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Impact of Ejection Fraction on the Therapeutic Effect of Omecamtiv Mecarbil in Patients with Heart Failure and Reduced Ejection Fraction: A Secondary Analysis From GALACTIC-HF

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Disclosures

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Background

GALACTIC-HF

- Omecamtiv mecarbil (OM)[1] is a novel, selective cardiac myosin activator ("myotrope"[2]) that improves cardiac structure/function and decreases heart rate and NT-proBNP in patients with Heart Failure and reduced Ejection Fraction (HFrEF)[3,4]
- In the GALACTIC-HF trial,[5] omecamtiv mecarbil improved the primary endpoint of heart failure events or cardiovascular death in patients with Heart Failure and reduced Ejection Fraction (EF ≤35%)

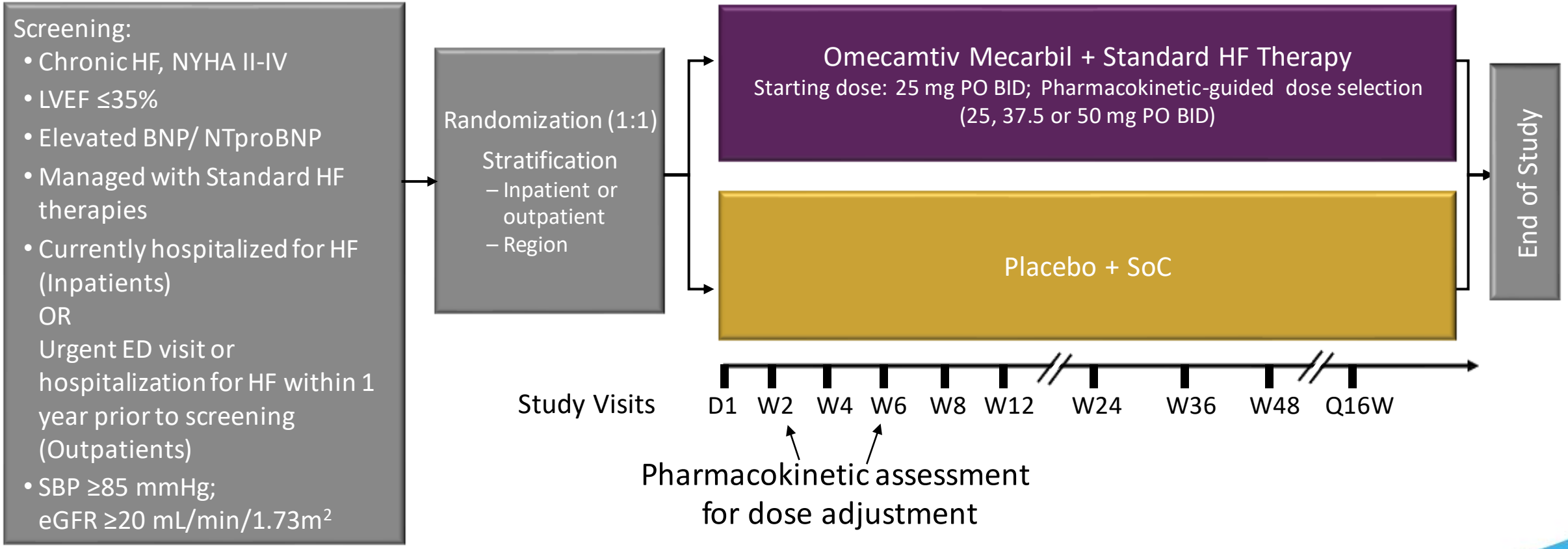
Analysis Question: Does the baseline Ejection Fraction (EF) modify the treatment effect of omecamtiv mecarbil?

[1]Malik FI, *et al. Science* 2011;331:1439–43; [2]Psotka MA, *et al. J Am Coll Cardiol* 2019;73:2345–53; [3]Teerlink JR, *et al. Lancet* 2016;388:2895–2903; [4]Teerlink JR, *et al. JACC Heart Fail* 2020;8:329–40; [5]Teerlink JR, *et al. N Engl J Med* 2021;384:105-116.

Trial Design

GALACTIC-HF

Hypothesis: Selectively improving cardiac function with the cardiac myosin activator, omecamtiv mecarbil, will improve clinical outcomes in patients with HFrEF



Multicenter, international, randomized, double-blind, placebo-controlled, event-driven Phase 3 study

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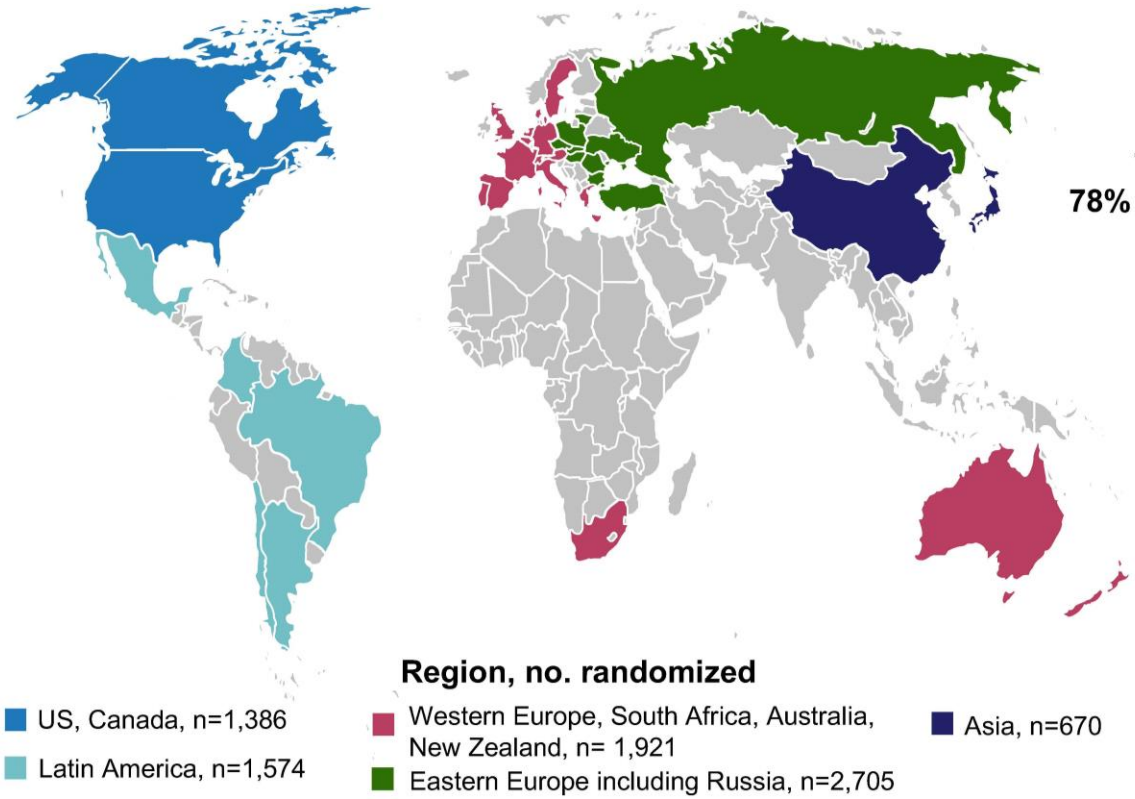
Teerlink JR, et al. *JACC Heart Fail* 2020;8:329–40.

Baseline Characteristics

GALACTIC-HF

Enrolled 8,256 Patients With HFrEF



Baseline Characteristics

79% Male, 21% Female,
78% White, 9% Asian, 7% Black,
65 yr mean age

25% Inpatient

27% Mean EF,
53% NYHA Class II,
47% NYHA Class III/IV

1971 pg/mL
median NT-proBNP,
117 mmHg mean SBP

87% ACEI/ARB/ARNi
(19% ARNi),
94% BB, 77% MRA

14% CRT and 32% ICD

Only one patient lost-to-follow-up for vital status

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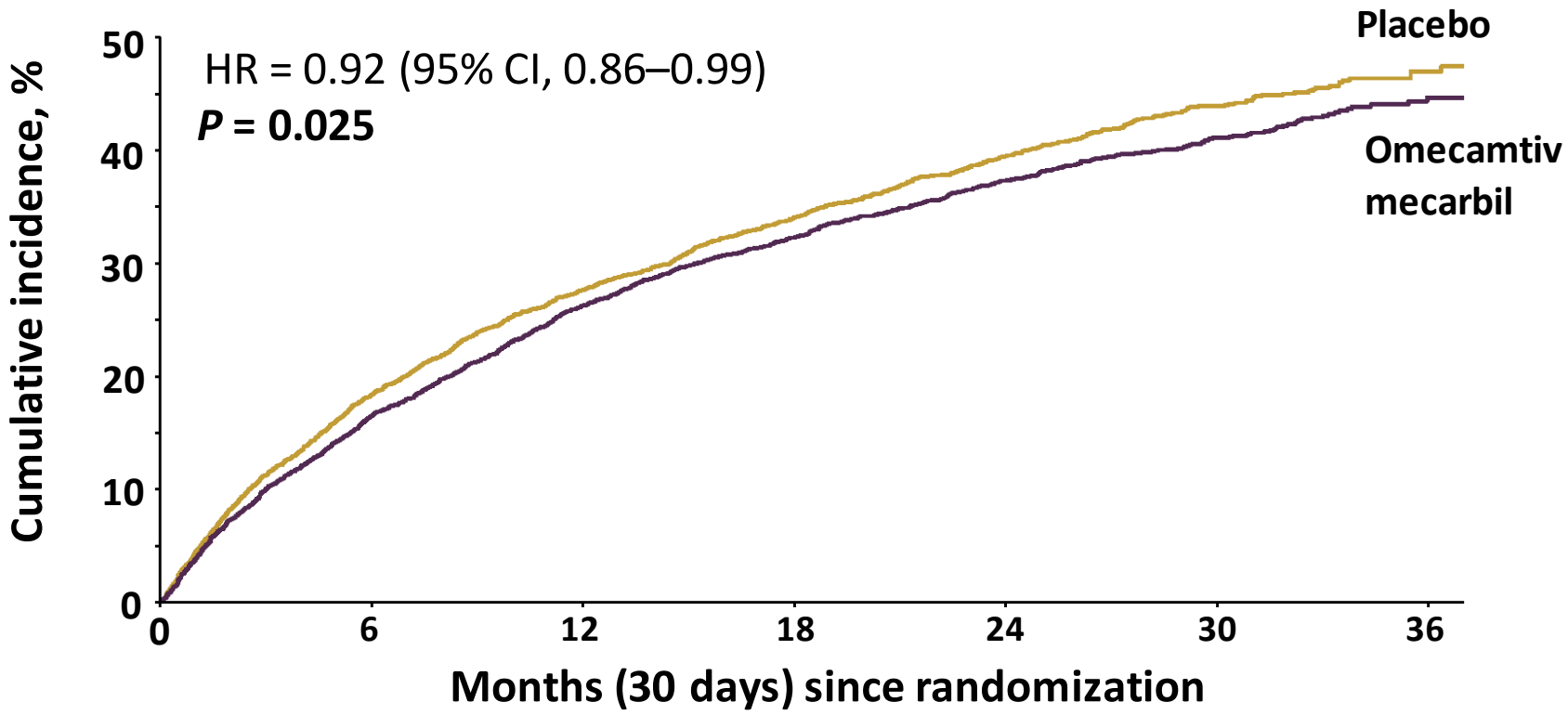
Teerlink JR, *et al. Eur J Heart Fail* 2020;22:2160-2171.

Primary Composite Endpoint

Time to First Heart Failure Event or Cardiovascular Death



Patients at risk, n							
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

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Teerlink JR, *et al. N Engl J Med* 2021;384:105-116.

Primary Outcome: Subgroup Results

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Subgroup	Hazard Ratio (95% CI)
Overall	0.92 (0.86, 0.99)
Randomization Setting	
Inpatient	0.89 (0.78, 1.01)
Outpatient	0.94 (0.86, 1.02)
Region	
Asia	0.80 (0.61, 1.05)
E. Europe with Russia	0.90 (0.80, 1.02)
Latin America	0.90 (0.75, 1.07)
US and Canada	0.85 (0.73, 0.99)
W. Europe, South Africa, and AUS	
Age	
< 65	
≥ 65	
Sex	
Female	
Male	
Race	
Asian	
Black or African American	
White	
Other	
Baseline NYHA Class	
II	
III/IV	0.88 (0.80, 0.97)
Diabetes at baseline	
No	0.91 (0.83, 1.01)
Yes	0.93 (0.84, 1.03)
Primary cause of HF	
Ischemic	0.90 (0.82, 0.98)
Non−ischemic	0.96 (0.86, 1.07)
History of MI	
No	0.93 (0.85, 1.03)
Yes	0.91 (0.83, 1.01)
Presence of Atrial fib/flutter	
No	0.86 (0.79, 0.94)
Yes	1.05 (0.93, 1.18)

0.5 0.7 0.9 1.0 1.1 1.3 1.5 1.7

Favors OM Favors Placebo

Subgroup	Hazard Ratio (95% CI)
Baseline LVEF	
≤ median (28%)	0.84 (0.77, 0.92)
> median (28%)	1.04 (0.94, 1.16)
Baseline NT−proBNP (excl. Afib)	
Inpatient + ≤ Median	0.97 (0.74, 1.28)
Inpatient + > Median	0.75 (0.61, 0.92)
Outpatient + ≤ Median	0.88 (0.73, 1.05)
Outpatient + > Median	0.85 (0.75, 0.97)
	0.91 (0.82, 1.01)
	0.93 (0.85, 1.03)
	0.90 (0.82, 0.99)
	0.95 (0.85, 1.05)
	0.98 (0.89, 1.07)
	0.84 (0.75, 0.94)
	0.94 (0.85, 1.03)
	0.90 (0.81, 1.00)
	0.91 (0.85, 0.99)
Yes	0.97 (0.83, 1.15)
Baseline use of MRA	
No	0.98 (0.85, 1.12)
Yes	0.91 (0.83, 0.98)
Baseline use of ARNi	
No	0.91 (0.84, 0.99)
Yes	0.97 (0.83, 1.13)
Baseline presence of CRT	
No	0.93 (0.86, 1.01)
Yes	0.84 (0.72, 0.99)
Baseline presence of ICD	
No	0.94 (0.86, 1.03)
Yes	0.88 (0.78, 0.98)

0.5 0.7 0.9 1.0 1.1 1.3 1.5 1.7

Favors OM Favors Placebo

Baseline LVEF

≤ median (28%)	0.84 (0.77, 0.92)
> median (28%)	1.04 (0.94, 1.16)

0.7 1.0 1.3

Interaction *P*-value = 0.003

Teerlink JR, *et al. N Engl J Med* 2021;384:105-116.

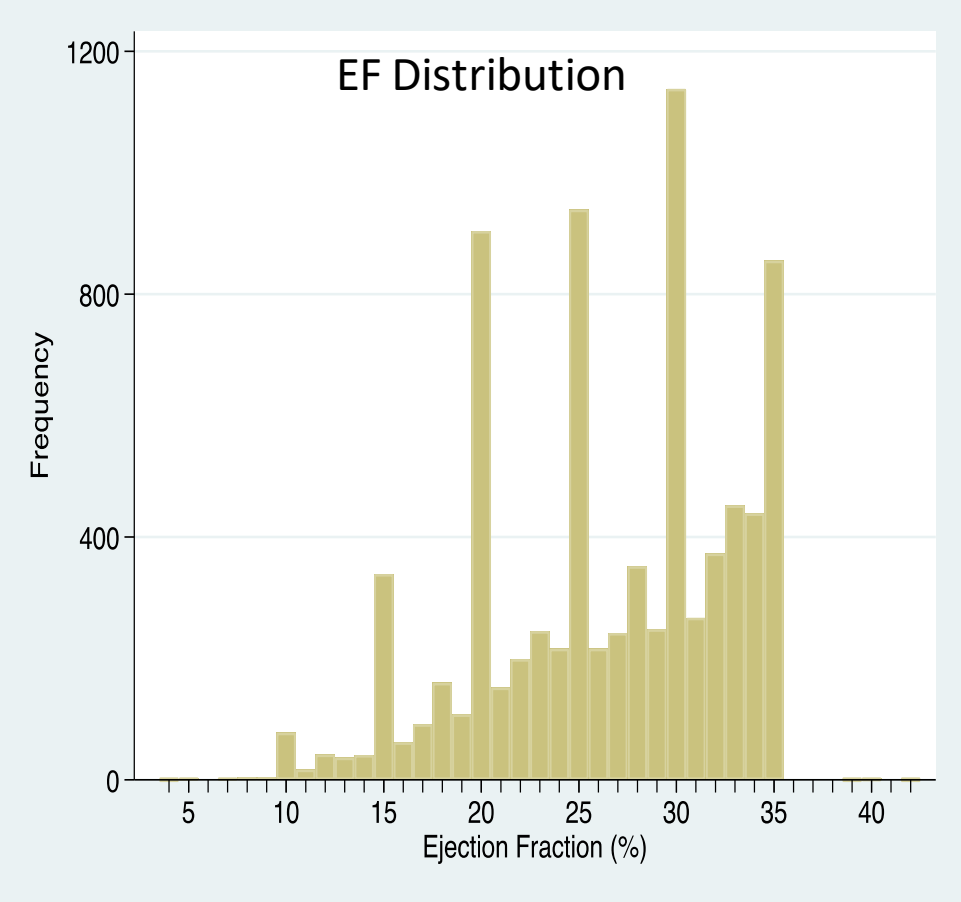
Baseline Ejection Fraction

GALACTIC-HF

Ejection Fraction (EF) ≤35%

- Most recent within 12 months
- ≥30 days after:
  1) Event likely to decrease EF (e.g., myocardial infarction, sepsis); or
  2) Intervention likely to increase EF (e.g., cardiac resynchronization therapy, coronary revascularization); or
  3) First ever presentation for HF.

>97% Baseline EFs from Echocardiograms
>70% Baseline EF's ≤30%



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Baseline Characteristics by EF Quartile (1)

GALACTIC-HF

Demographics	Q1: EF ≤22% (N=2246)	Q4: EF ≥33% (N=1750)	P-Value
Age (years), mean±SD	62.5 ± 12 ↓	66.4 ± 11	**<0.001**
Sex, female, n (%)	422 (19) ↓	421 (24)	**<0.001**
Race, n (%)			**<0.001**
Asian	171 (8)	136 (8)	
Black	243 (11) ↑	68 (4)	
Other*	200 (9) ↑	83 (5)	
White	1632 (73) ↓	1463 (84)	
Region, n (%)			**<0.001**
Asia	152 (7)	130 (7)	
Eastern Europe/ Russia	476 (21) ↓	805 (46)	
Latin and South America	438 (20) ↑	268 (15)	
US and Canada	581 (26) ↑	205 (12)	
Western Europe/ South Africa/ Australasia	599 (27) ↑	342 (20)	

Medical Conditions, n (%)	Q1: EF ≤22% (N=2246)	Q4: EF ≥33% (N=1750)	P-Value
Coronary artery disease	1267 (56) ↓	1218 (70)	**<0.001**
Atrial Fib/ Flutter (Screen)	547 (24) ↓	528 (30)	**<0.001**
Hypertension	1431 (64) ↓	1367 (78)	**<0.001**
Type 2 diabetes mellitus	869 (39) ↓	743 (43)	**<0.001**

Heart Failure History	Q1: EF ≤22% (N=2246)	Q4: EF ≥33% (N=1750)	P-Value
LVEF (%), median [Q1, Q3]	20 [15, 20]	34 [33, 35]	N/A
Time from last HF Hosp. (months; median [Q1,Q3]	3.0 [1.6, 5.9]	3.6 [1.6, 6.9]	**0.043**
MAGGIC Score, median (Q1, Q3)	25 [21, 30] ↑	21 [17, 25]	**<0.001**
NYHA III/IV, n (%)	1086 (48)	791 (45)	**0.016**
Ischemic HF etiology, n (%)	1033 (46) ↓	1088 (62)	**<0.001**
KCCQ TSS, median [Q1,Q3]	69 [48, 88]	69 [49, 85]	0.77

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Baseline Characteristics by EF Quartile (2)

GALACTIC-HF

Vitals and Laboratory Parameters	Q1: EF ≤22% (N=2246)	Q4: EF ≥33% (N=1750)	P-Value
Body mass index (kg/m^2), mean (SD)	27.9 (6.3) ↓	29.1 (6.1)	**<0.001**
SBP (mmHg), mean (SD)	112 (15) ↓	121 (14)	**<0.001**
Heart rate (beats/min), mean (SD)	74 (12) ↑	72 (12)	**<0.001**
NT-proBNP (pg/mL), median [Q1-Q3]	2524 ↑ [1250, 5296]	1615 [755, 3245]	**<0.001**
hsTnI (ng/L), median [Q3]	31 [58] ↑	23 [43]	**<0.001**
eGFR (mL/min/1.73m^2), median [Q1,Q3]	59 [44, 74]	58 [45, 74]	0.72

Medications and Cardiac Devices, n (%)	Q1: EF ≤22% (N=2246)	Q4: EF ≥33% (N=1750)	P-Value
ACEi, ARB or ARNi	1900 (85) ↓	1539 (88)	**<0.001**
ARNi	534 (24) ↑	248 (14)	**<0.001**
BB	2086 (93)	1655 (95)	**0.022**
MRA	1715 (76)	1305 (75)	0.10
(ACEi, ARB, or ARNi) + MRA + BB	1413 (63)	1114 (64)	0.37
Digitalis Glycosides	450 (20) ↑	251 (14)	**<0.001**
SGLT2 Inhibitors	64 (3)	43 (3)	0.19
Ivabradine	172 (8) ↑	90 (5)	**<0.001**
Cardiac Resynchronization Therapy	454 (20) ↑	152 (9)	**<0.001**
Implantable Cardioverter Defibrillator	972 (43) ↑	363 (21)	**<0.001**

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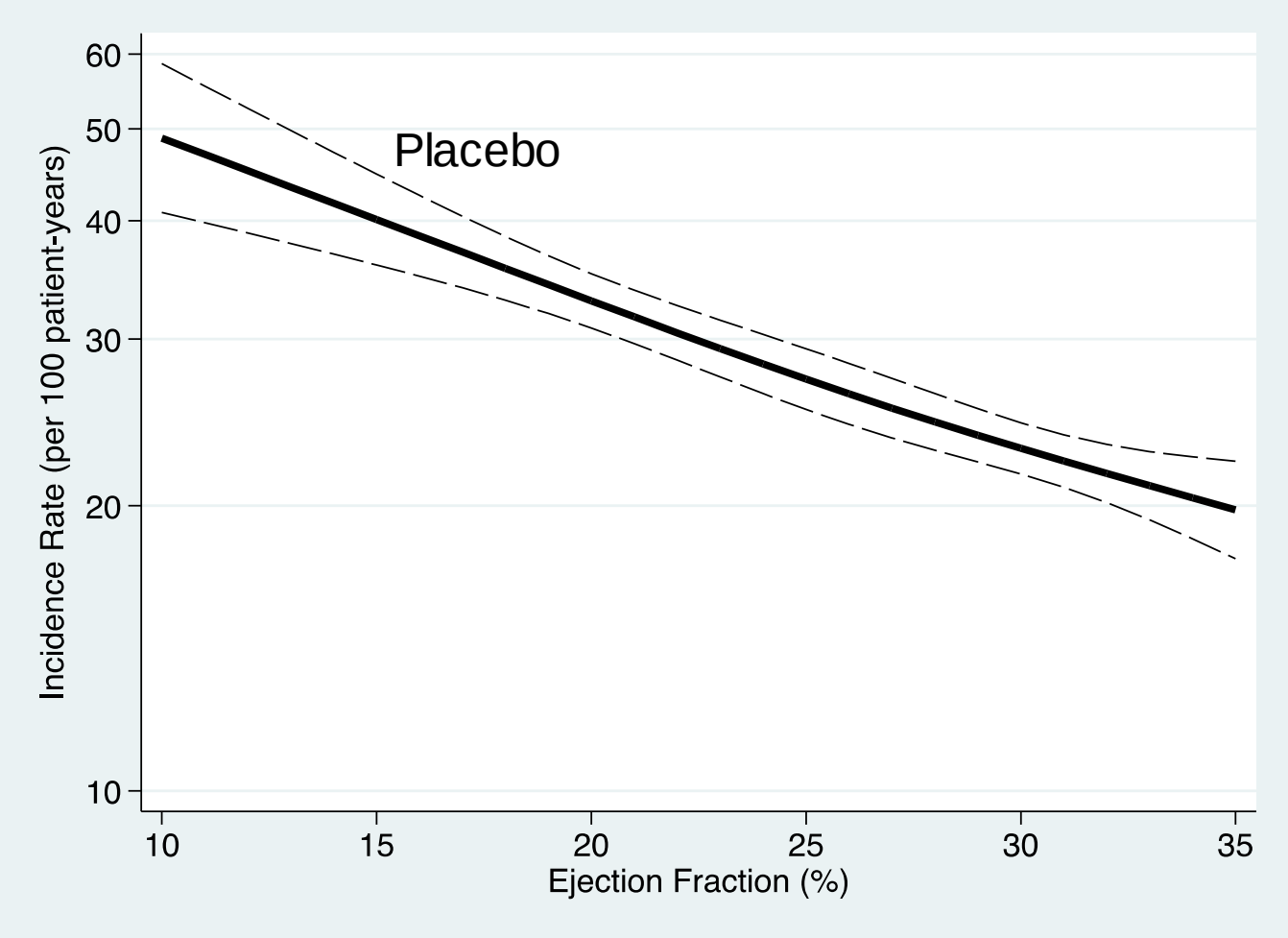
Incidence of Primary Composite Endpoint in Treatment Groups by Baseline Ejection Fraction

GALACTIC-HF



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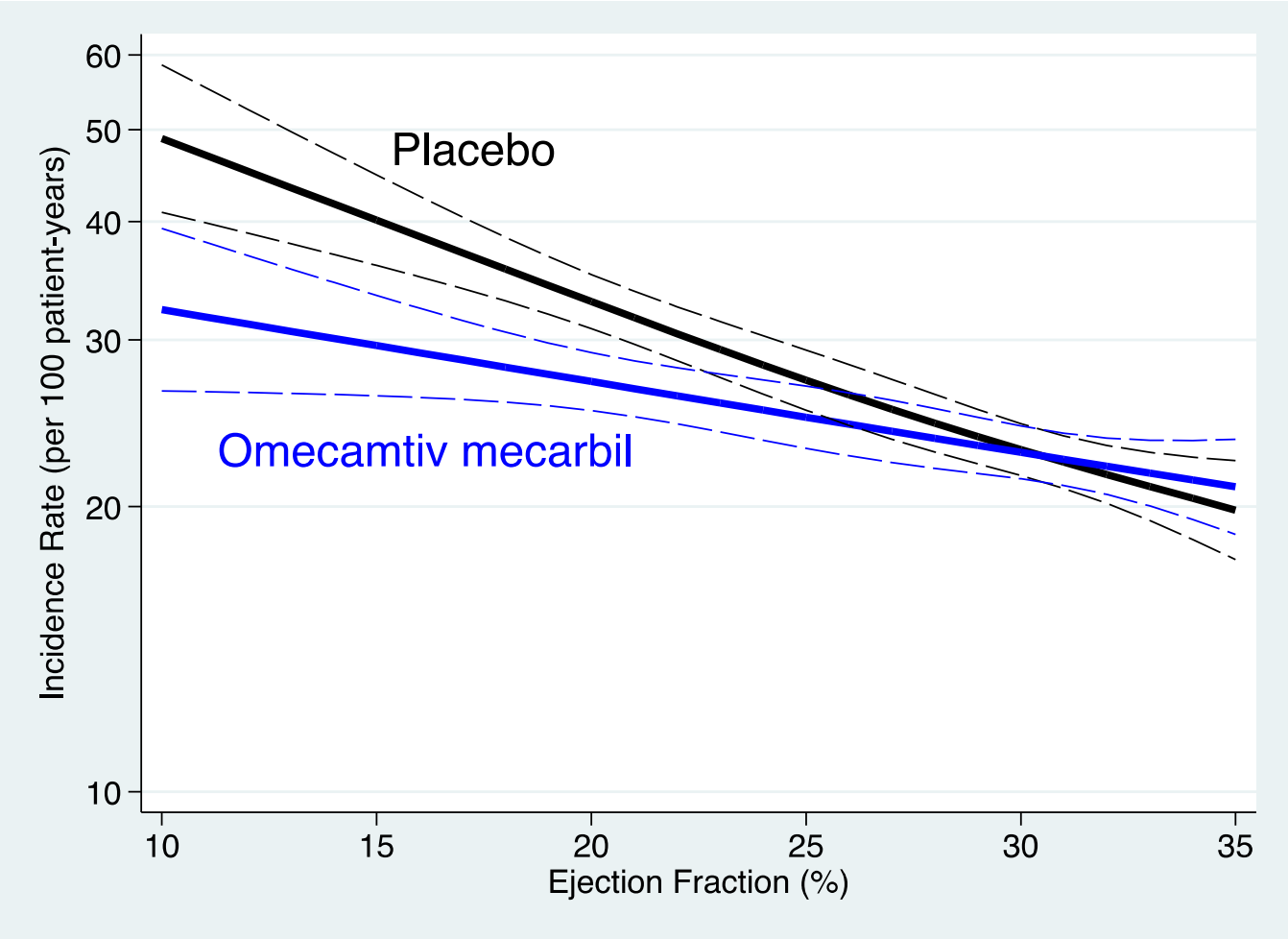

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Incidence of Primary Composite Endpoint in Treatment Groups by Baseline Ejection Fraction

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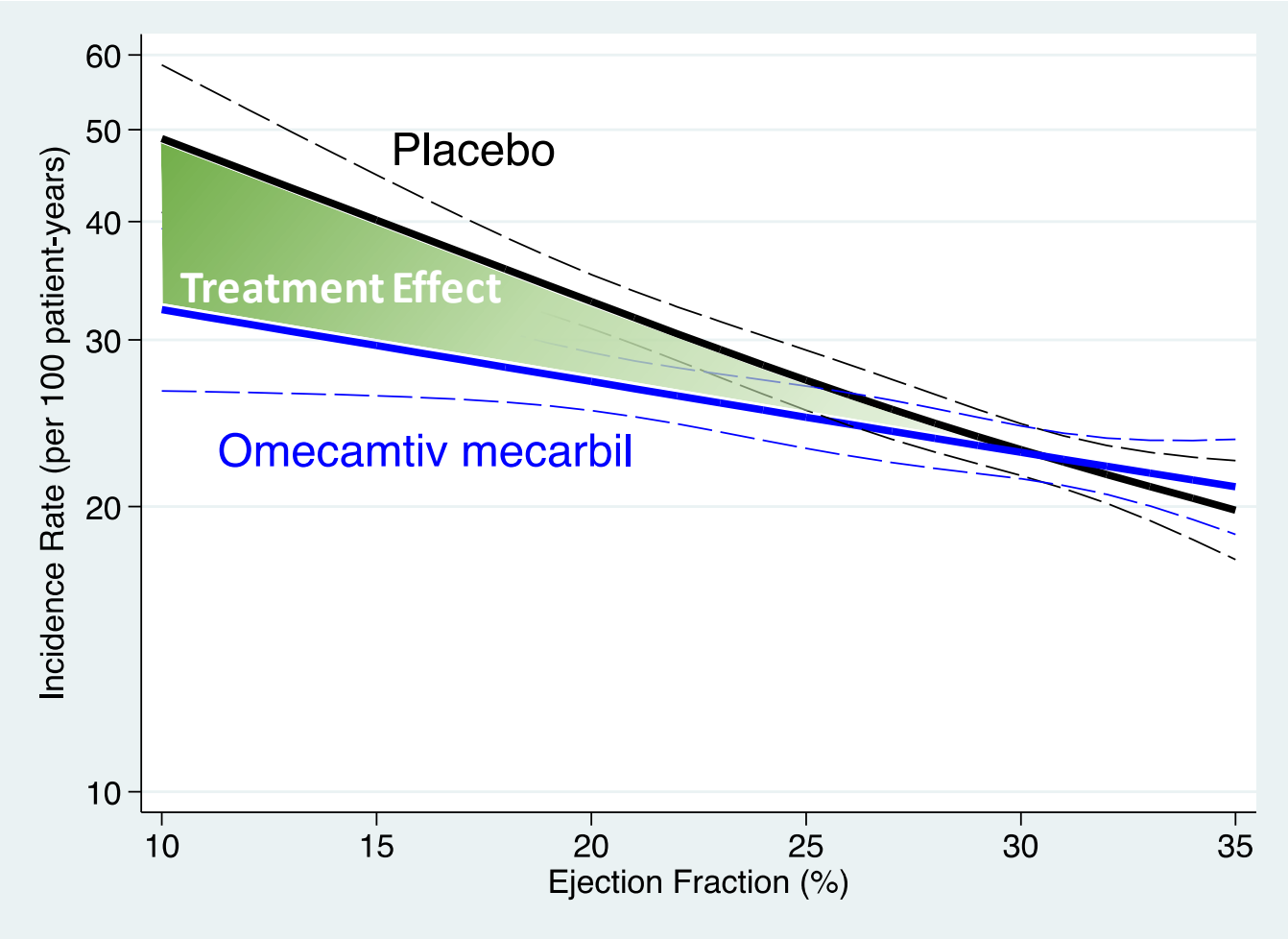

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Absolute and Relative Treatment Effect of Omecamtiv Mecarbil Compared to Placebo on Primary Composite Endpoint

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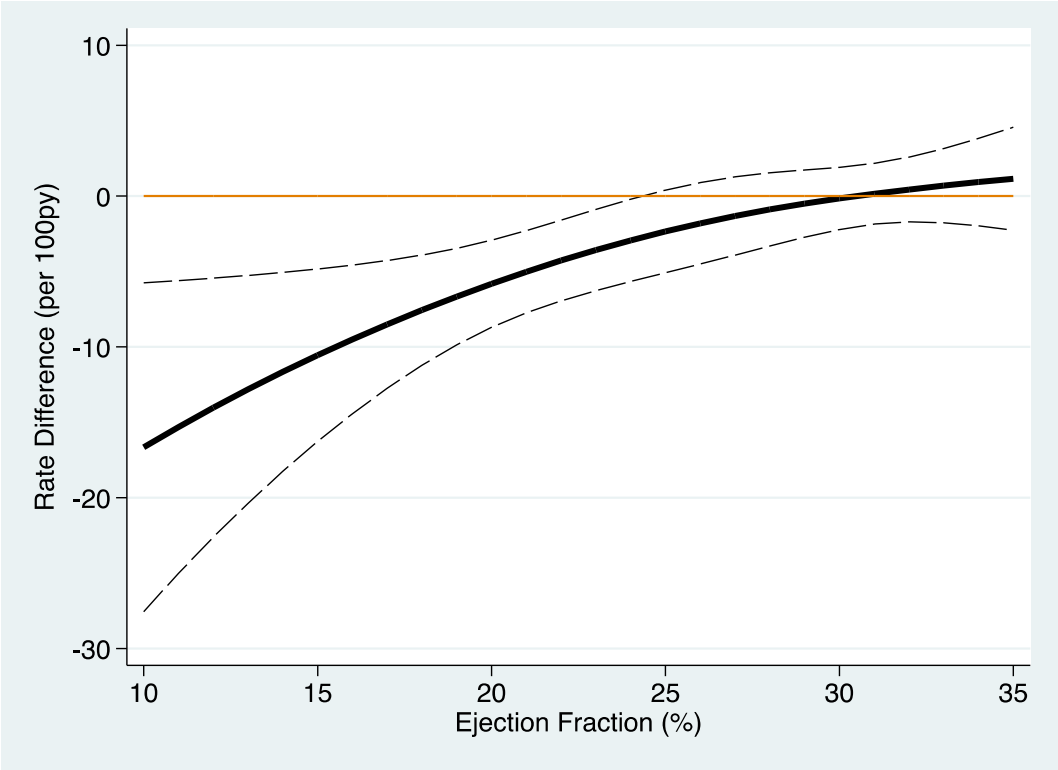
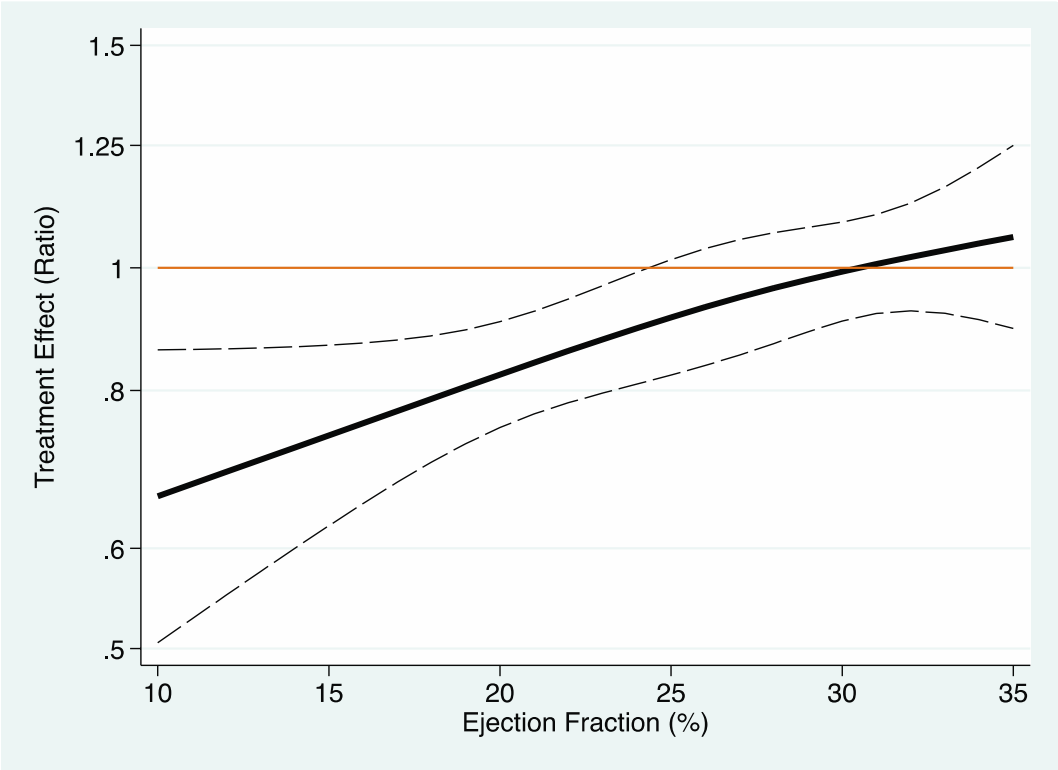
Incidence Rate Difference



Treatment Effect



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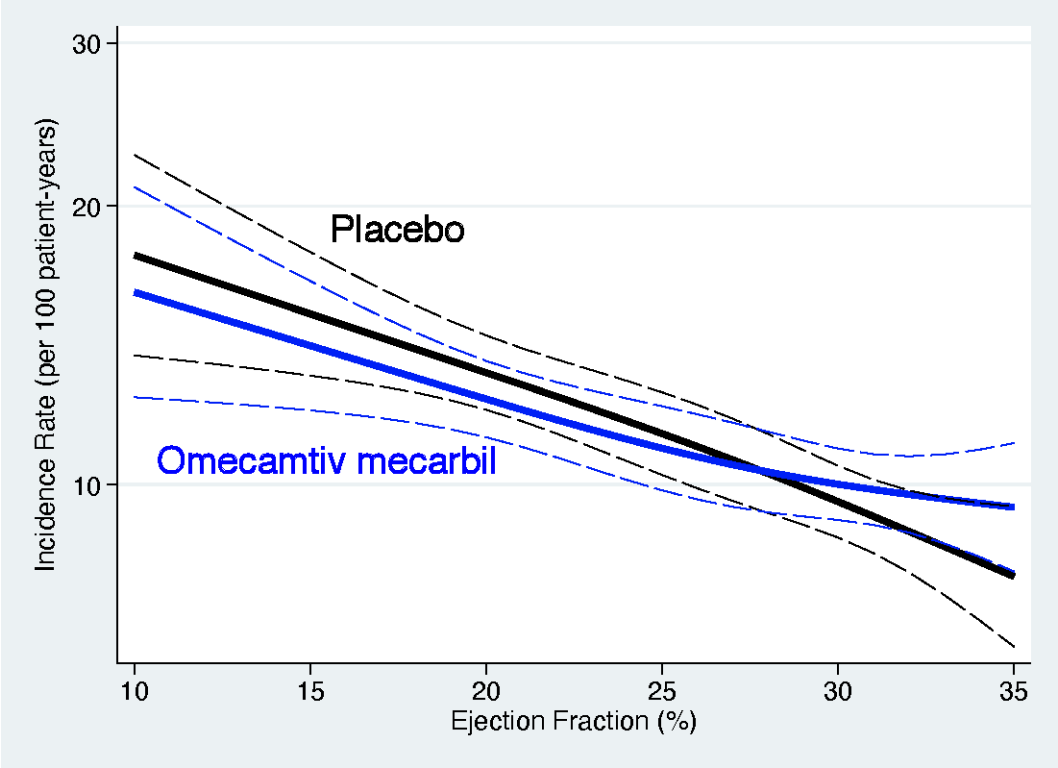
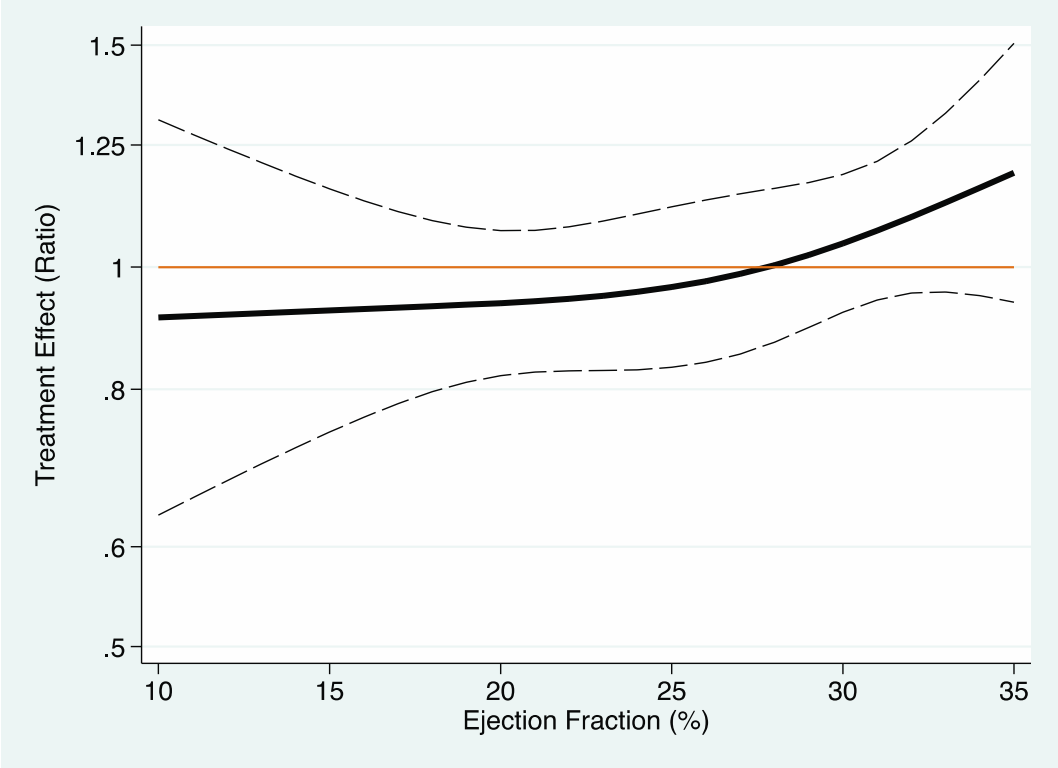
Absolute and Relative Treatment Effect of Omecamtiv Mecarbil Compared to Placebo on Cardiovascular Death

GALACTIC-HF

Incidence Rate



Treatment Effect



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Other Variables of Interest

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For Omecamtiv Mecarbil compared to Placebo:

- No significant difference in Systolic BP, Serum potassium, or Creatinine.
- Heart rate was significantly and similarly less in every EF quartile.
- NT-proBNP progressively decreased with decreasing EF.
- Troponin was minimally increased in every EF quartile.
- Serious Adverse Events and Adjudicated Arrhythmic and Ischemic Events were similar.

Treatment Difference at 24 Weeks (95% CI)	Q1: EF ≤22% (N=2246)	...	Q4: EF ≥33% (N=1750)	p-Value
Systolic BP (mmHg)	0.9 (-0.4, 2.2)		-1.2 (-2.7, 0.2)	0.038
Heart rate (bpm)	-1.6 (-2.5, -0.6)		-1.1 (-2.1, -0.1)	0.62
Potassium (mmol/L)	0.0 (-0.04, 0.05)		0.0 (-0.03, 0.06)	0.87
Creatinine (mg/dl)	0.0 (-0.04, 0.02)		0.0 (-0.01, 0.05)	0.22
NT-proBNP (Ratio)	0.78 (0.71, 0.85)		0.97 (0.89, 1.06)	<0.001
Troponin I (Ratio)	1.19 (1.11, 1.27)		1.27 (1.18, 1.37)	0.22
Troponin I (ng/L)	5 (4, 6)		3 (2, 4)	0.055

Conclusions

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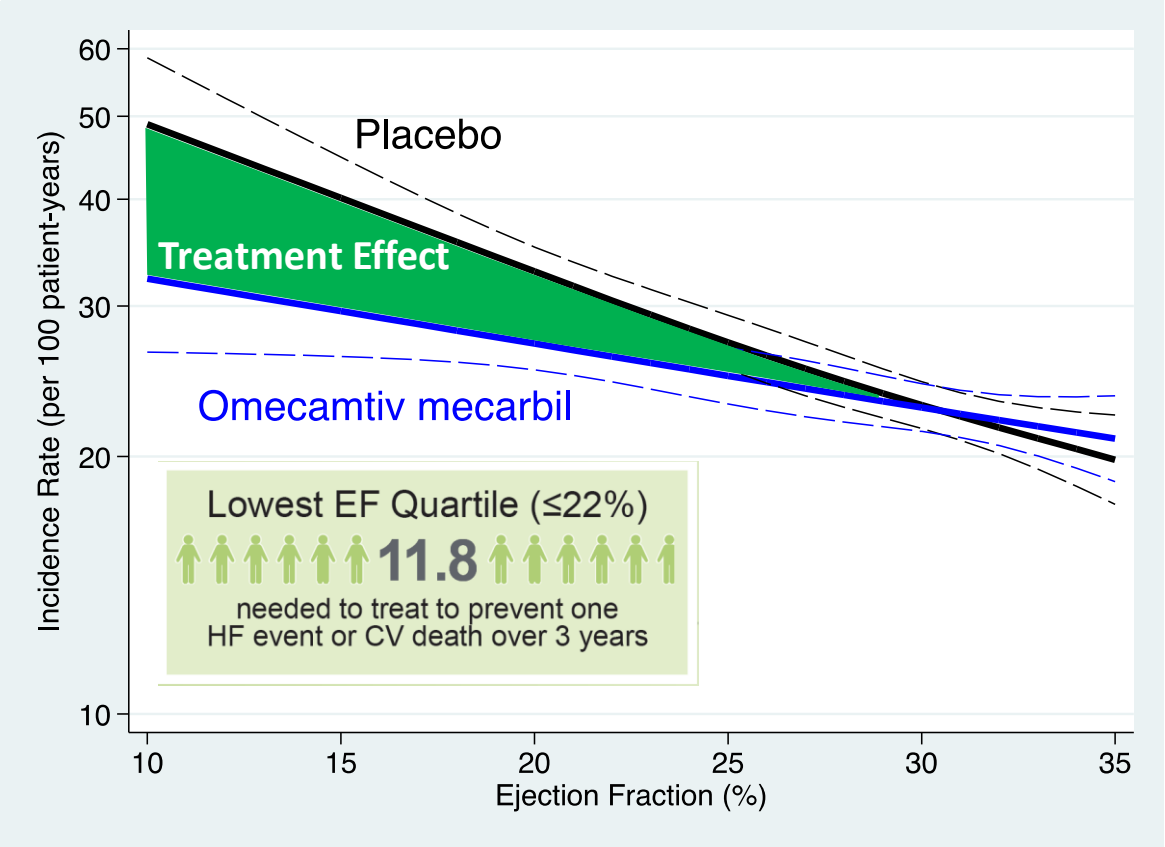
- In patients with HFrEF, omecamtiv mecarbil reduced the 1° composite outcome (first HF event or CV death)
- The treatment effect of omecamtiv mecarbil increased with decreasing EF
- There was no difference in Serious Adverse, Ischemic or Arrhythmic Events compared to Placebo across the range of EF
- There was no adverse effect on blood pressure, heart rate, potassium homeostasis or renal function



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ORIGINAL INVESTIGATIONS

GALACTIC-HF

Effect of Ejection Fraction on Clinical Outcomes in Patients treated with Omecamtiv Mecarbil in GALACTIC-HF

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945 Site Investigators in 35 Countries!!

Thank you!

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