Duke Clinical Research Institute

GALACTIC-HF

Omecamtiv Mecarbil in Patients with Severe Heart Failure: An Analysis from GALACTIC-HF

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Cytokinetics

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Background

- Omecamtiv mecarbil (OM) is a novel, selective cardiac myosin activator that improves cardiac structure/function and decreases heart rate and NT-proBNP in patients with heart failure and reduced ejection fraction (HFrEF)
- In the GALACTIC-HF trial of 8256 patients with HFrEF, omecamtiv mecarbil improved the primary endpoint of time to first heart failure event or cardiovascular death

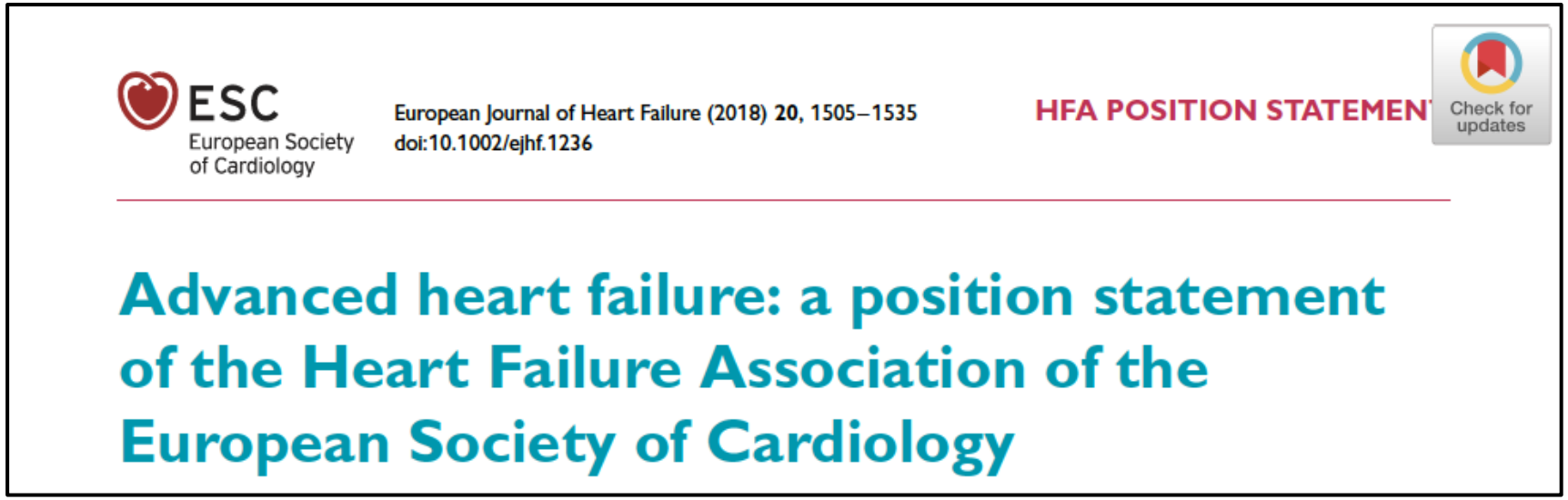
- *Current Analysis*: What is the efficacy and safety of omecamtiv mecarbil in patients with severe heart failure enrolled in the GALACTIC-HF study?

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

The Challenge of Severe Heart Failure

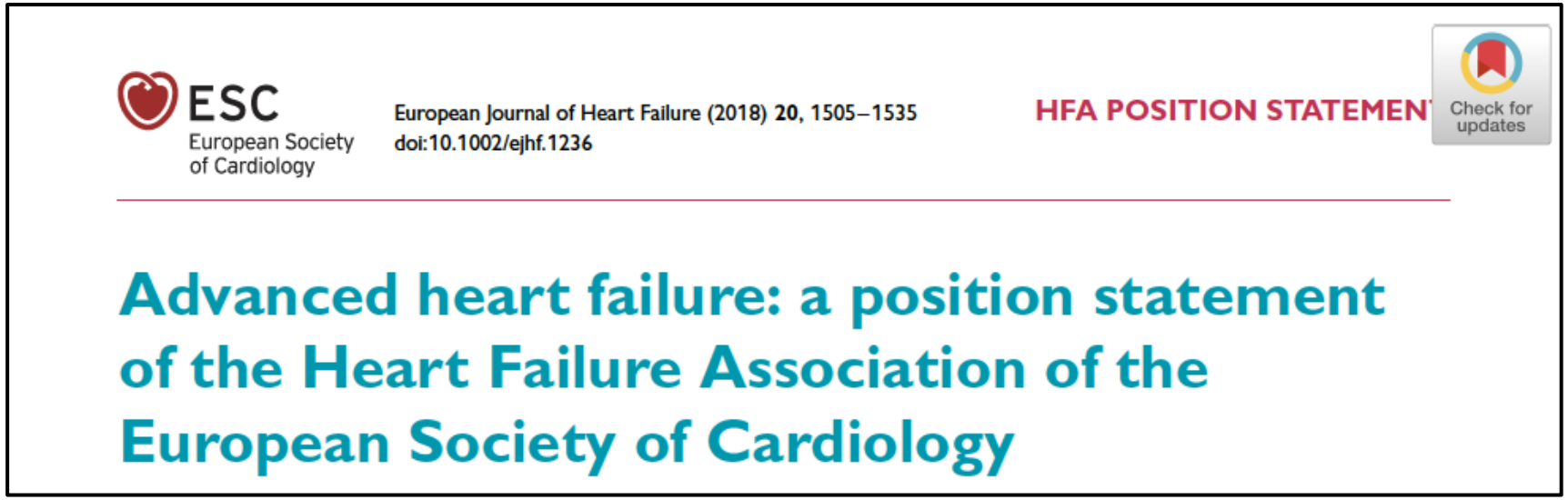
- Patient with more severe/advanced heart failure:
  - Have higher risk for mortality
  - Require frequent heart failure hospitalizations and unscheduled clinic visits
  - Suffer greater impairments in quality of life
  - May be progressively intolerant or ineligible for other effective medical therapies due to hypotension and renal dysfunction
  - Account for a large proportion of the economic burden of heart failure care

- Advanced therapies such as heart transplantation or mechanical cardiac support are available only to a small minority of patients with severe/advanced HF



- Despite optimal guideline-directed treatment
  - NYHA class III-IV symptoms
  - LVEF ≤ 30%
  - > 1 HF event (hospitalization or equivalent) within 12 months
  - Severe functional impairment (6 MWD < 300m or pVO2 (< 12-14 mL/kg/min)

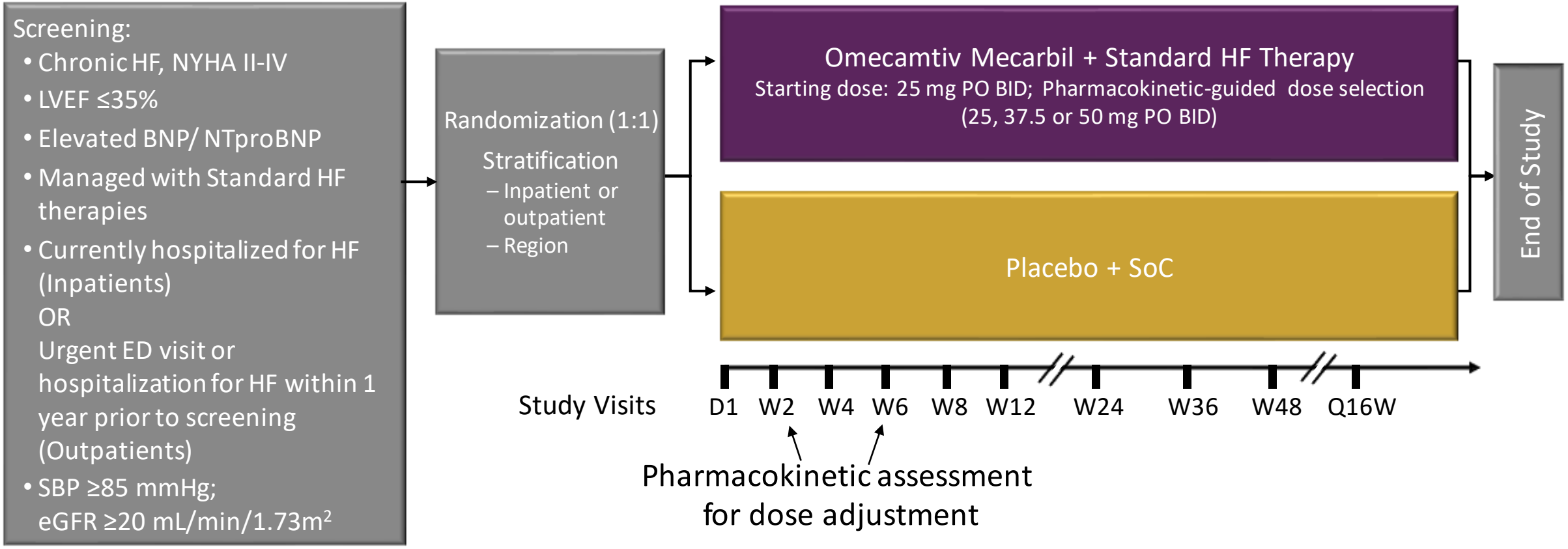
Crespo-Leiro, MG, et al. Eur J Heart Failure 2018



- Despite optimal guideline-directed treatment
  - NYHA class III-IV symptoms
  - LVEF ≤ 30%
  - ≥ 1 HF event (hospitalization or equivalent) within ~~12 months~~ 6 months
  - ~~Severe functional impairment (6 MWD < 300m or pVO2 (< 12-14 mL/kg/min)~~

GALACTIC-HF Trial Design

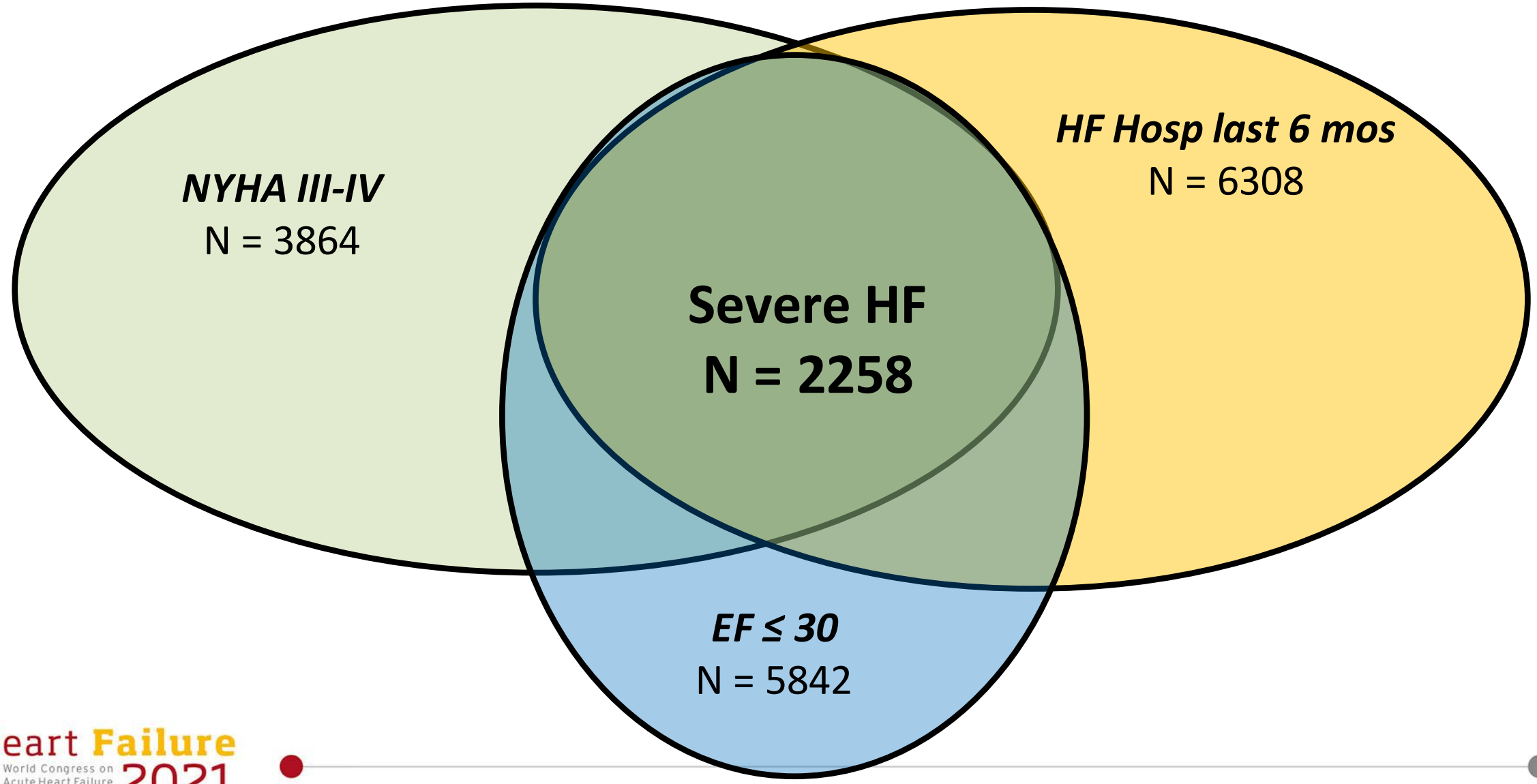
Hypothesis: Selectively improving cardiac function with the cardiac myosin activator, omecamtiv mecarbil, will improve clinical outcomes in patients with HFrEF



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

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

Criteria for Severe Heart Failure Classification



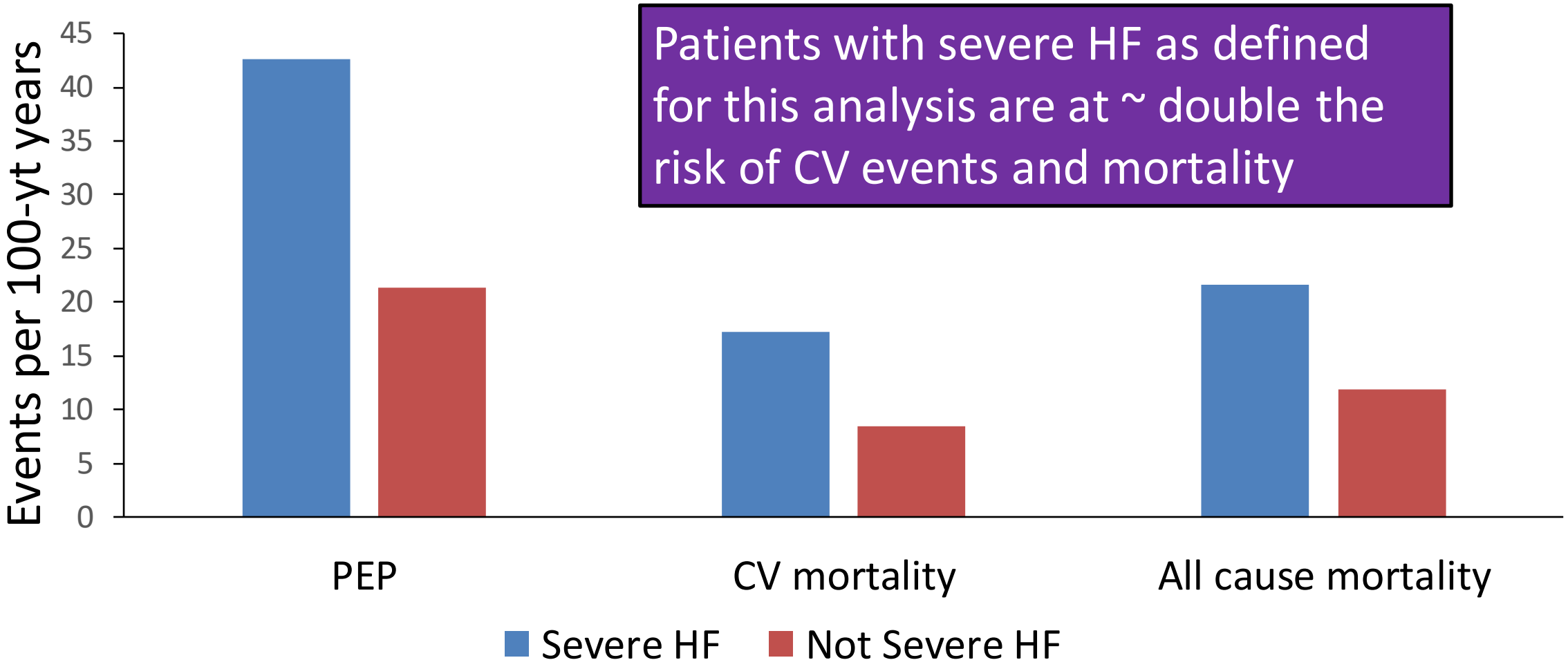
Key Baseline Differences by HF Severity

	Severe HF N= 2258	Not Severe HF N = 5974	
Atrial fib/flutter	717 (32%)	1528 (26%)	p<0.001
LVEF - %	23.4	27.8	p<0.001
KCCQ Total Symptom Score	56.2	74.0	p<0.001
SBP — mmHg	113.8	117.5	p<0.001
Heart rate — beats/min	74.3	71.7	p<0.001
NT-proBNP — pg/mL	2804	1768	p<0.001
Cardiac Troponin I — ng/L	34	24	p<0.001
eGFR — mL/min/1.73m2	55	60	p<0.001

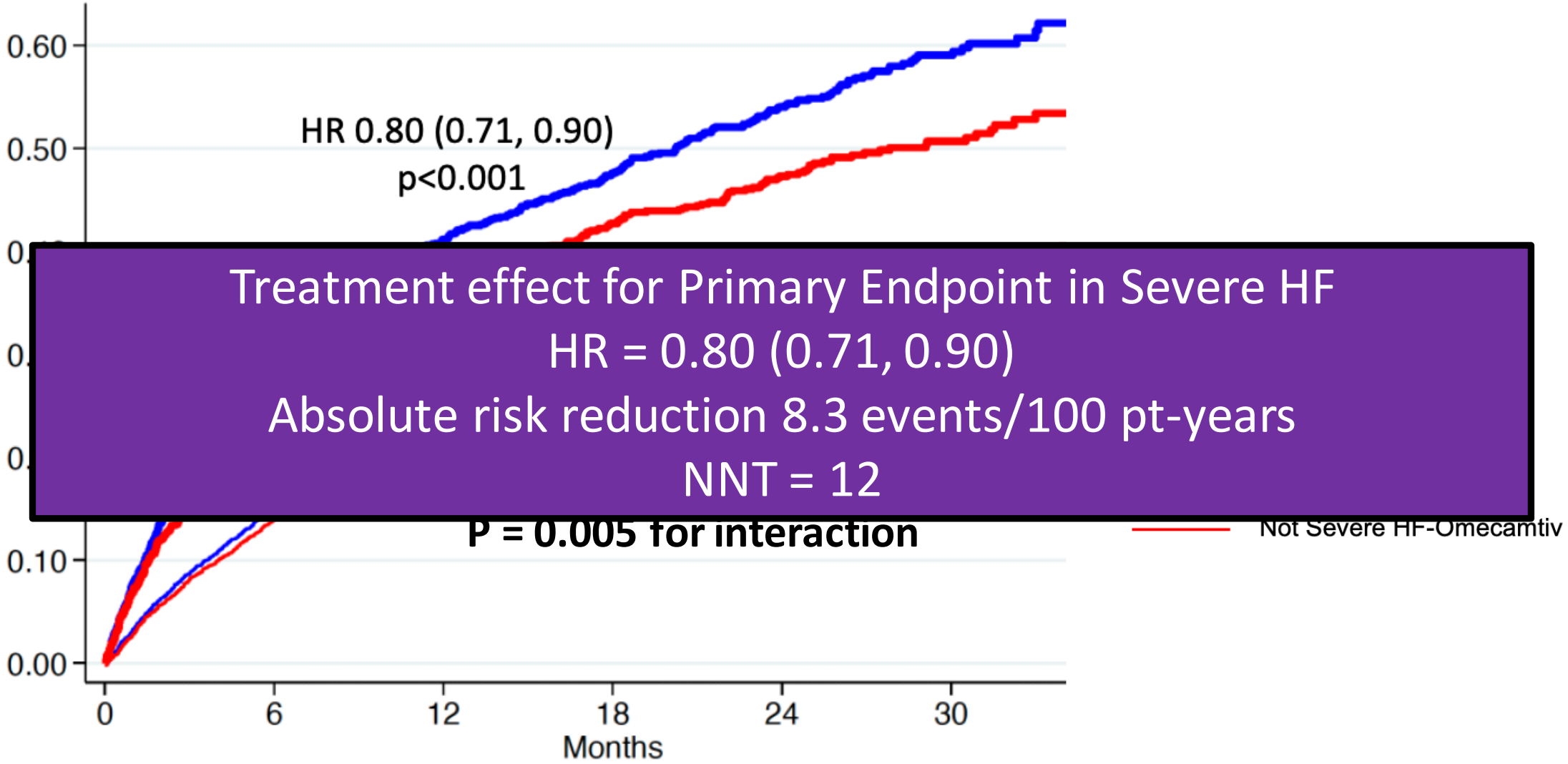
Background Medical Therapy by HF Severity

	Severe HF N= 2258	Not Severe HF N = 5974	
ACEi, ARB or ARNi	1873 (83%)	5286 (89%)	p<0.001
ARNi	447 (20%)	1154 (19%)	p=0.62
BB	2093 (93%)	5670 (95%)	p<0.001
MRA	1768 (78%)	4629 (78%)	p=0.43
SGLT2 Inhibitors	50 (2%)	168 (3%)	p=0.13
Ivabradine	188 (8%)	345 (6%)	p<0.001
Digitalis glycosides	436 (19%)	949 (16%)	p<0.001
Cardiac Resynchronization Therapy	372 (17%)	786 (13%)	p<0.001
Implantable Cardioverter Defibrillator	807 (36%)	1807 (30%)	p<0.001

Patients with Severe HF are at Higher Risk

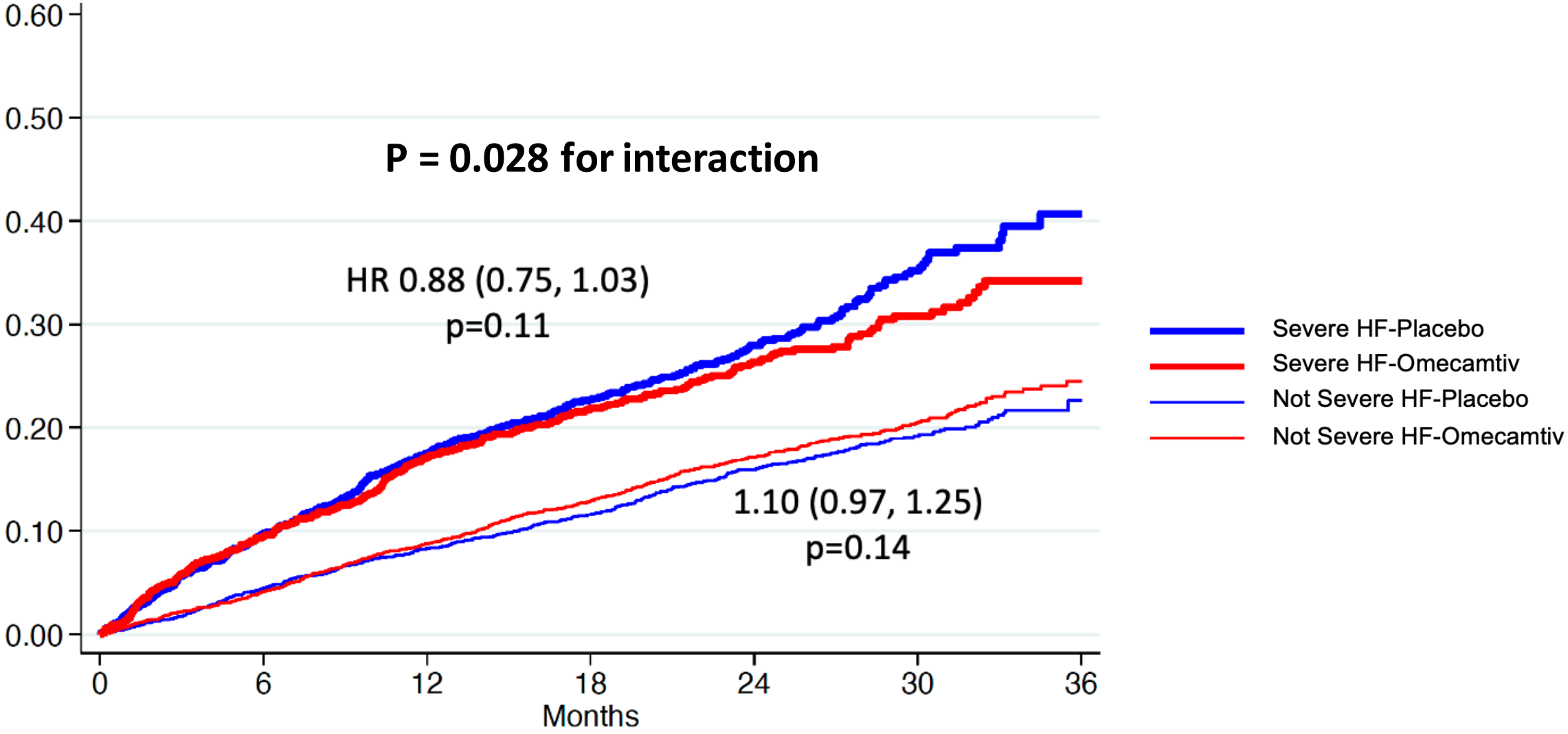


Treatment Effects by HF Severity: Primary Endpoint

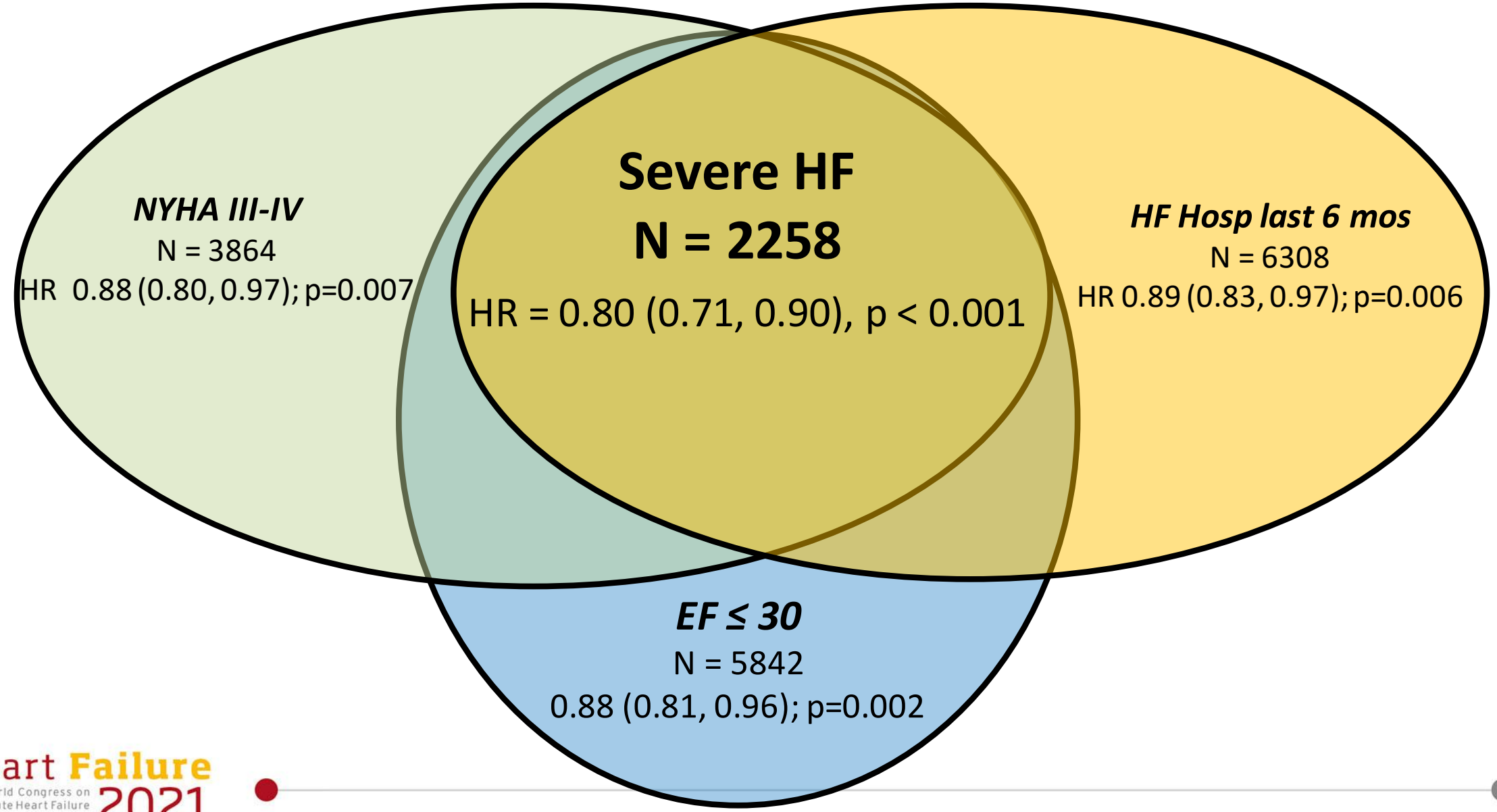


Treatment effect for Primary Endpoint in Severe HF
HR = 0.80 (0.71, 0.90)
Absolute risk reduction 8.3 events/100 pt-years
NNT = 12

Treatment Effects by HF Severity: CV Death



Benefit of Omecamtiv Mecarbil by Severe HF Criteria



Safety

	Omecamtiv	Placebo		Relative risk (95% CI)
Severe Heart Failure	n=1079	n=1132		
Any treatment-emergent serious adverse event	742 (67.3%)	790 (68.8%)	p=0.43	0.98 (0.92, 1.03)
AE: ventricular tachyarrhythmia	80 (8.0%)	86 (8.1%)	p=0.89	0.98 (0.73, 1.31)
Positively Adjudicated MI	42 (3.8%)	29 (2.5%)	p=0.08	1.51 (0.95, 2.40)
First Stroke	18 (1.6%)	31 (2.7%)	p=0.08	0.60 (0.34, 1.07)
Not Severe Heart Failure	n=2959	n=2920		
Any treatment-emergent serious adverse event	1631 (54.2%)	1645 (55.7%)	p=0.26	0.97 (0.93, 1.02)
AE: ventricular tachyarrhythmia	210 (7.9%)	218 (8.4%)	p=0.58	0.95 (0.79, 1.14)
Positively Adjudicated MI	80 (2.7%)	89 (3.0%)	p=0.41	0.88 (0.66, 1.19)
First Stroke	58 (1.9%)	81 (2.7%)	p=0.037	0.70 (0.50, 0.98)

Tolerability

Variable	Week 0		Week 24			
	OM	Placebo	OM	Placebo	Ratio or Difference	p-value
Severe HF						
Systolic BP (mm Hg)	114.0±15.3	113.5±14.7	116.7±17.3	116.0±17.7	0.6 (-0.7, 2.0)	p=0.35
HR (beats/min)	74.5±12.7	74.1±12.3	71.2±12.3	73.0±12.8	-1.9 (-2.9, -0.8)	p<0.001
Potassium (mmol/L)	4.53±0.57	4.56±0.56	4.52±0.57	4.56±0.58	-0.03 (-0.08, 0.02)	p=0.27
Creatinine (mg/dl)	1.39±0.50	1.36±0.48	1.37±0.55	1.38±0.56	-0.01 (-0.04, 0.02)	p=0.53
Not Severe HF						
Systolic BP (mm Hg)	117.1±15.4	117.9±15.4	118.4±16.8	119.6±17.9	-0.7 (-1.5, 0.1)	p=0.07
HR (beats/min)	71.7±12.0	71.6±11.9	69.6±11.3	71.0±11.6	-1.4 (-2.0, -0.9)	p<0.001
Potassium (mmol/L)	4.57±0.51	4.57±0.51	4.56±0.51	4.55±0.52	0.01 (-0.02, 0.03)	p=0.58
Creatinine (mg/dl)	1.27±0.45	1.28±0.45	1.29±0.49	1.28±0.48	0.01 (-0.00, 0.03)	p=0.14

Conclusions

- In HFrEF patients with severe HF by modified ESC-HFA criteria, treatment with omecamtiv mecarbil:
  - Reduced the risk of the of the primary endpoint of time to first HF event or CV death
  - Was well-tolerated with regard to blood pressure, renal function, and potassium homeostasis
- These data demonstrate a clinically important benefit of omecamtiv mecarbil on in patients with severe heart failure who may be less likely to tolerate other heart failure therapies