The effect of omecamtiv mecarbil on outcomes analysed using the win ratio: an exploratory analysis of GALACTIC-HF

Kieran F. Docherty, Alasdair D. Henderson, Pardeep S. Jhund, Genzhou Liu, Punag H. Divanji, Stephen B. Heitner, Stuart Kupfer, Fady I. Malik, G. Michael Felker, Scott D. Solomon, John R. Teerlink and John J.V. McMurray

on behalf of the GALACTIC-HF trial investigators and committees

University of Glasgow

GALACTIC-HF

NHS Greater Glasgow and Clyde

Heart Failure & World Congress on Acute Heart Failure 2025

Disclosures

My employer, the University of Glasgow, has been remunerated by AstraZeneca for work on clinical trials; I am National Leader (United Kingdom) for the COMET-HF trial sponsored by Cytokinetics; I have received speaker fees from AstraZeneca, Boehringer Ingelheim, Pharmacosmos, and Translational Medicine Academy; have served on advisory boards or performed consultancy for Abbott, FIRE-1, Us2.ai and Bayer AG; have served on a Clinical Endpoint Committee for Bayer AG; and have received research grant support (paid to my institution) from AstraZeneca, Roche Diagnostics, Novartis, and Boehringer Ingelheim.

The GALACTIC-HF trial was sponsored by Amgen, Cytokinetics, and Servier.

Introduction

- In the placebo-controlled GALACTIC-HF trial, the cardiac myosin activator omecamtiv mecarbil reduced the risk of time-to-first worsening heart failure event or cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF).

- Prespecified subgroup analyses suggested an attenuation of the effect of omecamtiv mecarbil in those with higher left ventricular ejection fraction, those in atrial fibrillation, and those with lower NT-proBNP concentrations.

- In this exploratory analysis, we examined the effect of omecamtiv mecarbil on clinical, patient-reported, and circulating biomarker outcomes using the hierarchical win ratio method in the overall trial population and subgroups of interest.

Teerlink JR, et al. NEJM 2021;384(2):105-116.

GALACTIC-HF Trial Design

Multicenter, international, randomized, double-blind, placebo-controlled, event-driven Phase 3 study

Hypothesis: Selectively improving cardiac function with the cardiac myosin activator, omecamtiv mecarbil, will improve clinical outcomes in patients with HFrEF

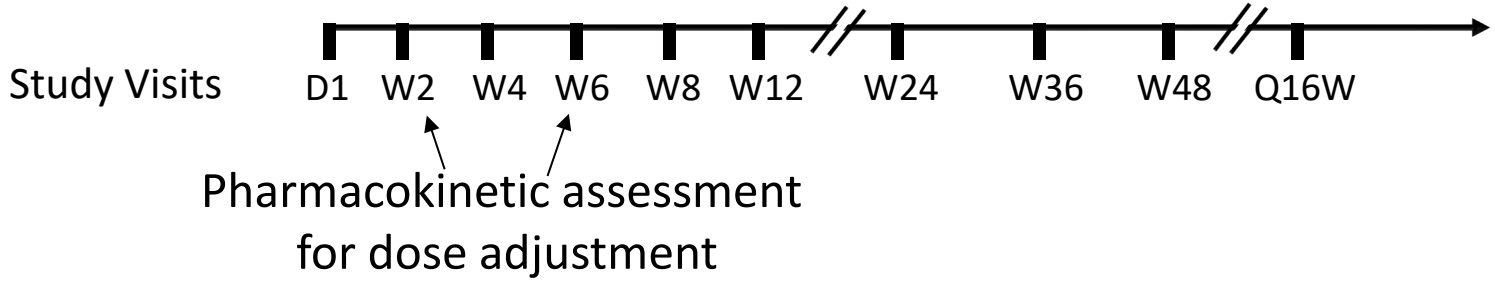
Screening:
- Chronic HF, NYHA II-IV
- LVEF ≤35%
- Elevated BNP/ NT-proBNP*
- Managed with standard HF therapies
- Currently hospitalized for HF (Inpatients)
  OR
  Urgent ED visit or hospitalization for HF within 1 year prior to screening (Outpatients)
- SBP ≥85 mmHg;
  eGFR ≥20 mL/min/1.73m^2

Randomization (1:1)

Stratification
– Inpatient or outpatient
– Region

Omecamtiv mecarbil + Standard HF therapy
Starting dose: 25 mg PO BID; Pharmacokinetic-guided dose selection (25, 37.5 or 50 mg PO BID)

Placebo + Standard HF therapy



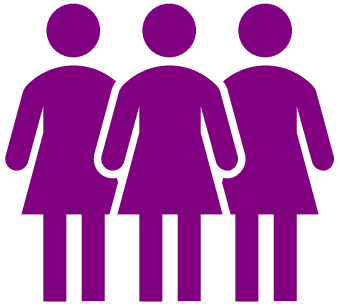
**NT-proBNP ≥400 pg/mL or BNP ≥125 pg/mL at screening (if in atrial fibrillation/ flutter: NT-proBNP ≥1,200 pg/mL or BNP ≥375 pg/mL).*

Teerlink JR, et al. JACC Heart Fail 2020;8:329–40

Methods

- We examined the effect of OM using the unmatched win ratio method on the following exploratory 5-tier hierarchical outcome:
    1) Cardiovascular death;
    2) The number of worsening HF events;
    3) A ≥5pt (outpatients) or ≥20pt (inpatients) KCCQ-TSS from baseline at 24 weeks;
    4) A ≥25% decrease in NT-proBNP from baseline at 24 weeks;
    5) The relative change in NT-proBNP from baseline at 24 weeks.
- The win ratio was calculated in the overall population and in subgroups of interest: ≤/> median LVEF (28%); AFF yes/no; and ≤/> median NT-proBNP overall (1998 pg/mL) and in sinus rhythm (1675 pg/mL).
- Multiple imputation for missing NT-proBNP and KCCQ-TSS data was performed.
- All analyses were stratified according to randomization setting and geographic region.

Win ratio



Omecamtiv mecarbil

Each patient from the OM arm paired with each patient from the placebo arm

↓

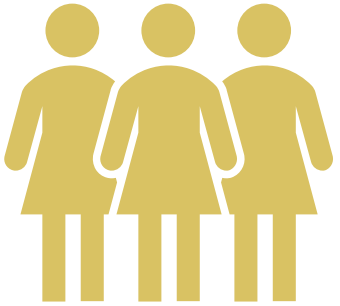
Comparison starts at the 1st of the 5 tiers

↓

A tie means that the comparison moves to the next tier of the hierarchy

↓

After 5 tiers the total number of wins and losses for OM are counted



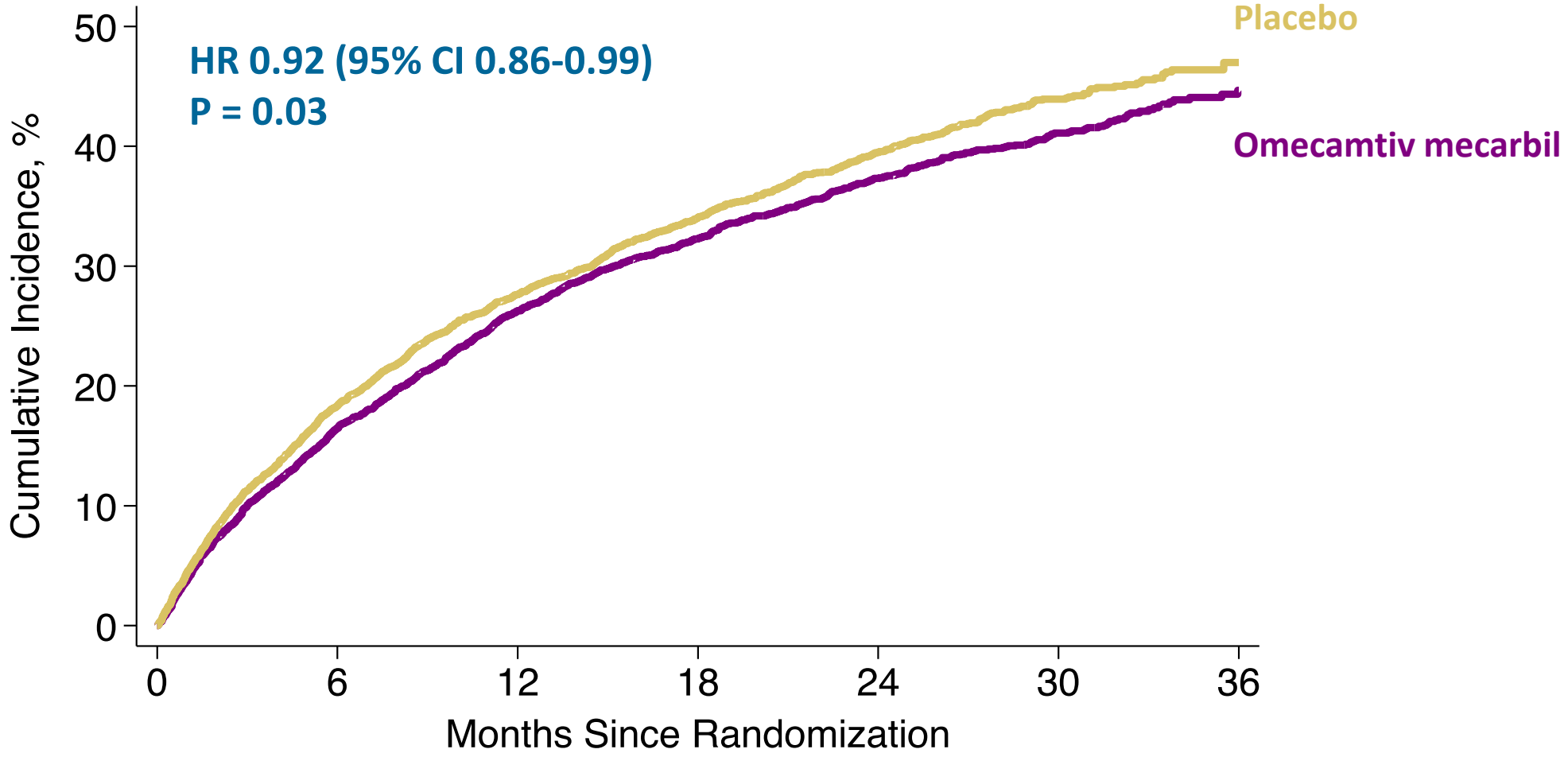
Placebo

Win ratio = Total Number of Wins / Total Number of Losses

Net Benefit = Sum of the difference in the win proportions across the tiers

GALACTIC-HF: Primary Composite Outcome

Time-to-first worsening heart failure event or cardiovascular death

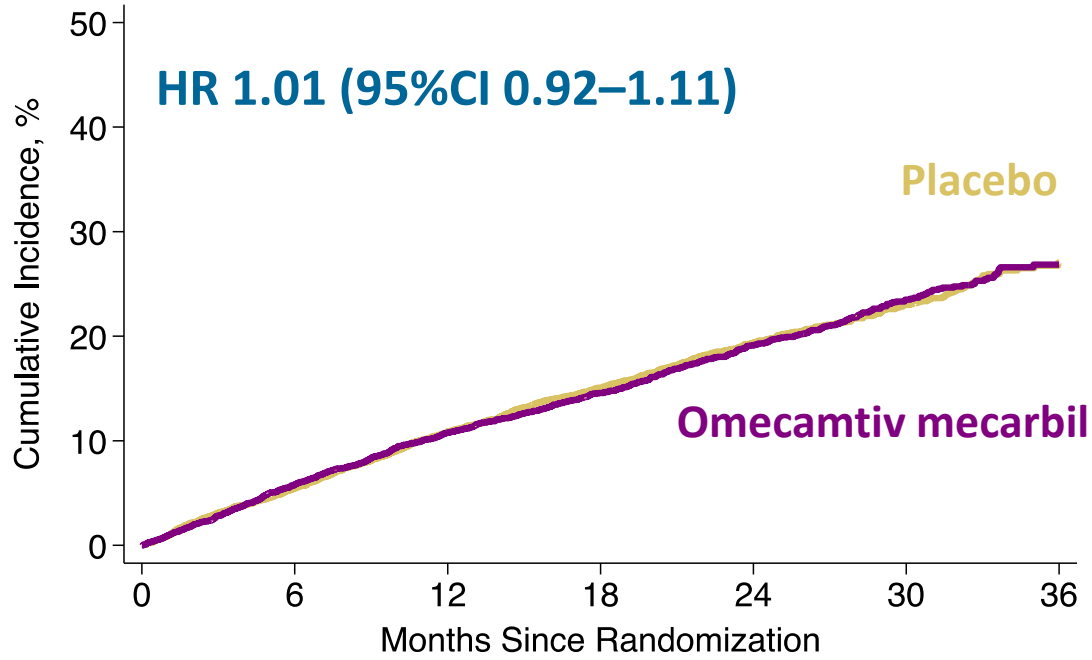


Number at risk							
Omecamtiv Mecarbil	4120	3391	2953	2158	1430	700	164
Placebo	4112	3310	2889	2102	1349	647	141

Teerlink JR, et al. NEJM 2021;384(2):105-116.

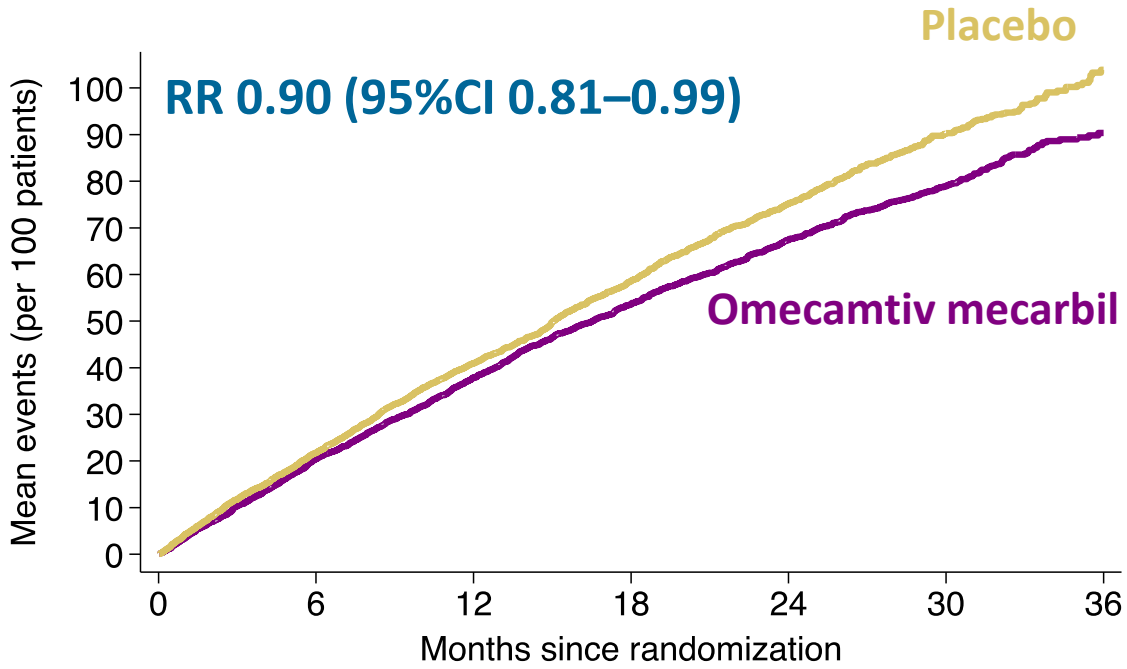
GALACTIC-HF: Clinical Components of Win Ratio

Cardiovascular death



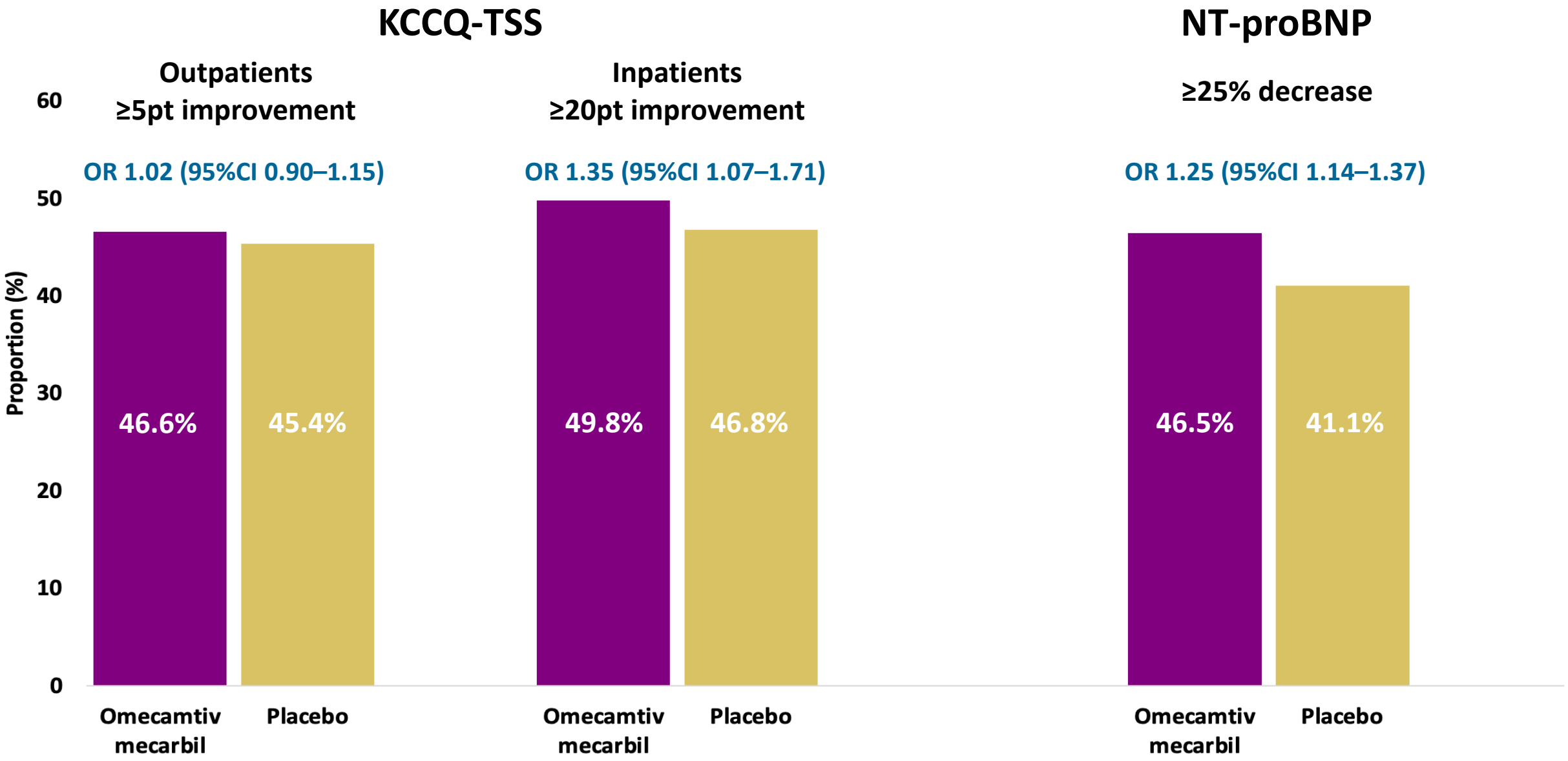
Number at risk							
Omecamtiv Mecarbil	4120	3838	3556	2710	1838	903	224
Placebo	4112	3821	3560	2722	1788	885	201

Total number of worsening HF events



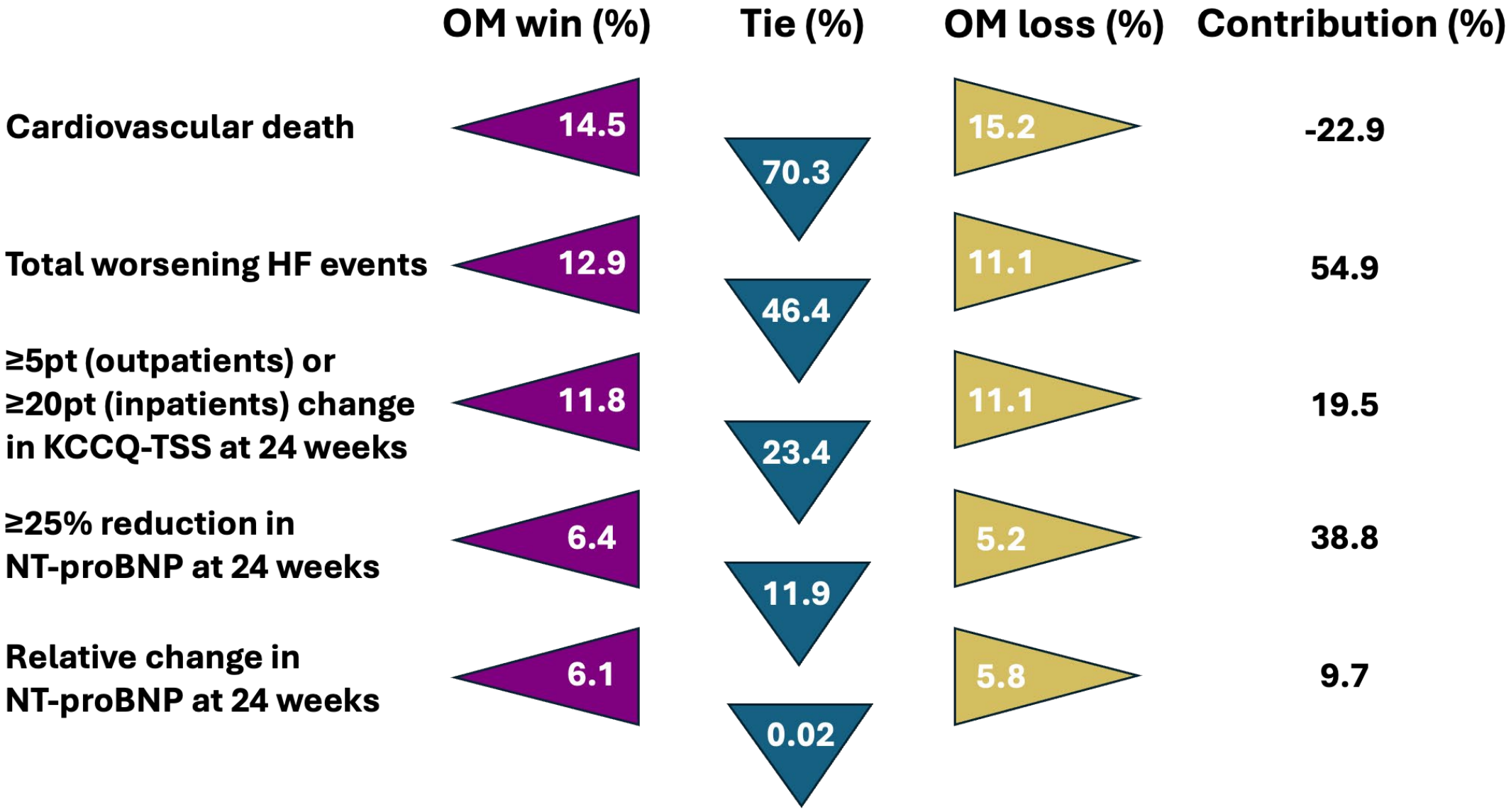
Number at risk							
Omecamtiv mecarbil	4120	3614	3190	2320	1525	738	172
Placebo	4112	3578	3145	2291	1453	696	150

GALACTIC-HF: KCCQ-TSS and NT-proBNP



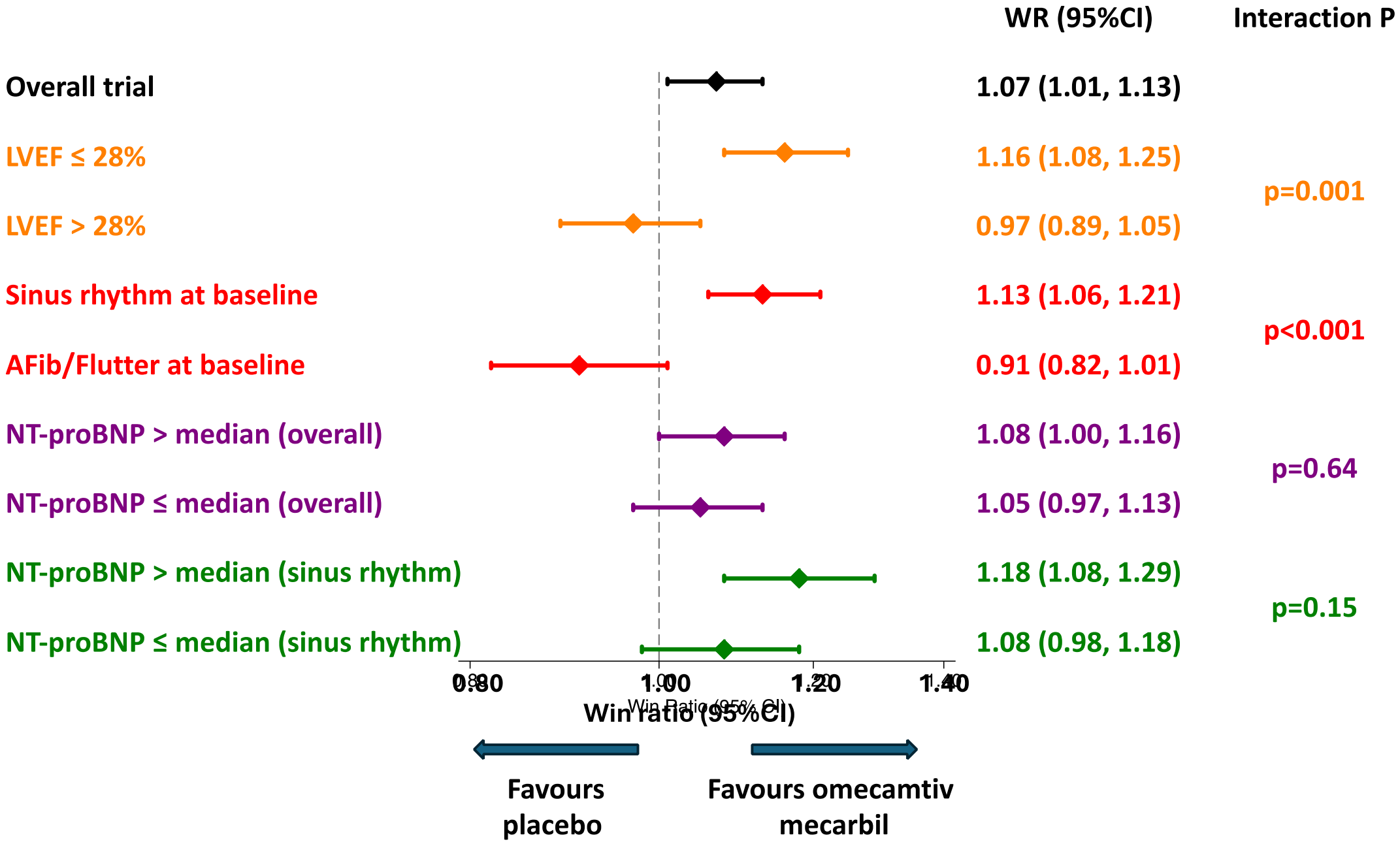
Analyses performed in those who were alive with available data at week 24

GALACTIC-HF – Overall Win Ratio



Win ratio = 1.07 (95%CI 1.01-1.13)
Net benefit = 3.3% (95%CI 0.6-6.0)

GALACTIC-HF – Win Ratio in Subgroups



Conclusions

- In GALACTIC-HF, the cardiac myosin activator omecamtiv mecarbil had a modest overall effect on an exploratory hierarchical outcome incorporating clinical, patient-reported, and circulating biomarker outcomes.
- There was evidence of a greater benefit of omecamtiv mecarbil in those with a lower LVEF and those in sinus rhythm.
- These data support ongoing research with omecamtiv mecarbil in the COMET-HF trial (Confirmation of Omecamtiv Mecarbil Efficacy Trial in HF [NCT06736574]), which is recruiting patients with the characteristics that appeared to benefit the most in GALACTIC-HF.