PLACE
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE
ROMA 2026

La CCM come opzione terapeutica il registro PREDICT

26 GIUGNO 2026

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Disclosure

Speaker honoraria (modest) from:

- ***Abbott***
- ***Biotronik***
- ***Boston Scientific***
- ***Medtronic***
- ***MicroPort***

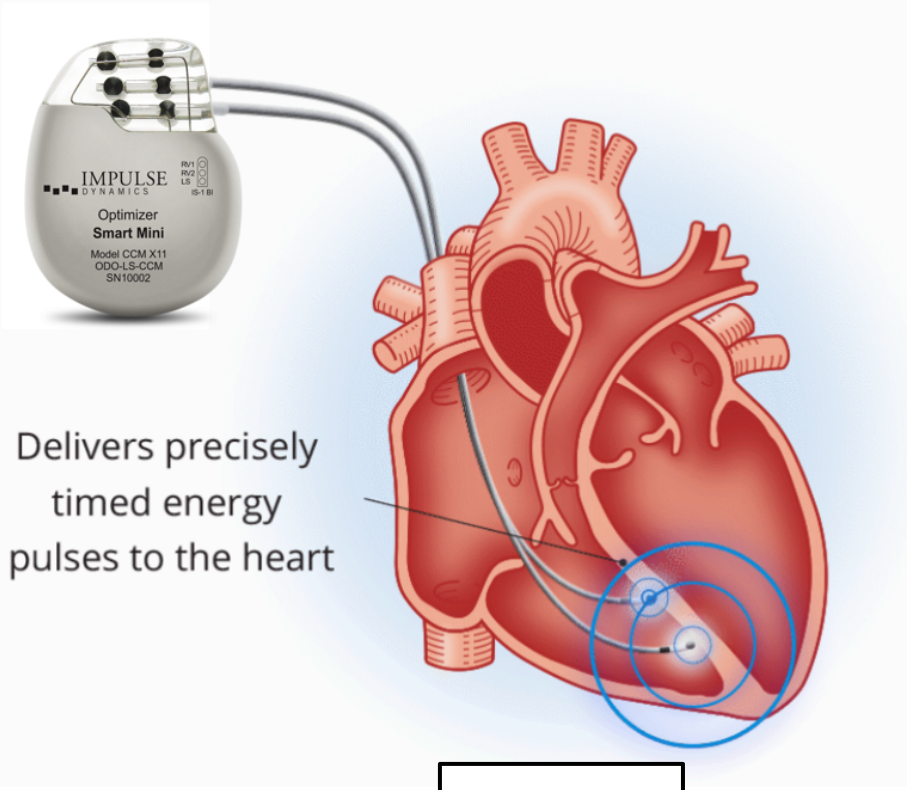
AGENDA

- CARDIAC CONTRACTILITY MODULATION (CCM)
- THE NEED OF PREDICTORS IN PATIENTS SELECTION
- THE ROLE OF CONTRACTILE RESERVE
- THE PREDICT-CCM STUDY

DISCLOSURES

Francesco Zanon reports (modest) speaker fees from Abbott, Biotronik, Boston Scientific, Medtronic, and Microport.

Cardiac Contractility Modulation (CCM)



OPTIMIZER

- Non-excitatory pulse – delivered during ventricular absolute refractory period (~ 30 ms delay)
- Bifasic
- Pulse Width 20 ms (at least)
- Programmable Amplitude, 4 to 7.5 V
- Max sync rate: 110bpm
- Rechargeable device
- 20 years longevity

CCM – Mechanism of action

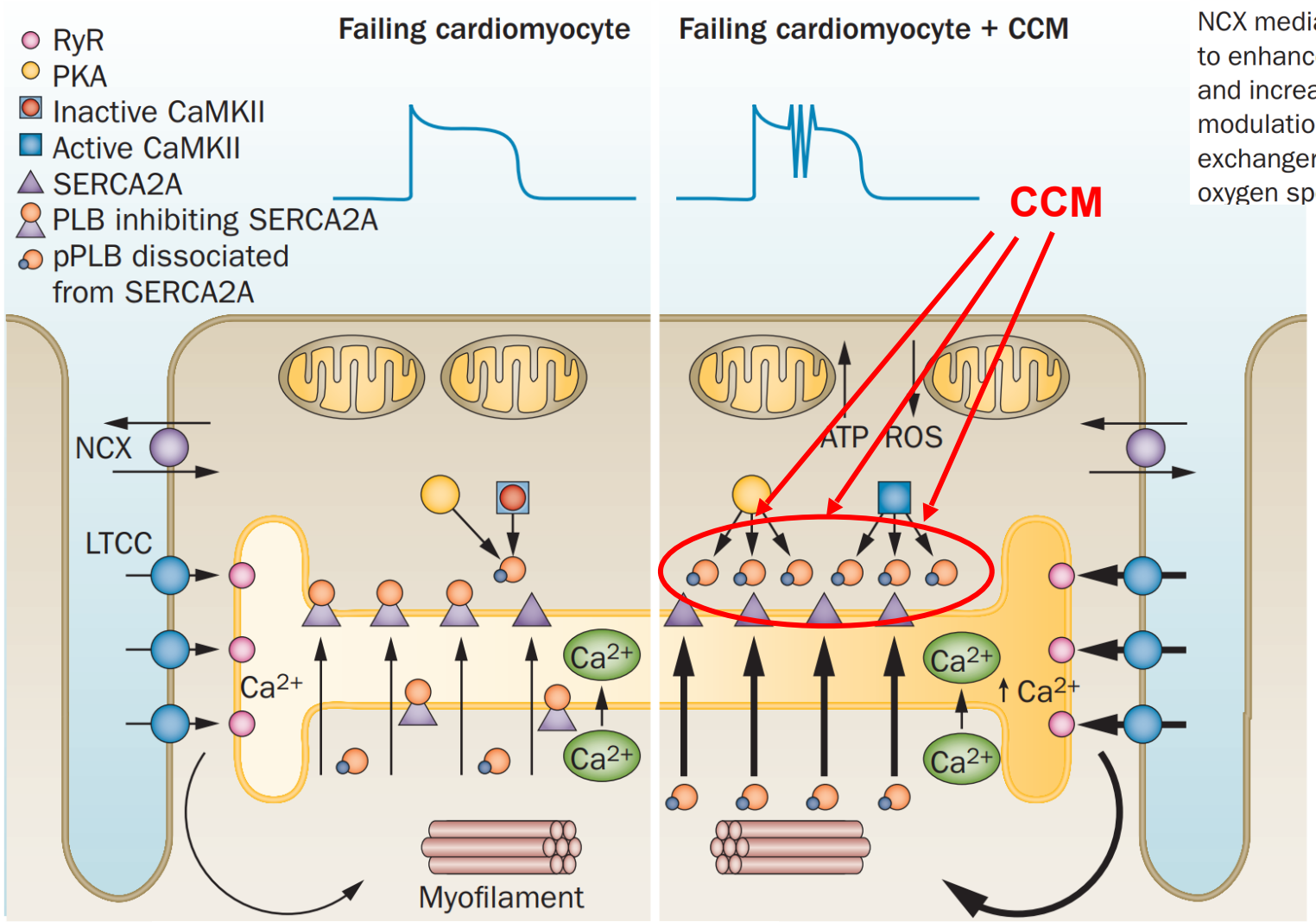
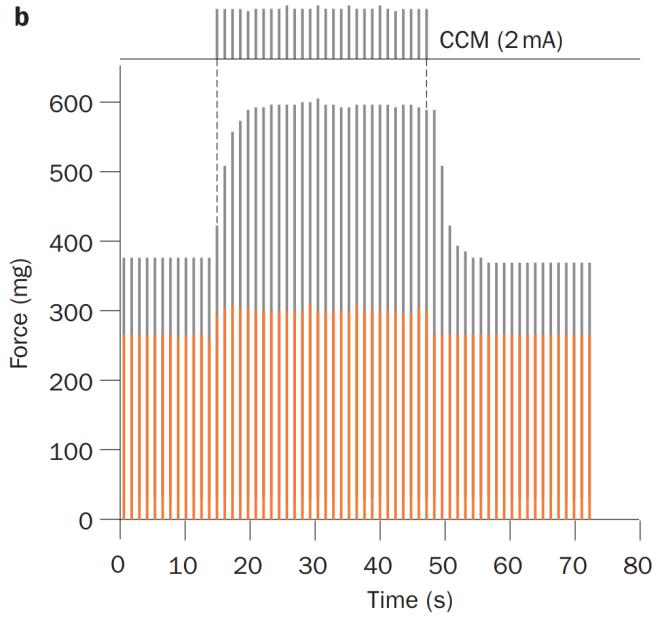


Figure 2 | Ca^{2+} cycling in the failing and CCM-treated cardiomyocyte, based on observations from preclinical studies of high-amplitude current pulses. In the failing cardiomyocyte (left), reduced LTCC-mediated Ca^{2+} entry, decreased sarcoplasmic reticulum Ca^{2+} load and release, severely impaired sarcoplasmic reticulum Ca^{2+} uptake, and enhanced Ca^{2+} clearance by sarcolemmal NCX, contribute to the phenotype. CCM therapy enhances LTCC-mediated Ca^{2+} entry, NCX mediated Ca^{2+} entry, PLB phosphorylation, and SERCA2 activity, contributing to enhanced efficiency of cytoplasmic–sarcoplasmic reticulum calcium transfer and increased contractile force (right). Abbreviations: CCM, cardiac contractility modulation; LTCC, L-type voltage-dependent Ca^{2+} channel; NCX, Na^{+},Ca^{2+} exchanger 1; PKA, protein kinase A; PLB, cardiac phospholamban; ROS, reactive oxygen species; SERCA2A, sarcoplasmic reticulum Ca^{2+} ATPase.

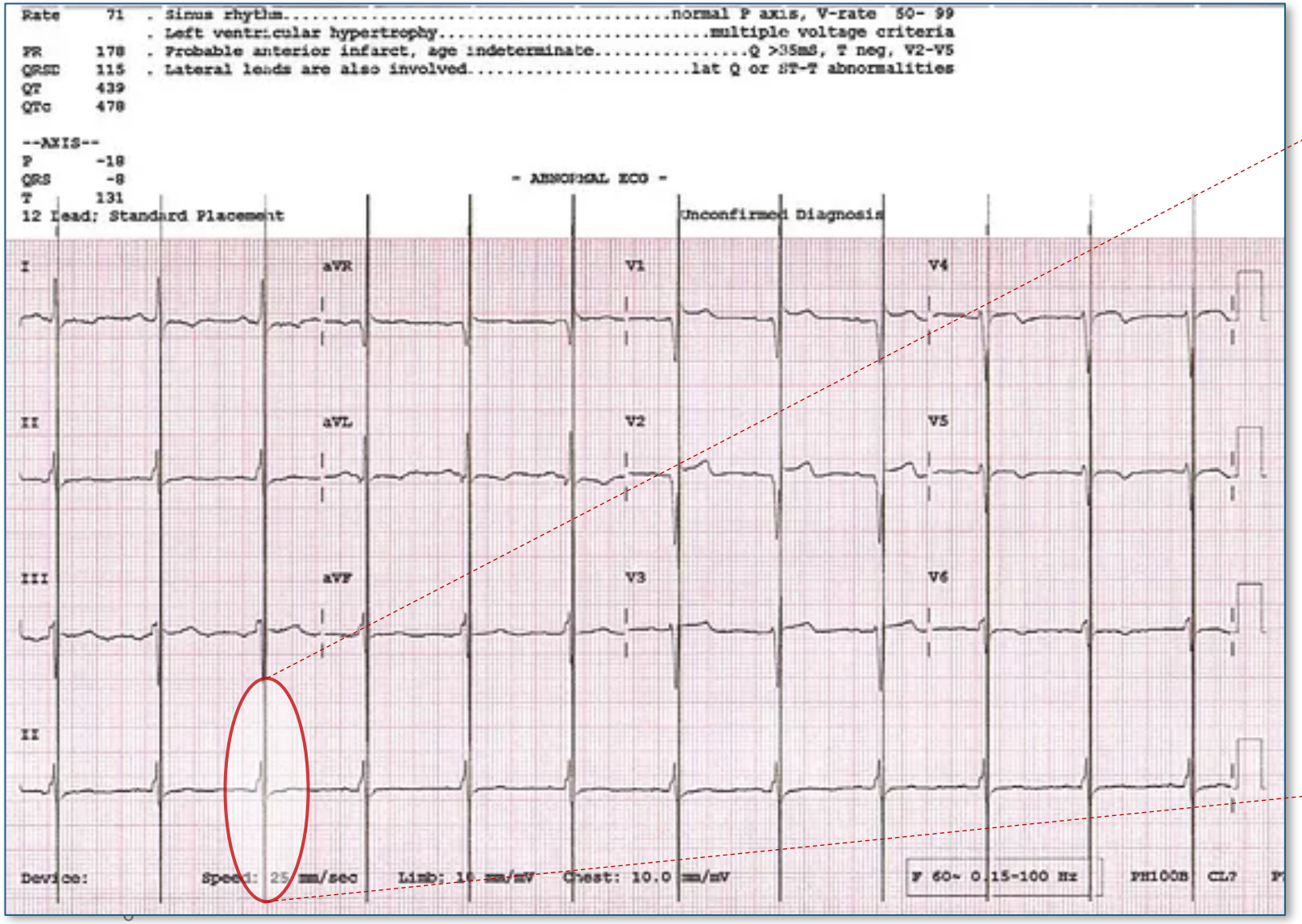


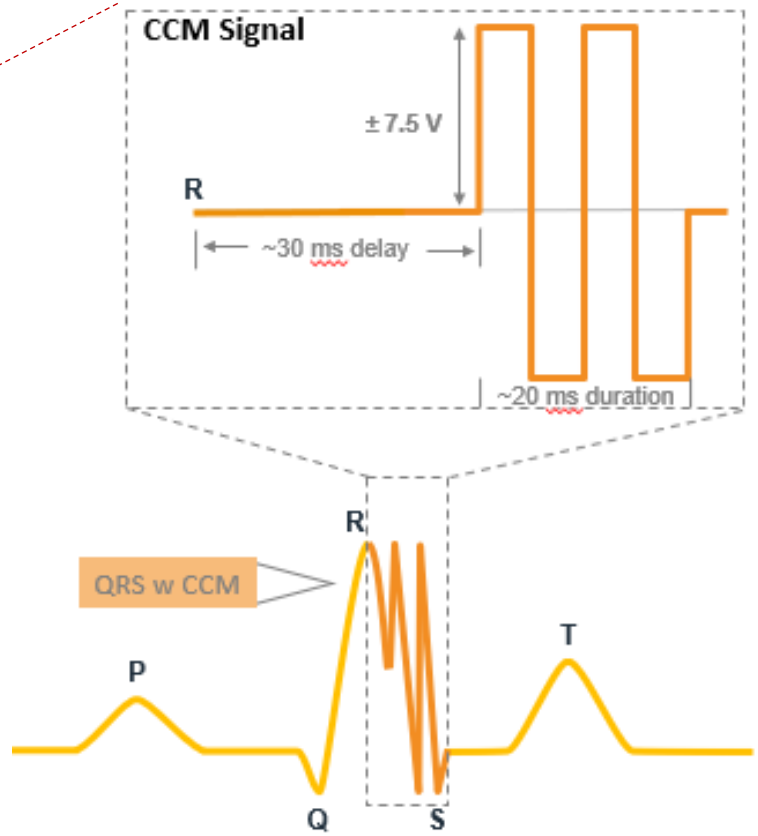
Cardiac contractility modulation therapy in advanced systolic heart failure

Alexander R. Lyon, Michael A. Samara and David S. Feldman

Nature, 2013

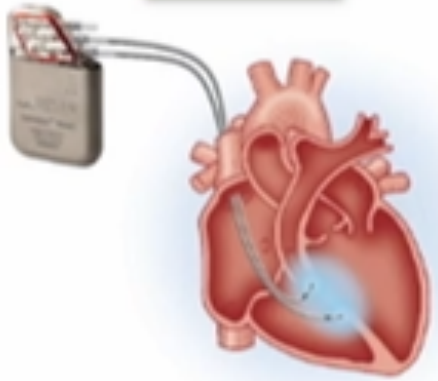
Cardiac Contractility Modulation (CCM)





CCM – Mechanism of action

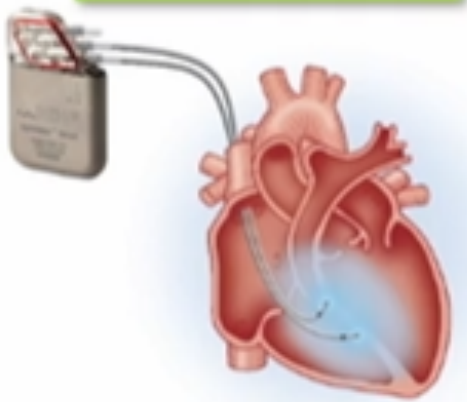
Rapid



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

- Improved calcium cycling and contractile force

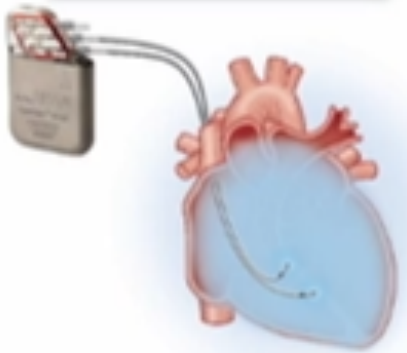
Intermediate



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

- Shift of gene program from heart failure to normal

Long-Term



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

- Beneficial effect on global ventricular properties and reverse remodeling

CCM – MAIN CLINICAL EVIDENCES

Herzschr Elektrophys
https://doi.org/10.1007/s00399-025-01118-1
Received: 11 July 2025
Accepted: 7 October 2025

Cardiac contractility modulation: an update

Jürgen Kuschyk[1] · Javed Butler[2] · Timothy Fendler[3] · Niraj Varma[4]

Table 1 Fix Heart Failure (FIX-HF) clinical trials summary

Clinical trials	Improvement in 6MHW[a]	Improvement in NYHA Class[b]	Improvement in QOL (MLWHFQ)[c]	Improvement in peak VO_2[d]
FIX-HF-4 [5] ($n = 164$) EF< 35%	Favor CCM treatment group	Not significant	–2.93 Points ($p = 0.03$)	+0.52 mL/kg/min ($p = 0.032$)
FIX-HF-5 [9] ($n = 428$) EF ≤ 35%	~ + 10 m ($p = N.S$)	CCM: 49.2% OMT: 34.4% ($p = 0.0026$)	–9.7 Points ($p < 0.0001$)	+0.65 mL/kg/min ($p = 0.024$)
FIX-HF-5C [1] ($n = 160$) EF: 25–45%	+33.7 m ($p = 0.0093$)	CCM: 81.2% OMT: 42.7% ($p < 0.0001$)	–11.7 Points ($p < 0.001$)	+0.84 mL/kg/min
FIX-HF-5C2 [18] ($n = 60$) EF: 25–45% two leads	*N*/A	CCM: 83.1% OMT: 42.7% ($p < 0.001$)	*N*/A	+1.72 mL/kg/min

[a] Positive value indicates improvement in 6MHW favoring CCM treatment
[b] Percent of subjects in each study group with NYHA class improved by ≥ 1 class
[c] Negative value indicates improvement in QOL favoring CCM treatment
[d] Positive value indicates improvement in peak VO_2 favoring CCM treatment
6MHW 6-Min Hall Walk, *CCM* cardiac contractility modulation, *NYHA* New York Heart Association, *MLWHFQ* Minnesota Living with Heart Failure Questionnaire, *N*/A not available, *OMT* optimal medical therapy, QOL Quality of life

CCM Guidelines

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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 Evidence in section 16).

ESC European Society of Cardiology
European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3150

POSITION PAPER

Integration of implantable device therapy in patients with heart failure. A clinical consensus statement from the Heart Failure Association (HFA) and European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC)

Wilfried Mullens[1,2]*, Jeroen Dauw[1,3], Finn Gustafsson[4], Alexandre Mebazaa[5],

In whom to implant cardiac contractility modulation?

Cardiac contractility modulation improved the quality of life and exercise capacity in symptomatic patients in sinus rhythm with LVEF <45% and QRS <130 ms in three open-label randomized trials,[68–70] but the effect was rather small. There are no blinded, sham-controlled trials limiting the robustness of the data to influence guidelines.[6] However, the AIM HIGHer clinical trial is a prospective, multicentre, randomized, quadruple-blind, sham-controlled, trial in subjects with HF and an LVEF ≥40% and ≤60% (NCT05064709).

CCM Guidelines

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European Journal of Heart Failure (2024)
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POSITION PAPER

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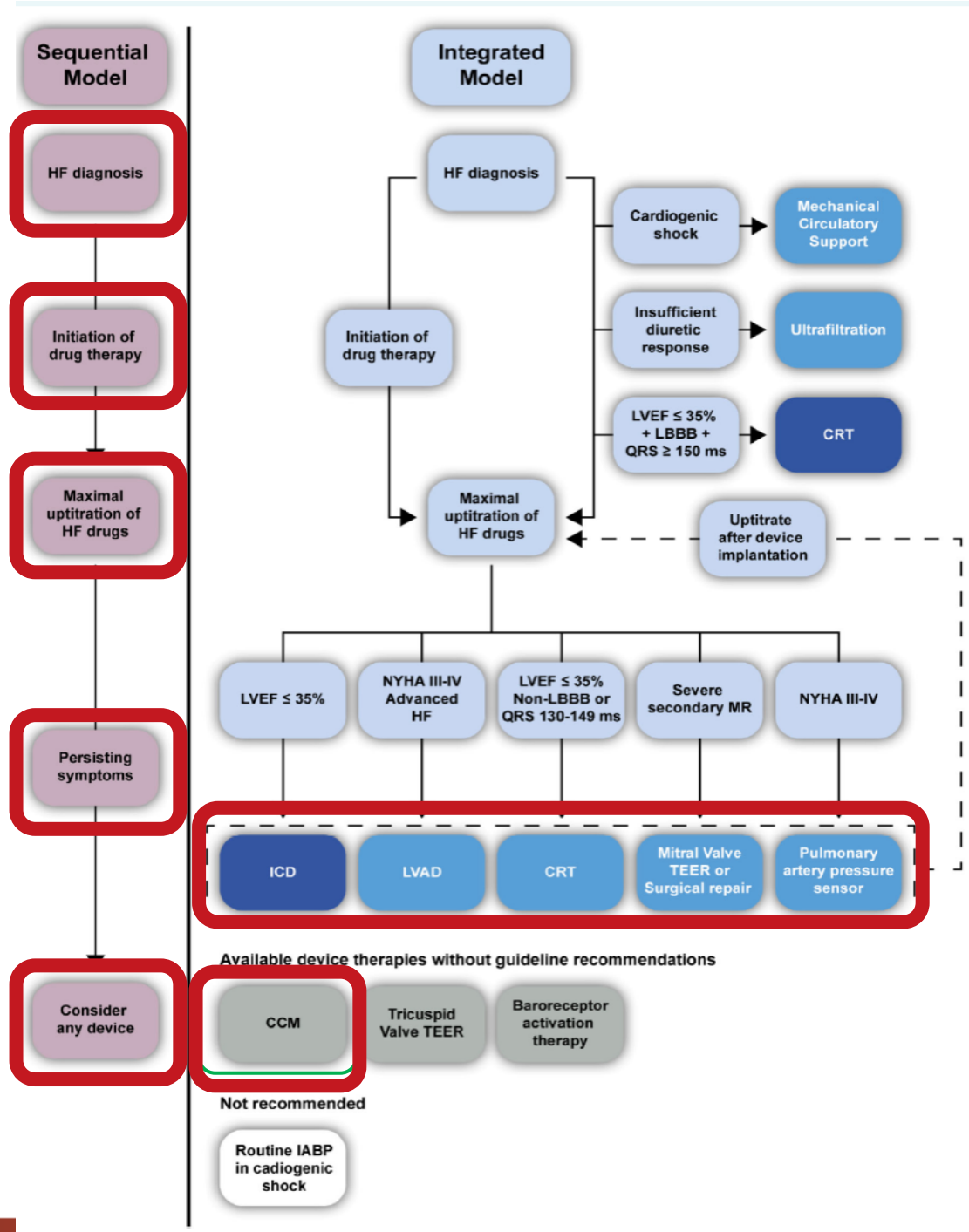


CCM Guidelines

GLOBAL CARDIOLOGY
Global Cardiology 2025
DOI: 10.4081/cardio.2025.70

GUIDELINES

iCARDIO Alliance Global Implementation Guidelines on Heart Failure 2025

Table 1. Grading and recommendations.

No.	Definition	Level of Recommendation
1-01	Evidence or consensus that a specific diagnostic test or treatment is effective, beneficial and valuable.	Strongly recommend (SR)
1-02	Majority of evidence or opinions support the benefits or effectiveness.	Recommend (R)
1-03	Usefulness or effectiveness is less clearly supported by evidence or opinion.	Suggest (Su)
1-04	Evidence or consensus suggests that it is ineffective and, in some cases, may even be harmful.	Do not do (DND)

No.	Guideline Statement	Level of Recommendation
5-08	Use CRT to reduce mortality and HF hospitalization, as well as to improve symptoms and QOL in patients with LVEF ≤35%; SR; non-LBBB pattern with QRS ≥150ms; and NYHA II-IV symptoms on maximally tolerated GDMT for at least 3 months.	R
5-09	Use CRT to reduce mortality and HF hospitalization, as well as improve symptoms and QOL in patients with high-degree or complete atrioventricular block and LVEF <50%.	Su
5-10	Use CRT to reduce mortality and HF hospitalization, as well as improve symptoms and QOL, for patients with LVEF ≤35%, SR, LBBB with a QRS duration of 130-149 ms, and NYHA class II-IV symptoms on maximally tolerated GDMT for at least 3 months.	Su
5-11	Use CRT in patients with LVEF ≤35% and have pre-existing RV pacing with symptoms of HF to reduce morbidity.	R
5-12	Use CRT to improve symptoms and QoL and reduce mortality and HF hospitalization in patients with AF and LVEF ≤ 35% on GDMT if: a) they need RV pacing of more than 20% or otherwise qualify for CRT, or b) AV nodal ablation or pharmacologic control will enable approximately 100% ventricular pacing with CRT.	R
5-13	Use CCM with the Optimizer Smart system to improve symptoms, QOL and exercise tolerance in patients with HF with LVEF 25-45% on GDMT not suitable for CRT.	R

LODO-CRT Trial

HeartRhythm Heart Rhythm Society

Volume 7, Issue 11 p1600-1605 November 2010

Presence of left ventricular contractile reserve predicts midterm response to cardiac resynchronization therapy—results from the LOw dose DObutamine Stress-Echo Test in Cardiac Resynchronization Therapy (LODO-CRT) Trial

Carmine Muto, MD * · Maurizio Gasparini, MD † · Carlo Peraldo Neja, MD ‡ · Saverio Iacopino, MD § · Mario Davinelli, PhD ¶ · Francesco Zanon, MD ‖ · Cosimo Dicandia, MD # · Giuseppe Distefano, MD ** · Roberto Donati, MD †† · Valeria Calvi, MD ‡‡ · Alessandra Denaro, MS ¶ · Bernardino Tuccillo, MD * Show less

LODO-CRT trial is a prospective, multicenter, observational study aimed at evaluating the role of DSE in selecting suitable candidates for CRT.

- Two hundred thirty-one patients were included in the analysis.
- LVCR (contractile reserve) presence was found in 185 subjects (80%)
- At follow-up, 170 (74%) patients responded to CRT,

  145/185 in the group with LVCR (78%) and 25/46 (54%) in the group without LVCR.
- Difference in responder proportion to CRT was 24% (P <.001).

CCM – REFINING PATIENT SELECTION

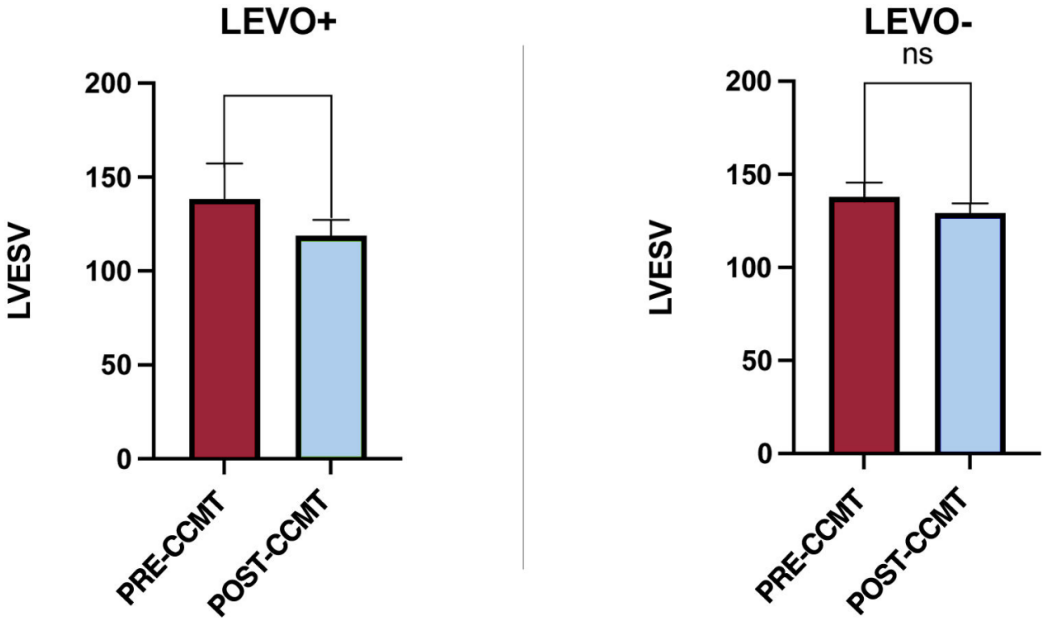
Response to levosimendan predicts response to cardiac contractility modulation therapy: a pilot study

La respuesta a levosimendán predice la respuesta a la terapia de modulación de la contractilidad cardiaca: un estudio piloto

Daniele Masarone[a,✉], Luigi Falco[a], Antonio d'Onofrio[b], Gerardo Nigro[c], Ernesto Ammendola[a], Giuseppe Pacileo[a]

REVISTA ESPAÑOLA DE CARDIOLOGÍA

- This study aimed to evaluate whether the echocardiographi response to levosimendan could predict clinical and echocardiographic response to CCMT.
- Levosimendan was administered in all patients (n.15) intravenously as a continuous infusion at 0.2mg/kg/min up t a total dose of 12.5 mg. The infusions were performed 72 hours before the Optimizer Smart implant
- After 6 months of CCMT, LVESV significantly decreased in the LEVO+ group (138.3±18.8 mL vs 119.7±8.1 mL; P < .05) compared with the LEVO- group (137.2±7.7 mL vs 129.5±9.8 mL; P = .48).
- At 1 year of follow-up, WHF episodes were significantly reduced post-CCMT in the LEVO+ group (14 vs 5; P = < .05).



Rev Esp Cardiol. 2024;77:703-5

The observation that **response to levosimendan predicts response to CCMT** could be because these patients have greater contractile reserve and less myocardial fibrosis and are consequently more responsive to both therapies.

Predict-CCM

ADVANCED HEART FAILURE: THE PREDICTIVE VALUE OF DOBUTAMINE ECHO-STRESS IN THE CLINICAL RESPONSE TO CARDIAC CONTRACTILITY MODULATION THERAPY (CCM)

Observational, multicenter, retrospective and prospective study

Rationale

- In patients with heart failure, CCM "recruits" cardiac contractility.
- Cardiac contractility is assessed simply and effectively with the dobutamine test, a test available in all Cardiology Units.
- The dobutamine test, if positive, should indicate the potential patient with contractility to be recruited and therefore a responder to CCM therapy.
- Centers that use CCM already use this test in clinical practice, but it needs to be clinically validated.

Predict-CCM

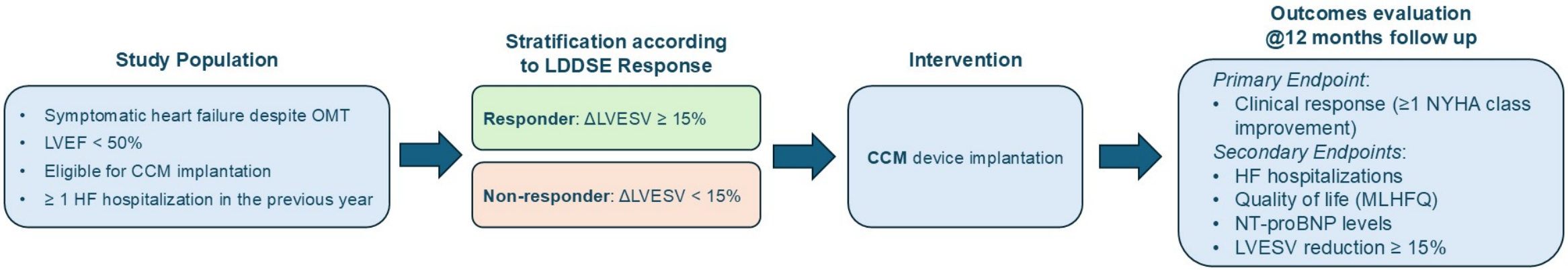
Study Objective

Endpoint evaluation will be performed in the entire cohort of enrolled subjects and in two subcohorts, divided based on their response to preimplantation low-dose dobutamine stress echocardiography:

- Subcohort "ΔESV >=15%", with a decrease in LVESV greater than or equal to 15%
- Subcohort "ΔESV <15%", with a decrease in LVESV less than 15%.

Primary endpoint

The percentage of subjects with a clinical response to CCM therapy at 12 months
(NYHA reduction ≥ 1 class + Reduction in HF hospitalizations)



PREDICT-CCM Study

Predict-CCM

45 Italian centers authorized by the Single Ethics Committee

National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

NCT06973902 Recruiting New

The Predictive Value of Dobutamine Echo-stress in the Clinical Response to **CCM** Therapy in Advanced HF

Conditions

Symptomatic Congestive Heart Failure

Locations

Rovigo, Italy, 45100
Recruiting
UO Cardiologia, S. Maria della Misericordia Hospital
Contact : Francesco Zanon, MD

Bologna, Emilia-Romagna, Italy
Recruiting
Policlinico S.Orsola, UO Cardiologia
Contact : Matteo Zacchi, Dott.

Vicenza, Veneto, Italy
Recruiting
UOC Cardiologia, Osp. S.Bortolo, Vicenza, ULSS 8 Berica
Contact : Antonio Rossillo, Dott.

EC approval 25/MAR/2025

1	Anzio	ASL Roma 6	Dr. Natale Di Belardino
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3	Avezzano	Osp. Civile Nicola e Filippo	Dr. Francesco Vetta
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14	Monza	San Gerardo	Dr Giovanni Rovaris
15	Nuoro	S. Francesco	Dr. Enrico Mura
16	Olbia	S.Giovanni di DIO	Dr.ssa Silvia Denti
17	Ostia	G.B. Grassi	Dr. Luca Santini
18	Paola	San Francesco	Dr.ssa Mariateresa Manes
19	Pescara	CDC Pierangeli	Dr. Stefano Guarracini
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22	Rovigo	S.Maria della Misericordia	Dr Francesco Zanon
23	San Gavino	N.S. di Bonaria	Dr. Roberto Floris
24	Saronno	Osp. Di Saronno	Dr Daniele Nassiacos
25	Sessa Aurunca	Ospedale S.Rocco	Dr Di Lorenzo
26	Siracusa	Umberto I	Dr.ssa Silvia Motta
27	Terni	S. Maria	Dr. Giovanni Carreras
28	Vicenza	S.Bortolo	Dr Antonio Rossillo
29	Villafranca	Magalini	Dr Gabriele Zanotto
30	Voghera	Osp di Voghera	Dr Pietro Broglia

EC approval 23/JUL/2025

31	Acquaviva delle I	Miulli	Dr . Vincenzo Caccavo
32	Bari	San Paolo	Dr. Luigi Mancini
33	Cagliari	Policlinico	Dr Vicenzo Nissardi
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41	Orbassano	AOU S.L. Gonzaga	Dr Matteo Bianco
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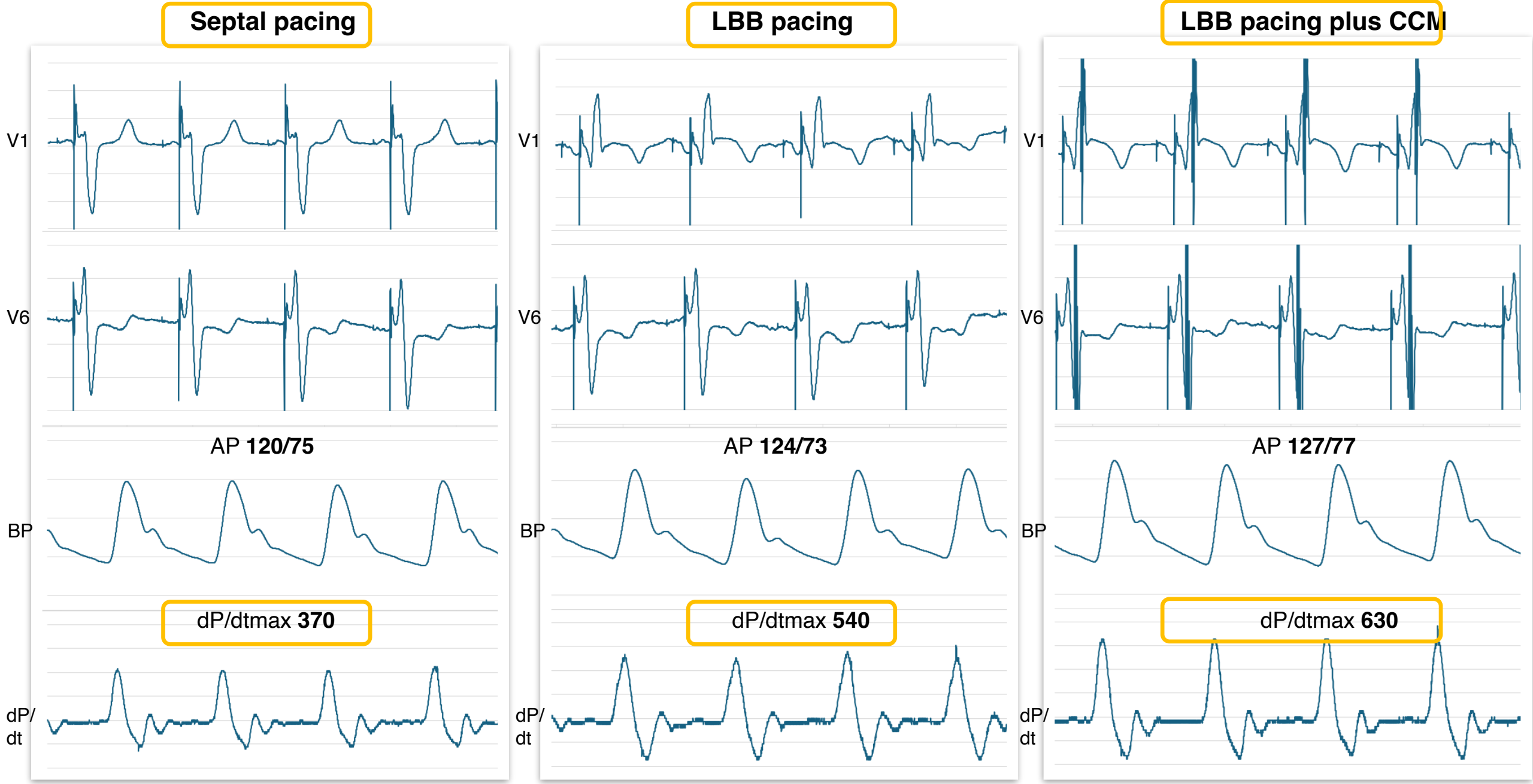
43	Rovereto	S.Maria del Carmine	Dr Maurizio del Greco
44	Taranto	SS.Annunziata	Dr. Cosimo Mandurino
45	Vercelli	ASL Vercelli/Borgosesia	Dr Francesco Rametta

Comitato etico Territoriale
Area Sud-Ovest Veneto (CET-ASOV

A CASE REPORT DESCRIBING SINERGY

- 71-year-old gentleman with post-infarction ischemic heart disease
- Previously implanted (2023) with a dual-chamber ICD (Rivacor DR, Biotronik) providing a physiologic left bundle branch pacing (**LBBP**)
- Evaluated for continuous **recurrences of heart failure**.
- Considering the persistence of symptoms (NYHA III) and repeated hospitalizations, in May 2024 it was decided to evaluate the left ventricle (LV) contractile reserve by means of **low-dose dobutamine stress echocardiography**.
- The LV end-systolic volume (LVESV) was reduced by 20%.
- Implantation of a CCM device (Optimizer Smart, Impulse Dynamics).



24 months after the implant the patient is currently in NYHA class II, no HF hospitalization occurred in the follow up period.

Journal of Clinical Medicine

MDPI

Study Protocol

Rationale and Design of the PREDICT-CCM Study: Predictive Value of Dobutamine Stress Echocardiography for Clinical Response to Cardiac Contractility Modulation Therapy in a Multicenter Italian Cohort

Francesco Zanon [1,*], Carlo Uran [2], Vincenzo Bonfantino [3], Natale Di Belardino [4], Antonio Lupo [5], Marzia Giaccardi [6], Procolo Marchese [7], Angelo Antonio Di Grazia [8], Luca Santini [9], Luigi Di Lorenzo [10], Giovanni Carreras [11], Luca Sgarra [12], Matteo Ziacchi [13], Leonardo Marinaccio [14], Luigi Mancini [15], Giovanni Bisignani [16], Mariateresa Manes [17], Stefano Guarracini [18], Amir Kol [19], Roberto Floris [20], Antonio Rossillo [21], Gabriele Zanotto [22], Lina Marcantoni [1] and Franco Noventa [23,*]

Published: 23 April 2026

J. Clin. Med. **2026**, 15, 3223

Predict-CCM Study

BASELINE

Partial data, updated as of June 26, 2026

Enrolled patients (to date)	**92**
Age (yrs)	69.5±10.9
Male sex	76,0%
BMI (kg/m2)	26.5±4.6
Ischaemic HF etiology	46,8%
Dilated cardiomyopathy	25,0%
Hypertensive cardiomyopathy	18,5%
Valvular heart disease	32,6%
Congenital heart disease	1,1%
Other heart disease	4,3%
Hypertension	60,9%
Diabetes	33,8%
Previous MI	32,6%
Angina	5,4%
Stroke	5,4%
CABG	9,8%
PCI	35,9%
Prior CIED	66,3%
CRT-D	15,2%
ICD	48,9%
PM	2,2%
History of AF	44,6%
COPD	10,6%

Predict-CCM Study

BASELINE

Partial data, updated as of June 26, 2026

HF symptoms	
Dyspnea on exertion	82,6%
Dyspnea at rest	41,3%
Dyspnea in the supine position	17,4%
Asthenia	41,3%
Limb edema	30,4%
Cough	2,2%
Abdominal swelling	17,8%
Abdominal pain	4,3%
Tachycardia	12,0%
Nocturia	18,5%
Mental confusion	12,0%
Memory deterioration	6,5%

NYHA CLASS II	21,7%
NYHA CLASS III	68,5%
NYHA CLASS IV	9,8%

Predict-CCM Study

BASELINE

Partial data, updated as of June 26, 2026

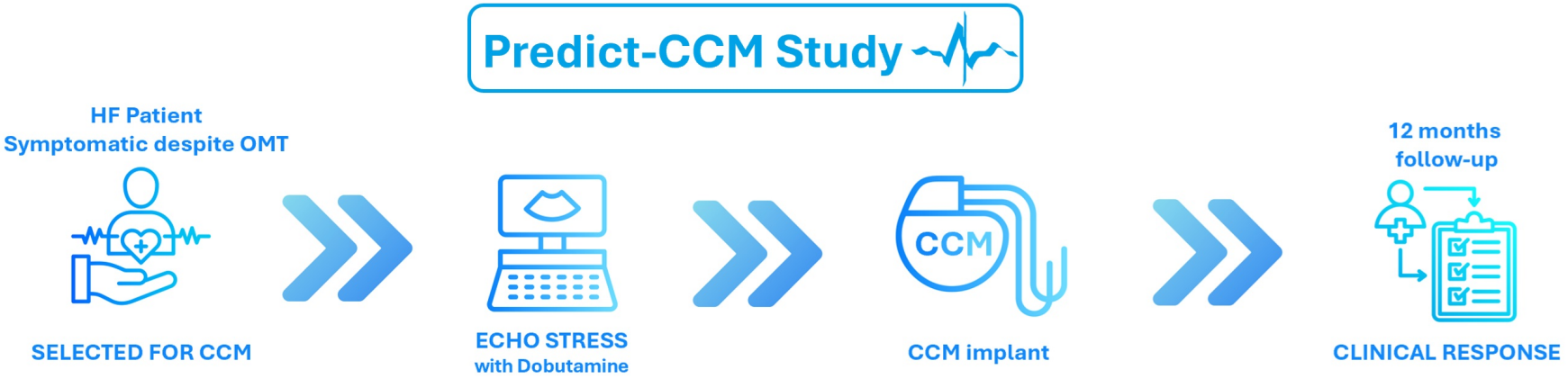
Baseline ECG	
Heart rate (bpm)	72±10
QRS duration (ms)	120±29
Sinus Rhythm	54,3%
Atrial fibrillation	27,2%
Atrial flutter	2,2%
Pacemaker induced	16,3%
QRS morphology	
Pacemaker-induced	16,3%
IVCD	7,6%
LBBB	10,9%
Narrow QRS	52,2%
RBBB	7,6%
Other	5,4%

LVEF (%)	31±8

NT pro-BNP (pg/mL)	6.588±9.780

MLHFQ	
Total score	52.7±20.8
Physical score	23.9±8.0
Emotional score	10.7±6.4

GRAZIE


Predict-CCM Study
HF Patient
Symptomatic despite OMT
SELECTED FOR CCM
ECHO STRESS
with Dobutamine
CCM
CCM implant
12 months
follow-up
CLINICAL RESPONSE