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GALACTIC-HF

- *Consulting Fee:* Abbott, **Amgen,** AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, **Cytokinetics,** Medtronic, Merck, Novartis, **Servier**, Verily, Windtree Therapeutics
- *Contracted Research:* Abbott, **Amgen,** AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, **Cytokinetics,** Medtronic, Novartis, Windtree Therapeutics

San Francisco VA Medical Center

UCSF University of California San Francisco

#AHA21

FS.01 - Rapid Fire Secondary Trial Analyses in Heart Failure

The Effect of Omecamtiv Mecarbil on Stroke in Patients With Heart Failure and Reduced Ejection Fraction in GALACTIC-HF

John R. Teerlink, Rafael Diaz, G. Michael Felker, John J.V. McMurray, Scott D. Solomon, Marco Metra, Zi Michael Miao, Brian Claggett, Stephen B. Heitner, Stuart Kupfer, Fady I. Malik, on behalf of the GALACTIC-HF Investigators and Patients

GALACTIC-HF

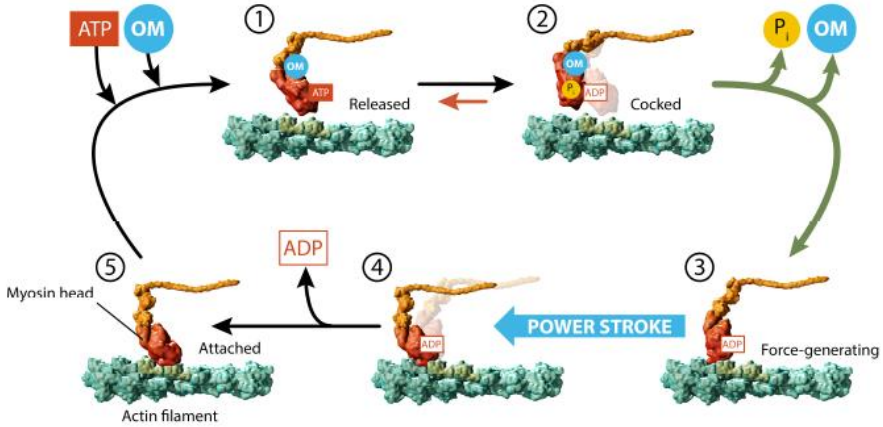
San Francisco VA Medical Center

UCSF University of California San Francisco

American Heart Association.

Omecamtiv Mecarbil (OM): A Novel Selective Cardiac Myosin Activator

Omecamtiv mecarbil stabilizes myosin in the Pre-Powerstroke State, increasing the entry rate of myosin into the tightly-bound, force-producing state with actin



Without omecamtiv mecarbil

With omecamtiv mecarbil

- More "hands" (myosin heads) to grasp the "rope" (actin filament) to produce more force

Malik FI, et al. *Science* 2011; 331:1439-43;
Shen YT, et al. *Circ Heart Fail* 2010;3:522-7;
Planelles-Herrero VJ, et al. *Nat Commun* 2017;8:190;
Teerlink JR, et al. *J Am Coll Cardiol HF* 2020;8:329-340.

Omecamtiv Mecarbil in Patients with Heart Failure with reduced Ejection Fraction (HFrEF)

GALACTIC-HF

Teerlink JR, *et al. N Engl J Med* 2021;384:105-116.

Enrolled 8,256 patients with:

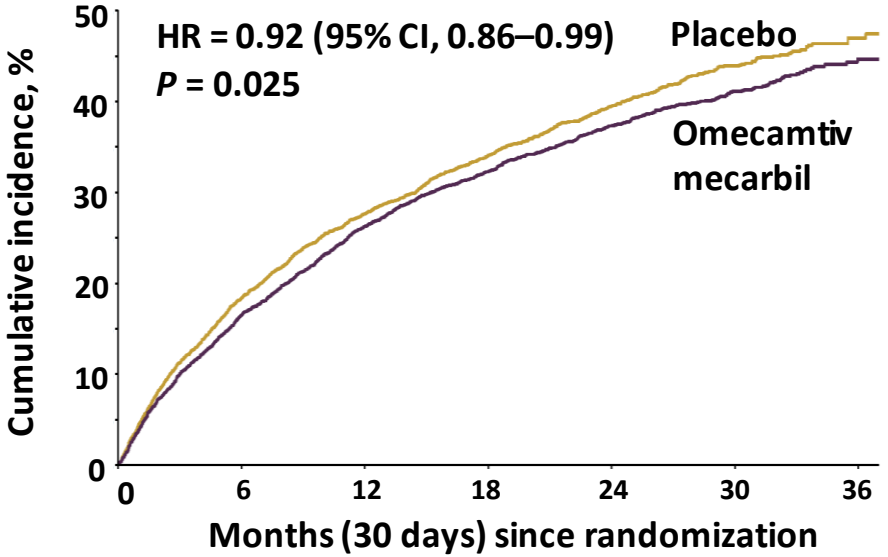
- Chronic HF, NYHA II-IV
- LVEF ≤35%
- Elevated BNP/ NTproBNP
- Managed with Standard HF therapies
- Inpatients (for HF) **OR** Outpatients (HF within 12 months)
- SBP ≥85 mmHg; eGFR ≥20 mL/min/1.73m^2

Randomized 1:1 to

- Placebo
- Omecamtiv mecarbil

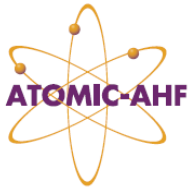
Median Follow-up: 21.8 months

Time to first Heart Failure event or Cardiovascular death



Biological Plausibility for Beneficial Effect of Omecamtiv Mecarbil on Stroke Events in Patients with HFrEF

Teerlink JR, *et al*. *J Am Coll Cardiol* 2016;67:1444-55; Teerlink JR, *et al*. *Lancet* 2016; 388: 2895-903; Biering-Sorensen T, *et al*. *Eur J Heart Fail* 2021;23:1052-56; Biering-Sorensen T, *et al. Circulation* 2016;134, Abstract.



In **ATOMIC-AHF** (606 pts with EF≤40% admitted for Acute HF treated with i.v. omecamtiv mecarbil or placebo for 48 hours):

- Adverse Event of Atrial fibrillation/flutter less frequent in patients treated with omecamtiv mecarbil: Placebo, 16 (5.3%) vs. OM 7 (2.3%).

In **COSMIC-HF** (448 pts with Chronic HF, EF≤40% treated with i.v. omecamtiv mecarbil or placebo for 20 weeks):

- Omecamtiv mecarbil increased LV, RV and LA function
- Omecamtiv mecarbil decreased LV and LA (nominal) volumes, heart rate (sympathetic drive) and NT-proBNP.

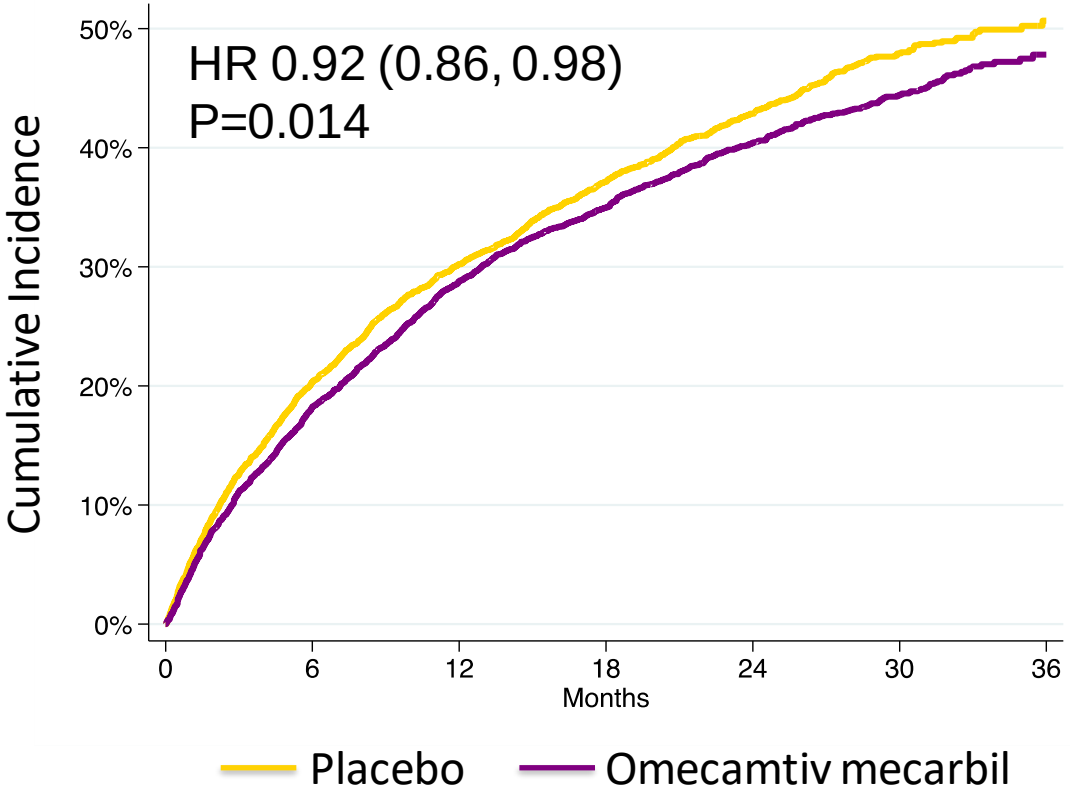
Stroke in HFrEF

GALACTIC-HF

- Patients with HFrEF have increased risk of stroke with significant morbidity and mortality
- Prior approaches to prevent stroke in HFrEF focused on anti-coagulation with associated bleeding risks
- Non-fatal and fatal stroke events were pre-specified, adjudicated endpoints in GALACTIC-HF
- Hypothesis: Can specifically and directly improving atrial and ventricular function prevent stroke in patients with HFrEF?

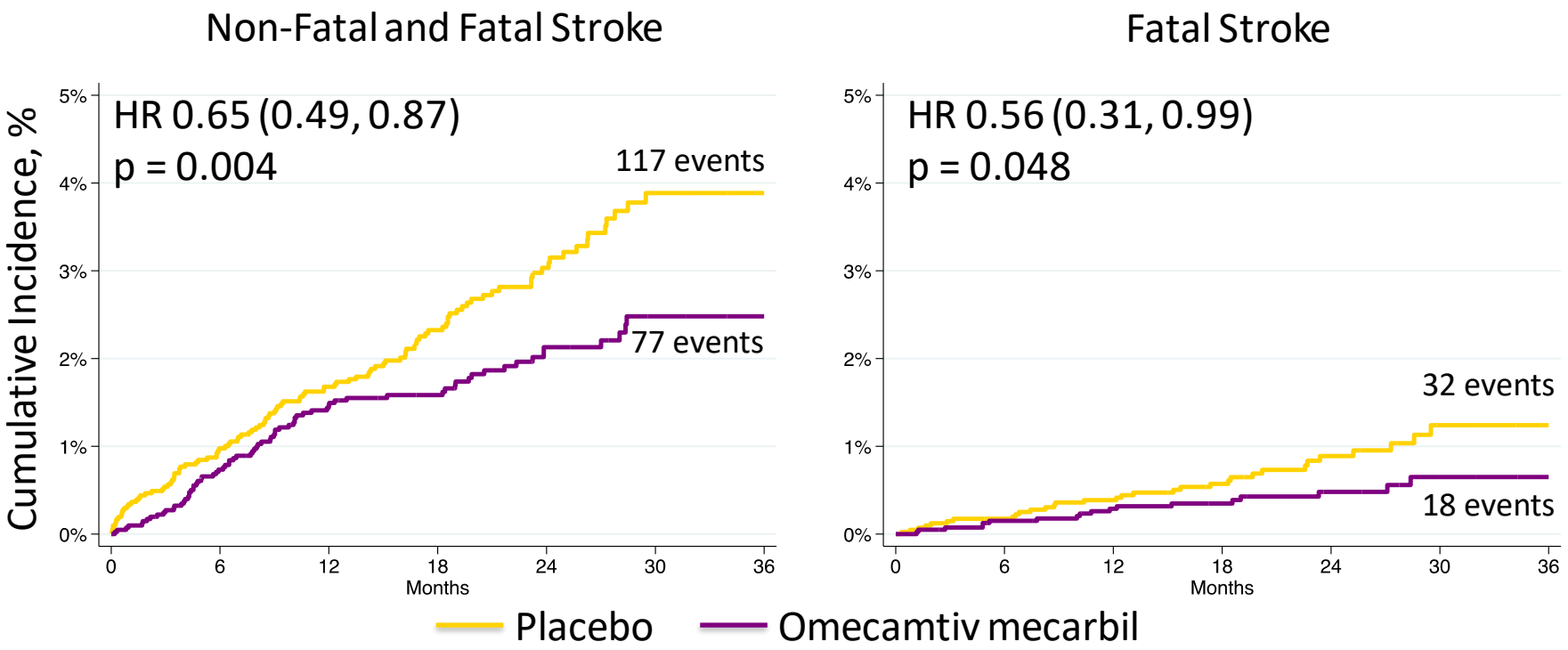
Time-to-First Adjudicated CV Death, HF Event, MI, Unstable Angina Hospitalization, Revascularization or Stroke

GALACTIC-HF



Effect of Omecamtiv Mecarbil on the Risk of Non-Fatal and Fatal Stroke

GALACTIC-HF



Total Recurrent Stroke events (Negative binomial regression): RR = 0.66 (0.49, 0.89), p=0.006

Adjudicated Type of First Stroke Event

GALACTIC-HF

	Omecamtiv Mecarbil (n = 4110)	Placebo (n = 4101)
Ischemic (Non-hemorrhagic)	65 (1.6 %)	84 (2.0 %)
Ischemic with hemorrhagic transformation	5 (0.1 %)	15 (0.4 %)
Hemorrhagic	3 (0.1 %)	9 (0.2 %)
Undetermined	3 (0.1 %)	4 (0.1 %)

Multivariate Predictors of Non-fatal and Fatal Stroke

GALACTIC-HF

Covariates	p-value	Hazard Ratio (95% CI)
Race (ref = White)	<0.001	
Asian		2.05 (1.33, 3.16)
Black		1.96 (1.20, 3.19)
Other		1.92 (1.17, 3.16)
History of stroke	0.002	1.85 (1.26, 2.71)
PCI	0.003	1.58 (1.17, 2.12)
Troponin (per doubling)	0.006	1.15 (1.04, 1.26)
AFF	0.008	1.51 (1.12, 2.05)
SBP (per 10 mmHg)	0.015	1.12 (1.02, 1.23)

Same variables selected if h/o Stroke is omitted

Effect of Omecamtiv Mecarbil on Risk of Non-Fatal and Fatal Stroke by History of Stroke

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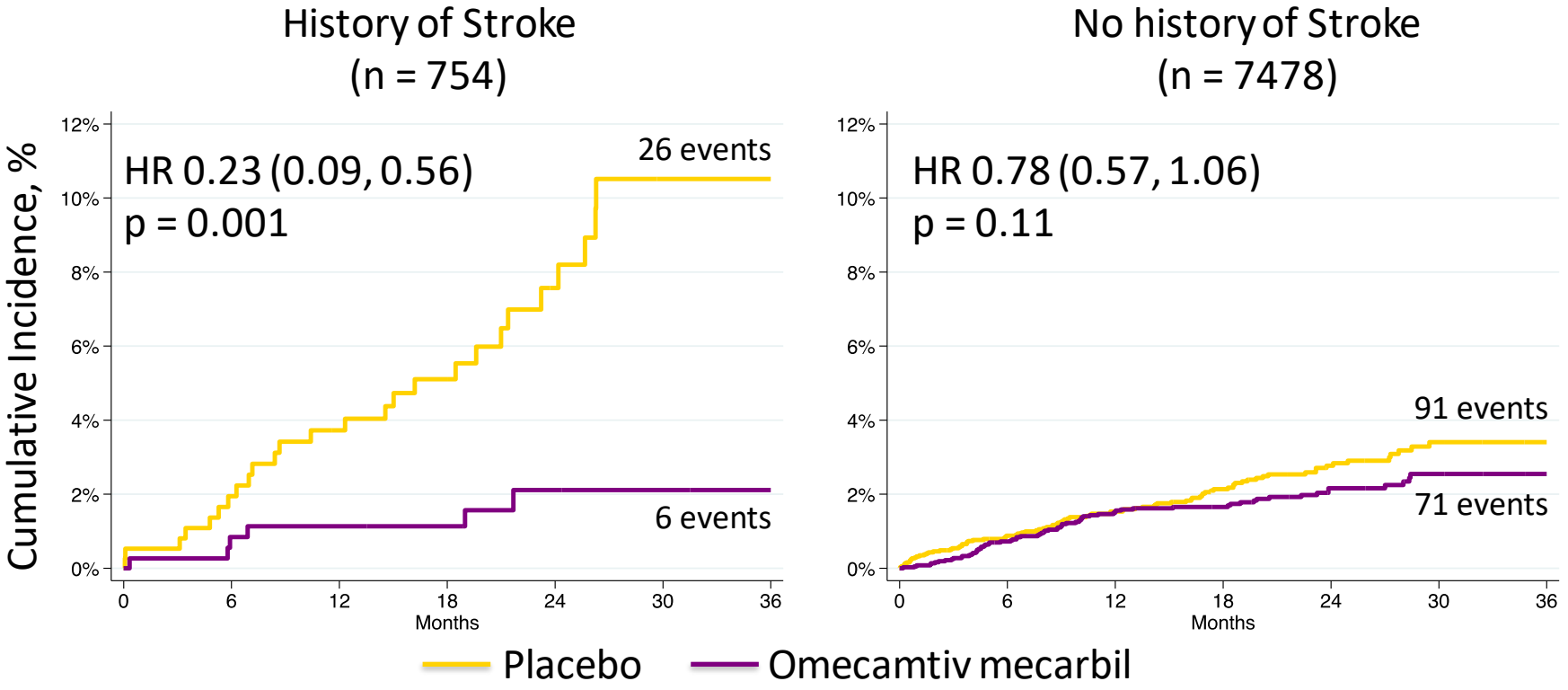
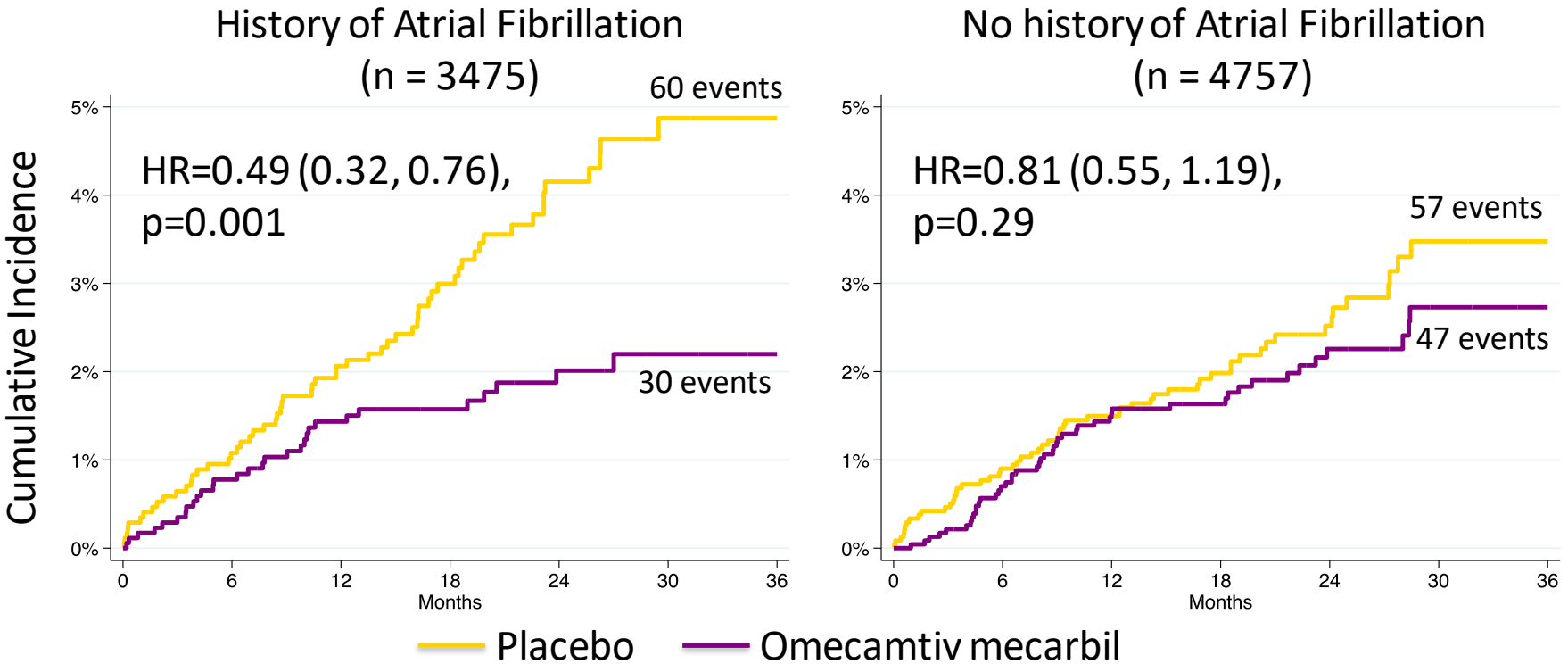
Interaction Effect, p= 0.01



Effect of Omecamtiv Mecarbil on Non-Fatal and Fatal Stroke by History of Atrial Fibrillation

GALACTIC-HF

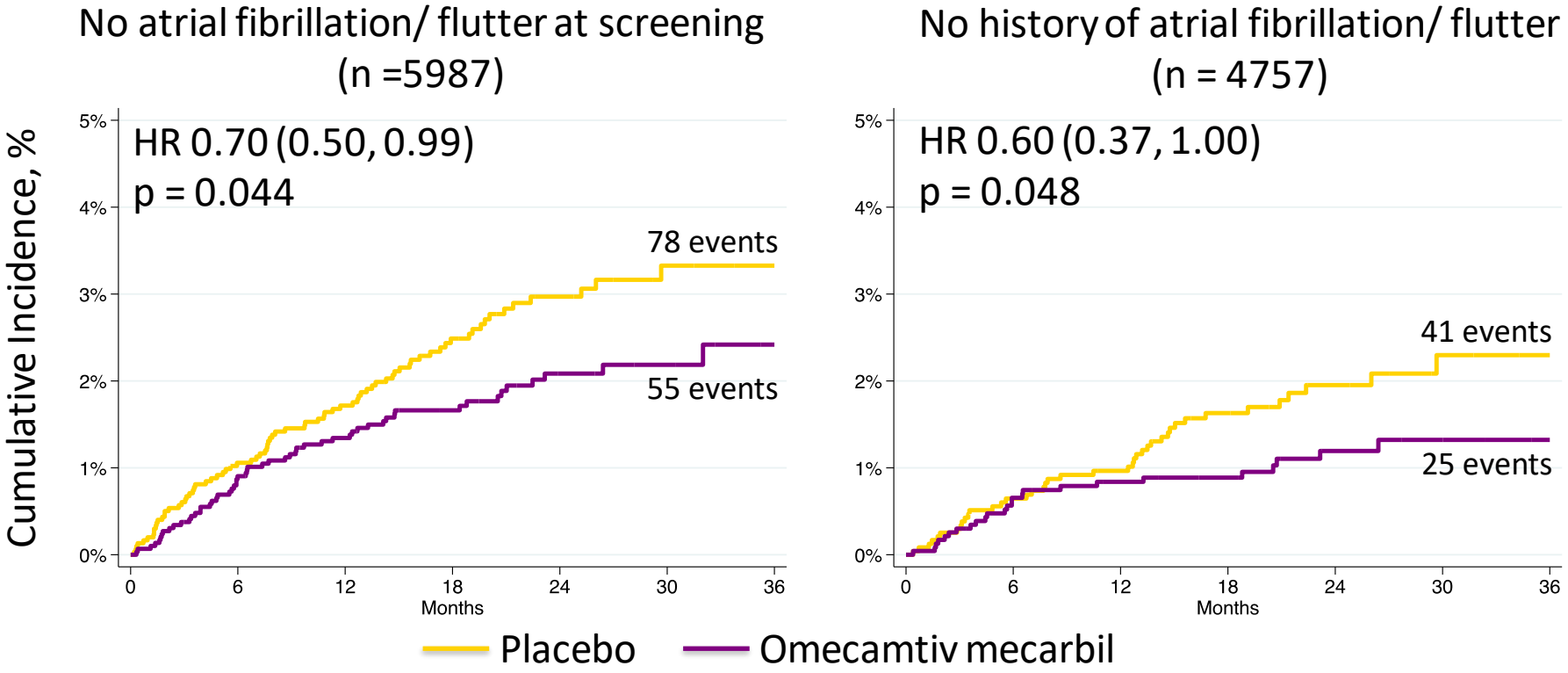
No significant interaction effect



Effect of Omecamtiv Mecarbil on New Onset Atrial Fibrillation/ Flutter

GALACTIC-HF

No significant interaction effect



Limitations

GALACTIC-HF

- Post-hoc analysis
  - Component of positive prespecified composite endpoint
  - Pre-specified Adjudication by CEC
- New onset Atrial Fibrillation determined by Serious Adverse Event reporting
  - Only includes events requiring hospitalization or intervention
- Severity of Stroke not assessed (only non-fatal vs. fatal)

Contemporary Trials of Stroke in HFrEF

Trial, year published (n)	Patient Population	All Strokes	Results
WATCH, 2009 (n= 1,587)	EF≤35% NYHA II-IV NSR	27	Primary: NS Total Strokes: Aspirin vs Warfarin: p=0.02 Clopidogrel vs Warfarin: p=0.02
WARCEF, 2012 (n=2,305)	EF≤35% NYHA I-IV NSR	91 (Stroke, ICH)	Primary: NS Ischemic Stroke: Aspirin vs. Warfarin: HR 0.52 (0.33-0.82); p=0.005
COMMANDER-HF, 2018 (n=5,022)	EF≤40% CAD; NSR Increased NP WHF within 21 days	127	Primary: NS Stroke: Rivaroxaban vs. Placebo: HR 0.66 (0.47-0.95)
GALACTIC-HF, 2021 (n=8,256)	EF≤35% NYHA II-IV Increased NP WHF within 12 mo.	194	Primary: p =0.025 Stroke: Omecamtiv mecarbil vs Placebo: HR 0.65 (0.49, 0.87) p = 0.004

Omecamtiv Mecarbil and the Risk of Stroke in Patients with HFrEF

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- There is biological plausibility for a beneficial effect of omecamtiv mecarbil on stroke events supported by decreased atrial fibrillation events in ATOMIC-AHF and improved LV, RV and LA function and decreased LV and LA volumes, sympathetic activation and NT-proBNP in COSMIC-HF.
- Omecamtiv mecarbil significantly reduced non-fatal and fatal strokes in patients with HFrEF in the context of significantly reducing new onset atrial fibrillation in GALACTIC-HF.
- These findings support a potential new approach to decreasing the risk of stroke in patients with HFrEF.

Thank you!

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Scientific Sessions

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