The Influence of QRS Duration and Resynchronization Status on the Efficacy and Safety of Omecamtiv Mecarbil in Heart Failure with Reduced Ejection Fraction: the GALACTIC-HF trial

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Introduction

Background

- Omecamtiv mecarbil (OM) is a first-in-class direct myosin activator[1]
- In GALACTIC-HF, OM reduced the risk of a composite endpoint of first HF event or cardiovascular death in patients with HF and reduced ejection fraction (HFrEF)[2]
- Subgroup analyses showed a greater treatment effect in patients with more severely reduced left ventricular ejection fraction and in those without atrial fibrillation treated with digoxin[3,4]
- Prolonged QRS duration is associated with an increased cardiovascular risk in patients with HFrEF, and in select patients, it is accompanied by electro-mechanical dyssynchrony[5]

Objectives

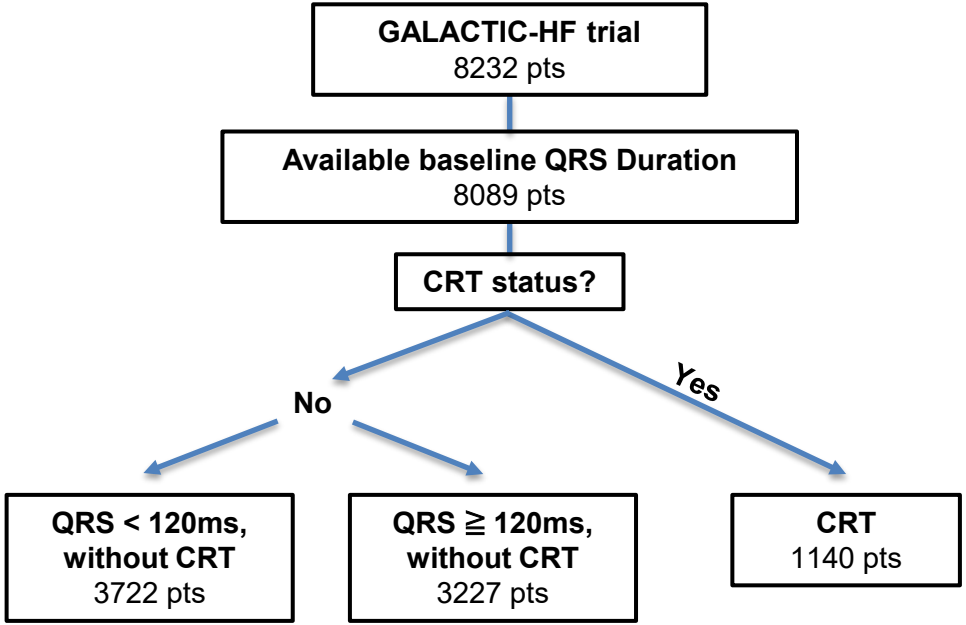
- Evaluate whether baseline QRS duration as well as the presence of cardiac resynchronization therapy (CRT) modifies the treatment effect of OM

Reference: [1]Teerlink JR et al. *JACC Heart Fail* 2020;8:329–340.; [2]Teerlink JR et al. N Engl J Med 2021;384:105–116.; [3]Teerlink JR et al. J Am Coll Cardiol 2021;78:97–108.; [4]Solomon SD et al. Eur Heart J 2022;43:2212–2220. [5]Kristensen SL et al. Eur J Heart Fail 2020;22:2370–2379.

Study Design & Methods

GALACTIC-HF Trial

- International, multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of OM in symptomatic HF patients (NYHA class II-IV), with reduced left ventricular ejection fraction (LVEF≤35%), elevated natriuretic peptide levels* and current or recent hospitalization for HF#



- Additional analyses

(I) QRS morphology and duration:

- QRS<120ms (*N=545*)
- QRS≥120ms and LBBB (*N=117*)
- QRS≥120ms and non-LBBB (N=213)

(II) Severe HF population†:

- Without Afib: LVEF<30% + NT-proBNP ≥ 1000 pg/mL
- With Afib: LVEF<25% + NT-proBNP ≥ 3000 pg/mL

- Survival analysis

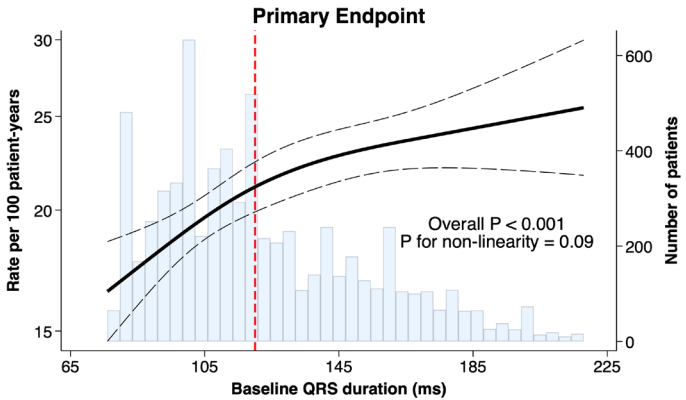
- Poisson regression (IR, RR)
- Cox proportional hazard models (HR)

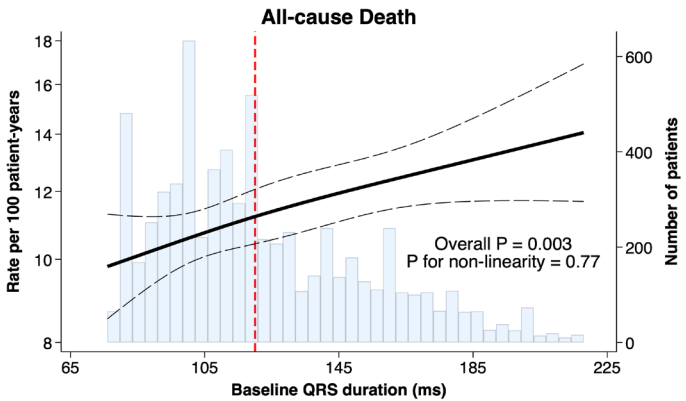
- Clinical Endpoints

- Primary: HF event or CV death
- HF hospitalization, CV death, All-cause death

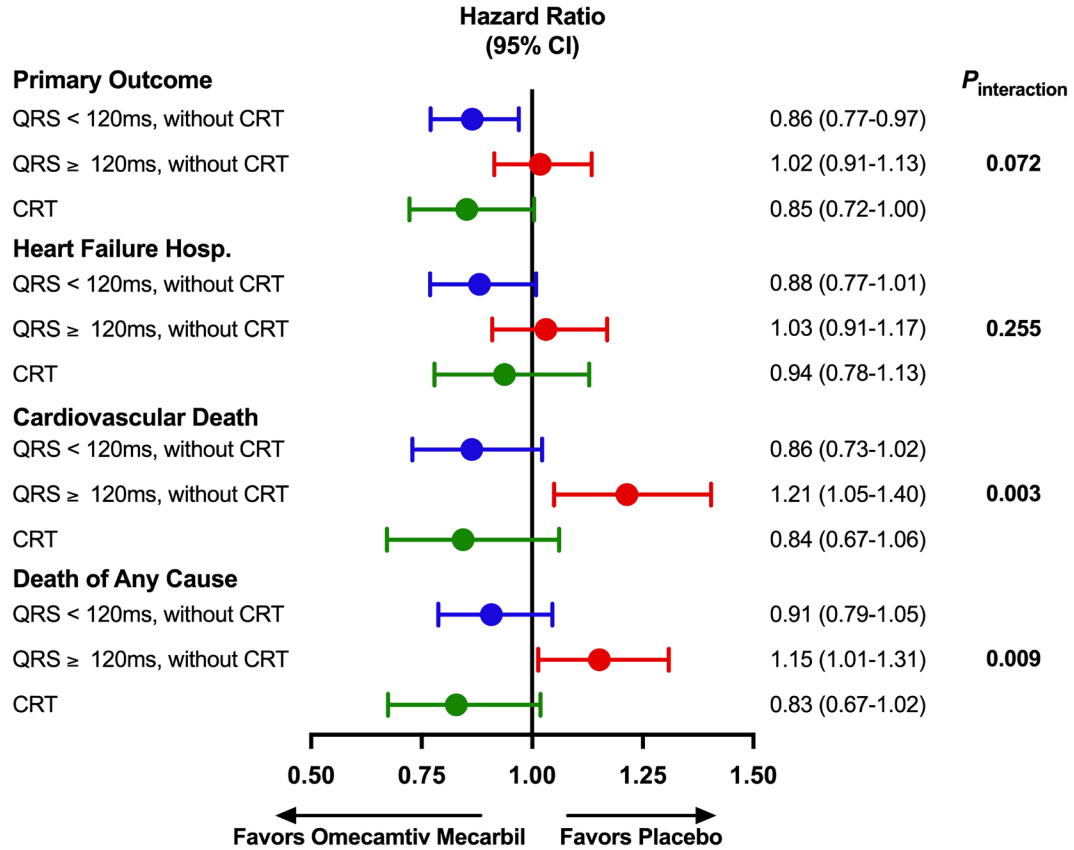
*N terminal pro–B-type natriuretic peptide (NT-proBNP) ≥400 pg/mL or BNP ≥125 pg/mL in patients without atrial fibrillation or flutter, and NT-proBNP ≥1,200 pg/mL or BNP ≥375 pg/mL in those with atrial fibrillation or flutter at baseline; #Currently hospitalized with a primary diagnosis of HF or to have received urgent treatment or been hospitalized for HF within the preceding year; † based on the COMET trial (NCT06736574)

Clinical outcomes across the QRS spectrum (without CRT)





The Treatment Effect of Omecamtiv Mecarbil was modified by baseline QRS duration and the presence of CRT



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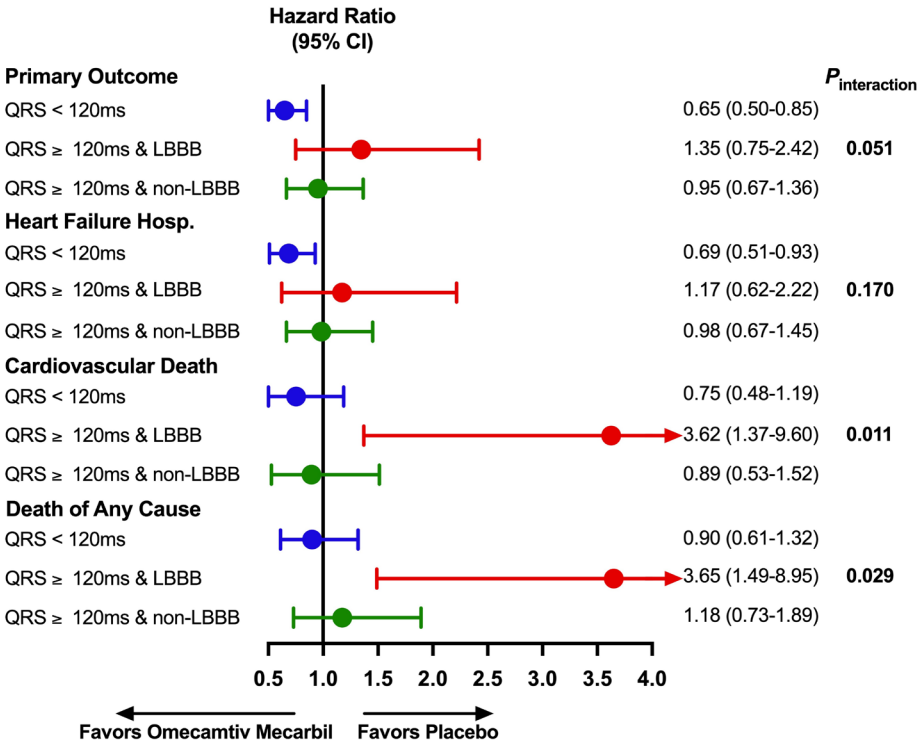
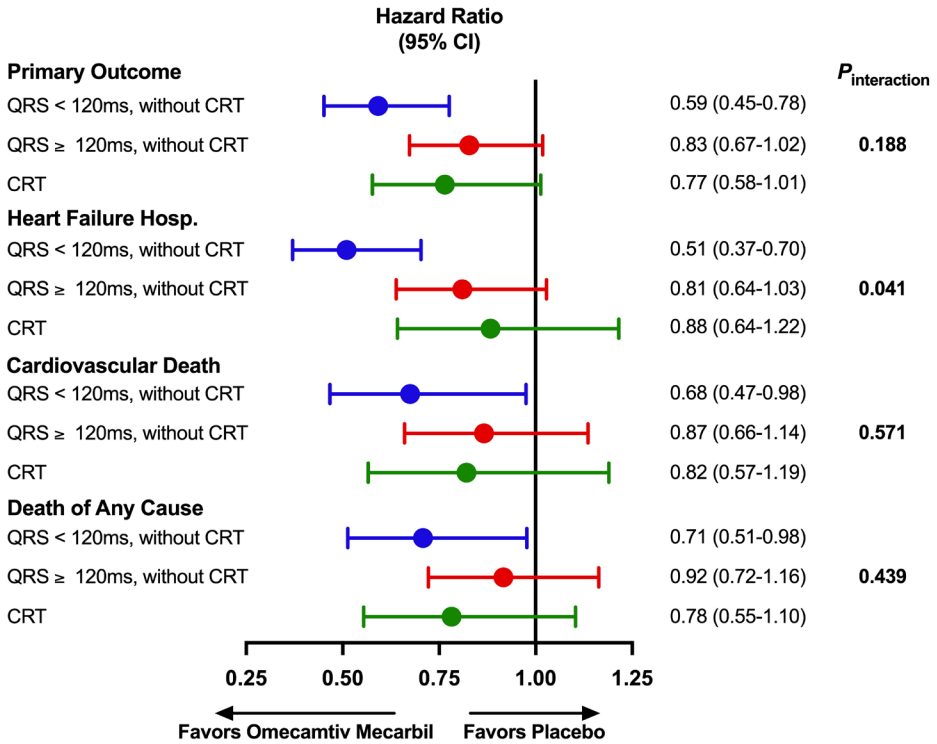
*Adjusted: age, sex, race, body mass index, estimated glomerular filtration rate (eGFR), atrial fibrillation/flutter at screening ECG, diabetes, ischemic etiology, chronic obstructive pulmonary disease, cerebrovascular disease, history of myocardial infarction, prior coronary artery bypass surgery, prior percutaneous coronary intervention, left ventricular ejection fraction, Kansas City Questionnaire – Total Symptom Score, systolic blood pressure, heart rate, NT-proBNP (on the log scale) and use of angiotensin converting enzyme inhibitor, angiotensin receptor blocker or angiotensin receptor blocker-neprilysin inhibitor, beta-blockers, sodium glucose co-transporter-2 inhibitors, mineralocorticoid antagonists and implantable cardioverter defibrillators

#Adjusted by eGFR and stratified by geographic region and randomization setting

The interaction was most evident among those with LBBB



Effect modification was not seen in patients with severe HF*



***Severe HF** Definition (Based on the COMET-HF Trial inclusion criteria (NCT06736574)
- Without Afib: LVEF<30% + NT-proBNP ≥ 1000 pg/mL or with Afib: LVEF<25% + NT-proBNP ≥ 3000 pg/mL + no digitalis use
- Minimum history of HF for 3 months; currently/within 6 months hospitalized for HF, receiving diuretics other than MRA
- Systolic blood pressure ≦ 130 mmHg; diastolic blood pressure ≦ 90 mmHg

Adjusted by eGFR and stratified by geographic region and randomization setting

Conclusions

1. In the GALACTIC-HF trial, baseline QRS duration in patients not treated with CRT appeared to modify the effect of OM, with wider QRS duration attenuating its treatment benefit.

2. This interaction was most pronounced among those with LBBB.

3. Patients with CRT at baseline experienced a consistent benefit from OM.

4. In a more advanced HF cohort with lower EF, there was no evidence of treatment heterogeneity according to baseline QRS duration or CRT status.

*We thank the patients, their families, investigators, staff, and all collaborators for their participation in **GALACTIC-HF**.*