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

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Background

- There are sex-specific differences in risk factors, prognosis, and treatment responses in the heart failure population.
- Women with heart failure with reduced ejection fraction (HFrEF) are undertreated with guideline recommended therapy and experience worse quality of life compared with men.
- Low enrollment of women in HFrEF outcomes trials has limited inferences about drug efficacy and safety in women.

Study Aim

To characterize baseline characteristics, clinical outcomes, efficiency and safety of omecamtiv mecarbil in men and women enrolled in GALACTIC-HF.

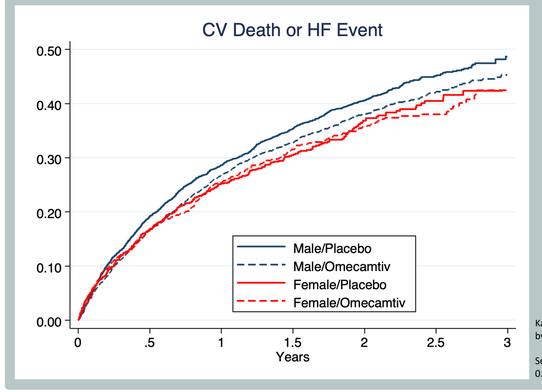
Methods

- The GALACTIC-HF trial evaluated treatment effects of omecamtiv mecarbil versus placebo in HFrEF with LVEF ≤ 35%.
- The primary study outcome was a composite of time to CV death or first heart failure event.
- Outcomes for male and female patients were compared using Cox proportional hazards models adjusted for 14 relevant covariates.
- Treatment effect of omecamtiv mecarbil compared to 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 estimated GFR as covariates.

Baseline characteristics, primary and secondary outcomes in women

Characteristic	Male	Female	
	n=6483	n=1749	
Age — years.	64.3 ± 11.2	65.4 ± 11.9	p < 0.001
Inpatient setting — no. (%)	1673 (25.8%)	411 (23.5%)	p = 0.049
Clinical features			
Atrial fibrillation or flutter — no. (%)	2828 (43.6%)	647 (37.0%)	p < 0.001
Type 2 diabetes mellitus — no. (%)	2680 (41.3%)	697 (39.9%)	p = 0.26
Ischemic heart failure — no. (%)	3688 (56.9%)	727 (41.6%)	p < 0.001
Left ventricular ejection fraction — %	26.4 ± 6.3	27.1 ± 6.2	p < 0.001
NYHA classification — no. (%)			p = 0.011
II	3495 (53.9%)	873 (49.9%)	
III	2799 (43.2%)	817 (46.7%)	
IV	189 (2.9 %)	59 (3.4 %)	
Mean total symptom score on KCCQ	67.5 ± 24.8	62.4 ± 25.9	p < 0.001
Median NT-proBNP (IQR) — pg/ml	1975.0 (995.0, 4028.0)	2091.0 (989.0, 4346.0)	p = 0.16
Median cardiac troponin I (IQR) — ng/liter	29.0 (16.0 , 53.0)	20.0 (10.0, 42.0)	p < 0.001
Mean eGFR — ml/min/1.73m2	61.5 ± 21.8	56.0 ± 21.7	p < 0.001
Heart-failure therapy — no. (%)			
ACE inhibitor	3252 (50.2%)	792 (45.3%)	p < 0.001
ARB	1177 (18.2%)	412 (23.6%)	p < 0.001
Mineralocorticoid-receptor antagonist	5061 (78.1%)	1336 (76.4%)	p = 0.13
Beta-blocker	6123 (94.4%)	1640 (93.8%)	p = 0.28
ARN inhibitor	1295 (20.0%)	306 (17.5%)	p = 0.020
SGLT2 inhibitor	191 (2.9 %)	27 (1.5 %)	p = 0.001
Cardiac-resynchronization therapy	956 (14.7%)	202 (11.5%)	p < 0.001
Implantable cardioverter-defibrillator	2186 (33.7%)	428 (24.5%)	p < 0.001

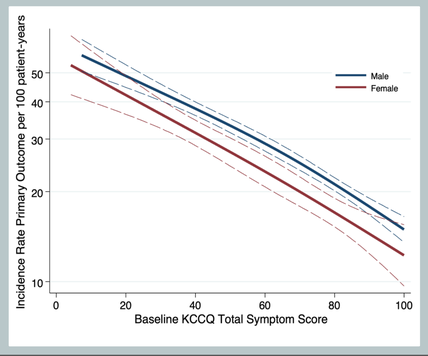
Primary endpoint and treatment effect by sex



Kaplan-Meier curves compared by log-rank testing.

Sex*treatment p interaction= 0.68

KCCQ-TSS at baseline predicts adverse outcomes in men and women participants



Adverse events and plasma levels of OM in women vs men

Variable	Male			Female			OR male vs female (95% CI)
	Omecamtiv mecarbil N= 3,245	Placebo N= 3,238	OR Omecamtiv mecarbil vs Placebo (95% CI)	Omecamtiv mecarbil N= 875	Placebo N= 874	OR Omecamtiv mecarbil vs Placebo (95% CI)	
Safety outcomes – no. (%)							
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) p=0.97
Serious adverse event	1890 (58.2%)	1962 (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) p=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) p<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) p<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) p=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) p=0.079
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) p=0.003

Key Findings

- Female participants with HFrEF had lower KCCQ scores at baseline and were undertreated with GDMT and devices as compared to men.
- KCCQ total symptom score 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 heart failure event as well as secondary outcomes.
- Women had lower rates of serious adverse events as compared to men including ventricular arrhythmias and adjudicated major cardiac ischemic events.

In this secondary analysis of the GALACTIC-HF trial, women had lower rates of the primary outcome of heart failure event or CV death despite being undertreated with guideline directed interventions and having lower quality of life at baseline. There was no difference in the treatment effect of omecamtiv mecarbil between sexes and this medication appears safe in women.