Omecamtiv mecarbil for patients with severe systolic dysfunction and hypotension

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This editorial refers to 'Effects of omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure: the GALACTIC-HF trial', by M. Metra *et al*., https://doi.org/10.1093/eurheartj/ehac293.

For patients with heart failure (HF) and reduced ejection fraction (HFrEF), thankfully, several treatments that improve clinical outcomes including survival are available and well established in clinical practice.[1] However, none of these evidence-based drugs address the underlying pathophysiological mechanism, which is a reduction of left ventricular (LV) contractility.

Over the years there has been great interest in developing treatments to increase cardiac contractility; classically these are referred to as inotropes.[2] Unfortunately, to date these agents have failed to demonstrate a survival benefit for patients.[3] Many of these drugs act on cAMP or intracellular calcium handling, increasing heart rate (HR) and myocardial oxygen consumption, causing arrhythmia, ischaemia, and a higher mortality.[3] A classification of drugs that improve myocardial contractility and contraction, based on three basic myocardial processes involved in these mechanisms, has been proposed: 'cardiac calcitropics' those agents that primarily alter calcium intracellular concentrations; 'myotropes', those that directly affect myosin or other components of the sarcomere including actin, the associated regulatory proteins, or other structural elements of the sarcomere through calcium-independent mechanisms; and 'cardiac mitotropes',

those that alter myocardiac energetics which are centred around mitochondrial energy production.[4]

Omecamtiv mecarbil is a myotrope, the first of a new class of direct cardiac myosin activators, with a unique mechanism of action that makes it distinct from traditional inotropes. It improves cardiac function through an increase in actin-myosin interaction without affecting the transient calcium and without greater oxygen consumption.[4] Early phase clinical studies showed that omecamtiv mecarbil increases left ventricular ejection fraction (LVEF), stroke volume, and systolic ejection time, and decreases left ventricular end-diastolic and end-systolic volumes.[5]

The GALACTIC HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial was the first to demonstrate a beneficial effect of omecamtiv mecarbil on cardiovascular outcomes.[6] In this study 8256 symptomatic patients, NYHA II-IV, with systolic heart failure and an LVEF ≤35%, were randomized to receive omecamtiv mecarbil or placebo in addition to optimal medical therapy. The patients included were currently hospitalized for HF or had either an urgent visit to the emergency department for HF or a hospitalization for HF within 1 year. A systolic blood pressure (SBP) of ≥85 mmHg and≤140 mmHg was required for eligibility. The main exclusion criteria were haemodynamic or clinical instability requiring mechanical or intravenous therapy, a diastolic blood pressure >90 mmHg, and estimated glomerular filtration rate <20 ml/min/1.73 m^2. The pre-specified primary endpoint was a composite of the time-to-first HF event or cardiovascular death. An ‘HF event’ was defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening HF leading to treatment intensification beyond a change in oral diuretic therapy. Secondary outcomes of interest included a first HF event, a first HF hospitalization, cardiovascular death, and all-cause death.

The primary endpoint of a first HF event or cardiovascular death was reduced by 8% (*P* = 0.03) with omecamtiv mecarbil. The between-group difference was driven by a larger effect among patients with an LVEF less than 28%. There was no effect on cardiovascular mortality, all-cause death, or hospitalization for HF.

The SBP at baseline in GALACTIC-HF was lower compared with that of all other trials enrolling either outpatients or patients hospitalized with HF.

In this issue of the *European Heart Journal*, Metra M *et al*. presented a subanalysis of the GALACTIC-HF trial[7] in which they aimed to evaluate the potential interaction between baseline SBP and the clinical benefit of omecamtiv mecarbil, on top of optimal medical therapy, compared with placebo, in patients with chronic HF. This subgroup analysis was not pre-specified in the protocol of the clinical trial. Patients were divided into two baseline categories according SBP: low defined as SBP ≤100 mmHg, and SBP >100 mmHg.

Among the 8232 patients analysed from the GALACTIC-HF trial, 1473 (17.9%) had anSBP ≤100 mmHg and 6759 (82.1%) had an SBP >100 mmHg. During a median follow-up of 21.8 months, the primary composite outcome occurred in 2415 (35.7%) patients with an SBP >100 mmHg vs. 715 (48.5%) patients with a low SBP, with an incidence of 23.0 vs. 37.9 per 100 patient-years in each group, respectively. Patients with an SBP >100 mmHg also had a significantly lower risk of a first HF event, cardiovascular death, all-cause death, and a first HF hospitalization

The investigational drug was associated with a statistically significant reduction of the primary combined endpoint cardiovascular death or HF event in the subgroup of patients with baseline systolic blood pressure ≤100 mm Hg [hazard ratio = 0.81; 95% confidence interval (CI) 0.70–0.94); *P* = .005]. However, no significant clinical benefit was observed among patients with baseline systolic blood pressure >100 mm Hg (hazard ratio = 0.95; 95% CI 0.88–1.03; *P* = .19). These results strongly suggest a differential treatment effect of omecamtiv mecarbil in patients with chronic HF, depending on the baseline systolic blood pressure; however, the interaction term remained at the edge of statistical significance (*P* = .051).

Despite the limitations, which are well stated in the article, (that it was a no pre-specified sub-analysis and that the SBP categories were arbitrarily defined), the study does have some interesting strengths.

First, severe impairment of systolic function is often associated with low SBP, and this makes treatment with evidence-based guideline-directed medical therapy for HFrEF difficult or even impossible for some patients. Indeed, a typical feature of advanced HF is both symptomatic hypotension and the reduced tolerability or inability to take neurohormonal modulators, which is also accompanied by a poorer prognosis.[8] This study confirms that patients with low SBP are at higher risk of adverse clinical outcomes.

Second, this study extends two previous subanalyses of GALACTIC-HF, in which the benefit of omecamtiv mecarbil is particularly seen in patients with more advanced disease and severe HF, defined as those having NYHA symptom class III to IV, an LVEF ≤30%, and a hospitalization for HF within the previous 6 months[9]; and in those with lower LVEF.[10] Omecamtiv mecarbil had a progressively greater relative and absolute treatment effect as baseline LVEF decreased, with a 17% relative risk reduction for the primary composite endpoint in patients with a baseline LVEF ≤22% compared with those with a LVEF ≥33%.[10]

Finally, the fact that in the group of patients with low SBP there was no evidence of a reduction in SBP and, in addition, no alteration in renal function or potassium levels after treatment with omecamtiv mecarbil, suggests that this drug may be useful in these sicker patients. Currently therapeutic options for patients with low SBP, low LVEF, or severe HF are very limited. The fact that omecamtiv mercarbil can be given orally sets it apart from other intravenous contractility-enhancing treatments. Careful selection of patients who may benefit from this drug will hopefully position its use in the near future.

Conflict of interest: M.G.C.-L.: Research grants and/or consulting fees from Amgen, Abbott, Medtronic, Novartis, AstraZeneca, Boehringer Ingelheim-Lilly, Vifor, and Rovi. Galactic HF National lead. T.A.M.: consulting fees from Edwards, Abbott and Boehringer Ingelheim. E.B.-C.: Consulting or personal fees from Abbott, AstraZeneca, Novartis, Boehringer Ingelheim-Lilly and Rovi. Galactic HF subinvestigator.

Data availability. No new data were generated or analysed in support of this research.

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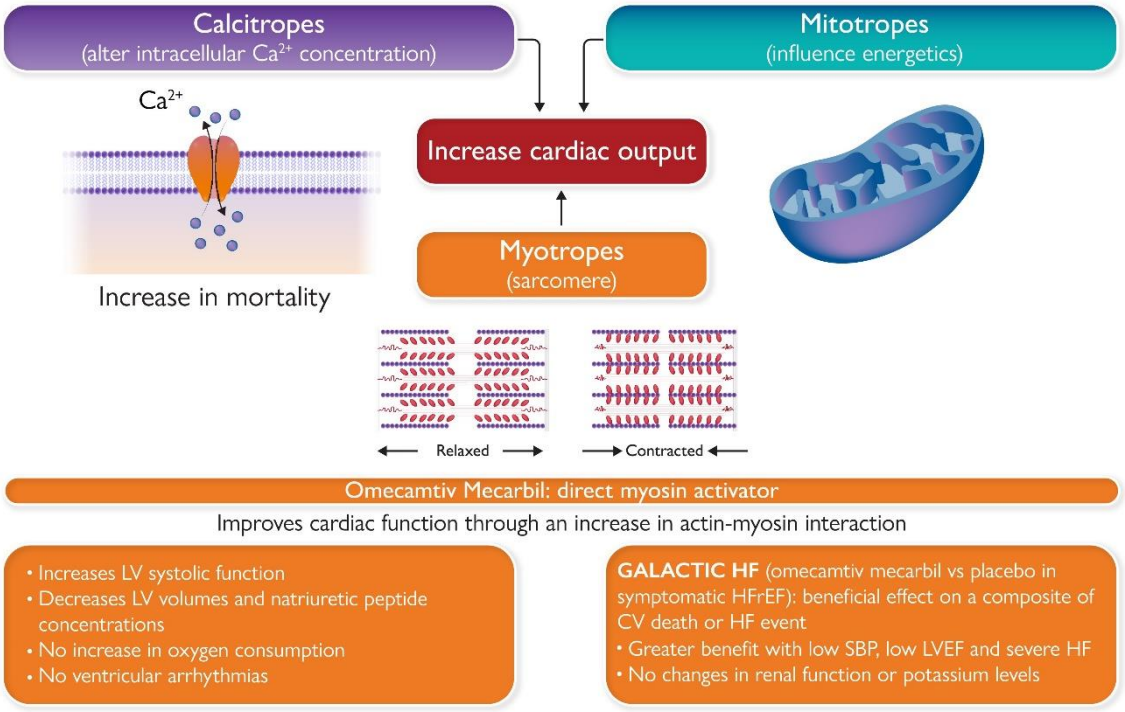

Graphical abstract. Classification of inotropic drugs according to mechanism of action: calcitropes, mitotropes and myotropes. Main effects and clinical outcomes of omecamtiv mecarbil. Modified from Psotka *et al.*[4] Ca^{2+}, calcium; LV, left ventricle; CV, cardiovascular; HFrEF, heart failure reduced ejection fraction; HF, heart failure; SBP, systolic blood pressure; LVEF, left ventricle ejection fraction.