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Sex Differences in Heart Failure With Reduced Ejection Fraction in the GALACTIC-HF Trial

Maria Pabon, MD,[a] Jon Cunningham, MD, MPH,[a] Brian Claggett, PhD,[a] G. Michael Felker, MD,[b] John J.V. McMurray, MD,[c] Marco Metra, MD,[d] Rafael Diaz, MD,[e] Xiaowen Wang, MD, MPH,[a] Alexandra Arias-Mendoza, MD,[f] Diana Bonderman, MD,[g] Maria Crespo-Leiro, MD, PhD,[h] Cândida Fonseca, MD, PhD,[i] Eva Goncalvesova, MD, PhD,[j] Mayanna Lund, MD,[k] Eileen O'Meara, MD,[l] Karen Sliwa-Hahnle, MD, PhD,[m] Fady I. Malik, MD, PhD,[n] Scott D. Solomon, MD,[a] John R. Teerlink, MD,[o] on behalf of the GALACTIC-HF Investigators

ABSTRACT

BACKGROUND Women with heart failure with reduced ejection fraction (HFrEF) receive less guideline-recommended therapy and experience worse quality of life than men.

OBJECTIVES The authors sought to assess differences in baseline characteristics, outcomes, efficacy, and safety of omecamtiv mecarbil between men and women enrolled in the GALACTIC-HF (Registrational Study With Omecamtiv Mecarbil [AMG 423] to Treat Chronic Heart Failure With Reduced Ejection Fraction) study.

METHODS In GALACTIC-HF, patients with symptomatic heart failure with EF of 35% or less, recent heart failure event, and elevated natriuretic peptides were randomized to omecamtiv mecarbil or placebo. The current analysis investigated differences in baseline characteristics, clinical outcomes, and efficacy and safety of omecamtiv mecarbil between men and women.

RESULTS Of 8,232 patients analyzed, 21.2% were women. Women more likely self-identified as being Black, had worse symptoms (lower Kansas City Cardiomyopathy Questionnaire Total Symptom Score [KCCQ-TSS]), and were less likely to be treated with angiotensin receptor/neprilysin inhibitor and devices at baseline. Compared with men, women had lower rates of the primary endpoint (adjusted HR: 0.80, 95% CI: 0.73-0.88). Sex did not significantly modify omecamtiv mecarbil's treatment effect (P interaction = 0.68). Women also had 20% less risk of cardiovascular death, heart failure event, and all-cause death. Women participants had lower rates of serious adverse events.

CONCLUSIONS Women participants of the GALACTIC-HF trial had worse quality of life and were less likely to be treated with guideline-based therapies at baseline. Despite KCCQ-TSS being predictive of poor outcomes in this population, women had a 20% lower risk of an HF event or cardiovascular death compared with men. The beneficial effect of omecamtiv mecarbil did not significantly differ by sex. (Registrational Study With Omecamtiv Mecarbil [AMG 423] to Treat Chronic Heart Failure With Reduced Ejection Fraction [GALACTIC-HF]; NCT02929329)
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From the [a]Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [b]Division of Cardiology, Duke University School of Medicine and Duke Clinical Research Institute, Durham, North Carolina, USA; [c]British Heart Foundation Cardiovascular Research Centre, Glasgow, United Kingdom; [d]University of Brescia, Brescia, Italy; [e]Estudios Clínicos Latino América, Rosario, Argentina; [f]Instituto Nacional de Cardiologìa, Mexico City, Mexico; [g]Medical University of Vienna, Vienna, Austria; [h]Unidad de Insuficiencia Cardiaca Avanzada y Trasplante Cardiaco, Complexo Hospitalario Universitario A Coruna, CHUAC, INIBIC, UDC, CIBERCV, La Coruna, Spain; [i]Department of Internal Medicine, Hospital São Francisco Xavier, Lisbon, Portugal; [j]Faculty of Medicine, Comenius University, Bratislava, Slovakia; [k]Middlemore Hospital, Auckland, New Zealand; [l]Montreal Heart Institute and Université de Montréal, Montreal, QC, Canada; [m]University of Cape Town, Johannesburg, South Africa; [n]Cytokinetics Inc, South San Francisco, California, USA; and the [o]San Francisco Veterans Affairs Medical Center and School of Medicine, University of California-San Francisco, San Francisco, California, USA.
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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SGLT2 = sodium-glucose cotransporter-2

Heart failure (HF) is a significant contributor to morbidity and mortality for both men and women in the United States.[1] Previous studies have shown that there are sex-specific differences in risk factors, prognosis, and treatment responses in the HF population. For instance, women with heart failure with reduced ejection fraction (HFrEF) tend to be older and have more comorbidities, worse quality of life, and greater functional and psychological impairment when compared with men.[2] Additionally, women with HFrEF continue to be undertreated with guideline-recommended medications and devices.[3] Furthermore, commonly used cardiovascular (CV) medications may have different effects in women than in men.[3-6] Women also remain underrepresented in HFrEF clinical trials relative to the disease prevalence, leading to underpowered subgroup analysis to detect differences in safety and efficacy of new HFrEF interventions.[7,8] Investigating sex differences in patients with HF may help improve the persistent disparities seen between men and women.

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The GALACTIC-HF (Registrational Study With Omecamtiv Mecarbil [AMG 423] to Treat Chronic Heart Failure With Reduced Ejection Fraction) study investigated the effect of omecamtiv mecarbil on clinical outcomes in patients with HFrEF. Omecamtiv mecarbil is a selective cardiac myosin activator that increases cardiac contractility by binding to the catalytic domain of myosin.[9,10] The main study found that omecamtiv mecarbil decreases the risk of an HF event or CV death among patients with HFrEF as compared with placebo.[11] The current analysis investigated differences in baseline characteristics, clinical outcomes, and the efficacy and safety of omecamtiv mecarbil between men and women enrolled in the GALACTIC-HF study.

METHODS

STUDY DESIGN AND PATIENT ELIGIBILITY. GALACTIC-HF was a multicenter international randomized placebo-controlled trial comparing omecamtiv mecarbil to placebo in 8,232 patients with HFrEF. The details of the study design, inclusion/exclusion criteria, and primary results have been previously published.[11,12] Briefly, patients with symptomatic HF (NYHA functional class II-IV) and left ventricular ejection fraction (LVEF) ≤35% on optimal medical therapy were enrolled in the trial if they had a history of HF hospitalization or urgent treatment in an emergency department for HF within a year before screening (outpatients) or were currently hospitalized for HF (inpatients). Patients were also required to have N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥400 pg/mL (or 1,200 pg/mL for patients in atrial fibrillation at screening) or elevation in BNP ≥125 pg/mL (or 375 pg/mL for patients in atrial fibrillation at screening). Per study protocol,[11] the omecamtiv mecarbil dosing was modified based on plasma concentrations targeting a level between 300 and 1,000 ng/mL. The study protocol was approved by the regulatory agencies in the participating countries and by the institutional review board or ethics committee at each trial center. All patients provided informed consent. Patient enrollment began on January 6, 2017, and the trial's primary completion date was September 14, 2020.

EXPOSURE AND OUTCOMES. Sex information was collected during initial visit. The primary study outcome was a composite of time to CV death or first HF event (defined as either a hospitalization for HF or an urgent nonhospitalized HF visit). Secondary outcomes included CV death, change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) at week 24, first hospitalization for HF, and death from any cause.

STATISTICAL ANALYSIS. Analysis of the treatment effect difference between sexes was prespecified in the statistical analysis plan. Additional post hoc analysis in this study included laboratory measures and omecamtiv mecarbil dosing, plasma concentrations, and safety outcomes. Baseline characteristics for male and female patients were presented using counts and percentages for categorical variables, mean ± SD for normally distributed continuous variables, and median (IQR) for non-normal continuous variables. To compare differences between groups, Pearson's chi-square tests, 2-sample Student's *t*-tests, and Wilcoxon rank sum tests were used, respectively. Time to event variables were summarized using

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Kaplan-Meier cumulative incidence curves. Outcomes for male and female patients were compared using Cox proportional hazards models adjusted for the following covariates: age, inpatient status, region, diabetes, estimated glomerular filtration rate (eGFR), ischemic etiology, body mass index, baseline KCCQ-TSS, heart rate, systolic blood pressure, LVEF, atrial fibrillation/flutter, hyperlipidemia, hypertension, and smoking status. Sex difference in the treatment effect of omecamtiv mecarbil compared with placebo was evaluated by the interaction term between sex and treatment group in Cox proportional hazards regression, with baseline hazards stratified according to the randomization setting (inpatient or outpatient) and geographic region, and with the treatment group, sex, and the baseline eGFR as covariates. Safety and tolerability data were summarized using descriptive statistics. Statistical analyses were performed using STATA version 16.1 software (StataCorp).

RESULTS

BASELINE CHARACTERISTICS. Of the 11,121 patients screened, a total of 8,256 underwent randomization. Twenty-four patients were excluded due to Good Clinical Practice violations. The screen failure rate was higher in women as compared with men (28.6% vs 25.2%; $P < 0.001$). Women were slightly more likely to be excluded given limited availability to complete and/or comply with all required study procedures and eGFR <20 mL/min/1.73 m^2 or receiving dialysis at screening (Supplemental Table 1). Of the 8,232 patients analyzed in the GALACTIC-HF trial, 1,749 (21.0%) were women (**Table 1**). Compared with men, women were more likely to be Black (10.8% vs 5.8%; $P < 0.001$) and less likely to have history of atrial fibrillation (37.0% vs 43.6%; $P < 0.001$), tobacco use (6.7% vs 12.5%; $P < 0.001$) or ischemic cardiomyopathy (41.6% vs 56.9; $P < 0.001$). Women had lower median troponin (20 vs 29 ng/L; $P < 0.001$), lower eGFR at baseline (56.0 vs 61.5 mL/kg/min; $P < 0.001$), and a slightly higher baseline LVEF (27% vs 26%; $P < 0.001$). Women also had worse HF symptoms as reflected in a lower KCCQ-TSS at baseline compared with men (62.4 vs 67.5; $P < 0.001$).

Regarding baseline medications, women were less likely than men to be treated with complete guideline-directed medical therapy at baseline (63% vs 67%; $P = 0.003$). This included triple therapy with beta-blockers, renin-angiotensin-aldosterone system inhibitors, and a mineralocorticoid receptor antagonist (MRA), but excluded SGLT2 inhibitors, per guideline recommendations at the trial's commencement (63% vs 67%; $P = 0.003$). Men and women were similarly treated with beta-blockers and MRAs, with no statistical difference in the doses used for both sexes (**Table 1**, Supplemental Table 2). Women were

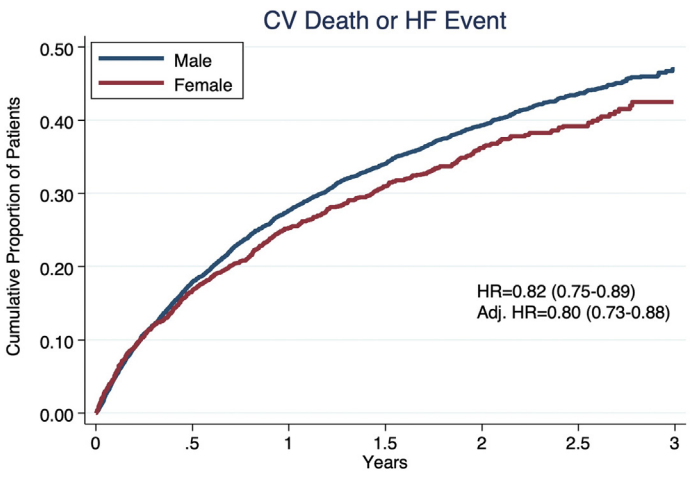
TABLE 1 Baseline Characteristics

	Male (n = 6,483)	Female (n = 1,749)	*P* Value
Age, y	64.3 ± 11.2	65.4 ± 11.9	<0.001
Race or ethnic group[a]			<0.001
White	5,149 (79.4)	1,248 (71.4)	
Asian	582 (9.0)	128 (7.0)	
Black	373 (5.0)	189 (10.8)	
Other	379 (5.0)	184 (10.5)	
Region			<0.001
Asia	547 (8.4)	123 (7.0)	
Eastern Europe or Russia	2,182 (33.7)	499 (28.5)	
Latin America	1,144 (17.6)	430 (24.6)	
United States and Canada	1,058 (16.3)	328 (18.8)	
Western Europe, South Africa, or Australasia	1,552 (23.9)	369 (21.1)	
Inpatient setting	1,673 (25.8)	411 (23.5)	0.049
Clinical features			
Atrial fibrillation or flutter	2,828 (43.6)	647 (37.0)	<0.001
Type 2 diabetes mellitus	2,680 (41.3)	697 (39.9)	0.26
Ischemic heart failure	3,688 (56.9)	727 (41.6)	<0.001
Body mass index	28.4 ± 5.9	28.7 ± 7.1	0.12
Left ventricular ejection fraction, %	26.4 ± 6.3	27.1 ± 6.2	<0.001
NYHA functional classification			0.011
II	3,495 (53.9)	873 (49.9)	
III	2,799 (43.2)	817 (46.7)	
IV	189 (2.9)	59 (3.4)	
Total symptom score on KCCQ	67.5 ± 24.8	62.4 ± 25.9	<0.001
Outpatient	53.6 ± 25.5	48.6 ± 25.0	<0.001
Inpatient	72.3 ± 22.7	66.6 ± 24.6	<0.001
Systolic blood pressure, mm Hg	116.4 ± 15.2	116.8 ± 15.8	0.35
Heart rate, beats/min	73.3 ± 12.7	74.8 ± 12.7	0.08
NT-proBNP, pg/mL	1,975 (995.0-4,028.0)	2,091 (989.0-4,346.0)	0.16
Cardiac troponin I, ng/L	29 (16.0-53.0)	20 (10.0-42.0)	<0.001
Median eGFR, mL/min/1.73 m^2	61.5 ± 21.8	56.0 ± 21.7	<0.001
Heart failure therapy			
Complete GDMT[b]	4,317 (66.7)	1,097 (62.9)	0.003
ACE inhibitor	3,252 (50.2)	792 (45.3)	<0.001
ARB	1,177 (18.2)	412 (23.6)	<0.001
ACE inhibitor or ARB	4,396 (67.8)	1,198 (68.5)	0.58
Mineralocorticoid receptor antagonist	5,061 (78.1)	1,336 (76.4)	0.13
Beta-blocker	6,123 (94.4)	1,640 (93.8)	0.28
ARN inhibitor	1,295 (20.0)	306 (17.5)	0.020
SGLT2 inhibitor	191 (2.9)	27 (1.5)	0.001
Cardiac resynchronization therapy	956 (14.7)	202 (11.5)	<0.001
Implantable cardioverter-defibrillator	2,186 (33.7)	428 (24.5)	<0.001

Values are mean ± SD, n (%), or median (IQR). [a]Race or ethnic group was reported by the patients. The category of Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple patient-identified races or ethnic groups. [b]Complete guideline-directed medical therapy (GDMT), inclusive of beta-blockers, mineralocorticoid receptor antagonists, and renin-angiotensin system inhibitors.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARN = angiotensin receptor-neprilysin; eGFR = estimated glomerular filtration rate; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter-2.

FIGURE 1 Primary Outcomes, Kaplan-Meier Curves Comparing Incidence of CV Death or HF Event Among Female vs Male Patients



The primary outcome was a composite of heart failure (HF) events (hospitalization or unscheduled urgent clinic, office, or emergency department visit resulting in intravenous therapy for heart failure) or death from cardiovascular (CV) causes. Adj = adjusted.

less likely to be treated with angiotensin-converting enzyme inhibitors as compared with men (45.3% vs 50.2%; $P < 0.001$), but more likely to be treated with angiotensin receptor blockers, (23.6% vs 18.2%; $P < 0.001$). For the combined variable of treatment with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, there was no statistically significant difference (67.8% of women and 68.5% of men; $P = 0.58$) (**Table 1**, Supplemental Table 2). Fewer women were using an angiotensin receptor neprilysin inhibitor (17.5% vs 20%; $P = 0.020$), sodium-glucose cotransporter 2 inhibitor (SGLT2 inhibitor) (1.5% vs 2.9%; $P = 0.001$), or had an implantable cardioverter-defibrillator (24.5% vs 33.7%; $P < 0.001$) or cardiac resynchronization therapy (11.5% vs 14.7%; $P < 0.001$).

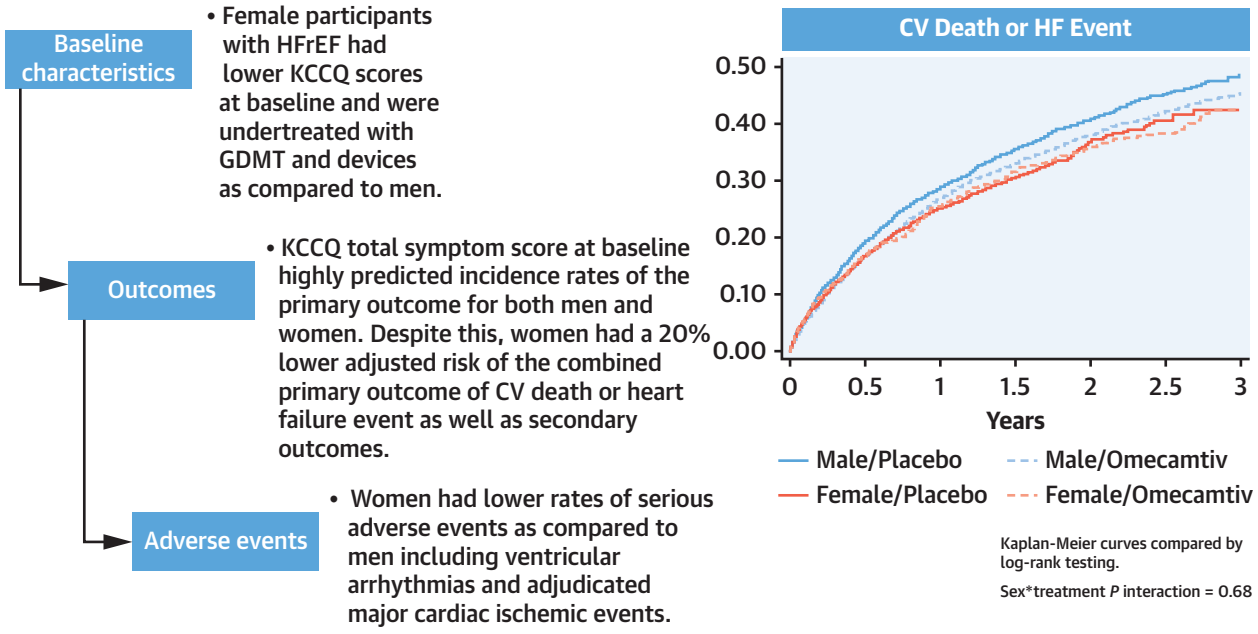
CLINICAL EVENT RATES. Median follow-up time was 22.0 months in women and 21.7 months in men. Women had lower rates of the primary endpoint of first HF event or CV death (22.9 events per 100 patient-years in women vs 25.9 events per 100 patient-years in men; HR: 0.89 [95% CI: 0.81-0.97]; $P = 0.01$). The risk of the primary endpoint was even lower for women after multivariable adjustment (HR: 0.80 [95% CI: 0.73-0.88]; $P < 0.001$) (**Figure 1**, **Central Illustration**). Women also had a lower risk of CV death during follow-up (HR: 0.78 [95% CI: 0.68-0.91]; $P < 0.001$), HF event (HR: 0.79 [95% CI: 0.72-0.88]; $P < 0.0001$), and all-cause death (HR: 0.79 [95% CI: 0.70-0.88]; $P < 0.001$) (**Table 2**). Notably, there was no statistically significant difference in incidence of stroke between men and women, although women had higher rates of CV death caused by stroke as compared with men (1% vs 0.5%, respectively; $P = 0.01$).

TREATMENT EFFECT OF OMECAMTIV MECARBIL IN FEMALE PARTICIPANTS. Sex did not significantly modify the treatment effect of omecamtiv mecarbil on the primary endpoint. The treatment effect among male participants for the primary outcome was a HR of 0.92 (95% CI: 0.85-0.99) compared with HR of 0.95; 95% CI: 0.81-1.12 in female participants (P-interaction = 0.68). Additionally, there was no significant difference in primary outcome treatment effect by sex when further adjusting for the known treatment interaction with severe HF (P interaction = 0.70). No significant treatment interaction by sex was observed on the secondary outcomes of CV death, HF event, and all-cause death (P interaction = 0.35, 0.32, and 0.16, respectively).

SEX DIFFERENCES IN KCCQ-TSS AND EVENT RATES. In this cohort of patients, baseline KCCQ-TSS was predictive of worse outcomes during follow-up for men and women; this association in particular was stronger among those enrolled in the outpatient setting (**Figure 2**, Supplemental Figure 1). A 10-point lower KCCQ-TSS at baseline was associated with an increased risk of the primary outcome regardless of sex (HR: 1.15 [95% CI: 1.13-1.16]; $P < 0.0001$). There was no significant difference between sexes in the mean change in KCCQ-TSS for patients enrolled in the inpatient setting, but among participants enrolled in the outpatient setting, women had greater improvement in KCCQ-TSS at weeks 24 and 48 as compared with men ($P = 0.02$ and $P = 0.002$, respectively) (**Table 2**). Despite improvements in mean KCCQ-TSS in both male and female participants during study follow-up, the mean KCCQ-TSS for women remained lower than for men throughout follow-up (**Figure 3**).

LABORATORY MEASURES. The effect of omecamtiv mecarbil on vital signs and key laboratory tests was similar between men and women (**Table 3**, Supplemental Table 3). There was no difference in the change in systolic blood pressure, creatinine, and potassium at 24 or 48 weeks of follow-up in either male or female patients. Omecamtiv mecarbil slightly decreased heart rate similarly in men and women. Also, both female and male patients treated with omecamtiv mecarbil had lower NT-proBNP levels and higher median change in troponin I at week 24 as compared with placebo, but there was no significant difference between sex groups.

CENTRAL ILLUSTRATION **Sex Differences in Heart Failure With Reduced Ejection Fraction in the GALACTIC-HF Trial**



Pabon M, et al. J Am Coll Cardiol HF. 2023;11(12):1729–1738.

CV = cardiovascular; GALACTIC-HF = Registrational Study With Omecamtiv Mecarbil [AMG 423] to Treat Chronic Heart Failure With Reduced Ejection Fraction; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire.

OMECAMTIV MECARBIL DOSING, PLASMA CONCENTRATIONS, AND SAFETY OUTCOMES. Women had higher plasma concentrations of omecamtiv mecarbil measured at week 2 (mean 184 ± 101 ng/mL vs 153 ± 87 ng/mL in men; $P < 0.0001$) (Supplemental Figure 2). Adjusting for weight attenuated this sex difference, although it remains statistically significant (difference of 17 ng/mL; 95% CI:

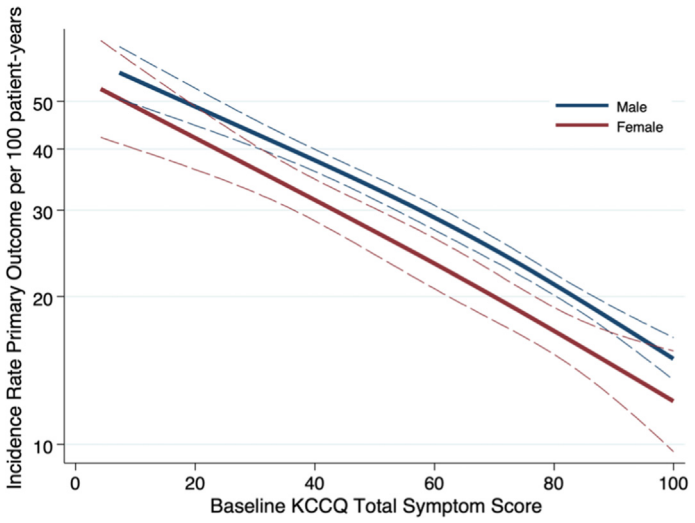
TABLE 2 **Primary and Secondary Outcomes in Female vs Male Participants (Adjusted HR)**

	Male (n = 6,483)		Female (n = 1,749)			
		Events (n/100 pt-yr)		Events (n/100 pt-yr)	HR or Difference	*P* Value
Primary composite outcome	2,517 (38.8)	25.9	613 (35)	22.9	0.80 (0.73 to 0.88)	<0.001
Secondary outcomes						
Cardiovascular death	1,291 (19.9)	11.1	315 (18)	9.9	0.80 (0.70 to 0.91)	0.001
Change in KCCQ total symptom score at wk 24[a]						
Inpatient	+22.0 ± 28.9	NA	+22.6 ± 28.5	NA	0.56 (−2.89 to +4.02)	0.75
Outpatient	+5.5 ± 20.5		+7.1 ± 22.5		1.60 (+0.25 to +2.96)	0.020
Change in KCCQ total symptom score at wk 48[a]						
Inpatient	+23.7 ± 28.0	NA	+24.7 ± 28.8	NA	1.00 (−2.56 to +4.56)	0.58
Outpatient	+5.2 ± 21.0	NA	+7.4 ± 21.9		2.21 (+0.79 to +3.63)	0.002
First hospitalization for heart failure	1,877 (28.9)	19.1	444 (25.4)	16.5	0.79 (0.71 to 0.88)	<0.0001
Death from any cause	1,723 (26.6)	14.8	409 (23.4)	12.9	0.79 (0.70 to 0.88)	<0.0001
Heart failure event	1,949 (30.1)	20.0	464 (26.5)	17.4	0.79 (0.72 to 0.88)	<0.0001

Values are n (%), mean ± SD, or median (IQR), except as noted. The primary outcome was a composite of heart failure events (hospitalization or unscheduled urgent clinic, office, or emergency department visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes. [a]All listed values are HRs except for the between-group differences in the changes in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

NA = not applicable; pt-yr = patient-year.

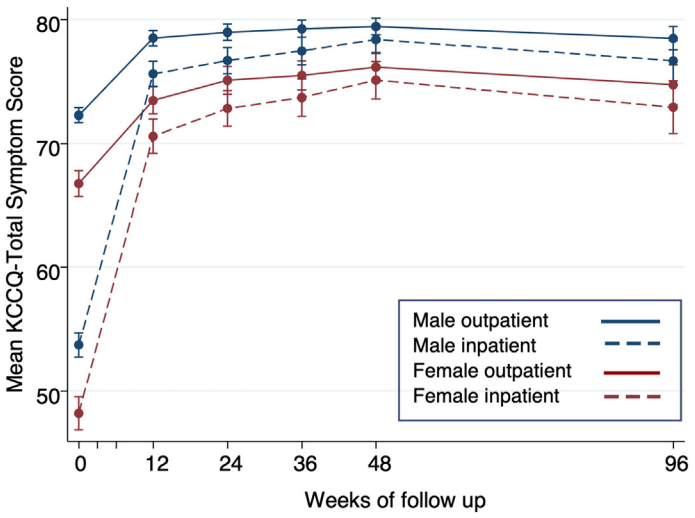
FIGURE 2 KCCQ-TSS at Baseline Is Associated to Incidence Rates of Primary Outcome



Incidence rate of primary outcome plotted against baseline Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS).

15.7-29.3 ng/mL; $P < 0.0001$). Subsequently, at study visit week 4, a greater proportion of male participants (55.4%) had their dose increased to 50 mg twice daily compared with 42.7% of females

FIGURE 3 Change in KCCQ-TSS During Study Follow-Up in Male and Female Participants



Mean KCCQ-TSS at weeks 0, 12, 24, 48, and 96 of follow-up in male and female participants of GALACTIC-HF (Registrational Study With Omecamtiv Mecarbil [AMG 423] to Treat Chronic Heart Failure With Reduced Ejection Fraction) by inpatient enrollment status. Abbreviation as in Figure 2.

($P < 0.0001$) (Supplemental Table 4). After dose adjustment at week 4, the mean dose of omecamtiv mecarbil was 39 ± 11 mg for females and 42 ± 11 mg for males ($P < 0.0001$). There was no statistically significant difference in total serious adverse events, ventricular arrhythmias, or discontinuation of study drug because of adverse events among women treated with omecamtiv mecarbil vs placebo (all $P > 0.05$) (Table 4). Women had lower rates of serious adverse events as compared with men (OR: 0.83; 95% CI: 0.75-0.92) including ventricular arrhythmia (OR: 0.55, 95% CI: 0.43-0.69), torsades de pointes/QT prolongation (OR: 0.46; 95% CI: 0.33-0.63), adjudicated major cardiac ischemic event (OR: 0.64; 95% CI: 0.48-0.85), and coronary revascularization (OR: 0.48; 95% CI: 0.32-0.72).

DISCUSSION

In this prespecified analysis of the GALACTIC-HF trial, we found that female participants with HFrEF were more symptomatic at baseline and received fewer guideline-recommended medications and devices compared with men. In this cohort of patients, KCCQ-TSS at baseline highly predicted incidence rates of the primary outcome for both men and women. Despite this, women had 20% lower adjusted risk of the combined primary outcome of CV death or HF event. Additionally, women had 22% lower risk of CV death and 21% lower risk of HF hospitalization and death from any cause. Female participants had lower rates of serious adverse events as compared with men, including ventricular arrhythmias and adjudicated major cardiac ischemic events. Overall, women and men had a similar benefit with omecamtiv mecarbil, and this medication seems to be safe in women.

Women represented only 21% of the population in GALACTIC-HF, which is consistent with the traditional proportion of women enrolled in HFrEF trials. Like in prior studies, women were less likely to have atrial fibrillation and ischemic cardiomyopathy.[2] They also had worse renal function (lower eGFR) and slightly higher LVEF at baseline as compared with men.[2] Women and men were equally treated with beta-blockers and MRAs, but women were less likely to be treated with more contemporary HF medications and devices such as angiotensin receptor neprilysin inhibitors, SGLT2 inhibitor, cardiac resynchronization therapy, and implantable cardioverter-defibrillators.

Notably, female patients had greater symptom burden and lower quality of life at baseline. This is interesting because despite baseline KCCQ-TSS being highly predictive of worse outcomes in both sexes,

TABLE 3 Changes in Vital Signs and Laboratory Measures at Week 24 of Follow-Up

	Male	Female	
	Difference (95% CI) Treatment vs Placebo	Difference (95% CI) Treatment vs Placebo	*P* Interaction
Systolic blood pressure, mm Hg	−0.4 (−1.2 to +0.3)	−0.1 (−1.5 to +1.4)	0.70
Heart rate, beats/min	−1.5 (−2.1 to −0.9)	−1.7 (−2.8 to −0.7)	0.70
Potassium, mmol/L	+0.00 (−0.02 to +0.03)	−0.01 (−0.06 to +0.04)	0.55
Creatinine, mg/dL	+0.00 (−0.01 to +0.02)	+0.01 (−0.01 to +0.05)	0.59
	Percentage Difference (95% CI) Treatment vs Placebo	Percentage Difference (95% CI) Treatment vs Placebo	
Change in NT-proBNP pmol/L at wk 24	−9% (−14% to −5%)	−15% (−23% to −6%)	0.21
Change in troponin I, ng/mL at wk 24	+24% (+18% to +31%)	+28% (+17% to +41%)	0.77

The plus and minus signs represent direction of change. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

NT-proBNP = N-terminal pro-B-type natriuretic peptide.

women had 20% lower risk of the primary and secondary outcomes as compared with men. This female HFrEF paradox of worse quality of life but better outcomes is consistent with prior reports, but the reason remains to be elucidated.[2,3,13-15] One possibility is the lower incidence of ischemic injury in women as compared with men, which can lead to more adverse remodeling in male patients with HFrEF.[16] Other determinants such as access to health care, socioeconomic status, and less caregiver support may also contribute to the female paradox observed in the HFrEF population.[2] Further research is needed to determine additional factors leading to this disproportionate burden of HF symptoms in women, because controlling these risk factors could lead to further improvement in quality of life and, ultimately, in outcomes among women with HF.

Although women represented only 21% of the participants in GALACTIC-HF, there were still 1,749 women with 613 primary outcome events, providing a robust population. The beneficial treatment effect of omecamtiv mecarbil was not modified by the sex of the participant. Women had higher plasma concentrations of omecamtiv mecarbil, and as such, women required lower doses of the study drug. Omecamtiv mecarbil was well-tolerated in women, and women had lower rates of serious adverse events, including ventricular arrhythmias and major adjudicated ischemic events, as compared with men, despite higher plasma level concentrations of the study drug. This difference could be partly explained by the lower incidence of ischemic disease in women leading to less myocardial scarring and arrhythmia substrate. Nevertheless, these results further support the selective effect of omecamtiv mecarbil on cardiac myosin leading to increased cardiac contractility without adverse events seen with other inotropic drugs such as arrhythmias and ischemic events.[10]

Our study contributes to the increasing recognition that women have different phenotypes of HF as compared with men with sex-specific risk factors

TABLE 4 Adverse Events in Male and Female Participants

	Male			Female			
Safety Outcomes	Omecamtiv Mecarbil (n = 3,245)	Placebo (n = 3,238)	Omecamtiv Mecarbil vs Placebo OR (95% CI)	Omecamtiv Mecarbil (n = 875)	Placebo (n = 874)	Omecamtiv Mecarbil vs Placebo OR (95% CI)	Male vs Female OR (95% CI), *P* Value
Discontinuation because of adverse event	345 (10.6)	357 (11)	0.96 (0.82-1.12)	95 (10.9)	94 (10.8)	1.01 (0.75-1.36)	0.99 (0.84-1.18), 0.97
Serious adverse event	1,890 (58.2)	1,962 (60.6)	0.91 (0.82-1.00)	485 (55.4)	476 (54.5)	1.04 (0.86-1.25)	0.83 (0.75-0.92), 0.0008
Ventricular tachyarrhythmia	248 (8.7)	265 (9.2)	0.94 (0.78-1.12)	42 (5.3)	39 (4.9)	1.07 (0.68-1.67)	0.55 (0.43-0.69), <0.0001
Torsades de pointes or QT prolongation	155 (5.4)	173 (6)	0.89 (0.72-1.12)	21 (2.6)	22 (2.8)	0.95 (0.52-1.72)	0.46 (0.33-0.63), <0.0001
Adjudicated major cardiac ischemic event	169 (5.2)	161 (4.9)	1.05 (0.84-1.31)	31 (3.5)	27 (3.1)	1.15 (0.69-1.93)	0.64 (0.48-0.85), 0.002
Myocardial infarction	100 (3.1)	100 (3.1)	0.99 (0.75-1.32)	22 (2.5)	18 (2.1)	1.22 (0.66-2.28)	0.73 (0.52-1.03), 0.079
Hospitalization for unstable angina	20 (0.6)	7 (0.2)	2.86 (1.24-6.61)	5 (0.6)	5 (0.6)	0.99 (0.31-3.23)	1.37 (0.67-2.80), 0.39
Coronary revascularization	100 (3.1)	105 (3.2)	0.95 (0.72-1.25)	15 (1.7)	12 (1.4)	1.25 (0.59-2.65)	0.48 (0.32-0.72), 0.003
Adjudicated stroke	62 (1.9)	87 (2.7)	0.70 (0.51-0.98)	14 (1.6)	25 (2.9)	0.55 (0.29-1.06)	0.97 (0.68-1.38), 0.86

Values are n (%) unless otherwise indicated. Adverse events in female and male participants compared by treatment arm and between sex groups. Data are reported as ORs for all safety outcomes.

and prognosis. These findings underscore the importance of increasing our understanding of the additional factors leading to the disparities seen in this HFrEF population. This also requires increasing the representation of women in HF clinical trials, which has remained low relative to the disease distribution.[7,17] Indeed, in the GALACTIC-HF trial, we found that women were more likely to be excluded due to their limited ability to complete and comply with study procedures. These results align with previous studies suggesting that a significant barrier to female participation in cardiovascular clinical trials is the concern over increased patient burden in terms of time and logistics.[17-19] As primary caregivers, women may benefit from efforts to decrease clinical trial burdens, such as reducing the number of in-person visits, offering telehealth follow-up or home visits, and providing transportation and ancillary services.[20] Reporting screen failures and pharmacokinetics by sex in future HF clinical trials may also help identify these barriers and ensure the safety of study medications in underrepresented populations.

Additionally, significant sex-related differences may exist in terms of cardiac contractile function and calcium regulation. Prior cellular models and animal studies suggest that women have smaller calcium currents that decay more rapidly, leading to lower excitation-contraction coupling gain compared with men.[21,22] This could explain why previous published reports suggest that women seem to derive less benefit from treatment with digoxin, whose inotropic effects are mediated via increased intracellular calcium.[23] Omecamtiv mecarbil could potentially serve as a better inotropic option for women because it increases contractility without altering intracellular calcium currents,[24] a mechanism notably different from traditional inotropes.

STUDY LIMITATIONS. First, the proportion of female patients was lower than male participants, which reduced the statistical power to detect differences in treatment effects. Also, patients enrolled in clinical trials may not be representative of the general population because they may be better managed and more closely monitored. Exclusion of patients with marked renal dysfunction (eGFR <20 mL/kg/min or on dialysis), hypotension (systolic blood pressure <85 mm Hg), or recent acute coronary syndrome may limit generalizability to a real-world population. GALACTIC-HF was conducted before SGLT2 inhibitor was being indicated for patients with HFrEF, so this treatment was low in both groups.

CONCLUSIONS

Women participants of GALACTIC-HF had lower rates of the primary outcome of HF event or CV death despite being undertreated with guideline directed interventions, having lower quality of life and higher burden of symptoms at baseline. There was no difference in the beneficial treatment effect of omecamtiv mecarbil between sexes, and this medication appears safe in women. These results highlight the importance of further characterizing the different phenotypes of HFrEF observed in men and women, as well as continuing with targeted efforts toward enrolling a representative proportion of women in HFrEF clinical trials.

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ADDRESS FOR CORRESPONDENCE: Dr Scott Solomon, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, USA. E-mail: ssolomon@rics.bwh.harvard.edu. @scottdsolomon.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HFrEF affects millions of people worldwide. It is associated with high morbidity, mortality, and health care costs. Despite advances in pharmacological and device therapies, many patients with HFrEF remain symptomatic and at risk of adverse outcomes. Sex differences in HFrEF have been increasingly recognized as an important factor that may influence the pathophysiology, presentation, prognosis, and response to treatment of this condition. However, women with HFrEF are often underrepresented in clinical trials and undertreated with guideline-directed medical therapy compared with men. In this prespecified analysis from the GALACTIC-HF trial, the authors report the results of sex differences in response, outcomes, and adverse effects to omecamtiv mecarbil. They found that omecamtiv mecarbil reduced the primary composite outcome similarly in both sexes and that there were no significant interactions between sex and treatment for any of the secondary outcomes or adverse effects.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: These findings have important implications for the management of HFrEF patients, especially women who tend to be undertreated with medical therapy and underrepresented in clinical trials. They suggest that omecamtiv mecarbil is an effective and safe option for both men and women with HFrEF and that sex-specific factors do not affect its benefits or risks. This study contributes to the existing published reports on sex differences in HFrEF by providing novel data from a large-scale clinical trial that has potential to change clinical practice and improve outcomes for HFrEF patients. Future research directions include: exploring whether omecamtiv mecarbil has different effects on quality of life or functional status across sexes; whether there are subgroups of patients who may benefit more or less from omecamtiv mecarbil based on sex-specific factors such as age, comorbidities, etiology, or phenotype, whether omecamtiv mecarbil interacts with other therapies such as sacubitril/valsartan or SGLT2 inhibitors, and whether there are any ethical, social, or cultural barriers to implementing omecamtiv mecarbil in different populations or groups.

TRANSLATIONAL OUTLOOK: Despite the distinct sex-related differences in baseline characteristics, pharmacokinetics did not differ between men and women. Future clinical trials should incorporate reports on screening failures and disparate pharmacokinetics among study populations. This will enhance our understanding of a drug's efficacy and safety in populations that are typically underrepresented in heart failure clinical trials.

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