7th Advances in Heart Failure 2024

10 e 11 de Outubro

FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

ORGANIZAÇÃO

PATROCÍNIO CIENTÍFICO

PCO

7th Advances in Heart Failure 2024
10 e 11 de Outubro
FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Novos insights da Insuficiência Cardíaca Avançada

Inotrópicos

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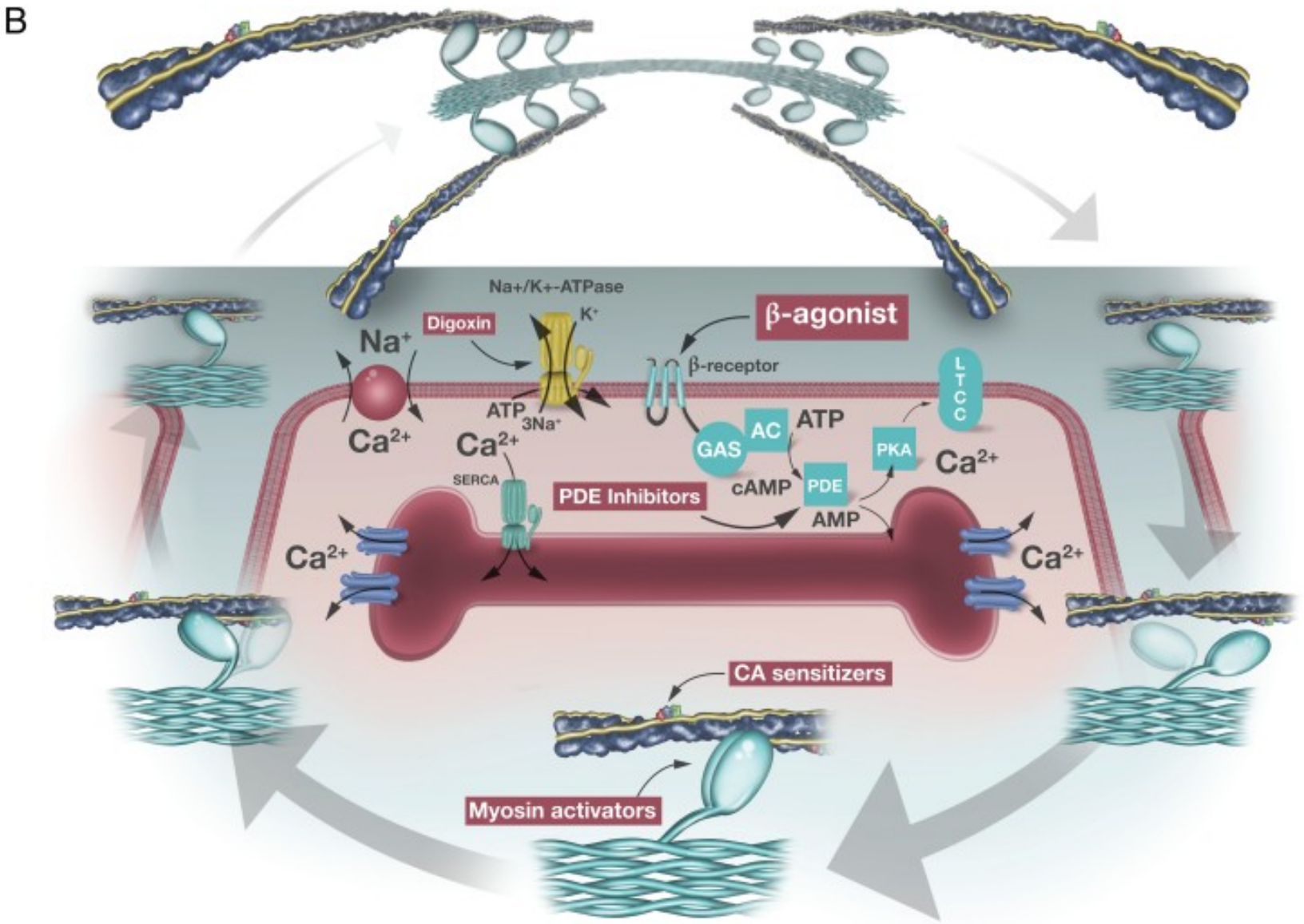
Inotropes



On the level of the actomyosin cross-bridge, inotropy relies largely on:

(i) the amount of calcium available to bind to troponin C **> Calcitropes**

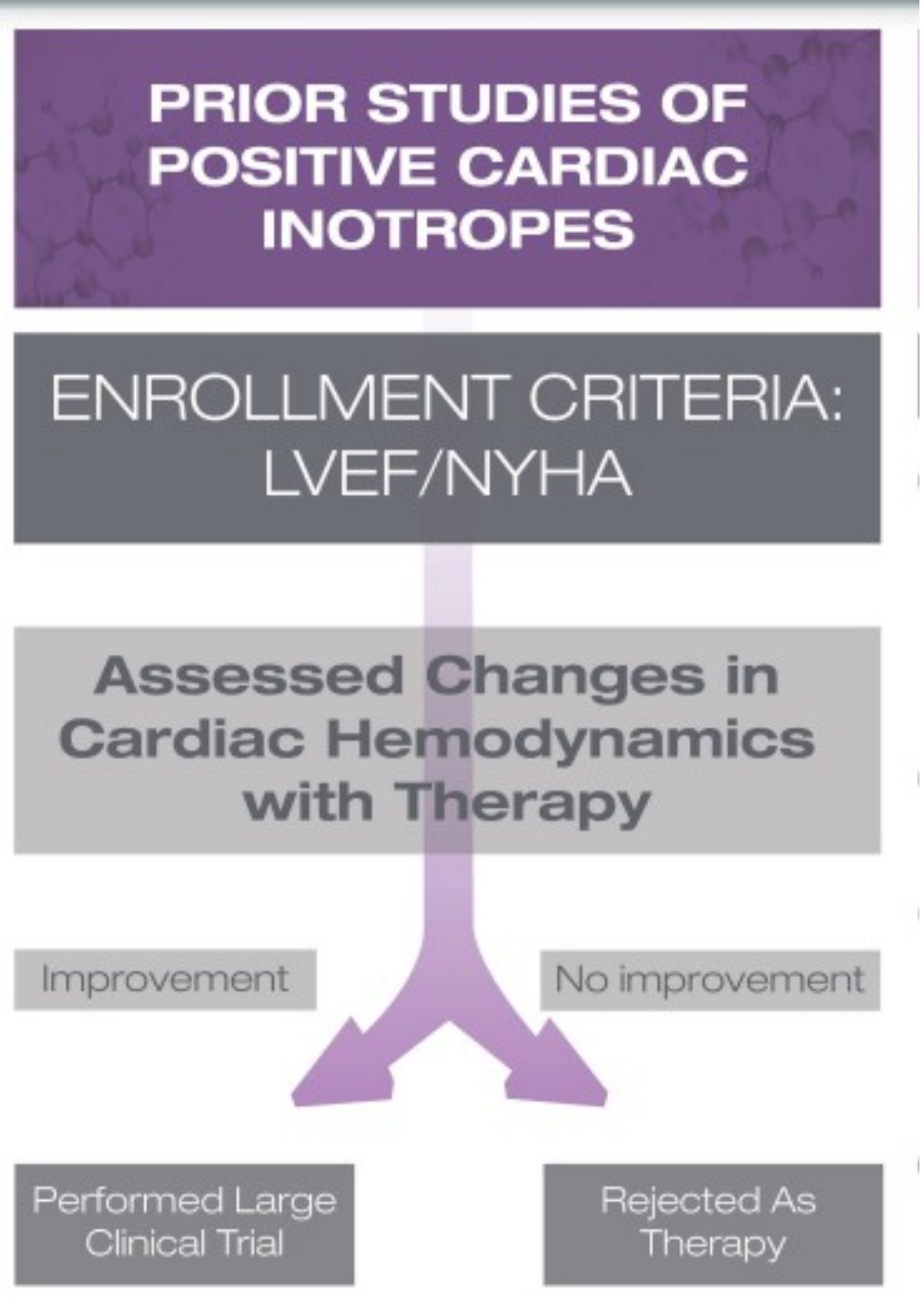
(ii) the calcium affinity of troponin C **> Myotropes**

(iii) the duration of the force-producing state with availability of high energy phosphates **> Mitotropes**

RESULTS OF CLINICAL TRIALS INVOLVING POSITIVE INOTROPES IN HEART FAILURE WITH REDUCED EF

Clinical trial	Comparator groups	Year	No. patients	Key inclusion criteria	Results
Amrinone Multicenter Trial[40]	Amrinone vs. placebo	1985	99	NYHA class III–IV, LVEF ≤ 40%	↑ Adverse events
Xamoterol in Severe Heart Failure[41]	Xamoterol vs. placebo	1990	516	LVEF < 35%, NYHA class III–IV	↑ Morbidity
PROMISE[42]	Milrinone vs. placebo	1991	1008	LVEF ≤ 35%, NYHA class III–IV	↑ Morbidity and mortality
PICO[43]	Pimobendan	1996	317	NYHA class II–III, LVEF ≤ 45%	↑ Exercise tolerance, ↑ mortality
PRIME II[44]	Ibopamine	1997	1906	NYHA class III–IV, LVEF < 35%	↑ Mortality
VEST[45]	Vesnarinone	1998	3833	LVEF ≤ 30%, NYHA class III–IV	Dose-dependent ↑mortality (potentially arrhythmias)
FIRST[46]	Dobutamine	1999	471	NYHA class IIIB–IV; LVEF < 30%	↑ Mortality
DICE[47]	Intermittent dobutamine vs. placebo	1999	38	NYHA class III–IV, cardiac index ≤2.2 L/min/m^2, and LVEF ≤ 30%	No improvement in functional status
OPTIME-CHF[48]	Milrinone	2002	951	ADHF with LVEF < 40%	↑ Adverse events, equivalent mortality
LIDO[49]	Levosimendan vs. dobutamine	2002	203	ADHF with LVEF < 35%, CI < 2.5 L/min/m^2, PCWP > 15 mmHg	↑ Haemodynamics, ↓ mortality with levosimendan
RUSSLAN[50]	Levosimendan vs. placebo	2002	504	LV failure complicating AMI	Low-dose levosimendan reduced the risk of worsening HF
SURVIVE[51]	Levosimendan vs. dobutamine	2007	1327	ADHF with LVEF ≤ 30%	↓ BNP with levosimendan but no impact on clinical outcomes
EMOTE[52]	Enoximone	2007	201	NYHA class IV, inotrope dependence, LVEF ≤ 25%	No difference is ability to wean patients off inotropes at 30 days
Enoximone Clinical Trials Program[14,53]	Enoximone	2009	1854	NYHA class III–IV, LVEF ≤ 35% (two trials)	No difference in mortality, CV hospitalizations, 6MWD, patient global assessment
HORIZON-HF[32]	Istaroxime	2008	120	ADHF with LVEF ≤ 35%	↓ PCWP, ↑ SBP, and ↓ diastolic stiffness
CUPID 2[34]	SERCA2a gene	2016	250	Chronic HF, NYHA class II–III, LVEF ≤ 35%, NT-proBNP > 1200 pg/mL[a]	No difference in time to recurrent events
REVIVE[54]	Levosimendan	2013	700	ADHF with LVEF ≤ 35%	↓ HF symptoms, ↑ risk of adverse CV events and 14-day mortality
ATOMIC-AHF[55]	Omecamtiv mecarbil	2016	606	ADHF with LVEF ≤ 40%, BNP > 400 pg/mL or NT-proBNP > 1600 pg/mL[a]	No difference in dyspnoea endpoint, ↑ SET, ↓ LVESD, ↑ troponin
COSMIC-HF[56]	Omecamtiv mecarbil	2016	448	Chronic HF, NYHA class II–III, LVEF ≤ 40%, NT-proBNP ≥ 200 pg/mL[a]	↑ SET, ↑ SV, ↓ LVESD, ↓ LVEDD, ↓ NT-proBNP
PROFILE[57]	Flosequinan	2017	2354	NYHA class III–IV, LVEF ≤ 35%	↑ Exercise tolerance, ↑ mortality

2019


PRIOR STUDIES OF POSITIVE CARDIAC INOTROPES
ENROLLMENT CRITERIA: LVEF/NYHA
Assessed Changes in Cardiac Hemodynamics with Therapy
Improvement
No improvement
Performed Large Clinical Trial
Rejected As Therapy

Some important conclusions….

- ✓No inotrope improves survival endpoints in patients with HF
- ✓Studies in refractory AdvHF patients have shown that treatment with intermittent low-dose dobutamine infusions improves QoL
- ✓Small studies have shown that repeated levosimendan administration also improves functional capacity and QoL in AdvHF
- ✓A meta-analysis of all available clinical trials, confirmed the effect of levosimendan on re-hospitalization in AdvHF on 3 months (**ESC Heart Fail. 2017**)
- ✓As a result, no positive inotrope is currently approved for long-term use in heart failure.

International Journal of Cardiology 297 (2019) 83–90

Some important conclusions….

Still, **inotropes are indispensable in the setting of AdvHF** as they do improve patients' symptoms/ QOL …

Inotropes and Advanced Heart Failure (AdvHF)

Continuous inotropes and/or vasopressors may be considered in patients with low cardiac output and evidence of organ hypoperfusion as bridge to MCS or heart transplantation.[389,390]	IIb	C

They <u>can be used</u> as palliative therapy for the relief of symptoms in patients without other treatment options.

Intermittent long-term use of inotropes <u>may be considered</u> in outpatients to improve functional class and QOL (IIb)

ESC Guidelines 2021

Eur J Heart Fail 2018;20:11281136.390.
Ambulatory inotrope infusions in advanced heart failure: a systematic review and meta-analysis. JACC Heart Fail

EDITORIAL

The Future for Inotropes in Heart Failure. Do Not Throw the Baby Out With the Bathwater!

Piero Pollesello, PhD and Zoltán Papp, MD, PhD†*

J Cardiovasc Pharmacol 2023

ESC European Society of Cardiology
European Journal of Heart Failure (2019) 21, 1064–1078
doi:10.1002/ejhf.1557
REVIEW

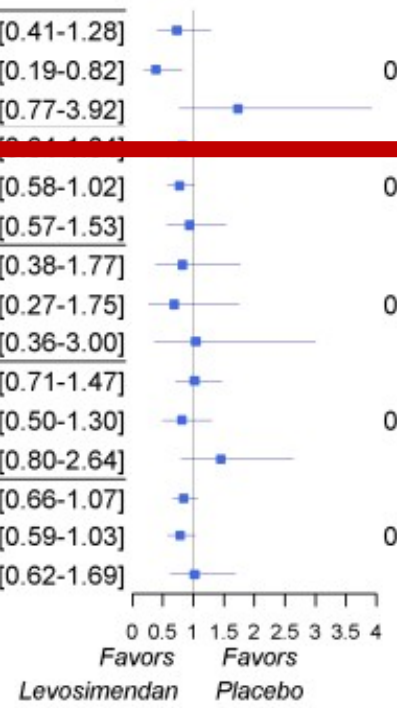
Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials

1) Improvements in short-term haemodynamics may not translate into longer-term mortality and morbidity benefits
2) Benefit from inotropes might only be restricted to sub-phenotypes of heart failure
3) The mechanism and dosage of inotropic agents can cause adverse effects
4) Medical treatment of patients in prior trials did not protect them from sudden cardiac death
5) Inotropes need to improve efficiency and not contractility…

*European Journal of Heart Failure (2019) **21**, 1064–1*

Prophylactic levosimendan in patients with low ejection fraction undergoing coronary artery bypass grafting: A pooled analysis of two multicentre randomised controlled trials

	Levosimendan (N=546)	Placebo (N=538)	HR/OR [CI95%]	P value interaction
90-day mortality	30 (5.5%)	42 (7.8%)	0.73 [0.41-1.28]	
Isolated CABG	12 (3.0%)	31 (7.4%)	0.39 [0.19-0.82]	0.004
CABG combined with valve surgery	18 (12.9%)	11 (8.2%)	1.73 [0.77-3.92]	
Isolated CABG	158 (38.9%)	182 (45.2%)	0.77 [0.58-1.02]	0.51
CABG combined with valve surgery	87 (62.1%)	86 (63.7%)	0.94 [0.57-1.53]	
Renal replacement therapy	21 (3.9%)	24 (4.5%)	0.82 [0.38-1.77]	
Isolated CABG	11 (2.7%)	15 (3.7%)	0.69 [0.27-1.75]	0.51
CABG combined with valve surgery	10 (7.1%)	9 (6.7%)	1.04 [0.36-3.00]	
Need for mechanical assist device	66 (12.1%)	64 (11.9%)	1.02 [0.71-1.47]	
Isolated CABG	34 (8.4%)	41 (10.2%)	0.81 [0.50-1.30]	0.13
CABG combined with valve surgery	32 (22.9%)	23 (17.0%)	1.45 [0.80-2.64]	
Combined endpoint	257 (47.1%)	276 (51.3%)	0.84 [0.66-1.07]	
Isolated CABG	165 (40.6%)	188 (46.7%)	0.78 [0.59-1.03]	0.35
CABG combined with valve surgery	92 (65.7%)	88 (65.2%)	1.02 [0.62-1.69]	



The subgroup of patients undergoing isolated CABG had a reduction in mortality at day 90, whereas there was no significant effect in combined surgery patients. This finding requires confirmation with a specific prospective trial.

Anaesth Crit Care Pain Med. 2022;41:101107

The Future for Inotropes in Heart Failure. Do Not Throw the Baby Out With the Bathwater!

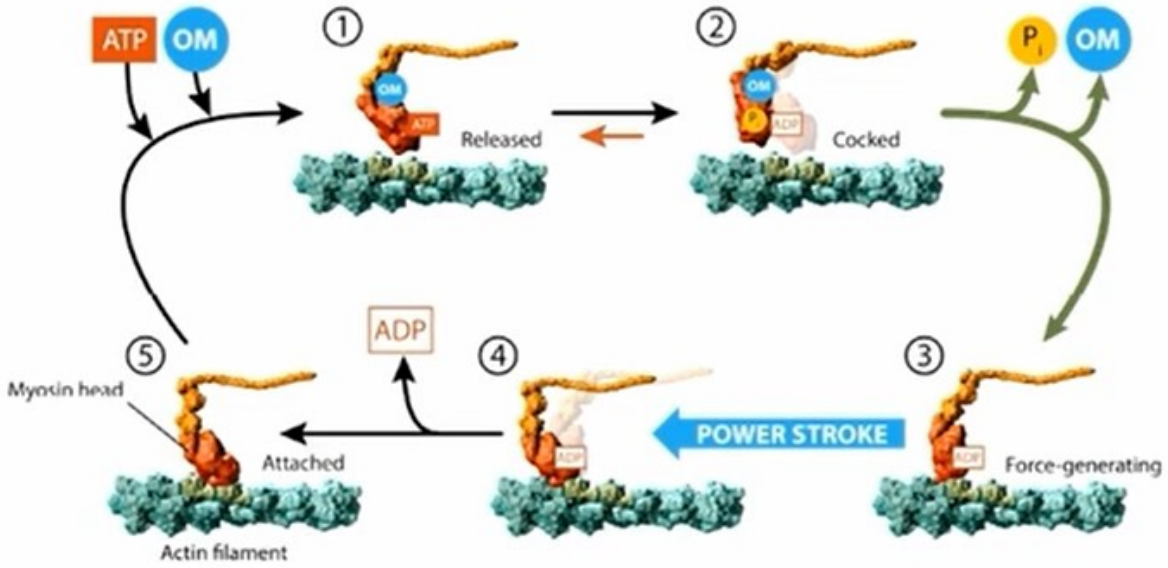
Piero Pollesello, PhD and Zoltán Papp, MD, PhD†*

- ***None of the established inotropes have been studied comprehensively in any closely-defined heart failure subsetting so far…***
- ***It depends on which inotrope and on which subtype of heart failure…***
- ***We must not throw the baby out with the bath water, just because in the past the clinical trials were not focused enough.***

2023

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 with no effect on intracellular calcium



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.

COSMIC-HF

Omecamtiv mecarbil in HFrEF

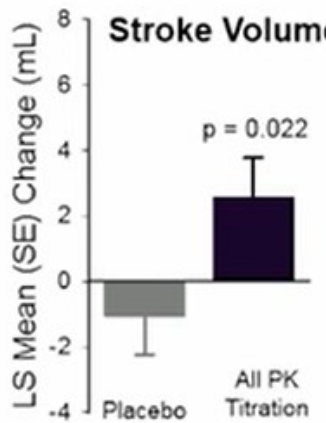
Teerlink JR, *et al*. *Lancet* 2016; 388: 2895-903.

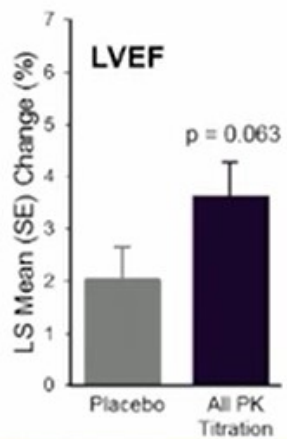
149 patients per group
- History of chronic HF
- Treated with stable, optimal HF Rx
- NYHA class II or III
- LVEF ≤ 40%
- NT-proBNP ≥ 200 pg/mL

20-weeks Oral therapy
- Placebo
- Omecamtiv mecarbil
  25 →50 mg BID (PK-titration)

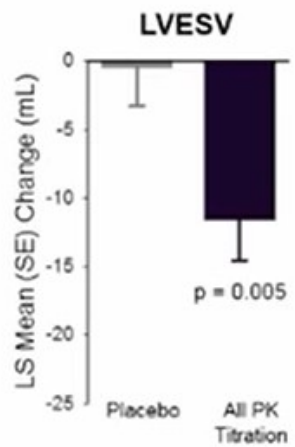
Serial Echocardiograms

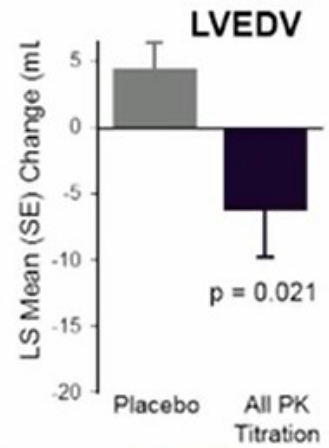
Improved LV Function



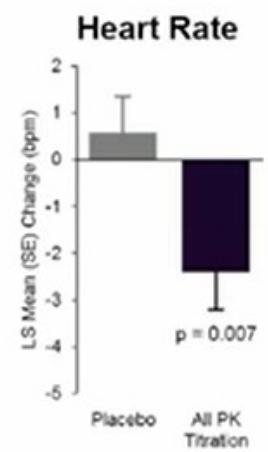


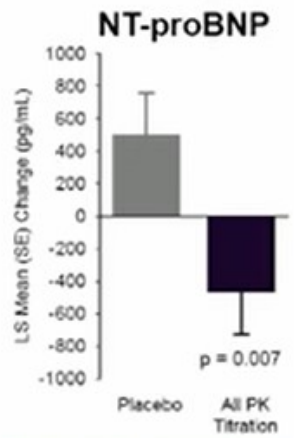
Decreased LV Volumes





Decreased Neuro-hormonal Activation

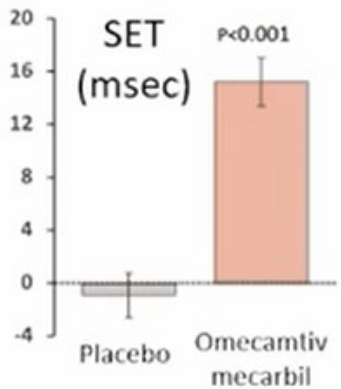


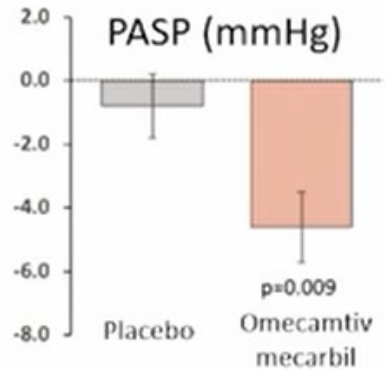


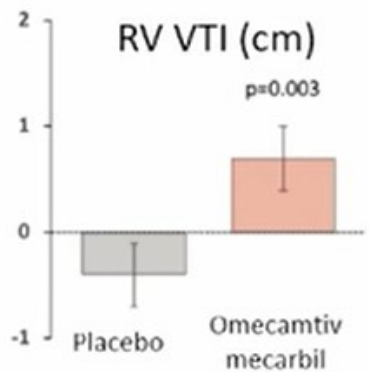
Improved Right Ventricular and Left Atrial Function

Biering-Sorensen T, *et al. Eur J Heart Fail* 2021;23:1052-1056; Biering-Sorensen T, *et al. Circulation* 2016;134, Abstract.

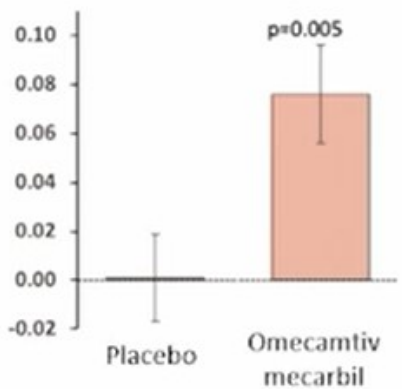
Right Ventricular Function



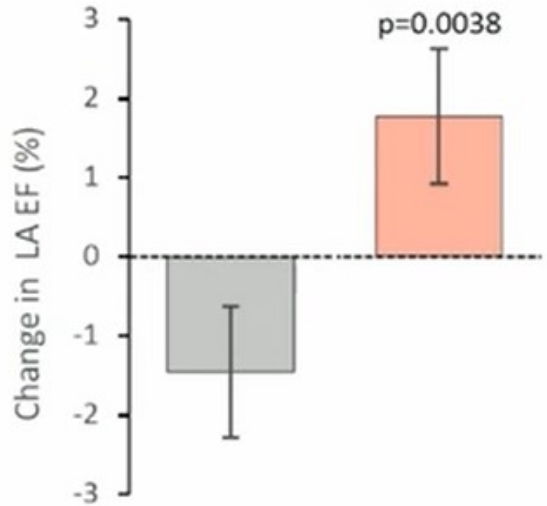




RVOT VTI/PASP ratio (cm/mmHg)



Left Atrial Function



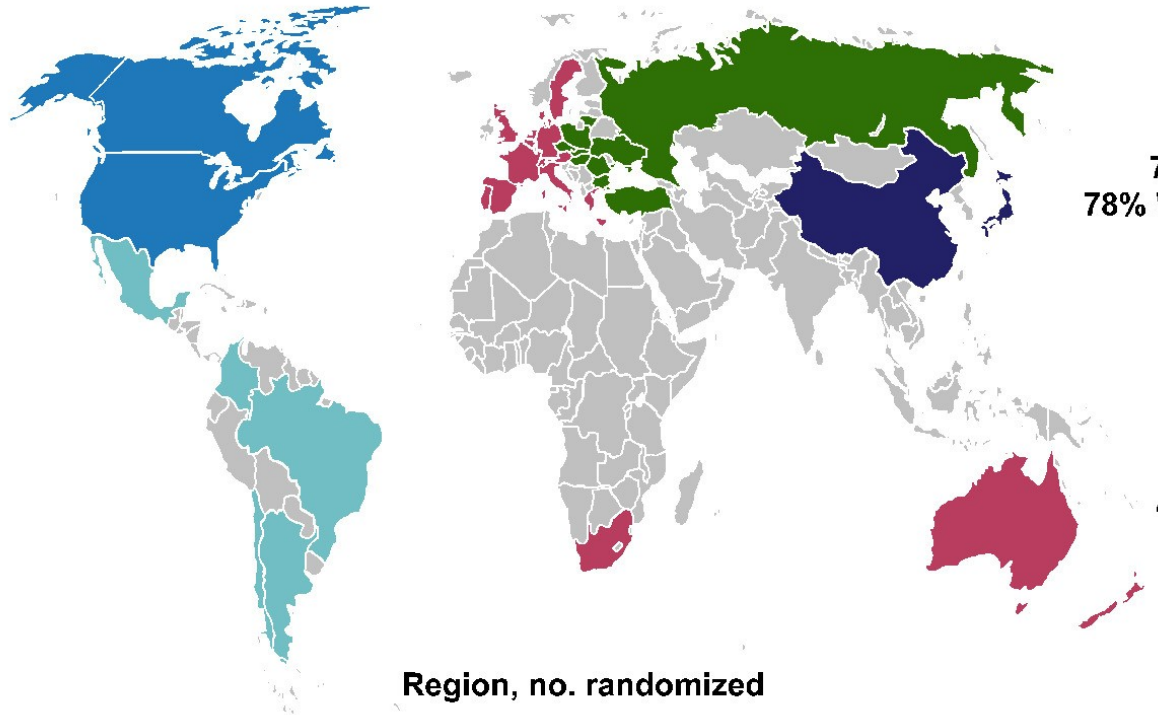
LAEF, Left atrial ejection fraction; PASP, Pulmonary artery systolic pressure; RV, Right ventricular; SE, standard error; SET, systolic ejection time; VTI, Velocity time integral (~Stroke volume).

CENTRAL ILLUSTRATION: Baseline Characteristics of GALACTIC-HF, Phase 3 Trial of Omecamtiv Mecarbil in Patients With HFrEF

GALACTIC-HF: Multicenter, randomized, double-blind, placebo-controlled, event-driven trial

- Assess effects of omecamtiv mecarbil, *a novel, selective cardiac myosin activator*, on clinical outcomes in both inpatients and outpatients with HFrEF **EjF < 35%**
- *Primary efficacy outcome*: Time to CV death or HF event, whichever occurs first

Enrolled 8,256 Patients With HFrEF



Baseline Characteristics

79% Male, 21% Female,
78% White, 9% Asian, 7% Black,
65 yr mean age

25% Inpatient

27% Mean EF,
53% NYHA Class II,
47% NYHA Class III/IV

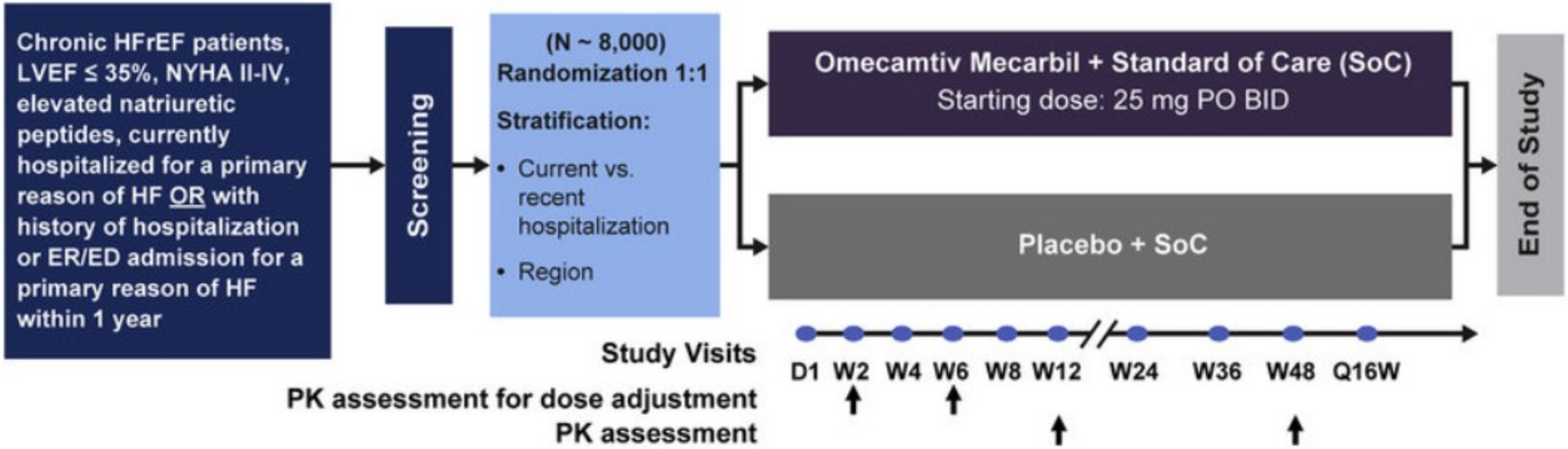
1971 pg/mL
median NT-proBNP,
117 mmHg mean SBP

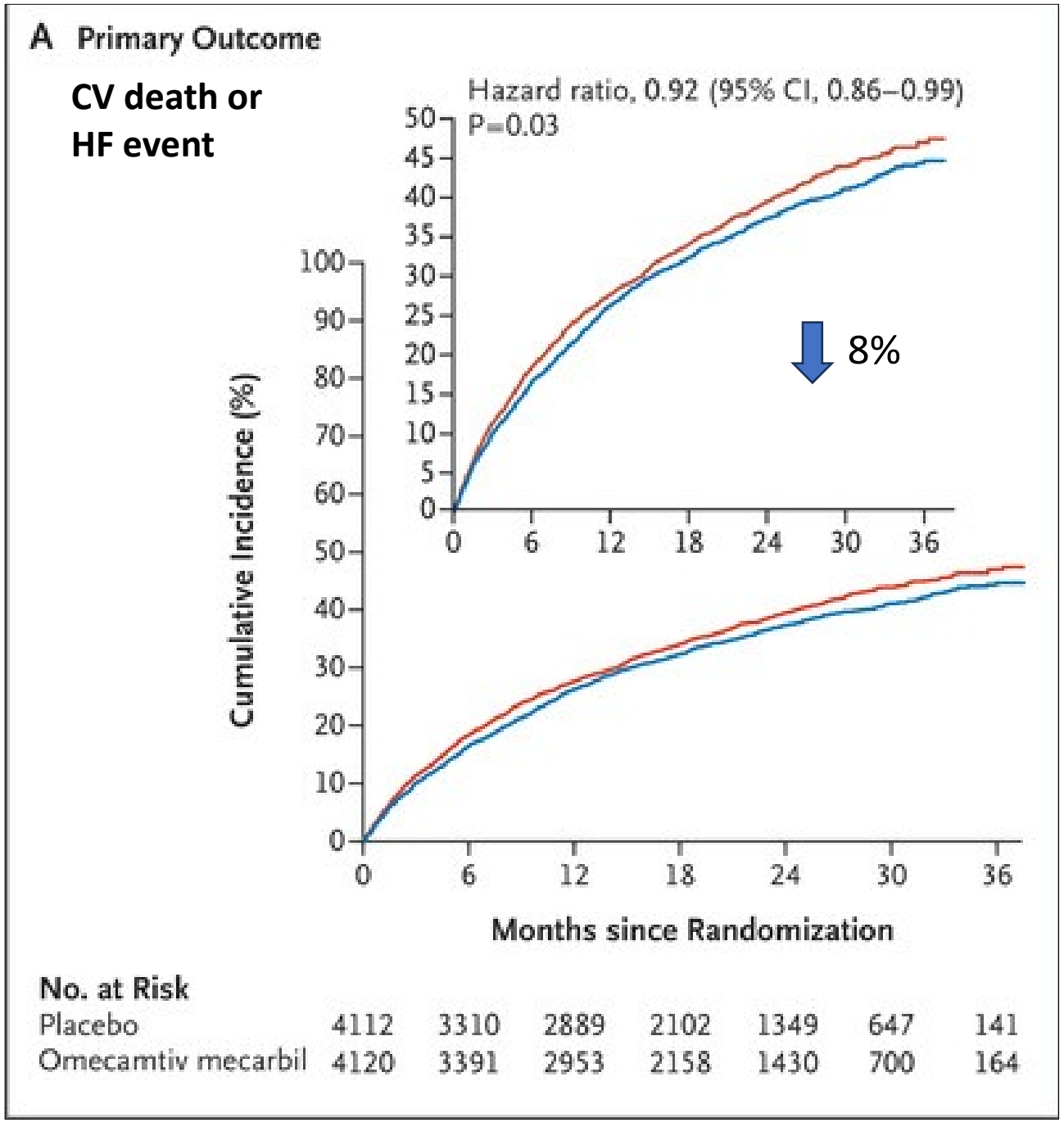
87% ACEI/ARB/ARNi
(19% ARNi),
94% BB, 77% MRA

14% CRT and 32% ICD

median Fup 21.8

Schematic of Study Design for the GALACTIC-HF Trial





N Engl J Med 2021; 384:105-116

Contemporary HF Outcome Trials

Primary Endpoint Absolute Rate Reduction

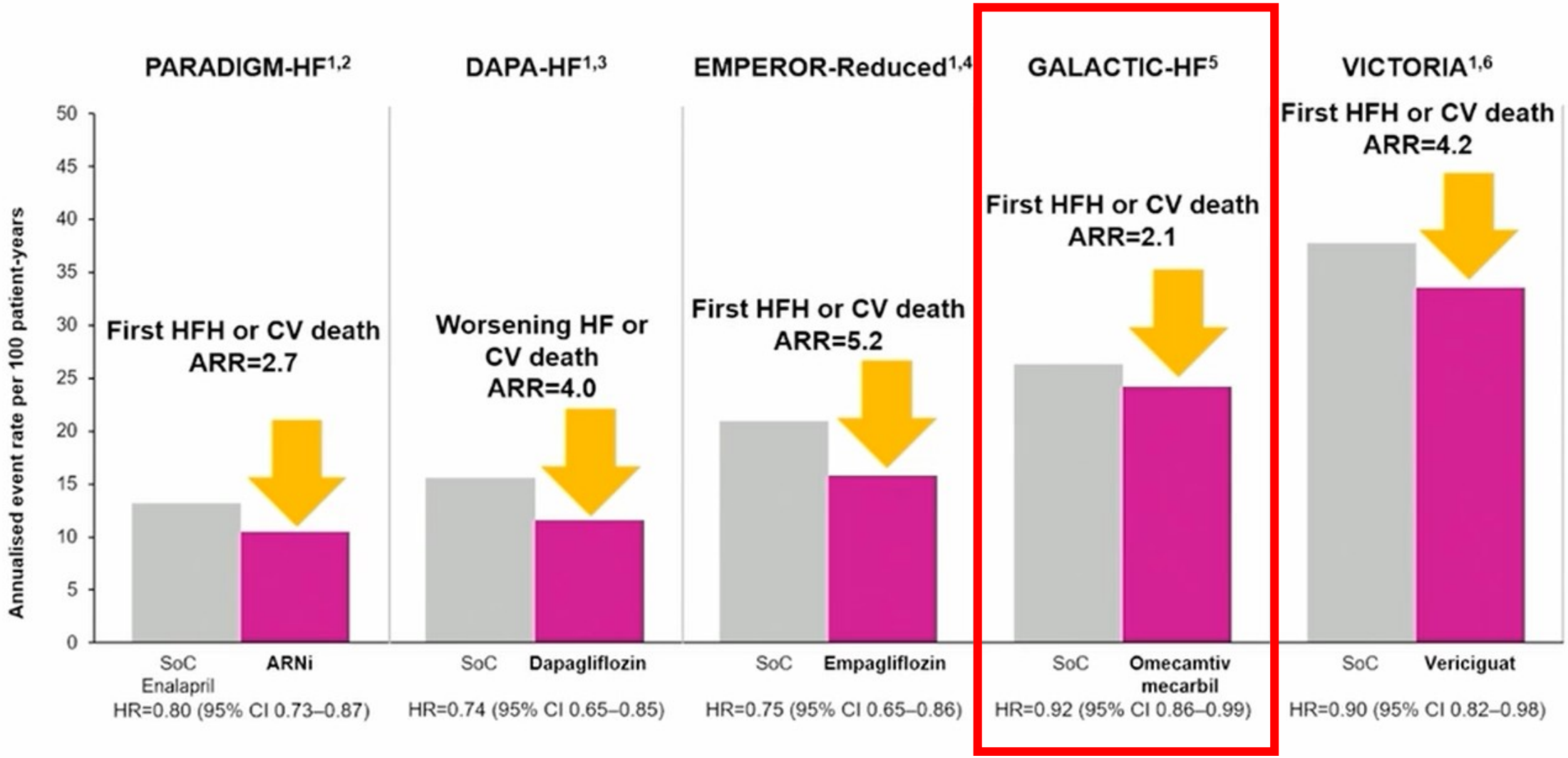


Table 2. Primary and Secondary Cardiovascular Outcomes.*

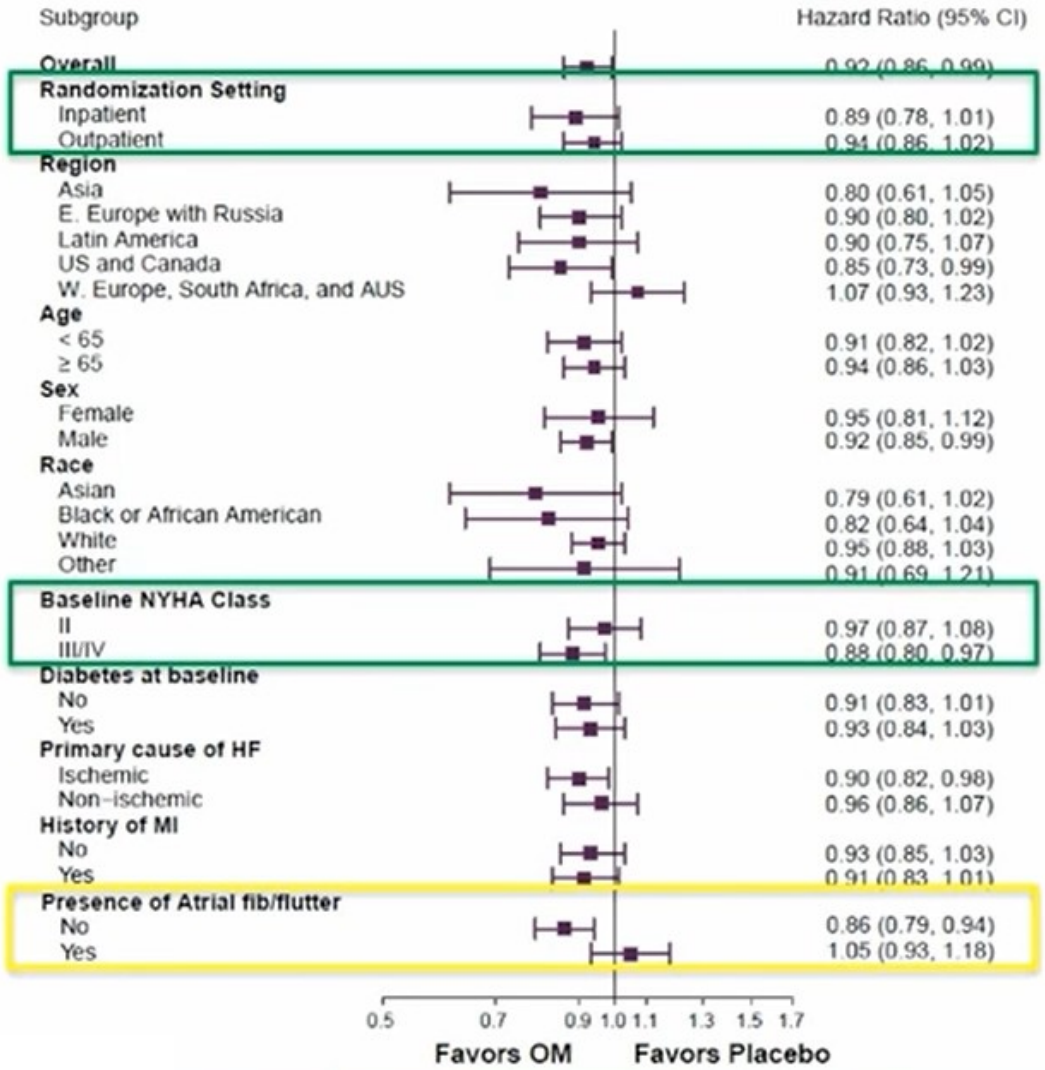
Variable	Omecamtiv Mecarbil (N=4120)		Placebo (N=4112)		Hazard Ratio or Difference (95% CI)†	P Value
	Value	Events	Value	Events		
		no./100 patient-yr		*no./100 patient-yr*		
Primary composite outcome — no. (%)‡	1523 (37.0)	24.2	1607 (39.1)	26.3	0.92 (0.86 to 0.99)	0.03
Cardiovascular death as first event	346 (8.4)		371 (9.0)			
Hospitalization for heart failure as first event	1107 (26.9)		1133 (27.6)			
Urgent outpatient visit for heart failure as first event	70 (1.7)		103 (2.5)			
Secondary outcomes						
Cardiovascular death — no. (%)	808 (19.6)	10.9	798 (19.4)	10.8	1.01 (0.92 to 1.11)	0.86§
Change in KCCQ total symptom score at wk 24						0.03§
Inpatients	23.7±0.7	NA	21.2±0.7	NA	2.5 (0.5 to 4.5)	
Outpatients	5.8±0.3	NA	6.3±0.3	NA	−0.5 (−1.4 to 0.5)	
First hospitalization for heart failure — no. (%)	1142 (27.7)	18.0	1179 (28.7)	19.1	0.95 (0.87 to 1.03)	NA
Death from any cause — no. (%)	1067 (25.9)	14.4	1065 (25.9)	14.4	1.00 (0.92 to 1.09)	NA
Exploratory outcome						
Heart-failure event — no. (%)	1177 (28.6)	18.7	1236 (30.1)	20.3	0.93 (0.86 to 1.00)	NA

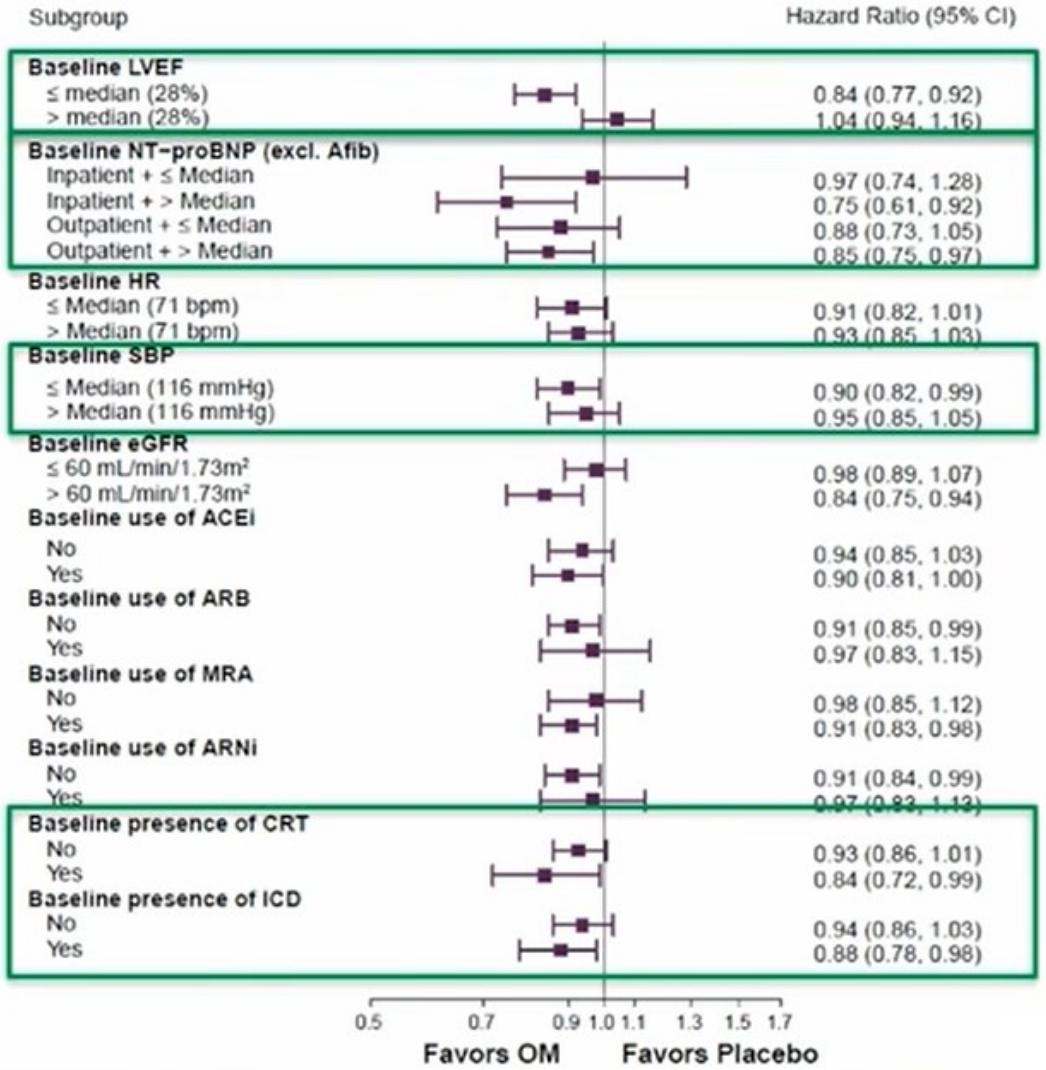
N Engl J Med 2021; 384:105-116

Cardiac Myosin Activator: Omecamtiv Mecarbil

GALACTIC-HF

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

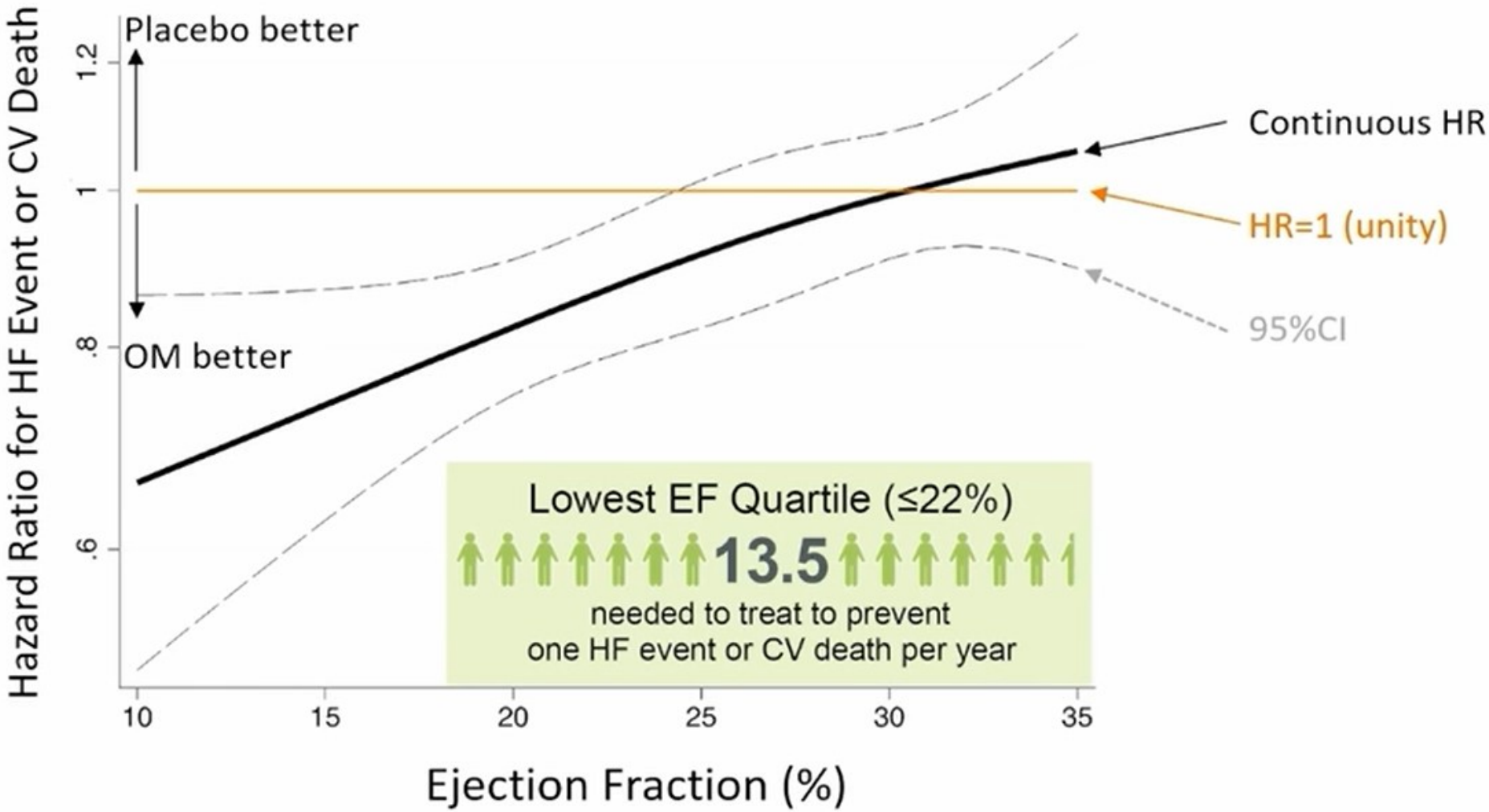




Primary Outcome: EF Subgroup Results

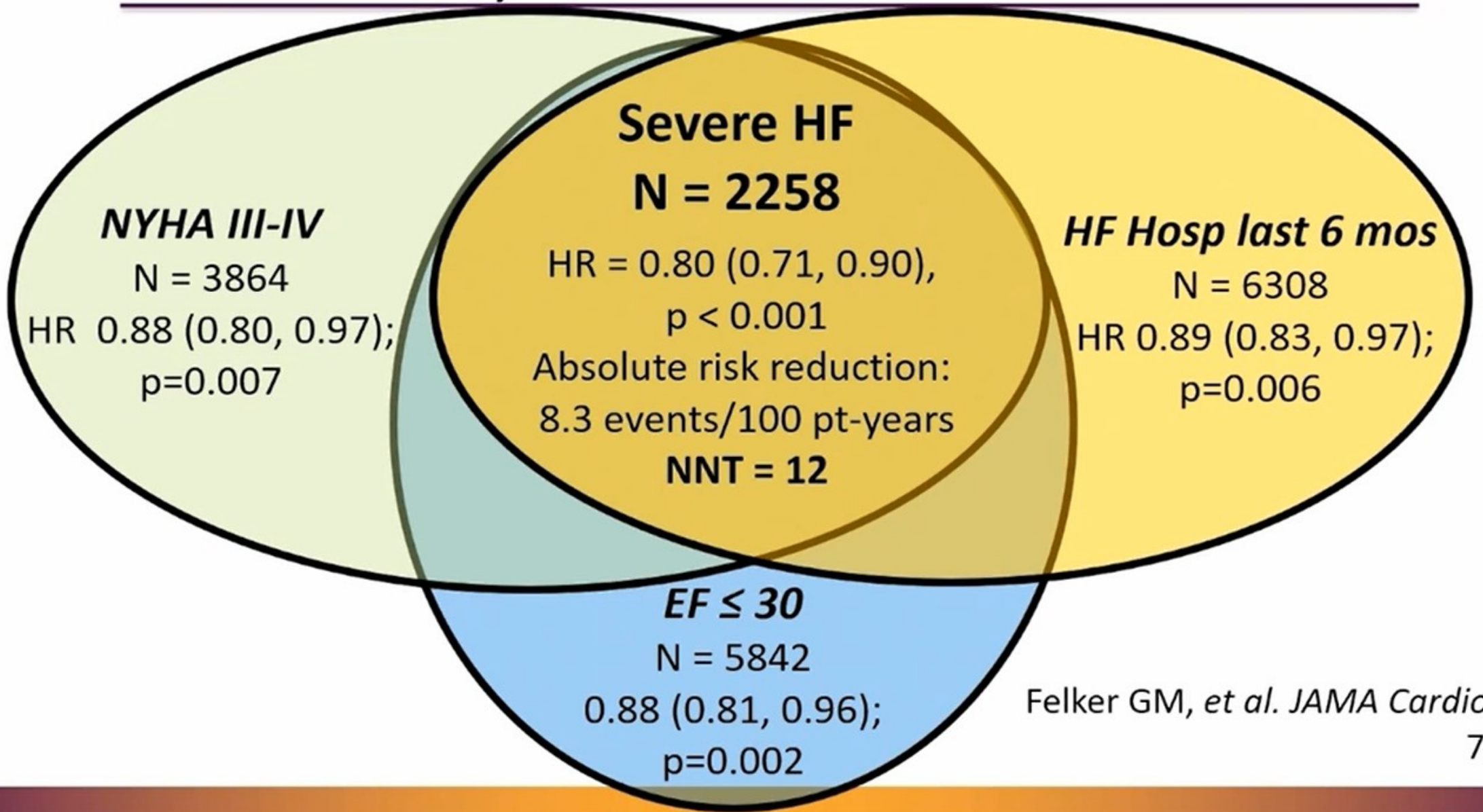
GALACTIC-HF

Teerlink JR, *et al. J Am Coll Cardiol* 2021:78:97-108.



Benefit of Omecamtiv Mecarbil by Severe HF Criteria

GALACTIC-HF



Felker GM, *et al. JAMA Cardiol* 2022; 7:26-34.

Vital Signs and Laboratory Results

GALACTIC-HF

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

Variable	Omecamtiv Mecarbil (N=4110)	Placebo (N=4101)	Relative Risk or Difference (95% CI)
Vital signs, laboratory values: change from baseline to Week 24			
Systolic BP, mmHg, mean (SD)	1.4 (15.3)	1.5 (15.6)	-0.1 (-0.9, 0.6)
Heart rate, bpm, mean (SD)	-2.1 (12.6)	-0.5 (12.8)	-1.6 (-2.2, -1.0)
Potassium, mmol/L, mean (SD)	-0.01 ± 0.57	-0.01 ± 0.57	0.00 (-0.03, 0.03)
Creatinine, mg/dL, mean (SD)	0.03 ± 0.33	0.02 ± 0.32	0.01 (-0.01, 0.02)
NT-proBNP, pg/mL, median (Q1, Q3)	-251 (-1180, 295)	-180 (-915, 441)	0.90 (0.86, 0.94)
Cardiac troponin I, ng/mL, median (Q1, Q3)	0.004 (-0.002, 0.021)	0.000 (-0.009, 0.008)	0.004 (0.003, 0.005)

No adverse impact on heart rate, blood pressure, renal function or potassium

Adverse Events

GALACTIC-HF

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

Adverse event	Omecamtiv Mecarbil (N=4110)	Placebo (N=4101)	Relative Risk (95% CI)
Any serious AE, n (%)	2373 (57.7)	2435 (59.4)	0.97 (0.94, 1.01)
Drug discontinuation due to AE, n (%)	371 (9.0)	382 (9.3)	0.97 (0.85, 1.11)
Adverse events of interest			
Ventricular tachyarrhythmias	290 (7.1)	304 (7.4)	0.95 (0.82, 1.11)
Torsade de pointes/QT prolongation	176 (4.3)	195 (4.8)	0.90 (0.74, 1.10)
SAE of ventricular arrhythmia requiring treatment	119 (2.9)	127 (3.1)	0.93 (0.73, 1.20)
Adjudicated major cardiac ischemic events, n (%)	200 (4.9)	188 (4.6)	1.06 (0.87, 1.29)
Myocardial infarction	122 (3.0)	118 (2.9)	--
Hospitalized for unstable angina	25 (0.6)	12 (0.3)	--
Coronary revascularization	115 (2.8)	117 (2.9)	--
Adjudicated Strokes	76 (1.8)	112 (2.7)	0.68 (0.51, 0.91)

No imbalance of AEs/SAEs (including cardiac ischemia and arrhythmias)

O que dizem as guidelines HF ESC 2021?

Cardiac myosin activator

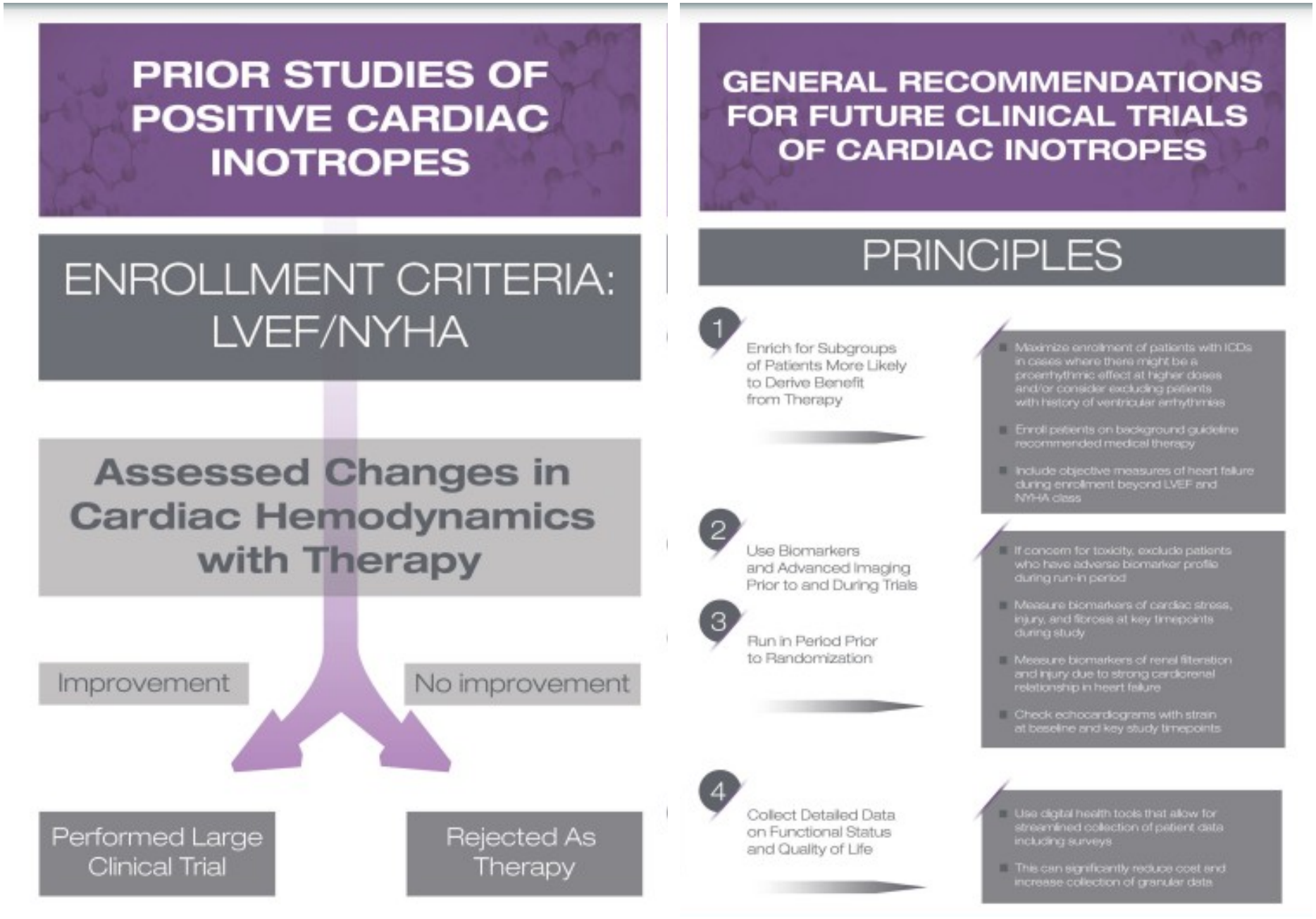
The GALACTIC-HF study assessed the efficacy and safety of the cardiac myosin activator, omecamtiv mecarbil, in HFrEF patients, enrolling patients in both the inpatient and outpatient settings. The primary endpoint of a first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug is not licensed for use in HF. However, in the future it may be able to be considered, in addition to standard therapy for HFrEF to reduce the risk of CV mortality and hospitalization for HF.[159]

FDA Declines Approval for Omecamtiv Mecarbil in HFrEF

Megan Brooks
March 01, 2023

The US Food and Drug Administration (FDA) has declined to approve omecamtiv mecarbil (Cytokinetics) for treatment of adults with chronic heart failure with reduced ejection fraction (HFrEF), citing a lack of evidence on efficacy.

Considerations for future trials testing positive inotropes



European Journal of Heart Failure (2019) ***21****, 1064–1078*

Sob T Médica Opt. (4 pilares) CDI/CRTD

Fej., NYHA, DC/ VS , CPWP, PAD

Fenótipos específicos

Biomarcadores stress/lesão miocárdica /fibrose

Biomarcadores de lesão e disfunção renal

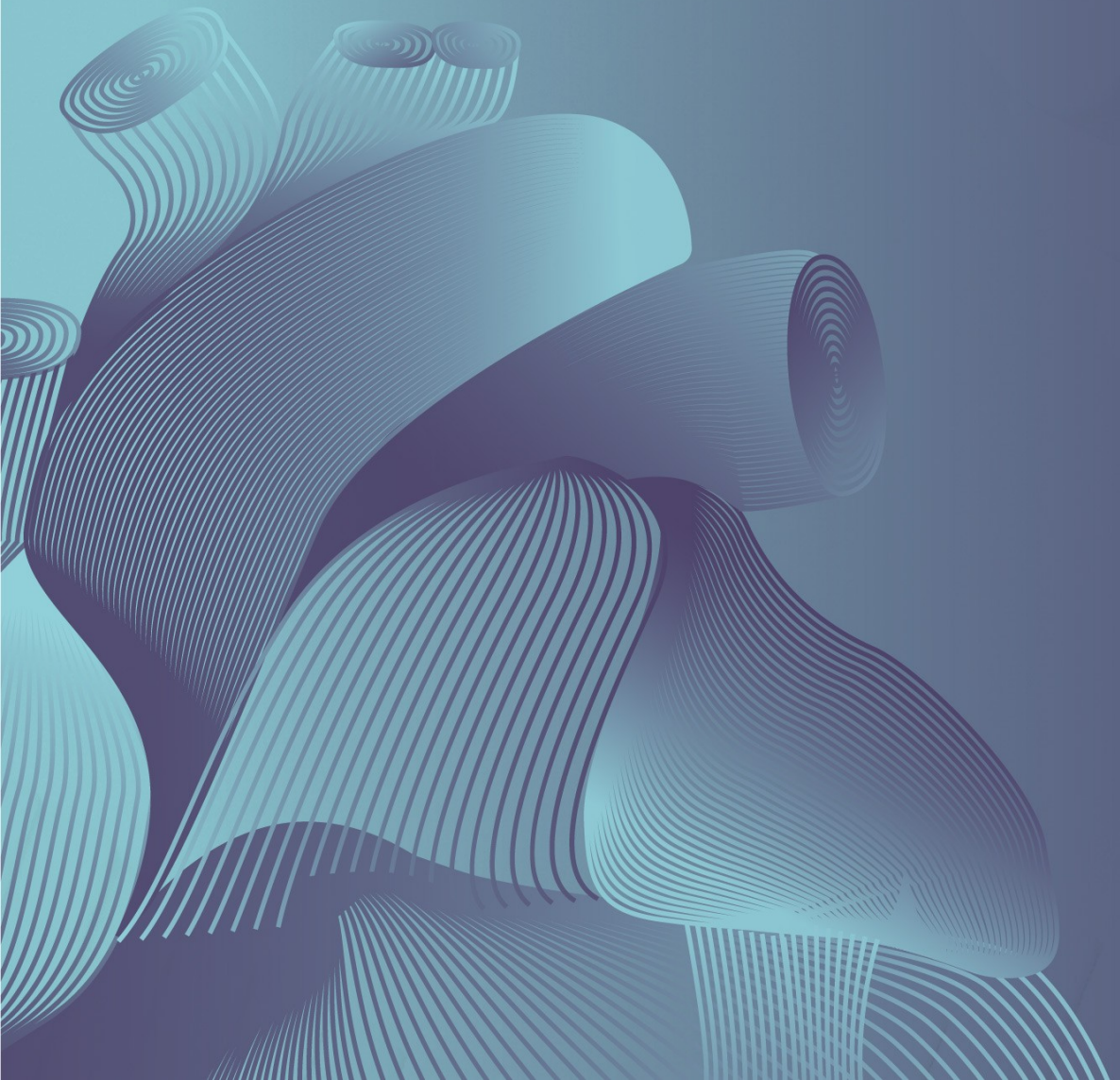
Técnicas avançadas de Imagem (echo /RMC)

Análise detalhada/objectiva da capacidade funcional e qualidade de vida, episódios de agudização de IC, sobrevida…

European Journal of Heart Failure (2019) ***21****, 1064–1078*

5 Take Home Messages

- ✓No positive inotrope is currently approved for long-term use in heart failure. Still, inotropes are indispensable in the setting of AdvHF.
- ✓None of the established inotropes have been studied comprehensively in any closely-defined heart failure subsetting so far.
- ✓There is a role for dobutamine and levosimendan in advanced heart failure.
- ✓Omecamtiv Mecarbil is a promising drug > It is necessary to phenotype who must benefit with it.
- ✓We need future (and different) trials testing positive inotropes!

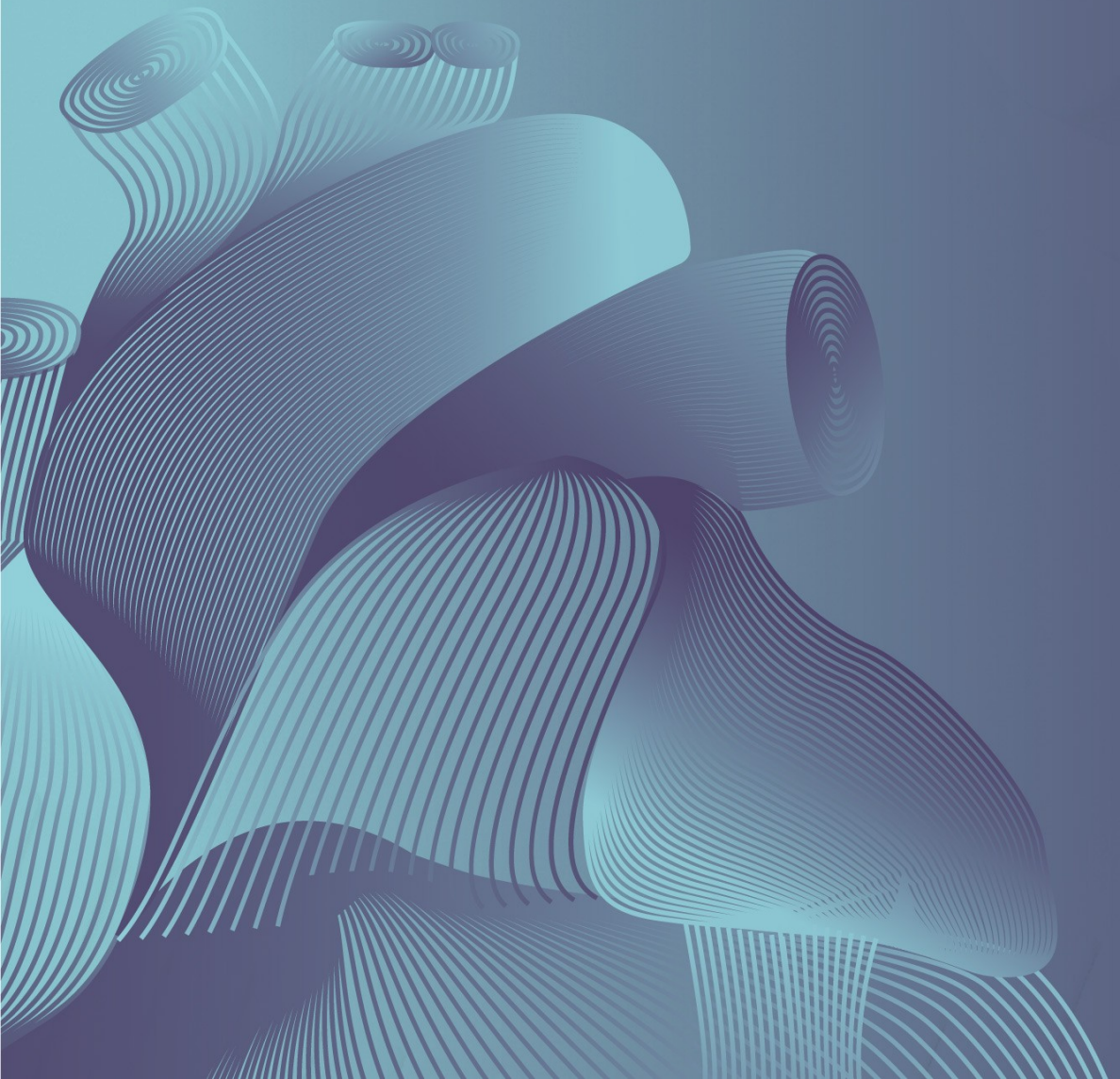


7th Advances in Heart Failure 2024

10 e 11 de Outubro

FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

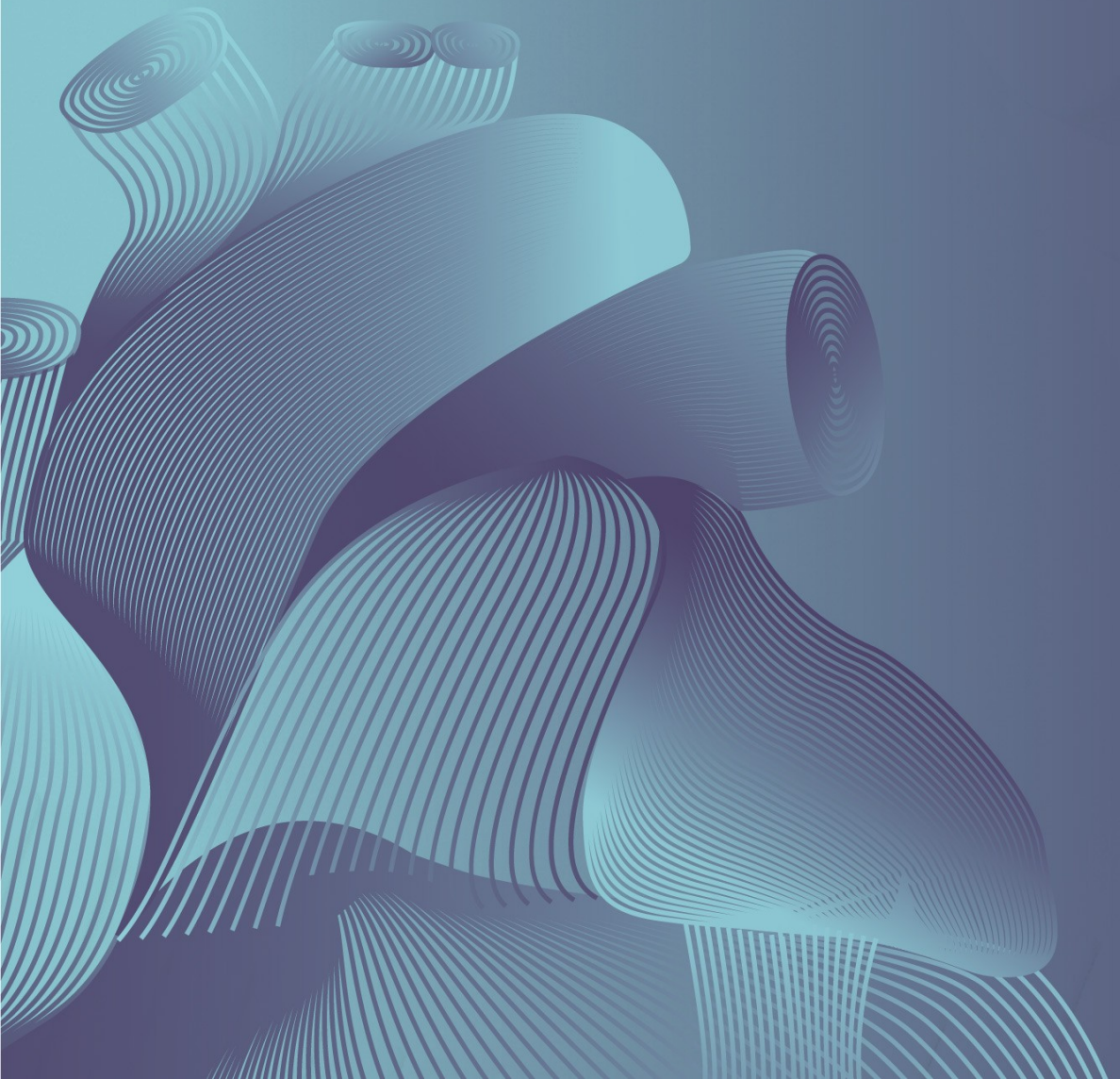
Obrigada



7th Advances in Heart Failure 2024

10 e 11 de Outubro

FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO



7th Advances in Heart Failure 2024

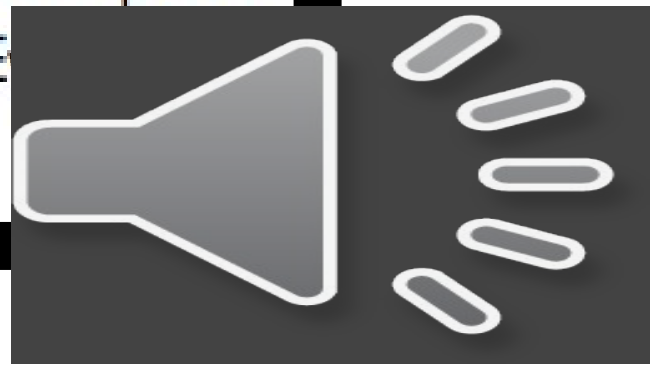
10 e 11 de Outubro

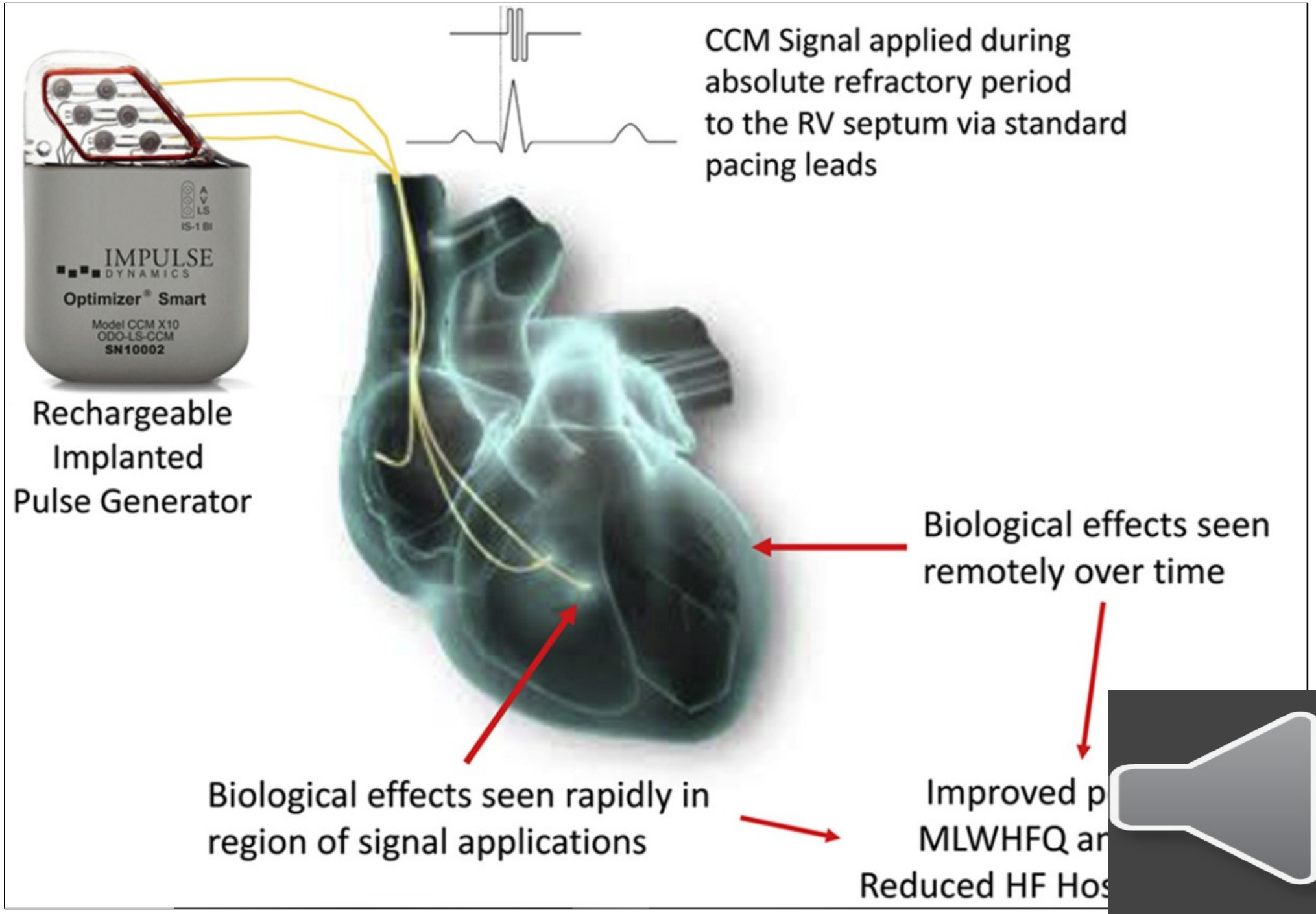
FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

6.3 Devices under evaluation

Cardiac contractility modulation (CCM) has been evaluated in patients with NYHA class III–IV HF, with an LVEF ≥25% to ≤45% and QRS duration <130 ms, and was associated with a small improvement in exercise tolerance and QOL.[241,242]

Technologies that involve modification of the activity of the autonomic nervous system, e.g. baroreflex activation therapy,[243,244] have also been shown to offer a modest improvement in effort capacity and QOL. However, currently, the evidence is considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization for these and a variety of other implantable electrical therapeutic technologies (see also Gaps in E
section 16).



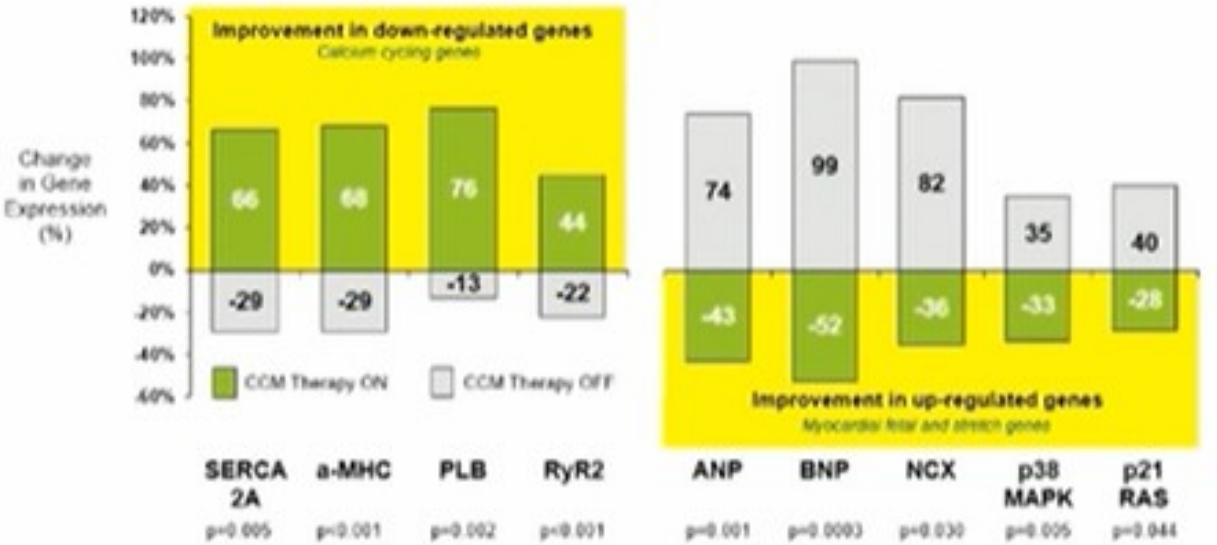

CCM Signal applied during absolute refractory period to the RV septum via standard pacing leads
IMPULSE DYNAMICS
Optimizer® Smart
Model CCM X10
ODO-LS-CCM
SN10002
Rechargeable Implanted Pulse Generator
Biological effects seen remotely over time
Biological effects seen rapidly in region of signal applications
Improved p
MLWHFQ ar
Reduced HF Hos

CCM therapy
Modes of action

There are thought to be two modes of actio

1. Improvement of calcium handling within the myo

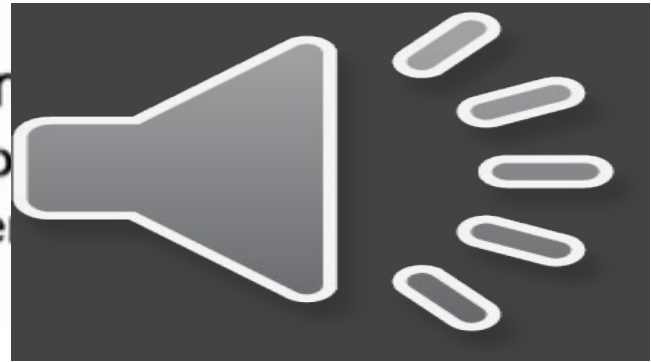
CCM therapy
Modes of action



Adapted from Butter, JACC 2008 FIX-HF-4 (N=11 patients):
Group 1: Therapy On > Off (n=7); Group 2: Therapy Off to On (n=4)

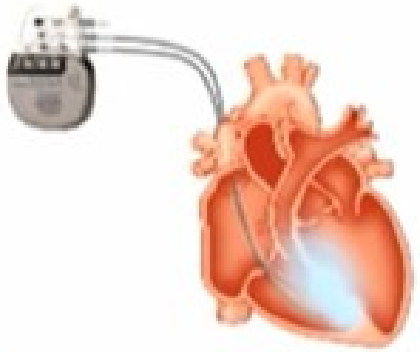
There are thought to be two modes of actio

1. Improvement of calcium handling within the myo
2. Normalization of abnormal gene expression see



Optimizer® Smart
Therapy effects

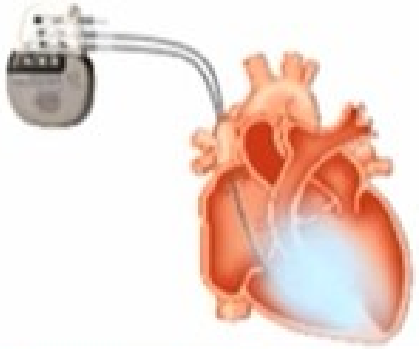
Rapid



Minutes to Hours$_{(1-3)}$

Improves contractility

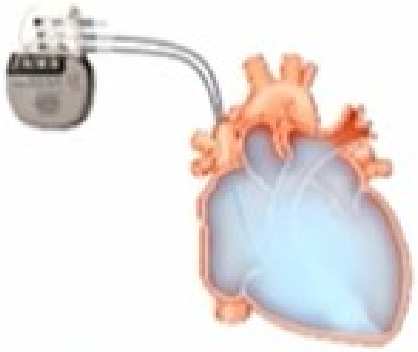
Intermediate



Hours to Weeks$_{(1-3)}$

Normalizes gene profile

Long-Term



Weeks to Months$_{(\sim 4)}$

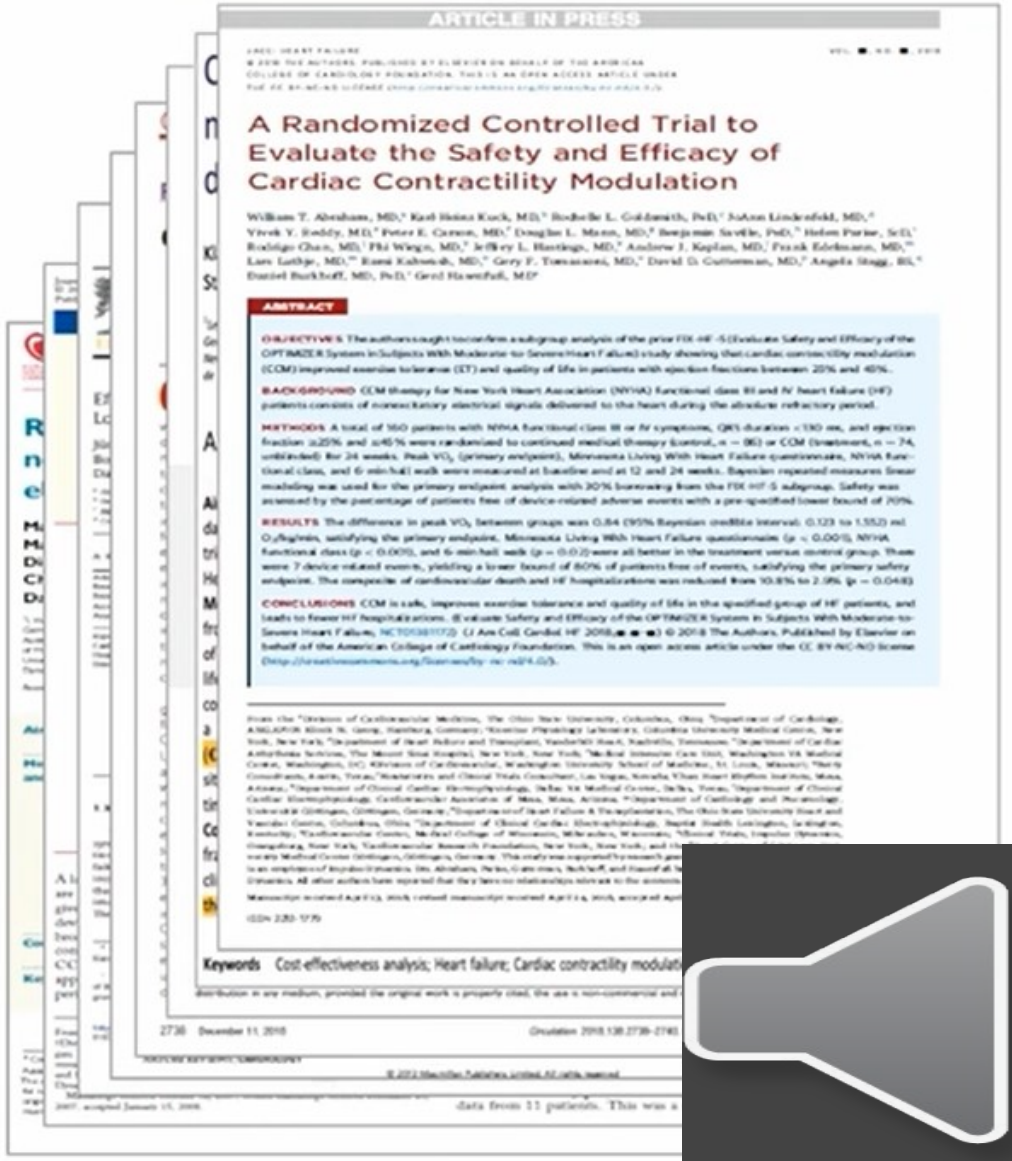
Reverse remodeling

The science behind CCM

More than 100 publications in peer-reviewed journals

Select Publications

- **Kuschyk et al:** "Long Term Clinical experience with cardiac contractility modulation delivered by the Optimizer Smart system" European Journal of Heart Failure, May 2021
- **Tschope -** Clinical effects of cardiac contractility modulation in heart failure with mildly reduced systolic function ESC Heart Failure December 2020
- **Abraham** et al: "A Randomized Control Trial to evaluate the safety and efficacy of Cardiac Contractility Modulation" JACC HF, May 2018
- **Tschope** et al: "Cardiac contractility modulation: mechanisms of action in heart failure with reduced ejection fraction and beyond" European Journal of Heart Failure, August 2018
- **Borggrefe** and **Mann**: "Cardiac Contractility Modulation in 2018" Circulation, December 2018
- **Butter** C: "Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients with heart failure" Journal of the American College of Cardiology, May 2008
- **Borggrefe** M.M. et al: "Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure" European Heart Journal, January 2008


ARTICLE IN PRESS

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

ABSTRACT

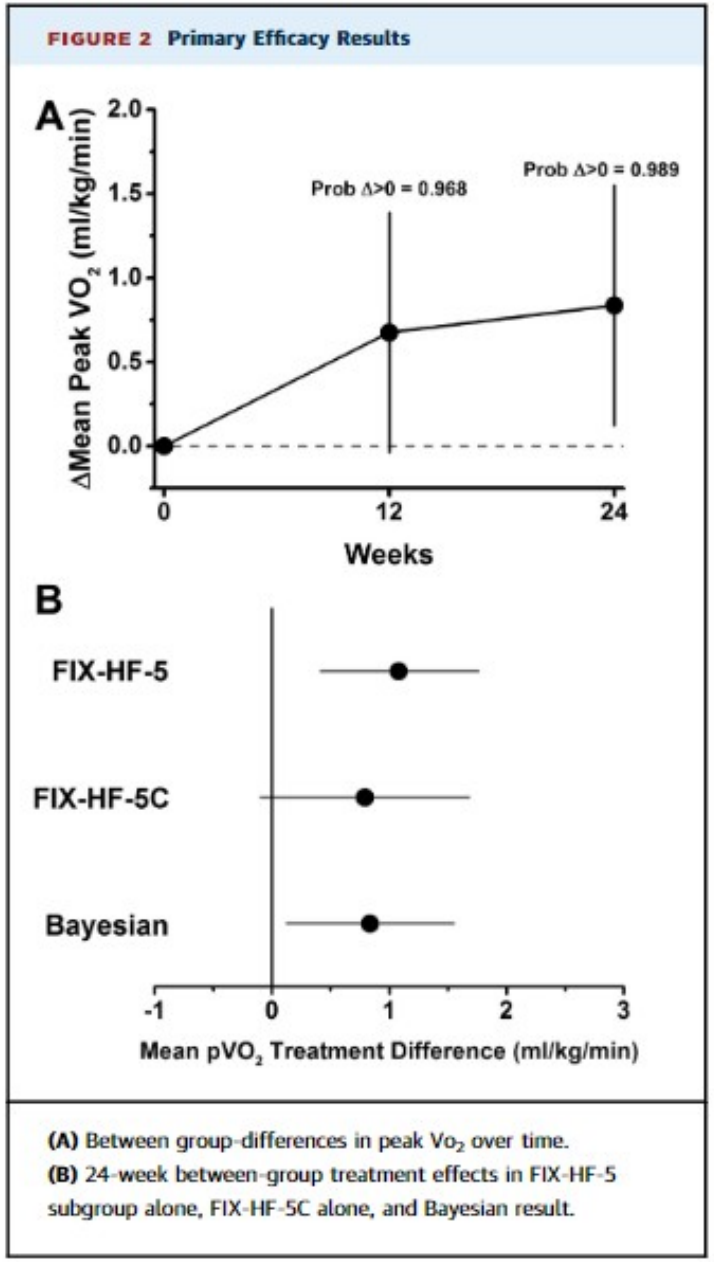
Keywords Cost-effectiveness analysis; Heart failure; Cardiac contractility modulat

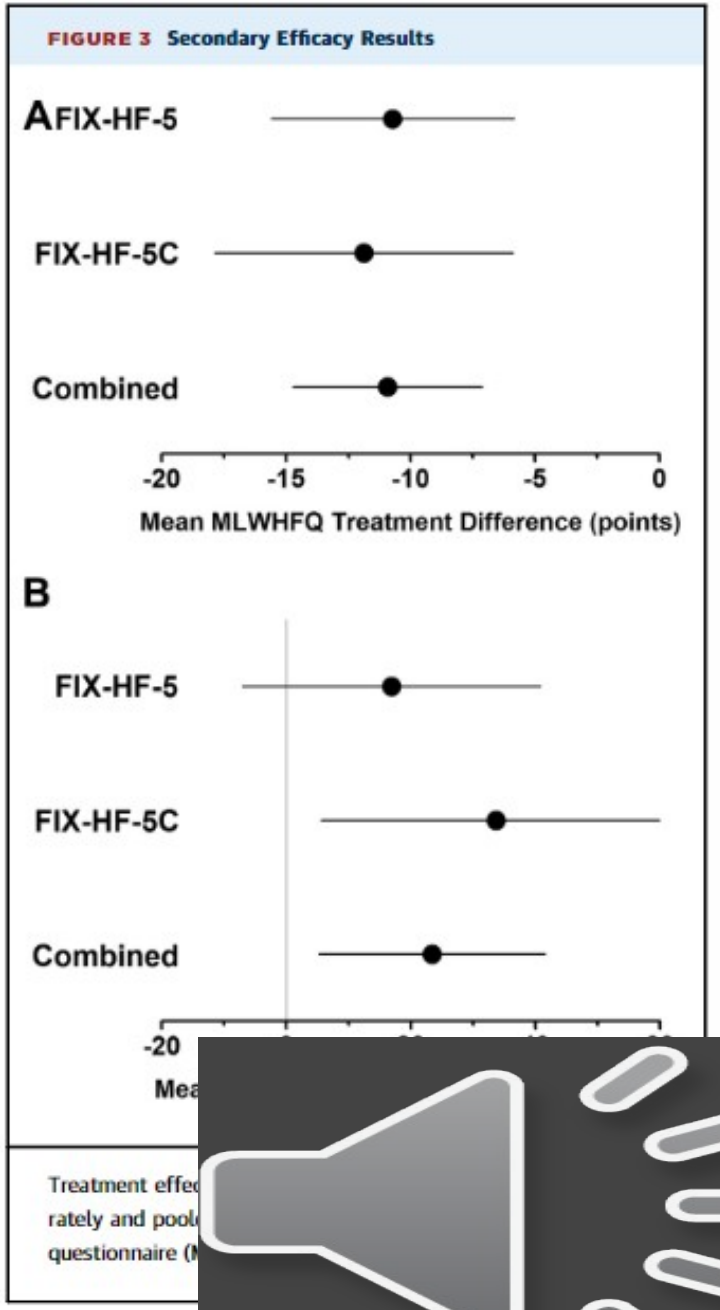
JACC: HEART FAILURE

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

160 patients
NYHA functional class III or IV symptoms
QRS duration<130 ms
Ejection fraction 25% and 45%

Continued medical therapy or CCM
Fup. 24 weeks.





A

FIGURE 4 Efficacy Results by EF Groups

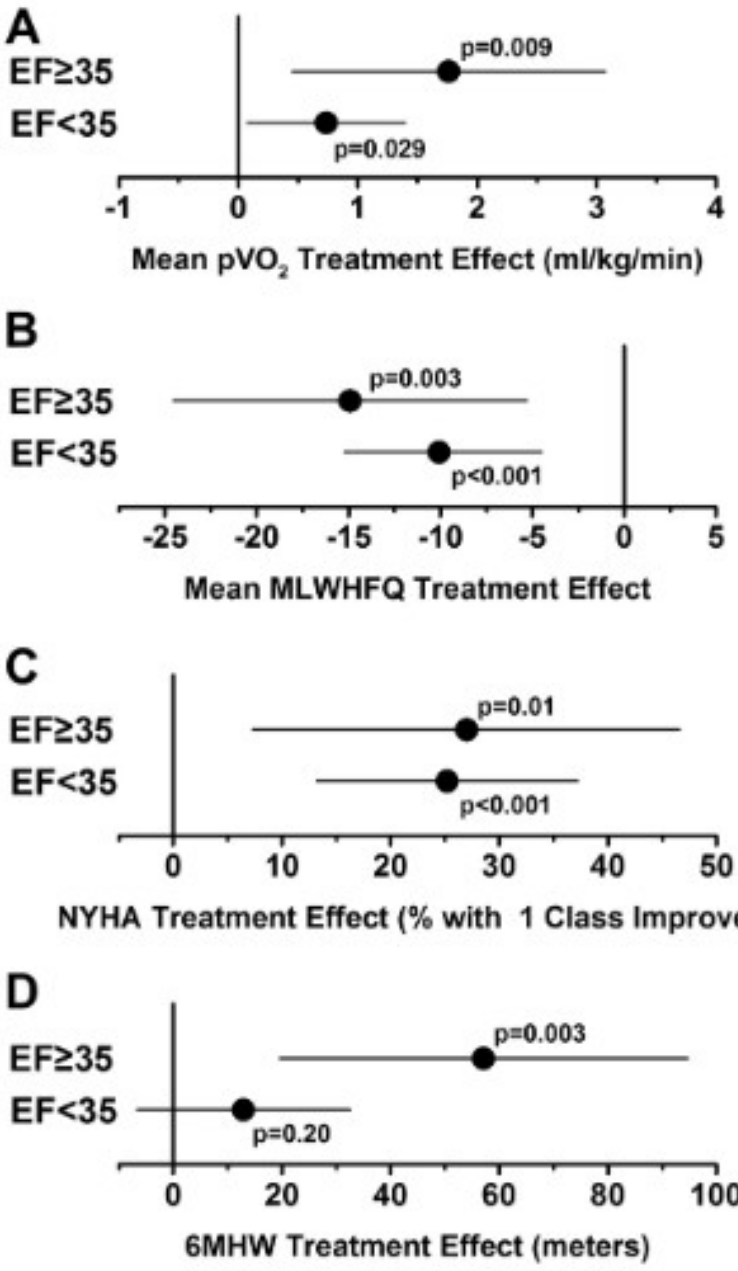
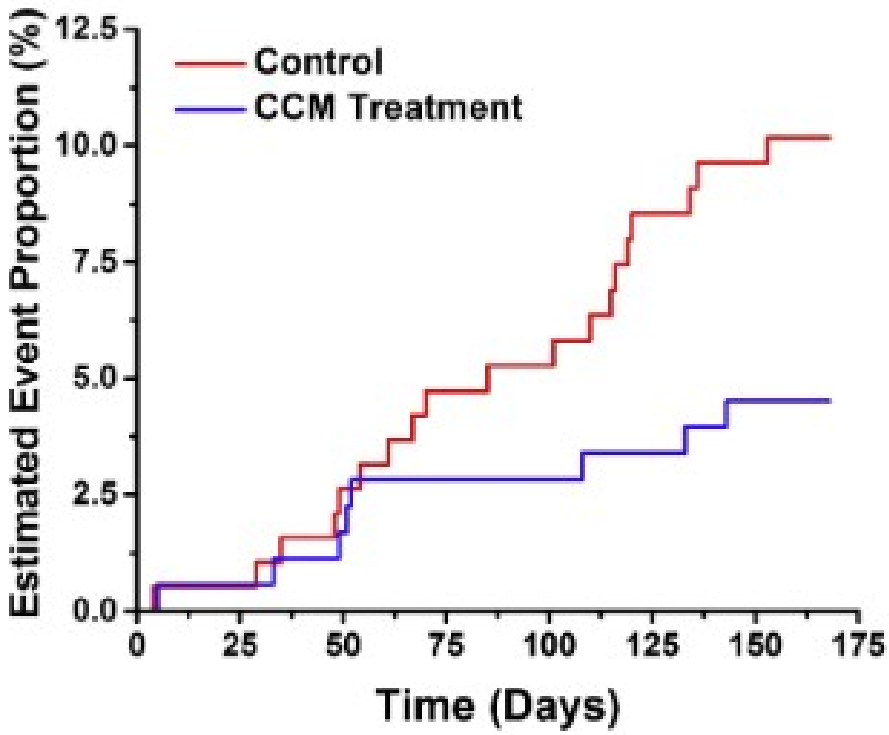
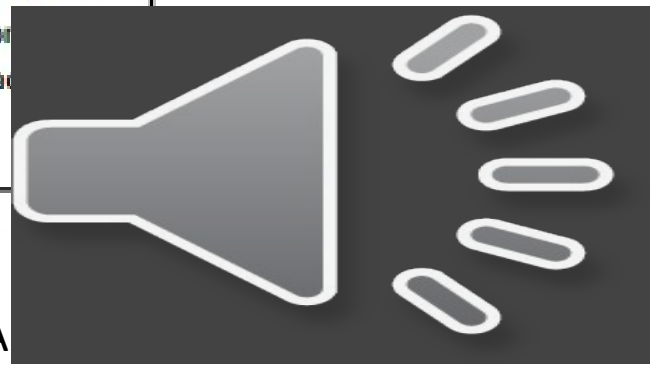


FIGURE 5 Heart Failure and Mortality Events



Comparison of estimated event proportions of the composite of cardiac death and heart failure hospitalizations between Control and Treatment; p = 0.042 by log-rank test and p = 0.036 when comparing 24 weeks using Greenwood's formula for variance. Further details in Online Table 6. CCM = cardiac contractility modulation.



ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 3531–3535
Published online 3 December 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13126

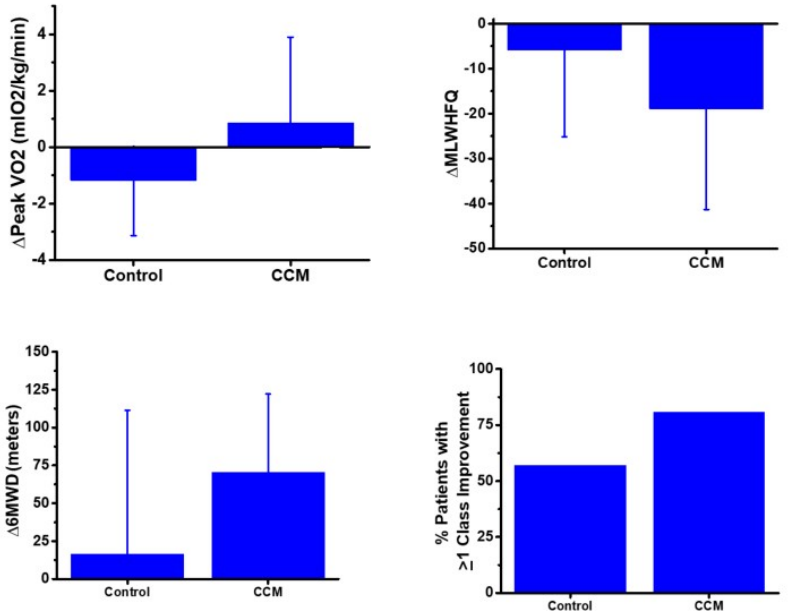
ORIGINAL RESEARCH ARTICLE

Clinical effects of cardiac contractility modulation in heart failure with mildly reduced systolic function

Carsten Tschöpe[1,2,3], Javed Butler[4], Dimitrios Farmakis[5], Deborah Morley[6], Ishu Rao[6] and Gerasimos Filippatos[7]*

53 patients with a LVEF of 40–45% recruited in previous CCM studies

Figure 1 Absolute changes in exercise capacity, quality of life, and functional status observed in the cardiac contractility modulation (CCM) group and the control group (6MWD, 6 min walk distance; MLWHFQ, Minnesota Living with Heart Failure Questionnaire).



CCM clinical outcomes

Real-world results in patients followed for 3 years

ESC European Society of Cardiology

European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2202

RESEARCH ARTICLE

Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer Smart system

Jürgen Kuschyk[1], Peter Falk[2], Thomas Demming[2], Oliver Marx[3], Deborah Morley[4], Ishu Rao[4], and Daniel Burkhoff[5]*

[1]1st Department of Medicine - Cardiology, University Medical Centre Mannheim, Germany; Partner Site Heidelberg/Mannheim, German Center for Cardiovascular Research (DZHK), Mannheim, Germany; [2]Herzzentrum Bad Bevensen, Bad Bevensen, Germany; [3]Elbe Klinikum Stade, Klinik für Innere Medizin, Kardiologie und Internistische Intensivmedizin, Stade, Germany; [4]Impulse Dynamics, Inc, Marlton, NJ, USA; and [5]Cardiovascular Research Foundation, New York, NY, USA

Received 4 February 2021; revised 18 March 2021; accepted 27 April 2021

Aims We assessed long-term effects of cardiac contractility modulation delivered by the Optimizer Smart system on quality of life, left ventricular ejection fraction (LVEF), mortality and heart failure and cardiovascular hospitalizations.

Methods and results CCM-REG is a prospective registry study including 503 patients from 51 European centres. Effects were evaluated in three terciles of LVEF (≤25%, 26–34% and ≥35%) and in patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). Hospitalization rates were compared using a chi-square test. Changes in functional parameters of New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and

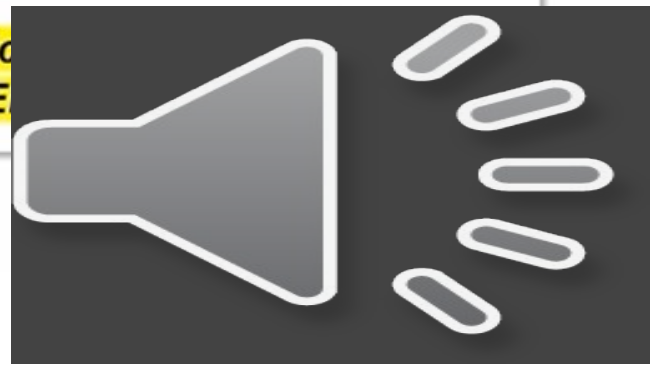
Aims:

To assess the long-term effects of CCM delivered by the Optimizer Smart system on:

- NYHA functional class
- quality of life
- left ventricular ejection fraction (LVEF)
- mortality and heart failure and cardiovascular hospitalizations

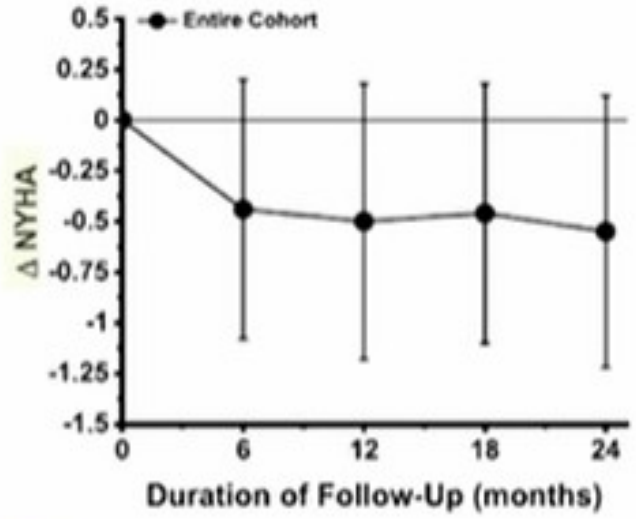
In 503 patients with CE Mark indications for CCM:

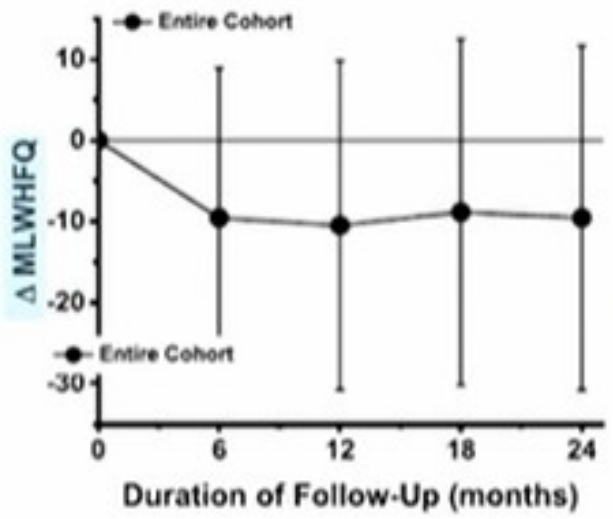
- ***"symptomatic***
  (NYHA II-IV, E

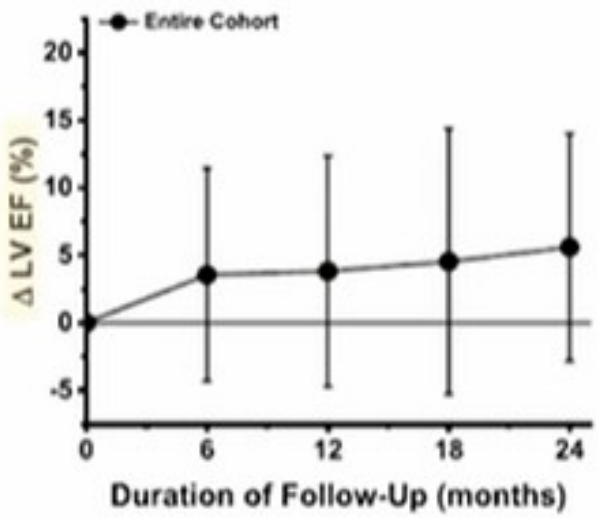


CCM clinical outcomes

Changes in NYHA, QoL, and LVEF







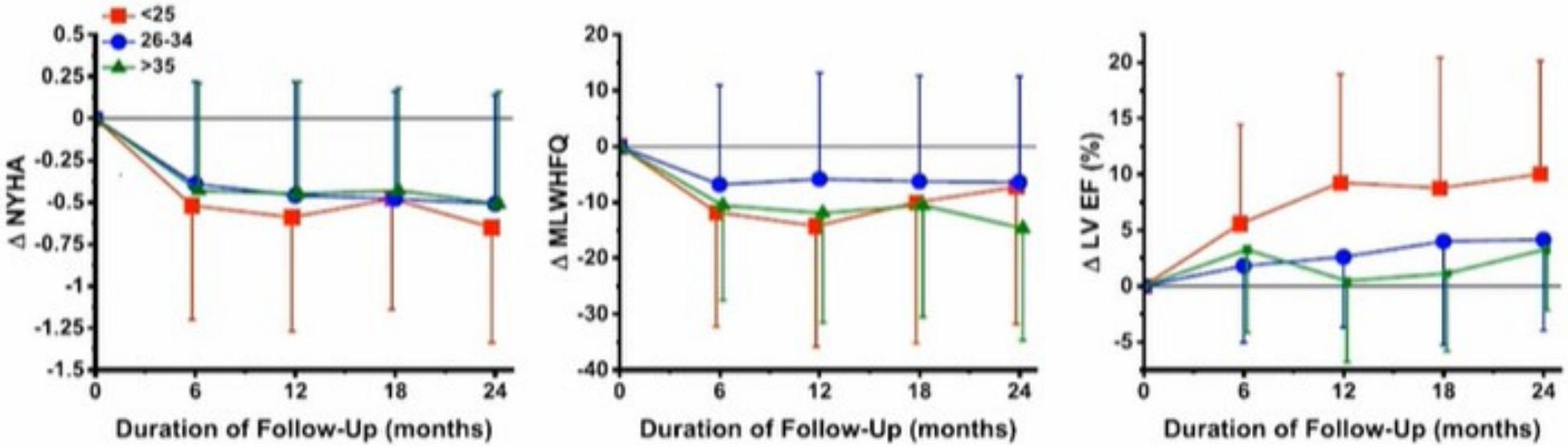
Average improvement @ 24 months ($p < 0.0001$)	0.6 ± 0.7	10 ± 21	5.6 ± 8.4%

European Journal Heart Fa

CCM Registry Study

Changes of NYHA, QoL, LVEF: LVEF subgroups

LVEF Subgroups



All subgroups statistically significant

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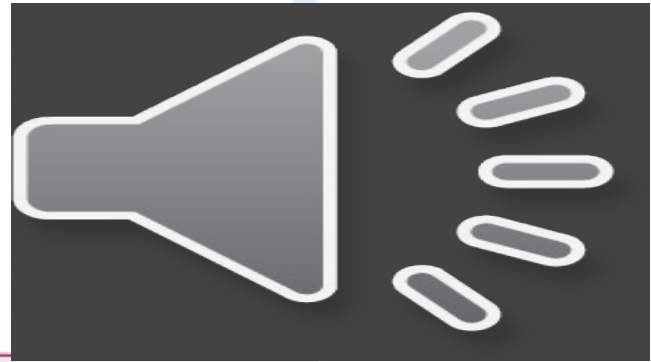
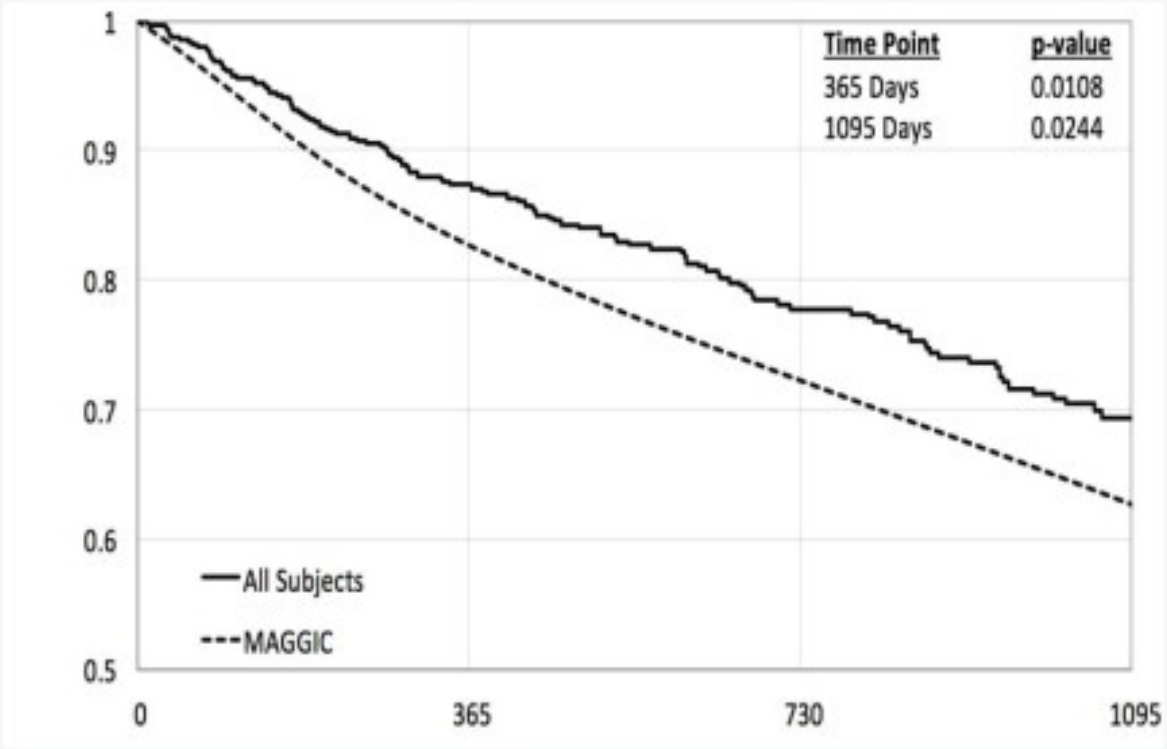
Table 3 Hospitalization rates the year prior to Optimizer implant compared to the 2 years following Optimizer implant in the entire cohort and in the five subgroups of interest

Subgroup	Pre-treatment (1 year prior)				Post-treatment (0–730 days)				
	Patients	Patient-years	Events	Event rate	Patients	Patient-years	Events	Event rate	*P*-value
All patients									
All cardiovascular events	503	503	523	1.04	503	729	287	0.39	<0.0001
Heart failure events			371	0.74			179	0.25	<0.0001
Non-heart failure cardiovascular events			152	0.30			108	0.15	<0.0001
LVEF ≤25%									
All cardiovascular events	178	178	227	1.28	178	233	123	0.53	<0.0001
Heart failure events			182	1.02			90	0.39	<0.0001
Non-heart failure cardiovascular events			45	0.25			33	0.14	0.0106
LVEF 26–34%									
All cardiovascular events	164	164	157	0.96	164	255	99	0.39	<0.0001
Heart failure events			102	0.62			59	0.23	<0.0001
Non-heart failure cardiovascular events			55	0.34			40	0.16	0.0002
LVEF ≥35%									
All cardiovascular events	161	161	139	0.86	161	242	65	0.27	<0.0001
Heart failure events			87	0.54			30	0.12	<0.0001
Non-heart failure cardiovascular events			52	0.32			35	0.14	0.0002
Normal sinus rhythm									
All cardiovascular events	349	349	342	0.98	349	530	200		
Heart failure events			229	0.66			130		
Non-heart failure cardiovascular events			113	0.32			70		
Atrial fibrillation									
All cardiovascular events	154	154	181	1.18	154	198	87		
Heart failure events			142	0.92			49		
Non-heart failure cardiovascular events			39	0.25			38		

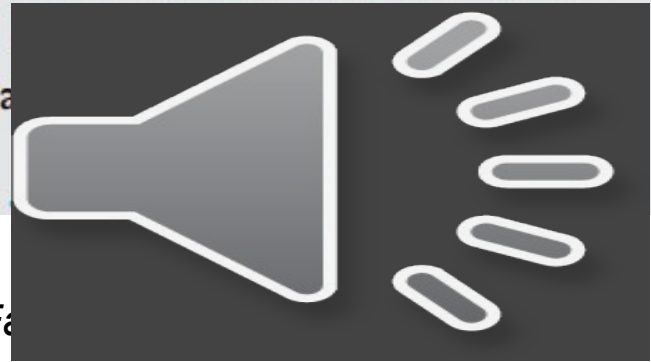


Improved Survival vs MAGGIC



Conclusions

Cardiac contractility modulation therapy improved functional status, quality of life, prior history, reduced heart failure hospitalization rates. Survival at 1 and 3 yea predicted by the MAGGIC risk score.



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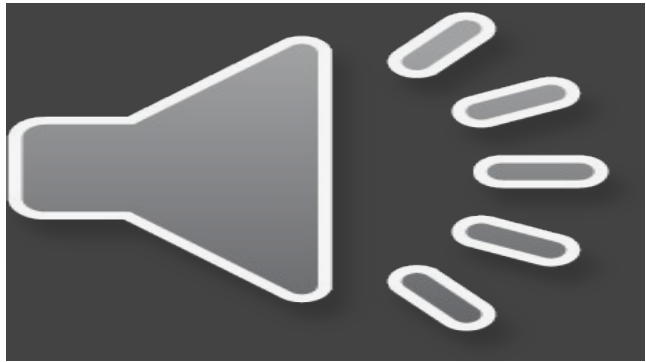
Indication

CE Mark Indications

- Patients >18 years with symptomatic HF due to systolic LVD despite appropriate medical therapy.
- CCM therapy as delivered by the OPTIMIZER system has been shown to:
  - Improve clinical status
  - Functional capacity and quality of life
  - and prevent hospital admissions
    - in patients with symptomatic left heart failure in carefully selected patients and in the hands of dedicated heart failure cardiologists.

US FDA Indications

- The Optimizer® Smart system is indicated to:
  - Improve 6-minute hall walk distance, and
  - Improve quality of life, and
  - Improve functional status
    - for NYHA Class III HF patients with LVEF 25% to 45% who remain symptomatic despite GDMT
    - who are not indicated for cardiac resynchronization therapy (CRT)



CCM-HFpEF Pilot Study

***CCM** in **H**eart **F**ailure With **P**reserved **E**jection **F**raction*

Presented at ESC HF Late Breaking Clinical Trial Session
Madrid, Spain
22 May 2022

Cecilia Linde, MD
Steering Committee
KAROLINSKA UNIVERSITY HOSPITAL

Study Objective

Assess the potential benefits of CCM in patients with HFpEF

Study Design

Prospective, multi-center, pilot study of CCM in patients with symptomatic HFpEF in 47 patients from 17 EU and AUS sites

Key Inclusion Criteria

- LVEF > 50% per core lab
- NYHA II or III on OMT for 30+d
- Stable OMT > 3 months
- NT pro-BNP > 220 pg/ml (SR) or > 600 pg/ml (AF)
- Per core lab:
- LAVi > 34 ml/m2 AND EITHER
- E/e' > 13 OR
- Septal e' < 7 cm/s or lateral e' < 10 cm/s

Primary Efficacy Endpoint

Mean change in KCCQ OSS from baseline to 24 weeks. 90% power to detect 12.5 point average improvement

Safety Endpoint

Device- and procedure-
rela
24 v

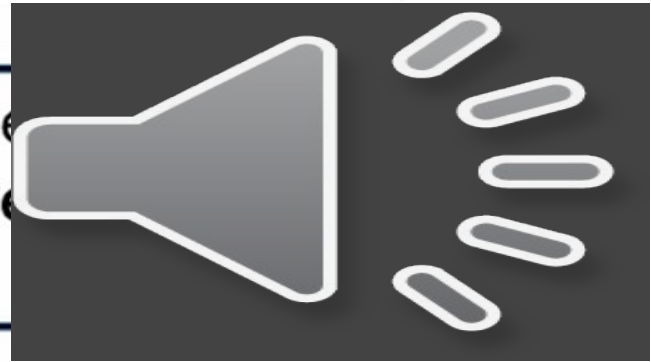
CCM-HFpEF Pilot Study: results

KCCQ overall summary score

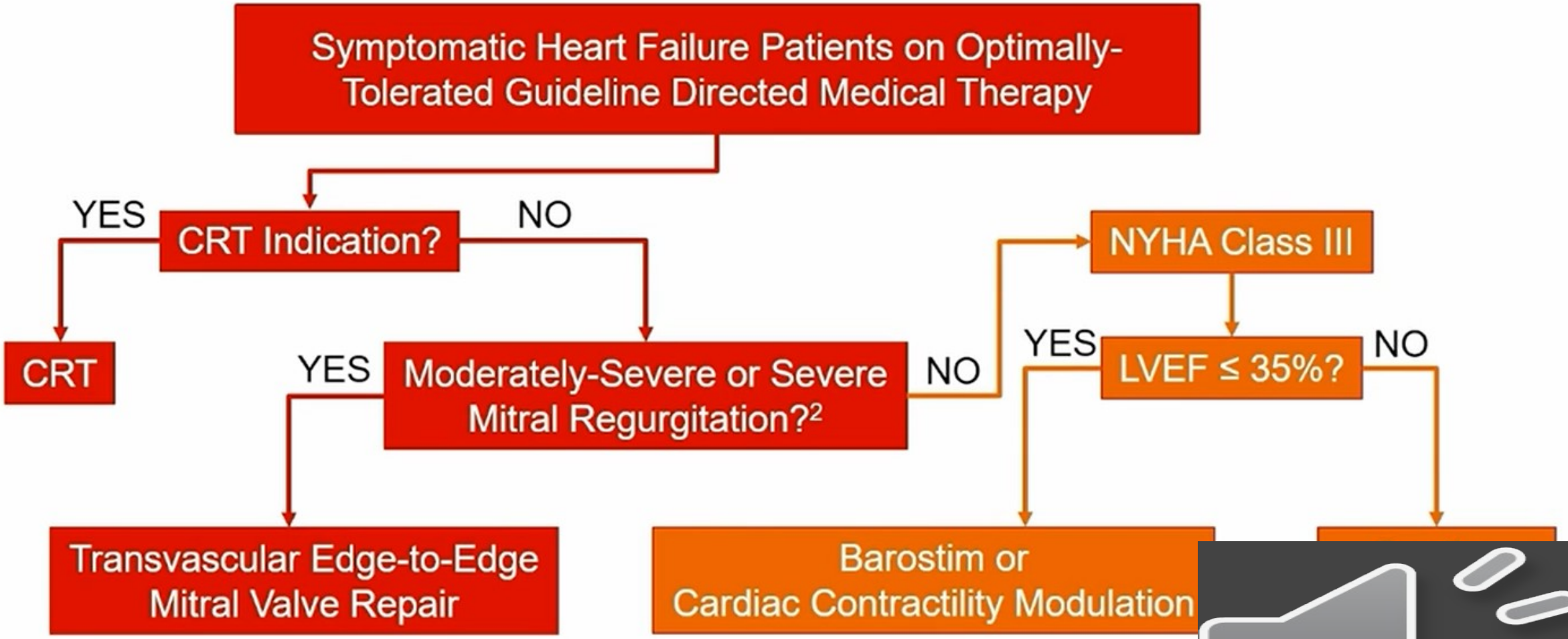
Baseline	12 weeks	BL-12wks (95% CI)	24 weeks	BL-24wks (95% CI)	T-test
48.9 ± 21.7	63.6 ± 21.2	14.5 ± 18.6 (9.0, 20.1)	67.0 ± 21.1	**18.0 ± 16.6 (13.1, 22.9)**	<0.001

Trial (year)	KCCQ change in sham	KCCQ change in treatment	Incremental difference over/under mean
MADIT-CRT (2012)	4.6 (ICD arm)	7.0 (CRT-D arm)	+2.4

Even assuming a **4.6-point placebo effect** improvement, the improvement would still be a greater than **13 point improve** between groups



Available Device Therapies for Heart Failure:
Who Should Be Considered for These Therapies?[1]



[1]Along with an ICD as indicated per guidelines; [2]And LVEF 20%-50%; [3]LVEF 36%-45%