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RESEARCH ARTICLE

Efficacy of omecamtiv mecarbil in heart failure with reduced ejection fraction according to N-terminal pro-B-type natriuretic peptide level: insights from the GALACTIC-HF trial

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Aim

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is predictive of both outcomes and response to treatment in patients with heart failure with reduced ejection fraction (HFrEF). The aim of this study was to examine the effect of the cardiac myosin activator omecamtiv mecarbil according to baseline NT-proBNP level in the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure trial (GALACTIC-HF).

Methods and results

The primary outcome was the composite of a worsening heart failure event (urgent clinic visit, emergency department visit, or hospitalization) or cardiovascular death. We prespecified analysis of the effect of treatment according to baseline NT-proBNP (≤median, >median), excluding individuals with atrial fibrillation/flutter (AF/AFL). Of the 8232 patients analysed, 8206 had an available baseline NT-proBNP measurement. Among the 5971 patients not in AF/AFL, the median (Q1–Q3) NT-proBNP level was 1675 (812–3579) pg/ml. Hazard ratios (HR) for the effect of omecamtiv mecarbil, compared with placebo, for the primary endpoint in patients without AF/AFL were: ≤median 0.94 (95% confidence interval [CI] 0.80–1.09), >median 0.81 (0.73–0.90) (p-interaction = 0.095); for the overall population (including patients with AF/AFL) the HRs were ≤median 1.01 (0.90–1.15) and >median 0.88 (0.80–0.96) (p-interaction = 0.035). There was an interaction between treatment and NT-proBNP, examined as a continuous variable, with greater effect of omecamtiv mecarbil on the primary outcome in patients with a higher baseline NT-proBNP (p-interaction = 0.086).

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Conclusions In GALACTIC-HF, the benefit of omecamtiv mecarbil appeared to be larger in patients with higher baseline NT-proBNP levels, especially in patients without AF/AFL.
Clinical Trial Registration: ClinicalTrials.gov Identifier NCT02929329; EudraCT number, 2016-002299-28.

Keywords Acute coronary syndromes • Atrial fibrillation • Calcium cycling/excitation–contraction coupling • Heart failure • Mortality/survival • Pharmacology • Treatment

Introduction

Natriuretic peptides are fundamental to the understanding of the pathophysiology of heart failure, its diagnosis, assessment of prognosis, and treatment. Elevation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is characteristic of heart failure with reduced ejection fraction (HFrEF) and higher blood concentrations of this and other natriuretic peptides are associated with higher rates of non-fatal and fatal outcomes.[1–5] Conversely, pharmacological therapies that are effective in reducing the risk of hospitalization for worsening heart failure or the risk of death in patients with HFrEF also reduce natriuretic peptides.[3–7] A newly developed therapy for HFrEF, omecamtiv mecarbil, directly augments cardiac contractility by selectively binding to cardiac myosin, increasing the number of myosin heads (force generators) that bind to the actin filament and initiating the power stroke at the start of systole.[8–14] In phase 2 trials in patients with HFrEF, both short-term intravenous treatment and longer-term oral therapy with omecamtiv mecarbil improved cardiac performance.[9–11] In the latter, oral omecamtiv mecarbil, over 20 weeks, reduced left ventricular systolic and diastolic volumes, plasma natriuretic peptide concentrations, and heart rate.[11] As a result, the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure trial (GALACTIC-HF) was conducted to assess whether treatment with omecamtiv mecarbil would improve outcomes in patients with HFrEF, enrolled either as outpatients or inpatients with decompensated heart failure.[12–14] Over a median of 22 months, omecamtiv mecarbil reduced the risk of the primary composite outcome of a worsening heart failure event or cardiovascular death by 8% (hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.86–0.99; $p = 0.025$).[14] We pre-specified that the effect of randomized treatment would be examined according to baseline NT-proBNP (≤ median, > median), according to the randomization setting (outpatient or inpatient), excluding individuals with atrial fibrillation/flutter (AF/AFL). Here we report the effect of omecamtiv mecarbil according to baseline NT-proBNP levels in patients without AF/AFL and in the overall population. In addition, we describe the effect of omecamtiv mecarbil using NT-proBNP as a continuous as well as a categorical measure and describe the effect of omecamtiv mecarbil on NT-proBNP level.

Methods

GALACTIC-HF was a randomized, double-blind, placebo-controlled trial in patients with HFrEF, evaluating the efficacy and safety of omecamtiv mecarbil, in addition to standard care. The design, baseline characteristics, and primary results of the trial are published.[12–14] The Ethics Committee of each of the 945 sites (in 35 countries) approved the protocol, and all patients gave written informed consent. The corresponding author had full access to the trial data and takes responsibility for its integrity and the data analysis. GALACTIC-HF is registered at ClinicalTrials.gov NCT02929329.

Patients

Patients were eligible if aged 18–85 years, in New York Heart Association (NYHA) functional class II–IV and had a left ventricular ejection fraction ≤35% despite optimized standard pharmacological and device therapy. Participants were also required to have an NT-proBNP concentration ≥400 pg/ml or B-type natriuretic peptide (BNP) ≥125 pg/ml (if in AF/AFL: NT-proBNP ≥1200 pg/ml or BNP ≥375 pg/ml). Patients could be enrolled as inpatients (i.e. be hospitalized for heart failure) or outpatients (but only if hospitalized for heart failure or had an urgent visit to an emergency department in the previous year). Key exclusion criteria included systolic blood pressure (SBP) <85 mmHg and estimated glomerular filtration rate (eGFR) <20 ml/min/1.73 m^2. Full details of the eligibility criteria are published elsewhere.[12–14]

Randomized treatment

Participants were randomized 1:1 to either placebo or omecamtiv mecarbil (pharmacokinetic-guided dosing: 25, 37.5, or 50 mg) twice daily. Patients and investigators were blinded to plasma concentrations and dose of omecamtiv mecarbil.

NT-proBNP measurements

NT-proBNP was measured at baseline and at 2, 6, 24, 48, and 96 weeks after randomization. Plasma NT-proBNP was measured in a central laboratory (Q Squared Solutions) using the Roche Elecsys NT-proBNP two-site electrochemiluminescence immunoassay (analytical range 50–35 000 pg/ml).

Study outcomes

The primary outcome was a composite of time to the first occurrence of a heart failure event or cardiovascular death. A heart failure event was defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening heart failure leading to intensification of treatment beyond the augmentation of oral diuretic therapy.[12] All deaths and heart failure events were centrally adjudicated by a blinded Clinical Endpoint Committee. Secondary outcomes included: cardiovascular death; change in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) from baseline to week 24; first heart failure hospitalization; and all-cause death. As described in the

primary results paper, the safety outcomes analysed included: ventricular arrhythmias (ventricular tachyarrhythmia, torsades de pointes or QT prolongation, and serious adverse ventricular arrhythmia leading to treatment), major cardiac ischaemic events (myocardial infarction, hospitalization for unstable angina, and coronary revascularization) and stroke.[14]

Statistical analysis

Although the primary outcome was a composite of a worsening heart failure event or cardiovascular death, the trial was designed to provide 90% power to detect a hazard ratio of 0.8 for cardiovascular death, giving a sample size of approximately 8000 patients. The trial was event-driven, with a target of approximately 1590 cardiovascular deaths. Efficacy analyses were performed according to randomized treatment group assignment (intention-to-treat) on the full analysis set which included all randomized patients except for 24 subjects from a single site excluded due to Good Clinical Practice violations. Baseline characteristics were summarized as frequencies with percentages, means with standard deviation (SD), or medians with interquartile ranges. Differences in baseline characteristics were tested using the Cochrane–Armitage trend test for categorical variables and the analysis of variance test for continuous variables. The difference between treatment groups in NT-proBNP at the time points after randomization in surviving patients was analysed using an analysis of covariance model, with the treatment-group assignment as a fixed-effect factor and baseline NT-proBNP as a covariate. The results of the analyses of covariance are presented as least-squares mean differences with the corresponding 95% CI. Time-to-event data were evaluated with Kaplan–Meier estimates and Cox proportional-hazards models with baseline hazards stratified by randomization setting and region and with treatment group and baseline eGFR as covariates. The safety analyses were performed in patients who underwent randomization and received at least one dose of omecamtiv mecarbil or placebo. All analyses were conducted using STATA version 15.1 (College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). A *p*-value of 0.05 was considered statistically significant.

Results

An NT-proBNP measurement at baseline was available for 8206 of the 8232 patients randomized. Of these, 5971 patients did not have AF/AFL on their baseline electrocardiogram. The median (Q1–Q3) NT-proBNP level at baseline was 1675 (812–3579) pg/ml among patients not in AF/AFL and 1998 (993–4079) pg/ml in all patients randomized (including patients with AF/AFL).

Patient characteristics according to median NT-proBNP level at baseline

Baseline characteristics according to median baseline NT-proBNP concentration are presented in *Table 1* for participants without AF/AFL and in the overall population. Compared to those with NT-proBNP level ≤ median, patients with a level > median were older, more often from Western Europe or Latin America, and less frequently from Asia. Participants with an NT-proBNP level > median had a lower mean body mass index, eGFR (and a larger proportion of patients with eGFR <60 ml/min/1.73 m^2), and systolic blood pressure, but higher heart rate and troponin I. They were also more likely to have a lower ejection fraction, and considerably worse NYHA functional class and KCCQ-TSS. These differences were seen both in participants without AF/AFL and in the overall population.

Some differences were only seen in patients without AF/AFL and not in the overall population. Participants without AF/AFL, with an NT-proBNP level > median, were more likely to have diabetes and an ischaemic aetiology, than those with an NT-proBNP ≤ median (these differences were not significant in the overall population).

Regarding heart failure treatment, patients with an NT-proBNP level > median were less often treated with renin–angiotensin system blockers (including sacubitril/valsartan), mineralocorticoid receptor antagonists, and beta-blockers, but were often prescribed a diuretic and digoxin (even in patients without AF/AFL) and were more likely to have an implanted cardiac device.

Generally, these differences were also observed whether patients were enrolled as an outpatient or an inpatient.

Hospitalization and mortality outcomes according to baseline concentration of NT-proBNP

Event rates were higher in patients with an NT-proBNP > median, compared with ≤ median, in participants without AF/AFL and the overall population, as shown by a comparison of the placebo groups in *Table 2*. When NT-proBNP was examined as a continuous variable, the rate of the primary endpoint rose steeply with increasing NT-proBNP concentration (*Figure 1*). The same was observed whether patients were enrolled as an outpatient or an inpatient (online supplementary *Figure S1*).

Effect of omecamtiv mecarbil on outcomes according to baseline concentration of NT-proBNP

Table 2 shows the effect of omecamtiv mecarbil on the pre-specified morbidity and mortality endpoints, according to baseline NT-proBNP level divided at the median, as pre-specified, in patients without AF/AFL and in the overall trial population. Additional analyses of the effect of omecamtiv mecarbil examining NT-proBNP as a continuous variable are shown in *Figure 2*.

Primary composite outcome

Among patients without AF/AFL, compared to placebo, omecamtiv mecarbil had more benefit on the primary endpoint in participants with an NT-proBNP > median (HR 0.81, 95% CI 0.73–0.90) than in patients with an NT-proBNP ≤ median (HR 0.94, 95% CI 0.80–1.09; *p* for interaction = 0.095). A similar interaction was seen in the overall population (HR 0.88, 95% CI 0.80–0.96 in patients with NT-proBNP > median and HR 1.01, 95% CI 0.90–1.15 in participants with an NT-proBNP ≤ median; *p* for interaction = 0.035). We performed a sensitivity analysis in the overall population using specific median values for patients with

Table 1 Baseline characteristics of patients according to pre-randomization N-terminal pro-B-type natriuretic peptide level (≤ median or > median) in the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and in all patients randomized

	No AF/AFL			All patients		
	≤ median (*n* = 2987)	> median (*n* = 2984)	*p*-value	≤ median (*n* = 4105)	> median (*n* = 4101)	*p*-value
Age (years), mean (SD)	61.6 ± 11.4	64.9 ± 11.5	<0.001	62.5 ± 11.3	66.5 ± 11.0	<0.001
Male sex, *n* (%)	2334 (78.1)	2300 (77.1)	0.33	3259 (79.4)	3203 (78.1)	0.15
Race, *n* (%)			<0.001			<0.001
Asian	316 (10.6)	240 (8.0)		402 (9.8)	308 (7.5)	
Black	234 (7.8)	249 (8.3)		290 (7.1)	266 (6.5)	
White	2238 (74.9)	2262 (75.8)		3159 (77.0)	3220 (78.5)	
Other	199 (6.7)	233 (8.2)		254 (6.2)	307 (7.5)	
Geographic region, *n* (%)			<0.001			<0.001
Asia	300 (10.0)	222 (7.4)		382 (9.3)	288 (7.0)	
Western Europe	587 (19.7)	718 (24.1)		827 (20.1)	1086 (26.5)	
Eastern Europe	972 (32.5)	818 (27.4)		1408 (34.3)	1273 (31.0)	
North America	586 (19.6)	542 (18.2)		757 (18.4)	611 (14.9)	
Latin America	542 (18.1)	684 (22.9)		731 (17.8)	843 (20.6)	
Randomized as an inpatient, *n* (%)	569 (19.0)	776 (26.0)	<0.001	871 (21.2)	1188 (29.0)	<0.001
Physiological measures						
Systolic blood pressure (mmHg), mean (SD)	119.0 ± 14.8	115.0 ± 15.9	<0.001	118.5 ± 14.8	114.4 ± 15.7	<0.001
Heart rate (bpm)	69.9 ± 10.9	72.8 ± 11.9	<0.001	70.8 ± 11.4	73.9 ± 12.7	<0.001
BMI (kg/m^2)	29.6 ± 6.2	27.2 ± 5.8	<0.001	29.6 ± 6.3	27.3 ± 5.8	<0.001
eGFR (ml/min/1.73 m^2), mean (SD)	67.4 ± 21.8	57.0 ± 22.0	<0.001	66.0 ± 21.4	54.9 ± 21.0	<0.001
eGFR <60 ml/min/1.73 m^2, *n* (%)	1163 (38.9)	1764 (59.1)	<0.001	1705 (41.5)	2599 (63.4)	<0.001
Ischaemic aetiology, *n* (%)	1624 (54.4)	1708 (57.2)	0.026	2185.0 (53.2)	2216.0 (54.0)	0.46
LVEF, mean (SD)	27.4 ± 6.0	25.3 ± 6.4	<0.001	27.4 ± 6.0	25.7 ± 6.4	<0.001
NYHA class, *n* (%)			<0.001			<0.001
II	1893 (63.4)	1454 (48.7)		2484 (60.5)	1875 (45.7)	
III	1045 (35.0)	1418 (47.5)		1539 (37.5)	2060 (50.2)	
IV	49 (1.6)	112 (3.8)		82 (2.0)	166 (4.0)	
KCCQ-TSS, mean (SD)	71.9 ± 23.3	64.4 ± 25.7	<0.001	70.7 ± 23.8	62.3 ± 25.7	<0.001
AF/AFL*, *n* (%)	–	–	–	725 (17.7)	1510 (36.8)	
Medical history, *n* (%)						
Hypertension	2085 (69.8)	2038 (68.3)	0.21	2908 (70.8)	2854 (69.6)	0.22
Type 2 diabetes	1188 (39.8)	1288 (43.2)	0.008	1662.0 (40.5)	1702.0 (41.5)	0.35
Previous MI	1315 (44.0)	1361 (45.6)	0.22	1727 (42.1)	1696 (41.4)	0.51
Treatment, *n* (%)						
ACEI/ARB/ARNI	2752.0 (92.1)	2481.0 (83.1)	<0.001	3752.0 (91.4)	3388.0 (82.6)	<0.001
ARNI	629.0 (21.1)	536.0 (18.0)	0.003	862.0 (21.0)	728.0 (17.8)	<0.001
Beta-blocker	2865.0 (95.9)	2771.0 (92.9)	<0.001	3921.0 (95.5)	3819.0 (93.1)	<0.001
MRA	2377.0 (79.6)	2238.0 (75.0)	<0.001	3279.0 (79.9)	3101.0 (75.6)	<0.001
Diuretic	2541 (85.1)	2732 (91.6)	<0.001	3554 (86.6)	3801 (92.7)	<0.001
Digoxin	319 (10.7)	372 (12.5)	0.031	610 (14.9)	771 (18.8)	<0.001
ICD	893.0 (29.9)	1012.0 (33.9)	<0.001	1222.0 (29.8)	1380.0 (33.7)	<0.001
CRT-P/CRT-D	352.0 (11.8)	460.0 (15.4)	<0.001	480.0 (11.7)	672.0 (16.4)	<0.001

Percentages may not total 100 because of rounding.
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CRT-P/D, cardiac resynchronization therapy with pacemaker/defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score (range from 0 to 100, with higher scores indicating fewer symptoms); LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.

Table 2 Outcomes according to baseline N-terminal pro-B-type natriuretic peptide level (≤ median or > median) according to randomized treatment assignment in the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and all patients randomized

	No AF/AFL (n = 5971)						All patients (n = 8206)					
	Placebo (n = 3006)		OM (n = 2965)		HR (95% CI)	p-value	Placebo (n = 4099)		OM (n = 4107)		HR (95% CI)	p-value
	n (%)	Rate	n (%)	Rate			n (%)	Rate	n (%)	Rate		
Primary outcome												
≤ median NT-proBNP	352 (23)	13.42	328 (22)	12.42	0.94 (0.80, 1.09)	0.392	518 (25)	14.84	537 (26)	15.00	1.02 (0.90, 1.15)	0.790
> median NT-proBNP	748 (50)	38.85	650 (44)	31.30	0.81 (0.73, 0.90)	0.000	1080 (52)	41.59	981 (48)	36.52	0.88 (0.81, 0.96)	0.003
HF hospitalization												
≤ median NT-proBNP	263 (17)	10.02	254 (17)	9.62	0.97 (0.82, 1.15)	0.728	399 (20)	11.43	424 (20)	11.84	1.04 (0.91, 1.19)	0.565
> median NT-proBNP	570 (38)	29.62	483 (32)	23.26	0.79 (0.70, 0.89)	0.000	830 (40)	31.97	750 (37)	27.93	0.88 (0.79, 0.97)	0.008
Cardiovascular death												
≤ median NT-proBNP	141 (9)	4.85	135 (9)	4.64	0.96 (0.76, 1.22)	0.761	202 (10)	5.13	227 (11)	5.63	1.11 (0.92, 1.34)	0.296
> median NT-proBNP	405 (27)	16.32	363 (24)	14.29	0.87 (0.75, 1.00)	0.047	591 (29)	17.18	578 (28)	17.15	0.99 (0.88, 1.11)	0.811
All-cause death												
≤ median NT-proBNP	205 (14)	7.05	196 (13)	6.74	0.96 (0.79, 1.17)	0.715	292 (14)	7.42	327 (16)	8.11	1.10 (0.94, 1.29)	0.223
> median NT-proBNP	530 (35)	21.35	474 (32)	18.67	0.86 (0.76, 0.97)	0.017	766 (37)	22.27	737 (36)	21.87	0.97 (0.88, 1.07)	0.544

Numbers of patients in subgroups. No AF/AFL: NT-proBNP ≤ median: placebo = 1511/OM = 1476. NT-proBNP > median: placebo = 1495/OM = 1489. All patients: NT-proBNP ≤ median: placebo = 2032/OM = 2073. NT-proBNP > median: placebo = 2067/OM = 2034. The primary outcome was a composite of time to HF event or cardiovascular death, whichever came first. Rate is per 100 person-years.
AF, atrial fibrillation; AFL, atrial flutter; HF, heart failure; CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OM, omecamtiv mecarbil.

or without AF/AFL (HR 0.86, 95% CI 0.79–0.94 in patients with NT-proBNP > median and HR 1.05, 95% CI 0.93–1.18 in participants with an NT-proBNP ≤ median; p for interaction = 0.007).

When NT-proBNP was examined as a continuous variable, the increasing beneficial effect of omecamtiv mecarbil with increasing NT-proBNP became clearer as shown in *Figure 2*.

Qualitatively similar findings were seen in participants enrolled in both the outpatient and inpatient setting (online supplementary *Figure S2*).

Secondary outcomes

Examination of the hospitalization and mortality secondary outcomes in patients without AF/AFL suggested the interaction between baseline NT-proBNP level and the effect of omecamtiv mecarbil was more evident for heart failure hospitalization than for cardiovascular or all-cause death (*Table 2*, *Figure 2*). While both hospitalization and mortality were reduced by omecamtiv mecarbil in participants without AF/AFL and an NT-proBNP > median, the mortality benefits were lost when the overall population was analysed, because of the absence of an effect of omecamtiv mecarbil in patients with AF/AFL. Even the larger benefit of omecamtiv mecarbil on heart failure hospitalization was attenuated by the addition of patients with AF/AFL in the overall population.

Effect of omecamtiv mecarbil on physiologic measures and plasma biomarkers according to baseline concentration of NT-proBNP

Table 3 shows the effect of omecamtiv mecarbil on physiologic measures and plasma biomarkers according to baseline NT-proBNP level divided at the median, in patients without AF/AFL, and in the overall trial population. Changes from baseline to the 24-week visit are provided. Omecamtiv mecarbil did not have a significant effect on systolic blood pressure in any subgroup but did reduce heart rate, significantly, by 1–2 bpm in all four patient subgroups. Treatment with omecamtiv mecarbil also led to a small but significant increase in troponin I in all subgroups other than non AF/AFL patients with < median NT-proBNP (in whom there was a smaller decrease with omecamtiv mecarbil as compared with the placebo group) and the proportional between-group difference was similar in all four patient subgroups. By contrast, omecamtiv mecarbil reduced NT-proBNP only in patients with a baseline value NT-proBNP > median at baseline, as shown in more detail in *Figure 3*.

Association between reduction in NT-proBNP and effect of omecamtiv mecarbil

We conducted landmark analyses, in participants who had both a baseline and a 6-week NT-proBNP level and were event-free at that point. Among those without AF/AFL, the unadjusted HR for the primary outcome after day 45 was 0.86 (95% CI 0.78–0.95). After adjusting for the change in NT-proBNP between baseline and 6 weeks, the HR was 0.91 (95% CI 0.83–1.00).

The corresponding HRs in the overall population were 0.91 (95% CI 0.85–0.99) and 0.96 (95% CI 0.89–1.04), respectively.

Safety outcomes

The occurrence of adverse events according to treatment assignment according to NT-proBNP category is shown in *Table 4*.

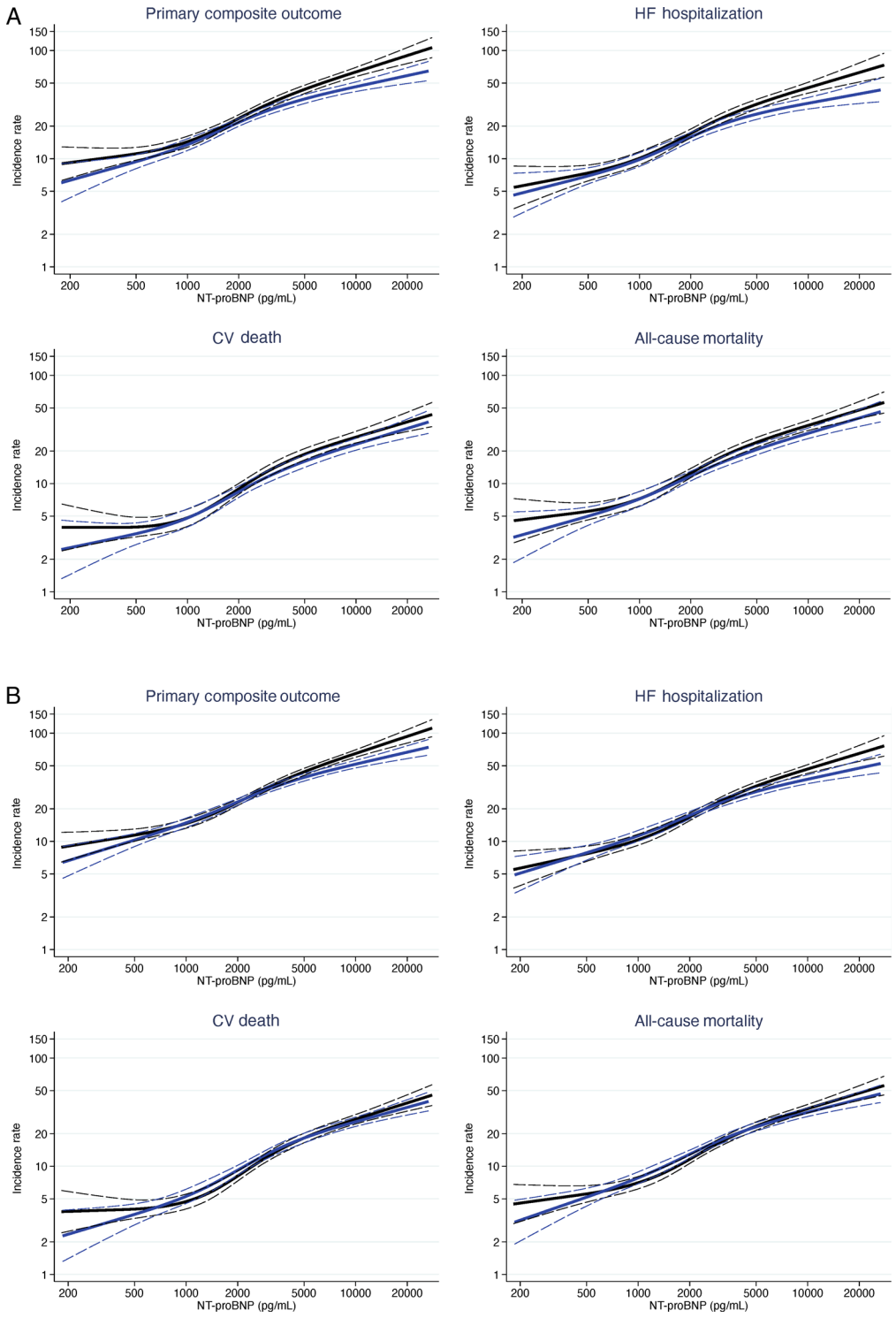

Figure 1 Outcomes according to baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) level in (*A*) the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and (*B*) all patients randomized (including patients with atrial fibrillation/flutter at baseline). The *y*-axis shows the incidence rate per 100 person-years and the *x*-axis NT-proBNP level (ng/L). CV, cardiovascular; HF, heart failure. Black line = patients randomly assigned to placebo; blue line = patients randomly assigned to omecamtiv mecarbil.

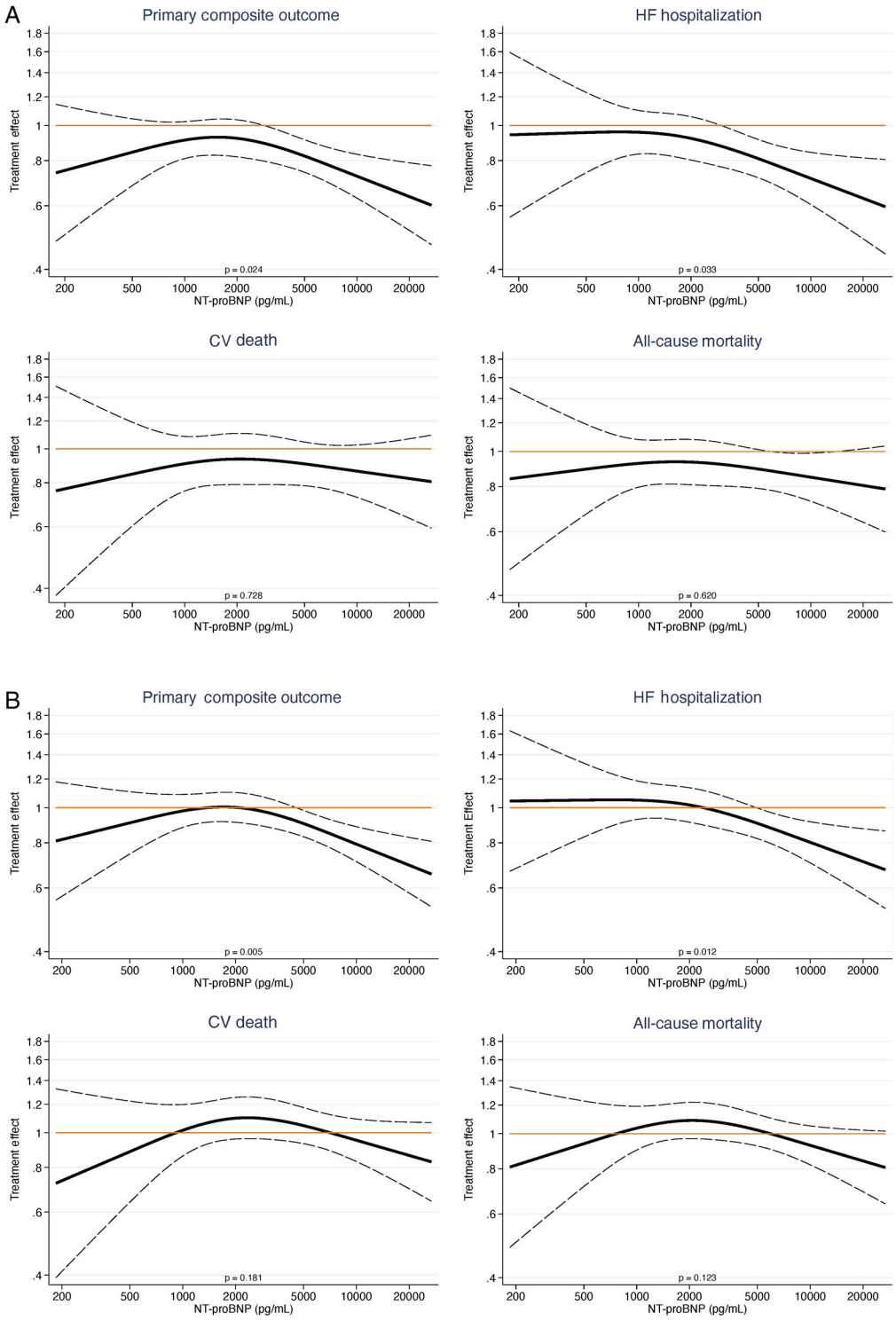

Figure 2 Effect of randomized treatment on outcomes according to baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) level in (*A*) the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and (*B*) all patients randomized (including patients with atrial fibrillation/flutter at baseline). CV, cardiovascular; HF, heart failure. Solid black line = continuous hazard ratio; interrupted black lines = 95% confidence interval. Horizontal solid brown line = unity (hazard ratio = 1). A hazard ratio of less than 1 indicates a benefit of omecamtiv mecarbil over placebo.

Table 3 **Change from baseline to 24 weeks in physiologic measures and biomarkers according to baseline N-terminal pro-B-type natriuretic peptide level (≤ median or > median) according to randomized treatment assignment in the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and all patients randomized**

	No AF/AFL (n = 5971)						All patients (n = 8206)					
	Placebo (n = 3006)		OM (n = 2965)		Difference/ratio	p-value	Placebo (n = 4099)		OM (n = 4107)		Difference/ratio	p-value
	Baseline	24 weeks	Baseline	24 weeks			Baseline	24 weeks	Baseline	24 weeks		
Systolic BP (mmHg)												
≤ median NT-proBNP	119 (15)	122 (18)	119 (15)	120 (16)	−1.0 (−2.1, 0.1)	0.06	119 (14)	121 (17)	118 (15)	120 (16)	−0.8 (−1.7, 0.2)	0.11
> median NT-proBNP	115 (16)	117 (19)	115 (16)	117 (18)	0.3 (−0.8, 1.4)	0.59	114 (16)	116 (18)	114 (16)	116 (17)	−0.1 (−1.0, 0.9)	0.88
Heart rate (bpm)												
≤ median NT-proBNP	70 (11)	70 (11)	70 (11)	69 (11)	−1.5 (−2.2, −0.8)	<0.001	71 (12)	71 (12)	71 (11)	70 (11)	−1.5 (−2.2, −0.09)	<0.001
> median NT-proBNP	73 (12)	71 (11)	73 (12)	70 (12)	−1.7 (−2.5, −0.9)	<0.001	74 (12)	72 (12)	74 (13)	70 (12)	−1.6 (−2.3, −0.8)	<0.001
Creatinine (mg/dl)												
≤ median NT-proBNP	1.19 (0.40)	1.18 (0.40)	1.16 (0.36)	1.17 (0.42)	0.02 (−0.00, 0.04)	0.07	1.20 (0.40)	1.20 (0.39)	1.19 (0.37)	1.21 (0.43)	0.02 (0.00, 0.04)	0.019
> median NT-proBNP	1.37 (0.50)	1.40 (0.56)	1.39 (0.52)	1.37 (0.50)	−0.01 (−0.03, 0.02)	0.66	1.40 (0.49)	1.43 (0.57)	1.42 (0.52)	1.43 (0.56)	−0.01 (−0.03, 0.02)	0.54
NT-proBNP (pg/ml)												
≤ median NT-proBNP	829 (535, 1174)	691 (332, 1150)	791 (506, 1176)	614 (332, 1150)	0.95 (0.88, 1.01)	0.11	914 (610, 1444)	818 (410, 1480)	992 (592, 1469)	772 (385, 1472)	0.95 (0.90, 1.01)	0.10
> median NT-proBNP	3574 (2387, 6312)	2754 (1424, 5241)	3586 (2364, 6353)	2302 (1146, 4689)	0.83 (0.76, 0.90)	<0.001	4065 (2798, 6952)	3207 (1766, 5774)	4100 (2732, 6972)	2809 (1474, 5145)	0.84 (0.78, 0.89)	<0.001
Troponin I (ng/L)[a]												
≤ median NT-proBNP	19 (10, 37)	16 (10, 35)	18 (10, 35)	16 (10, 35)	1.25 (1.18, 1.31)	<0.001	20 (10, 39)	18 (10, 37)	19 (10, 38)	24 (10, 50)	1.28 (1.22, 1.34)	<0.001
> median NT-proBNP	33 (18, 61)	31 (16, 56)	36 (18, 67)	40 (20, 78)	1.23 (1.16, 1.31)	<0.001	35 (19, 64)	34 (17, 62)	37 (19, 67)	44 (22, 81)	1.23 (1.17, 1.29)	<0.001

Data are presented as mean (standard deviation) and median (25th, 75th centile) as appropriate.

AF, atrial fibrillation; AFL, atrial flutter; BP, blood pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OM, omecamtiv mecarbil.

[a] Measured using the Siemens ADVIA Centaur Ultra Troponin I assay (lower limit of detection, 6 ng/L; upper reference limit, 40 ng/L).

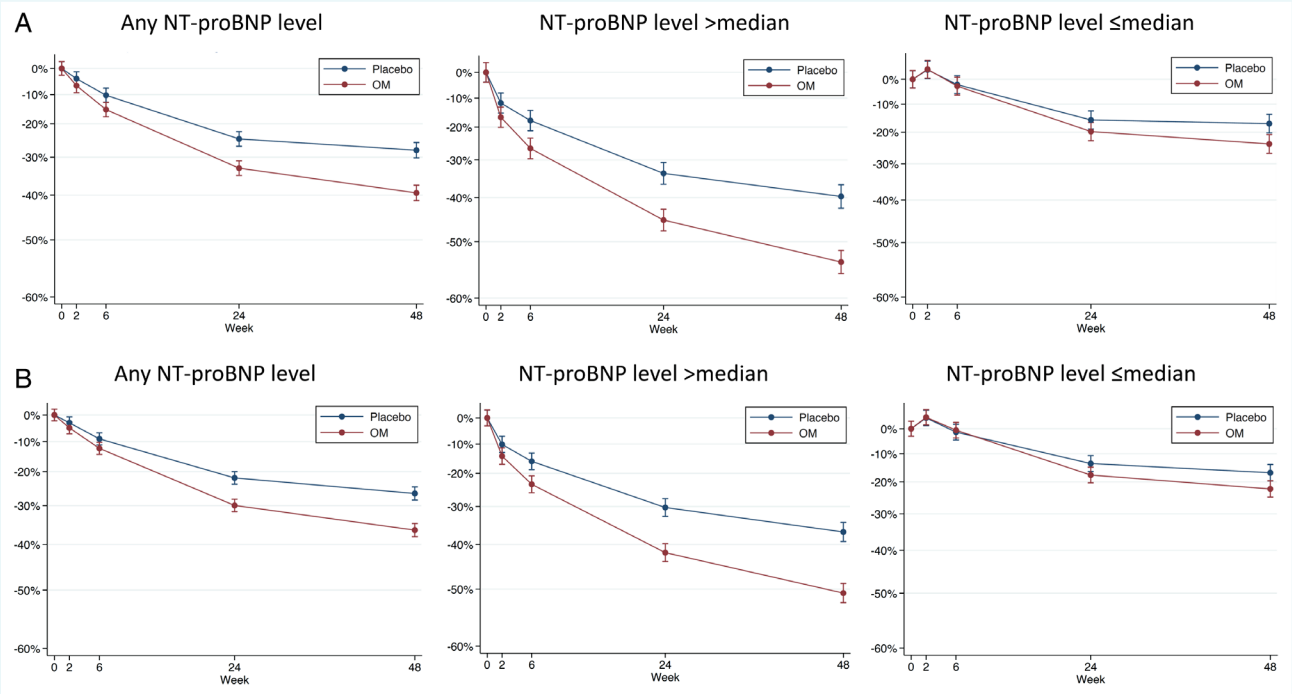

Figure 3 Effect of omecamtiv mecarbil (OM), compared with placebo, on N-terminal pro-B-type natriuretic peptide (NT-proBNP) after randomization. Figures show the percent change in NT-proBNP from baseline according to treatment assignment in (*A*) the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and (*B*) all patients randomized (including patients with atrial fibrillation/flutter at baseline). In each population, three panels are shown – all patients, irrespective of NT-proBNP level, and patients with an NT-proBNP level either above or at or below the median value.

Table 4 Adverse events according to baseline N-terminal pro-B-type natriuretic peptide level (≤ median or > median) according to randomized treatment assignment in the pre-specified analysis population (no atrial fibrillation/flutter at baseline) and all patients randomized

	No AF/AFL (*n* = 5971)				All patients (*n* = 8206)			
	Placebo (*n* = 3006)	OM (*n* = 2965)	RR	*p*-value	Placebo (*n* = 4099)	OM (*n* = 4107)	RR	*p*-value
Ventricular tachyarrhythmia								
≤ median NT-proBNP	104 (8.1)	84 (6.7)	0.82 (0.62, 1.09)	0.17	142 (8.2)	130 (7.3)	0.89 (0.71, 1.12)	0.32
> median NT-proBNP	112 (8.2)	115 (8.6)	1.05 (0.82, 1.35)	0.69	161 (8.4)	160 (8.7)	1.03 (0.83, 1.27)	0.79
Torsade/QT prolongation								
≤ median NT-proBNP	57 (4.4)	47 (3.7)	0.84 (0.58, 1.23)	0.37	86 (4.9)	78 (4.4)	0.88 (0.65, 1.19)	0.41
> median NT-proBNP	72 (5.2)	71 (5.3)	1.01 (0.73, 1.39)	0.95	108 (5.6)	98 (5.3)	0.94 (0.72, 1.23)	0.64
Ventricular tachyarrhythmia leading to treatment								
≤ median NT-proBNP	44 (2.9)	29 (2.0)	0.67 (0.42, 1.07)	0.09	58 (2.9)	51 (2.5)	0.86 (0.59, 1.25)	0.43
> median NT-proBNP	43 (2.9)	49 (3.3)	1.15 (0.77, 1.72)	0.51	68 (3.3)	68 (3.4)	1.02 (0.73, 1.42)	0.91
Major cardiac ischaemic events								
≤ median NT-proBNP	76 (5.0)	86 (5.8)	1.16 (0.86, 1.56)	0.34	101 (5.0)	114 (5.5)	1.10 (0.85, 1.43)	0.46
> median NT-proBNP	77 (5.2)	83 (5.6)	1.08 (0.80, 1.47)	0.60	87 (4.2)	85 (4.2)	0.99 (0.74, 1.33)	0.97
Stroke								
≤ median NT-proBNP	31 (2.1)	25 (1.7)	0.83 (0.49, 1.39)	0.47	52 (2.6)	36 (1.7)	0.68 (0.44, 1.03)	0.07
> median NT-proBNP	40 (2.7)	29 (2.0)	0.73 (0.45, 1.17)	0.19	59 (2.9)	40 (2.0)	0.69 (0.46, 1.03)	0.07

Numbers of patients in subgroups. All patients: NT-proBNP ≤ median: placebo = 2032/OM = 2073. NT-proBNP > median: placebo = 2067/OM = 2034. No AF/FL NT-proBNP ≤ median: placebo = 1511/OM = 1476. NT-proBNP > median: placebo = 1495/OM = 1489. Rate is per 100 person-years.
AF, atrial fibrillation; AFL, atrial flutter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OM, omecamtiv mecarbil; RR, relative risk.

Comparison of the placebo groups showed no substantial difference in the incidence of any adverse event in patients with a baseline NT-proBNP concentration > median compared to ≤ median. Similarly, there was no strong or consistent evidence that any adverse event was more common with omecamtiv mecarbil, compared to placebo, in any of the four subgroups of patients.

Discussion

In this pre-specified analysis of patients without AF/AFL enrolled in GALACTIC-HF, we found that omecamtiv mecarbil reduced the risk of the primary endpoint to a greater extent in those who had higher NT-proBNP levels, compared to lower NT-proBNP levels, at baseline. Omecamtiv mecarbil reduced the risk of both components of the primary endpoint in patients with higher NT-proBNP levels. Omecamtiv mecarbil also reduced NT-proBNP to a significantly greater extent in those with a baseline concentration > median, compared to those with a baseline NT-proBNP level ≤ median. In other words, it appeared that NT-proBNP concentration at baseline identified patients likely to respond more favourably to omecamtiv mecarbil (i.e. those with a high baseline level), and reduction in NT-proBNP represented a surrogate for the efficacy of omecamtiv mecarbil, as seen with other treatments.[3–7,15]

Plasma natriuretic peptide concentrations reflect cardiac chamber wall stress, blood volume, heart rhythm, and kidney function.[1–3,16] Therefore, in patients with HFrEF, natriuretic peptides provide an integrated measure of cardiac preload and afterload, chamber size, wall thickness, and systolic function, as well as the systemic consequences of pump dysfunction. It is not surprising, therefore, that selectively targeting the cardiac sarcomere to improve pump function might have the most benefit in those with elevated NT-proBNP levels, by identifying the individuals with the greatest cardiac dysfunction. The present observations are consistent with and extend our findings that the benefits of omecamtiv mecarbil were most evident in patients with the lowest ejection fractions.[17]

In the pre-specified analysis population (patients without AF/AFL), treatment with omecamtiv mecarbil led to a relative risk reduction of 19% (95% CI 10–27%) in the primary endpoint, with a somewhat larger reduction in heart failure hospitalization (21%, 11–30%) than in cardiovascular mortality (13%, 0–25%), in those with a baseline NT-proBNP > median, with no clear benefit in participants with NT-proBNP ≤ median. To explore this interaction further, we conducted additional *post hoc* analyses examining the effect of omecamtiv mecarbil using NT-proBNP as a continuous measure. These analyses suggested a linear interaction above a threshold of around 2000 pg/ml (below which there was no suggestion of benefit), with a steadily increasing benefit of omecamtiv mecarbil as the NT-proBNP level increased across the remaining range of baseline values (up to approximately 20 000 pg/ml). The benefits of omecamtiv mecarbil related to NT-proBNP levels were consistent in both inpatients and outpatients.

In the overall trial population, the benefits of omecamtiv mecarbil were smaller than seen in participants without AF/AFL, possibly because of the interplay between AF/AFL, NT-proBNP level, and left ventricular ejection fraction.[18] Atrial arrhythmias elevate natriuretic peptides and, for a given natriuretic peptide level, the degree of left ventricular systolic dysfunction is less in patients with AF/AFL than in patients in sinus rhythm.[19,20] Consequently, patients with AF/AFL may have 'diluted' the prevalence of significant left ventricular systolic dysfunction in the overall trial population with an NT-proBNP > median, compared to participants without AF/AFL with an NT-proBNP > median.

Just as natriuretic peptides increase with cardiac chamber dilatation, elevated wall stress, and reduced systolic function, reversal of these abnormalities with effective therapy is paralleled by a decrease in natriuretic peptides. Consequently, the clinical benefits of omecamtiv mecarbil should have been accompanied by a corresponding reduction in NT-proBNP level during treatment.[3–7,15] This is what we observed, and the greater clinical benefits in patients with a baseline NT-proBNP > median was reflected in a greater reduction in NT-proBNP in such patients (and, indeed, little change in NT-proBNP in participants with a value ≤ median at baseline). In patients with an NT-proBNP > median at baseline, the proportional reduction in NT-proBNP in the omecamtiv mecarbil, compared with placebo, group was approximately 17%. In a prior analysis of 18 therapeutic interventions in heart failure, a 17% reduction in natriuretic peptide concentration was associated with an approximately 20% relative risk reduction in heart failure hospitalization and 13% reduction in mortality, estimates close to the actual reductions observed in GALACTIC-HF.[6]

Although treatment with omecamtiv mecarbil led to a small, but statistically significant, increase in troponin I, which has been observed before, there was no associated increase in cardiac ischaemic events or any other adverse event of interest.[10,11]

The findings presented have potentially important clinical implications. Patients with very high natriuretic peptide levels are at especially high risk and often have other clinical features such as low blood pressure and poor renal function causing intolerance of some recommended therapies.[21–24] Any additional therapeutic option is attractive for these individuals and it is often in these patients that inotropic therapy is resorted to, or even use of mechanical support or transplantation.[21–24] The present findings support evidence from another analysis that omecamtiv mecarbil may be of particular value in such patients with more advanced heart failure.[25] In this context, it is of interest that a contrasting observation was made with another new therapy, vericiguat, where treatment efficacy declined at higher NT-proBNP concentrations.[26]

Limitations

The findings of this study should be viewed in the context of potential limitations. Although NT-proBNP was a pre-defined subgroup analysis, the utilization of baseline NT-proBNP as a continuous measure was done *post hoc*. The pre-specified inclusion and exclusion criteria, although less restrictive than most prior HFrEF trials, reduce the generalizability of our results.

Conclusions

In GALACTIC-HF, the benefit of omecamtiv mecarbil appeared to be larger in patients with higher baseline NT-proBNP levels, especially in patients without AF/AFL.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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