoms (≥3-point decrease in PHQ-9), in the model that excluded KCCQ-OS and medications, independent predictors were higher PHQ-9 scores at baseline, male sex, lack of COPD, and randomization to spironolactone (**Table 3**). When KCCQ-OS and medications were added to the model, higher baseline PHQ-9 scores, male sex, lack of COPD, and randomization to

TABLE 2 Baseline Characteristics Stratified by Category Changes in Depressive Symptoms (≥3-Point Changes in PHQ-9) From Baseline to 12 Months

	Worse (ΔPHQ-9 ≥3-Point Increase; n = 222)	Same (ΔPHQ-9 −2 to 2 Points; n = 563)	Better (ΔPHQ-9 ≥3-Point Decrease; n = 358)	p Trend
Baseline PHQ-9	5.0 ± 4.6	4.3 ± 4.4	10.6 ± 5.3	<0.001
Change in PHQ-9	6.0 ± 3.3	-0.2 ± 1.2	-6.6 ± 3.7	NA
KCCQ overall score	59.1 ± 23.1	67.2 ± 22.0	49.7 ± 21.8	<0.001
Age, yrs	70.5 ± 9.9	73.4 ± 9.3	70.1 ± 9.8	0.17
Men	115 (52)	292 (52)	192 (54)	0.63
Race category				0.004
White	179 (81)	462 (82)	258 (72)	
Black	34 (15)	81 (14)	77 (22)	
Others	9 (4)	20 (4)	23 (6)	
Medical history				
Hypertension	202 (91)	501 (89)	330 (92)	0.47
Atrial fibrillation	83 (37)	281 (50)	165 (46)	0.11
Angina	72 (32)	169 (30)	116 (32)	0.89
Myocardial infarction	55 (25)	136 (24)	80 (22)	0.47
PCI	50 (23)	138 (25)	82 (23)	0.99
CABG	51 (23)	121 (21)	75 (21)	0.58
Stroke	17 (8)	51 (9)	40 (11)	0.14
ICD	6 (3)	23 (4)	6 (2)	0.31
Pacemaker	30 (14)	86 (15)	53 (15)	0.73
Diabetes	116 (52)	237 (42)	192 (54)	0.35
COPD	43 (19)	94 (17)	55 (15)	0.22
Asthma	25 (11)	54 (10)	56 (16)	0.05
Chronic kidney disease	117 (53)	273 (48)	172 (48)	0.32
Body mass index, kg/m^2	34.8 ± 8.0	33.6 ± 7.9	35.2 ± 9.4	0.34
NYHA functional classes III and IV	85 (38)	186 (33)	138 (39)	0.7
LVEF, %	58.2 ± 7.8	58.0 ± 7.5	57.9 ± 7.4	0.62
Potassium, mg/dl	4.1 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	0.34
eGFR, ml/min/1.73 m^2	58.4 (47.5, 75.6)	60.6 (48.8, 74.1)	61.3 (50.3, 79.2)	0.12
Hemoglobin, g/dl	12.8 ± 1.5	12.9 ± 1.6	12.7 ± 1.6	0.39
Current smoker	19 (9)	20 (4)	23 (6)	0.53
Alcoholic drinks/week				0.77
0	171 (77)	386 (69)	272 (76)	
1-10	46 (21)	158 (28)	77 (22)	
>10	5 (2)	19 (3)	8 (2)	
Activity (AHA definition)				0.14
Poor	162 (73)	384 (69)	273 (77)	
Intermediate	34 (15)	93 (17)	49 (14)	
Ideal	26 (12)	82 (15)	33 (9)	
Currently living alone	72 (32)	174 (31)	94 (26)	0.09
Currently living with spouse	122 (55)	332 (59)	216 (60)	0.22
Medical treatment				
Diuretic	200 (90)	495 (88)	323 (90)	0.8
ACE inhibitor	104 (47)	273 (48)	182 (51)	0.33
ARB	75 (34)	180 (32)	116 (32)	0.78
β-blocker	188 (85)	453 (80)	285 (80)	0.16
Hypoglycemic agent	107 (48)	219 (39)	178 (50)	0.35
Aspirin	131 (59)	347 (62)	207 (58)	0.64
Warfarin	80 (36)	232 (41)	130 (36)	0.82
Antidepressants	49 (22)	68 (12)	60 (17)	0.24
Randomization to spironolactone	103 (46)	277 (49)	198 (55)	0.027

Values are mean ± SD, n (%), or median (25th, 75th percentiles).

ACE = angiotensin angiotensin-converting enzymes; AHA = American Heart Association; ARB = aldosterone receptor blocker; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NA = not applicable; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PHQ-9 indicates Patient Health Questionnaire-9.

spironolactone remained as significant predictors. Of note, patients with baseline PHQ-9 ≤2 were excluded because it was difficult to improve upon minimal depressive symptoms (n = 338).

IMPACT OF SPIRONOLACTONE ON DEPRESSIVE SYMPTOMS. There were no significant differences in mean PHQ-9 scores between the treatment groups at the prespecified endpoint of 12 months (5.6 ± 5.3 for placebo, 5.3 ± 5.2 for spironolactone; p = 0.25). After adjustments of baseline PHQ-9, the differences remained statistically insignificant, although they trended toward lower PHQ-9 in the spironolactone arm (5.2 ± 0.2 vs. 5.7 ± 0.2, respectively; p = 0.09). However, overall, there was a significant reduction of PHQ-9 score associated with randomization to spironolactone (longitudinal p = 0.014) (Figure 3). As reported above, randomization to spironolactone was also independently associated with clinically meaningful improvement in depressive symptoms.

BASELINE DEPRESSIVE SYMPTOMS ON CARDIOVASCULAR OUTCOMES. Over a mean follow-up of 3.3 years, 446 patients experienced the primary composite event (CV death, HF hospitalization, and aborted cardiac arrest). In unadjusted models, baseline PHQ-9 score was not associated with an incidence of primary composite event, CV death, HF hospitalization, and all-cause mortality (Table 4). However, when adjusted for CV comorbidities, higher baseline PHQ-9 score was associated with all-cause mortality (hazard ratio [HR]: 1.09; 95% confidence interval [CI]: 1.02 to 1.16; p = 0.011) but not with other CV outcomes. Non-CV death made up 43% of mortality in this study. Higher baseline PHQ-9 score was significantly associated with non-CV deaths in the model adjusted for CV comorbidities (HR: 1.13 per 3-point increase; 95% CI: 1.03 to 1.24; p = 0.012).

12-MONTH CHANGE IN DEPRESSIVE SYMPTOMS AND SUBSEQUENT CARDIOVASCULAR OUTCOMES. For this analysis, patients who had a CV event for each respective analysis between baseline and 12 months and patients who had baseline PHQ-9 ≤2 were excluded. There were no significant differences among the 3 groups in the primary composite events and heart failure hospitalizations (Table 5). However, after baseline PHQ-9 scores were adjusted, patients who had worsening depressive symptoms had a significantly higher incidence of CV death and all-cause mortality than those with no significant changes. These differences persisted after adjustment for comorbidities and randomization to spironolactone.

In sensitivity analysis, in which the 5-point improvement was included as a clinically meaningful change (Supplemental Table 3), associations between clinical worsening in PHQ-9 and CV death and all-cause mortality remained statistically significant in baseline-adjusted and fully adjusted models. Associations between clinical improvement in PHQ-9 and CV death and all-cause mortality became marginally statistically significant in the fully adjusted models. In sensitivity analysis, in which a PHQ-9 follow-up score <10 and a 50% improvement in PHQ-9 score as clinically significant improvement were used, there was no significant association between change in PHQ-9 with any outcome (Supplemental Table 4).

Baseline PHQ-9 score was marginally associated with permanent drug discontinuation (HR: 1.04 per 3-point increase; 95% CI: 1.00 to 1.08; p = 0.050), whereas clinical worsening of PHQ-9 (≥3-point increase) was significantly associated with permanent drug discontinuation (HR: 1.51; 95% CI: 1.13 to 2.02; p = 0.006). In on-treatment analysis, baseline PHQ-9

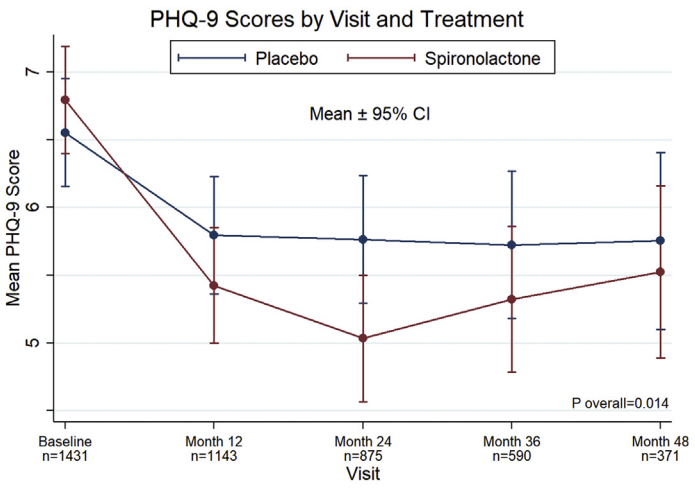
TABLE 3 Independent Predictors of Continuous Improvement in Depressive Symptoms (Decreasing PHQ-9) and Clinically Meaningful Improvement in Depressive Symptoms (≥3-Point Decrease in PHQ-9) Between Baseline and 12 Months (n = 805)

	Estimate	95% CI		|Z| Score
Continuous improvement in depressive symptoms (linear decrease in PHQ-9)				
Without KCCQ-OS or medications				
Baseline PHQ-9 (per 3 points)	1.54	1.34	1.74	15.2
NYHA functional classes III/IV	−0.86	−1.54	−0.19	2.5
COPD	−0.85	−1.72	0.02	1.9
With KCCQ-OS and medications				
Baseline PHQ (per 3 points)	1.74	1.50	1.98	14.3
Antidepressant use	−1.38	−2.26	−0.51	3.1
KCCQ-overall score (per 5 points)	0.14	0.05	0.23	2.9
Clinically meaningful improvement in depressive symptoms (≥ 3-point decrease in PHQ-9)				
Without KCCQ-OS or medications				
Baseline PHQ-9 (per 3 points)	0.46	0.36	0.56	9.0
Male	0.39	0.08	0.69	2.5
COPD	−0.53	−0.95	−0.12	2.5
Randomization to spironolactone	0.36	0.06	0.66	2.4
Asthma	0.51	0.05	0.98	2.2
NYHA functional classes III/IV	−0.34	−0.65	−0.03	2.1
With KCCQ-OS and medications				
Baseline PHQ-9 (per 3 points)	0.46	0.36	0.56	9.0
Male	0.39	0.08	0.69	2.5
COPD	−0.53	−0.95	−0.12	2.5
Randomization to spironolactone	0.36	0.06	0.66	2.4
Asthma	0.51	0.05	0.98	2.2
NYHA functional classes III/IV	−0.34	−0.65	−0.03	2.1

All p values <0.05. Patients with baseline PHQ≤2 were excluded (n = 338).

COPD = chronic obstructive pulmonary disease; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; NYHA = New York Heart Association; PHQ-9 = Patient Health Questionnaire-9.

FIGURE 3 Longitudinal Analysis of PHQ-9 Scores



Within the overall course of the trial, there was a significant reduction of PHQ-9 scores associated with randomization to spironolactone. PHQ-9 = Patient Health Questionnaire-9.

score was no longer associated with any outcome including all-cause mortality (Supplemental Table 5). In the fully adjusted model, association between clinical worsening of PHQ-9 (≥3-point increase) and CV death remained significant but attenuated, whereas its relationship with all-cause mortality was no longer significant (Supplemental Table 6).

DEPRESSIVE SYMPTOMS ON HRQL. Patients with at least moderate depressive symptoms (PHQ-9 ≥10) were more likely to report a clinically meaningful improvement in KCCQ-OS (≥5 points) at 12 months (odds ratio [OR]: 2.32; 95% CI: 1.76 to 3.05; $p < 0.001$) compared to patients without baseline clinical depression (PHQ-9 <10). Patients who were clinically depressed at baseline had similar odds of improving their quality of life when randomized to spironolactone (OR: 1.33; 95% CI: 0.82 to 2.16; $p = 0.24$) as patients who were not depressed (OR: 1.11; 95% CI: 0.85 to 1.45; $p = 0.45$) (p value for interaction = 0.51).

TABLE 4 Associations of Baseline PHQ-9 Scores (per 3-Point Increase) With Cardiovascular Outcomes (n = 1,431)

		Unadjusted Model			Adjusted Model*		
	Events	HR	95% CI	p Value	HR	95% CI	p Value
Primary composite event	446	1.04	0.99–1.09	0.11	0.99	0.94–1.05	0.73
Cardiovascular death	177	1.04	0.96–1.13	0.29	1.06	0.97–1.15	0.21
Heart failure hospitalization	352	1.02	0.97–1.08	0.44	0.96	0.90–1.02	0.22
Aborted cardiac arrest	6	-	-	-	-	-	-
All-cause mortality	312	1.05	0.99–1.11	0.11	1.09	1.02–1.16	0.011

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; PHQ-9 indicates = Patient Health Questionnaire-9. *Adjusted for age, sex, race, hypertension, diabetes, body mass index, history of myocardial infarction, history of stroke, previous hospitalization for heart failure, NYHA functional class, chronic kidney disease, and randomization to spironolactone.

DISCUSSION

In this large contemporary randomized clinical trial of patients with symptomatic chronic HFpEF, 27% of patients reported at least moderate depressive symptoms at baseline. Independent predictors of clinically meaningful improvement in depressive symptoms included higher baseline depressive symptoms, male sex, lack of COPD, and randomization to spironolactone. While not statistically significant at 12 months, randomization to spironolactone was associated with modest but statistically significant reduction in depressive symptoms over the entire course of the trial. Worse baseline PHQ-9 score was associated with all-cause mortality, and patients who had worsening depressive symptoms had higher incidence of CV death and all-cause mortality despite adjusting for comorbidities (**Central Illustration**).

In the TOPCAT study, factors associated with clinical depression at baseline included female sex, COPD, worse NYHA functional class, and worse KCCQ scores (8). The present study builds upon those findings by showing that those aforementioned factors associated with clinical depression at baseline remain associated with significant changes in depressive symptoms over 12 months. Additionally, randomization to spironolactone was significantly associated with clinically meaningful improvement in depressive symptoms, which may provide physicians another tool with which to improve depressive symptoms. The data also showed that patients with lower KCCQ-OS were more likely to have worse depressive symptoms and vice versa, consistent with a prior HFrEF study (22).

Female sex was an independent predictor of worsening depressive symptoms. Secondary analysis of SADHART-CHF showed that male patients with HFrEF were more likely to experience depression remission (23), consistent with the present findings. Findings that COPD and greater NYHA functional class were independent predictors of worsening depressive symptoms was consistent with their prior associations with baseline clinical depression and worsening HRQL as shown in the previous TOPCAT study (13). Smoking status was not predictive of worsening depressive symptoms, a finding that differed from a prior study in patients with HFrEF (24). In both analyses of categorical and continuous changes, baseline PHQ-9 score, better NYHA

TABLE 5 Impact of Categorical Changes in PHQ-9 Scores From Baseline to 12 Months on Cardiovascular Outcomes, Excluding Patients With Baseline PHQ-9 ≤2

			Adjusted for Baseline PHQ-9 Hazard Ratio (95% CI) p Value			Adjusted for Baseline PHQ-9 and Other Comorbidities* Hazard Ratio (95% CI) p Value		
	N	Number of Events	Worse ΔPHQ-9 ≥+3	Same ΔPHQ-9 <|3|	Better ΔPHQ-9 ≤−3	Worse ΔPHQ-9 ≥+3	Same ΔPHQ-9 <|3|	Better ΔPHQ-9 ≤−3
Primary composite event	686	161	1.36 (0.86–2.15) 0.18	Ref.	1.15 (0.80–1.65) 0.45	1.25 (0.78–1.99) 0.36	Ref.	1.10 (0.76–1.58) 0.62
Cardiovascular death	769	79	2.73 (1.49–5.01) 0.001	Ref.	1.84 (1.05–3.23) 0.034	2.47 (1.32–4.63) 0.005	Ref.	1.71 (0.96–3.04) 0.07
Heart failure hospitalization	687	117	1.39 (0.83–2.34) 0.21	Ref.	1.09 (0.71–1.66) 0.70	1.34 (0.78–2.29) 0.28	Ref.	1.08 (0.70–1.66) 0.72
Aborted cardiac arrest	767	3	-	Ref.	-	-	Ref.	-
All-cause mortality	778	141	1.79 (1.13–2.83) 0.014	Ref.	1.45 (0.97–2.16) 0.07	1.82 (1.13–2.93) 0.014	Ref.	1.39 (0.92–2.09) 0.12

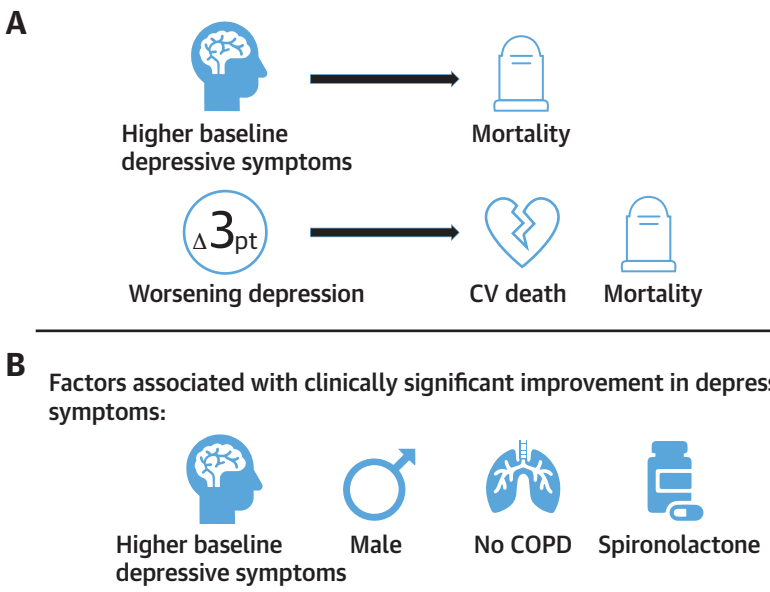
*Adjusted for age, sex, race, hypertension, diabetes, body mass index, history of myocardial infarction, history of stroke, previous hospitalization for heart failure, NYHA functional class, chronic kidney disease, and randomization to spironolactone

CI = confidence interval; NYHA = New York Heart Association; PHQ-9 = Patient Health Questionnaire-9.

functional class, and lack of COPD were consistent independent predictors of improvement in PHQ-9. Randomization to spironolactone was only associated with clinically meaningful improvement. This could be due to a threshold effect through which spironolactone interacts with depressive symptoms.

The present study was one of the first to examine the impact of a mineralocorticoid receptor antagonist on depressive symptoms in patients with HFpEF. Similar to the ALSO-DHF (ALDOsterone receptor blockade in Diastolic Heart Failure) study (5), spironolactone did not improve depressive symptoms at the prespecified time of 12 months. However, randomization to spironolactone was an independent predictor of clinically meaningful improvement in depressive symptoms. Randomization to

CENTRAL ILLUSTRATION Association Between Depressive Symptoms and Outcomes



Chandra, A. et al. J Am Coll Cardiol HF. 2020;8(12):1009–20.

Higher baseline depressive symptoms and worsening depressive symptoms were associated with all-cause mortality. Independent predictors of clinically meaningful improvement in depressive symptoms include higher baseline PHQ-9, male sex, lack of COPD, and randomization to spironolactone. COPD = chronic obstructive pulmonary disease; CV = cardiovascular; PHQ-9 = Patient Health Questionnaire-9; Δ3pt = 3-point change in PHQ-9.

spironolactone was also associated with modest but statistically significant improvement in depressive symptoms longitudinally over the course of the entire trial. Patients with major depression have been shown to have high activity of the mineralocorticoid system causing an imbalance in the mineralocorticoid-to-glucocorticoid ratio which affects the brain serotonin systems (25). In a mouse model, spironolactone prevented chronic corticosterone-induced depression-like behavior (26). Patients with depression exhibit greater cognitive empathy, and spironolactone was shown to reduce cognitive empathy in depressed patients to the level of patients without depression (27). There are biologically plausible mechanisms through which spironolactone may improve depressive symptoms.

Prior HF trials have shown that cognitive behavioral therapy (28), exercise (29), and disease management programs (30) could improve depressive symptoms in patients with HF, whereas antidepressants may not be as effective (6,7). The present study reaffirmed that the use of antidepressants was not associated with improvement in depressive symptoms. Thus, this study suggests that physicians may treat depressive symptoms in HF more effectively by focusing on treatments directed at both heart failure symptoms and the depressive symptoms.

Previous studies have suggested that HFpEF patients with depressive symptoms at baseline are at an increased risk of adverse clinical outcomes (9). This study did not find a significant relationship between higher baseline PHQ-9 score and incidence of CV events. However, higher PHQ-9 scores were associated with all-cause mortality. Higher baseline PHQ-9 score was significantly associated with non-CV death, which caused 43% of mortality in this analysis, similar to that in other HFpEF studies (31). Our study is the first to report an association between worsening depressive symptoms over time and adverse clinical outcomes in a HFpEF trial. This relationship is consistent with changes in depressive symptoms in HFrEF population. A study in 147 HFrEF outpatients reported that a ≥3-point worsening of depressive symptoms using the Beck Depression Inventory over 1 year was associated with a 2-fold risk of a composite of death or CV hospitalization (32). Further studies also showed this relationship in HFrEF in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) (33), and in inpatients in COACH (Comparison of Outcomes and Access to Care for Heart Failure Trial) (34). On-treatment analysis showed weaker associations between baseline depression and changes in depressive symptoms on the subsequent CV outcome than with intention-to-treat. It suggests that depressive symptoms and worsening depressive symptoms were associated with permanent study drug discontinuation, which in turn led to worse outcomes.

Prior to analysis, clinically meaningful changes were defined as a change of ±3 points in PHQ-9 at 12 months, which corresponded to interquartile intervals of 12-month change scores. In sensitivity analysis, there were no significant associations between clinically significant changes in PHQ-9 and any outcome as defined by a post-treatment score of <10 and 50% improvement in PHQ-9. However, it was difficult to meaningfully interpret these results due to a lack of power because only 25% of patients (n = 289) had a PHQ-9 score ≥10 at baseline. In sensitivity analysis, in which a 5-point improvement was used as a clinically meaningful improvement, associations of clinically significant worsening depressive symptoms with CV death and all-cause mortality remained statistically significant. The associations of clinical improvement in PHQ-9 with CV death and all-cause mortality also became marginally statistically significant likely due to the fact that patients with milder depressive symptoms and fewer CV comorbidities were excluded. Also, patients who had clinically significant improvement in PHQ-9 had higher baseline PHQ-9 scores; thus, despite statistical adjustment for baseline, they were still at higher risk for unmeasured CV comorbidities.

STUDY LIMITATIONS. PHQ-9 has been demonstrated to be a valid measurement of depressive symptoms in patients with HFpEF (5,8,17). However, due to the symptom overlap between depression and HF, some of the changes in depressive symptoms could be attributed to improvement in HF symptoms. Ultimately, it was up to the patients to determine the extent to which their symptoms were caused by depression. Because PHQ-9 was only given to participants from the United States and Canada, these findings may not be generalizable to an international HFpEF population. No adjustment was made for multiple testing in this analysis, which may increase the chance of declaring significance or overestimating importance of perceived differences. There was a substantial decline in PHQ-9 and KCCQ completion rates beyond 36 months, which may have created a healthier cohort over time and limited the ability to detect differences among treatment groups at later time points. Given that many enrolled patients had relatively few depressive symptoms at baseline, it was impossible for many patients to have a 3-point decrease in depressive symptoms. Thus, caution is recommended in comparing patients whose depressive symptoms improved versus those whose

worsened because a patient could only have a 3-point decrease if they had at least a PHQ-9 of 3 at baseline.

CONCLUSIONS

At least moderate depressive symptoms are common in patients with HFpEF. This represents an important target for therapy in contemporary HFpEF trials. Randomization to spironolactone was associated with modest reduction in depressive symptoms over the course of the trial, while antidepressant use was not. Higher baseline depressive symptoms and worsening depressive symptoms were associated all-cause mortality.

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients who had worsening depressive symptoms had a higher incidence of CV death and all-cause mortality, despite adjustments made for other comorbidities. Randomization to spironolactone was associated with modest reduction in depressive symptoms over the course of the trial, whereas antidepressant use was not. This study suggests that physicians may treat depressive symptoms in heart failure patients more effectively by focusing on treatments directed at both heart failure symptoms and depressive symptoms.

TRANSLATIONAL OUTLOOK: In this large contemporary randomized clinical trial of patients with symptomatic chronic HFpEF, at least moderate depressive symptoms are common in patients with HFpEF. This represents an important target for therapy in future HFpEF trials. In animal and human studies, spironolactone has been shown to reduce depressive symptoms and behaviors. In the present study, randomization to spironolactone was associated with modest but statistically significant improvement in depressive symptoms over the course of the entire trial. Future research on the association between depression and the mineralocorticoid pathway activity in patients with HFpEF is needed.

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KEY WORDS age, depression, HFpEF, quality of life, spironolactone, TOPCAT

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