XII Meeting. State of the Art in

HEART FAILURE

CLINICAL PRACTICE AND ORGANIZATIONAL MODELS

Venue: Hotel Meliá María Pita, A Coruña

A Coruña 26-27 September 2025

A Coruña Heart Failure Academy

#ACORUÑAHF2025

Cardiac contractility modulation in heart failure. Mechanism of action and clinical data.

David Couto Mallón. MD, PhD || Complexo Hospitalario Universitario A Coruña. CIBERCV

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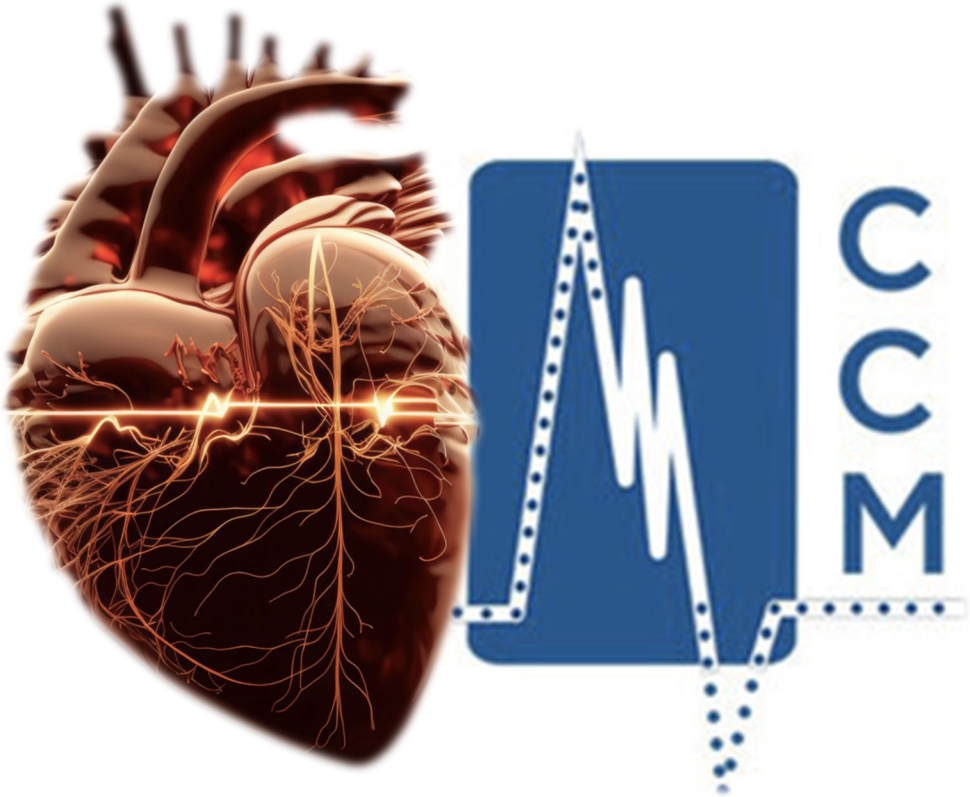
I have no financial disclosures regarding to this presentation

Cardiac contractility modulation (CCM) in HF

Agenda



- What is CCM?
- Mechanisms of action of CCM
- Results derived from clinical studies
- Patient selection for CCM therapy
- Future directions

What is cardiac contractility modulation?

Cardiac contractility modulation (CCM) is an electrical device-based therapy for symptomatic HF patients and no indication for CRT (narrow QRS)

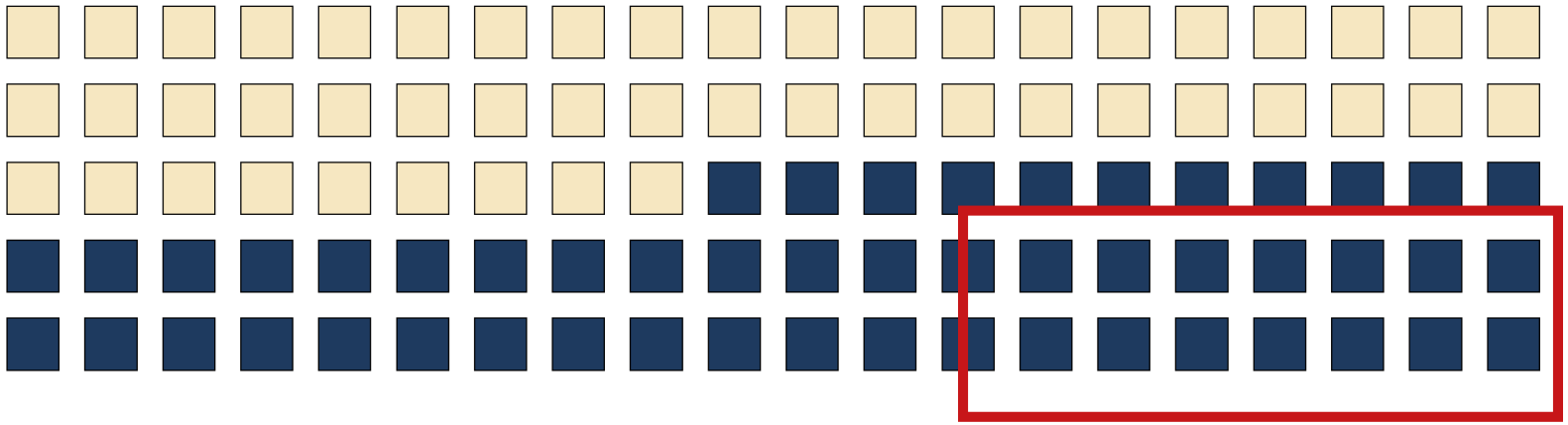
New answer for unresolved needs

HF population

HFpEF

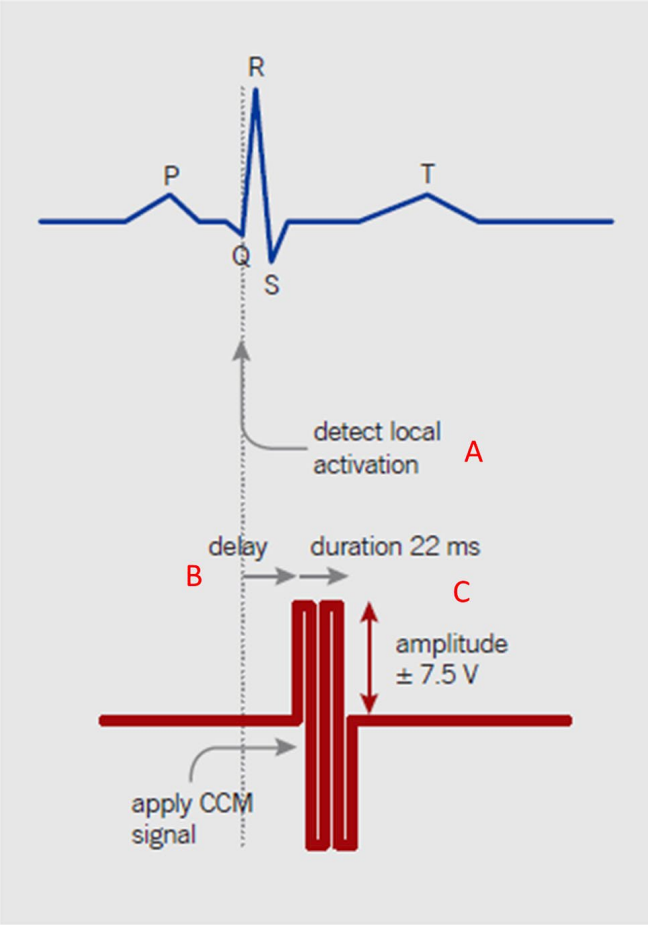
HFrEF

≈ 70% HFrEF patients who remained symptomatic despite GDMT may benefit from this technology



≈ 30% meet criteria for CTR

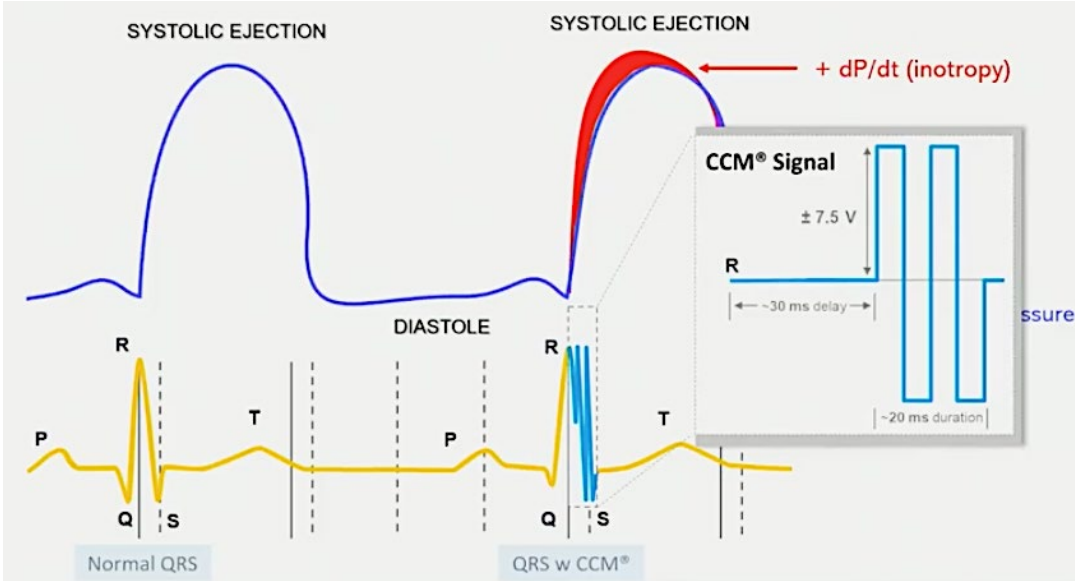
What is cardiac contractility modulation?



Electrical CCM signals are biphasic and high voltage **non-excitatory** electrical signals applied during the **cardiac absolute refractory period.**

Electrical stimulation during refractory period modulates cardiac contractility.

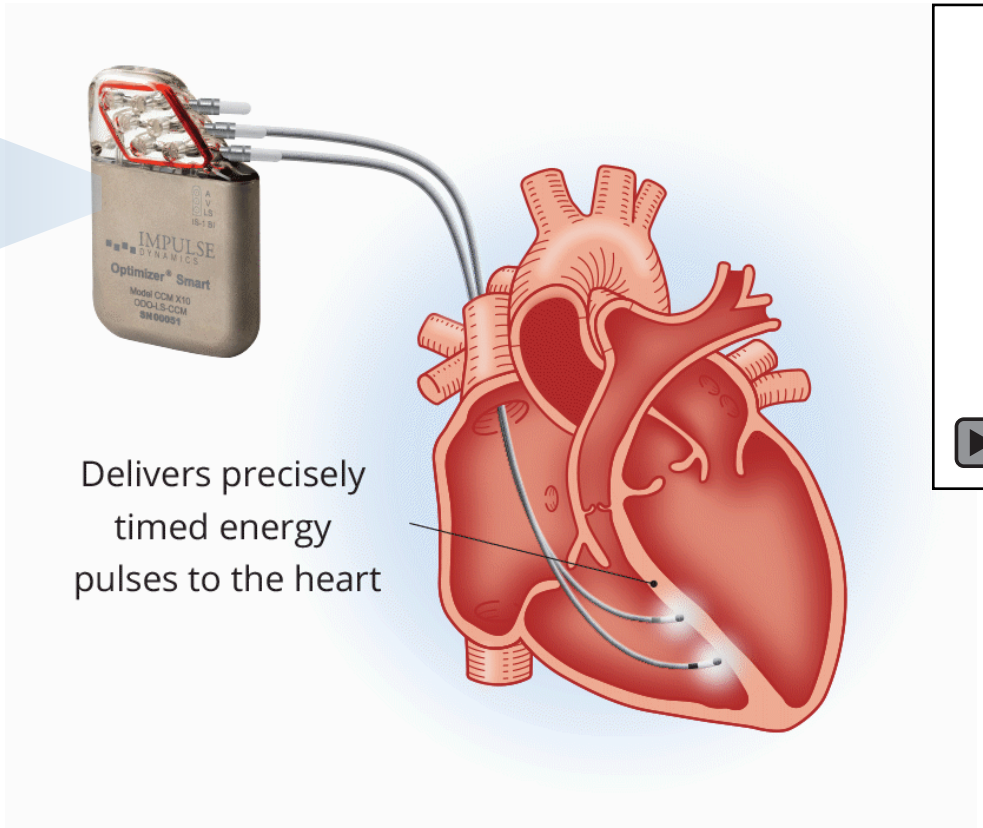
Cardiac cycle and CCM

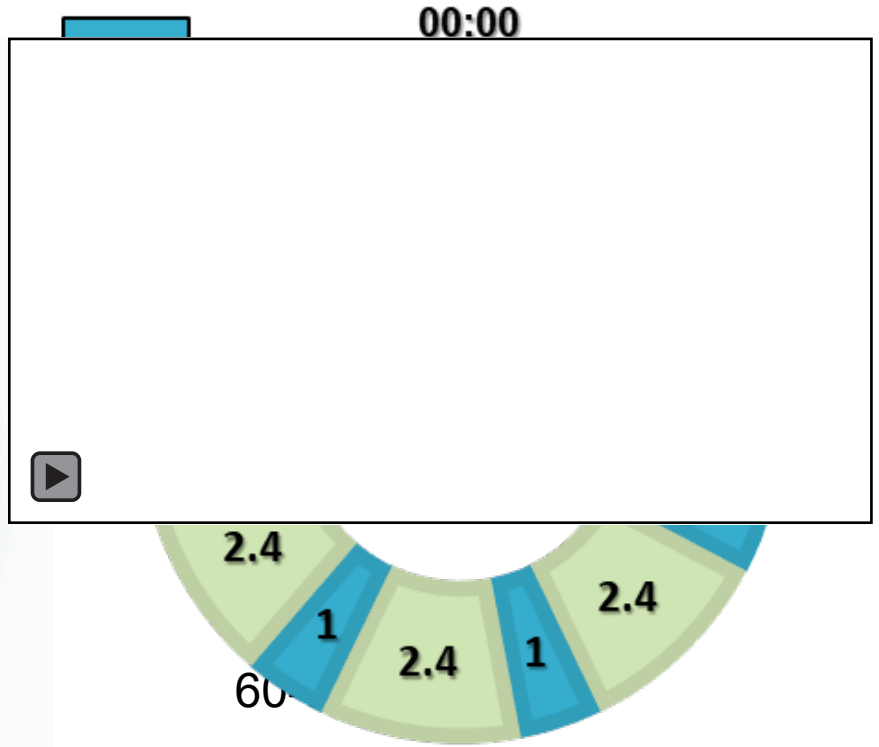


What is cardiac contractility modulation?

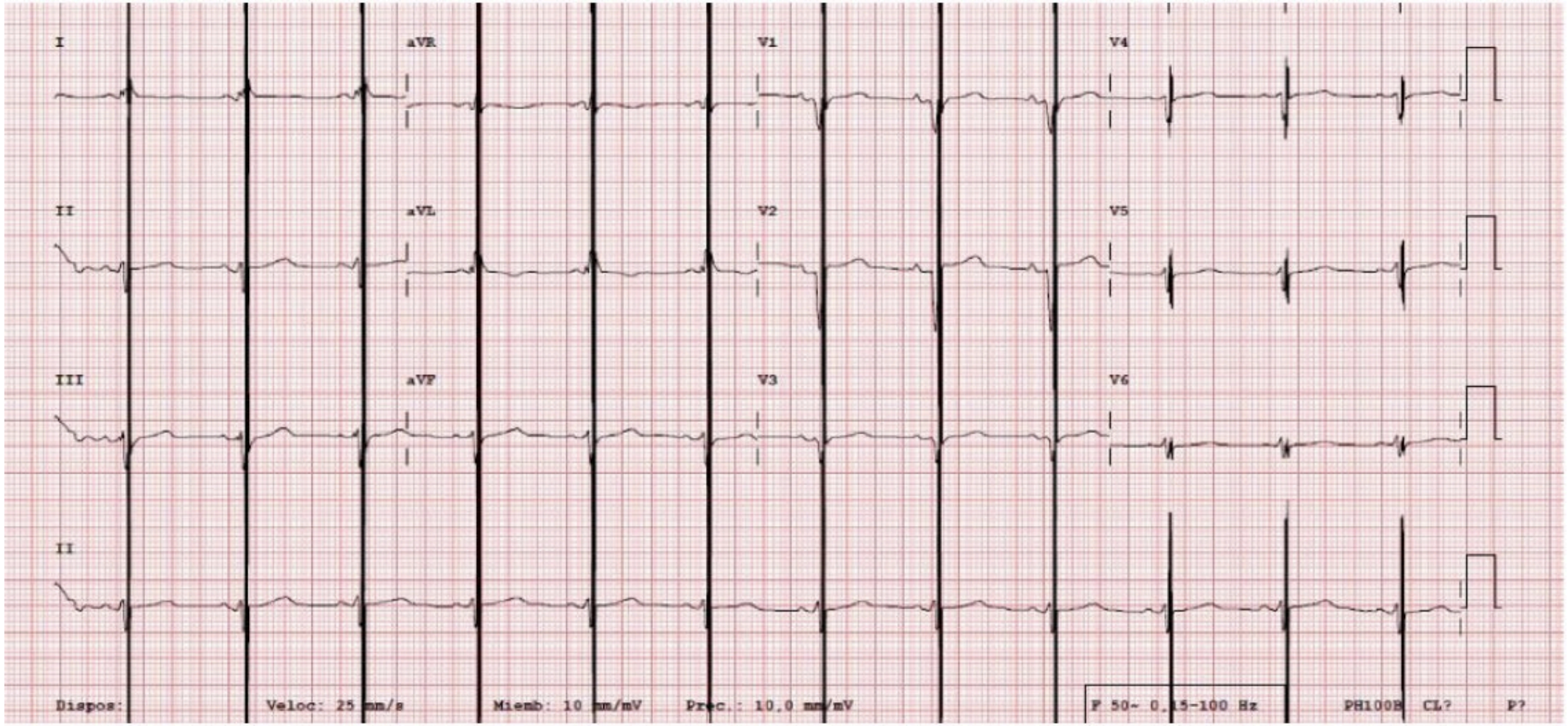
CCM signals are delivered to the heart from an implanted pulse generator through two ventricular leads: one for sensing timing of local electrical activation and other for delivering CCM signals *

Rechargeable battery
20 years of duration





What is cardiac contractility modulation?



Cardiac contractility modulation: mechanisms of action

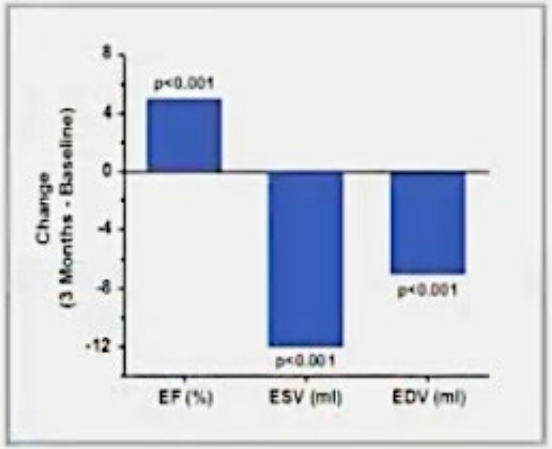
Improvement in contractility (minutes-hours)

Rapid, local effect on septal wall

Biochemical and gene profile normalization (hours-weeks)

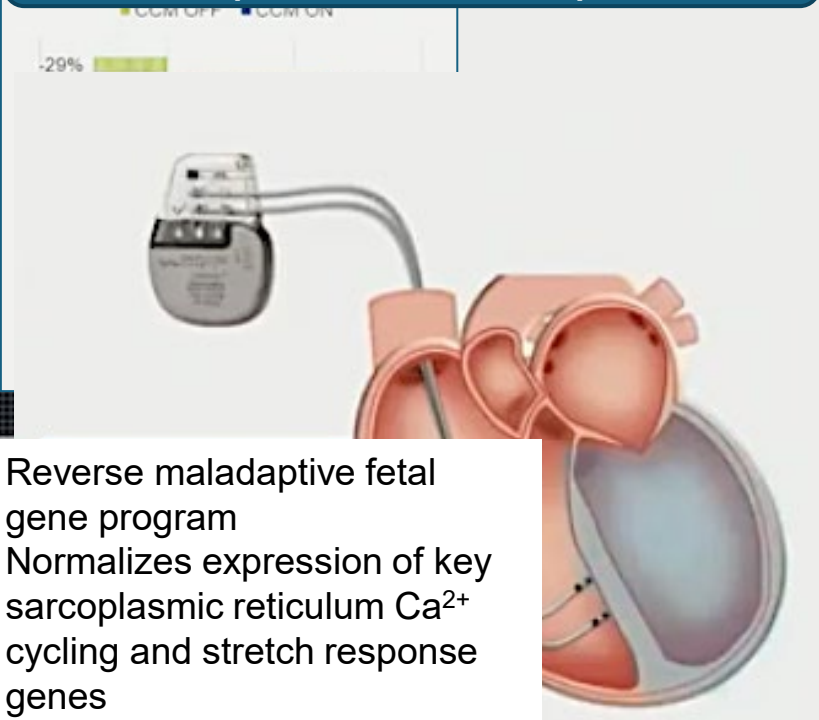
- Intracellular Ca^{2+} metabolism

- Normalization of matrix metalloproteinases
- ↓ replacement and interstitial fibrosis.
- ↑ LV systolic reserve



J Am Coll Cardiol Img 2009;2:1341–9

Reverse remodeling (weeks-months)



- Reverse maladaptive fetal gene program
- Normalizes expression of key sarcoplasmic reticulum Ca^{2+} cycling and stretch response genes
- ↑ Phosphorilation of PLB, myofilaments (TnI, MBP) and titin.
- ↓ Sympathetic nerve activity

J Heart Fail 2019;21: 14-22

Cardiac contractility modulation: clinical evidence

Journal of Cardiovascular Electrophysiology
THE OFFICIAL JOURNAL OF THE WORLD SOCIETY OF ARRHYTHMIAS

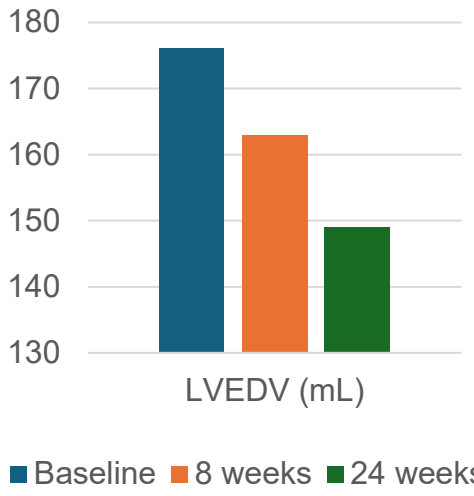
First Human Chronic Experience with Cardiac Contractility Modulation by Nonexcitatory Electrical Currents for Treating Systolic Heart Failure:

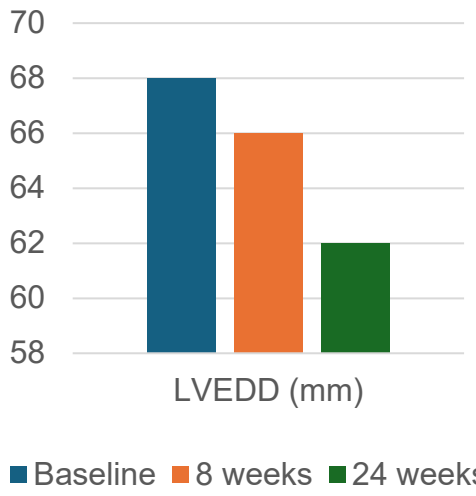
Mid-Term Safety and Efficacy Results from a Multicenter Study

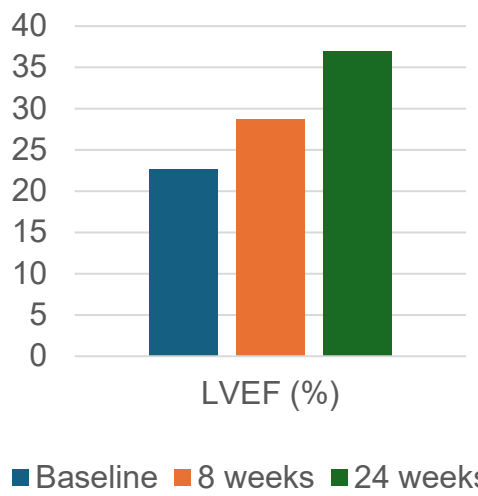
CARLO PAPPONE M.D., Ph.D., GIUSEPPE AUGELLO M.D., SALVATORE ROSANIO M.D., Ph.D., GABRIELE VICEDOMINI M.D., VINCENZO SANTINELLI M.D., MASSIMO ROMANO M.D. ... See all authors

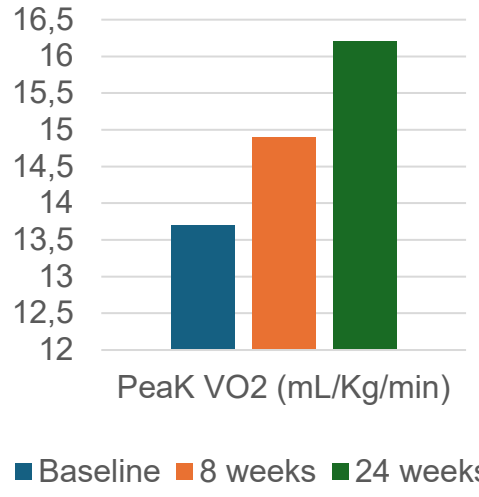
First published: 13 April 2004 | https://doi.org/10.1046/j.1540-8167.2004.03580.x | Citations: 75

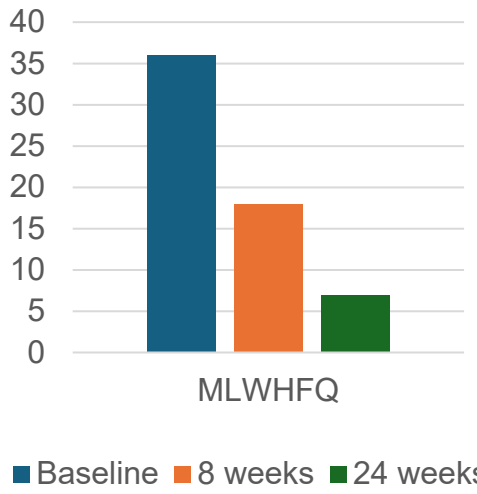
Compared with the period previous to inclusion 54% absolute risk reduction for HF hospitalization and WHF





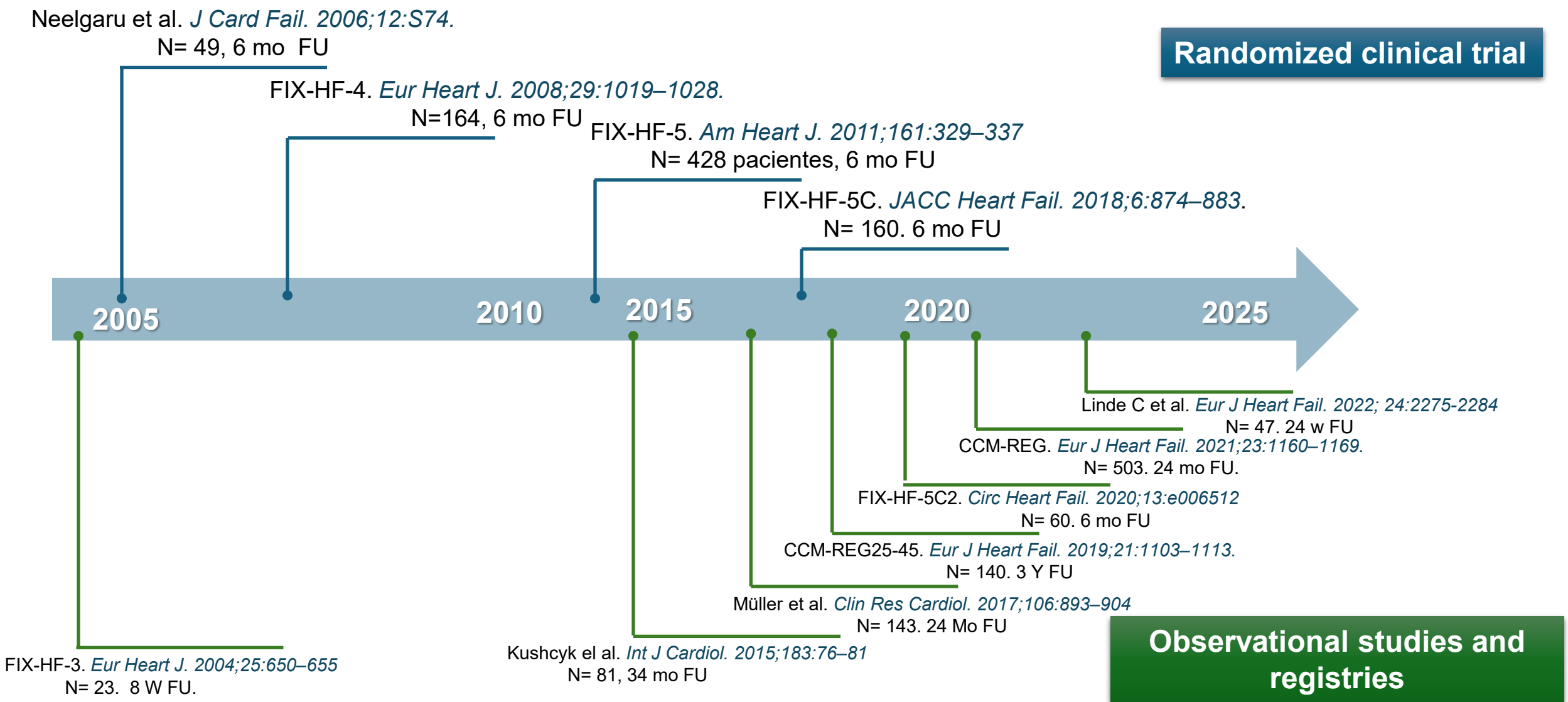






J Cardiovasc Electrophysiol 2004; 15, . 418-427

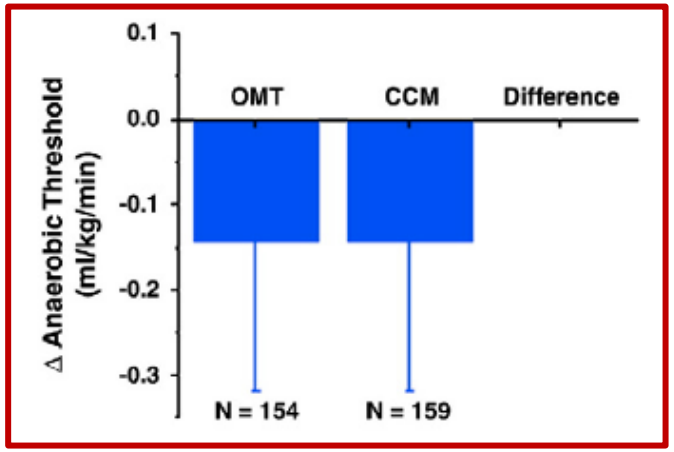
Cardiac contractility modulation: clinical evidence



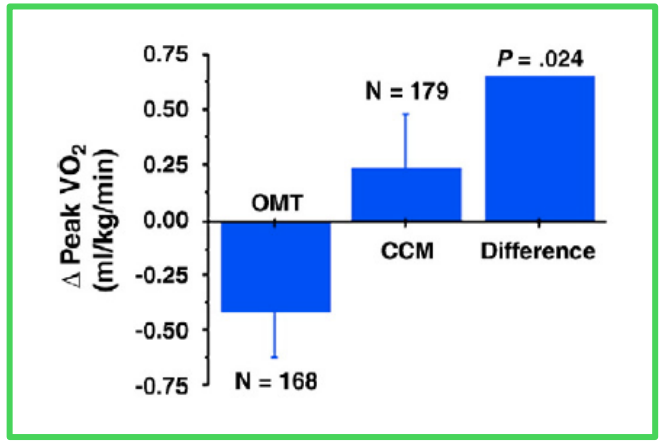
Cardiac contractility modulation: clinical evidence

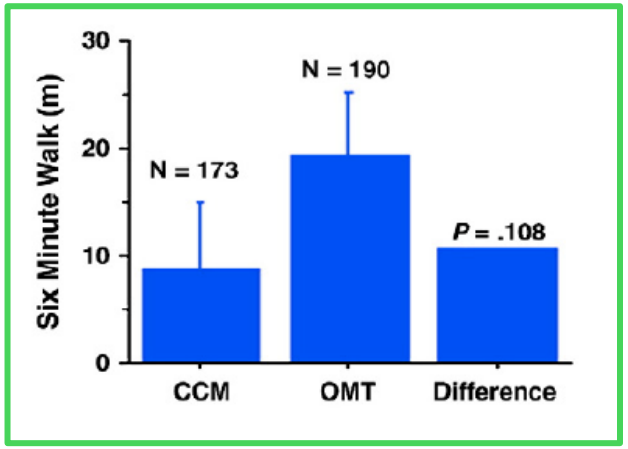
A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure

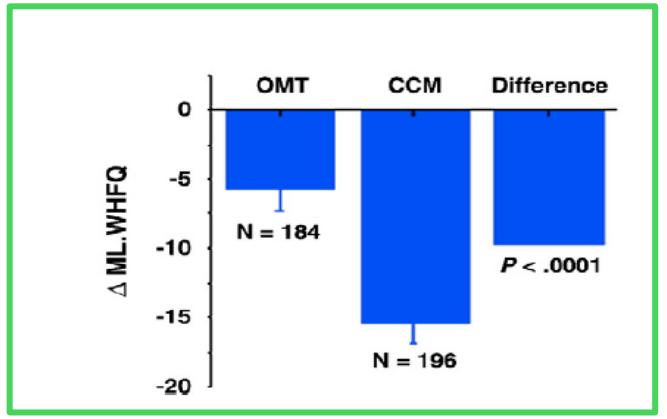
FIX-HF-5 trial
- 428 patients 6 months
- NYHA III-VI
- QRS < 130 mseg and LVEF <35%

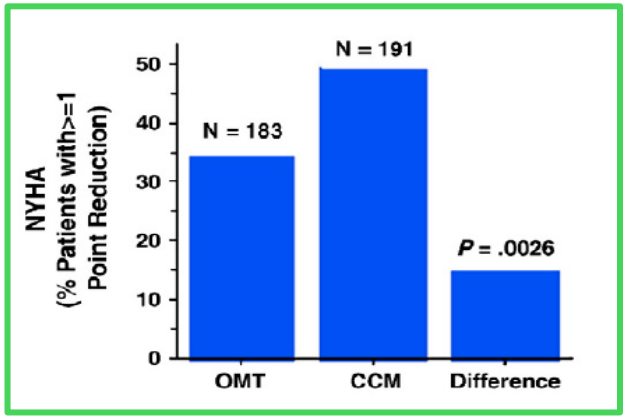


Patients with LVEF ≥ 25% and NYHA III benefit the most from CCM therapy







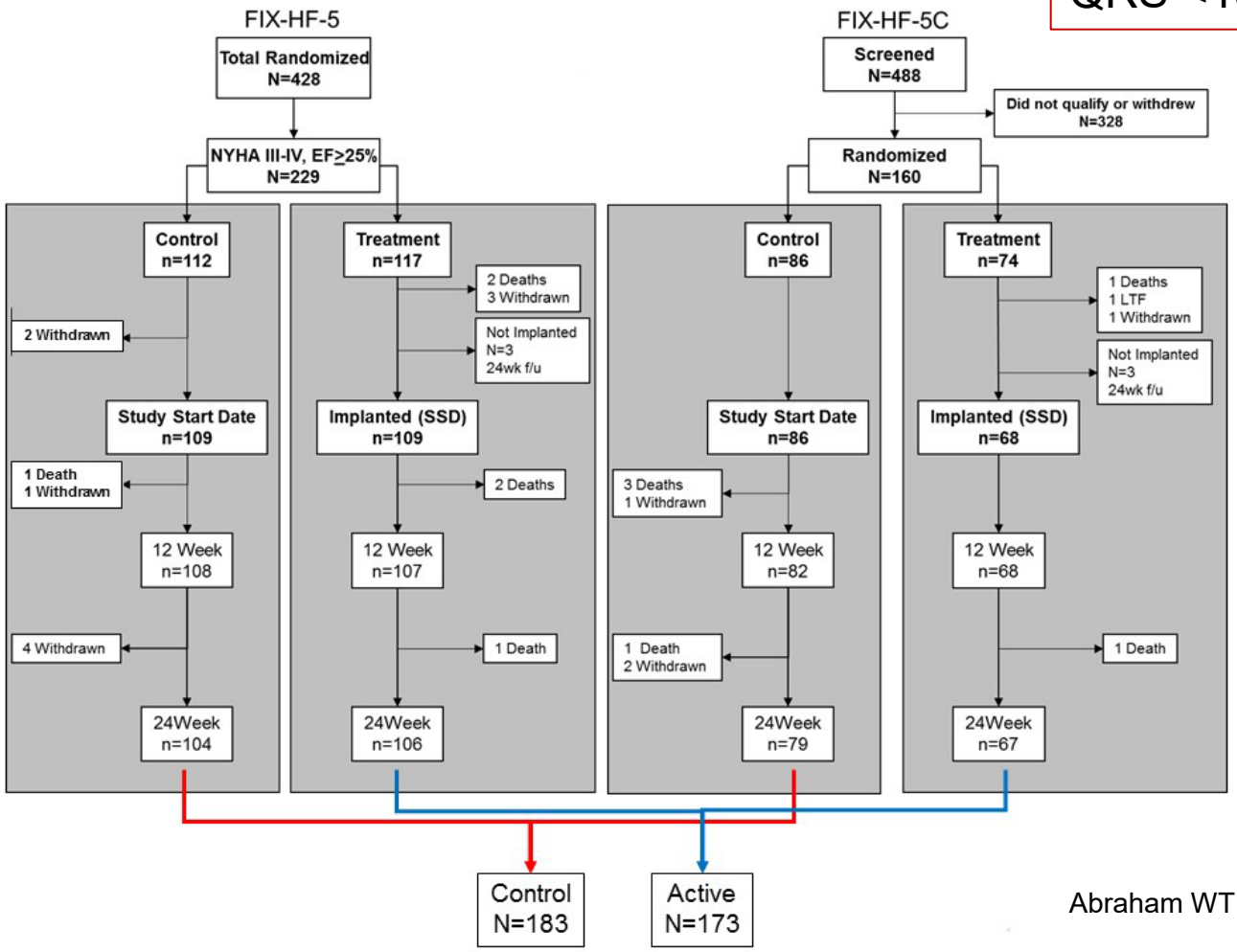


Kadish A et a. Am Heart J. 2011;161:329–337

Cardiac contractility modulation: clinical evidence

FIX-HF-5 ➡ FIX-HF-5C

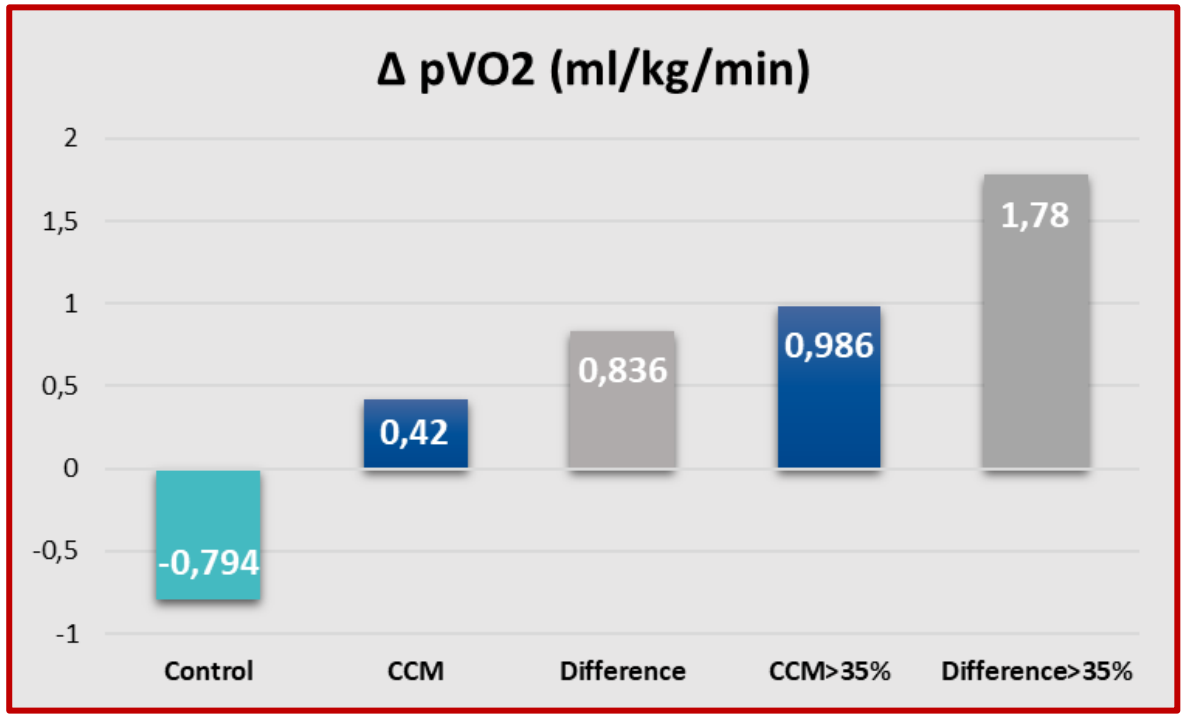
160 patients. ≥ 25% LVEF ≤ 45%
NYHA III-IV.
QRS <130 mseg



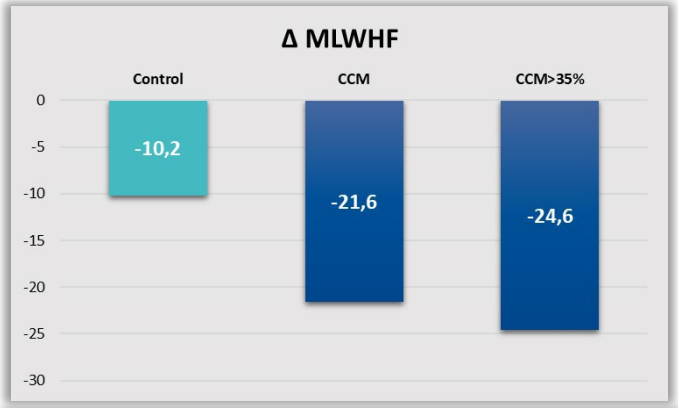
Abraham WT et al JACC Heart Fail. 2018;6:874–883

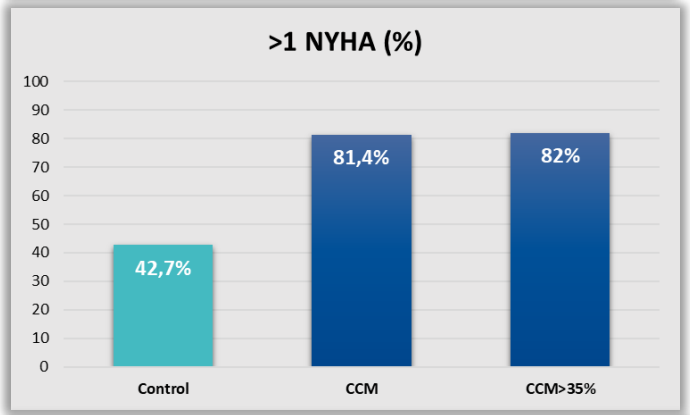
Cardiac contractility modulation: clinical evidence

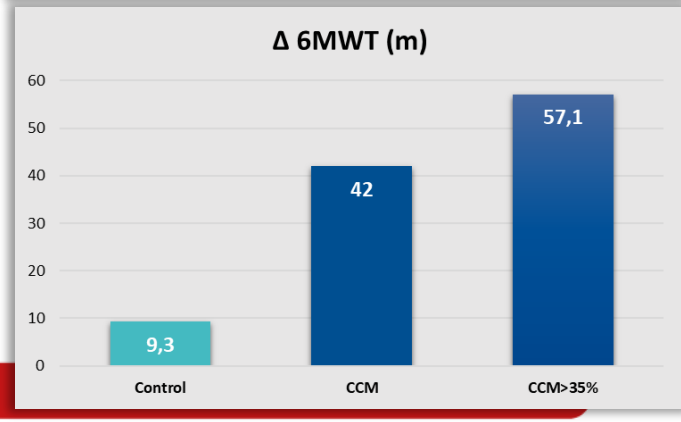
FIX-HF-5C Trial



Significant improvement for NYHAIII patients
Greater effect on LVEF > 35%



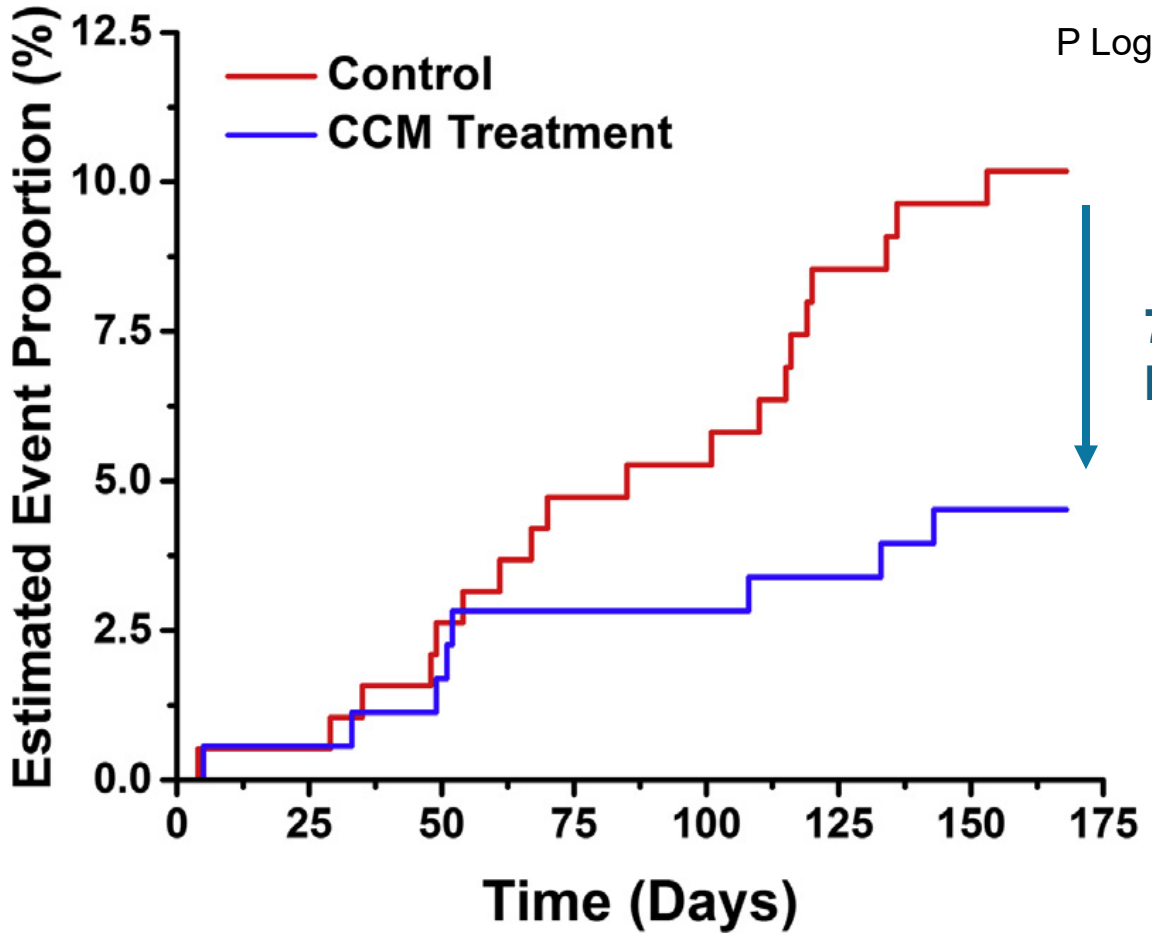




Abraham WT et al JACC Heart Fail. 2018;6:874–883

Cardiac contractility modulation: clinical evidence

Exploratory analysis of composite cardiac death and HF hospitalization
N= 371



P Log Rank= 0.0042

73% lower rate of death or HF hospitalization

Abraham WT et al JACC Heart Fail. 2018;6:874–883

Cardiac contractility modulation: clinical evidence

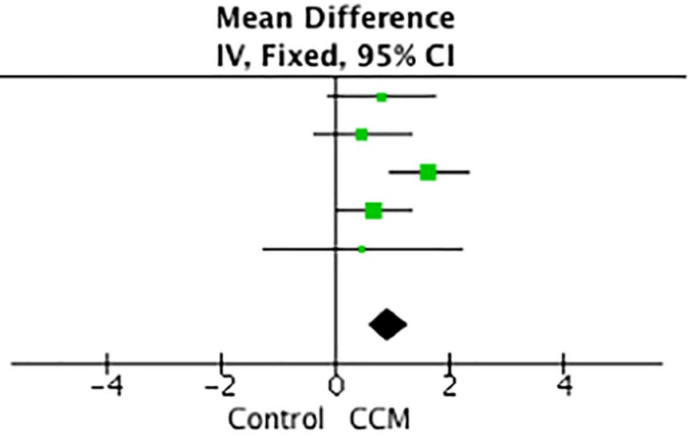
Meta-analysis of randomized controlled clinical trials. N= 861

Peak VO_2 (mL/Kg/min)

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	0.39	3.47	84	-0.44	2.59	80	15.5%	0.83 [-0.10, 1.76]
FIX-CHF-5C	-0.026	2.74	66	-0.504	2.36	71	18.3%	0.48 [-0.38, 1.34]
FIX-CHF-5C2	1.12	1.49	52	-0.504	2.36	71	29.0%	1.62 [0.94, 2.31]
FIX-HF-5	0.28	3.16	176	-0.4	2.91	167	32.7%	0.68 [0.04, 1.32]
FIX-HF-5 Pilot (24 weeks)	-0.96	2.6	23	-1.43	3.01	19	4.6%	0.47 [-1.25, 2.19]
Total (95% CI)			**401**			**408**	**100.0%**	**0.93 [0.56, 1.30]**

Heterogeneity: $Chi^2 = 5.94$, $df = 4$ ($P = 0.20$); $I^2 = 33\%$

Test for overall effect: $Z = 4.96$ ($P < 0.00001$)

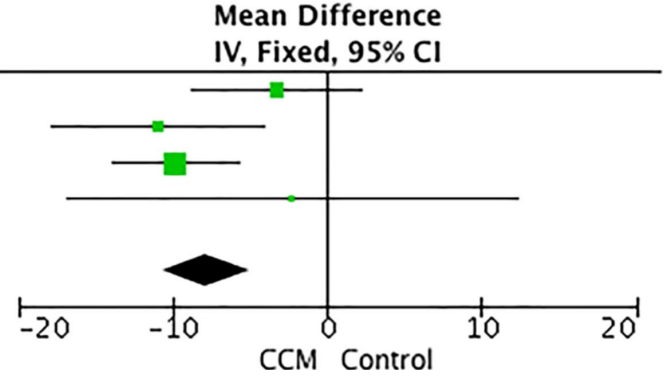


MLWHFQ

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	-10.07	16.73	84	-6.78	18.41	78	28.7%	-3.29 [-8.72, 2.14]
FIX-CHF-5C	-21.2	23.7	70	-10.2	18.5	78	17.7%	-11.00 [-17.91, -4.09]
FIX-HF-5	-15.56	19.15	180	-5.76	21.24	188	49.6%	-9.80 [-13.93, -5.67]
FIX-HF-5 Pilot (24 weeks)	-18.29	23.47	24	-15.96	27.87	24	4.0%	-2.33 [-16.91, 12.25]
Total (95% CI)			**358**			**368**	**100.0%**	**-7.85 [-10.76, -4.94]**

Heterogeneity: $Chi^2 = 4.92$, $df = 3$ ($P = 0.18$); $I^2 = 39\%$

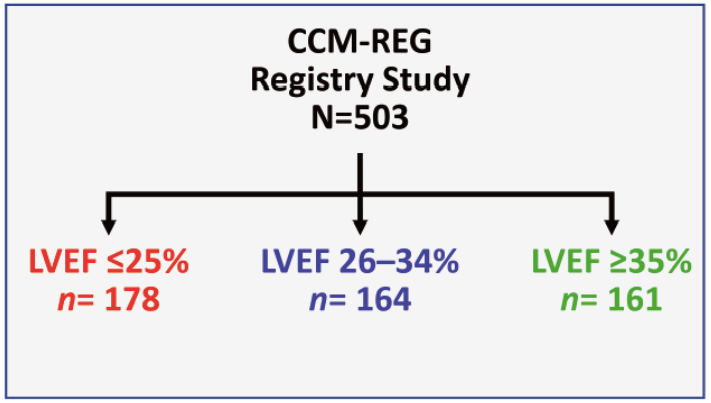
Test for overall effect: $Z = 5.29$ ($P < 0.00001$)

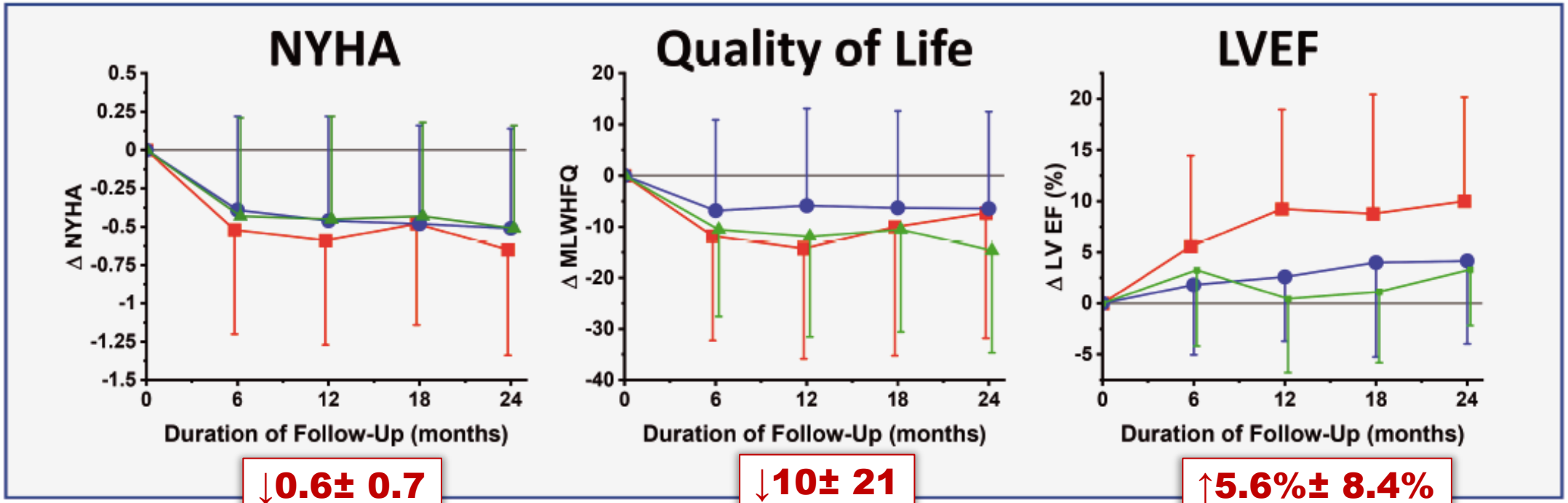


Giallauria F et al. ESC Heart Fail 2020; 7: 2922–2932

Cardiac contractility modulation: clinical evidence

Real world data: CCM-REG Registry





↓0.6± 0.7

↓10± 21

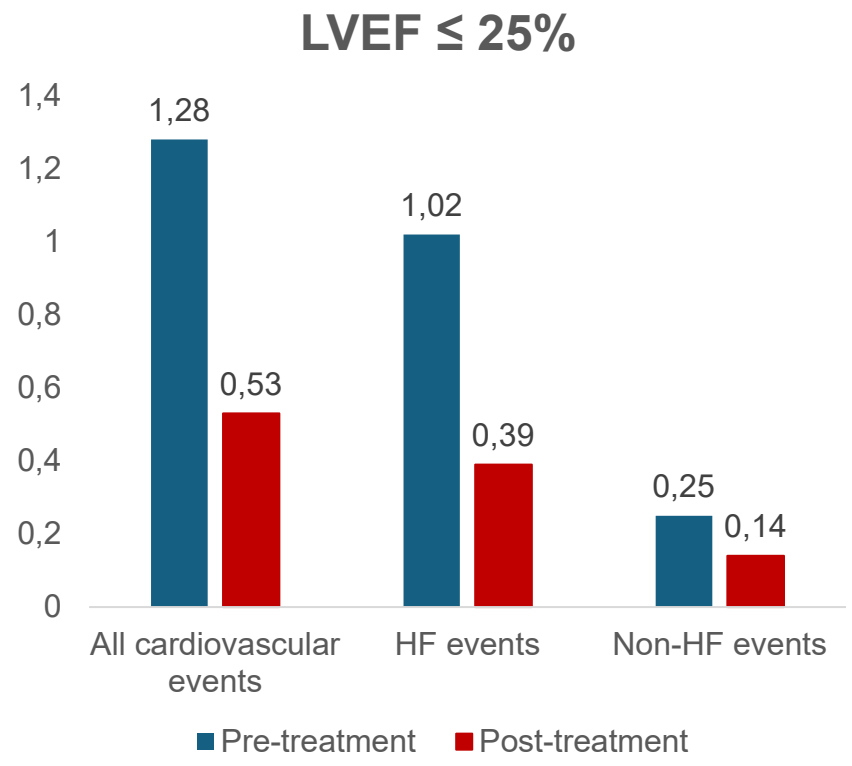
↑5.6%± 8.4%

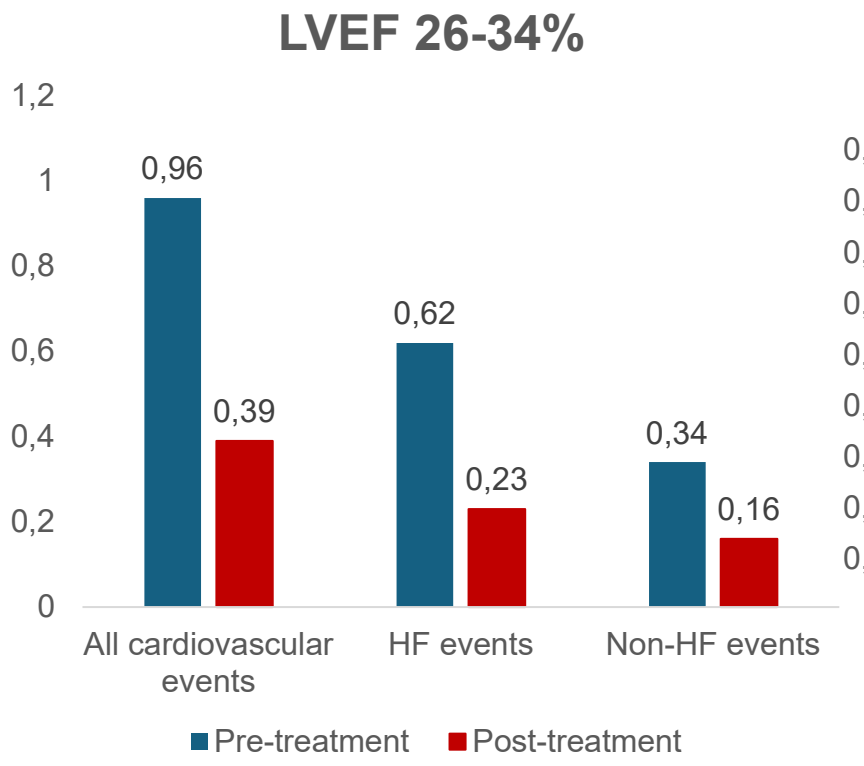
Kuschyk J et al. Eur J Heart Fail. 2021;23:1160–1169

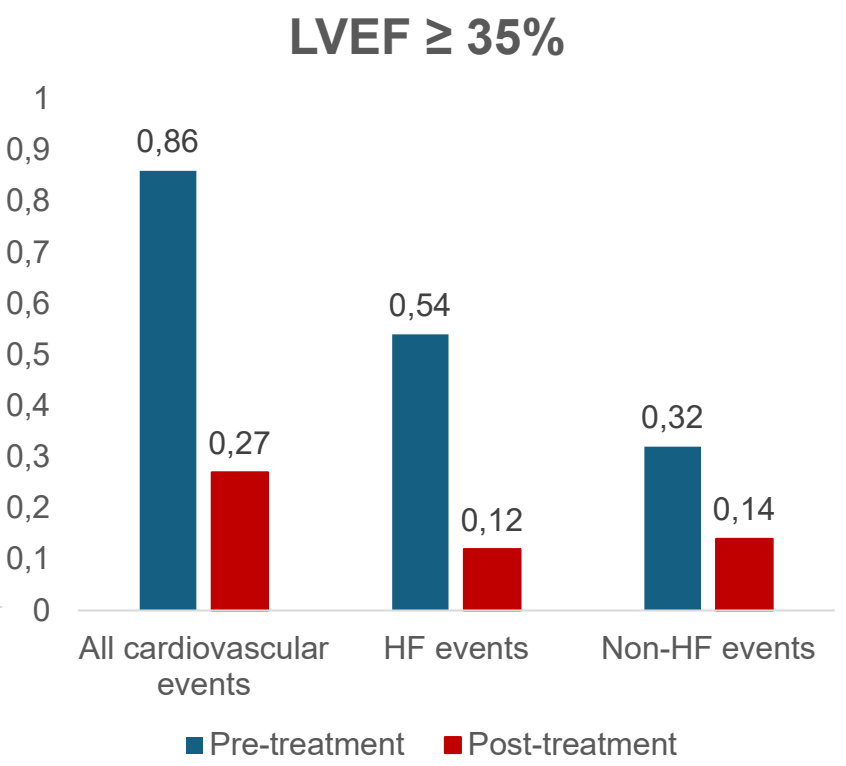
Cardiac contractility modulation: clinical evidence

Real world data: CCM-REG Registry

Incidence rate of events (cardiovascular, HF and non-HF events)*







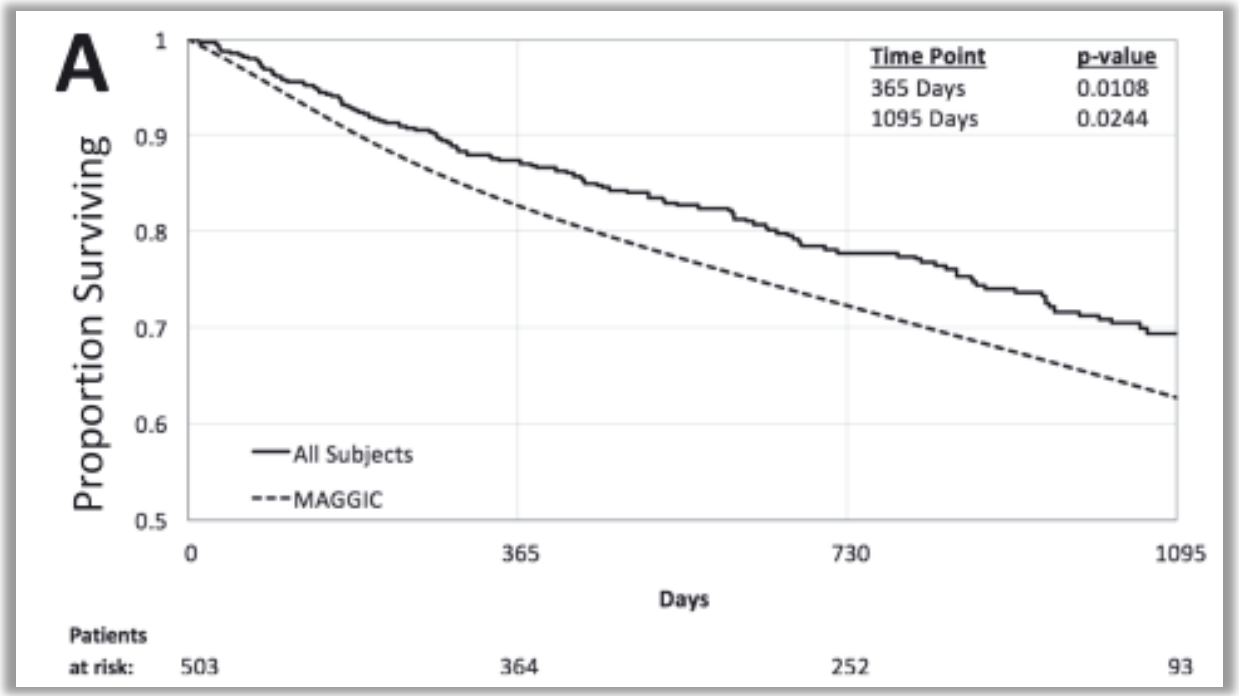
** All differences were statistically significant*

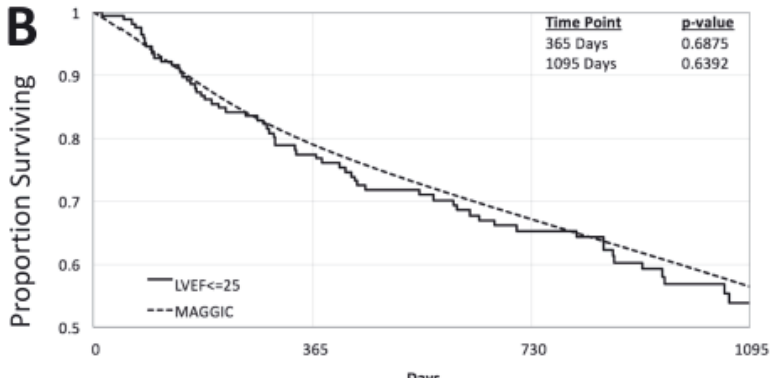
Kuschyk J et al. Eur J Heart Fail. 2021;23:1160–1169

Cardiac contractility modulation: clinical evidence

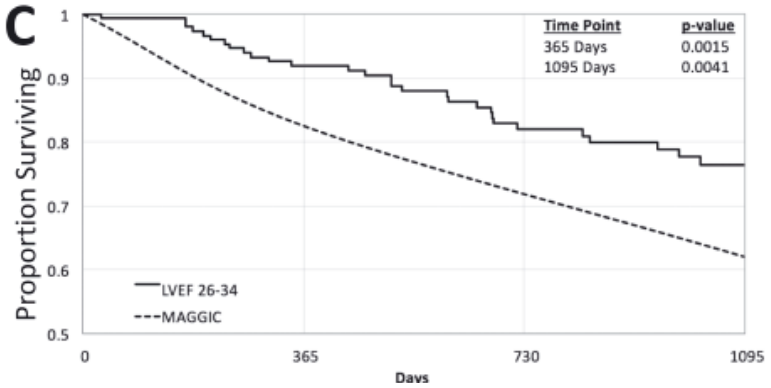
Real world data: CCM-REG Registry

Observed survival vs. **predicted** survival for the MAGGIC risk score

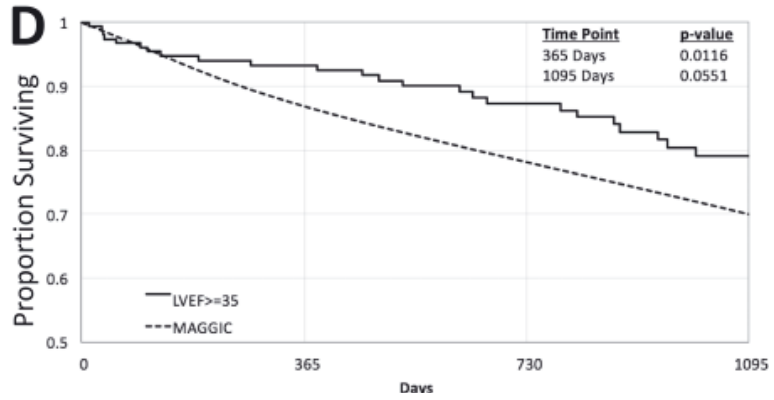




LVEF ≤ 25%



LVEF 26-34%



LVEF ≥ 35%

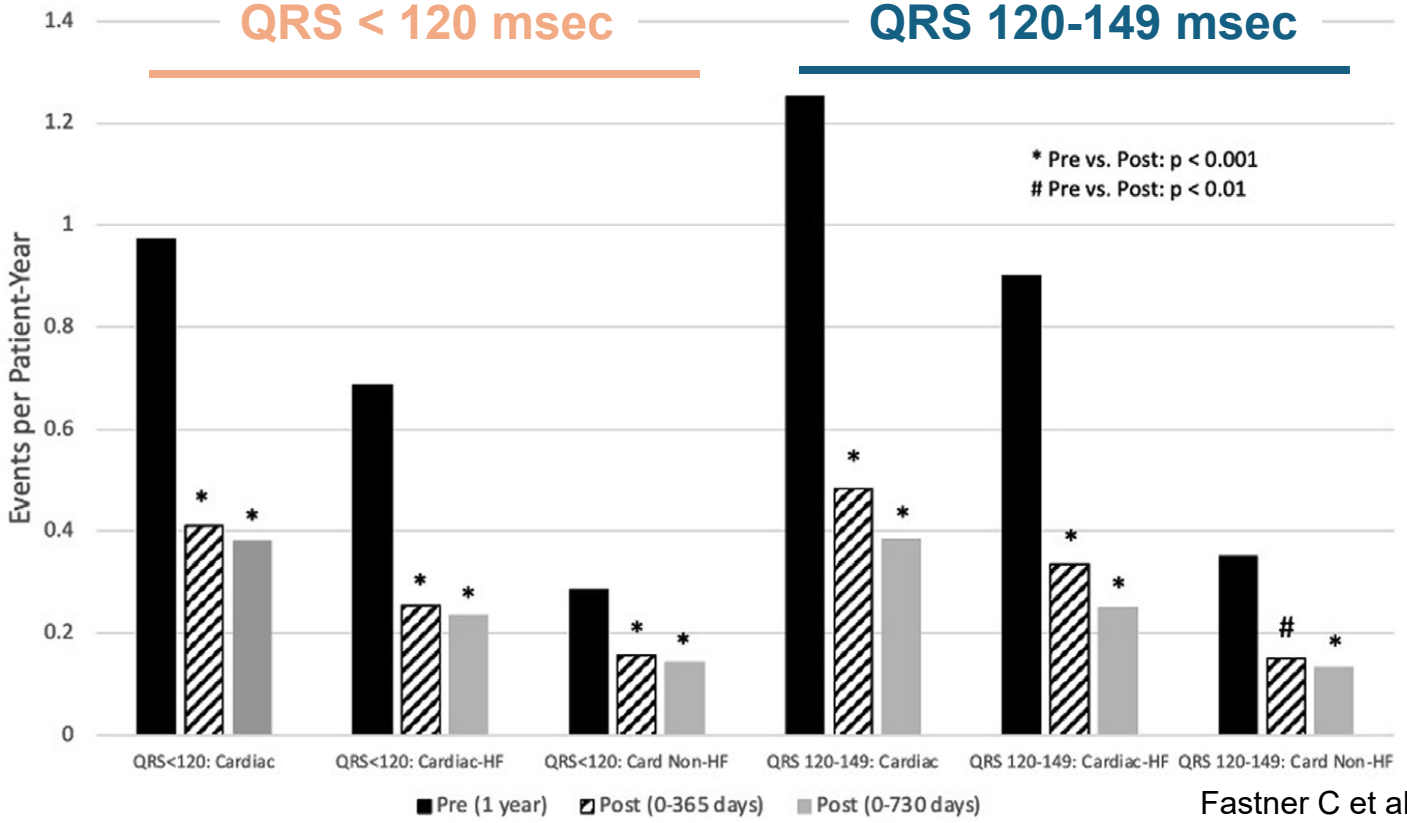
Kuschyk J et al. Eur J Heart Fail. 2021;23:1160–1169

Cardiac contractility modulation: clinical evidence

Real world data: CCM-REG Registry

CCM effect was maintained in patients with **intermediate QRS duration** (120-149 msec)

Total cardiac, HF related and cardiac non-HF related hospitalization event rates

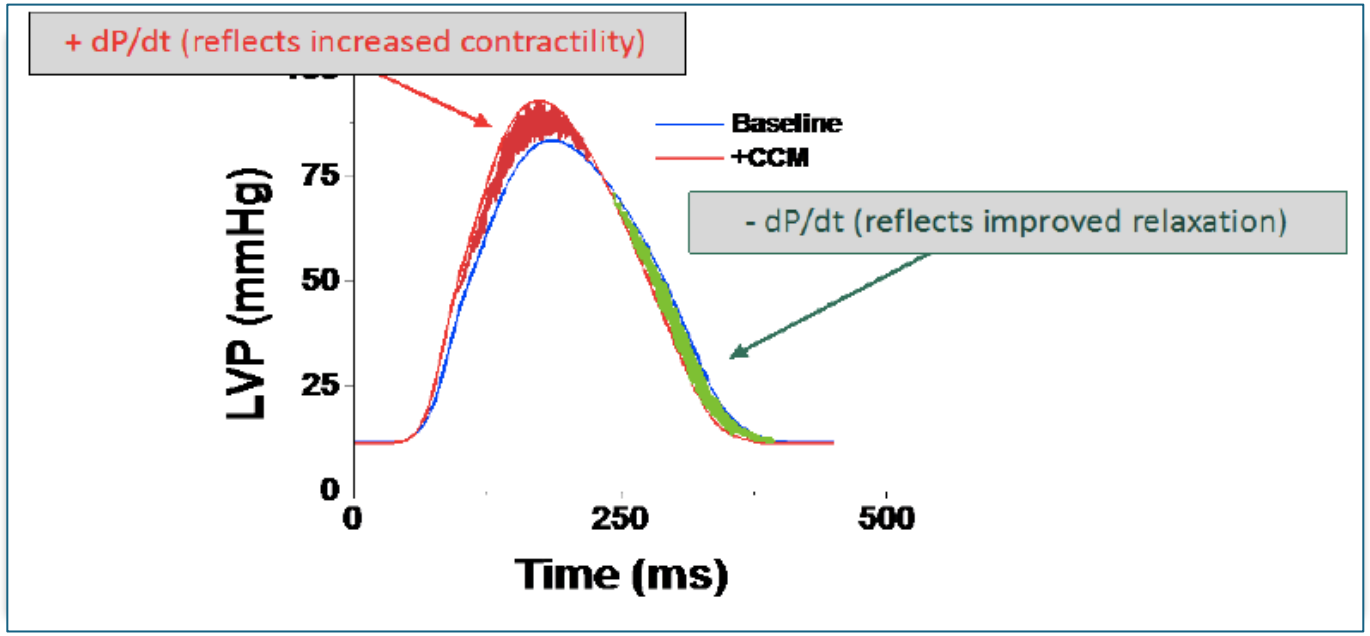


Fastner C et al. Heart Rhythm 2025; 22:1756-1762

Cardiac contractility modulation: clinical evidence

May be CCM therapy useful beyond HFrEF?

RCT and registries showed a **greater effect** with **higher EF**



From FIX-HF-5

Calcium metabolism

- Phosphorylation of PLB → ↓SERCA2a inhibition→ ↑intracelular Ca^{2+} reuptake → ↑ **lusitropism**

Myofilaments

- ↑ PKA and PKG titin phosphorilation → ↑ **titin compliance** and **recoil**
- ↑ Binding of HSP27/αB-crystallin to titin → ↓ titin aggregation → ↓ **stiffness**

Extracellular matrix

- Normalization of metalloproteinases
- ↓ **fibrosis** and collagen depostion

Mohri S et al. Am J Physiol Heart Circ Physiol 2003;284:H1119-23

Tschöpe K et al. Eur J Heart Fail 2019; 21: 14–22
Talha KM et al. J Cardiac Fail 2022;28:17171726

Cardiac contractility modulation: clinical evidence

CCM-HFpEF pilot study

AIM

To assess the benefits of CCM therapy on safety and health status in patients with HFpEF

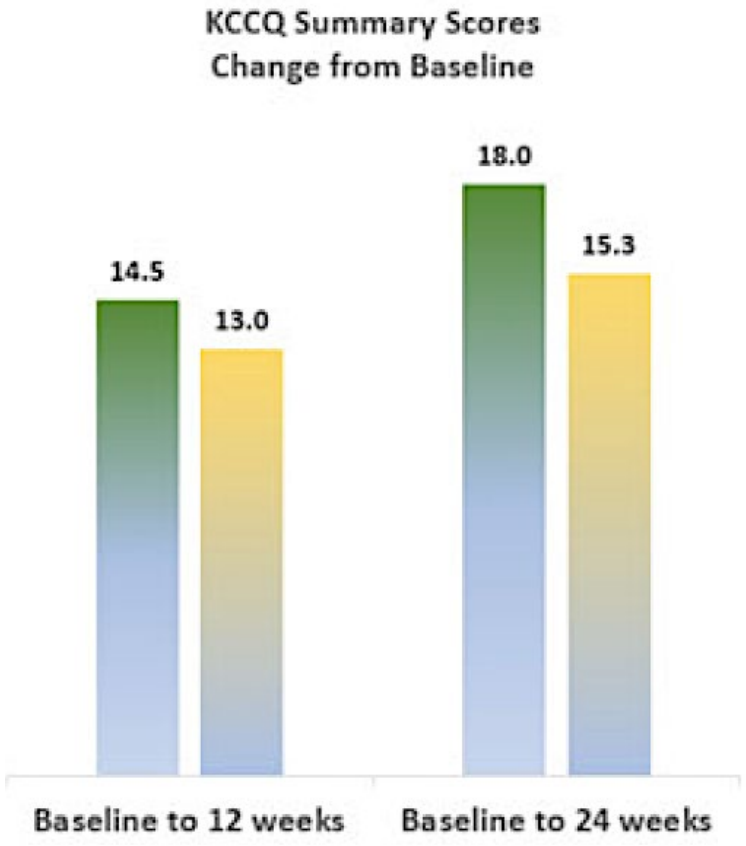
METHODS

47 HFpEF patients implanted with CCM

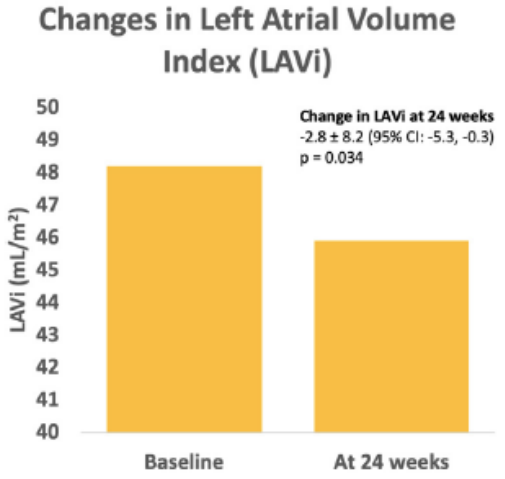
17 centres in EU and Australia

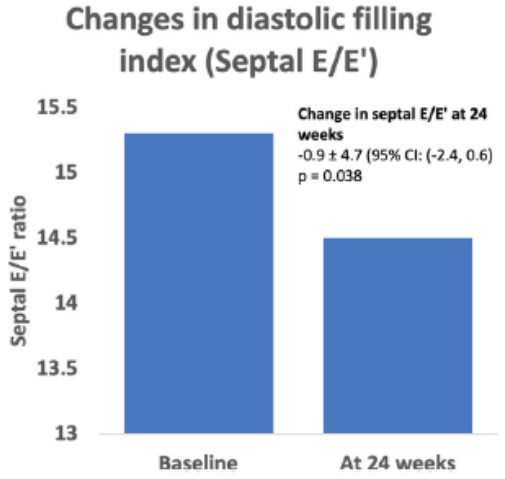
LVEF ≥ 50% per Core Lab

Health status (KCCQ) and safety



P-value for change from baseline – 24 weeks <0.001 for both KCCQ TSS and CSS

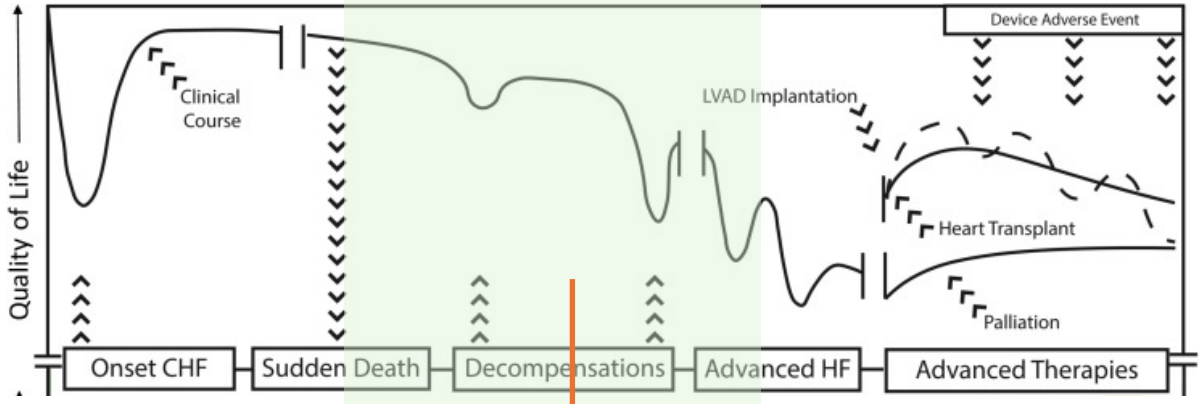




Linde C et al. Eur J Heart Fail 2022;24:2275-2284

Cardiac contractility modulation: patient selection

Beta-blockers
ACEi/ARB/ARNi
ARM
SLGT2 inhibitors
Vericiguat



Exclude CRT

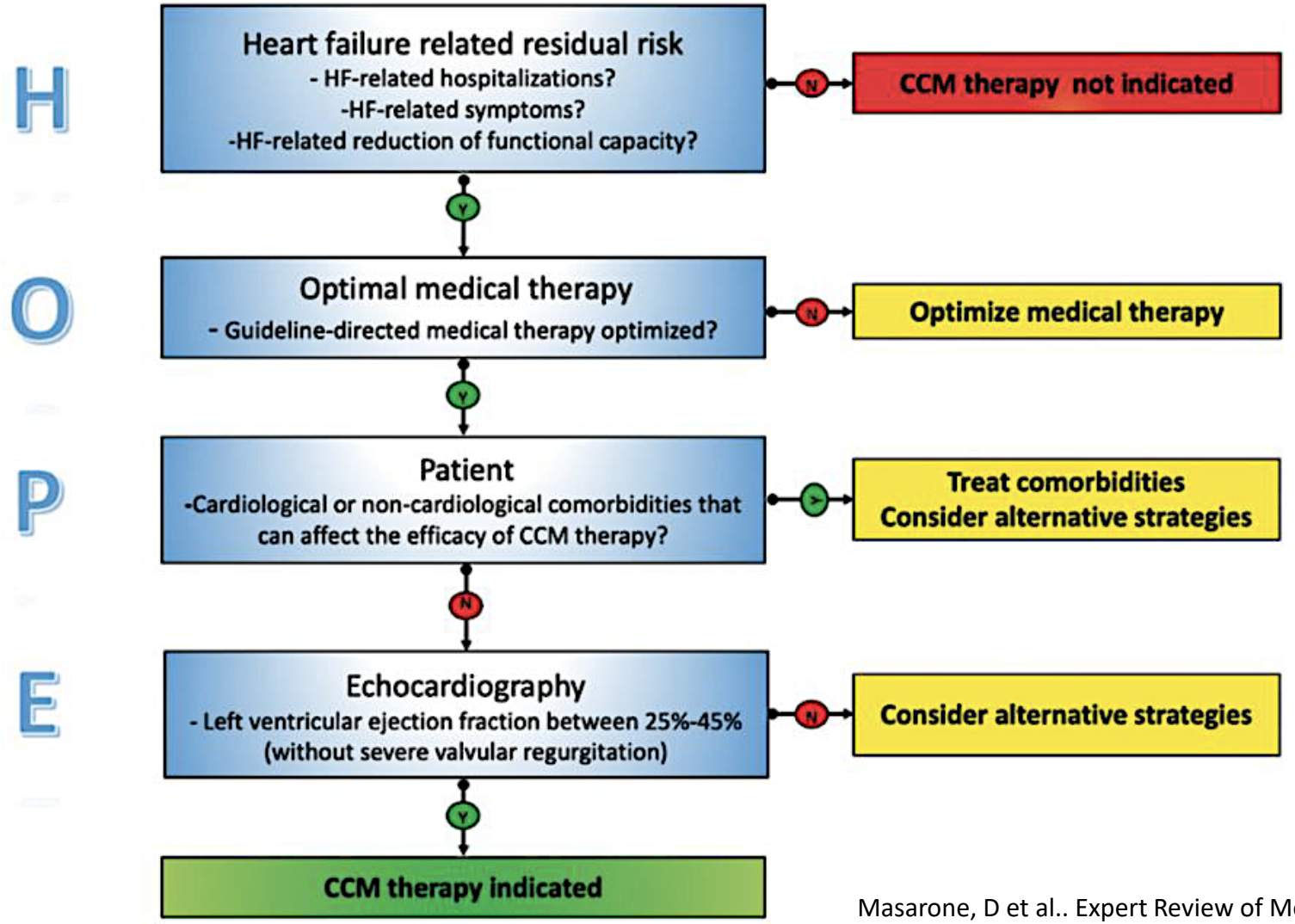
Window for intervention

HF patients candidates for CCM therapy

- Stable NYHA class III despite optimal GDMT
- LVEF 25-45%. Specially recommended for LVEF 35%-45%[1].
- No pacemaker dependent and QRS < 130 msec[2].
- No candidates for CRT.
- Low ventricular arrhythmias burden (less tan 8000 VE/24 hours).
- No severe concomitant valve disease (except secondary mitral regurgitation)

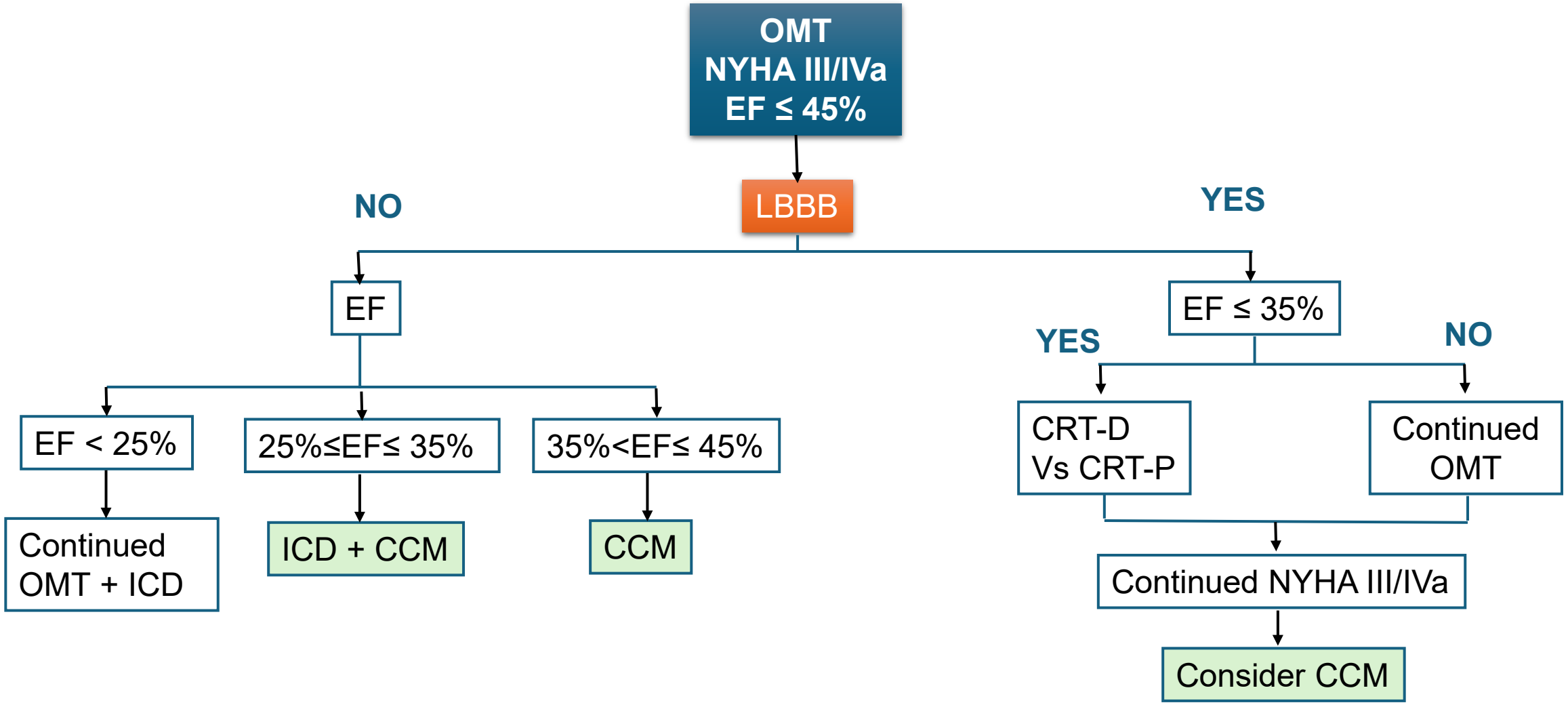
1. CCM is approved in Europe for HFpEF patients
2. QRS may be > 130 msec if patient is not candidate for CRT

Cardiac contractility modulation: patient selection



Masarone, D et al.. Expert Review of Medical Devices 2023; 20, 525–528

Cardiac contractility modulation: patient selection



Borggrefe M et al. Circulation. 2018;138:2738–2740

Cardiac contractility modulation: future directions

INTEGRA–D Trial

Combining CCM® with ICD Therapy- Safety & Efficacy Trial

Study Objective

Evaluate the safety and efficacy of a combined Cardiac Contractility Modulation (CCM) therapy and Internal Cardioverter-Defibrillator (ICD) device.

Key Inclusion/Exclusion Criteria

- LVEF ≤ 40%
- Symptomatic HF (NYHA Class II-IV)
- On GDMT ≥ 90-days
- Class I indication for ICD
- Not indicated for CRT-D or PPM

Study Design

Prospective, multi-center, non-randomized, single arm open label study of 300 subjects

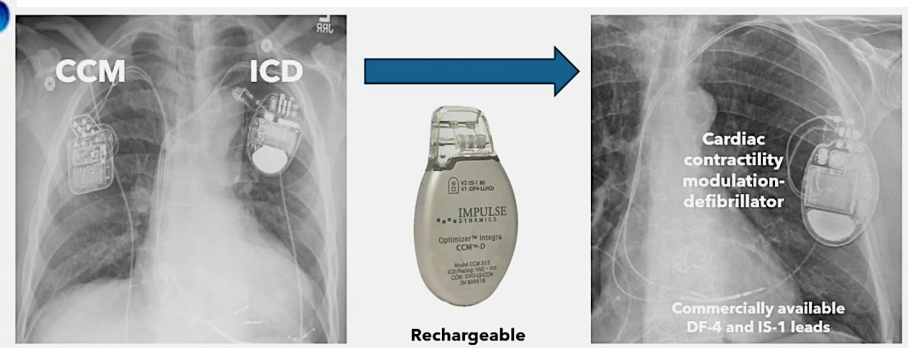
Primary Efficacy Endpoint

Rate of successful Defibrillation Efficacy (DE) testing on the first 100 subjects implanted

Safety Endpoints

Device-related complication and inappropriate shock-free rate at 6-months post implant

INTEGRA-D



Cardiac contractility modulation: future directions

Study Objective

Evaluate the safety and efficacy of Cardiac contractility Modulation (CCM) therapy in patients w/ **symptomatic HF with LVEF 40-70%** (inclusive)

Study Design

Multicenter, **randomized, quadruple-blind, sham** controlled, 2-part, embedded IDE clinical trial with **1500 subjects** at 150-200 US sites

Part I: Primary Efficacy Endpoint

(n=450)

- Change in 6MWD from baseline to 6 months
- Change in KCCQ CSS from baseline to 6 months

Part II: Primary Efficacy Endpoint

(n=1500)

- Hierarchical composite of:
  CV mortality, HF hospitalizations, urgent HF visits requiring IV therapy through 18 months
- KCCQ CSS through 12 months

Safety Endpoint

Freedom from Optimizer device or procedure-related serious adverse events through 12 months

Take home messages

- CCM improves both systolic and diastolic function and promotes reverse remodeling in HF patients.
- In chronic HF, CCM therapy improves symptoms, exercise capacity and quality of life.
- Patients with LVEF ≥ 35% and functional class NYHA III benefit the most from CCM therapy.
- Larger randomized controlled trials are needed for assessing impact of CCM in survival and HF hospitalizations.

Thank you