Efficacy of omecamtiv mecarbil in HFrEF according to NT-proBNP level: Insights from the GALACTIC-HF trial

John J.V. McMurray, Brian L Claggett; Rafael Diaz, G Michael Felker, Marco Metra, Siddique A. Abbasi, Stephen B Heitner, Stuart Kupfer, Fady Malik, Scott D Solomon; John R Teerlink, on behalf of the GALACTIC-HF Investigators

University of Glasgow

British Heart Foundation

NHS Greater Glasgow and Clyde

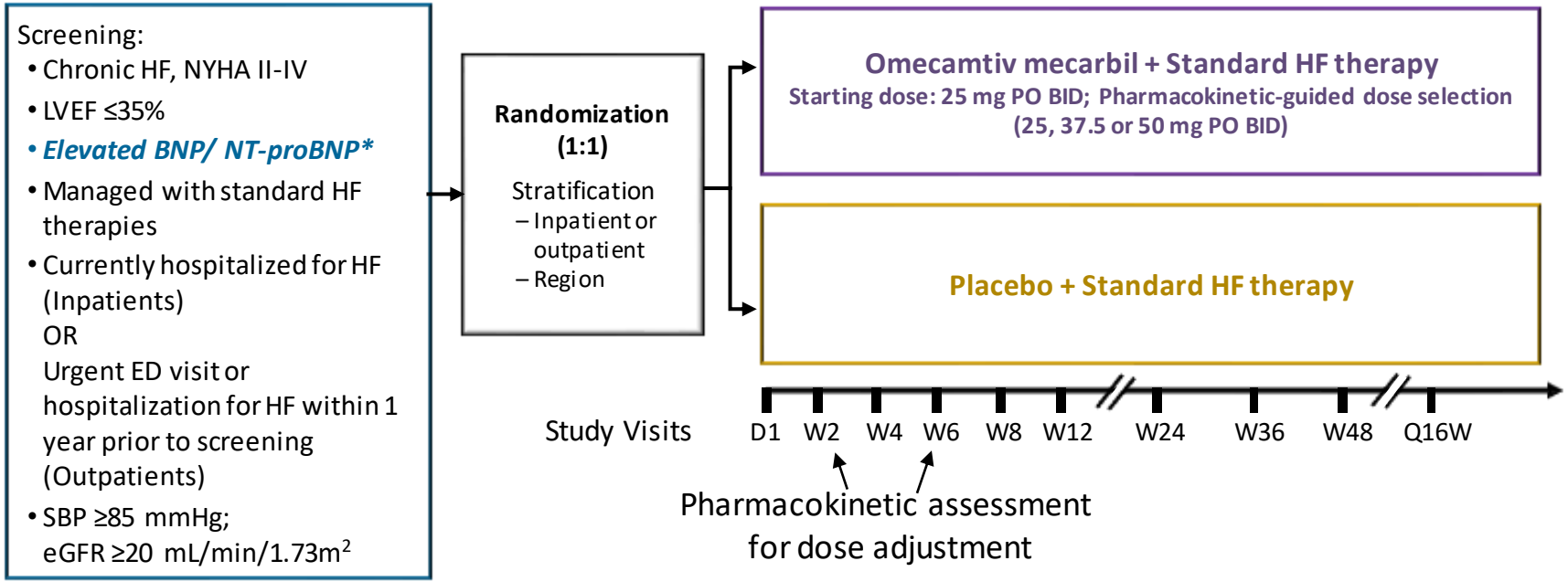
Background: GALACTIC-HF NT-proBNP analysis

- Patients with more severe heart failure have higher NT-proBNP levels than those with less severe heart failure.
- NT-proBNP is a powerful and independent prognostic biomarker in heart failure.
- Treatments that improve outcomes in heart failure usually also reduce NT-proBNP (and the extent of reduction in NT-proBNP correlates with the magnitude of clinical benefit).
- **Prespecified subgroup analysis: Does baseline NT-proBNP level modify the treatment effect of OM in patients not in atrial fibrillation/flutter (AF/F)?**

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

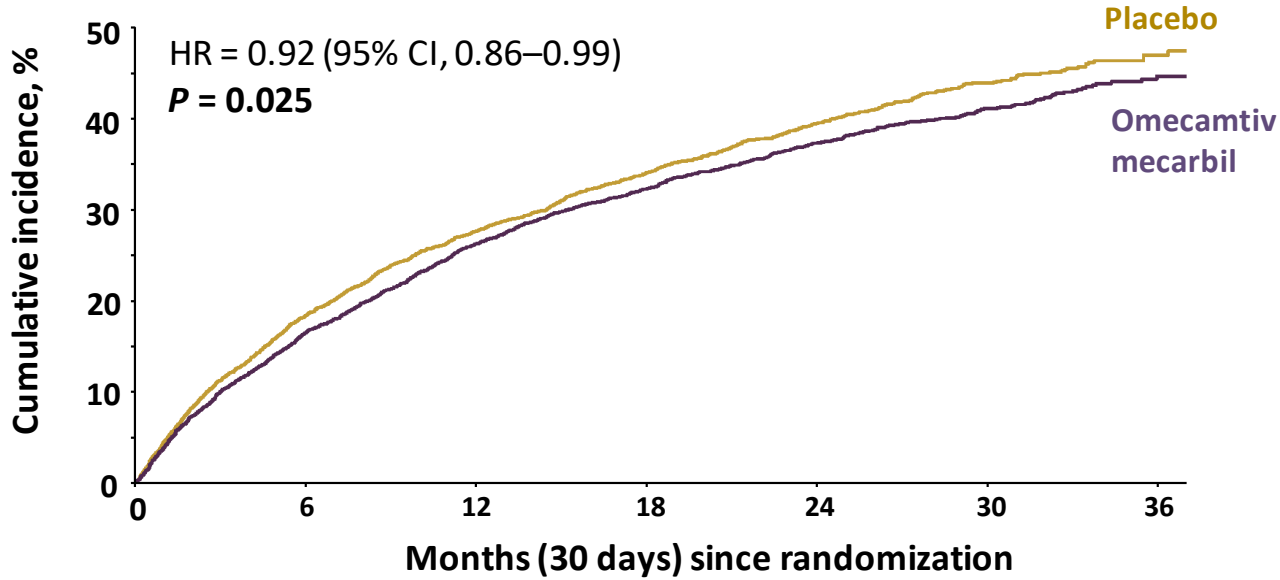


**NT-proBNP ≥400 pg/mL or BNP ≥125 pg/mL at screening (if in atrial fibrillation/ flutter: NT-proBNP ≥1,200 pg/mL or BNP ≥375 pg/mL).*

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

GALACTIC-HF: Primary Composite Endpoint

Time to first heart failure event or cardiovascular death



Patients at risk, n							
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

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

GALACTIC-HF NT-proBNP Results: Outline

- Baseline characteristics according to baseline NT-proBNP level.
- Effect of OM on NT-proBNP level (change from baseline to 48 months).
- Effect of OM on outcomes according to baseline NT-proBNP level
  - a] Prespecified analysis: subgroup ≤median *versus* >median, excluding individuals with AF/F (n=5971)
  - b] Examining NT-proBNP as a continuous measure

GALACTIC-HF NT-proBNP analysis: Baseline characteristics

	No AF/F (n=5971)			*All patients (n=8206)*		
NT-proBNP	**≤ median* N=2987**	**>median* N=2984**	**P-value**	*≤ median N=4105*	*>median N=4101*	*P-value*
Age (years), mean (SD)	62±11	65±12	<0.001	*63±11*	*67±11*	*<0.001*
Male sex, N (%)	78	77	0.33	*79*	*78*	*0.15*
Randomized as an inpatient, (%)	19	26	<0.001	*21*	*29*	*<0.001*
Physiological measures						
Systolic BP (mmHg), mean (SD)	119±15	115±16	<0.001	*119±15*	*114±16*	*<0.001*
Heart rate (bpm)	70±11	73±12	<0.001	*71±11*	*74±13*	*<0.001*
BMI (kg/m^2)	30±6	27±5	<0.001	*30±6*	*27±6*	*<0.001*
eGFR (mL/min/1.73m^2), mean (SD)	67±22	57±22	<0.001	*66±21*	*55±21*	*<0.001*
eGFR <60 mL/min/1.73m^2, (%)	39	59	<0.001	*42*	*63*	*<0.001*
Ischemic etiology, N (%)	54	57	0.026	*53*	*54*	*0.46*

**Median 1675 (Q1, Q3 812-3579) pg/ml*

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LVEF, mean (SD)	27.4±6.0	25.3±6.4	<0.001	*27.4±6.0*	*25.7±6.4*	*<0.001*
NYHA class, (%)			<0.001			*<0.001*
II	63	49		*61*	*46*	
III/IV	35/1.6	48/3.8		*38/2.0*	*50/4.0*	
KCCQ-TSS, mean (SD)	72±23	64±26	<0.001	*71±24*	*62±26*	*<0.001*
Atrial fibrillation/flutter*, (%)	--	--	--	*17.7*	*36.8*	
Medical history, (%)						
Hypertension	70	68	0.21	*71*	*70*	*0.22*
Type 2 diabetes	40	43	0.008	*41*	*42*	*0.35*
Previous MI	44	46	0.22	*42*	*41*	*0.51*
ICD	30	34	<0.001	*30*	*34*	*<0.001*
CRT-P/CRT-D	12	15	<0.001	*12*	*16*	*<0.001*

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Treatment, (%)						
ACEI/ARB/ARNI	92	83	<0.001	*91*	*83*	*<0.001*
ARNI	21	18	0.003	*21*	*18*	*<0.001*
Beta-blocker	96	93	<0.001	*96*	*93*	*<0.001*
MRA	80	75	<0.001	*80*	*76*	*<0.001*
Diuretic	85	92	<0.001	*87*	*93*	*<0.001*
Digoxin	11	13	0.031	*15*	*19*	*<0.001*
ICD	30	34	<0.001	*30*	*34*	*<0.001*
CRT-P/CRT-D	12	15	<0.001	*12*	*16*	*<0.001*

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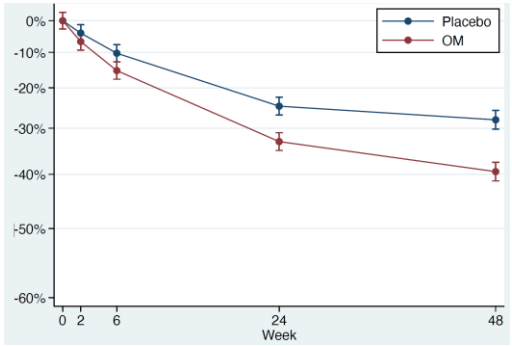
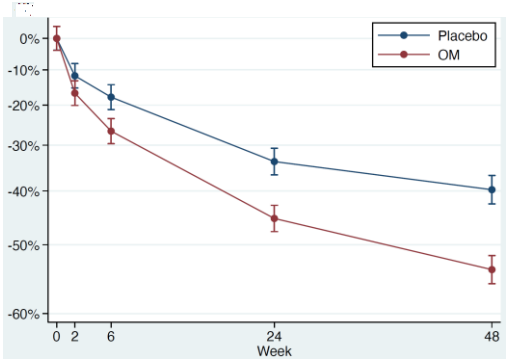
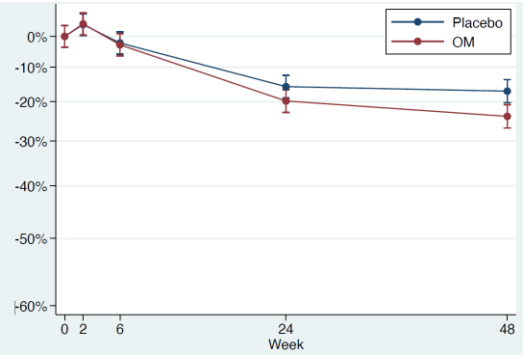
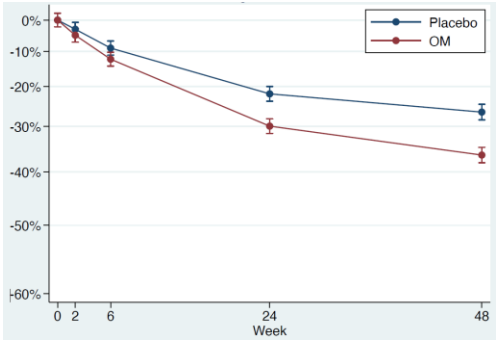
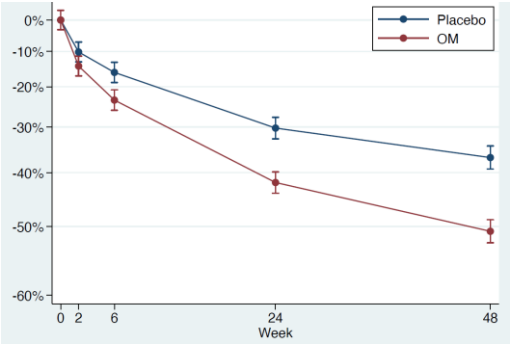
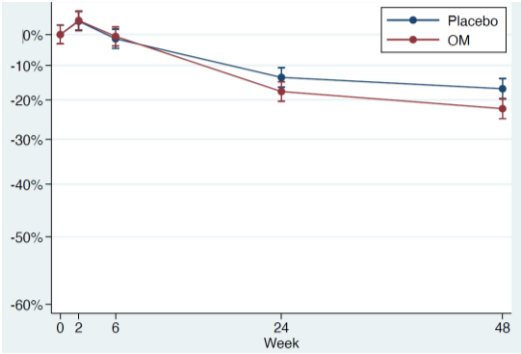
GALACTIC-HF: Effect of OM on NT-proBNP

	All NT-proBNP concentrations	NT-proBNP >median	NT-proBNP ≤median
Patients not in AF/F			
All patients			

Placebo

OM

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GALACTIC-HF: Pre-specified NT-proBNP subgroup analysis*

	Placebo (n=3006)		OM (n=2965)		HR (95% CI)	Within subgroup P-value	Interaction P-value
	n (%)	*Rate*⁺	n (%)	*Rate*⁺			
Primary outcome							
≤ median NTproBNP	352 (23)	*13.42*	328 (22)	*12.42*	0.94 (0.80,1.09)	0.392	0.102
> median NTproBNP	748 (50)	*38.85*	650 (44)	*31.30*	0.81 (0.73,0.90)	0.000	
HF hospitalization							
≤ median NTproBNP	263 (17)	*10.02*	254 (17)	*9.62*	0.97 (0.82,1.15)	0.728	**0.042**
> median NTproBNP	570 (38)	*29.62*	483 (32)	*23.26*	0.79 (0.70,0.89)	0.000	
Cardiovascular death							
≤ median NTproBNP	141 (9)	*4.85*	135 (9)	*4.64*	0.96 (0.76,1.22)	0.761	0.399
> median NTproBNP	405 (27)	*16.32*	363 (24)	*14.29*	0.87 (0.75,1.00)	0.047	
All-cause death							
≤ median NTproBNP	205 (14)	*7.05*	196 (13)	*6.74*	0.96 (0.79,1.17)	0.715	0.294
> median NTproBNP	530 (35)	*21.35*	474 (32)	*18.67*	0.86 (0.76,0.97)	0.017	

⁺Rate is per 100 person-years **Patients not in atrial fibrillation/flutter – median 1675 (Q1, Q3 812-3579) pg/ml*

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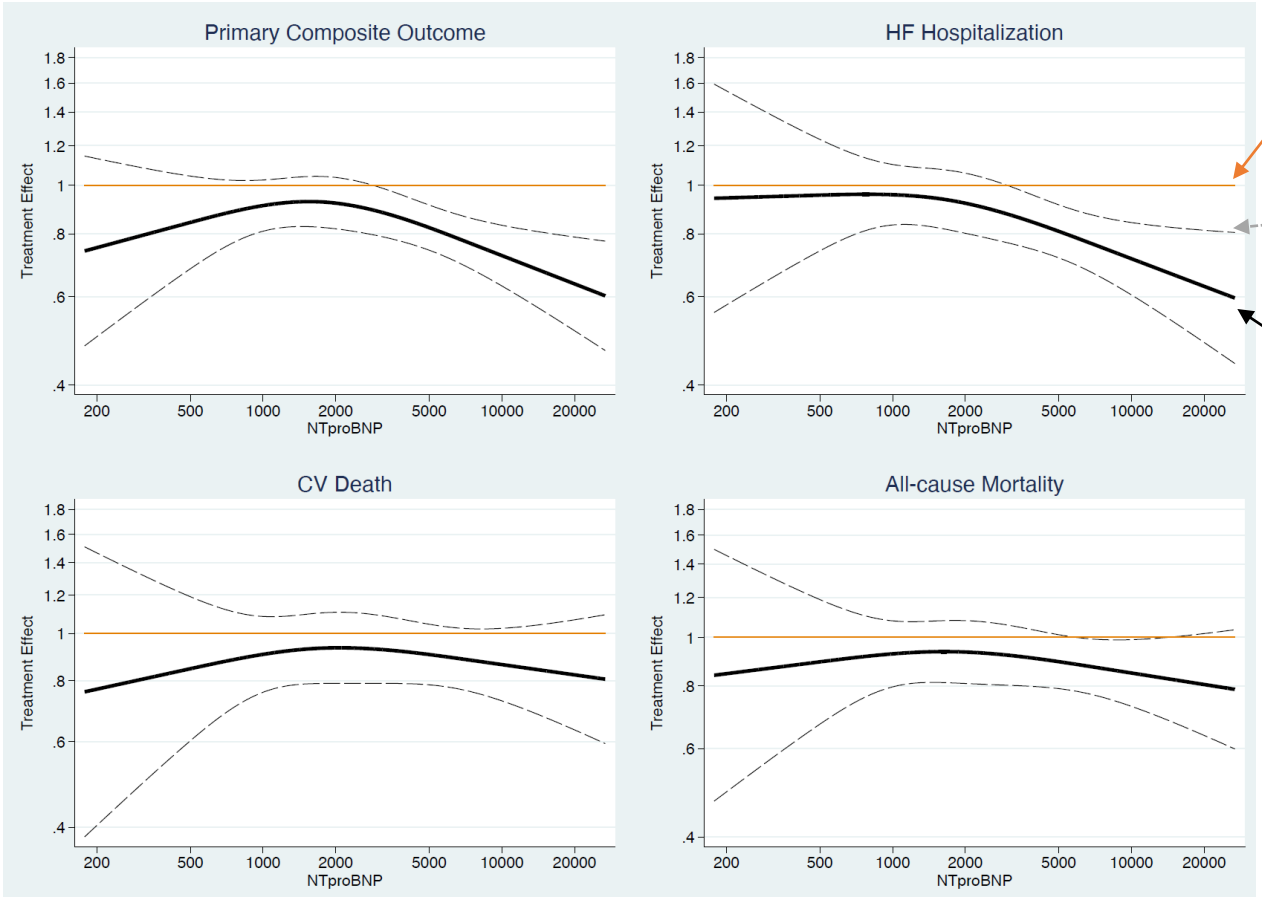
GALACTIC-HF: Effect according to baseline NT-proBNP in patients not in AF/F

Placebo better

HR=1 (unity)

OM better



HR=1 (unity)

95%CI

Continuous HR

GALACTIC-HF NT-proBNP analysis: Summary and conclusions

- In a prespecified subgroup analysis, baseline NT-proBNP level appeared to modify the effect of OM in patients without AF/F.
- The relative (and absolute) risk-reduction with OM was greater in patients with a NT-proBNP level >median (compared to ≤median).
- This finding is consistent with the other analyses of GALACTIC-HF suggesting that OM has a greater benefit in patients with more severe HFrEF