Circulation: Heart Failure

ORIGINAL ARTICLE

Effects of Omecamtiv Mecarbil on Symptoms and Health-Related Quality of Life in Patients With Chronic Heart Failure

Results From the COSMIC-HF Study

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BACKGROUND: Chronic heart failure with reduced ejection fraction impairs health-related quality of life (HRQL). Omecamtiv mecarbil (OM)—a novel activator of cardiac myosin—improves left ventricular systolic function and remodeling and reduces natriuretic peptides. We sought to evaluate the effect of OM on symptoms and HRQL in patients with chronic heart failure with reduced ejection fraction and elevated natriuretic peptides enrolled in the COSMIC-HF trial (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure).

METHODS: Patients (n=448) were randomized 1:1:1 to placebo, 25 mg of OM BID, or to pharmacokinetically guided dose titration (OM-PK) for 20 weeks. The Kansas City Cardiomyopathy Questionnaire was administered to assess HRQL at baseline, 16 weeks, and 20 weeks. The primary scores of interest were the Total Symptom Score, Physical Limitation Scale, and Clinical Summary Score.

RESULTS: Mean change in score from baseline to 20 weeks for the Total Symptom Score was 5.0 (95% CI, 1.8–8.1) for placebo, 6.6 (95% CI, 3.4–9.8) for OM 25 mg (P=0.32 versus placebo), and 9.9 (95% CI, 6.7–13.0) for OM-PK (P=0.03 versus placebo); for the Physical Limitation Scale, it was 3.1 for placebo (95% CI, −0.3 to 6.6), 6.0 (95% CI, 3.1–8.9) for OM 25 mg (P=0.12), and 4.3 (95% CI, 0.7–7.9) for OM-PK (P=0.42); for the Clinical Summary Score, it was 4.1 (95% CI, 1.4–6.9) for placebo, 6.3 (95% CI, 3.6–9.0) for OM 25 mg (P=0.19), and 7.0 (95% CI, 4.1–10.0) for OM-PK (P=0.14). Differences between OM and placebo were greater in patients who were more symptomatic at baseline.

CONCLUSIONS: HRQL as measured by the Total Symptom Score improved in patients with heart failure with reduced ejection fraction assigned to the OM-PK group relative to placebo. Ongoing trials are prospectively testing whether OM improves symptoms and HRQL in heart failure with reduced ejection fraction.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01786512.

Key Words heart failure ■ longitudinal studies ■ quality of life ■ stroke volume ■ systole

Chronic heart failure (HF) is characterized by both a high risk of mortality and morbidity and by impairments in functional capacity and health-related quality of life (HRQL). For patients with HF and reduced ejection fraction (HFrEF), the development of effective treatments (collectively called guideline-directed medical therapy) has resulted in progressive improvements in morbidity and mortality. Improvement in functional capacity and HRQL

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WHAT IS NEW?

- Omecamtiv mecarbil is a novel potential treatment for heart failure with reduced ejection fraction that works by directly targeting cardiac myosin to improve systolic function.
- The phase II COSMIC study (Chronic Oral Study of Myosin Activation to Increase Contractility) demonstrated that omecamtiv mecarbil lowers natriuretic peptide concentrations and induces favorable ventricular remodeling.
- The current report presents additional data from COSMIC on the effects of omecamtiv mecarbil on health-related quality of life. Twenty weeks of treatment with omecamtiv mecarbil resulted in numerically improved Kansas City Cardiomyopathy Questionnaire scores for the Total Symptom Score, Physical Limitations Score, and Clinical Summary Score compared with placebo, which was statistically significant for the Total Symptom Score.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Impaired quality of life is a major problem for patients with heart failure with reduced ejection fraction.
- If the magnitude of improvements in Kansas City Cardiomyopathy Questionnaire scores reported here are confirmed in larger studies such as the ongoing Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility and Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure trials, omecamtiv mecarbil would represent a significant advance in medical therapy for heart failure with reduced ejection fraction.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
CARE-HF	Cardiac Resynchronisation-Heart Failure
COSMIC-HF	Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure
CSS	Clinical Summary Score
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HRQL	health-related quality of life
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	left ventricle
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OM	omecamtiv mecarbil
OM-PK	Omecamtiv Mecarbil Pharmacokinetically guided dose titration
PLS	Physical Limitation Score
TSS	Total Symptom Score

with these therapies has been less well documented. Many patients with chronic HFrEF continue to have a high symptom burden and poor HRQL despite current treatments. Improving symptom burden and HRQL, especially in highly symptomatic patients, is, therefore, an important goal of treatment in HF,[1] as has been recently emphasized in regulatory guidance for drug development in HF.[2]

Omecamtiv mecarbil (OM) is a selective cardiac myosin activator (myotrope) that improves cardiac contraction by binding to cardiac myosin and increasing the probability of force generating interactions between myosin and actin during the cardiac cycle.[3,4] This pharmacology has been shown to result in dose-dependent increases in stroke volume in both healthy volunteers[5] and patients with HF.[6] Given that impaired systolic performance could be a major contributor to symptom burden in patients with HFrEF, there is substantial interest in the effect of OM on symptoms in patients with HF. The COSMIC-HF study (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) was a phase II study of OM in chronic HFrEF evaluating its effects on pharmacodynamics, cardiac remodeling, natriuretic peptides, and patient-reported outcomes. The results of COSMIC-HF demonstrated dose-dependent improvements in cardiac function, plasma concentrations of natriuretic peptides, and left ventricular (LV) remodeling after 20 weeks of treatment with OM compared with placebo.[7] Herein we present data describing the effects of OM on the prespecified exploratory end point of HF symptoms and HRQL in the COSMIC-HF study.

METHODS

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request. Details of the design and primary results of the COSMIC-HF study (https://www.clinicaltrials.gov; unique identifier: NCT01786512) have been published.[7] Briefly, this study evaluated the effects 20 weeks of OM in patients with stable HF in 448 outpatients with chronic symptomatic HFrEF (New York Heart Association II or III), LV ejection fraction ≤40%, and elevated natriuretic peptides NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≥200 pg/mL (≥1200 pg/mL if the patient was in atrial fibrillation). Patients were randomized 1:1:1 to placebo, 25 mg of oral OM BID (25 mg), or pharmacokinetically guided dose titration (OM-PK; initial 25 mg BID dose, increased to 50 mg BID depending on plasma concentrations after 2 weeks). The entry criteria for COSMIC-HF mandated clinical stability and optimized background HF therapy at the time of study entry, making it well suited to assess the effects of OM on HRQL in HFrEF. The study was approved by the relevant institutional review boards or ethics committees at participating sites, and all patients provided written informed consent.

Patient-Reported Outcome Measurements

Participants completed self-administered Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, 16 weeks, and 20 weeks. The KCCQ is a 23-item self-administered, disease-specific HRQL instrument that has demonstrated good measurement properties in patients with HFrEF.[8] The KCCQ is made up of 8 domains evaluating specific aspects of the patient experience. The 8 domains include physical limitation, symptom stability, symptom frequency, symptom burden, Total Symptom Score (TSS), HRQL, self-efficacy, and social limitations. The TSS is a composite of symptom frequency and symptom burden. The Physical Limitations Score (PLS) measures specific physical limitations (eg, dressing, showering). The Clinical Summary Score (CSS) is a composite of the TSS and the PLS. The TSS, PLS, and CSS were recently qualified by the Food and Drug Administration for use in measuring these concepts in drug development.[9] Each domain and summary score is scaled from 0 to 100, with higher scores indicating better health status. Based on prior work, ≥5 points is generally considered a minimally clinically meaningful difference in KCCQ scores.[10] In addition to the KCCQ, patients and clinicians also assessed the overall burden of symptoms using the Patient Global Rating of Severity and Clinician Global Rating of Severity, which are 6 point Likert scale assessments rating the severity of symptoms from none to very severe. In additional analyses assessing the effect of baseline symptoms severity on the treatment effect of OM, we grouped patients by whether they had rated their baseline symptoms as none, very mild, or mild (n=242) or as moderate, severe, or very severe (n=202).

Statistical Analysis

Descriptive statistics are presented as means (SD), medians (interquartile range), and percentages, as appropriate. Summary statistics were produced using observed data only without applying models or imputation. Participants with missing data were considered nonresponders in categorical responder analyses. $P<0.05$ was considered to represent statistical significance. There was no adjustment for multiple comparisons.

Treatment group differences for changes in TSS, PLS, and CSS were estimated by using a repeated measures model (ANOVA) fitted separately for each variable and included the stratification factor of the presence or absence of atrial fibrillation/flutter at randomization, baseline value, treatment group, visit, and the treatment group by visit interaction. An unstructured covariance matrix was used to account for the correlation between visits within a subject. Pearson correlation coefficients were calculated to measure the correlation of QOL with natriuretic peptides and LV dimensions.

RESULTS

Baseline characteristics dichotomized by patient-reported symptom severity (as assessed by Patient Global Rating of Severity) are shown in Table 1. In general, patients with less severe symptoms and patients with more severe symptoms at baseline were broadly similar, except for KCCQ scores. For placebo, OM 25 mg, and OM-PK groups, the median baseline TSS was 70.8 (56.3–87.5), 74.5 (52.1–90.6), and 68.8 (53.1–85.4), respectively; the median baseline PLS was 62.5 (45.8–83.3), 66.7 (50.0–83.3), and 62.5 (45.8–85.0), respectively, and the median baseline CSS was 69.2 (52.1–82.3), 68.7 (49.9–85.4), and 67.2 (50.0–83.3), respectively. These scores are consistent with moderate limitation in health status and represented more symptomatic patients compared with those reported in other recent trials in chronic HFrEF (eg, median CSS was 72 in Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and 76 in Prospective Comparison of ARNI [Angiotensin Receptor -Neprilysin Inhibitor] with ACEI [Angiotensin-Converting -Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial).[11,12] Rates of missingness for KCCQ data were generally low (≤20 missing values for each treatment group and time point).

Effect of OM on Symptoms and HRQL

The overall effects of OM on TSS, PLS, and CSS measured at 16 and 20 weeks are shown in Figure 1. For the TSS, the mean change in score from baseline to 20 weeks was 5.0 for placebo, 6.6 for OM 25 mg ($P=0.32$ versus placebo), and 9.9 for OM-PK ($P=0.03$ versus placebo). For the PLS, the mean change in score from baseline to 20 weeks was 3.1 for placebo, 6.0 for OM 25 mg ($P=0.12$ versus placebo), and 4.3 for OM-PK ($P=0.42$ versus placebo). For the CSS, the mean change in score from baseline to 20 weeks was 4.1 for placebo, 6.3 for OM 25 mg ($P=0.19$ versus placebo), and 7.0 for OM-PK (0.14 versus placebo). As shown in Figure 1, these trends on KCCQ were evident by 16 weeks of treatment and persisted to week 20. Given that a 5-point change in KCCQ score has been proposed as a minimum clinically important change, we assessed the proportion of patients with an improvement of that amount or greater in each group for each domain (ie, responders). In this analysis, the proportion of responders did not differ significantly between placebo and OM for any of the KCCQ scores (Table 2).

Change in Symptoms and HRQL by Baseline Symptoms Severity

Since the COSMIC-HF study enrolled patients with a spectrum of symptoms (from minimally to highly symptomatic), we performed additional analyses stratifying the population by severity of baseline symptoms. The rationale for these analyses was that patients who were more symptomatic at baseline had a greater opportunity for improvement than those with milder symptoms at baseline. For these analyses, we utilized the baseline Patient Global Rating of Severity score, in which patients rated their symptom burden on a 6-point Likert scale from none to very severe, to stratify participants based on their self-reported symptom severity. We grouped patients by whether they had rated their symptoms as none, very mild, or mild (n=242) or as moderate, severe, or very severe (n=202). In this analysis, the improvement in

Table 1. Baseline Characteristics Stratified by Symptom Severity

	PGR-S: none, very mild, or mild symptoms			PGR-S: moderate, severe, or very severe symptoms		
	Placebo (n=81)	OM 25 mg BID (n=86)	OM-PK titration group (n=75)	Placebo (n=67)	OM 25 mg BID (n=64)	OM-PK titration group (n=71)
Age, y	64.0±9.8	63.5±9.9	63.0±10.4	63.2±9.8	61.8±10.6	62.6±13.0
Men, n (%)	65 (80.2)	74 (86.0)	63 (84.0)	54 (80.6)	53 (82.8)	59 (83.1)
White race, n (%)	73 (90.1)	81 (94.2)	70 (93.3)	62 (92.5)	61 (95.3)	68 (95.8)
Systolic blood pressure, mm Hg	119.7±15.0	121.4±17.1	120.6±16.3	118.9±14.1	120.0±15.3	116.2±15.6
Heart rate, beats/min	69.3±10.4	68.6±11.5	69.6±10.8	70.4±10.1	70.2±10.6	71.3±11.5
Ejection fraction, %	30.1±7.0	30.2±7.0	28.9±7.2	28.4±7.9	28.1±8.0	28.8±7.4
HF characteristics						
Ischemic heart disease, n (%)	47 (58.0)	56 (65.1)	50 (66.7)	42 (62.7)	41 (64.1)	50 (70.4)
Years from HF diagnosis	8.5±7.0	8.8±8.6	7.3±6.5	7.4±7.2	6.2±6.6	8.2±6.5
Hospitalized for HF in past 12 mo, n (%)	22 (27.2)	24 (27.9)	17 (22.7)	16 (23.9)	27 (42.2)	20 (28.2)
Comorbidities						
History						
Persistent AFib/flutter, n (%)	16 (19.8)	13 (15.1)	11 (14.7)	17 (25.4)	15 (23.4)	12 (16.9)
Diabetes, n (%)	33 (40.7)	44 (51.2)	32 (42.7)	28 (41.8)	26 (40.6)	23 (32.4)
Hypertension, n (%)	59 (72.8)	56 (65.1)	53 (70.7)	51 (76.1)	39 (60.9)	45 (63.4)
Laboratory variables†						
Troponin I, ng/mL; median (Q1–Q3)	0.024 (0.016–0.039)	0.023 (0.016–0.042)	0.019 (0.016–0.041)	0.028 (0.016–0.042)	0.021 (0.016–0.035)	0.024 (0.016–0.042)
NT-proBNP, pg/mL; median (Q1–Q3)	1377.0 (690.7–2837.0)	1398.4 (634.0–2962.0)	1550.9 (699.0–3165.0)	1942.4 (915.0–3373.1)	1644.2 (628.4–3754.9)	1847.6 (983.1–3151.0)
eGFR, mL/min per 1.73 m^2	62.95±17.82	63.07±19.76	65.21±18.93	66.96±20.72	63.42±17.51	64.66±18.64
Heart failure therapies, n (%)						
ACE inhibitor or ARB	77 (95.1)	81 (94.2)	67 (89.3)	62 (92.5)	61 (95.3)	68 (95.8)
β-Blockers	80 (98.8)	83 (96.5)	72 (96.0)	65 (97.0)	63 (98.4)	70 (98.6)
MRAs	46 (56.8)	44 (51.2)	47 (62.7)	41 (61.2)	43 (67.2)	46 (64.8)
Diuretics other than MRAs	65 (80.2)	72 (83.7)	67 (89.3)	59 (88.1)	56 (87.5)	65 (91.5)
ICD only	30 (37.0)	40 (46.5)	32 (42.7)	22 (32.8)	18 (28.1)	28 (39.4)
CRT without ICD	3 (3.7)	2 (2.3)	1 (1.3)	2 (3.0)	0 (0.0)	0 (0.0)
CRT with ICD	22 (27.2)	20 (23.3)	18 (24.0)	8 (11.9)	19 (29.7)	19 (26.8)
KCCQ, median (IQR)						
PLS	75.0 (58.3–87.6)	75.0 (60.0–91.7)	79.2 (62.5–91.7)	50.0 (37.5–70.8)	50. 0 (33.3–62.5)	50.0 (37.5–62.5)
TSS	81.3 (64.6–89.6)	84.9 (68.8–93.8)	81.3 (66.7–91.7)	60.4 (44.8–76.0)	54.2 (53.3–63.4)	55.2 (40.6–70.8)
CSS	76.6 (62.5–87.0)	81.0 (65.6–91.7)	77.0±16.3	52.6 (41.2–69.8)	50.8 (41.7–67.5)	50.0 (40.6–67.7)

Mean±SD, unless otherwise noted. ACE indicates angiotensin-converting enzyme; AFib, atrial fibrillation; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; CSS, Clinical Summary Score; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardiac defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OM, omecamtiv mecarbil; PGR-S, Patient Global Rating of Severity; PK, pharmacokinetic; PLS, Physical Limitations Score; and TSS, Total Symptom Score.

†Laboratory variables, heart failure therapies, and echocardiographic variables exclude 3 patients who were randomized but not dosed.

symptoms with OM compared with placebo was greater for those with more severe symptoms (Figure 2). Similarly, the differences in the proportion of responders (≥5-point improvement in the KCCQ score) between OM and placebo were numerically greater in patients with moderate to severe symptoms at baseline, although none of these differences were statistically significant.

Correlation of QOL With Natriuretic Peptides and LV Dimensions

Given that an important objective of the COSMIC-HF study was to assess the impact of OM on ventricular remodeling and natriuretic peptides, we assessed the relationship between improvements in KCCQ and changes in both ventricular remodeling and NT-proBNP

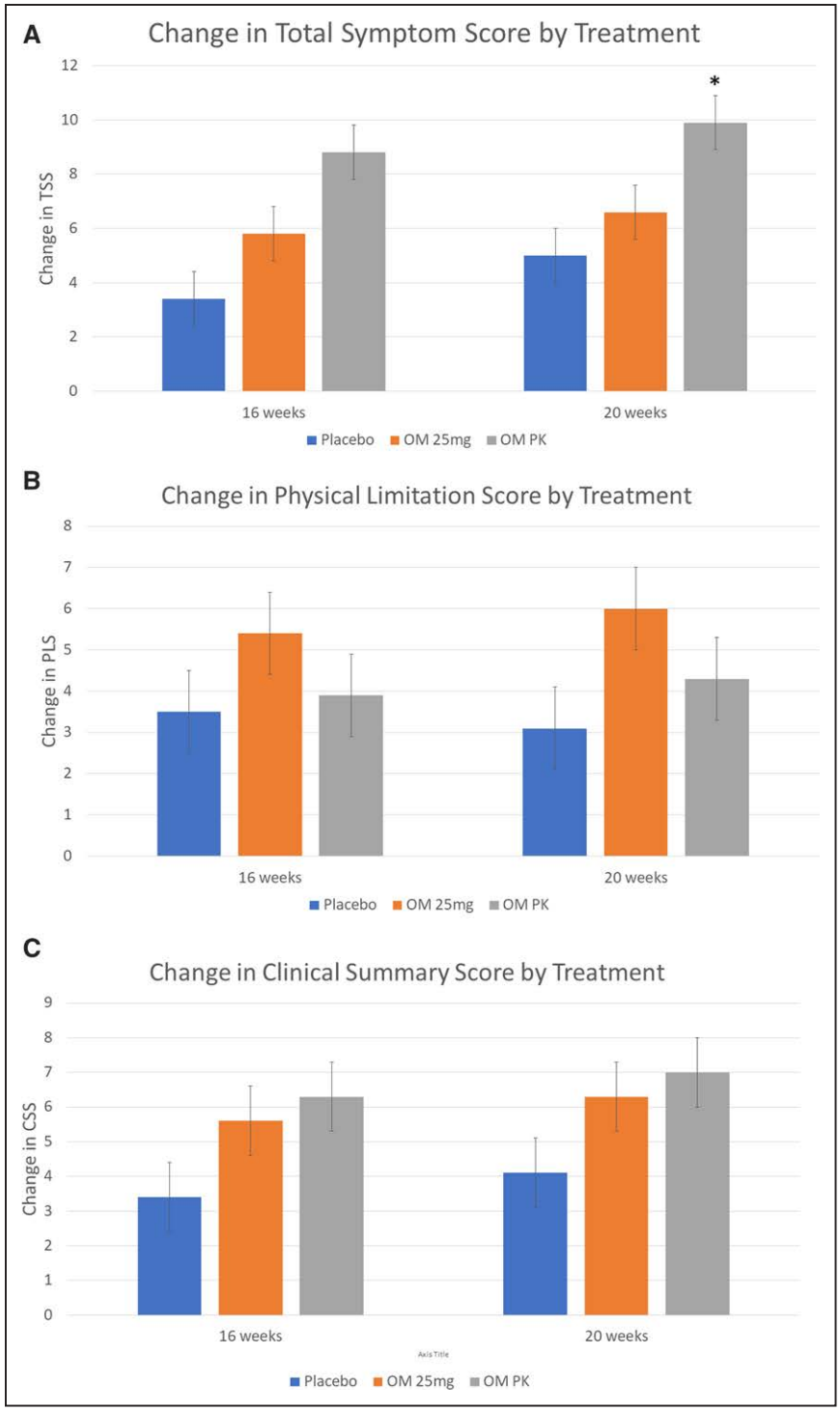

Figure 1. Mean change in Kansas City Cardiomyopathy Questionnaire from baseline through weeks 16 and 20 for Total Symptom Score (TSS), Physical Limitations Score (PLS), and Clinical Summary Score (CSS).
Error bars show ±SE. OM indicates omecamtiv mecarbil; and PK, pharmacokinetic. *$P \leq 0.05$, all other comparisons, $P > 0.05$. Placebo = blue bars, OM 25mg = Orange bars, OM PK = Grey bars.

observed in COSMIC-HF. As reported previously, treatment with OM in COSMIC-HF improved LV remodeling (ventricular volumes and LV ejection fraction) and reduced plasma NT-proBNP compared with placebo.[7] In the current analysis, there was a modest relationship between improvements in KCCQ and decrease in NT-proBNP for PLS (r=−0.08, P=0.098), CSS (r=−0.14, P=0.007), and TSS (r=−0.15, P=0.002). These relationships were the strongest for patients assigned to the pharmacokinetic titration arm; PLS (r=−0.15, P=0.093), CSS (r=−0.23, P=0.009), and TSS (r=−0.26, P=0.003). There was no significant relationship between changes in LV remodeling and changes in KCCQ scores (data not shown).

DISCUSSION

Improvement in patient-reported outcomes is an important goal in the management of HF. In the current analysis,

Table 2. Proportion of Patients With Minimally Clinically Important Difference in Kansas City Cardiomyopathy Questionnaire Scores by Treatment, Stratified by Baseline Symptom Severity

	Placebo (n=149)	OM 25 mg BID (n=150)	*P* value vs placebo	OM-PK titration group (n=146)	*P* value vs placebo
PLS, n (%)	54 (36%)	70 (47%)	0.09	60 (41%)	0.46
PLS–mild symptoms, n (%)	26 (32%)	34 (40%)	0.40	27 (36%)	0.73
PLS–mod-severe symptoms, n (%)	28 (42%)	36 (56%)	0.14	33 (47%)	0.70
TSS, n (%)	68 (46%)	68 (45%)	1.00	70 (48%)	0.78
TSS–mild symptoms, n (%)	34 (42%)	31 (36%)	0.53	29 (39%)	0.80
TSS–mod-severe symptoms, n (%)	34 (51%)	37 (58%)	0.52	41 (58%)	0.51
CSS, n (%)	61 (41%)	69 (46%)	0.44	66 (45%)	0.53
CSS–mild symptoms, n (%)	32 (40%)	32 (37%)	0.88	25 (33%)	0.53
CSS–mod-severe symptoms, n (%)	29 (43%)	37 (58%)	0.14	41 (58%)	0.13

CSS indicates Clinical Summary Score; mod, moderate; OM, omecamtiv mecarbil; PK, pharmacokinetic; PLS, Physical Limitations Score; and TSS, Total Symptom Score.

administration of OM improved HRQL as measured by the TSS compared with placebo. Other domains of the KCCQ were not significantly different. This analysis focused on those domains of the KCCQ, specifically the TSS, PLS, and CSS, that have recently been qualified by the Food and Drug Administration for assessing the benefits of interventions for HF. As might be anticipated, observed changes were the greatest in patients who were most symptomatic at baseline, whereas the changes in KCCQ in patients with no or minimal symptoms at baseline were negligible.

These data should be compared with reports of the effects of other interventions for HFrEF on KCCQ scores. In general, effective HF therapies have a variable effect on HRQL. For older therapies such as β-blockers and ACE (angiotensin-converting enzyme) inhibitors, there are few data directly assessing HRQL compared with placebo and none using the KCCQ. β-Blockers have notable effects on ventricular remodeling, morbidity, and mortality but appear to exert little or no effect on improving HFQoL.[13] More recently developed therapies for HFrEF had undergone more rigorous assessment of their effect on HRQL. The largest reported effects are in the 2- to 3-point improvement in KCCQ range, specifically for dapagliflozin,[11] or exercise training.[14] The CARE-HF study (Cardiac Resynchronisation-Heart Failure) of cardiac resynchronization therapy showed a more marked improvement on HRQL but used the Minnesota Living With Heart Failure Score,[15] as did the African American Heart Failure Trial study of nitrates and hydralazine in self-identified Black patients.[16] Notably, the angiotensin receptor blocker/neprilysin inhibitor sacubitril-valsartan improved the CSS by a more modest mean change of 0.9 points after 8 months of treatment compared with enalapril,[12] despite the large observed differences in morbidity and mortality between the two treatment arms.[17] In this context, the improvements seen in HRQL for the OM-PK titration group over placebo at 20 weeks of treatment by TSS (4.9 points) equal or exceed those of common effective HF therapies. These improvements are numerically greater when limited to the subgroup of patients who were more symptomatic at baseline (6.5 for TSS).

The specific mechanisms underlying the improvements in QOL with effective HF therapies are poorly defined and probably diverse. Given the mechanism of action of OM is to improve LV performance, we analyzed whether improvement in symptoms and HRQL might mirror changes in LV remodeling or natriuretic peptides, both of which were improved by OM treatment compared with placebo in COSMIC. However, we found only modest relationships between improvements in KCCQ scores and declines in plasma NT-proBNP and none with changes in ventricular function or remodeling. These results underscore the complex nature of symptom and HRQL improvement in HF.

Limitations

COSMIC-HF was a phase 2 trial and was not powered to provide definitive evidence of beneficial effects on symptoms or HRQL for OM. Given the smaller sample size and shorter duration of treatment (20 weeks), and the violation of normality (changes from the baseline of PLS), the CIs around the effect estimates on HRQL are broad in comparison to those from larger phase 3 studies of other therapies, and most of the observed differences in KCCQ did not reach statistical significance. It is possible that our results are related to the play of chance rather than a true treatment effect. Given the sample size of COSMIC-HF and the modest number of clinical events, we are not able to assess the relationship between the observed KCCQ improvements and clinical outcomes.

Conclusions

In COSMIC-HF, randomization to OM led to —statistically significant improvement in TSS in the OM-PK titration group compared with placebo. Point estimates of the effect of KCCQ were of a similar or greater magnitude to those

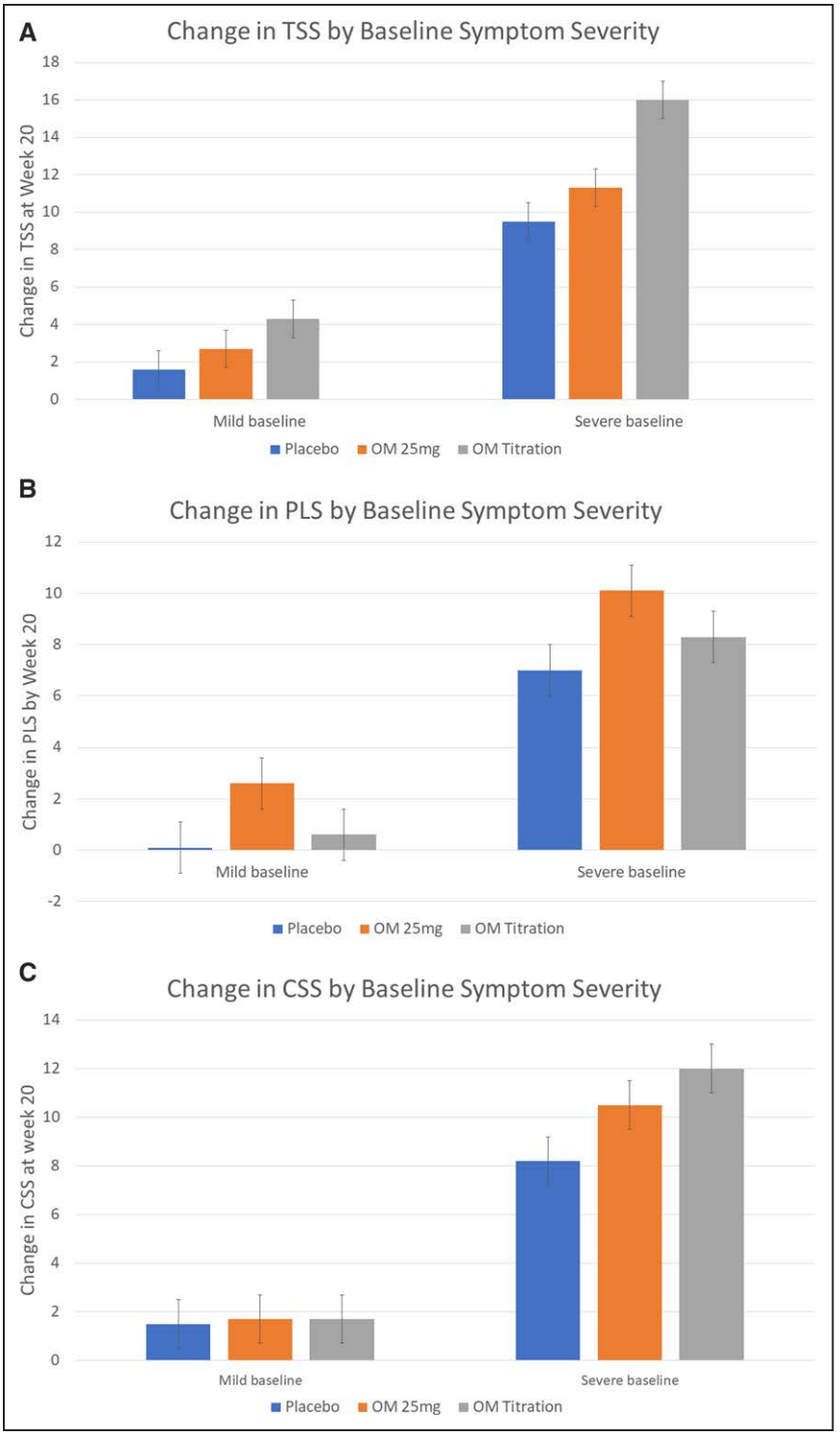

Figure 2. Change in Total Symptom Score (TSS), Physical Limitations Score (PLS), and Clinical Summary Score (CSS) based on symptom severity at baseline. Placebo = blue bars, OM 25mg = Orange bars, OM PK = Grey bars. OM indicates omecamtiv mecarbil; and PK, pharmacokinetic.

seen with other effective pharmacological interventions for HF. The effect of OM on HF symptoms, specifically the TSS of the KCCQ, is being further tested prospectively as a predefined secondary end point, in ongoing trials focused on morbidity and mortality (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure; https://www.clinicaltrials.gov; unique identifier: NCT02929329)[18]and exercise capacity (Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure; https://www.clinicaltrials.gov; unique identifier: NCT03759392), which will further inform the clinical benefits of this potential therapy in patients with HFrEF.

ARTICLE INFORMATION

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