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## **Omecamtiv Mecarbil: a Personalized Treatment for Patients with Severely Impaired Ejection Fraction**

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Omecamtiv mecarbil is a first-in-class “myotrope” that selectively binds to cardiac myosin increasing cardiac sarcomere function, which can lead to an improvement of myocardial contractility, particularly by augmenting the power stroke at the start of the systole and the contractile function of the atria.<sup>1, 2</sup>

In the Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) phase 2 trial, treatment with omecamtiv mecarbil for 20 weeks increased left ventricular systolic ejection time and stroke volume, reduced end-systolic and diastolic diameters, and decreased NT-pro BNP levels.<sup>3</sup> These encouraging findings prompted the conduct of the phase 3 Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) trial to test the efficacy and safety of omecamtiv mecarbil (vs. placebo) in patients with heart failure and a left ventricular ejection fraction (LVEF) of 35% or less.<sup>4</sup>

GALACTIC-HF included 8256 symptomatic patients with elevated natriuretic peptide levels, who were randomized both in the hospital and in ambulatory settings and followed for a median of 22 months. The primary outcome, a composite of a first heart failure (HF) event (hospitalization or urgent visit for HF) or death from cardiovascular causes, occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group, with a corresponding HR of 0.92; 95%CI, 0.86 to 0.99. The primary outcome rate reduction with omecamtiv mecarbil was due to reduction of HF events, without impact on cardiovascular mortality: HR, 1.01; 95%CI, 0.92-1.11.<sup>5</sup>

Among the multiple subgroups tested (24 in total) LVEF ( $\leq 28\%$  vs.  $>28\%$ , median) showed a significant interaction for the effect of omecamtiv mecarbil on the primary

outcome, whereby patients with a LVEF  $\leq 28\%$  could have benefited more from omecamtiv mecarbil therapy (vs. placebo) than patients with a LVEF  $>28\%$ : HR, 0.86; 95%CI, 0.79 to 0.94 for patients with a LVEF  $\leq 28\%$  and HR, 1.04; 95%CI, 0.94 to 1.16 for patients with a LVEF  $>28\%$ ; interaction P =0.004. Atrial fibrillation (AFib, yes vs. no) was the other subgroup where a similar qualitative interaction was found, suggesting a greater benefit of omecamtiv mecarbil among patients in sinus rhythm compared with patients in AFib: HR, 0.86; 95%CI, 0.79 to 0.94 for patients in sinus rhythm and HR, 1.05; 95%CI, 0.93 to 1.18 for patients in AFib.<sup>5</sup> Beyond the directionally opposite effects, there is a strong biological plausibility suggesting that these interactions are not a product of chance. Omecamtiv mecarbil increases systolic stroke power and the atrial contractile function; therefore, it is plausible that the drug only benefits patients with a severely impaired LVEF in sinus rhythm, in whom the increment in ventricular and atrial contraction may produce a meaningful and beneficial impact on outcomes.

In this issue of the *Journal*, Teerlink J.R. and colleagues study in detail the influence of baseline LVEF on the therapeutic effect of omecamtiv mecarbil. Beyond the findings shown in the primary report,<sup>5</sup> the authors expand the analysis assessing the effect of omecamtiv mecarbil across quartiles and the continuous spectrum of LVEF; but unfortunately, they do not report the interplay between the LVEF and atrial rhythm. Given the qualitative treatment by LVEF and atrial rhythm interactions backed by the pharmacologic action of omecamtiv mecarbil on myocardial and atrial contractility, one might expect a most pronounced treatment effect among patients with a severely impaired systolic function in sinus rhythm.

Notwithstanding, it is interesting to observe that the treatment effect on the study primary outcome is similar between patients with a LVEF of 23% to 28% (HR, 0.85;

95%CI 0.74 to 0.97) and those with a LVEF  $\leq$ 22% (HR, 0.83; 95%CI, 0.73 to 0.95), but very different than the treatment effect observed in patients with a LVEF of 29% to 32% (HR, 1.11; 95%CI, 0.96 to 1.28) and in patients with a LVEF  $\geq$ 33% (HR, 0.99; 95%CI, 0.84 to 1.16); interaction P =0.013. Accordingly, the analysis with LVEF as a continuous covariate suggest that the beneficial effect of omecamtiv mecarbil is most pronounced among patients with a LVEF below 25%; interaction P =0.004 by LVEF as continuous variable. Omecamtiv mecarbil had no effect on cardiovascular (including sudden) or all-cause death, regardless of ejection fraction.

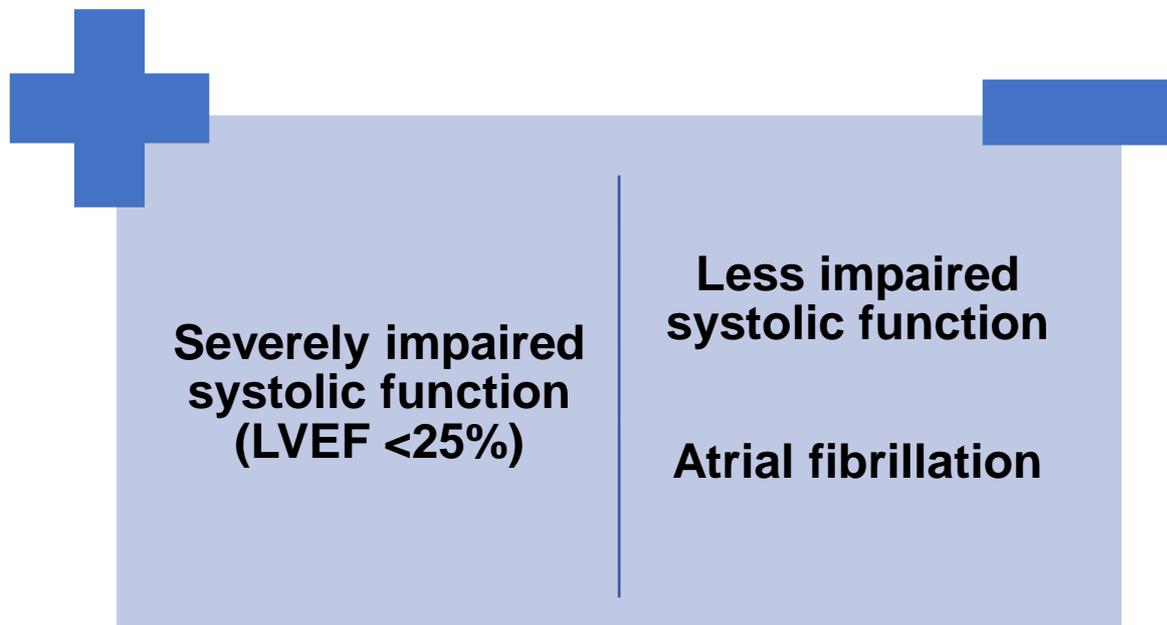
In GALACTIC-HF, the placebo primary outcome event-rates (per 100 patient-years) were 27.2 and 35.6 in patients with a LVEF from 23 to 28% and  $\leq$ 22%, respectively; much higher than the event-rate of 20.0 seen in patients with a LVEF  $\geq$ 33%. These subgroups, with a LVEF from 23 to 28% and  $\leq$ 22%, experienced primary outcome relative reductions of 15 to 17%, and absolute reductions (per 100 patient-years) of 3.3 and 7.4. For example, twelve patients with a LVEF  $\leq$ 22% need to be treated over a 3-year period to prevent one HF hospitalization.

GALACTIC-HF enrolled more than 8200 patients of whom 4456 had a LVEF  $\leq$ 28% and 1821 experienced a primary outcome event (within the LVEF  $\leq$ 28% subgroup), providing enough power to assume a benefit only to patients with a severely impaired systolic function. For comparison, in the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) and EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trials the total primary outcome events (composite of HF hospitalization or cardiovascular death) were less than half (888 and 823 patients, respectively) of the events experienced by patients with a LVEF  $\leq$ 28% in GALACTIC-HF.<sup>6, 7</sup>

In an era where adding more treatments to the therapeutic armamentarium of patients with HFrEF is increasingly difficult, personalized treatment approaches are necessary to cover unmet needs, benefit patients who need the most, and also to be cost-effective and generate return of investment.<sup>8</sup> Ejection fraction (and atrial rhythm) are probably the best means to stratify and identify patients responsive to omecamtiv mecarbil in a manner that is completely aligned with the biological mechanisms of the drug and using widely available and inexpensive biomarkers (an echo- and electrocardiogram).

Based on LVEF as a continuous variable, the “sweet spot” where the effect of omecamtiv mecarbil begins to occur is below 25%; therefore, based on the large number of patients and events among those with severely impaired ejection fraction in GALACTIC-HF, omecamtiv mecarbil should be recommended to patients with a LVEF <25% to reduce HF hospitalizations. *Figure 1.* Whether atrial rhythm should be part of the decisional algorithm should be explored in further studies.

Figure 1. Omecamtiv mecarbil benefits patients with severely impaired ejection fraction



Legend: LVEF, left ventricular ejection fraction; +, more benefit; -, less benefit.

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