

# Effects of omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure: the GALACTIC-HF trial

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## Abstract

### Aim

Patients with heart failure with reduced ejection fraction and low systolic blood pressure (SBP) have high mortality, hospitalizations, and poorly tolerate evidence-based medical treatment. Omecamtiv mecarbil may be particularly helpful in such patients. This study examined its efficacy and tolerability in patients with SBP  $\leq 100$  mmHg enrolled in the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF).

### Methods and results

The GALACTIC-HF enrolled patients with baseline SBP  $\geq 85$  mmHg with a primary outcome of time to cardiovascular death or first heart failure event. In this analysis, patients were divided according to their baseline SBP ( $\leq 100$  vs.  $> 100$  mmHg). Among the 8232 analysed patients, 1473 (17.9%) had baseline SBP  $\leq 100$  mmHg and 6759 (82.1%) had SBP  $> 100$  mmHg. The primary outcome occurred in 715 (48.5%) and 2415 (35.7%) patients with SBP  $\leq 100$  and  $> 100$  mmHg, respectively. Patients with lower SBP were at higher risk of adverse outcomes. Omecamtiv mecarbil, compared with placebo, appeared to be more effective in reducing the primary composite endpoint in patients with SBP  $\leq 100$  mmHg [hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.70–0.94] compared with those with SBP  $> 100$  mmHg (HR, 0.95; 95% CI, 0.88–1.03; *P*-value for interaction = 0.051). In both groups, omecamtiv mecarbil did not change SBP values over time and did not increase the risk of adverse events, when compared with placebo.

### Conclusion

In GALACTIC-HF, risk reduction of heart failure outcomes with omecamtiv mecarbil compared with placebo was large and significant in patients with low SBP. Omecamtiv mecarbil did not affect SBP and was well tolerated independent of SBP values.

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**Structured Graphical Abstract**

**Key Question**

Patients with heart failure with reduced ejection fraction (HFrEF) and low systolic blood pressure (SBP) are at high risk of death or heart failure (HF) hospitalizations and poorly tolerate evidence-based treatments. Omecamtiv mecarbil, a selective cardiac myosin activator, may be particularly helpful in patients with low SBP

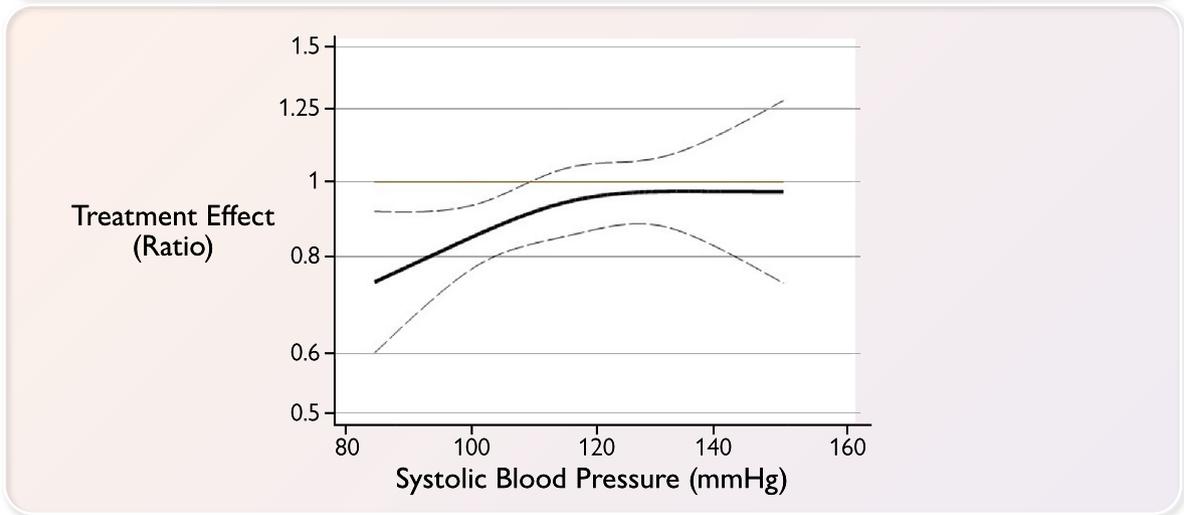
**Key Finding**

Compared with placebo, omecamtiv mecarbil reduced the primary endpoint of cardiovascular death or first HF event in patients with SBP  $\leq 100$  mmHg (HR, 0.81; 95% CI, 0.70-0.94) and was well tolerated with no difference in side effects.

**Take Home Message**

Omecamtiv mecarbil provides significant improvements in clinical outcomes in patients with HFrEF and low SBP ( $\leq 100$  mmHg), predominantly through a reduction HF events. In these difficult to treat patients, omecamtiv mecarbil doesn't decrease blood pressure and was well-tolerated.

**Relative treatment effect of omecamtiv mecarbil, according to baseline SBP, on the primary endpoint (CV death or first HF event)**



- Interaction p-value for SBP >100 mmHg versus SBP  $\leq 100$  mmHg = 0.051
- NNT for patients with SBP  $\leq 100$  mmHg = 10.2 patients for 1 year to prevent one CV death or first HF event

In Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF), treatment with omecamtiv mecarbil compared with placebo was associated with a large and significant reduction in the risk of the composite endpoint of cardiovascular death or first HF event in patients with low baseline SBP ( $\leq 100$  mmHg).

CI = confidence interval; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NNT = number needed to treat; SBP = systolic blood pressure.

**Keywords**

Heart failure • Omecamtiv mecarbil • Inotrope • Myotrope • Cardiovascular outcomes trial

**Introduction**

Major advances have occurred in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF). However, none of the drugs

currently indicated to improve outcome directly affects impaired myocardial function, the primary abnormality leading to HF.<sup>1-3</sup> Traditional inotropic agents (calcitropes) have not improved outcomes in patients with HFrEF, and their untoward effects are related

**Table 1** Baseline characteristics of GALACTIC-HF patients across systolic blood pressure subgroups

	SBP ≤100 mmHg (N = 1473)	SBP >100 mmHg (N = 6759)	P-value
<b>Demographics</b>			
Age (years), mean (SD)	63.4 ± 11.9	64.8 ± 11.2	<0.001
Sex, female, n (%)	314 (21.3)	1435 (21.2)	0.94
Race, n (%)			<0.001
Asian	202 (13.7)	508 (7.5)	
Black or African American	89 (6.0)	473 (7.0)	
Other <sup>a</sup>	103 (7.0)	460 (6.8)	
White	1079 (73.3)	5318 (78.7)	
Geographic Region, n (%)			<0.001
Asia	190 (12.9)	480 (7.1)	
Eastern Europe/Russia	244 (16.6)	2437 (36.1)	
Latin and South America	302 (20.5)	1272 (18.8)	
US and Canada	278 (18.9)	1108 (16.4)	
Western Europe/South Africa/Australasia	459 (31.2)	1462 (21.6)	
Randomization setting: inpatient	449 (30.5)	1635 (24.2)	<0.001
<b>Clinical characteristics</b>			
<b>Medical conditions, n (%)</b>			
History of myocardial infarction	599 (40.7)	2836 (42.0)	0.36
History of coronary artery bypass surgery	251 (17.0)	1066 (15.8)	0.23
History of percutaneous coronary revascularization	433 (29.4)	2005 (29.7)	0.84
Stroke	147 (10.0)	607 (9.0)	0.23
Atrial fibrillation or flutter at screening	438 (29.7)	1807 (26.7)	0.019
Hypertension	753 (51.1)	5031 (74.4)	<0.001
Type 2 diabetes mellitus	533 (36.2)	2776 (41.1)	<0.001
<b>Heart failure history</b>			
LVEF (%), mean (SD)	24.3 ± 6.3	27.0 ± 6.2	<0.001
NYHA classification, n (%)			<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)	
Ischaemic heart failure aetiology	709 (48.1)	3706 (54.8)	<0.001
KCCQ total symptom score, median (Q1, Q3)	66.7 (45.8, 87.5)	69.8 (50.0, 87.5)	0.002
Outpatient	72.9 (55.2, 89.6)	75.0 (55.2, 91.7)	0.09
Inpatient	51.0 (30.2, 71.9)	54.2 (33.3, 70.8)	0.34
<b>Vitals and laboratory parameters</b>			
SBP (mmHg), mean (SD)	94.4 ± 5.1	121.3 ± 12.3	<0.001
Heart rate (bpm), mean (SD)	72.4 ± 12.3	72.4 ± 12.1	1.00
NT-proBNP (pg/mL), median (Q1, Q3)	2829 (1432, 5592)	1856 (924, 3770)	<0.001
Cardiac Troponin I (ng/L), median (Q1, Q3)	29 (14, 55)	26 (14, 50)	0.035

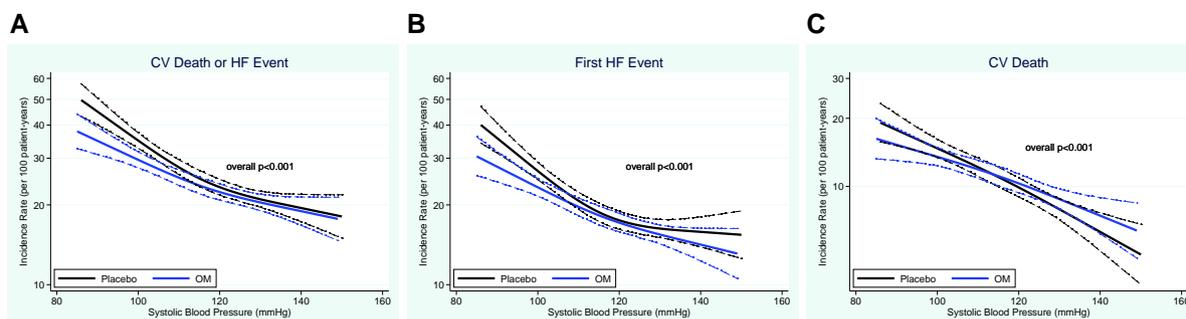
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**Table 1 Continued**

	SBP ≤100 mmHg (N = 1473)	SBP >100 mmHg (N = 6759)	P-value
eGFR (mL/min/1.73 m <sup>2</sup> ), median (Q1, Q3)	55.3 (40.7, 71.6)	59.4 (44.9, 74.4)	<0.001
<b>Medications and cardiac devices, n (%)</b>			
ACEi, ARB, or 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
SGLT2 inhibitors	52 (3.5)	166 (2.5)	0.020
Ivabradine	109 (7.4)	424 (6.3)	0.11
Digitalis glycosides	287 (19.5)	1098 (16.2)	0.003
Cardiac resynchronization therapy	322 (21.9)	836 (12.4)	<0.001
Implantable cardioverter defibrillator	632 (42.9)	1982 (29.3)	<0.001

<sup>a</sup>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; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2.



**Figure 1** Incidence rate of clinical outcomes according to baseline systolic blood pressure. The figure shows the incidence rate of the primary composite endpoint (A), first heart failure event (B), and cardiovascular death (C) according to baseline SBP systolic blood pressure in patients treated with omecamtiv mecarbil or placebo. CV = cardiovascular; HF = heart failure; SBP = systolic blood pressure.

to the increase in intracellular free calcium concentrations.<sup>4</sup> Omecamtiv mecarbil is a myotrope and the first of a new class of direct cardiac myosin activators, improving cardiac function through an increase in actin–myosin interaction without affecting calcium transients.<sup>4–7</sup> Omecamtiv mecarbil increased left ventricular (LV) systolic function and decreased LV volumes, natriuretic peptide concentrations, and heart rate without meaningful changes in blood pressure in prior clinical studies.<sup>8,9</sup> The Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial has demonstrated its beneficial effect on a composite of cardiovascular death or first HF event in 8256 patients with symptomatic chronic HFrEF.<sup>10</sup>

Low systolic blood pressure (SBP) is reported in 10–20% of patients with HFrEF.<sup>11</sup> It can be a sign of severely impaired LV systolic function,<sup>11</sup> an independent predictor of outcome,<sup>11–19</sup> and a major cause of medication intolerance and lack of titration to target doses of

evidence-based medical therapy in patients with HFrEF.<sup>20–25</sup> Treatment of patients with HFrEF and low SBP remains a major challenge for clinical practice. The unique mechanism of action of omecamtiv mecarbil, based on direct improvement of LV systolic function without direct effects on SBP, makes it potentially attractive for patients with low SBP.<sup>26,27</sup> In GALACTIC-HF, an SBP of ≥85 and ≤140 mmHg was required for eligibility and SBP at baseline was lower compared with that of all other trials enrolling either outpatients or patients hospitalized with HF.<sup>28,29</sup> In addition, and unlike other HFrEF therapies, the beneficial effects of omecamtiv mecarbil tend to increase incrementally as LV ejection fraction (LVEF) decreases and with more severe HF.<sup>10,28,30,31</sup> The aim of the present analysis was to evaluate the safety and efficacy of omecamtiv mecarbil in patients with HFrEF enrolled in the GALACTIC-HF trial (NCT02929329; EudraCT number 2016-002299-28) who had a low SBP at baseline.

## Methods

### Study design

The design, baseline characteristics and main results of the GALACTIC-HF trial have been previously reported.<sup>10,28,29</sup> In brief, this Phase 3, global, double-blind, placebo-controlled randomized clinical trial compared omecamtiv mecarbil with placebo in 8256 patients with symptomatic HF<sub>rEF</sub> [New York Heart Association (NYHA) functional Class II to Class IV and LVEF  $\leq 35\%$ ]. Included patients were currently hospitalized for HF (inpatients) or had either an urgent visit to the emergency department for HF or a hospitalization for HF within 1 year (outpatients). All participants were on optimized background HF therapy and were required to have elevated natriuretic peptides [N-terminal pro-B-type natriuretic peptide (NT-proBNP) level  $\geq 400$  pg/mL (1200 pg/mL for patients in atrial fibrillation) or B-type natriuretic peptide (BNP)  $\geq 125$  pg/mL (375 pg/mL for patients in atrial fibrillation)]. Key exclusion criteria were haemodynamic or clinical instability requiring mechanical or intravenous therapy, SBP  $< 85$  or  $> 140$  mmHg, diastolic blood pressure  $> 90$  mmHg, estimated glomerular filtration rate (eGFR)  $< 20$  mL/min/1.73 m<sup>2</sup>, a recent acute coronary syndrome or cardiovascular procedure (including planned procedures), and other conditions that would adversely affect participation in the trial. All participants provided informed consent and the study protocol was approved by the relevant local ethics committees.

### Study outcomes

The pre-specified primary endpoint was a composite of the time-to-first HF event or cardiovascular death. Secondary outcomes of interest included first HF event, first HF hospitalization, cardiovascular death, and all-cause death. An HF event was defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening HF leading to treatment intensification beyond change in oral diuretic therapy.<sup>29</sup> Additional exploratory outcomes and safety outcomes have also been published.<sup>10,29</sup> All deaths, HF events, major cardiac ischaemic events, and strokes were adjudicated by an independent external Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions.<sup>32</sup>

### Statistical analysis

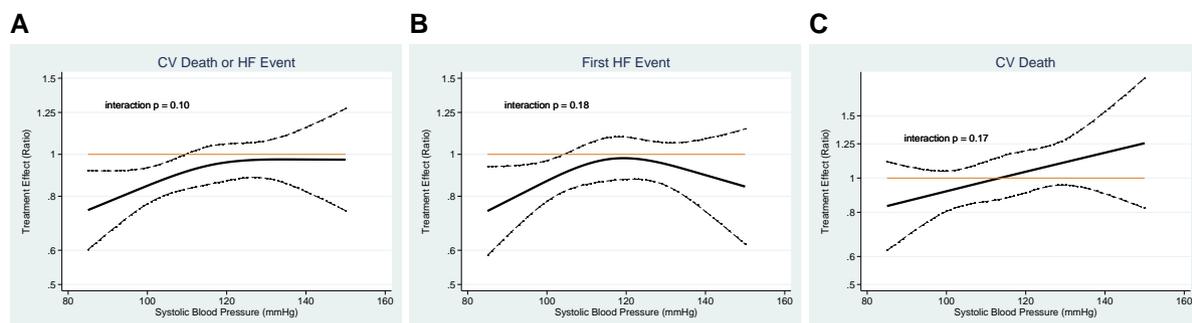
In the present analysis, patients were divided into two baseline SBP categories: (i) low SBP, defined as SBP  $\leq 100$  mmHg, and (ii) SBP  $> 100$  mmHg. Continuous variables are reported as mean values and

standard deviations or medians and interquartile ranges, as appropriate. Categorical variables are reported as number and percentages. Treatment effects on continuous outcomes were assessed via linear regression or quantile regression (for troponin) 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 hazard models to estimate hazard ratios (HRs) adjusted for eGFR and stratified by region and inpatient status, as in the primary GALACTIC-HF analysis. Kaplan–Meier methods were used to construct cumulative incidence curves for time-to-event data. To allow for potentially non-linear associations between SBP and time-to-event outcomes, restricted cubic splines with 3 knots were applied to the Poisson regression models. Treatment effect modification was assessed via the introduction of interaction terms between randomized treatment assignment and baseline SBP categories. All analyses were performed using STATA version 16 (StataCorp, College Station, TX, USA). All *P*-values  $< 0.05$  were considered statistically significant. All *P*-values were two-sided.

## Results

### Study population

Among the 8232 patients analysed from the GALACTIC-HF trial, 1473 (17.9%) had SBP  $\leq 100$  mmHg and 6759 (82.1%) had SBP  $> 100$  mmHg. Mean baseline SBP values were  $94.4 \pm 5.1$  and  $121.3 \pm 12.3$  mmHg in each group, respectively. As shown in [Table 1](#), patients with low SBP were younger and less likely to be from Eastern Europe and Russia. They were also more frequently randomized as inpatients and more likely to have atrial fibrillation/flutter, NYHA III–IV functional class, higher NT-proBNP values, and lower LVEF, Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score and eGFR values. Conversely, patients with SBP  $> 100$  mmHg were more likely to have history of hypertension, Type 2 diabetes mellitus, and ischaemic aetiology of HF. Regarding HF therapy, patients with low SBP were less likely to be treated with a beta-blocker plus either an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNi), though they had a higher use of ARNi alone. Patients with low SBP were also more likely to be treated with mineralocorticoid receptor antagonists, sodium-



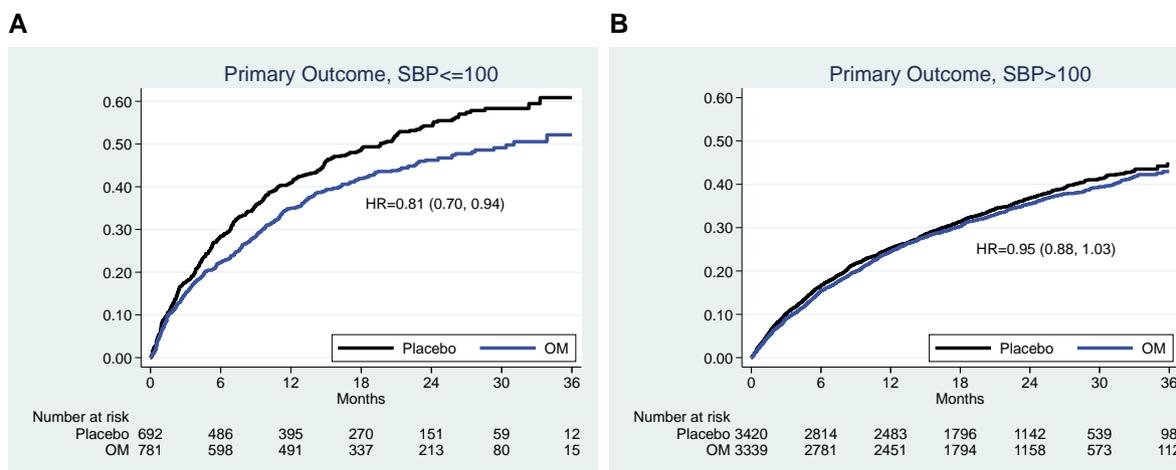
**Figure 2** Relative treatment effect of omecamtiv mecarbil, according to baseline systolic blood pressure, on clinical outcomes. The figure shows the relative treatment effect of omecamtiv mecarbil vs. placebo, according to baseline systolic blood pressure, on the primary composite endpoint (A), first heart event (B), and cardiovascular death (C). CV = cardiovascular; HF = heart failure; SBP = systolic blood pressure.

**Table 2 Clinical outcomes**

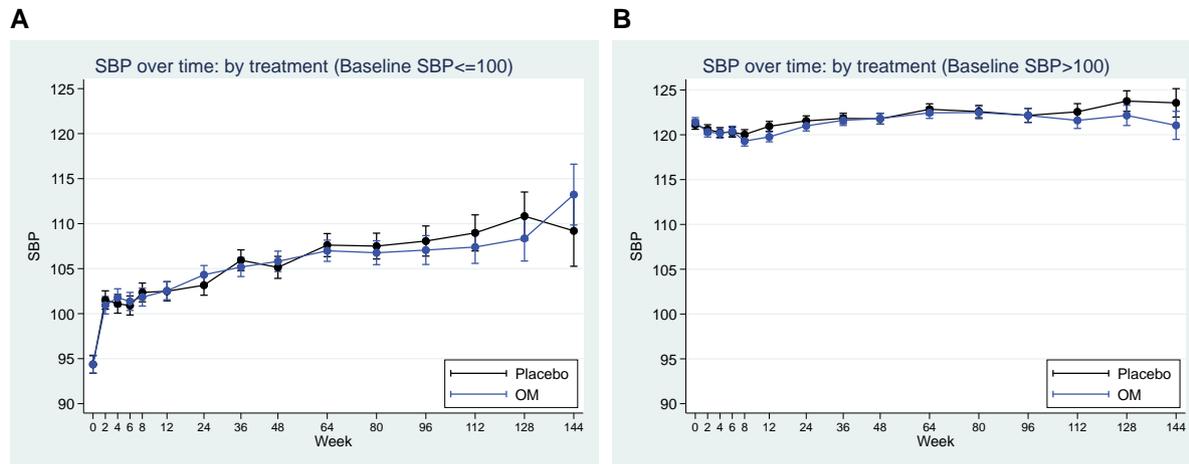
Outcome by SBP	Omecamtiv mecarbil		Placebo		HR (95% CI); P-value	ARR (per 100 pt-yrs)
	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)		
<b>Primary outcome</b>					Interaction P = 0.051	
SBP ≤100 mmHg	350/781 (45%)	33.4	365/692 (53%)	43.2	0.81 (0.70, 0.94); P = 0.005	9.8
SBP >100 mmHg	1173/3339 (35%)	22.4	1242/3420 (36%)	23.6	0.95 (0.88, 1.03); P = 0.19	1.2
<b>First HF event</b>					Interaction P = 0.08	
SBP ≤100 mmHg	273/781 (35%)	26.1	284/692 (41%)	33.6	0.81 (0.69, 0.96); P = 0.013	7.5
SBP >100 mmHg	904/3339 (27%)	17.3	952/3420 (28%)	18.1	0.95 (0.87, 1.04); P = 0.30	0.9
<b>First HF hospitalization</b>					Interaction P = 0.16	
SBP ≤100 mmHg	264/781 (34%)	24.9	267/692 (39%)	30.6	0.85 (0.71, 1.00); P = 0.06	5.6
SBP >100 mmHg	878/3339 (26%)	16.6	912/3420 (27%)	17.2	0.97 (0.88, 1.06); P = 0.49	0.6
<b>CV death</b>					Interaction P = 0.27	
SBP ≤100 mmHg	195/781 (25%)	15.0	192/692 (28%)	17.0	0.91 (0.75, 1.12); P = 0.38	1.9
SBP >100 mmHg	613/3339 (18%)	10.0	606/3420 (18%)	9.7	1.03 (0.92, 1.15); P = 0.59	-0.3
<b>All-cause death</b>					Interaction P = 0.28	
SBP ≤100 mmHg	245/781 (31%)	18.9	241/692 (35%)	21.3	0.91 (0.76, 1.09); P = 0.31	2.4
SBP >100 mmHg	822/3339 (25%)	13.4	824/3420 (24%)	13.2	1.02 (0.92, 1.12); P = 0.75	-0.3

Data are reported as n/N (%), rate (per 100 patient-years), HR with 95% CI and ARR. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SBP, systolic blood pressure.

glucose co-transporter 2 (SGLT2) inhibitors, digitalis glycosides, cardiac resynchronization therapy, and implantable cardioverter defibrillators, compared with the higher SBP group. Detailed baseline characteristics in patients with SBP ≤100 and SBP >100 mmHg, according to randomization status (omecamtiv mecarbil vs. placebo), are shown in [Supplementary material online, Table S1](#).



**Figure 3** Kaplan–Meier curves for the primary endpoint by systolic blood pressure categories. The figure shows Kaplan–Meier curves for the primary composite endpoint according to treatment with omecamtiv mecarbil or placebo in patients with baseline systolic blood pressure ≤100 mmHg (A) and in those with baseline systolic blood pressure >100 mmHg (B). Hazard ratios and 95% confidence intervals are also reported. HR = hazard ratio; OM = omecamtiv mecarbil; SBP = systolic blood pressure.



**Figure 4** Trend of systolic blood pressure over time. The figure shows the trend of systolic blood pressure over time according to treatment with omecantiv mecarbil or placebo in patients with baseline systolic blood pressure  $\leq 100$  mmHg (A) and in those with baseline systolic blood pressure  $> 100$  mmHg (B). OM = omecantiv mecarbil; SBP = systolic blood pressure.

**Table 3** Treatment effects of omecantiv mecarbil vs. placebo on selected vital signs and laboratory values from baseline to Week 24

Difference (95% CI); P-value	SBP $\leq 100$ mmHg (N = 1473)	SBP $> 100$ mmHg (N = 6759)	P-value
SBP (mmHg)	+1.1 (−0.5, +2.7); 0.17	−0.6 (−1.4, +0.1); 0.09	0.06
Heart rate (b.p.m.)	−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

Values represent treatment effects as evaluated by between-group differences of change from baseline to Week 24. CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

## Impact of systolic blood pressure on outcomes

During a median follow-up of 21.8 months (interquartile range, 15.4–28.6 months), the primary composite outcome of first HF event or cardiovascular death occurred in 2415 (35.7%) patients with SBP  $> 100$  mmHg vs. 715 (48.5%) patients with low SBP [HR, 0.70; 95% confidence interval (CI), 0.64–0.76;  $P < 0.001$ ]. The incidence of the primary composite endpoint was 23.0 per 100 patient-years in the SBP  $> 100$  mmHg group vs. 37.8 per 100 patient-years in the low SBP group. Patients with SBP  $> 100$  mmHg also had a lower risk of first HF event (HR, 0.70; 95% CI, 0.64–0.78;  $P < 0.001$ ), cardiovascular death (HR, 0.67; 95% CI, 0.59–0.75;  $P < 0.001$ ), all-cause death (HR, 0.72; 95% CI, 0.65–0.80;  $P < 0.001$ ), and first HF hospitalization (HR, 0.71; 95% CI, 0.65–0.79;  $P < 0.001$ ), when compared with those with low SBP.

As shown in [Figure 1A](#), the incidence of the primary endpoint increased in both the omecantiv mecarbil and placebo groups with

decreasing SBP. A similar trend was observed for the incidence rate of first HF event ([Figure 1B](#)) and cardiovascular death ([Figure 1C](#)). The HR per each 5 mmHg decrease of SBP for the primary composite endpoint was of 1.07 (95% CI, 1.06–1.08;  $P < 0.001$ ). After adjustment for several covariates (age, female sex, race, region, inpatient setting, myocardial infarction, coronary artery bypass graft, percutaneous coronary revascularization, stroke, atrial fibrillation or flutter, diabetes mellitus, LVEF, NYHA class, ischaemic HF aetiology, KCCQ, heart rate, NT-proBNP, troponin, eGFR), lower SBP remained independently associated with a higher risk of the primary composite endpoint (adjusted HR per each 5 mmHg decrease, 1.05; 95% CI, 1.03–1.06;  $P < 0.001$ ). Regarding secondary endpoints, in the overall population lower SBP was significantly associated with a higher risk of cardiovascular death (adjusted HR per each 5 mmHg decrease, 1.08; 95% CI, 1.06–1.09;  $P < 0.001$ ), all-cause death (adjusted HR per each 5 mmHg decrease, 1.06; 95% CI, 1.04–1.07;  $P < 0.001$ ), first HF event (adjusted HR per each 5 mmHg

**Table 4 Safety outcomes**

OM: n (%) Placebo: n (%) RR (95% CI) P-value	SBP ≤100 mmHg (N = 1473)	SBP >100 mmHg (N = 6759)
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
Adverse event: 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
Serious adverse event: 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 ischaemic 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

Values are presented as n (%) and RR with 95% CI. CI, confidence interval; OM, omeamtiv mecarbil; P, placebo; RR, relative risk; SBP, systolic blood pressure.

decrease, 1.04; 95% CI, 1.03–1.06;  $P < 0.001$ ), and first HF hospitalization (adjusted HR per each 5 mmHg decrease, 1.04; 95% CI, 1.03–1.06;  $P < 0.001$ ).

### Impact of systolic blood pressure on the treatment effect of omeamtiv mecarbil

Omeamtiv mecarbil administration lead to an 8% reduction in the primary composite endpoint (HR, 0.92; 95% CI, 0.86–0.99;  $P = 0.025$ ) in the overall study group in GALACTIC-HF.<sup>28</sup> In a multivariable analysis of continuous covariate interactions of the pre-specified subgroups on the primary endpoint, SBP (per 10 mmHg) was not a significant modifier of the treatment effect of omeamtiv mecarbil ( $P = 0.74$ ). However, with respect to the univariate impact of SBP as a continuous variable, an inverse relationship was observed between the treatment effect of omeamtiv mecarbil for the primary endpoint and baseline SBP modelled as restricted cubic spline, with a larger treatment effect in patients with lower baseline SBP, particularly for SBP values below 100 mmHg (Figure 2A,  $P = 0.098$ ). A similar trend between the treatment effect of omeamtiv mecarbil and baseline SBP was observed for the secondary endpoint of first HF

event alone, with a larger treatment effect in patients with SBP  $\leq 100$  mmHg (Figure 2B). Regarding cardiovascular death, an inverse relationship between the treatment effect of omeamtiv mecarbil and baseline SBP was observed, but the effect of omeamtiv mecarbil was not significant across the whole SBP spectrum, since the 95% CI of the treatment effect did not cross 1.00 for any SBP value (Figure 2C).

Univariate subgroup analysis showed a 19% relative risk reduction in the primary composite endpoint among patients with SBP  $\leq 100$  mmHg randomized to omeamtiv mecarbil, when compared with placebo (HR, 0.81; 95% CI, 0.70–0.94), with an absolute risk reduction of 9.8 events per 100 patient-years in this subgroup (Table 2, Figure 3). Among patients with SBP  $> 100$  mmHg, no significant difference in the primary outcome was observed between those randomized to omeamtiv mecarbil vs. placebo (HR, 0.95; 95% CI, 0.88–1.03; interaction  $P$ -value for SBP  $> 100$  vs. SBP  $\leq 100$  mmHg = 0.051).

The beneficial effect of treatment with omeamtiv mecarbil in patients with SBP  $\leq 100$  mmHg was driven predominantly by a reduction in first HF event (Figure 2B). Although there was not a significant interaction between SBP as two categories covariate ( $\leq 100$  vs.  $> 100$  mmHg) and treatment with omeamtiv mecarbil for first HF event (interaction  $P$ -value = 0.08), a larger reduction in first HF event was observed with omeamtiv mecarbil in patients with SBP  $\leq 100$  mmHg (HR, 0.81; 95% CI, 0.69–0.96) than in those with SBP  $> 100$  mmHg (HR, 0.95; 95% CI, 0.87–1.04; Table 2). No significant impact of omeamtiv mecarbil, when compared with placebo, was observed for the secondary endpoints of first HF hospitalization, cardiovascular death and all-cause death, considered alone, across the two SBP categories (Table 2).

### Trend of systolic blood pressure over time, other outcomes, and safety of omeamtiv mecarbil by systolic blood pressure

The trend of SBP over time in patients randomized to omeamtiv mecarbil or placebo is depicted in Figure 4, showing a similar increase in SBP among patients in both groups ( $P < 0.001$  in all groups). From baseline to Week 24 (Table 3), there was no significant effect of omeamtiv mecarbil on SBP when compared with placebo across both SBP categories (interaction  $P$ -value = 0.06). Reduction in NT-proBNP by omeamtiv mecarbil was observed in both SBP categories (interaction  $P$ -value = 0.06), with an 18% (95% CI, 10–26%) reduction in patients with SBP  $\leq 100$  mmHg ( $P < 0.001$ ) and a 9% (95% CI, 5–13%) reduction in patients with SBP  $> 100$  mmHg ( $P = 0.004$ ; Table 3). Furthermore, a small reduction in heart rate and a small increase in troponin I were observed with omeamtiv mecarbil, which did not differ across SBP categories (interaction  $P$ -value = 0.18 for heart rate, interaction  $P$ -value = 0.89 for troponin I).

No significant differences were observed in adverse events between omeamtiv mecarbil and placebo groups across the two SBP categories, except for the incidence of any treatment-emergent serious adverse events and of adjudicated first stroke, which were significantly lower among patients with SBP  $\leq 100$  mmHg treated with omeamtiv mecarbil (Table 4).

## Discussion

Our results show that omecamtiv mecarbil, compared with placebo in GALACTIC-HF, had a greater effect on the primary outcome of cardiovascular death or first HF event in patients with a baseline SBP  $\leq 100$  mmHg, with a 19% relative risk reduction and a 9.8 events per 100 patient-years absolute risk reduction in these patients (*Structured Graphical Abstract*). A numerically larger reduction in NT-proBNP values was also observed in these patients with an 18% reduction of NT-proBNP at Week 24. In addition, omecamtiv mecarbil had no significant effect on SBP and was well tolerated in all patients, independent of baseline SBP values.

The SBP is related to stroke volume and peripheral hypoperfusion and is a powerful independent prognostic marker in patients with HF.<sup>11,33,34</sup> The lack of decrease in SBP with omecamtiv mecarbil, compared with placebo, and the benefit and tolerance of this drug in patients with the lowest SBP are consistent with its unique mechanism of action based on a direct improvement in cardiac systolic function with no direct effect on neurohormonal mechanisms and peripheral resistance.<sup>4,9</sup> These results are consistent with other recent analyses of GALACTIC-HF demonstrating a greater benefit of omecamtiv mecarbil in patients with lower baseline LVEF<sup>30</sup> and in those with evidence of more severe HF.<sup>31</sup>

The GALACTIC-HF enrolled the largest proportion of patients with SBP  $\leq 100$  mmHg out of any HFrEF studies to date, and we therefore used this cut-off to define our patient groups. Recent randomized trials investigating ARNI in patients with HFrEF did not include patients with SBP  $< 95$  or  $100$  mmHg at screening or randomization, respectively.<sup>35–37</sup> Similarly, previous trials with beta-blockers, with the notable exception of carvedilol prospective randomized cumulative survival (COPERNICUS) trial, and recent trials with SGLT2 inhibitors or vericiguat also excluded patients with SBP  $< 95$ – $100$  mmHg.<sup>38–43</sup> In contrast, GALACTIC-HF included patients with SBP  $\geq 85$  mmHg, thus providing data on 1473 enrolled patients with SBP  $\leq 100$  mmHg. In our study, patients with low SBP at baseline were less likely to receive evidence-based medical therapy, including ACEi, ARBs, and beta-blockers, and had baseline characteristics consistent with more severe HF, as shown by their higher NYHA classes, lower LVEF, worse KCCQ total symptom score, and higher NT-proBNP levels. However, omecamtiv mecarbil showed progressively greater reduction in the incidence of the primary composite outcome as baseline SBP decreased, consistent with its direct effect on myocardial function and the critical role of impaired LV systolic function in the patients with more severe HF.<sup>7–10,28–31</sup> A lowest value of SBP of 85 mmHg for study enrolment was used also in COPERNICUS trial. The absolute benefit from treatment with carvedilol, vs. placebo, was the greatest in patients with the lowest SBP, consistently with the long-term improvement in cardiac function with this agent.<sup>40,44</sup>

The beneficial effects of omecamtiv mecarbil in patients with low SBP are particularly relevant when considering that these patients are less likely to tolerate evidence-based medical therapy of HFrEF.<sup>11,15,16,20–25</sup> Interestingly, among the 2079 patients with HFrEF who did not complete the pre-randomization run-in period in the recent Prospective Comparison of Angiotensin Receptor-Nephrilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and

Morbidity in Heart Failure (PARADIGM-HF) trial, hypotension was one of the most frequent reasons for study drug discontinuation (29.4 and 22.5% of patients who discontinued the study for adverse events during enalapril and sacubitril/valsartan run-in period, respectively).<sup>23</sup> Moreover, although very effective in patients who were able to tolerate it, sacubitril/valsartan was associated with a higher risk of symptomatic hypotension when compared with enalapril among the 8442 patients with HFrEF who completed the run-in period and were randomized in the PARADIGM-HF trial (14.0% with sacubitril/valsartan vs. 9.2% with enalapril,  $P < 0.001$ ).<sup>37</sup> Thus, SBP reduction is not an untoward event by itself but it may rather reduce tolerability of neurohormonal modulators when it becomes symptomatic. Also in COPERNICUS, although the absolute benefit of treatment with carvedilol was the greatest in the patients with the lowest SBP at baseline, the patients with lower initial SBP were more likely to have an adverse event, be intolerant to high doses of the study drug or require its permanent withdrawal ( $P < 0.001$  for all).<sup>44</sup> The SGLT2 inhibitors seem to be less likely to cause hypotension than neurohormonal modulators.<sup>26,45,46</sup> The effects of omecamtiv mecarbil in patients with low SBP in GALACTIC-HF are therefore of major value, since they indicate that omecamtiv mecarbil is both well tolerated and has increasing treatment effect at lower SBP with beneficial effects on outcome in patients who often cannot tolerate a neurohormonal modulator. Of note, SBP increased from baseline in both treatment groups, though with a numerically larger extent with omecamtiv mecarbil. However, survivor bias might have impacted these results since omecamtiv mecarbil numerically decreased risk of poor outcomes in patients with low SBP, so that there were more patients with low SBP in this group.

## Study limitations

The present study has some limitations. First, it represents a post-hoc analysis of the GALACTIC-HF randomized trial since no subgroup analysis was pre-specified according to the reported SBP categories ( $\leq 100$  vs.  $> 100$  mmHg). The SBP categories chosen in our study were arbitrary, although they are clinically meaningful and appear to be useful in clinical practice. Furthermore, subgroup analyses may have limited statistical power because of limited sample size and number of events. However, the analyses of SBP as a continuous variable were performed on the entire GALACTIC-HF population ( $n = 8232$  patients). Another potential limitation is that baseline SBP was investigator reported. Finally, other patients' characteristics may influence the treatment effect of omecamtiv mecarbil in patients with HFrEF.

## Conclusion

Treatment of patients with HFrEF and low SBP is a major challenge as they do not often tolerate evidence-based treatment. Among patients with symptomatic, chronic HFrEF, enrolled in GALACTIC-HF, treatment with omecamtiv mecarbil compared with placebo was associated with a large and significant reduction in the risk of the composite endpoint of cardiovascular death or first HF event in patients with low baseline SBP ( $\leq 100$  mmHg). Omecamtiv mecarbil was safe and well tolerated across different baseline SBP values and did not significantly affect SBP over time.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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**Conflict of interest:** M.M. has received funding to his institution from Amgen and Cytokinetics as participant to the Executive Committee during the trial and for patients' enrolment; 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. B.L.C. has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. R.D. has received research grants and other payment or honoraria from Amgen. G.M.F. has received grant funding to his institution from American Heart Association, Amgen, Bayer, Bristol Myers Squibb, CSL-Behring, Cytokinetics, Merck, Myokardia, and National Institutes of Health; has received consulting fees from Abbott, American Regent, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cardionomic, Cytokinetics, Medtronic, Myovant, Novartis, Reprieve, Sequana, Windtree Therapeutics, and WhiteSwell; and has participated on Data Safety Monitoring boards or advisory boards for EBR Systems, LivaNova, Medtronic, Siemens, Rocket Pharma, and V-Wave. J.J.V.M. has received funding to his institution from Amgen and Cytokinetics for his participation in the Steering Committee for the ATOMIC-HF, COSMIC-HF, and GALACTIC-HF trials and meetings and other activities related to these trials; has received personal fees from Abbott, Alkerm Metabolics, Eris Lifesciences, Hikma, Lupin, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, Sun Pharmaceuticals, and The Corpus; and has received funding paid to his institution for activities related to trials or other activities from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, DalCor, GlaxoSmithKline, Ionis Pharmaceuticals, KBP Biosciences, Novartis, and Theracos. S.D.S. has received grant funding to his institution from Actelion, Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis Pharmaceuticals, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, US2AI; and has received consulting fees from Abbott, Action, Akros, Alnylam, American Regent, Amgen, Anacardio, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimensions, Cardior, Cardurion, CellProthera, Corvia, Cytokinetics, Daiichi Sankyo, Dinaqor, GlaxoSmithKline, Janssen, Lexicon, Lilly, Merck, Moderna, Myokardia, Novartis, Puretech Health, Quantum Genomics, Roche, Sanofi Pasteur, Sarepta, Tenaya, Theracos, and Tremeau. D.B. has received research grants from Abbott, Bayer, Boehringer Ingelheim, Novartis, Pfizer, SOBI, and Zoll; has received consulting fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Ionis Pharmaceuticals, Novartis, Novo Nordisk, Pfizer, SOBI, and Zoll; has received speaker fees or honoraria and support for attending meetings and/or travels from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Ionis Pharmaceuticals, MSD, Novartis, Pfizer, SOBI, and Zoll; and is in the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function. J.C.F. has served on the Board of Directors for the Heart Failure Society of America. C.F. has received personal fees for consulting

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### Data availability

Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, a statistical analysis plan, data requirements, a publication plan, and qualifications of the researcher(s). Requests are reviewed by a committee of internal and external advisors. If approved, information necessary to address the research question will be provided under the terms of a data sharing agreement. Data sharing requests will be considered after applications for marketing authorization in the US and Europe have been reviewed and final decisions rendered. There is no end date for eligibility to submit a data sharing request for this study. Requests may be submitted to [medicalaffairs@cytokinetics.com](mailto:medicalaffairs@cytokinetics.com).

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