GALACTIC-HF

Effects of Omecamtiv Mecarbil in Patients with HFrEF and Low Blood Pressure: Results from GALACTIC-HF

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Disclosures

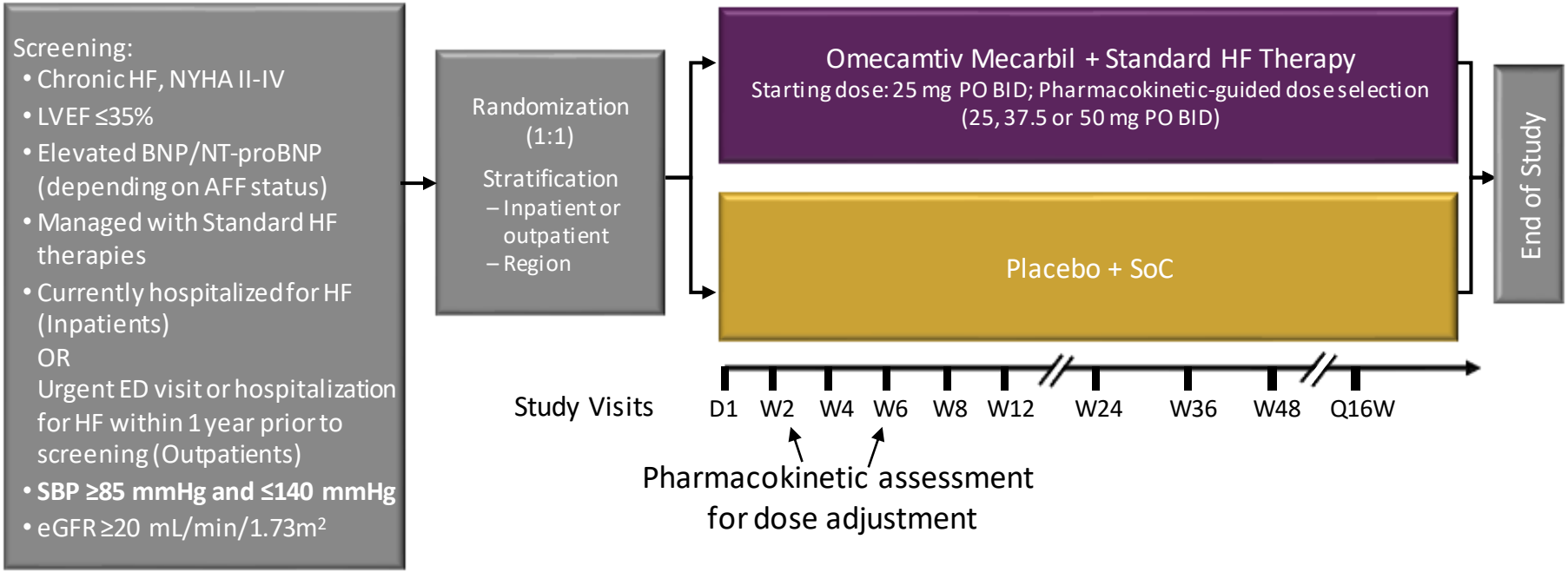
- Prof. Metra has received funding to his institution from Amgen and Cytokinetics as participant to the Executive Committee during the trial and for patients' enrollment; has received consulting fees for participation to advisory boards from AstraZeneca, Bayer, and Boehringer Ingelheim; has received personal fees as member of Executive or Data Monitoring Committees of sponsored clinical trials from LivaNova and Vifor Pharma; has received speaker fees from Abbott Vascular and Edwards Therapeutics for speeches at sponsored meetings; and has participated on Data Safety Monitoring boards for Actelion.

Background and Study Aim

- Low SBP identifies patients with HFrEF at increased risk of clinical events and who poorly tolerate guideline-directed medical therapy
- Yet, these patients are typically excluded from HFrEF trials due to hypotensive effects of many therapies for HFrEF
- Omecamtiv mecarbil, a selective cardiac myosin activator, directly improves cardiac function without reducing blood pressure and may be useful in these difficult to treat patients
- We evaluated the efficacy and tolerability of omecamtiv mecarbil in HFrEF patients with SBP ≤100 mmHg enrolled in GALACTIC-HF

Study 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

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

Primary Endpoint

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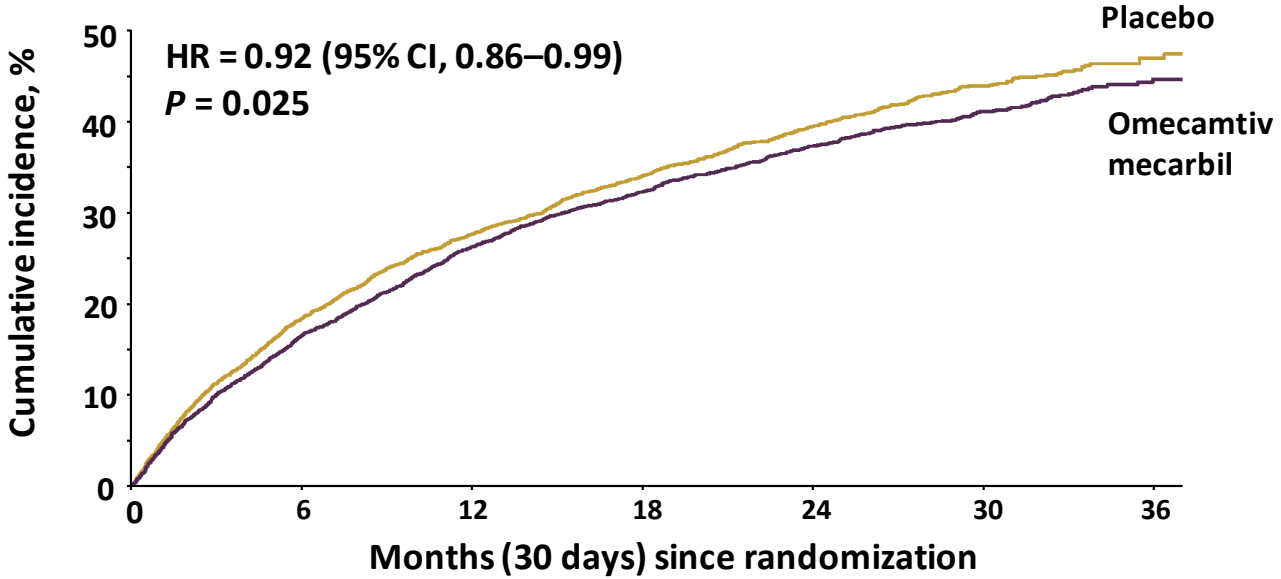
Time to first Heart Failure event or Cardiovascular death



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

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

GALACTIC-HF SBP Substudy Design

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- 8,232/8,232 patients with available data on baseline SBP:
  - 1,473 patients (17.9%) with SBP ≤100 mmHg (*low SBP group*)
  - 6,759 patients (82.1%) with SBP >100 mmHg
- Primary endpoint: composite of CV death or first HF event
- Secondary endpoints: first HF event, first HF hospitalization, CV death, all-cause death
- Additional exploratory and safety outcomes

Baseline Characteristics by Blood Pressure

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	SBP ≤100 mmHg (N=1,473)	SBP >100 mmHg (N=6,759)	p-value
Age (years)	63.4 ± 11.9	64.8 ± 11.2	**<0.001**
Women	314 (21.3%)	1435 (21.2%)	0.94
Inpatient setting	449 (30.5%)	1635 (24.2%)	**<0.001**
Comorbidities and HF history			
History of MI	599 (40.7%)	2836 (42.0%)	0.36
Stroke	147 (10.0%)	607 (9.0%)	0.23
AF/flutter (screening)	438 (29.7%)	1807 (26.7%)	**0.019**
Hypertension	753 (51.1%)	5031 (74.4%)	**<0.001**
Type 2 DM	533 (36.2%)	2776 (41.1%)	**<0.001**
LVEF (%)	24.3 ± 6.3	27.0 ± 6.2	**<0.001**
NYHA class			**<0.001**
Class II	728 (49.4%)	3640 (53.9%)	
Class III	678 (46.0%)	2938 (43.5%)	
Class IV	67 (4.5%)	181 (2.7%)	
Ischemic HF etiology	709 (48.1%)	3706 (54.8%)	**<0.001**

	SBP ≤100 mmHg (N=1,473)	SBP >100 mmHg (N=6,759)	p-value
Vitals and laboratory data			
SBP (mmHg)	94.4 ± 5.1	121.3 ± 12.3	**<0.001**
HR (beats/min)	72.4 ± 12.3	72.4 ± 12.1	1.00
NT-proBNP (pg/ml)	2829 [1432, 5592]	1856 [924, 3770]	**<0.001**
eGFR (ml/min/1.73m^2)	55.3 [40.7, 71.6]	59.4 [44.9, 74.4]	**<0.001**
Baseline HF therapy			
ACEi/ARB/ARNi	1249 (84.8%)	5910 (87.4%)	**0.006**
ARNi	416 (28.2%)	1185 (17.5%)	**<0.001**
BB	1357 (92.1%)	6406 (94.8%)	**<0.001**
MRA	1192 (80.9%)	5205 (77.0%)	**0.001**
SGLT2i	52 (3.5%)	166 (2.5%)	**0.020**
Ivabradine	109 (7.4%)	424 (6.3%)	0.11
Digoxin	287 (19.5%)	1098 (16.2%)	**0.003**
CRT	322 (21.9%)	836 (12.4%)	**<0.001**
ICD	632 (42.9%)	1982 (29.3%)	**<0.001**

Results – Impact of SBP on Outcomes

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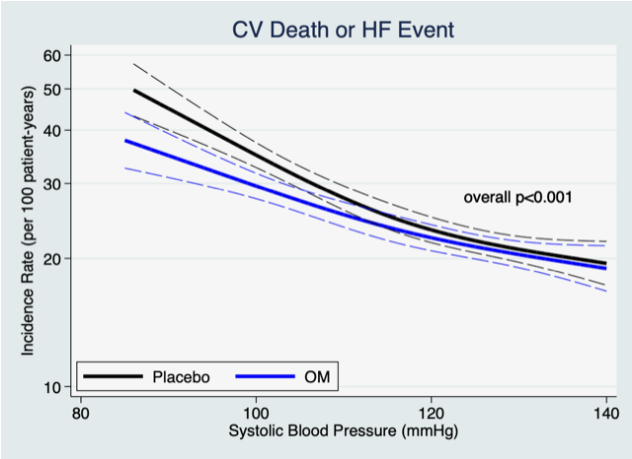
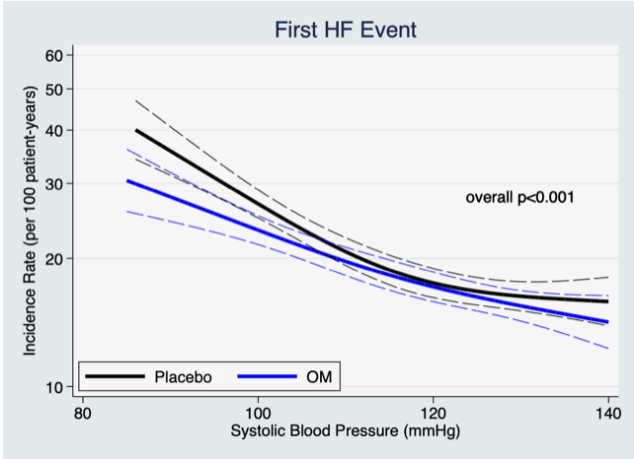
Primary Endpoint



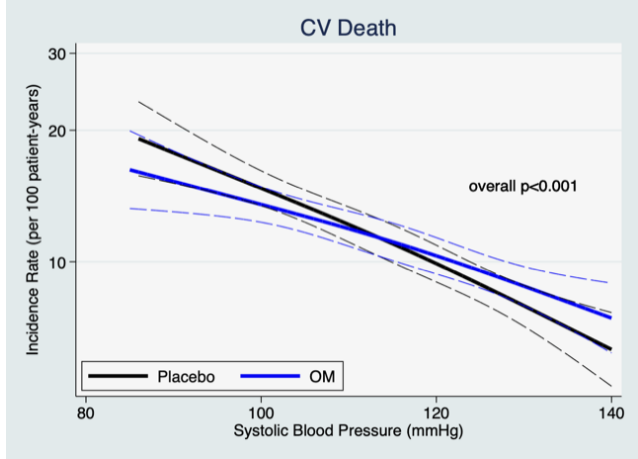
Adjusted HR* per 5-mmHg SBP decrease, **1.05**; 95% CI, **1.03 to 1.06**; p<0.001

First HF Event



Adjusted HR* per 5-mmHg SBP decrease, **1.04**; 95% CI, **1.03 to 1.06**; p<0.001

CV Death



Adjusted HR* per 5-mmHg SBP decrease, **1.08**; 95% CI, **1.06 to 1.09**; p<0.001

*Adjustment for age, sex, race, region, inpatient setting, MI, CABG, PCI, stroke, AF/flutter, diabetes mellitus, LVEF, NYHA class, ischemic HF etiology, KCCQ, HR, NT-proBNP, troponin, eGFR

Results – Impact of SBP on Omecamtiv Mecarbil Treatment Effect

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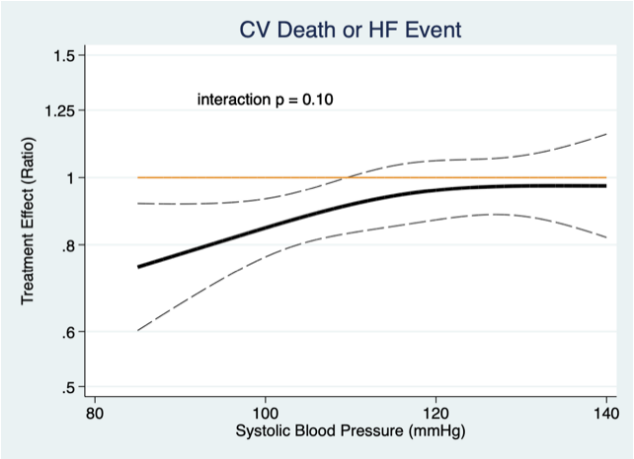
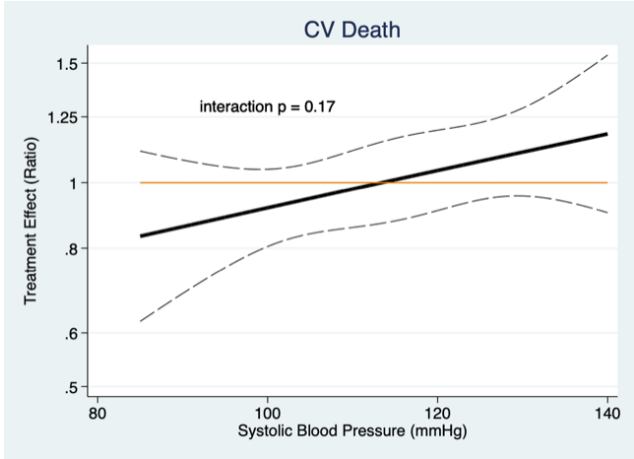
Primary Endpoint



First HF Event

CV Death



Results – KM Curves for the Primary Endpoint by SBP Subgroups

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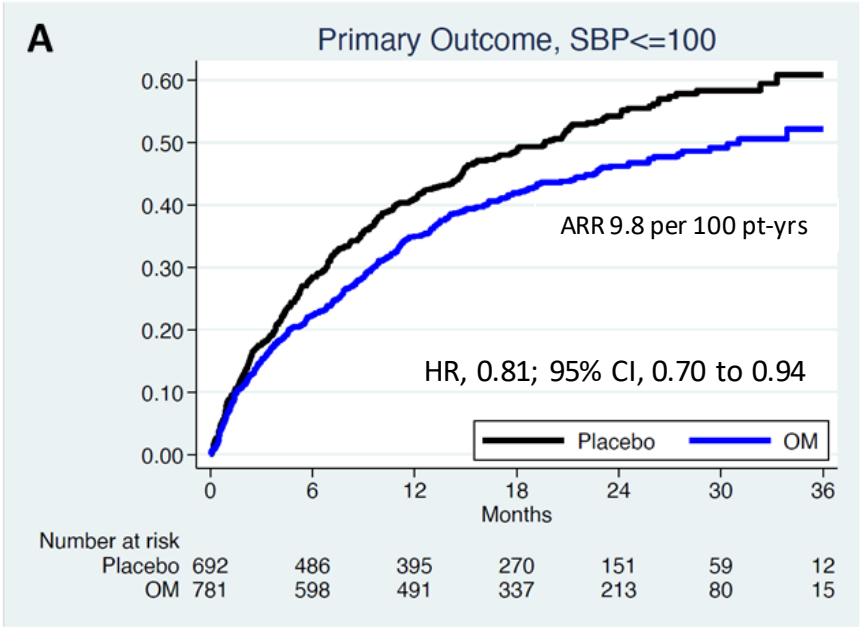

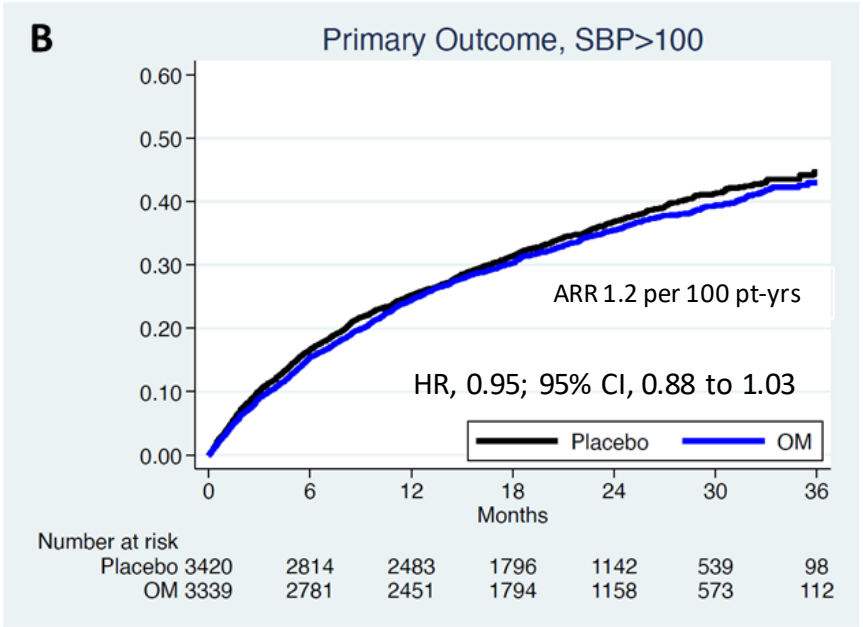

Interaction p-value for SBP ≤100 mmHg vs. SBP >100 mmHg = 0.051

SBP Values Over Time during Omecamtiv Mecarbil or Placebo Treatment

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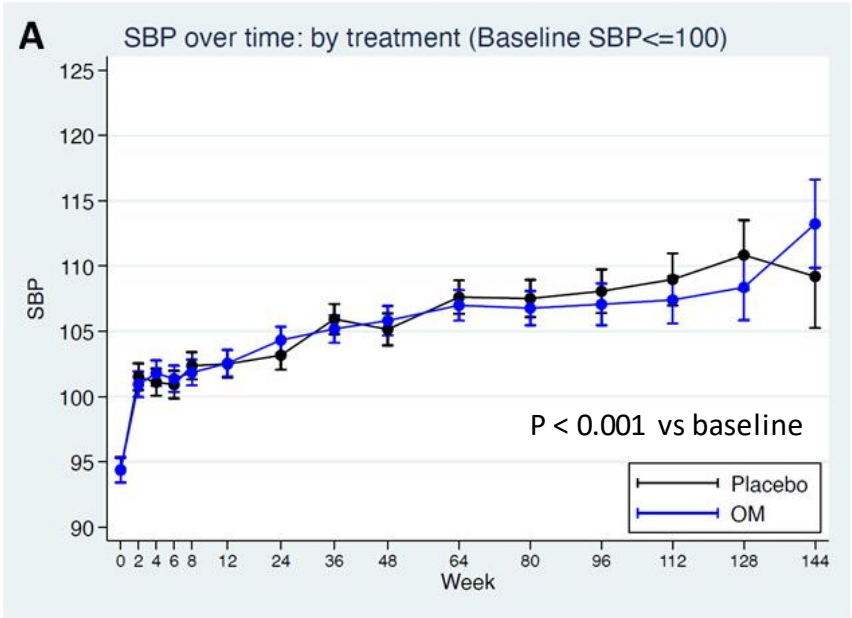

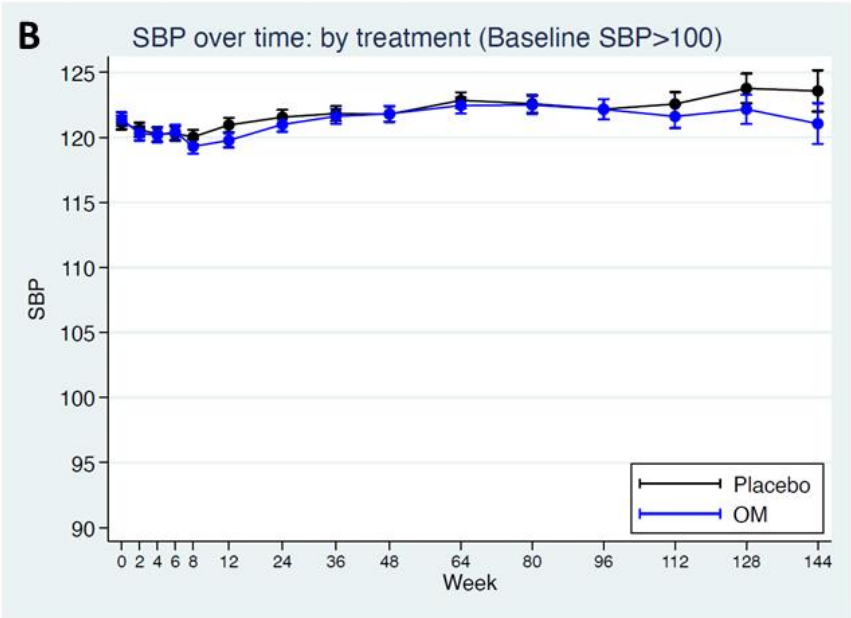

Effects of Omecamtiv Mecarbil on Selected Vital Signs and Laboratory Values

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Placebo-Corrected Change from Baseline to Week 24

Variable Difference (95% CI) p-value	SBP ≤100 mmHg (N=1,473)	SBP >100 mmHg (N=6,759)	p-value
SBP (mmHg)	+1.1 (-0.5, +2.7) 0.17	-0.6 (-1.4, +0.1) 0.09	0.06
HR (bpm)	-2.3 (-3.5, -1.1) <0.001	-1.4 (-1.9, -0.9) <0.001	0.18
Potassium (mmol/l)	-0.02 (-0.08, 0.04) 0.43	+0.01 (-0.02, +0.03) 0.69	0.36
Creatinine (mg/dl)	-0.02 (-0.06, +0.02) 0.36	0.01 (-0.00, +0.03) 0.15	0.13
NT-proBNP (pg/ml; Ratio)	0.82 (0.74, 0.90) <0.001	0.91 (0.87, 0.95) <0.001	0.06
Troponin I (ng/L)	+5 (+3, +7) <0.001	+4 (+3, +5) <0.001	0.89

Effects of Omecamtiv Mecarbil on Safety Outcomes by Blood Pressure Groups

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Omecamtiv Mecarbil: n (%) Placebo: n (%) RR (95% CI); p-value	SBP ≤100 mmHg (N=1,473)	SBP >100 mmHg (N=6,759)
Any Treatment-Emergent Serious Adverse Events	OM: 495 (63.5%) P: 496 (72.0%) RR 0.88 (0.82, 0.95); p <0.001	OM: 1878 (56.4%) P: 1939 (56.8%) RR 0.99 (0.95, 1.03); p = 0.72
AE: Ventricular Tachyarrhythmia	OM: 70 (9.8%) P: 75 (11.5%) RR 0.85 (0.63, 1.16); p = 0.32	OM: 220 (7.5%) P: 229 (7.6%) RR 0.99 (0.83, 1.18); p = 0.88
SAE: Ventricular Arrhythmia Requiring Treatment	OM: 28 (3.6%) P: 32 (4.6%) RR 0.77 (0.47, 1.27); p = 0.31	OM: 91 (2.7%) P: 95 (2.8%) RR 0.98 (0.74, 1.30); p = 0.90
Adjudicated First Major Cardiac Ischemic Events	OM: 28 (3.6%) P: 26 (3.8%) RR 0.95 (0.56, 1.61); p = 0.85	OM: 172 (5.2%) P: 162 (4.7%) RR 1.09 (0.88, 1.34); p = 0.43
Positively Adjudicated Myocardial Infarction	OM: 18 (2.3%) P: 17 (2.5%) RR 0.94 (0.49, 1.80); p = 0.84	OM: 104 (3.1%) P: 101 (3.0%) RR 1.06 (0.81, 1.38); p = 0.70
Adjudicated First Stroke	OM: 6 (0.8%) P: 17 (2.5%) RR 0.31 (0.12, 0.79); p = 0.009	OM: 70 (2.1%) P: 95 (2.8%) RR 0.75 (0.56, 1.02); p = 0.07

Conclusions

- Treatment of the patients with HFrEF and low SBP remains a major challenge

- Among patients with symptomatic, chronic HFrEF enrolled in GALACTIC-HF, patients with low baseline SBP (≤100 mmHg) experienced:
  - Increased risk of HF outcomes compared with patients with SBP >100 mmHg
  - Large absolute risk reduction (9.8%) of the primary composite endpoint of CV death or first HF event with omecamtiv mecarbil compared with placebo
  - Similar safety and tolerability profile with omecamtiv mecarbil compared with placebo