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REVIEW

Cardiac myosin activators for heart failure therapy: focus on omecamtiv mecarbil

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Abstract

Heart failure continues to be a major global health problem with a pronounced impact on morbidity and mortality and very limited drug treatment options especially with regard to inotropic therapy. Omecamtiv mecarbil is a first-in-class cardiac myosin activator, which increases the proportion of myosin heads that are tightly bound to actin and creates a force-producing state that is not associated with cytosolic calcium accumulation. Phase I and phase II studies have shown that it is safe and well tolerated. It produces dose-dependent increases in systolic ejection time (SET), stroke volume (SV), left ventricular ejection fraction (LVEF), and fractional shortening. In the ATOMIC-AHF trial, intravenous (IV) omecamtiv mecarbil did not improve dyspnoea overall but may have improved it in a high-dose group of acute heart failure patients. It did, however, increase SET, decrease left ventricular end-systolic diameter, and was well tolerated. The COSMIC-HF trial showed that a pharmacokinetic-based dose-titration strategy of oral omecamtiv mecarbil improved cardiac function and reduced ventricular diameters compared to placebo and had a similar safety profile. It also significantly reduced plasma N-terminal-pro B-type natriuretic peptide compared with placebo. The GALACTIC-HF trial is now underway and will compare omecamtiv mecarbil with placebo when added to current heart failure standard treatment in patients with chronic heart failure and reduced LVEF. It is expected to be completed in January 2021. The ongoing range of preclinical and clinical research on omecamtiv mecarbil will further elucidate its full range of pharmacological effects and its clinical usefulness in heart failure.

Keywords: heart failure, myosin activator, omecamtiv mecarbil.

Citation

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Introduction

Heart failure continues to be a leading public health problem with an estimated global prevalence of over 26 million patients and a sustained growing incidence mainly due to the aging of the population [1]. In the United States alone, the number of patients suffering from chronic heart failure is close to 6 million with an expected increase to over 8 million by 2030 [2,3]. Also in the United States, acutely decompensated heart failure (ADHF) is the primary cause for the hospitalisation of individuals aged 65 years and over, which results in around 1 million hospitalisations annually [3,4]. The overall mortality rate associated with heart failure in western populations approximates 50% within 5 years of diagnosis [5], a figure in excess of most malignancies [6].

Neurohumoral axis activation

When myocardial contractility starts to fail, neurohumoral axis activation occurs (i.e., sympathetic nervous system and renin-angiotensin-aldosterone system activation) as a compensatory mechanism; however, long-term and sustained overactivation results in a maladaptive process (cardiac remodelling) that leads to chronic heart failure progression [7–9].

Blocking the neurohumoral axis at different levels has shown some therapeutic success [10]. For example, significant improvements of morbidity and mortality have been obtained with angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARB), β-blockers (BB) and mineralocorticoid receptor antagonists (MRA) [10,11]. More recently, the combination of sacubitril (neprilysin inhibitor) plus valsartan (an ARB), has been found to significantly reduce cardiovascular (CV) and all-cause mortality as well as heart failure hospitalisations in comparison with enalapril (an ACEi) [12].

Inotropic agents

Myocardial contractility impairment is at the core of heart failure progression, and cardiac output (CO) is characteristically

compromised during its evolution, initially upon effort and in late stages at rest [13]. Hypothetically, it was reasonable to believe that inotropic agents that directly improve cardiac contractility should have been clinically beneficial [14]; however, they have consistently failed to meet expectations. Their use has been marked by serious concerns regarding increased morbidity and mortality connected with an augmented risk of ventricular arrhythmia, atrial fibrillation, hypotension, induced myocardial ischaemia, increased myocardial oxygen consumption and direct myocyte toxicity due to intracellular calcium overload [14,15].

Current options for their use are covered in a recent article by Tariq and Aronow [15]. They support inotropic intravenous (IV) administration to stabilise hospitalised individuals showing clinical expressions of ADHF or as intermittent home or hospital infusions for limited numbers of chronic heart failure patients with, in general, a permanent ambulatory advanced New York Heart Association (NYHA) functional class. Additionally, IV inotropes may be used as bridge therapy in different settings such as coronary revascularisation, mechanical circulatory support, heart transplantation, and device therapy.

Indications for their use per national guidelines reflect all of their weaknesses and uncertainties. For example, the European Society of Cardiology (2016) classifies digoxin (which is still the only oral positive inotrope available) as 'other treatments with less certain benefits in symptomatic patients with heart failure with reduced left ventricular ejection fraction (LVEF)' and it should be considered 'in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a BB and an MRA, to reduce the risk of hospitalisation (both all-cause and heart failure hospitalisations)'. Digoxin receives a class IIb, level B recommendation in which class IIb implies 'usefulness/efficacy is less well established by evidence/opinion' and level B indicates that supporting data are derived from 'a single randomised clinical trial' [11]. They also state that IV inotropic agents (e.g. dobutamine, dopamine, levosimendan and phosphodiesterase III inhibitors) should be considered 'in patients with hypotension (systolic blood pressure <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase CO, increase blood pressure, improve peripheral perfusion and maintain end-organ function'. These agents are classified as class IIb, level C recommendation in which (class IIb was already described) level C indicates that data are 'coming from consensus of opinion of experts and/or small studies, retrospective studies, registries' [11].

The search for new drugs

Currently available heart failure treatments have severe clinical efficacy shortcomings and safety problems. There is a clear need for new agents that can provide symptom relief and improvement in long-term outcomes.

Serelaxin (RLX030), a recombinant form of human relaxin-2 hormone, is in phase II trials. It showed promise in the RELAX-AHF trial when it was shown to improve dyspnoea, but in the RELAX-AHF-2 trial it failed on its two main endpoints: worsening of heart failure after 5 days of therapy, and CV death after 10 days [16,17].

The novel vasodilator, ularitide, is being studied in the phase III TRUE-AHF trial. Results showed that short-term treatment did not improve long-term outcomes in acute heart failure patients [18]. The study is ongoing; however, there have been concerns over enrolment and ineligibility [19].

TRV027 is a beta-arrestin-biased ligand. It is being studied in the dose-ranging phase IIb BLAST-AHF trial in hospitalised patients with ADHF. Results show it did not provide any benefit in the primary composite endpoint including the time from baseline to death through day 30 and from baseline to heart failure rehospitalisation through day 30 [20].

Omecamtiv mecarbil is a first-in-class cardiac myosin activator that increases the proportion of myosin heads that are tightly bound to actin and creates a force-producing state that is not connected with cytosolic calcium accumulation [21]. This review looks at the clinical development to-date of omecamtiv mecarbil and its future prospects.

Omecamtiv mecarbil

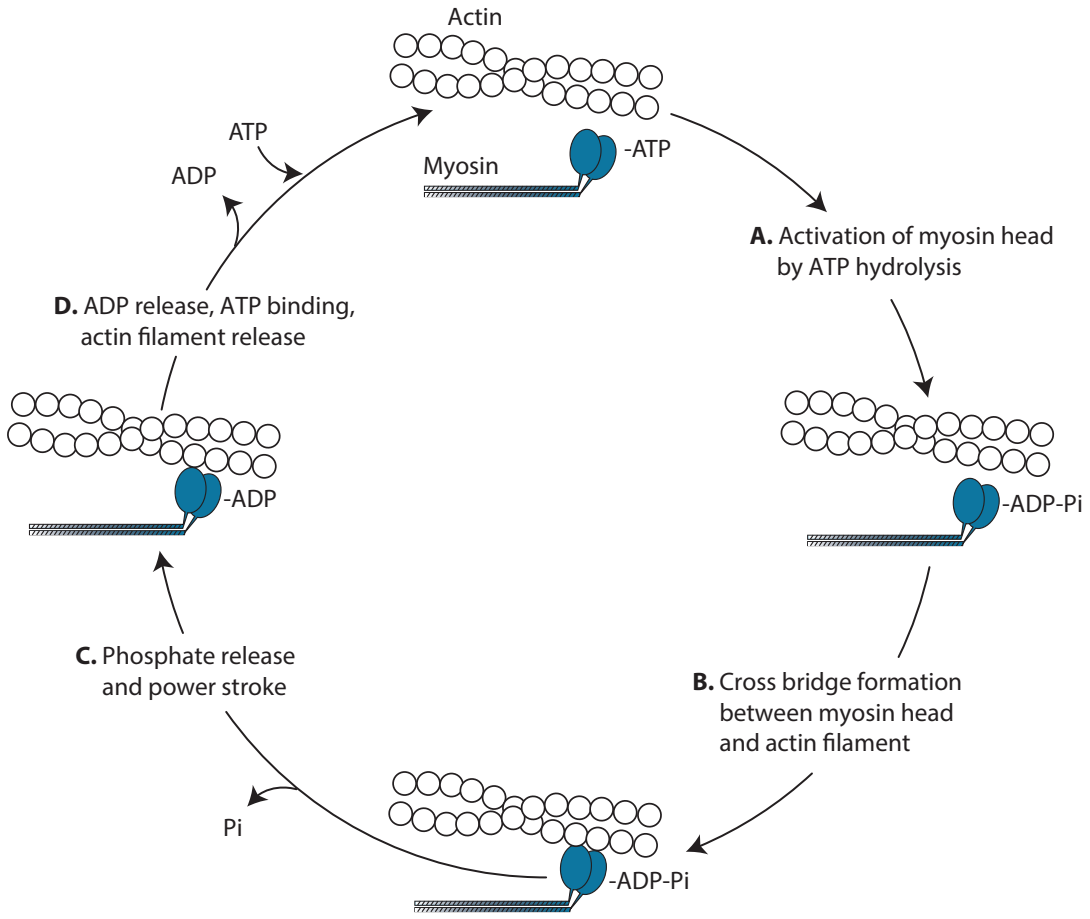
Background

Physiologically, binding between myosin-ATP to actin filaments is weak until hydrolysis of ATP to adenosine diphosphate (ADP) and inorganic phosphate (Pi) occurs. The Pi is released from myosin, and the remaining myosin-ADP complex remains firmly attached to actin in a very stable force-generating complex – its slow dissociation happens once a molecule of ATP binds myosin inducing a conformational change [21]. Thus, hydrolysis of ATP to ADP-Pi and subsequent Pi release from myosin reflects the transition from a weakly actin-binding state to a strongly actin-binding state, and this transition is decisive, because it implies a rate-limiting step during the whole actin-myosin ATPase cycle (Figure 1) [22,23].

Pharmacology and mechanism of action

Omecamtiv mecarbil formerly known as CK-1827452 [24] is a selective cardiac myosin activator (molecular weight 401.43) that specifically binds the catalytic S1 domain of cardiac myosin but without any significant effect over other types of myosin (smooth or skeletal muscle) [21]. The omecamtiv mecarbil binding site is a narrow cleft between the N-terminal 25-K domain and the lower portion of the 50-K domain that result in different reversible allosteric changes that explain how the drug modulates cardiac myosin activity [25]. The binding site is the amino acid serine 148, which is about 6.5 ηm from the actin-binding interface and about 3 ηm from the nucleotide-binding pocket [21]. These conformational changes augment the speed of ATP hydrolysis with consequent Pi release and so accelerate the transition rate from a weakly bound to a strongly

Figure 1. Myocardiocyte contractile cycle. Calcium binds TnC (inhibiting TnI) inducing a conformational change that displaces tropomyosin from binding sites and exposing active sites between actin and myosin. Myosin heads activation occurs by ATP hydrolysis (ADP+Pi) which is no longer inhibited (TnI) and enables cross-bridge formation between myosin heads and active sites on actin (A/B). Release of Pi reinforces these interactions (myosin and actin) triggering the 'power stroke,' which is another conformational change that firmly pulls myosin against actin in a very stable force-generating association (B/C). Complex myosin-ADP-actin dissociates when an ATP molecule binds myosin heads liberating ADP and releasing actin filaments (D). Calcium dissociation from troponin occurs when its cytosolic levels decrease and tropomyosin returns to its original state (blocking actin binding sites).



ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, inorganic phosphate; TnC, troponin C; TnI, troponin I.

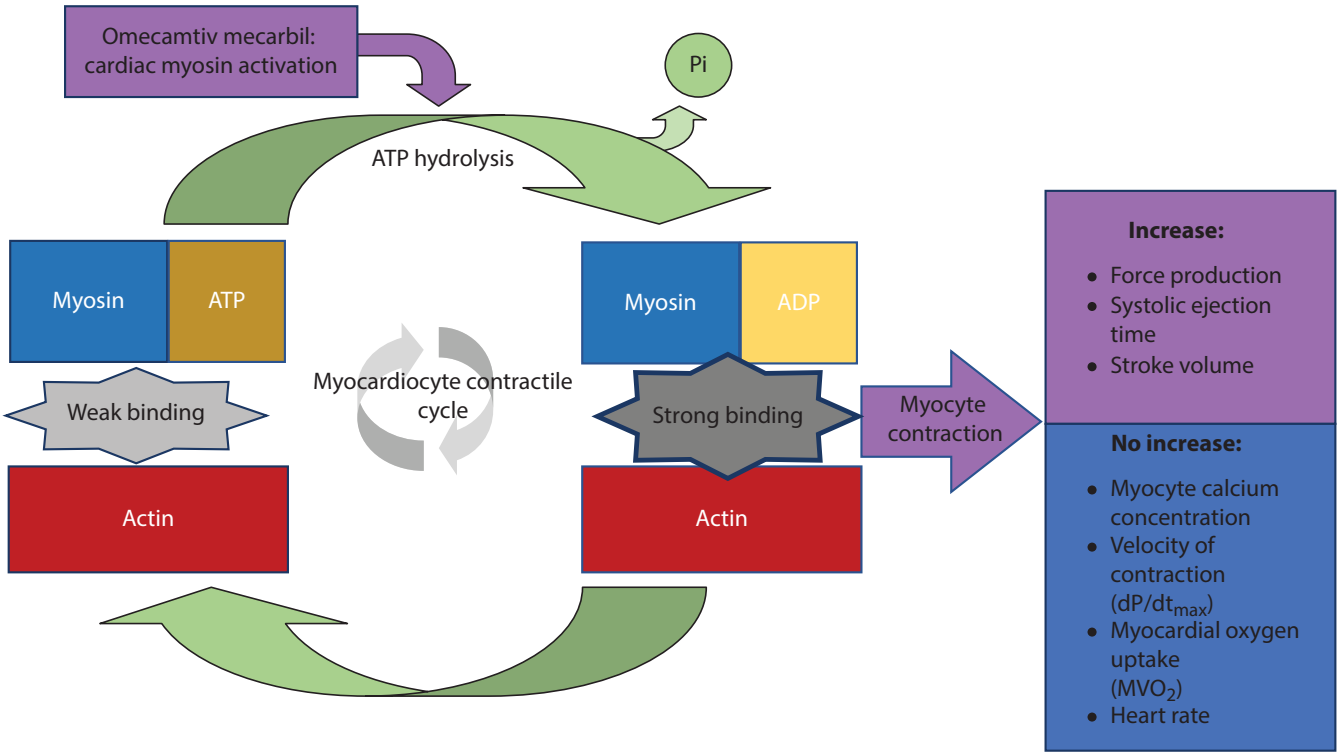
bound force-producing state (Figure 1). As a result, the total number of myosin heads bound to actin filaments increases thus boosting force production [21,26]. This mechanism is central to understanding omecamtiv mecarbil's action, because in a normal systole, only about 10–30% of total cardiac myosin heads interact with actin filaments [27]. From a functional point of view, omecamtiv mecarbil prolongs total systole duration by enhancing entry rate of myosin into a force-generating state, which implies more active cross-bridges formation and thus, a stronger cardiac contraction (Figure 2) [21,26].

In two experimental canine models of heart failure, omecamtiv mecarbil (bolus and 24-hour perfusion) was capable of reducing heart rate, vascular peripheral resistance, mean left atrial pressure, and left ventricular end diastolic pressure, whereas, systolic wall thickening, stroke volume (SV) and CO improved. Omecamtiv mecarbil increased systolic ejection time (SET) as well as cardiac myocyte fractional shortening but without any significant increase of LV dP/dt_{max}, myocardial oxygen consumption and myocyte intracellular calcium [28].

Clinical trials with omecamtiv mecarbil

Currently, omecamtiv mecarbil has been studied in nine phase I clinical trials (over 200 healthy volunteers) and four phase II clinical trials (more than 1300 heart failure patients) [29].

Figure 2. Omecamtiv mecarbil activates cardiac myosin and augments the speed of ATP hydrolysis, thus accelerating the production of a strong actin-myosin complex, which leads to increased force production.



ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, inorganic phosphate.

A first-in-man phase I dose-escalating crossover study in 34 healthy men was published in 2011 [30]. It sought to establish the maximum tolerated dose and plasma concentrations following omecamtiv mecarbil infusion (0.005–1 mg/kg/h). Secondary objectives were to record pharmacokinetic and pharmacodynamic data, and safety and tolerability of the drug. A dose-dependent augmentation of different cardiac systolic function markers (all $p<0.0001$) was documented including: SET, 85±5 ms; SV, 15±2 mL; left ventricular fractional shortening (LVFS), 8±1%; LVEF, 7±1%. Heart rate was not modified. The maximum tolerated dose was 0.5 mg/kg/h, whilst doses >0.75 mg/kg/h were associated with myocardial ischaemia (troponin elevation).

Cleland and colleagues studied the effects of omecamtiv mecarbil on cardiac function in a double-blind, placebo-controlled, crossover and dose-ranging phase II study [31]. A total of 45 patients (LVEF <40%) were divided into 5 cohorts (8–10 subjects) to receive omecamtiv mecarbil (2, 24 and 72 hours) in escalating infusion doses (loading and maintenance). A direct proportional relation (all $p<0.0001$) was observed between omecamtiv mecarbil plasma concentration (ηg/mL) and the augmentation (from baseline) of SET (up to 80 ms/>100 ηg/mL) and SV (up to 9.7 mL/>200 ηg/mL). Higher plasma concentrations (>500 ηg/mL) were linked with the reduction of both, LV end-systolic volume (LVESV) (15 mL; $p=0.0026$) and LV end-diastolic volume (LVEDV) (16 mL, $p=0.0096$). Induction of ischaemia was observed in two patients at very high concentrations (1750 and 1350 ηg/mL).

The safety and tolerability of omecamtiv mecarbil during exercise was studied in heart failure patients with ischaemic cardiomyopathy and active angina in a double-blind, randomised, placebo-controlled trial published in 2015 [32]. Patients (mean age 63±9) were randomised to receive omecamtiv mecarbil ($n=65$) or placebo ($n=29$) in two sequential cohorts at escalating doses previously shown to improve systolic function. Two symptom-limited exercise treadmill tests (ETTs) were performed at baseline (ETT1, ETT2) and one before the end of the 20-hour omecamtiv mecarbil infusion (ETT3). Omecamtiv mecarbil was dosed to target plasma levels ~295 ηg/mL (24 mg/h for 2 hours plus 6 mg/h for 18 hours) in cohort 1 ($n=31$) and to levels ~550 ηg/mL (48 mg/h for 2 hours plus 11 mg/h for 18 hours) in cohort 2 ($n=34$). Patients who tolerated IV infusion continued receiving (3 times daily) 12.5 mg (cohort 1) or 25 mg (cohort 2) of oral omecamtiv mecarbil or placebo for 7 days (any additional ETT was performed). The predefined safety endpoint was the proportion of patients needed to

stop ETT3 due to angina at a stage earlier than baseline. Only one patient in the placebo arm stopped ETT3 due to angina (none in both omecamtiv mecarbil cohorts) and no dose-dependent differences were found in the proportion of patients stopping ETT3 for any reason (one in placebo, four in cohort 1 and two in cohort 2 groups, respectively). The authors concluded that omecamtiv mecarbil is well tolerated in heart failure patients with ischaemic cardiomyopathy and angina with no evidence of induced myocardial ischaemia.

ATOMIC-AHF trial

Results of the ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) trial were published in 2016 [33]. This was a double-blind, randomised, placebo-controlled sequential cohort phase IIb study designed to investigate the safety, pharmacokinetics/pharmacodynamics and efficacy of IV omecamtiv mecarbil in hospitalised patients due to an ADHF.

Dyspnoea improvement (patient-reported 7-level Likert scale) through 48 hours was its primary efficacy endpoint ('responder': defined as minimally, moderately, or markedly improved dyspnoea by 6 hours after infusion start and moderately or markedly improved dyspnoea at 24 and 48 hours without experiencing worsening heart failure or death from any cause by 48 hours).

Eligible patients (history of heart failure and LVEF ≤40%) were those who had been hospitalised due to ADHF showing dyspnoea at rest or with minimal effort ≥2 hours after IV diuretics. Increased plasma concentrations of B-type natriuretic peptide (BNP) or N-terminal (NT)-proBNP (NT-proBNP) were also required, and individuals receiving IV inotropic agents (other than dopamine ≤5 mg/kg/min) were excluded. There were 606 patients who were treated in three sequential cohorts (approximately 200 patients per cohort) with a 48-hour omecamtiv mecarbil infusion in three escalating dose regimens targeting a mean plasma concentration of 115, 230 and 310 ηg/mL.

The primary endpoint was not achieved, because the response rates of dyspnoea relief within 48 hours amongst the placebo groups of the three treatment cohorts were not statistically different (p=0.316). There was a suggestion of greater dyspnoea relief in the high-dose omecamtiv mecarbil cohort compared with its placebo-concurrent group (assessed by both Likert and numeric-rating scales).

More patients randomised to omecamtiv mecarbil had elevated troponins compared to placebo, though no clear relationship to omecamtiv mecarbil concentrations was found. In an echocardiographic substudy, LVESD was found to be reduced (p<0.05) and a plasma concentration-dependent increase in SET caused by omecamtiv mecarbil (p<0.0001) was observed. Mean placebo-corrected increase in SET was 23, 34, and 53 ms for omecamtiv mecarbil concentration oscillating from 88 to 200 ηg/mL, 201 to 300 ηg/mL and >300 ηg/mL, respectively (p<0.005 for the difference *versus* placebo for all ranges).

At 30 days, the rates for serious adverse events (mostly related to heart failure) were similar in both pooled groups (placebo n=70 [23%] *versus* omecamtiv mecarbil n=66 [22%]) as well as all-cause rehospitalisation (placebo n=47 [15.5%] *versus* omecamtiv mecarbil n=39 [12.9%]) and heart failure rehospitalisation (placebo n=19 [6.3%] *versus* omecamtiv mecarbil n=22 [7.3%]). Within the same period, there were 18 CV deaths (placebo=10, omecamtiv mecarbil=8) and 77 by 6 months (placebo=39, omecamtiv mecarbil=38). A total of 20 (6.6%) episodes of supraventricular tachyarrhythmia were observed in patients taking placebo compared with 11 (3.6%) in the omecamtiv mecarbil group (predominantly atrial fibrillation or flutter), whilst the incidence of ventricular tachyarrhythmia was similar in both pooled groups (placebo n=18 [5.9%] *versus* omecamtiv mecarbil n=16 [5.2%]). Finally, there were 3 (1.0%) post-randomisation myocardial infarctions in the placebo group compared with 7 (2.3%) in the omecamtiv mecarbil cohorts.

Thus, IV omecamtiv mecarbil did not improve dyspnoea overall but may have improved it in the high-dose group of acute heart failure patients. It did, however, increases SET, decrease LVESD and was well tolerated. ATOMIC-AHF was a dose-finding study and underpowered to look at clinical outcomes, and the serial enrolment of cohorts limited analyses; however, the results were sufficient to warrant further investigation of omecamtiv mecarbil as an oral treatment in chronic heart failure patients.

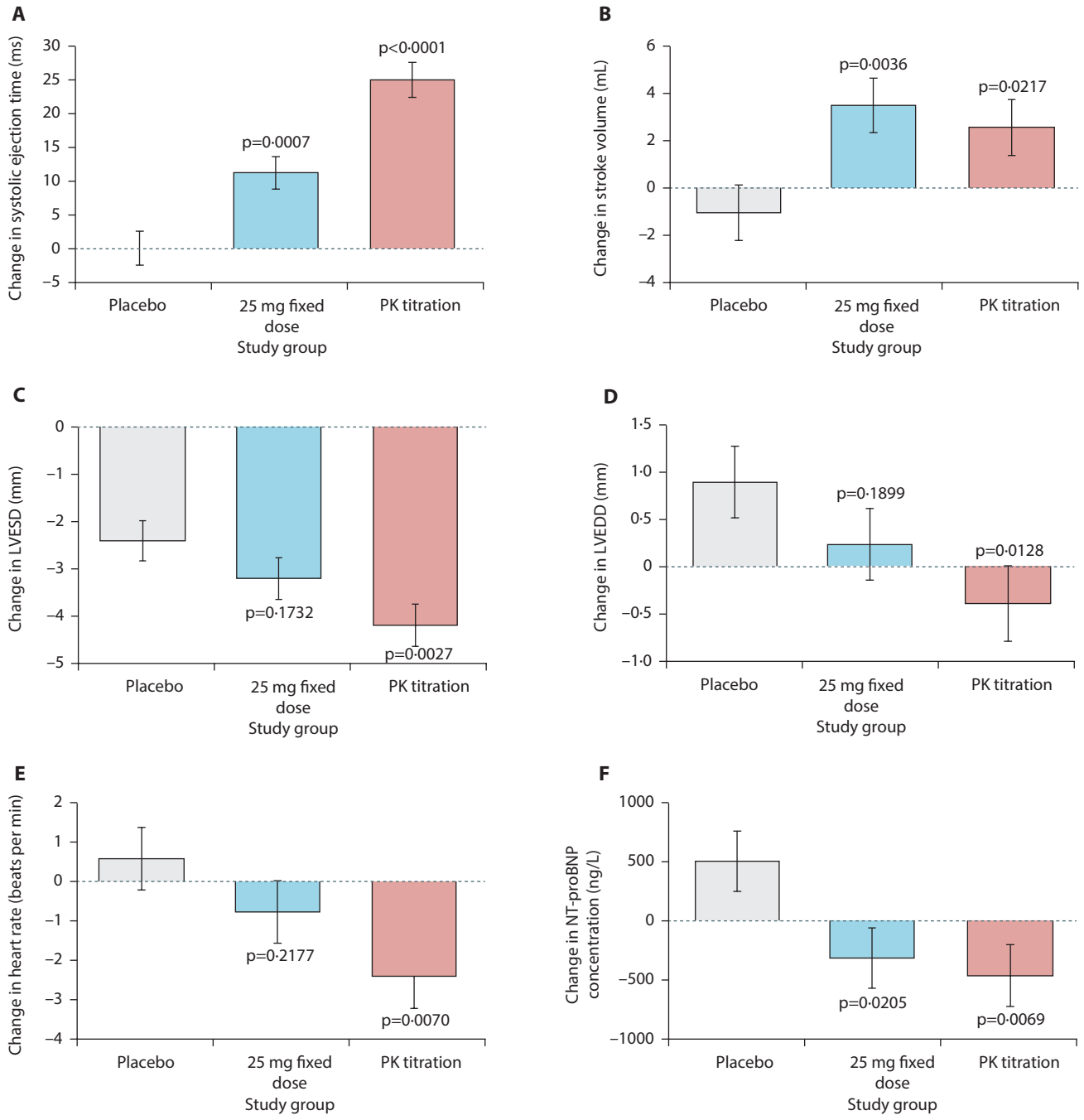
COSMIC-HF trial

The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF trial) was a randomised, parallel-group, double-blind, placebo-controlled phase II study conducted over 87 sites in 13 countries [34]. Its primary pharmacokinetic objective was to dose titrate omecamtiv mecarbil so that patients received the drug over a targeted plasma concentration range for the duration of the study, with a secondary endpoint of its effect on cardiac function.

Eligible patients were aged 18–85 years with chronic heart failure (NYHA II or III) who had an optimal specific treatment for at least 4 weeks. There were 448 patients randomised 1:1:1 to receive oral placebo or omecamtiv mecarbil (fixed-dose group: 25 mg twice daily; pharmacokinetic [PK]-titration group: 25 mg with escalation to 50 mg, depending on omecamtiv mecarbil plasma concentration). Patients were visited at weeks 2 and 8, and then every 4 weeks until week 24 and intensive pharmacokinetic sampling was performed at the end of weeks 2 and 12, over a period of 8 hours on each day. At week 8, 78 patients (53%) of 146 in the PK-titration group were escalated to dose of 50 mg twice daily and at week 12.

At 20 weeks, both omecamtiv mecarbil groups showed significant improvements over placebo in SET (fixed-dose group: +11 ms, p=0.007; PK-titration group: +25 ms, p<0.001) and SV (fixed-dose group: +5 mL, p=0.0036; PK-titration group: + 4 mL, p=0.0217). Individually, the PK-titration group had

Figure 3. COSMIC-HF study: least squares mean (SE) changes from baseline to 20 weeks in efficacy endpoints. All prespecified secondary efficacy endpoints in the PK-titration group differed significantly from those in the placebo group at week 20. (A) SET (systolic ejection time). (B) SV (stroke volume). (C) LVESD (left ventricular end systolic diameter). (D) LVEDD (left ventricular end diastolic diameter). (E) Heart rate. (F) NT-proBNP (N-terminal-pro B-type natriuretic peptide). PK, pharmacokinetic.



The p values are for comparisons with the placebo group. Reproduced with permission [34].

significantly reduced LVESD (–1.8 mm, p=0.0027) and LVEDD (–1.3 mm, p=0.0128), heart rate (–3 beats per minute, p=0.0070) as well as LVESV, LVEDV and an augmented LVFS. LVEF was significantly improved in the fixed-dose group (p=0.025) but only reached a positive tendency towards improvement in the PK-titration group (p=0.063). Plasma concentrations of NT-proBNP at 20 weeks were reduced in both omecamtiv mecarbil groups (fixed-dose group: –822 pg/mL, p=0.0205; PK-titration

group: –970 pg/mL, p=0.0069) and this effect persisted 4 weeks after omecamtiv mecarbil discontinuation (fixed-dose group: –1327 pg/mL, p=0.0004; PK-titration group: –1306 pg/mL, p=0.0006) suggesting a progressive reduction in myocardial wall stress (Figure 3).

Adverse and clinical events in patients on omecamtiv mecarbil were comparable to placebo. There were a total of eight deaths (four on placebo, one in the fixed-dose group, and three in the PK-titration group) and three myocardial infarctions (two on placebo and one in the PK-titration group), whereas unstable angina was documented only in one patient of the fixed-dose group. Other cardiac adverse and noncardiac events were mostly balanced between placebo and treatment groups. There were 91 (61%) reported adverse events on placebo, 92 (61%) in the fixed-dose group, and 95 (65%) in the PK-titration group (pooled 187), whereas the adjudicated serious adverse events, were 30 in the placebo arm (20%), 36 (24%) in the fixed-dose group and 32 (22%) in the PK-titration group (pooled 68).

Cardiac troponin median change from baseline at week 20 increased compared with placebo by 0.001 ηg/mL in the fixed-dose and by 0.006 ηg/mL in the PK-titration group (unchanged in the placebo group). There were a total 278 events of increased troponin affecting all treatment groups, but none of them were judged to be due to an episode of myocardial ischaemia or infarction.

A further analysis of data from COSMIC-HF looked at omecamtiv mecarbil response with regard to ischaemic and nonischaemic heart failure aetiologies and found similar findings between aetiologies with regard to pharmacodynamic response, and efficacy and safety endpoints (Table 1) [35].

In summary, COSMIC-HF showed that an omecamtiv mecarbil PK-based dose-titration strategy produced an improvement in cardiac function as well as a reduction of ventricular diameters compared to placebo, and with a similar safety profile.

GALACTIC-HF

GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) is a phase III, double-blind, randomised, placebo-controlled multicentre clinical trial which started recruiting in January 2017 and is due for completion in January 2021 [36]. It is designed to compare omecamtiv mecarbil with placebo when added to current heart failure standard treatment in patients with chronic heart failure and reduced ejection fraction. Its primary endpoint is a composite of time-to-cardiovascular death or first heart-failure event, whichever occurs first. Secondary endpoints include measurement of patient-reported outcomes (Kansas City Cardiomyopathy Questionnaire, KCCQ); time to first heart-failure hospitalisation; and time to all-cause death. GALACTIC-HF will recruit approximately 8000 symptomatic chronic heart

Table 1. Effects of omecamtiv mecarbil in patients with ischaemic and nonischaemic heart failure aetiology in COSMIC-HF (placebo-corrected change from baseline at 20 weeks in the PK-group) [33]. A total of 287 (64%) patients had ischaemic aetiology of heart failure, whilst 161 (36%) had a nonischaemic origin. The main statistically significant changes in all prespecified secondary efficacy endpoints (compared to placebo) were documented in the PK-group (20 weeks). In this group there were 100 patients with an ischaemic aetiology (placebo 89) and 46 with a nonischaemic one (placebo 60). Reproduced with permission [34].

Variable	Ischaemic (*n*:100) LSmean (95% CI)	Nonischaemic (*n*:46) LSmean (95% CI)	Interaction (*p*-value)
SET (ms)	24 (16, 32)	25 (14, 37)	0.89
SV (mL)	4.9 (1.0, 8.7)	1.2 (–4.2, 6.7)	0.28
LVEDD (mm)	–1.2 (–2,5, 0.1)	–1.7 (–3.4, 0.1)	0.66
LVESD (mm)	–1.6 (–3.1, –1.0)	–2.2 (–4.2, –0.3)	0.61
LVSF (%)	1.4 (–0.2, 3.0)	2.1 (–0.0, 4.1)	0.59
LVEDV (mL)	–10.3 (–21.1, 0.5)	–12.8 (–29.9, 4.3)	0.81
LVESV (mL)	–10.5 (–19.3, –1.6)	–14.2 (–29.2, 0.8)	0.67
LVEF (%)	1.4 (–0.8, 3.5)	2.1 (–0.7, 5.0)	0.67
HR (bpm)	–4.1 (–6.7, –1.5)	–0.6 (–4.5, 3.3)	0.15
NTproBNP (pg/mL)	–695 (–1526, 136)	–1249 (–2499, 2)	0.47
TnI (ηg/mL)	0.024 (0.011, 0.037)	0.022 (–0.008, 0.052)	0.91

HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVSF, left ventricular shortening fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PK, pharmacokinetic; SET, systolic ejection time; SV, stroke volume; TnI, troponin I.

failure patients in over 800 sites in 34 countries and, in order to be eligible, these individuals should have LVEF ≤35%, NYHA II–IV, and elevated BNP or NT-proBNP levels. Patients will be randomised to oral omecamtiv mecarbil or placebo: omecamtiv mecarbil starting dose of 25 mg twice daily and then followed by a PK-guided dose optimisation to one of three target doses (25, 37.5 and 50 mg twice daily). This is an event-driven study in which patients will be followed indefinitely until the accumulation of pre-estimated CV death events is reached (90% powered for CV mortality).

Conclusions and future prospects

The first-in-class cardiac myosin activator, omecamtiv mecarbil, augments the speed of ATP hydrolysis, thus accelerating the production of a strong actin-myosin complex, which leads to increased force production. It produces dose-dependent increases in SET, SV, ejection fraction and fractional shortening.

The ATOMIC-AHF trial showed that IV omecamtiv mecarbil did not improve dyspnoea overall but may have improved it in a high-dose group of acute heart failure patients. It did, however, increase SET, decrease LVESD and was well tolerated. The COSMIC-HF trial showed that a pharmacokinetic-based dose-titration strategy improved cardiac function and reduced ventricular diameters compared to placebo, and had a similar safety profile. It also significantly reduced plasma NT-proBNP compared with placebo. Minimal troponin release without evidence of ischaemia observed will no doubt be further studied in the phase III trial [30,37].

The GALACTIC-HF phase III trial is comparing omecamtiv mecarbil with placebo when added to current heart failure standard treatment in patients with chronic heart failure and reduced ejection fraction and is expected to be completed in January 2021.

Preclinical and clinical pharmacology studies are continuing to look at the exact mechanism of omecamtiv mecarbil and will no doubt help to interpret clinical results and guide future clinical use of the drug [38].

Thus, the ongoing range of preclinical and clinical research on omecamtiv mecarbil will further elucidate its full range of pharmacological effects and its clinical usefulness in heart failure.

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