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ORIGINAL INVESTIGATIONS

Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF

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on behalf of the GALACTIC-HF Investigators

ABSTRACT

BACKGROUND In GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) (n = 8,256), the cardiac myosin activator, omecamtiv mecarbil, significantly reduced the primary composite endpoint (PCE) of time-to-first heart failure event or cardiovascular death in patients with heart failure and reduced ejection fraction (EF) (≤35%).

OBJECTIVES The purpose of this study was to evaluate the influence of baseline EF on the therapeutic effect of omecamtiv mecarbil.

METHODS Outcomes in patients treated with omecamtiv mecarbil were compared with placebo according to EF.

RESULTS The risk of the PCE in the placebo group was nearly 1.8-fold greater in the lowest EF (≤22%) compared with the highest EF (≥33%) quartile. Amongst the pre-specified subgroups, EF was the strongest modifier of the treatment effect of omecamtiv mecarbil on the PCE (interaction as continuous variable, p = 0.004). Patients receiving omecamtiv mecarbil had a progressively greater relative and absolute treatment effect as baseline EF decreased, with a 17% relative risk reduction for the PCE in patients with baseline EF ≤22% (n = 2,246; hazard ratio: 0.83; 95% confidence interval: 0.73 to 0.95) compared with patients with EF ≥33% (n = 1,750; hazard ratio: 0.99; 95% confidence interval: 0.84 to 1.16; interaction as EF by quartiles, p = 0.013). The absolute reduction in the PCE increased with decreasing EF (EF ≤22%; absolute risk reduction, 7.4 events per 100 patient-years; number needed to treat for 3 years = 11.8), compared with no reduction in the highest EF quartile.

CONCLUSIONS In heart failure patients with reduced EF, omecamtiv mecarbil produced greater therapeutic benefit as baseline EF decreased. These findings are consistent with the drug's mechanism of selectively improving systolic function and presents an important opportunity to improve the outcomes in a group of patients at greatest risk. (Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure With Reduced Ejection Fraction [GALACTIC-HF]; NCT02929329)
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ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

NYHA = New York Heart Association

Many therapies have been developed that improve cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF). However, none of the currently available drugs directly improve the central defect of HFrEF: reduced systolic function. Moreover, severe impairment of systolic function is often associated with lower blood pressure and greater difficulty tolerating target doses of guideline-directed medical therapies. Myotropes (1) represent a new class of drugs that improve myocardial function by directly augmenting cardiac sarcomere function. The cardiac myosin activator, omecamtiv mecarbil (2,3), is the first of this class, and it increases systolic function by selectively facilitating the actin-myosin interaction, increasing contractile force without altering the cardiomyocyte calcium transient (4). In patients with chronic HFrEF enrolled in COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure), omecamtiv mecarbil increased left ventricular systolic function, as reflected by increased systolic ejection time and ejection fraction (EF) and improved myocardial strain, while decreasing left ventricular systolic and diastolic volumes, natriuretic peptide concentrations, and heart rate (5,6). The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial was the first trial to demonstrate a beneficial effect of selectively increasing cardiac contractility on cardiovascular outcomes in patients with HFrEF (7–9). Here, we examine the impact of baseline EF, a pre-specified subgroup, as a modifier of the effect of omecamtiv mecarbil on clinical outcomes and safety in patients enrolled in GALACTIC-HF (NCT02929329; EudraCT number 2016-002299-28).

METHODS

GALACTIC-HF STUDY DESIGN. The design, baseline characteristics, and primary results of the trial have been previously published (7–9). Briefly, GALACTIC-HF was a phase 3, global, double-blind, placebo-controlled randomized clinical trial that compared omecamtiv mecarbil to placebo in 8,256 patients with symptomatic (New York Heart Association [NYHA] functional class II to IV) HFrEF and EF ≤35% as per the patient's most recent medical record within 12 months prior to screening. The most recent qualifying EF was to be at least 30 days after any of the following, if applicable: 1) an event likely to decrease EF (eg, myocardial infarction, sepsis); 2) an intervention likely to increase EF (eg, cardiac resynchronization therapy, coronary revascularization); or 3) the first ever presentation for heart failure. All participants were required to have elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] level ≥400 pg/ml [1,200 pg/ml for patients in atrial fibrillation] or B-type natriuretic peptide [BNP] ≥125 pg/ml [375 pg/ml for patients in atrial fibrillation]) and were on optimized background heart failure therapy. Participants were currently hospitalized for heart failure (inpatients) or within 1 year had either an urgent visit to the emergency department for heart failure or a hospitalization for heart failure (outpatients). Key exclusion criteria included current hemodynamic or clinical instability requiring mechanical or intravenous medication, systolic blood pressure <85 mm Hg, estimated glomerular filtration rate <20 ml/min/1.73 m^2, recent acute coronary syndrome events or cardiovascular procedures (including planned procedures), and other conditions with reduced life expectancy <2 years or that would adversely affect participation in the trial. The study protocol was approved by the relevant local ethics committees, and all participants provided informed consent.

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STUDY OUTCOMES. The primary outcome was a composite of the time-to-first heart failure event or death due to cardiovascular causes. Secondary outcomes included the time to cardiovascular death; change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) from baseline to week 24 using a scale from 0 to 100, with a higher score indicating fewer symptoms; time to first heart failure hospitalization; and time to all-cause death. Additional exploratory outcomes have been

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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published (9). All deaths, HF events, major cardiac ischemic events (myocardial infarction/unstable angina hospitalization and coronary revascularization), and strokes were adjudicated by an independent external Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions (10).

STATISTICAL ANALYSIS. The initial analysis plan defined subgroups according to median baseline EF; however, for the purposes of this paper, we further evaluated baseline characteristics for patients by quartiles of EF. Continuous variables were summarized via means and SDs or medians and interquartile ranges, as appropriate. Categorical variables are summarized with counts and percentages. Tests of trend across categories were conducted via linear regression, Cuzick's nonparametric trend test, and chi-square tests of trend, respectively. Treatment effects on continuous outcomes were assessed via linear regression models adjusted for the corresponding baseline value of the parameter of interest. Survival analyses were conducted using Poisson regression models to estimate incidence rates, rate differences, and rate ratios and Cox proportional hazards models to estimate hazard ratios (HRs). Treatment effect HRs were adjusted for estimated glomerular filtration rate and stratified by region and inpatient status as in the primary GALACTIC-HF analysis. To allow for potentially nonlinear associations between EF and time-to-event outcomes, restricted cubic splines were utilized in the Poisson regression models with 3 knots. Treatment effect modification was assessed via the introduction of interaction terms between randomized treatment assignment and the corresponding EF model covariates (eg, linear, quartile, or cubic spline). All analyses were conducted using STATA version 16 (StataCorp, College Station, Texas). All p values <0.05 were considered statistically significant. Due to the exploratory nature of these analyses, no adjustments were made for multiple comparisons.

RESULTS

STUDY PATIENTS. All of the 8,232 participants had reported EFs with over 97% measured by echocardiogram (Supplemental Table 1, Supplemental Figures 1 and 2), and there were 4,456 patients with an EF ≤28%, the median EF in the trial. Due to digit preference for EF assessment, over 70% of the patients had an EF ≤30%. When assessed by quartiles (**Table 1,** Supplemental Table 2), patients with lower EFs were younger; more likely to be male and non-White; less likely to be enrolled in Eastern Europe or Russia; and more likely to be enrolled in the United States, Canada, Western Europe, South Africa, or Australasia. Patients with lower EF were more likely to have a nonischemic etiology of heart failure, NYHA functional class III/IV, lower body mass index, lower systolic blood pressure, higher heart rate, higher NT-proBNP, and higher cardiac troponin I, and were less likely to have coronary artery disease, hypertension, type 2 diabetes mellitus, or atrial fibrillation/flutter. Lower EF was associated with greater symptom burden in patients enrolled as inpatients (lower KCCQ-TSS), but there was no meaningful difference in the outpatients. There was no difference in the proportion of patients receiving triple therapy ([angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor] + mineralocorticoid receptor antagonist + beta-blocker) among the EF quartiles. Patients with lower EFs had higher use of angiotensin-receptor neprilysin inhibitor, ivabradine, digitalis glycosides, cardiac resynchronization therapy, and implantable cardioverter-defibrillators compared with patients with higher EFs.

RELATIONSHIP BETWEEN EF AND CLINICAL OUTCOMES. Within the group of patients with HFrEF enrolled in the GALACTIC-HF trial, the incidence of clinical outcomes increased with decreasing EF (**Table 2**). As noted by the rates in the placebo group, the incidence of the primary outcome of first heart failure event or cardiovascular death in patients in the lowest EF quartile (EF ≤22%; 35.6 per 100 patient-years) was almost 80% greater than in the highest EF quartile (EF ≥33%; 20 per 100 patient-years). The incidence of first heart failure event was 90% greater (28.3 events vs 14.9 events per 100 patient-years) and of cardiovascular death was 68% greater (14.1 deaths vs 8.4 deaths per 100 patient-years) in the lowest EF compared to the highest EF quartile. Participants in the placebo group had significant improvements in the KCCQ-TSS at week 24 compared with baseline, with greater improvements in those enrolled as inpatients, but there was no modification of this effect by EF quartile (Supplemental Table 3).

INFLUENCE OF EF ON THE TREATMENT EFFECT OF OMECAMTIV MECARBIL. Omecamtiv mecarbil significantly decreased the primary endpoint of the time-to-first heart failure event or cardiovascular death in the overall trial population (HR: 0.92; 95% confidence interval [CI]: 0.86-0.99; p = 0.025) (8). The statistical analysis plan pre-specified the assessment of the primary endpoint in the EF subgroups above and below the median value (≤28%), and there was a significant modification of the treatment effect of

TABLE 1 Baseline Characteristics of GALACTIC-HF Patients' Ejection Fraction Quartiles

	EF ≤22% (n = 2,246)	EF 23%–28% (n = 2,210)	EF 29%–32% (n = 2,026)	EF ≥33% (n = 1,750)	p Value
Demographics					
Age, yrs	62.5 ± 11.8	64.1 ± 11.6	65.7 ± 10.9	66.4 ± 10.5	<0.001
Female	422 (18.8)	451 (20.4)	455 (22.5)	421 (24.1)	<0.001
Race					<0.001
Asian	171 (7.6)	224 (10.1)	179 (8.8)	136 (7.8)	
Black or African American	243 (10.8)	156 (7.1)	95 (4.7)	68 (3.9)	
Other*	200 (8.9)	162 (7.3)	118 (5.8)	83 (4.7)	
White	1,632 (72.7)	1,668 (75.5)	1,634 (80.7)	1,463 (83.6)	
Geographic region					<0.001
Asia	152 (6.8)	214 (9.7)	174 (8.6)	130 (7.4)	
Eastern Europe/Russia	476 (21.2)	617 (27.9)	783 (38.6)	805 (46.0)	
Latin and South America	438 (19.5)	504 (22.8)	364 (18.0)	268 (15.3)	
United States and Canada	581 (25.9)	341 (15.4)	259 (12.8)	205 (11.7)	
Western Europe/South Africa/Australasia	599 (26.7)	534 (24.2)	446 (22.0)	342 (19.5)	
Randomization setting: in-patient	592 (26.4)	552 (25.0)	487 (24.0)	453 (25.9)	0.50
Clinical characteristics					
Medical conditions					
Coronary artery disease	1,267 (56)	1,320 (60)	1,323 (65)	1,218 (70)	<0.001
Stroke	214 (10)	194 (9)	250 (12)	161 (9)	0.80
Atrial fibrillation or flutter history	912 (41)	884 (40)	889 (44)	790 (45)	<0.001
Atrial fibrillation or flutter at screening	547 (24.4)	561 (25.4)	609 (30.1)	528 (30.2)	<0.001
Hypertension	1,431 (64)	1,483 (67)	1,503 (74)	1,367 (78)	<0.001
Type 2 diabetes mellitus	869 (39)	880 (40)	817 (40)	743 (43)	<0.001
Chronic obstructive pulmonary disease	352 (16)	360 (16)	332 (16)	301 (17)	0.21
Heart failure history					
LVEF, %	20 (15, 20)	25 (25, 27)	30 (30, 31)	34 (33, 35)	N/A
Time from last HF event, months (outpatients only)	2.9 (1.6, 5.8)	3.1 (1.6, 6.1)	3.3 (1.6, 6.5)	3.4 (1.5, 6.8)	0.039
Time from last HF hospitalization, months (outpatients only)	3.0 (1.6, 5.9)	3.2 (1.6, 6.2)	3.4 (1.7, 6.6)	3.6 (1.6, 6.9)	0.043
MAGGIC score	25 (21, 30)	24 (20, 28)	22 (17, 26)	21 (17, 25)	<0.001
NYHA functional classification					0.016
II	1,160 (52)	1,164 (53)	1,085 (54)	959 (55)	
III	1,007 (45)	968 (44)	889 (44)	752 (43)	
IV	79 (4)	78 (4)	52 (3)	39 (2)	
Ischemic heart failure etiology	1,033 (46)	1,153 (52)	1,141 (56)	1,088 (62)	<0.001
KCCQ total symptom score	69 (48, 88)	70 (49, 88)	71 (50, 88)	69 (49, 85)	0.77
Outpatient	75 (56, 92)	75 (54, 92)	75 (56, 92)	73 (54, 90)	0.05
Inpatient	51 (29, 69)	53 (33, 73)	55 (35, 72)	54 (31, 74)	0.022
Vitals and laboratory parameters					
Body mass index, kg/m^2	27.9 ± 6.3	28.2 ± 6.2	28.9 ± 6.0	29.1 ± 6.1	<0.001
SBP, mm Hg	112 ± 15	115 ± 15	119 ± 15	121 ± 14	<0.001
Heart rate, beats/min	74 ± 12	72 ± 12	72 ± 12	72 ± 12	<0.001
NT-proBNP, pg/ml	2,524 (1,250, 5,296)	2,035 (1,057, 4,157)	1,866 (924, 3,655)	1615 (755, 3,245)	<0.001
hsTnI (ng/l), median (Q3)	31 (58)	29 (55)	26 (48)	23 (43)	<0.001
eGFR, ml/min/1.73 m^2	59 (44, 74)	59 (44, 75)	59 (43, 74)	58 (45, 74)	0.72

Continued on the next page

omecamtiv mecarbil by EF (interaction p = 0.004). This significant interaction persisted (p = 0.009) after further adjustment for all potential effect modifiers reported previously as pre-specified subgroups (8). In patients with EF ≤28%, there was a 16% reduction in the time-to-first heart failure event or cardiovascular death (HR: 0.84; 95% CI: 0.77-0.92; p = 0.0003) compared with no difference in patients with EF >28% (HR: 1.04; 95% CI: 0.94-1.16; p = 0.45). Analysis by quartiles of EF of the modifying effect on the primary composite endpoint (interaction p = 0.013) (**Table 2,** Supplemental Figure 3) by treatment with omecamtiv mecarbil demonstrated a 15% (HR: 0.85; 95% CI: 0.74-0.97; p = 0.016) and 17% (HR: 0.83; 95% CI: 0.73-0.95; p = 0.005) relative risk reduction in the lower 2 quartiles of EF, respectively, compared with no difference in the upper 2 quartiles. Analysis of EF as a continuous variable demonstrated a

TABLE 1 Continued

	EF ≤22% (n = 2,246)	EF 23%–28% (n = 2,210)	EF 29%–32% (n = 2,026)	EF ≥33% (n = 1,750)	p Value
Medications and cardiac devices					
ACEi, ARB, or ARNi	1,900 (85)	1,933 (88)	1,787 (88)	1,539 (88)	<0.001
ARNi	534 (24)	468 (21)	351 (17)	248 (14)	<0.001
BB	2,086 (93)	2,101 (95)	1,922 (95)	1,655 (95)	0.022
MRA	1,715 (76)	1,792 (81)	1,585 (78)	1,305 (75)	0.10
(ACEi, ARB, or ARNi) + MRA + BB	1,413 (63)	1,511 (68)	1,387 (68)	1,114 (64)	0.37
Digitalis glycosides	450 (20)	380 (17)	304 (15)	251 (14)	<0.001
SGLT2 inhibitors	64 (3)	67 (3)	44 (2)	43 (3)	0.19
Ivabradine	172 (8)	165 (8)	106 (5)	90 (5)	<0.001
Cardiac resynchronization therapy	454 (20)	321 (15)	231 (11)	152 (9)	<0.001
Implantable cardioverter-defibrillator	972 (43)	745 (34)	534 (26)	363 (21)	<0.001

Values are mean ± SD, n (%), or median (Q1, Q3), unless otherwise indicated. *Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or multiple self-identified races.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; CRT = cardiac resynchronization therapy; ED = emergency department; eGFR = estimated glomerular filtration rate; hsTnI = high-sensitivity troponin I; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MAGGIC = Meta-Analysis Global Group in Chronic HF; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; SGLT2 = sodium-glucose co-transporter 2.

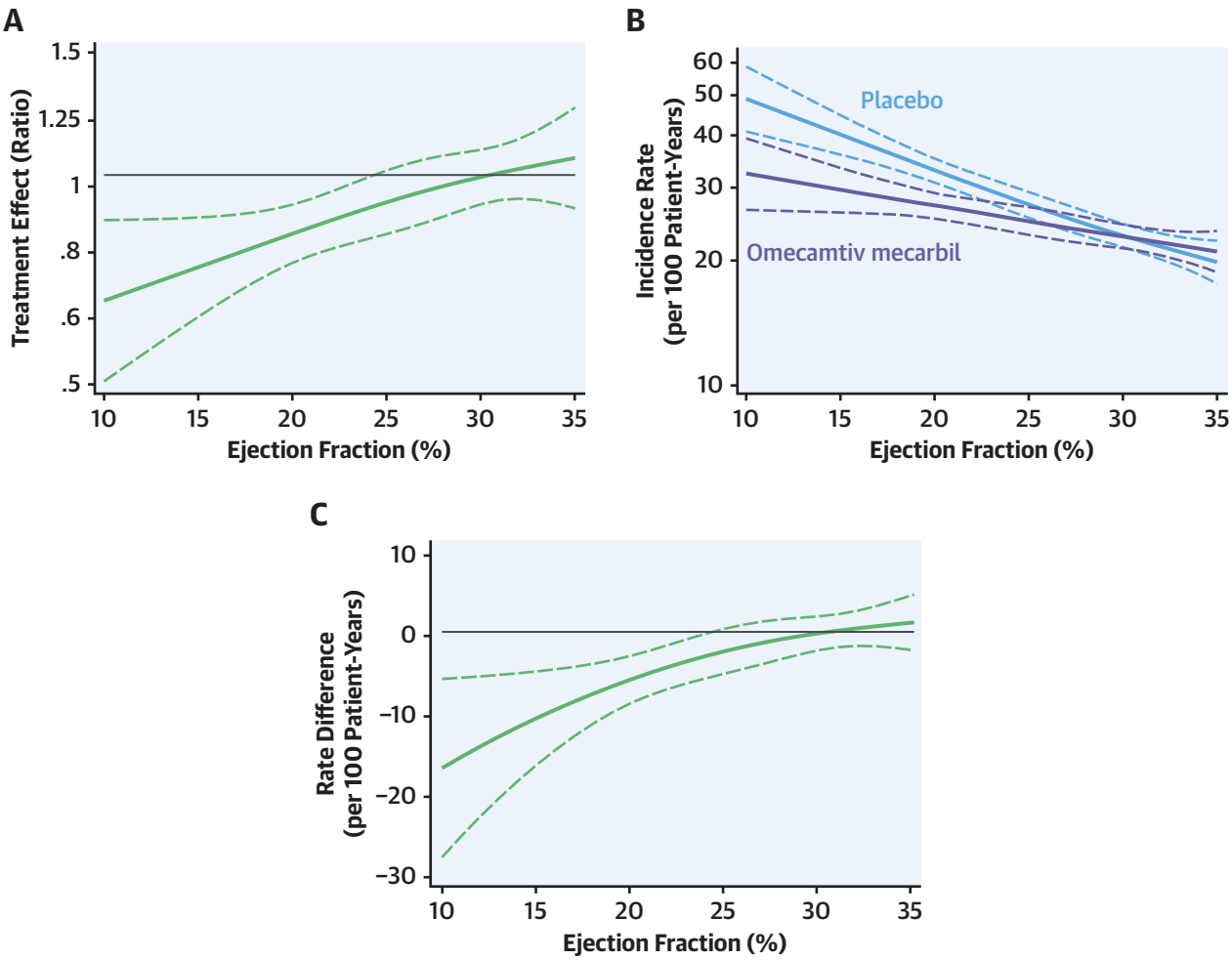
progressively larger treatment effect of omecamtiv mecarbil with decreasing EF (interaction p = 0.004) (**Central Illustration A, Table 2**). The difference in the incidence of the primary composite endpoint increased disproportionately between the placebo and omecamtiv mecarbil treatment groups with lower EFs (**Central Illustration B**), such that absolute risk reduction by omecamtiv mecarbil progressively

TABLE 2 Clinical Outcomes

	Omecamtiv Mecarbil		Placebo			
Outcome by EF Quartiles	n/N (%)	Rate (per 100 patient-yrs)	n/N (%)	Rate (per 100 patient–yrs)	HR (95% CI)	ARR (per 100 patient-yrs)
Primary outcome					Interaction p = 0.013	
EF ≥33%	298/892 (33)	20.5	280/858 (33)	20.0	0.99 (0.84–1.16)	−0.4
EF 29%–32%	375/1,015 (37)	23.8	356/1,011 (35)	22.4	1.11 (0.96–1.28)	−1.4
EF 23%–28%	393/1,086 (36)	24.0	449/1,124 (40)	27.2	0.85 (0.74–0.97)	3.3
EF ≤22%	457/1,127 (41)	28.3	522/1,119 (47)	35.6	0.83 (0.73–0.95)	7.4
First HF event					Interaction p = 0.004	
EF ≥33%	236/892 (26)	16.2	208/858 (24)	14.9	1.04 (0.86–1.25)	−1.3
EF 29%–32%	286/1,015 (28)	18.2	269/1,011 (27)	16.9	1.13 (0.96–1.33)	−1.3
EF 23%–28%	304/1,086 (28)	18.5	345/1,124 (31)	20.9	0.84 (0.72–0.98)	2.4
EF ≤22%	351/1,127 (31)	21.7	414/1,119 (37)	28.3	0.81 (0.70–0.93)	6.6
First HF hospitalization					Interaction p = 0.004	
EF ≥33%	228/892 (26)	15.5	201/858 (23)	14.3	1.03 (0.85–1.24)	−1.2
EF 29%–32%	279/1,015 (27)	17.6	251/1,011 (25)	15.5	1.19 (1.01–1.42)	−2.1
EF 23%–28%	295/1,086 (27)	17.8	327/1,124 (29)	19.6	0.86 (0.74–1.01)	1.8
EF ≤22%	340/1,127 (30)	20.9	400/1,119 (36)	26.9	0.82 (0.71–0.94)	6.1
CV death					Interaction p = 0.14	
EF ≥33%	153/892 (17)	9.0	136/858 (16)	8.4	1.06 (0.84–1.33)	−0.6
EF 29%–32%	196/1,015 (19)	10.5	162/1,011 (16)	8.5	1.26 (1.02–1.55)	−2.0
EF 23%–28%	207/1,086 (19)	10.8	235/1,124 (21)	11.8	0.88 (0.73–1.07)	1.0
EF ≤22%	252/1,127 (22)	13.0	265/1,119 (24)	14.1	0.96 (0.80–1.14)	1.1
All-cause death					Interaction p = 0.38	
EF ≥33%	200/892 (22)	11.8	189/858 (22)	11.7	0.98 (0.80–1.20)	−0.1
EF 29%–32%	260/1,015 (26)	13.9	226/1,011 (22)	11.9	1.19 (0.99–1.42)	−2.0
EF 23%–28%	278/1,086 (26)	14.4	315/1,124 (28)	15.8	0.89 (0.76–1.05)	1.4
EF ≤22%	329/1,127 (29)	17.0	335/1,119 (30)	17.8	0.98 (0.84–1.14)	0.8

CI = confidence interval; CV = cardiovascular; EF = ejection fraction; HF = heart failure; HR = hazard ratio.

CENTRAL ILLUSTRATION **Primary Composite Endpoint**



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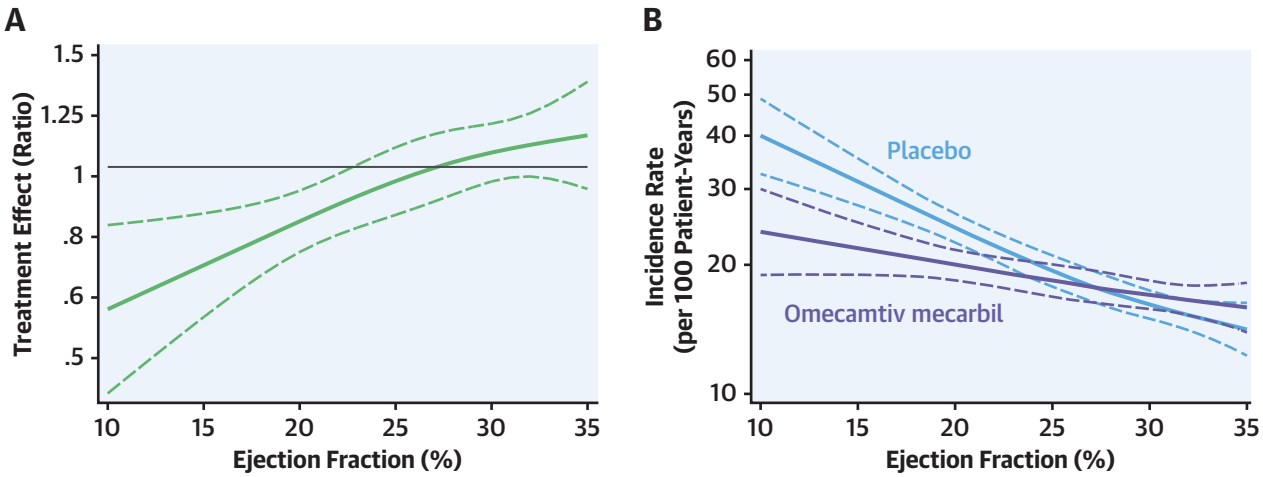
Estimates from Poisson regression models with ejection fraction expressed via restricted cubic spline **(solid line)** **(dashed line**, 95% confidence interval) demonstrated the increasing beneficial relative treatment effect of omecamtiv with decreasing ejection fraction for the primary composite endpoint of time-to-first heart failure or cardiovascular death event (interaction p = 0.004 by ejection fraction as continuous variable) **(A)**. Incidence rates **(B)** (events/100 patient-years) of primary composite endpoint increased with decreasing ejection fraction in both the placebo **(blue lines)** and omecamtiv mecarbil group **(purple lines)**. Omecamtiv mecarbil progressively increases the absolute rate reduction in the primary composite endpoint with decreasing ejection fraction **(C)**.

increased with decreasing EF (Central Illustration C). In the lowest EF quartile, omecamtiv mecarbil resulted in an absolute reduction of 7.4 events per 100 patient-years, with a number-needed-to-treat of 11.8 patients over 3 years necessary to prevent an event (Table 2), compared with no reduction in the highest EF quartile.

The beneficial effect of treatment with omecamtiv mecarbil on the primary outcome was driven predominantly by the significant reduction in heart failure events, and EF was a significant modifier of this treatment effect (interaction p = 0.004 by EF quartile, interaction p = 0.001 by EF as continuous variable) (Table 2). Ejection fraction had a similar modifying effect on the progressive reduction of heart failure hospitalizations by omecamtiv mecarbil (interaction p = 0.004 by EF quartile, interaction p = 0.001 by EF as continuous variable) (Figure 1A, Table 2). Consistent with the primary composite endpoint, the incidence rate of heart failure hospitalizations increases with decreasing EF in both the placebo and omecamtiv mecarbil-treated patients (Figure 1B), but was

FIGURE 1 Heart Failure Hospitalizations



Estimates from Poisson regression models with ejection fraction expressed via restricted cubic spline (interaction p = 0.001 by ejection fraction as continuous variable) **(solid line) (dashed line**, 95% confidence interval) demonstrated the increasing beneficial relative treatment effect of omecamtiv with decreasing ejection fraction for the time-to-first heart failure hospitalization **(A)**. Incidence rates **(B)** (events/100 patient-years) of heart failure hospitalizations increased with decreasing ejection fraction in both the placebo **(blue lines)** and omecamtiv mecarbil group **(purple lines)**.

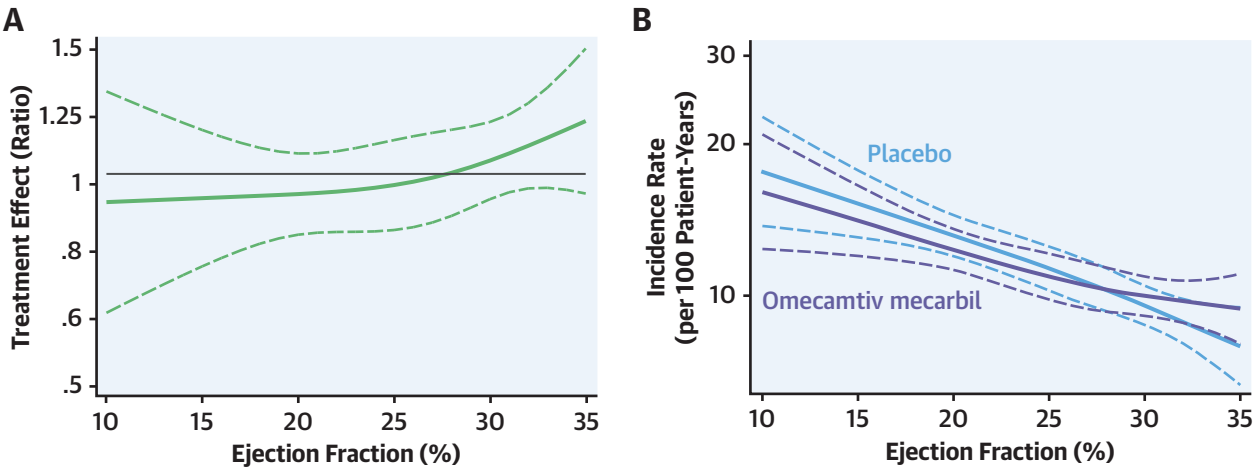
significantly affected by treatment with omecamtiv mecarbil, and showed a progressively greater reduction in the absolute difference with decreasing EF. EF significantly modified the treatment of effect of omecamtiv mecarbil on total heart failure events and hospitalizations as well (interaction p = 0.006 and p = 0.009, respectively) (Supplemental Table 4). Omecamtiv mecarbil had no overall effect on cardiovascular death, either in the overall population or as a function of baseline EF (interaction p = 0.14 by EF quartile) (**Figure 2A, Table 2**). As expected, the incidence of cardiovascular death increased comparably in both the placebo and omecamtiv mecarbil arms with decreasing EF (**Figure 2B, Table 2**). Similarly, there was no effect of omecamtiv mecarbil on all-cause mortality (**Table 2**). The proportional hazards assumption was evaluated for all HRs presented in **Table 2** via a test of Schoenfeld residuals. No significant violations were detected (all p > 0.20).

OTHER OUTCOMES AND SAFETY OF OMECAMTIV MECARBIL BY EF. Despite the reduction in heart failure events with omecamtiv mecarbil, there was no consistent beneficial effect on symptoms as a function of EF as assessed by the KCCQ-TSS in either the subjects enrolled from the inpatient or outpatient settings. However, there was a greater reduction in NT-proBNP by omecamtiv mecarbil in patients with lower EF such that the lowest EF quartile had a 22% reduction (p < 0.001), whereas the highest EF quartile showed only a 3% change (p = 0.54; interaction p < 0.001) (**Table 3**). Omecamtiv mecarbil treatment resulted in a small reduction in heart rate (treatment difference of 1.1 to 1.9 beats/min across the EF quartiles) and increase in troponin I (median 3 to 5 ng/l across the EF quartiles; limit of detection, 6 ng/l; upper reference limit 40 ng/l), which did not differ by EF quartile. There was no significant effect on systolic blood pressure, serum potassium, or creatine across the EF quartiles compared with placebo. There were also no significant differences noted in the incidence of adverse events between the omecamtiv mecarbil and placebo-treated groups, except for an apparent reduction in the incidence of adjudicated stroke for patients treated with omecamtiv mecarbil (**Table 4**).

DISCUSSION

In the GALACTIC-HF trial, selectively increasing systolic function in patients with HFrEF improved cardiovascular outcomes (primary composite endpoint HR: 0.92; p = 0.025), predominantly through reducing heart failure events (8). Given the unique mechanism of action of omecamtiv mecarbil, we investigated the influence of EF on the observed treatment effects. Omecamtiv mecarbil provided progressively greater benefit by reducing heart failure events in patients with lower baseline EF such that patients with an EF below the median (≤28%) had an 16% reduction in the primary endpoint. We also observed greater

FIGURE 2 Cardiovascular Death



Estimates from Poisson regression models with ejection fraction expressed via restricted cubic spline **(solid line) (dashed line**, 95% confidence interval) showed no relative treatment effect of omecamtiv with decreasing ejection fraction for the time-to-cardiovascular death (interaction p = 0.25 by ejection fraction as continuous variable) **(A)**. Incidence rates **(B)** (events/100 patient-years) of cardiovascular death increased with decreasing ejection fraction in both the placebo **(blue lines)** and omecamtiv mecarbil group **(purple lines)**.

reductions in NT-proBNP with decreasing EF, with a 22% reduction of NT-proBNP at week 24 in the lowest EF quartile (≤22%). Patients with EF in the lowest quartile had a relative risk reduction of 17% and an absolute risk reduction of 7.4 events per 100 patient-years (number-needed-to-treat for 3 years = 11.8) for the primary composite endpoint.

IMPROVING CARDIAC FUNCTION WITH THE MYOTROPE OMECAMTIV MECARBIL. Although multiple drugs have been developed to improve inotropy (11), omecamtiv mecarbil is the first drug to specifically increase systolic function by targeting the sarcomere without any direct vascular, electrophysiological, or neurohormonal effects and without increasing mortality. It exerts this effect by selectively binding to myosin, stabilizing its lever arm in a primed position resulting in an accumulation of cardiac myosin heads in the pre-powerstroke state prior to onset of cardiac contraction (4). This mechanism increases the number of force generators (myosin heads) that can bind to the actin filament and undergo a powerstroke once the cardiac cycle starts without altering the cardiomyocyte calcium transient. Intravenous omecamtiv mecarbil improved cardiac performance in early clinical studies (12–14), and as noted in the previous text, oral omecamtiv mecarbil increased systolic function in patients with chronic HFrEF in the COSMIC-HF trial (5,6). The GALACTIC-HF trial provided the first opportunity to evaluate the effect of improving cardiac function on outcomes in patients with HFrEF. Given its mechanism of action, there is biological plausibility to the hypothesis that patients with greater systolic dysfunction would derive greater benefit. In the pre-specified subgroup analyses, EF was the most significant variable to modify the treatment effect of omecamtiv mecarbil.

INFLUENCE OF EF ON TREATMENT EFFECTS OF OTHER DRUGS. Reviewing data from other contemporary drug trials in patients with HFrEF, the relationship between treatment effect and baseline EF has been variable. In the 11,186 patients with heart failure and an EF ≤34% in sinus rhythm evaluated in a patient-level meta-analysis of beta-blocker trials (15), beta-blocker therapy resulted in greater relative risk reductions in cardiovascular hospitalizations as well as the combined endpoint of cardiovascular hospitalizations and cardiovascular death with decreasing baseline EF. This pattern was not as evident for cardiovascular or all-cause mortality, and interestingly, there was no beneficial effect of beta-blocker therapy noted in the patients in atrial fibrillation. In analyses incorporating data from the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and PARAGON-HF (Prospective comparison of Angiotensin Receptor-

TABLE 3 Omecamtiv Mecarbil Treatment Effects from Baseline to Week 24 of Selected Vital Signs and Laboratory Values

	EF ≤22% (n = 2,246)	EF 23%-28% (n = 2,210)	EF 29%-32% (n = 2,026)	EF ≥33% (n = 1,750)	p Value
KCCQ total symptom score	+1.6 (−0.2 to +3.3)	−0.6 (−2.3 to +1.2)	+0.3 (−1.4 to +2.0)	−1.0 (−2.8 to +0.9)	0.10
Inpatient	+4.9 (+0.8 to +8.9)	+0.2 (−3.7 to +4.1)	+4.8 (+0.6 to +8.9)	−0.0 (−3.9 to +3.9)	0.33
Outpatient	+0.7 (−1.2 to +2.6)	−0.6 (−2.5 to +1.2)	−0.8 (−2.6 to +1.1)	−1.5 (−3.5 to +0.5)	0.12
Systolic BP, mm Hg	0.9 (−0.4 to 2.2)	−0.6 (−1.9 to 0.8)	−0.6 (−1.9 to 0.7)	−1.2 (−2.7 to 0.2)	0.038
Heart rate, beats/min	−1.6 (−2.5 to −0.6)	−1.7 (−2.7 to −0.8)	−1.9 (−2.9 to −0.9)	−1.1 (−2.1 to −0.1)	0.62
Potassium, mmol/l	0.01 (−0.04 to 0.05)	−0.01 (−0.06 to 0.03)	−0.01 (−0.06 to 0.03)	0.02 (−0.03 to 0.06)	0.87
Creatinine, mg/dl	−0.01 (−0.04 to 0.02)	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)	0.02 (−0.01 to 0.05)	0.22
NT-proBNP ratio	0.78 (0.71 to 0.85)	0.90 (0.83 to 0.98)	0.95 (0.87 to 1.04)	0.97 (0.89 to 1.06)	<0.001
Troponin I ratio	1.19 (1.11 to 1.27)	1.29 (1.21 to 1.38)	1.27 (1.18 to 1.36)	1.27 (1.18 to 1.37)	0.22
Troponin I, ng/l	5 (4 to 6)	4 (3 to 5)	4 (3 to 5)	3 (2 to 4)	0.055

Values represent treatment effects as evaluated by between-group differences of change from baseline to week 24 (95% confidence interval). Troponin I assay had limit of detection of 6 ng/l with an upper reference limit of 40 ng/l.

Abbreviations as in Table 1.

neprilysin inhibitor with Angiotensin receptor blocker Global Outcomes iN HF with Preserved Ejection Fraction) trials (16,17), there was no effect modification by EF on the treatment effect of sacubitril/valsartan for heart failure events or cardiovascular death in patients with EF ≤42.5%, with a trend toward less treatment benefit on total heart failure hospitalizations and cardiovascular death with decreasing baseline EF in these patients. Similarly, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, the treatment effect of dapagliflozin on the primary outcome and heart failure events in patients with an EF ≤35% mildly increased with decreasing EF, and then also had a decreasing treatment effect in patients with EF of approximately ≤18% (18). In the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, which evaluated the effect of vericiguat on patients with HFrEF and EF ≤45%, there was a decreased hazard ratio for the primary endpoint of time-to-first heart failure hospitalization or cardiovascular death in the lower 2 EF quartiles (EF 24% to 29% and EF ≤23%) (19).

DIFFERENCES IN BASELINE CHARACTERISTICS BY EF SUBGROUPS. Different baseline characteristics, defined by EF subgroup, have been noted in multiple prior heart failure studies, including the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trials (20), the beta-blocker trials (15), PARADIGM-HF (16) and DAPA-HF (18). In GALACTIC-HF, patients with lower EFs were more likely to be younger, to be men, and to have a nonischemic etiology of heart failure, whereas they were less likely to have atrial fibrillation, hypertension, or diabetes mellitus. Patients with lower EF also had indicators of more severe heart failure, such as worse NYHA functional class and MAGGIC (Meta-Analysis Global Group in Chronic HF) score, more recent pre-randomization heart failure event, greater NT-proBNP concentrations, as well as higher heart rates and lower systolic blood pressure. These characteristics typically interfere with initiation and uptitration of guideline-directed medical therapy, and as was observed in other trials, there was also an increasing risk of heart failure hospitalizations and cardiovascular death with decreasing EF in GALACTIC-HF. Thus, these severely affected patients with increasing risk are often least likely to receive or tolerate heart failure therapies.

CLINICAL IMPLICATIONS OF THE MODIFYING EFFECT OF EF IN GALACTIC-HF. In GALACTIC-HF, omecamtiv mecarbil reduced the risk of heart failure events in patients with EFs no >35%. The current analysis demonstrates that this treatment effect increases with decreasing EF and suggests that patients with EFs approximately ≤30% are most likely to benefit from this therapy. Additional analyses will need to be performed to identify the patients with EFs >30% who may also derive benefit. Although omecamtiv mecarbil did not reduce cardiovascular death, consistent with the overall findings in GALACTIC-HF, omecamtiv mecarbil had no adverse effect on blood pressure, heart rate, potassium homeostasis, or renal function when assessed by EF quartile. The small reduction in heart rate, believed to be due to the secondary effect of sympathetic withdrawal, was consistent across the EF groups. As noted in prior trials, a minor increase in troponin I was noted across EF subgroups with no modifying effect by EF; however, there was no evidence of adverse clinical consequences (5,14). There was no difference in the relative risk of treatment for emergent adverse

TABLE 4 Other Outcomes and Adverse Events of Special Interest

Safety Outcomes	EF ≤22% (n = 2,246)	EF 23%–28% (n = 2,210)	EF 29%–32% (n = 2,026)	EF ≥33% (n = 1,750)
Any treatment emergent serious adverse events				
Omecamtiv mecarbil	683 (60.7)	616 (56.9)	579 (57.3)	495 (55.5)
Placebo	719 (64.6)	666 (59.3)	585 (58.0)	465 (54.3)
Relative risk (95% CI)	0.94 (0.88–1.00)	0.96 (0.89–1.03)	0.99 (0.92–1.07)	1.02 (0.94–1.11)
Adverse event: ventricular tachyarrhythmia				
Omecamtiv mecarbil	97 (9.8)	80 (8.3)	62 (6.9)	51 (6.4)
Placebo	99 (9.8)	85 (8.5)	65 (7.2)	55 (7.3)
Relative risk (95% CI)	1.00 (0.76–1.30)	0.98 (0.73–1.31)	0.96 (0.69–1.34)	0.88 (0.61–1.27)
Serious adverse event: ventricular arrhythmia requiring treatment				
Omecamtiv mecarbil	41 (3.6)	35 (3.2)	21 (2.1)	22 (2.5)
Placebo	46 (4.1)	35 (3.1)	27 (2.7)	19 (2.2)
Relative risk (95% CI)	0.88 (0.58–1.33)	1.04 (0.65–1.65)	0.78 (0.44–1.37)	1.11 (0.61–2.04)
Adjudicated first major cardiac ischemic events				
Omecamtiv mecarbil	54 (4.8)	47 (4.3)	41 (4.1)	58 (6.5)
Placebo	45 (4.0)	49 (4.4)	38 (3.8)	56 (6.5)
Relative risk (95% CI)	1.19 (0.81–1.75)	1.00 (0.67–1.47)	1.08 (0.70–1.66)	0.99 (0.70–1.42)
Positively adjudicated myocardial infarction				
Omecamtiv mecarbil	37 (3.3)	29 (2.7)	22 (2.2)	34 (3.8)
Placebo	30 (2.7)	34 (3.0)	22 (2.2)	32 (3.7)
Relative risk (95% CI)	1.22 (0.76–1.96)	0.89 (0.54–1.44)	1.00 (0.56–1.79)	1.02 (0.64–1.64)
Adjudicated first stroke				
Omecamtiv mecarbil	17 (1.5)	19 (1.8)	24 (2.4)	16 (1.8)
Placebo	26 (2.3)	37 (3.3)	29 (2.9)	20 (2.3)
Relative risk (95% CI)	0.65 (0.35–1.18)	0.53 (0.31–0.92)	0.83 (0.48–1.41)	0.77 (0.40–1.47)

Values are n (%) unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

events, tachyarrhythmias, or cardiac ischemic events compared with placebo. Thus, therapy with omecamtiv mecarbil could be initiated in appropriate patients at any time in their clinical course without interfering with the initiation or up-titration of life-saving guideline directed medical therapy.

STUDY LIMITATIONS. Although the analysis of GALACTIC-HF by EF was pre-specified, subgroup analyses have inherent limitations. Many subgroup analyses have limited sample sizes and number of events. The evaluation of EF by quartiles in the current analysis has subgroups of approximately 2,000 patients with 578 to 979 events in each quartile, subgroups in themselves larger than many studies. These investigations are supported by analyses of EF as a continuous variable incorporating the data from all 8,232 patients. Although the statistical analysis plan from GALACTIC-HF pre-specified multiple subgroups for evaluation and is subject to issues related to multiplicity testing, the univariate interaction p value for the treatment-covariate interaction was 0.004 and was 0.009 after adjustment for all other pre-specified subgroups, making it highly unlikely to be due to chance. In addition, there is biological plausibility for this effect modification, and the findings are internally consistent. Other potential limitations are that the EF was the investigator-reported, the most recent value within 12 months prior to randomization, and it was not measured by a core laboratory or immediately prior to randomization. Although this approach is more consistent with clinical practice, where EFs are measured in response to specific clinical events, there is the possibility that the reported EF is not reflective of the baseline EF at the time of enrollment. To mitigate this possibility, investigators were instructed to repeat the measurement if there had been an intervening event that might have changed its value. This analysis only assesses the influence of 1 variable, the baseline EF, on

the treatment effect of omecamtiv mecarbil. Clearly, other baseline characteristics can influence the response to a therapy in patients with HFrEF. As noted in the previous text, in the large analysis of patients with heart failure treated with beta-blockers, patients with atrial fibrillation at baseline had minimal to no beneficial clinical effect regardless of baseline EF (15). Similarly, other comorbidities or markers of disease severity may modify the treatment effect of omecamtiv mecarbil.

CONCLUSIONS

In GALACTIC-HF, treatment with omecamtiv mecarbil was associated with greater reductions in heart failure events in patients with lower baseline EF. Combined with the high risk of heart failure events in these patients, patients treated with omecamtiv mecarbil displayed an even greater relative treatment effect and a progressively larger absolute risk reduction for the primary composite endpoint of heart failure events and cardiovascular death with lower baseline EF. These findings support the concept that patients with more severe heart failure derive greater clinical benefit from cardiac myosin activator therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: In patients with left ventricular EF ≤35% receiving guideline-directed therapy, those with more severe ventricular systolic dysfunction exhibit the greatest reductions in heart failure hospitalization or cardiovascular death during treatment with the cardiac myosin activator omecamtiv mecarbil.

TRANSLATIONAL OUTLOOK: Further analyses could identify patient characteristics other than EF that are associated with greater clinical responsiveness to omecamtiv mecarbil and define its place in the optimum sequence of pharmacological interventions for patients with HFrEF of various etiologies.

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KEY WORDS cardiovascular outcomes trial, heart failure with reduced ejection fraction, myotrope

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