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RESEARCH ARTICLE

Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: GALACTIC-HF baseline characteristics and comparison with contemporary clinical trials

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Aims The safety and efficacy of the novel selective cardiac myosin activator, omecamtiv mecarbil, in patients with heart failure with reduced ejection fraction (HFrEF) is being tested in the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial. Here we describe the baseline characteristics of participants in GALACTIC-HF and how these compare with other contemporary trials.

Methods and results Adults with established HFrEF, New York Heart Association (NYHA) functional class ≥II, ejection fraction ≤35%, elevated natriuretic peptides and either current hospitalization for heart failure or history of hospitalization/emergency department visit for heart failure within a year were randomized to either placebo or omecamtiv mecarbil (pharmacokinetic-guided dosing: 25, 37.5, or 50 mg bid). A total of 8256 patients [male (79%), non-white (22%), mean age 65 years] were enrolled with a mean ejection fraction 27%, ischaemic aetiology in 54%, NYHA class II 53% and III/IV 47%, and median N-terminal pro-B-type natriuretic peptide 1971 pg/mL. Heart failure therapies at baseline were among the most effectively employed in contemporary heart failure trials. GALACTIC-HF randomized patients representative of recent heart failure registries and trials with substantial numbers of patients also having characteristics understudied in previous trials including more from North America ($n = 1386$), enrolled as inpatients ($n = 2084$), systolic blood pressure <100 mmHg ($n = 1127$), estimated glomerular filtration rate <30 mL/min/1.73 m^2 ($n = 528$), and treated with sacubitril/valsartan at baseline ($n = 1594$).

Conclusions GALACTIC-HF enrolled a well-treated, high-risk population from both inpatient and outpatient settings, which will provide a definitive evaluation of the efficacy and safety of this novel therapy, as well as informing its potential future implementation.

Keywords Heart failure • Omecamtiv mecarbil • Cardiac myosin activator • Inotrope • Myotrope • Cardiovascular outcomes trial

Introduction

The pathogenesis of heart failure with reduced ejection fraction (HFrEF) is characterized primarily by a decrease in systolic function independent of the specific aetiology. Contemporary therapies do not directly address this fundamental defect, but rather act on the compensatory pathways that are stimulated by this loss of function. Omecamtiv mecarbil[1] is a cardiac myosin activator[2] and the first of a novel class of myotropes,[3] agents that directly improve myocardial function by selectively increasing cardiac sarcomere function. Clinical studies in healthy volunteers[4] and patients with stable chronic[5] and acute heart failure[6] show that omecamtiv mecarbil improves cardiac performance. In the COSMIC-HF study,[7] patients with chronic HFrEF treated with omecamtiv mecarbil for 20 weeks had improved systolic function and structure demonstrated by increased systolic ejection time,[8–10] fractional shortening, ejection fraction and stroke volume as well as decreased left ventricular systolic dimensions and volumes. Omecamtiv mecarbil treatment also led to reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and heart rate, consistent with decreased ventricular stress and less neurohormonal activation. Importantly, the significant reductions in left ventricular diastolic and systolic dimensions and volumes were suggestive of beneficial reverse ventricular remodelling. These findings suggest that omecamtiv mecarbil might reduce both heart failure hospitalizations[11] and mortality.[12]

The Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial is the first to examine whether selectively increasing cardiac contractility in patients with HFrEF will result in improved clinical outcomes.[13] Due to the absence of adverse effects on blood pressure, heart rate, renal function or potassium homeostasis with omecamtiv mecarbil, GALACTIC-HF enrolled a broad range of patients from both the inpatient and outpatient settings, many of whom have been specifically excluded in other contemporary heart failure trials. GALACTIC-HF tests the hypotheses that omecamtiv mecarbil can safely improve symptoms, prevent clinical heart failure events, and delay cardiovascular death in patients with HFrEF.

Methods

The GALACTIC-HF (ClinicalTrials.gov NCT02929329; EU Clinical Trials Register 2016-002299-28) trial is a multicentre, randomized, double-blind, placebo-controlled, event-driven cardiovascular outcomes trial to evaluate the efficacy, safety and tolerability of omecamtiv mecarbil in patients with chronic HFrEF.[13]

Summary of GALACTIC-HF design

People aged 18–85 years with a history of symptomatic [New York Heart Association (NYHA) functional class II–IV] HFrEF (ejection fraction ≤ 35%), optimally treated with standard of care pharmacologic and device therapy for HFrEF were eligible. Participants were currently hospitalized for heart failure (inpatients; approximately 25% of enrolment) or within 1 year had either an urgent visit to the emergency department for heart failure or a hospitalization for heart failure (outpatients). In addition, patients had NT-proBNP concentration ≥400 pg/mL or B-type natriuretic peptide (BNP) ≥125 pg/mL at screening (if in atrial fibrillation/flutter: NT-proBNP ≥1200 pg/mL or BNP ≥375 pg/mL).

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Key exclusion criteria included: current haemodynamic or clinical instability requiring mechanical or intravenous medication, systolic blood pressure (SBP) <85 mmHg, estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2, recent acute coronary syndrome events or cardiovascular procedures (including planned procedures), and other conditions with reduced life expectancy <2 years or that would adversely affect participation in the trial. A full description of the eligibility criteria has been published.[13]

Participants were randomized 1:1 to oral administration of either placebo or omecamtiv mecarbil twice daily (pharmacokinetic-guided dosing: 25, 37.5, or 50 mg bid). The primary objective of the GALACTIC-HF trial is to determine in patients with HFrEF on standard of care heart failure therapy whether omecamtiv mecarbil is superior to placebo in reducing cardiovascular death or heart failure events. A heart failure event is defined as an urgent, unscheduled clinic/office/emergency department visit or hospital admission with a primary diagnosis of heart failure where the patient exhibited new or worsening symptoms of heart failure on presentation, had objective evidence of new or worsening heart failure, and received initiation or intensification of treatment specifically for heart failure. Additional secondary and exploratory outcomes have been published.[13] The study is endpoint-driven and will end after accumulation of approximately 1590 cardiovascular deaths.

Comparator studies

Three recent registries [European Society of Cardiology Heart Failure Long-Term Registry (ESC HF Long-Term Registry),[14] Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry,[15,16] Change the Management of Patients with Heart Failure (CHAMP-HF) registry[17,18]] from varied international regions were reviewed to provide 'real-world' context for the GALACTIC-HF population. Moreover, patient characteristics from four contemporary Phase III clinical trials of heart failure pharmacologic therapies [Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF),[19] Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF),[20] Vericiguat global study in subjects with heart failure with reduced ejection fraction (VICTORIA)[21] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced)[22]] were compared to those in GALACTIC-HF. GALACTIC-HF was designed to enrol patients with HFrEF from both the inpatient and outpatient settings. While many Phase III trials have been conducted to evaluate new intravenous therapies for patients with acute heart failure, three major trials [Efficacy of Vasopressin Antagonism In Heart Failure Outcome Study with Tolvaptan (EVEREST),[23,24] Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT),[25] and Comparison of Sacubitril-Valsartan vs. Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF)[26]] have enrolled patients stabilized during an admission for heart failure and treated with chronic oral therapies. These trials have been used to provide the context for GALACTIC-HF participants enrolled as inpatients.

Results

GALACTIC-HF baseline characteristics

Nearly 11 000 people were screened for enrolment in GALACTIC-HF and approximately 25% did not meet eligibility criteria (online supplementary *Table S1*). From 6 January 2017 to 9 July 2019, 8256 participants were randomized at 945 sites in 35 countries. The baseline characteristics of these participants are presented in *Table 1* and in *Figure 1*. The participants were on average 65 years of age, 21% female, and 78% self-identified white race recruited from a wide range of regions (33% Eastern Europe/Russia; 23% Western Europe/South Africa/Australasia; 19% Latin and South America; 17% North America; 8% Asia). Comorbidities were common in the participants, including 62% with coronary artery disease, 42% history of atrial fibrillation/flutter, 70% hypertension, and 40% diabetes mellitus. The median (Q1–Q3) eGFR was 59 (44–74) mL/min/1.73 m^2 and 52% had chronic kidney disease stage III–V. The mean left ventricular ejection fraction was 27%, predominantly due to an ischaemic aetiology (54%). Participants had mild–moderate symptom limitation, with 53% patients in NYHA functional class II and 47% in NYHA functional class III/IV. The mean Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) was 66 (where 100 is the least symptom burden). Mean (standard deviation) SBP was 117 (15) mmHg and the mean heart rate was 72 (12) bpm. NT-proBNP was substantially elevated [median (Q1–Q3): 1971 (961–4033) pg/mL], with modestly elevated high-sensitivity troponin I [median (Q3): 0.030 (0.049) ng/mL; upper limit of 95% confidence interval: 0.014 ng/mL]. Patients were well treated with guideline-recommended heart failure therapies at baseline with 87% receiving an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin receptor–neprilysin inhibitor (ARNi) (19.3% ARNi), 94% beta-blocker, and 77% mineralocorticoid receptor antagonist (MRA). Approximately two-thirds of the participants were receiving triple therapy (ACEi/ARB/ARNi + beta-blocker + MRA). Almost 32% of the patients had an implantable cardioverter defibrillator and 14% had cardiac resynchronization therapy at baseline.

Participants in GALACTIC-HF were enrolled from both the inpatient and outpatient clinical settings. Of the 8256 participants, 2084 (25.2%) were enrolled as inpatients after stabilization during a hospitalization for heart failure with a greater percentage of the inpatient cohort enrolled in Eastern Europe and Russia (*Table 1*). As might be anticipated, the participants enrolled during a heart failure hospitalization also had a higher prevalence of chronic kidney disease and history of atrial fibrillation/flutter, had more symptomatic heart failure (worse baseline NYHA functional class, MAGGIC score, and KCCQ total symptom score), lower SBP and eGFR, and higher NT-proBNP and high sensitivity troponin I concentrations compared to those enrolled as outpatients. Although the use of heart failure therapy was lower at baseline in the participants enrolled as inpatients, 83% were treated with ACEi/ARB/ARNi (16% ARNi), 93% with beta-blockers, 81% with MRA and 65% with triple therapy [(ACEi/ARB/ARNi) + beta-blocker + MRA].

The absence of adverse effects on renal function and blood pressure in prior studies with omecamtiv mecarbil permitted enrolment of patients in GALACTIC-HF with eGFR and SBP lower than levels often excluded from HFrEF clinical trials. Over 500 patients with eGFR <30 mL/min/1.73 m^2 participated (*Table 2*) and there were over 1100 participants in GALACTIC-HF with SBP <100 mmHg (*Table 2*). GALACTIC-HF will provide important insights into these two groups of patients that

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Table 1 Baseline characteristics of GALACTIC-HF patients

	Overall (n = 8256)	Current HF hospitalization ('Inpatient') (n = 2084)	Recent HF hospitalization or ED visit within 1 year ('Outpatient') (n = 6172)
Demographics			
Age (years), mean (SD)	64.5 (11.3)	65.0 (11.3)	64.4 (11.4)
Female sex, *n* (%)	1756 (21.3)	411 (19.7)	1345 (21.8)
Race, *n* (%)			
White	6421 (77.8)	1706 (81.9)	4715 (76.4)
Asian	710 (8.6)	184 (8.8)	526 (8.5)
Black or African American	562 (6.8)	105 (5.0)	457 (7.4)
Other[a]	563 (6.8)	89 (4.3)	474 (7.7)
Ethnicity, Hispanic/Latino, *n* (%)	1771 (21.5)	355 (17.0)	1416 (22.9)
Geographic region, *n* (%)			
Eastern Europe/Russia	2705 (32.8)	915 (43.9)	1790 (29.0)
Western Europe/South Africa/Australasia	1921 (23.3)	486 (23.3)	1435 (23.3)
Latin and South America	1574 (19.1)	326 (15.6)	1248 (20.2)
US and Canada	1386 (16.8)	180 (8.6)	1206 (19.5)
Asia	670 (8.1)	177 (8.5)	493 (8.0)
Clinical characteristics			
Medical conditions, *n* (%)			
Coronary artery disease	5144 (62.3)	1317 (63.2)	3827 (62.0)
Myocardial infarction	3457 (41.9)	893 (42.9)	2564 (41.5)
Percutaneous coronary intervention	2452 (29.7)	599 (28.7)	1853 (30.0)
Coronary artery bypass grafting	1319 (16.0)	320 (15.4)	999 (16.2)
Peripheral artery disease	847 (10.3)	215 (10.3)	632 (10.2)
Stroke	753 (9.1)	197 (9.5)	556 (9.0)
Atrial fibrillation or flutter history	3472 (42.1)	995 (47.7)	2477 (40.1)
Hypertension	5800 (70.3)	1495 (71.7)	4305 (69.8)
Hypercholesterolaemia	4553 (55.1)	1094 (52.5)	3459 (56.0)
Type 2 diabetes mellitus	3313 (40.1)	870 (41.7)	2443 (39.6)
Chronic kidney disease	2977 (36.1)	809 (38.8)	2168 (35.1)
Chronic obstructive pulmonary disease	1344 (16.3)	354 (17.0)	990 (16.0)
Asthma	440 (5.3)	92 (4.4)	348 (5.6)
HF history			
LVEF (%), mean (SD)	26.6 (6.3)	26.5 (6.4)	26.6 (6.2)
MAGGIC score, mean (SD)	23.3 (6.3)	25.0 (6.3)	22.8 (6.3)
NYHA class, *n* (%)			
II	4391 (53.2)	767 (36.8)	3624 (58.7)
III	3616 (43.8)	1190 (57.1)	2426 (39.3)
IV	248 (3.0)	126 (6.0)	122 (2.0)
Ischaemic HF aetiology, *n* (%)	4458 (54.0)	1148 (55.1)	3310 (53.6)
KCCQ total symptom score, mean (SD)	66.4 (25.1)	52.6 (25.4)	71.0 (23.2)
Vitals and laboratory parameters			
Body mass index (kg/m^2), mean (SD)	28.5 (6.2)	28.0 (6.1)	28.6 (6.2)
SBP (mmHg), mean (SD)	117 (15)	114 (14)	117 (16)
Heart rate (bpm), mean (SD)	72 (12)	73 (12)	72 (12)
NT-proBNP (pg/mL), median (Q1–Q3)	1971 (961–4033)	2457 (1185–5073)	1858 (900–3749)
hsTnI (ng/mL), median (Q3)	0.030 (0.049)	0.036 (0.066)	0.029 (0.044)
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	59 (44–74)	54 (41–70)	60 (45–75)
Stage ≤2: >60	3922 (47.7)	838 (40.2)	3084 (50.0)
Stage 3: 30–59	3806 (46.1)	1077 (51.7)	2729 (44.2)
Stage 4: 15–29	523 (6.3)	169 (8.1)	354 (5.7)
Stage 5: <15	5 (<0.1)	0 (0.0)	5 (<0.1)
Medications and cardiac devices, *n* (%)			
ACEi, ARB, or ARNi	7161 (86.7)	1729 (83.0)	5432 (88.0)
ARNi	1594 (19.3)	328 (15.7)	1266 (20.5)
BB	7763 (94.0)	1931 (92.7)	5832 (94.5)
MRA	6358 (77.0)	1686 (80.9)	4672 (75.7)
(ACEi, ARB, or ARNi) + MRA + BB	5367 (65.0)	1360 (65.3)	4007 (64.9)
Digitalis glycosides	1380 (16.7)	356 (17.1)	1024 (16.6)
SGLT2 inhibitors	219 (2.7)	56 (2.7)	163 (2.6)
Ivabradine	533 (6.5)	156 (7.5)	375 (6.1)
CRT	1156 (14.0)	267 (12.8)	889 (14.4)
ICD	2614 (31.7)	598 (28.7)	2016 (32.7)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT, cardiac resynchronization therapy; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; hsTnI, high-sensitivity troponin I; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; 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.

[a] Includes American Indian or Alaska native, native Hawaiian or other Pacific Islander, or multiple self-identified races.

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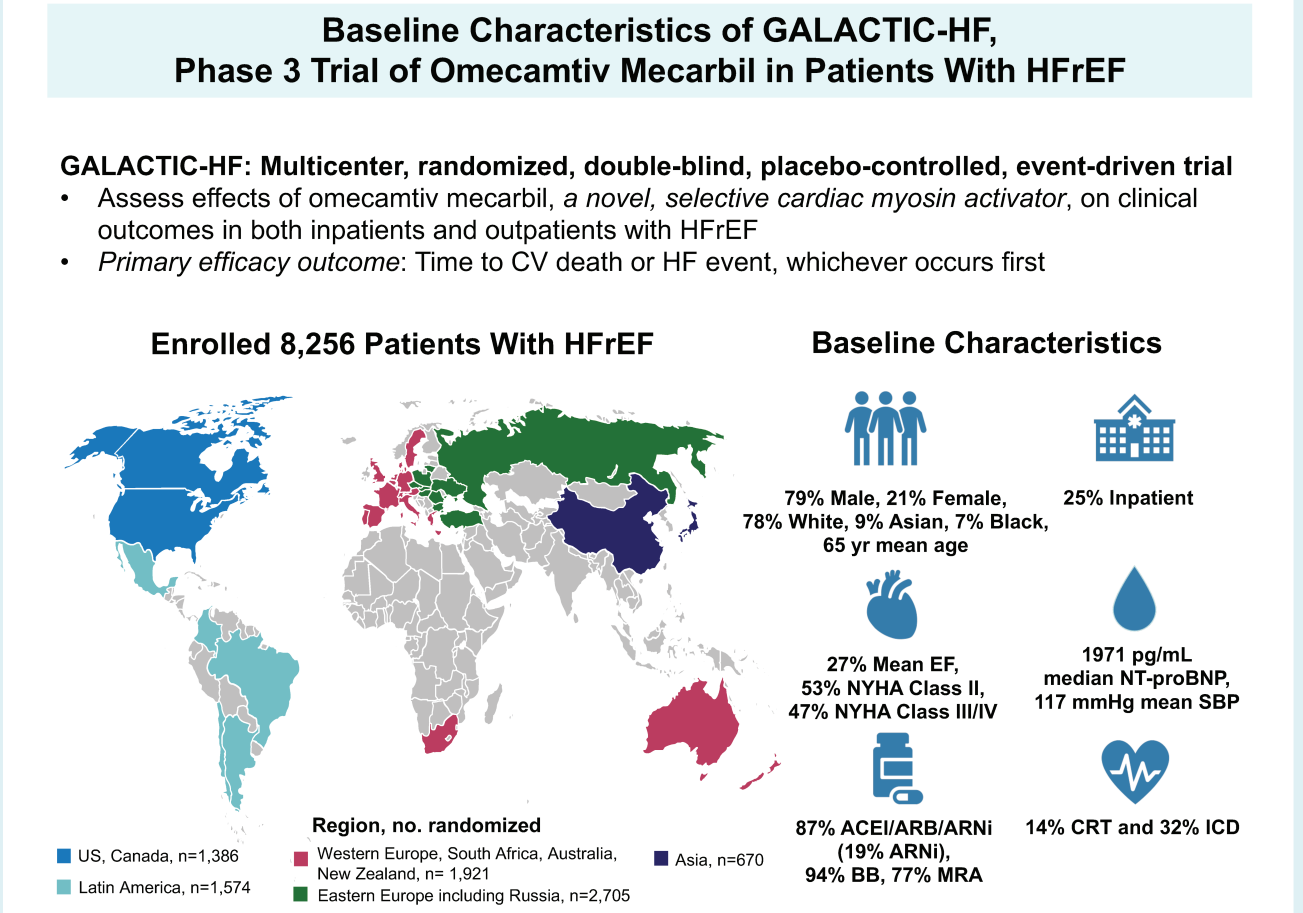


Figure 1 Graphical representation of the GALACTIC-HF trial design, enrolment and baseline characteristics. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CRT, cardiac resynchronization therapy (biventricular pacemaker); CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, Hew York Heart Association; SBP, systolic blood pressure.

have been underrepresented in other contemporary clinical trials.

Comparison of GALACTIC-HF baseline characteristics to other heart failure populations

The baseline characteristics of participants in GALACTIC-HF are compared to the population of patients in a number of registries (online supplementary *Table S2*) as well as four major contemporary trials (PARADIGM-HF, DAPA-HF, VICTORIA and EMPEROR-Reduced) of pharmacologic therapies in participants enrolled as outpatients with HFrEF (*Table 3*). To provide context for GALACTIC-HF participants enrolled in-hospital, their baseline characteristics were compared to patients from the EVEREST, ASTRONAUT, and PIONEER-HF trials (*Table 4*). The key selection criteria for these trials are presented in online supplementary *Table S3*.

Discussion

The GALACTIC-HF trial was designed to provide a comprehensive assessment of the effect of chronic therapy with the cardiac myosin activator omecamtiv mecarbil on cardiovascular mortality, heart failure hospitalizations and quality of life in people with HFrEF. Participants in GALACTIC-HF were randomized from a diverse international population representing a wide spectrum of the HFrEF clinical course. Their clinical characteristics are similar to those of patients in contemporary registries (online supplementary *Table S2*), although GALACTIC-HF patients tended to be more symptomatic and received more guideline-recommended medical therapy.

GALACTIC-HF randomized patients with many similarities to those in other chronic heart failure trials (*Table 3*), though there are some interesting differences, some of which were generated by differences in the eligibility criteria (online supplementary *Table S3*). The mean ages of patients in these contemporary HFrEF

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Table 2 Selected subgroups in GALACTIC-HF

	Renal function		SBP	
	eGFR <30 mL/min/m^2 (n = 528)	eGFR ≥30 mL/min/m^2 (n = 7728)	<100 mmHg (n = 1127)	≥100 mmHg (n = 7129)
Demographics				
Age (years), mean (SD)	70.5 (8.8)	64.1 (11.4)	63.3 (11.9)	64.7 (11.3)
Female sex, *n* (%)	175 (33.1)	1581 (20.5)	248 (22.0)	1508 (21.2)
Race, *n* (%)				
White	450 (85.2)	5971 (77.3)	789 (70.0)	5632 (79.0)
Asian	19 (3.6)	691 (8.9)	188 (16.7)	522 (7.3)
Black or African American	24 (4.5)	538 (7.0)	72 (6.4)	490 (6.9)
Other[a]	35 (6.6)	528 (6.8)	78 (6.9)	485 (6.8)
Geographic region, *n* (%)				
Eastern Europe/Russia	139 (26.3)	2566 (33.2)	136 (12.1)	2569 (36.0)
Western Europe/South Africa/Australasia	196 (37.1)	1725 (22.3)	363 (32.2)	1558 (21.9)
Latin and South America	86 (16.3)	1488 (19.3)	214 (19.0)	1360 (19.1)
US and Canada	90 (17.0)	1296 (16.8)	237 (21.0)	1149 (16.1)
Asia	17 (3.2)	653 (8.4)	177 (15.7)	493 (6.9)
Clinical characteristics				
Medical conditions, *n* (%)				
Coronary artery disease	397 (75.2)	4747 (61.4)	627 (55.6)	4517 (63.4)
Myocardial infarction	282 (53.4)	3175 (41.1)	455 (40.4)	3002 (42.1)
Peripheral artery disease	88 (16.7)	759 (9.8)	99 (8.8)	748 (10.5)
Stroke	63 (11.9)	690 (8.9)	111 (9.8)	642 (9.0)
Atrial fibrillation or flutter history	282 (53.4)	3190 (41.3)	509 (45.2)	2963 (41.6)
Hypertension	403 (76.3)	5397 (69.8)	551 (48.9)	5249 (73.6)
Hyperlipidaemia	352 (66.7)	4201 (54.4)	568 (50.4)	3985 (55.9)
Type 2 diabetes mellitus	287 (54.4)	3026 (39.2)	404 (35.8)	2909 (40.8)
Chronic kidney disease	466 (88.3)	2511 (32.5)	407 (36.1)	2570 (36.0)
Chronic obstructive pulmonary disease	92 (17.4)	1252 (16.2)	152 (13.5)	1192 (16.7)
HF history				
LVEF (%), mean (SD)	26.7 (6.2)	26.6 (6.3)	24.0 (6.2)	27.0 (6.2)
Ischaemic HF, *n* (%)	353 (66.9)	4105 (53.1)	542 (48.1)	3916 (54.9)
NYHA class, *n* (%)				
II	210 (39.8)	4181 (54.1)	557 (49.4)	3834 (53.8)
III	295 (55.9)	3321 (43.0)	523 (46.4)	3093 (43.4)
IV	23 (4.4)	225 (2.9)	47 (4.2)	201 (2.8)
KCCQ total symptom score, mean (SD)	60.2 (26.7)	66.8 (25.0)	64.3 (26.0)	66.7 (25.0)
MAGGIC score, mean (SD)	30.4 (5.5)	22.9 (6.1)	26.1 (6.5)	22.9 (6.2)
Vitals and laboratory parameters				
Body mass index (kg/m^2), mean (SD)	28.7 (5.7)	28.5 (6.2)	26.28 (5.6)	28.81 (6.2)
SBP (mmHg), mean (SD)	114.4 (16.7)	116.6 (15.2)	92.6 (4.6)	120.2 (12.8)
Heart rate (bpm), mean (SD)	70.4 (11.5)	72.5 (12.2)	72.5 (12.2)	72.3 (12.1)
NT-proBNP (pg/mL), median (Q1–Q3)	4525.0 (2082.0–8435.0)	1885.0 (924.0–3768.0)	2927.0 (1466.5–5835.0)	1858.0 (903.0–3775.0)
hsTnI (ng/mL), median (Q3)	0.040 (0.075)	0.030 (0.048)	0.030 (0.052)	0.030 (0.049)
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	25.7 (23.1–28.0)	60.4 (47.3–75.4)	55.2 (40.7–70.6)	59.3 (44.7–74.4)
Stage ≤2: >60	–	3922 (50.8)	461 (40.9)	3461 (48.5)
Stage 3: 30–59	–	3806 (49.2)	561 (49.8)	3245 (45.5)
Stage 4: 15–29	523 (99.1)	–	104 (9.2)	419 (5.9)
Stage 5: <15	5 (0.9)	–	1 (<0.1)	4 (<0.1)
Medications and cardiac devices, *n* (%)				
ACEi, ARB, or ARNi	379 (71.8)	6782 (87.8)	957 (84.9)	6204 (87.0)
ARNi	110 (20.8)	1484 (19.2)	344 (30.5)	1250 (17.5)
BB	480 (90.9)	7283 (94.2)	1030 (91.4)	6733 (94.4)
MRA	294 (55.7)	6064 (78.5)	893 (79.2)	5465 (76.7)
(ACEi, ARB, or ARNi) + MRA + BB	217 (41.1)	5150 (66.6)	711 (63.1)	4656 (65.3)
Digitalis glycosides	54 (10.2)	1326 (17.2)	223 (19.8)	1157 (16.2)
SGLT2 inhibitors	7 (1.3)	212 (2.7)	44 (3.9)	175 (2.5)
Ivabradine	40 (7.6)	493 (6.4)	79 (7.0)	454 (6.4)
CRT	130 (24.6)	1026 (13.3)	248 (22.0)	908 (12.7)
ICD	235 (44.5)	2379 (30.8)	502 (44.5)	2112 (29.6)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; hsTnI, high-sensitivity troponin I; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; 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.

[a] Includes American Indian or Alaska native, native Hawaiian or other Pacific Islander, or multiple self-identified races.

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Table 3 Baseline characteristics and treatments in GALACTIC-HF, EMPEROR-Reduced, VICTORIA, DAPA-HF and PARADIGM-HF trials

	GALACTIC-HF (*n* = 8256)	EMPEROR-Reduced (*n* = 3730)	VICTORIA (*n* = 5050)	DAPA-HF (*n* = 4744)	PARADIGM-HF (*n* = 8442)
Demographics					
Age (years), mean (SD)	64.5 (11.3)	66.9 (11.0)	67.3 (12.2)	66.4 (11)	63.8 (11.4)
Female sex, *n* (%)	1756 (21.3)	893 (23.9)	1208 (23.9)	1109 (23.4)	1832 (22.0)
Race, *n* (%)					
White	6421 (77.8)	2629 (70.5)	3239 (64.2)	3333 (70.3)	5544 (65.7)
Asian	710 (8.6)	672 (18.0)	1132 (22.4)	1116 (23.5)	1509 (17.9)
Black or African American	562 (6.8)	257 (6.9)	249 (4.9)	226 (4.8)	428 (5.1)
Geographic region, *n* (%)					
Eastern Europe/Russia	2705 (32.8)	All Europe 1353 (36.3)	1694 (33.5)	1604 (33.8)	2826 (33.5)
Western Europe/South Africa/Australasia	1921 (23.3)		889 (17.6)	550 (11.6)	2051 (24.3)
Latin and South America	1574 (19.1)	1286 (34.5)	724 (14.3)	817 (17.2)	1433 (17.0)
US and Canada	1386 (16.8)	425 (11.4)	560 (11.1)	677 (14.3)	602 (7.1)
Asia Pacific	670 (8.1)	493 (13.2)	1183 (23.4)	1069 (23.1)	1487 (17.6)
Index event, *n* (%)					
Inpatient for HF	2084 (25.2)	N/A	[a]	N/A	N/A
HF hospitalization within 3 months	2992 (36.2)		3366 (66.7)	368 (7.8)	1611 (19.1)
IV diuretic for HF within 3 months (no hospitalization)	N/A		813 (16.1)	N/A	N/A
HF hospitalization 3–6 months	1523 (18.4)		871 (17.2)	410 (8.6)	1009 (12.0)
HF hospitalization >6 months	1636 (19.8)		N/A	1473 (31.0)	2632 (31.2)
Clinical characteristics					
Medical conditions, *n* (%)					
Coronary artery disease	5144 (62.3)	1710 (45.8)	2944 (58.3)	–	4796 (57.1)
Myocardial infarction	3457 (41.9)	1623 (43.5)		1977 (44.5)	3634 (43.0)
Peripheral artery disease	847 (10.3)	261 (7.0)	630 (12.5)	324 (6.8)	
Stroke	753 (9.1)	421 (11.3)	578 (11.5)	472 (9.9)	725 (8.7)
Atrial fibrillation or flutter history	3472 (42.1)	1369 (36.7)	2268 (44.9)	1818 (38.3)	3091 (37.0)
Hypertension	5800 (70.3)	2698 (72.3)	3995 (79.1)	(74)	5940 (71.2)
Type 2 diabetes mellitus	3313 (40.1)	1856 (49.8)	2369 (46.9)	1983 (41.8)	2907 (34.9)
Chronic obstructive pulmonary disease	1344 (16.3)	443 (11.9)	867 (17.2)	585 (12.3)	1080 (12.9)
HF history					
LVEF (%), mean (SD)	26.6 (6.3)	27.5 (6.1)	28.9 (8.3)	31.1 (6.8)	29.5 (6.2)
Ischaemic HF aetiology, *n* (%)	4458 (54.0)	1929 (51.7)		2674 (56.4)	5036 (59.7)
NYHA class, *n* (%)					
I	0	0	2 (0.0)	0	389 (4.7)
II	4391 (53.2)	2800 (75.1)	2975 (59.0)	3203 (67.5)	5919 (70.9)
III	3616 (43.8)	910 (24.4)	2003 (39.7)	1498 (31.6)	2018 (24.1)
IV	248 (3.0)	20 (0.5)	66 (1.3)	43 (0.9)	60 (0.7)
KCCQ total symptom score, median (Q1–Q3)	68.8 (49.0–87.5)			77.1 (58.3–91.7)	83.3 (67.7–95.8)
MAGGIC score, median (Q1– Q3)	23 (19–28)		23 (18–27)	22 (18, 25)	20 (16–24)
Vitals and laboratory parameters					
Body mass index (kg/m^2), mean (SD)	28.5 (6.2)	27.9 (5.4)	27.8 (5.9)	28.2 (6.0)	28.2 (5.5)
SBP (mmHg), mean (SD)	117 (15)	122 (15)	121 (16)	122 (16)	121 (15)
Heart rate (bpm), mean (SD)	72.4 (12.1)	71.3 (11.8)	73.1 (13.0)	71.5 (11.7)	72 (12)
NT-proBNP (pg/mL), median (Q1–Q3)	1971 (962–4033)	E: 1887 (1077–3429) P: 1926 (1153–3525)	2816 (1556–5314)	1437 (857–2649)	1608 (886–3221)
eGFR (mL/min/1.73 m^2), mean (SD)	60.3 (21.8)	62.0 (21.6)	61.5 (27.2)	65.8 (19.4)	70 (20)
Stage ≤2: ≥60	3922 (47.5)	1929 (51.7)	2335 (47.1)	2782 (58.6)	5654 (67.0)
Stage ≥3: <60	4334 (52.5)	1799 (48.3)	2624 (52.0)	1962 (40.2)	2745 (33.0)
Medications and cardiac devices, *n* (%)					
ACEi, ARB, or ARNi	7161 (86.7)	3327 (89.2)	3700 (73.4)	4476 (94.4)	8339 (100)
ARNi	1594 (19.3)	727 (19.5)	731 (14.5)	508 (10.7)	N/A
BB	7763 (94.0)	3533 (94.7)	4691 (93.1)	4558 (96.1)	7811 (93.6)
MRA	6358 (77.0)	2661 (71.3)	3545 (70.3)	3370 (71.0)	4671 (55.3)
(ACEi, ARB, or ARNi) + MRA + BB	5367 (65.0)		3009 (59.7)	3097 (65.3)	(≤55.3)
Digitalis glycosides	1380 (16.7)	594 (15.9)		887 (18.7)	2539 (30.2)
ICD	2614 (31.7)	1171 (31.4)	1399 (27.8)	1242 (26.2)	1243 (14.9)
CRT	1156 (14.0)	442 (11.8)	739 (14.7)	354 (7.5)	574 (6.8)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT, cardiac resynchronization therapy; E, empagliflozin group; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; P, placebo group; SBP, systolic blood pressure; SD, standard deviation.

[a]VICTORIA also enrolled inpatients, although these data were not available at this time.

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Table 4 Baseline characteristics and treatment in stabilized inpatients in contemporary trials

	GALACTIC-HF ('inpatient') (n = 2084)	EVEREST (n = 4133)	ASTRONAUT (n = 1615)	PIONEER-HF (n = 881)
Demographics				
Age (years), mean (SD) or median (Q1–Q3)	65.0 (11.3)	65.8 (11.8)	64.6 (12.2)	62 (53–71)
Female sex, *n* (%)	411 (19.7)	25.6	368 (22.7)	246 (27.9)
Race, *n* (%)				
White	1706 (81.9)	3533 (85.5)	1140 (70.6)	515 (58.5)
Asian	184 (8.8)	N/A	336 (20.8)	
Black or African American	105 (5.0)	310 (7.5)	78 (4.8)	316 (35.9)
Other[b]	89 (4.3)	290 (7.0)	61 (3.8)	50 (5.7)
Hispanic ethnicity, *n* (%)	355 (17.0)	201 (4.9)		75 (8.5)
Geographic region, *n* (%)				
Eastern Europe/Russia	915 (43.9%)	1619 (39.2)	498 (30.4)	–
Western Europe/South Africa/Australasia	486 (23.3%)	564 (13.6)	407 (24.8)	–
Latin and South America	326 (15.6%)	699 (16.9)	165 (10.1)	–
US and Canada	180 (8.6%)	1251 (30.2)	124 (7.6)	881 (100)
Asia	177 (8.5%)	–	445 (27.2)	–
Clinical characteristics				
Medical conditions, *n* (%)				
Coronary artery disease	1317 (63.2)	2911 (70.4)	881 (54.6)	244 (27.7)
Myocardial infarction	893 (42.9)	2084 (50.4)	689 (42.7)	62 (7.0)
Percutaneous coronary intervention	599 (28.7)	738 (17.9)	323 (20.0)	8 (0.9)
Coronary artery bypass grafting	320 (15.4)	862 (20.9)	279 (17.3)	35 (4.0)
Peripheral artery disease	215 (10.3)	866 (21.0)		95 (10.8)
Stroke	197 (9.5)	471 (11.4)		87 (9.9)
Atrial fibrillation or flutter history	995 (47.7)	1790 (43.3)	676 (41.9)	407 (46.2)
Hypertension	1495 (71.7)	2932 (70.9)	1225 (75.9)	753 (85.6)
Type 2 diabetes mellitus	870 (41.7)	1598 (38.7)	662 (41.0)	168 (19.1)
Chronic kidney disease	809 (38.8)	1107 (26.8)	332 (20.6)	250 (29.1)
Chronic obstructive pulmonary disease	354 (17.0)	416 (10.1)	322 (19.9)	
HF history				
LVEF (%), mean (SD) or median (Q1–Q3)	26.5 (6.4)	27.5 (8.1)	27.9 (7.3)	25 (20–30)
Ischaemic HF aetiology, *n* (%)	1148 (55.1)	2672 (64.6)	1027 (63.6)	
NYHA class at randomization, *n* (%)				
II	767 (36.8)		513 (31.8)	112 (19.4)
III	1190 (57.1)	2404 (59.4)	903 (55.9)	297 (51.6)
IV	126 (6.0)	1622 (40.1)	139 (8.6)	54 (9.4)
Vitals and laboratory parameters				
Body mass index (kg/m^2), mean (SD) or median (Q1, Q3)	28.0 (6.1)		27.2 (6.2)	30 (26–37)
SBP (mmHg), mean (SD) or median (Q1, Q3)	114 (14)	121 (19)	123 (13)	118 (110–132)
Heart rate (bpm), mean (SD) or median (Q1, Q3)	73 (12)	80	78 (16)	80 (72–91)
NT-proBNP (pg/mL), median (Q1–Q3) at randomization	2457 (1185–5073)		2718 (1531–5235)	2701 (1490–5218)
hsTnI (ng/mL), median (Q3)	0.036 (0.066)		0.035 (0.08)	0.032 (0.050)
eGFR (mL/min/1.73 m^2), mean (SD) or median (Q1–Q3)	54.4 (41.3–70.2)		66.7 (19.9)	59 (48–71)
Medications and cardiac devices, *n* (%)				
ACEi, ARB, or ARNi	1729 (83.0)	3479 (84.2)	1360 (84.2)	422 (47.9)[a]
BB	1931 (92.7)	2903 (70.2)	1333 (82.5)	525 (59.6)
MRA	1686 (80.9)	2242 (54.2)	921 (57.0)	88 (10.0)
(ACEi, ARB, or ARNi) + MRA + BB	1360 (65.3)	(≤54.2)	(≤57.0)	502 (57.0)[a]
Digitalis glycosides	356 (17.1)	1815 (43.9)	628 (38.9)	76 (8.6)
CRT	267 (12.8)		109 (6.7)	76 (8.6)
ICD	598 (28.7)	600 (14.5)	253 (15.7)	250 (28.3)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; hsTnI, high-sensitivity troponin I; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

[a]Note that PIONEER-HF enrolled *de novo* HF patients and patients on ARNi were excluded, so this value represents patients on ACEi or ARB at baseline.

[b]Includes American Indian or Alaska native, native Hawaiian or other Pacific Islander, or multiple self-identified races.

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trials ranged from 64–67 years and 21–24% of the participants were females. Racial characteristics differed amongst the trials, with GALACTIC-HF enrolling a high percentage of self-identified Black participants (6.8%) compared to the other trials (4.8–6.9%), but a substantially lower proportion of Asian patients (8.6% vs. 17.9–23.5%). These proportions reflect the geographic distribution of recruitment, where GALACTIC-HF enrolled more patients from the United States and Canada (16.8% vs. 7.1–14.3%), but fewer participants from Asia (8.1% vs. 13.2–23.4%). Given the size of GALACTIC-HF, these proportions translated into substantially greater absolute numbers of patients (nearly twice as many as the comparators) in North America where recruitment has been historically challenging. Comorbidities were common and similar in all of the trials with a history of atrial fibrillation present in about 37–45%, type 2 diabetes mellitus in 35–50% and hypertension in 70–79% of subjects. The participants in GALACTIC-HF had a slightly lower ejection fraction than the other trials (26.6% vs. 27.5–31.1%) and higher NT-proBNP concentrations compared to PARADIGM-HF, DAPA-HF and EMPEROR-Reduced, the latter being potentially related to enrolling inpatients. As opposed to the other trials which enrolled patients with predominantly mild symptoms (59–75% NYHA class II), patients with a broader range of symptoms are represented in GALACTIC-HF from mild (NYHA class II, 53%) to moderate–severe (NYHA class III/IV, 47%) symptoms.

The GALACTIC-HF cohort is a unique population, comprising patients enrolled from both the inpatient and outpatient settings. For comparison, the VICTORIA trial[21] specifically randomized patients ($n = 3366$; 66.7%) in the high-risk period within 3 months of hospitalization for heart failure. GALACTIC-HF also has a robust representation of these high-risk patients ($n = 4976$; 60.3%). In the Phase 2 trial of omecamtiv mecarbil in patients with acute heart failure, ATOMIC-AHF,[6] 606 patients were randomized to a 48 h infusion of placebo or omecamtiv mecarbil in ascending dose cohorts. In these acutely ill inpatients, omecamtiv mecarbil had a side-effect profile similar to placebo and improved dyspnoea in the high-dose group. In the context of these safety data and with the recognition that early initiation of disease-modifying therapies would optimize medication adherence and its potential benefit, GALACTIC-HF randomized 2084 patients (25.2%) in the inpatient setting. A greater proportion of subjects enrolled as inpatients had a history of atrial fibrillation/flutter and chronic renal disease compared to the outpatient cohort. While this inpatient group had the same left ventricular ejection fraction as those randomized as outpatients, the inpatients were more symptomatic as represented by worse NYHA functional class and KCCQ total symptom scores and also had lower blood pressure, worse renal function, and higher NT-proBNP and troponin I concentrations. Three other large multicentre trials have enrolled stabilized inpatients with HFrEF who were hospitalized for acute heart failure (*Table 4*; online supplementary *Table S3*). The international trials EVEREST[23,24] and ASTRONAUT[25] enrolled patients with a history of HFrEF who had baseline characteristics similar to the inpatient group from GALACTIC-HF, except for the worse renal function and lower SBP in GALACTIC-HF. The lower heart rate in GALACTIC-HF compared to these other trials may be reflective of the higher use of beta-blockers at baseline. PIONEER-HF[26] also enrolled patients who were haemodynamically stable while hospitalized for acute decompensated heart failure but only in the United States. PIONEER-HF had a higher representation of women and Blacks compared to the other three trials, as well as higher prevalence of obesity and hypertension. Patients in PIONEER-HF had a much lower use of renin–angiotensin system inhibitors (48% ACEi/ARB vs. 83% ACEi/ARB/ARNi), beta-blockers (60% vs. 94%) and MRA (10% vs. 81%) compared to the inpatient group from GALACTIC-HF, although PIONEER-HF randomized patients with *de novo* heart failure such that only 65.4% of patients had a prior history of heart failure.

Adverse effects on renal function are a major impediment to the initiation, up-titration and maintenance of many current heart failure therapies. Omecamtiv mecarbil has demonstrated no significant difference from placebo with respect to renal function or related adverse events in Phase I or II clinical studies. Consequently, the entry criterion for renal function in GALACTIC-HF was among the lowest of any contemporary clinical trial, enrolling patients with an eGFR $\geq$20 mL/min/1.73 m^2 who were not on dialysis. GALACTIC-HF enrolled 528 patients with eGFR <30 mL/min/1.73 m^2, representing 6.4% of total enrolment. These patients are a distinct group with a greater proportion being women and older age, enrolled as inpatients with lower SBP, more comorbidities and ischaemic aetiology of heart failure, more symptomatic heart failure (worse NYHA class, MAGGIC and KCCQ total symptom scores) and markedly higher NT-proBNP, increased troponin, on less guideline-recommended medical therapy, yet a greater proportion of device therapy, compared to those with better renal function. Patients with an eGFR $\geq$20 mL/min/1.73 m^2 were also enrolled in EMPEROR-Reduced. These patients are typically a poorly studied group in HFrEF therapeutic trials and were excluded from ASTRONAUT,[25] PARADIGM-HF,[19] PIONEER-HF[26] and DAPA-HF.[27] In the VICTORIA trial[21] of the soluble guanylate cyclase activator vericiguat, patients with an eGFR $\geq$15 mL/min/1.73 m^2 were enrolled and there were 506 patients enrolled with an eGFR $\leq$30 mL/min/1.73 m^2 (10.2% of total enrolment).

Many patients with HFrEF have lower blood pressure, especially those on maximal neurohormonal antagonist therapy, yet due to the hypotensive effects of many investigational therapies, these patients have been excluded from contemporary clinical trials. Trials with aliskiren (ASTRONAUT,[23,24] SBP <110 mmHg), sacubitril/valsartan (PARADIGM-HF,[19] PIONEER-HF[26]), vericiguat (VICTORIA[21]) and empagliflozin (EMPEROR-Reduced[22]) excluded patients with SBP <100 mmHg, while DAPA-HF[27] (dapagliflozin) excluded those with SBP <95 mmHg. Omecamtiv mecarbil has no vasodilating properties and does not adversely affect blood pressure, so the GALACTIC-HF trial was able to study patients with SBP $\geq$85 mmHg, randomizing 1127 patients (13.7%) with a baseline SBP <100 mmHg. These patients were slightly younger and more frequently enrolled as inpatients, with lower left ventricular ejection fraction, mildly increased NT-proBNP and troponin, decreased eGFR, fewer with ischaemic aetiology of heart failure, and more symptomatic heart failure (worse NYHA class, MAGGIC and KCCQ total symptom scores), compared to participants

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with higher SBP. GALACTIC-HF provides a unique opportunity to prospectively evaluate a therapy in this large, but underserved group of patients with HFrEF.

Comprehensive background heart failure therapy is not only important for the appropriate care of the participants but is also essential to the evaluation of the additional therapeutic benefit of a study drug. Patients in GALACTIC-HF received amongst the most comprehensive baseline heart failure therapy in contemporary clinical trials. Implantable cardioverter defibrillators were in 32% (15–31% in PARADIGM-HF, DAPA-HF, VICTORIA, and EMPEROR-Reduced) and cardiac resynchronization therapy was present in 14% of patients in GALACTIC-HF at baseline (7–15% in the other four trials). In terms of baseline medical therapies employed, 87% of participants in GALACTIC-HF received an ACEi, ARB or ARNi, compared to 73–94% in PARADIGM-HF, DAPA-HF, VICTORIA, and EMPEROR-Reduced. Beta-blockers were administered to 94% of patients in GALACTIC-HF, similar to the 93–96% of patients in the other trials. MRA administration was more common in GALACTIC-HF (77% compared to 55–71% in the other trials). The absence of adverse effects of omecamtiv mecarbil on potassium homeostasis may have accounted for the investigators' comfort in enrolling patients with the highest percentage of MRA use in any contemporary clinical trial. Unlike the PARADIGM-HF, PIONEER-HF, ASTRONAUT, and EVEREST trials, GALACTIC-HF had no exclusion criterion for potassium plasma concentrations. Triple therapy (ACEi/ARB/ARNi + beta-blocker + MRA) was present in 65% of the GALACTIC-HF patients compared to less than 55% to 65% in the other three contemporary trials. Relative to DAPA-HF (n = 508, 11%), VICTORIA (n = 731, 14%) and EMPEROR-Reduced (n = 727; 19.5%), almost 1600 patients (over 19%) in GALACTIC-HF were treated with sacubitril/valsartan at baseline. As might be expected given the different timing of regulatory approvals and accessibility of sacubitril/valsartan worldwide, there was considerable regional variation in baseline ARNi use, ranging from approximately 5% of patients in Eastern Europe to almost one-third of patients in North America and Western Europe.

A recent study demonstrated that failure to initiate or up-titrate guideline-recommended medical therapies to target doses is most frequently due to physiologic factors, such as blood pressure, heart rate, renal function, or potassium concentrations rather than physician inertia.[28] In Phase I and II clinical studies of omecamtiv mecarbil, there was no adverse effect on blood pressure, heart rate, renal function, or potassium homeostasis. These findings suggest that omecamtiv mecarbil should not interfere with baseline guideline-recommended medical therapy and has the potential to facilitate initiation or up-titration of these therapies through improved cardiac function.

Limitations

GALACTIC-HF is one of the most inclusive contemporary clinical trials, but there are some important limitations. Underrepresentation of racial groups and women in clinical trials is a continuing concern.[29] Only 7% of the GALACTIC-HF participants were Black; however, a total of 562 Black participants were enrolled, representing over 100 more Black patients than were randomized in PARADIGM-HF and over twice that enrolled in VICTORIA (n = 249), DAPA-HF (n = 226) or EMPEROR-Reduced (n = 257). Moreover, in the United States, over 29% of the GALACTIC-HF participants self-reported race as Black, more than twice the corresponding proportion of U.S. population (13.4%). Asian, Pacific Islander and other non-white racial groups have limited representation in this trial. In addition, women continue to constitute a minority of patients with HFrEF in both registries and clinical trials.[30] Approximately 21% of the participants in GALACTIC-HF were female, constituting a database of over 1700 women with HFrEF in whom the effects of omecamtiv mecarbil can be evaluated. The recent compelling trial results from DAPA-HF[27] and EMPEROR-Reduced[22] have established a role for the sodium–glucose co-transporter 2 (SGLT2) inhibitors in the treatment of patients with HFrEF, but these data did not enter clinical practice or guidelines until after GALACTIC-HF had completed enrolment. Only 219 (2.7%) patients in GALACTIC-HF were on SGLT2 inhibitors at baseline, but given that the mechanism of action of the cardiac myosin activator omecamtiv mecarbil has no apparent significant overlap with that of the SGLT2 inhibitors, there is minimal biological plausibility that they would interfere with the other's effects on clinical outcomes, and there is the suggestion that they could be complementary or even synergistic.

Conclusion

GALACTIC-HF is the first trial to test the hypothesis that directly improving cardiac function with the novel, selective cardiac myosin activator omecamtiv mecarbil can safely improve symptoms, prevent clinical heart failure events, and reduce the risk of cardiovascular death in patients with HFrEF. To this end, the trial enrolled patients with a wide range of symptomatic HFrEF receiving excellent medical and device heart failure therapy who were similar to those enrolled in other contemporary heart failure trials and registries. GALACTIC-HF also randomized patients typically excluded from chronic heart failure trials including inpatients and those with severely reduced renal function or low blood pressure. GALACTIC-HF will provide a definitive evaluation of the efficacy and safety of this novel therapy, and, if effective, inform its future implementation.

Supplementary Information

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

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