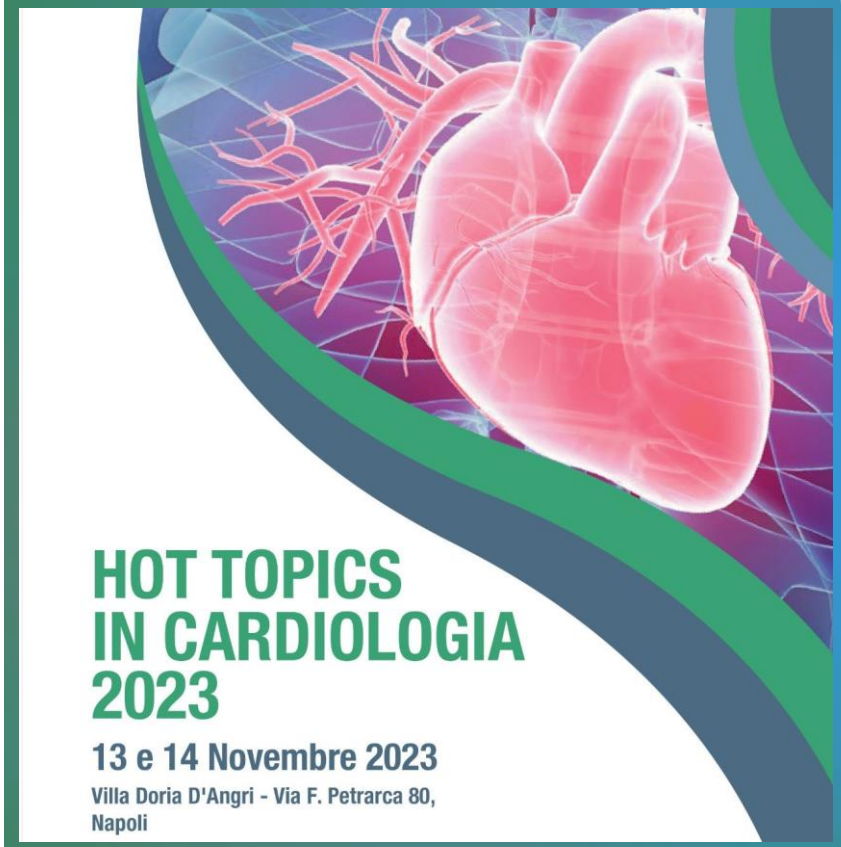


CCM nello scompenso cardiaco: HFrEF/HFpEF candidato ideale

Dott. Daniele Masarone

UOSD Scompenso Cardiaco

AOS dei Colli

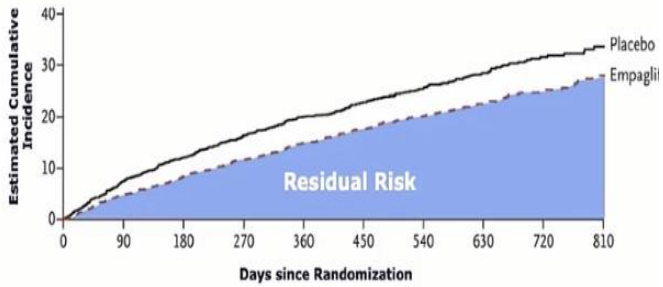
Ospedale Monaldi

DISCLOSURE

SONO UN CARDIOLOGO CLINICO!!!

The war against heart failure: the *Lancet* lecture

Eugene Braunwald

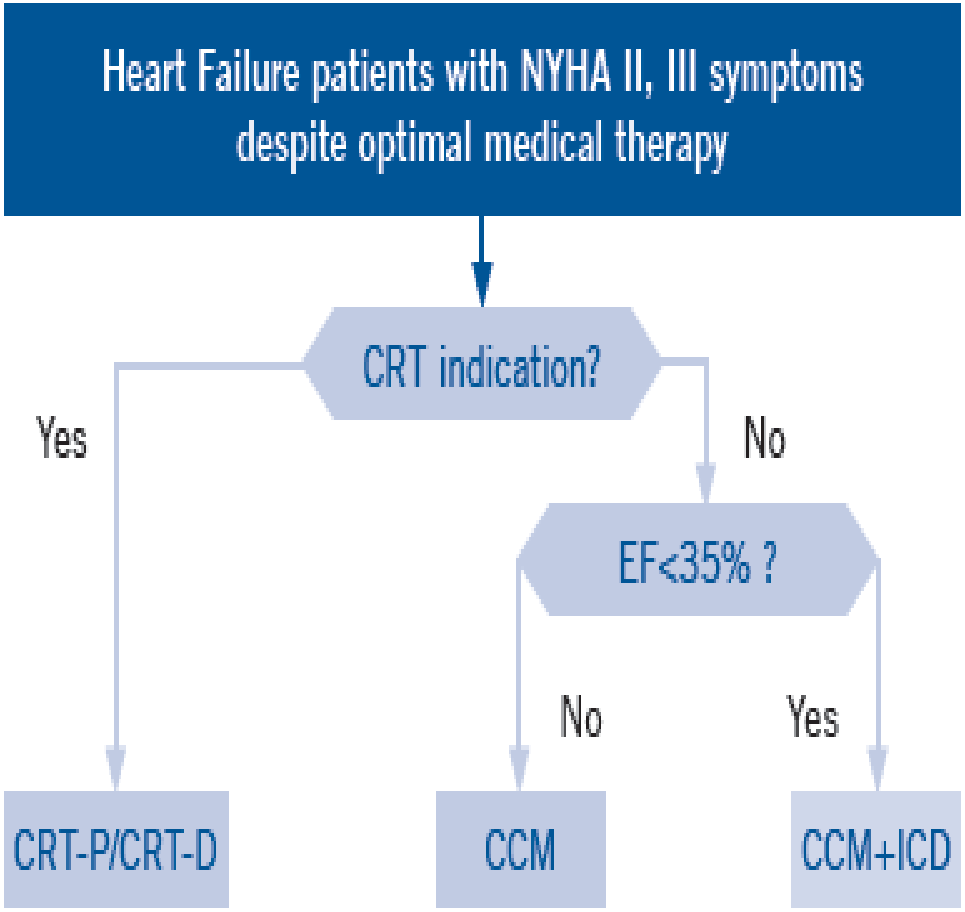


19.4%

Residual risk of CV death or hospitalization despite optimal GDMT

Packer M NEJM 2020

CCMT solves an unmet need in the treatment of HF



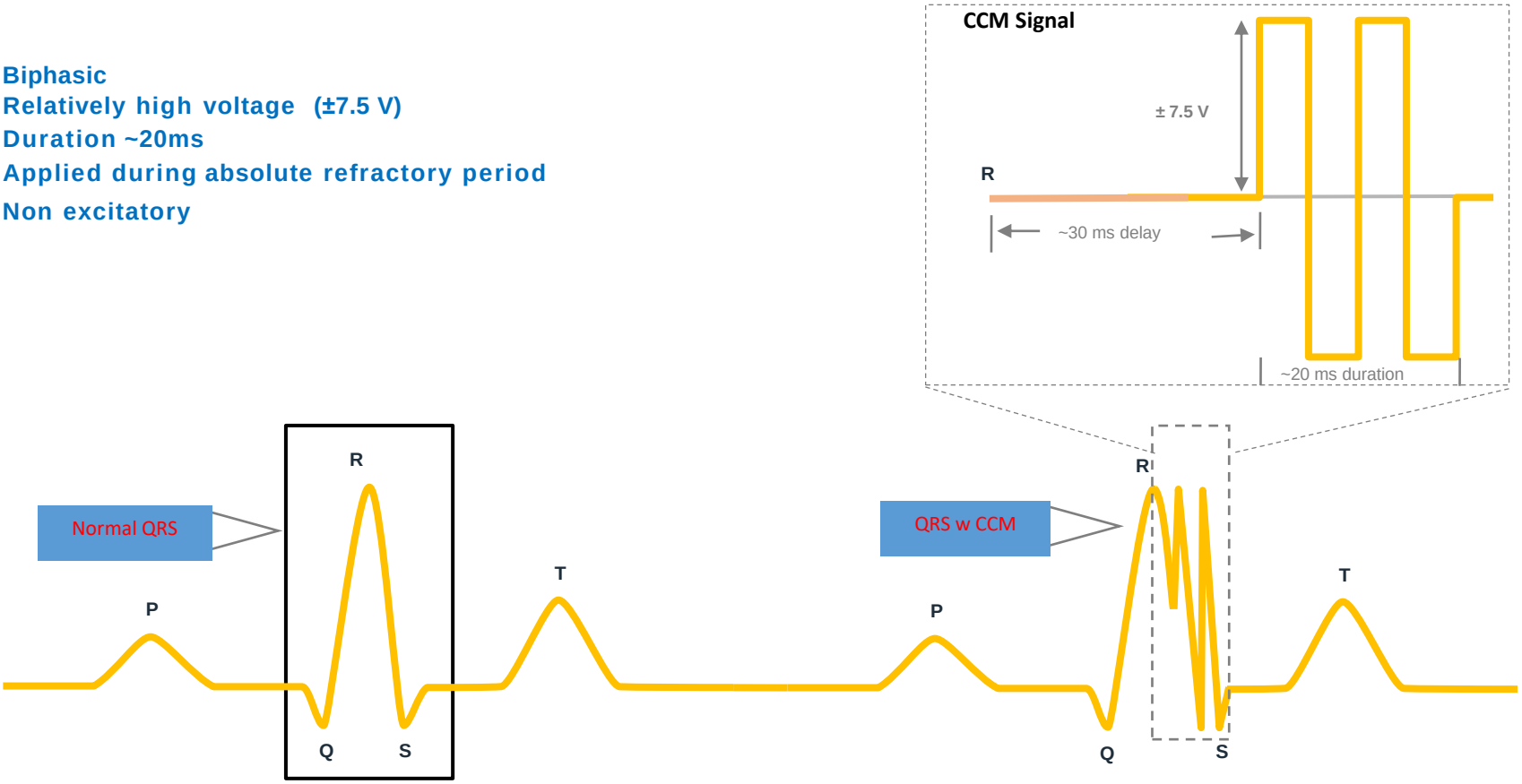
More than 17m patients globally with NYHA II/III despite OMT

- 30% eligible for CRT
- 70% eligible for CCM

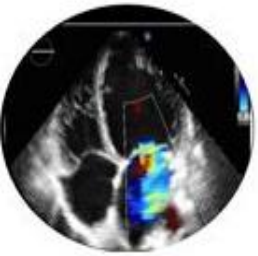
Abraham WT. Heart Fail. Clin. 2021

CCMT
Mechanism of Action

- Biphasic
- Relatively high voltage (±7.5 V)
- Duration ~20ms
- Applied during absolute refractory period
- Non excitatory



CCM
Mechanism of Action



Minutes

- Upregulation of SERCA2a
- Increased phosphorylation of titin
- Increased phosphorylation of PLB
- Increased phosphorylation of PKA and PKG

Hours

- Reverse of the maladaptive fetal gene program
- Reduction of cardiac fibrosis
- Decreased sympathetic activity

Months

- Improved ejection fraction reserve
- Improved diastolic filling index

Masarone D . Hear Rhytm 2023

Optimizer®: Randomized Clinical Trial History

- All randomized studies showed significant impact on exercise tolerance and quality of life
- Peak VO2 endpoint consistently positive across all trials
- Subgroup analyses (whether or not pre-specified) demonstrated greatest benefits in HF patients with moderately reduced ejection fractions ranging from 35% to 45%

CCM-REG	CCM Registry		Opt IVs, Smart	Germany, Russia, France	503
FIX-HF-5C2	2-Lead CCM Device		OptSmart (2-lead)	US, Germany	60
HFpEF Pilot	FE>50%		OptSmart (2-lead)	EU, Australia	47
Total					1,751

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

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PhD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PhD,[h] Helen Parise, ScD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PhD,[r] Gerd Hasenfuß, MD[s]

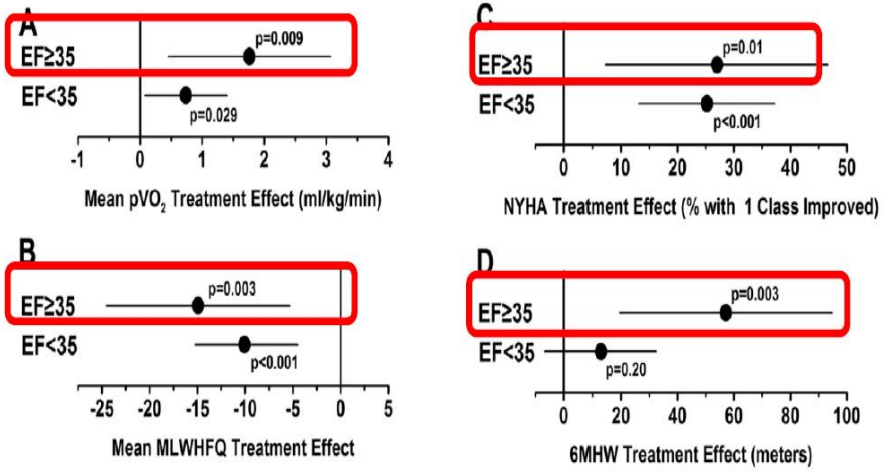
OBJECTIVES *The authors sought to confirm a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) study showing that cardiac contractility modulation (CCM) improved exercise tolerance (ET) and quality of life in patients with ejection fractions between 25% and 45%.*

- 160 patients **randomized** 1:1: at 20 US sites and 8 EU sites
- Target population: Heart failure patients with **EF 25% to 45%**
- **Primary Efficacy Endpoint:** Improvement in **peak VO2**
- **Primary Safety Endpoint:** Proportion of Treatment group that did **not** experience an Optimizer device or Optimizer procedure related **complication** through 24-weeks greater than **70%**
- Major **Secondary Efficacy Endpoint:**
  - Minnesota Living with Heart Failure **Quality of Life** (QoL) Score
- Granted Expedited Access Pathway by the FDA qualifying for priority review

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

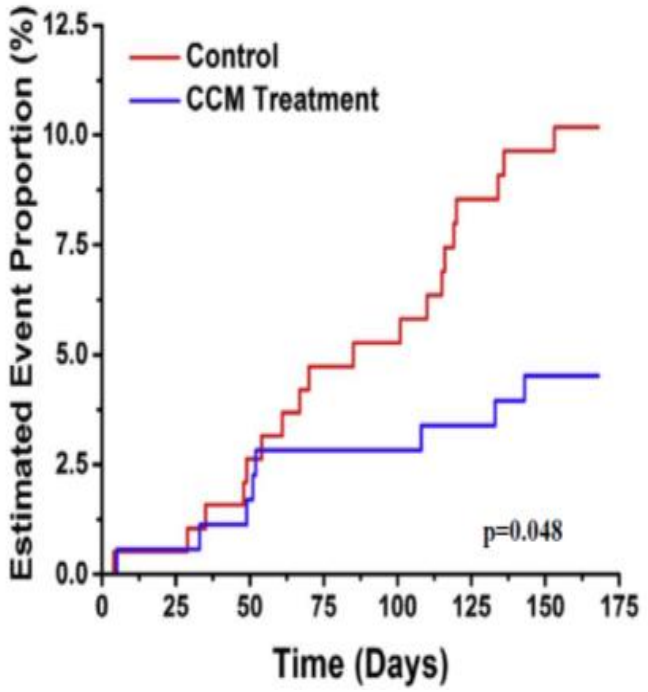
(J Am Coll Cardiol HF 2018;6:874-83)

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PhD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PhD,[h] Helen Parise, ScD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PhD,[r] Gerd Hasenfuß, MD[s]



- CCM improve functional capacity irrespictive of EF
- Better response in patients with EF (increase of Voi2 peak. **+1,76 mL/Kg/min vs +0,9 mL/Kg/min** in the overall population)

FIGURE 5 Heart Failure and Mortality Events



A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life

Francesco Giallauria[1]*, Gianluigi Cuomo[1], Alessandro Parlato[1], Nirav Y. Raval[2], Jürgen Kuschyk[3] and Andrew JS Stewart Coats[4]

	RX-HF-5 pilot		FIX-CHF-4		FIX-HF-5		FIX-HF-5C		FIX-HF-5C2	
First author	Neelagaru SB[26]		Borggrefe MM[27]		Kadish A[28]		Abraham WT[29]		Wiegn P[32]	
Year of publication	2006		2008		2011		2018		2020	
Total study cohort sample size (*N*)	49		164		428		160		60	
Randomized	Yes		Yes		Yes		Yes		No	
Double blinded	No		Yes		Yes		No		No	
	COM	Control	COM	Control	COM	Control	COM	Control[c]	COM	Control[c]
Age (years)	52 ± 15	60 ± 12	59 ± 10	60 ± 10	58 ± 13	59 ± 12	63 ± 11	63 ± 11	66 ± 9	63 ± 11
Male (%)	68	71	89	81	73	71	73	79	88	79
Ischaemic CHF (%)	64	67	64	56	65	67	62	59	68	59
EF (%)[a]	24.9 ± 6.5	31.4 ± 7.4	29.3 ± 6.6	29.8 ± 7.8	25.7 ± 6.6	26.1 ± 6.5	33 ± 6	33 ± 5	34 ± 6	33 ± 5
NYHA class III (%)	100	96	72	80	91	86	86	91	98	91
Peak VO_2 (mL/kg/min)	14.3 ± 2.8	16.0 ± 2.9	14.1 ± 3.0	13.6 ± 2.7	14.7 ± 3.0	14.7 ± 2.9	15.5 ± 2.6	15.4 ± 2.8	15.0 ± 2.9	15.4 ± 2.8
6MWT (m)	321 ± 82	352 ± 95	386 ± 103	394 ± 102	326 ± 82	324 ± 92	317 ± 88	324 ± 90	NA	324 ± 90
MLWHFQ score	56.4 ± 24.8	52.1 ± 21.4	38.9 ± 27.4	36.5 ± 27.1	60.5 ± 23.0	57.4 ± 22.6	56 ± 23	57 ± 23	NA	57 ± 23
Interventions	COM (OPTIMIZER system) signals *on*; control: signals *off*		COM (OPTIMIZER system) allocated to on/off (Group 1: *on* to *off*; Group 2: *off* to *on*)		COM (OPTIMIZER system) and optimal medical therapy[b] vs. optimal medical therapy alone (control)		COM (OPTIMIZER system) and optimal medical therapy vs. optimal medical therapy alone (control)		The OPTIMIZER Smart system with 2-lead	
Outcomes	Peak VO_2, 6MWT, MLWHFQ Others: NYHA classification, Holter monitoring		Peak VO_2, 6MWT, MLWHFQ Others: NYHA classification, LV function		Peak VO_2, 6MWT, MLWHFQ Others: NYHA classification, LVEF, LV end-diastolic dimension, VAT, composite of all-cause mortality and all-cause hospitalizations		Peak VO_2, 6MWT, MLWHFQ Others: safety		Peak VO_2 Others: NYHA, safety	
Follow-up visits	12, 24 weeks		Phase I: 12 weeks; Phase II: 24 weeks		12, 24, 50 weeks		12, 24 weeks		12, 24 weeks	

A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life

Francesco Giallauria[1]*, Gianluigi Cuomo[1], Alessandro Parlato[1], Nirav Y. Raval[2], Jürgen Kuschyk[3] and Andrew JS Stewart Coats[4]

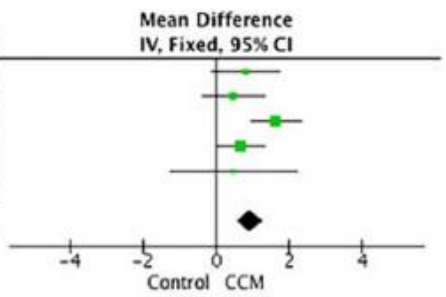
ESC HEART FAILURE
ESC Heart Failure (2020)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12902

ORIGINAL RESEARCH ARTICLE

Panel A. 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]**

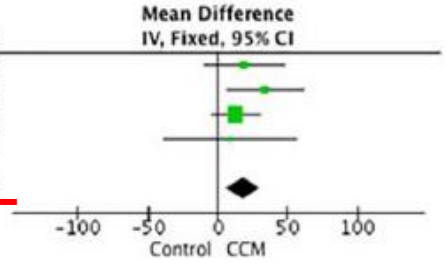
Heterogeneity: $Chi^2 = 5.94$, $df = 4$ ($P = 0.20$); $I^2 = 33\%$
Test for overall effect: $Z = 4.96$ ($P < 0.00001$)



Panel B. 6MWT distance (m)

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)	23.09	81.69	82	4.1	99	76	19.3%	18.99 [-9.44, 47.42]
FIX-CHF-5C	43	80.7	69	9.3	87.4	73	20.4%	33.70 [6.05, 61.35]
FIX-HF-5	21.1	77.9	185	8.3	85.7	170	53.4%	12.80 [-4.29, 29.89]
FIX-HF-5 Pilot (24 weeks)	49.1	97.1	24	40.5	64.5	21	6.9%	8.60 [-39.05, 56.25]
Total (95% CI)			**360**			**340**	**100.0%**	**17.97 [5.48, 30.46]**

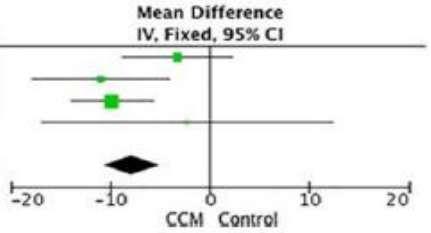
Heterogeneity: $Chi^2 = 1.75$, $df = 3$ ($P = 0.63$); $I^2 = 0\%$
Test for overall effect: $Z = 2.82$ ($P = 0.005$)



Panel C. 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: $Z = 5.29$ ($P < 0.00001$)



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

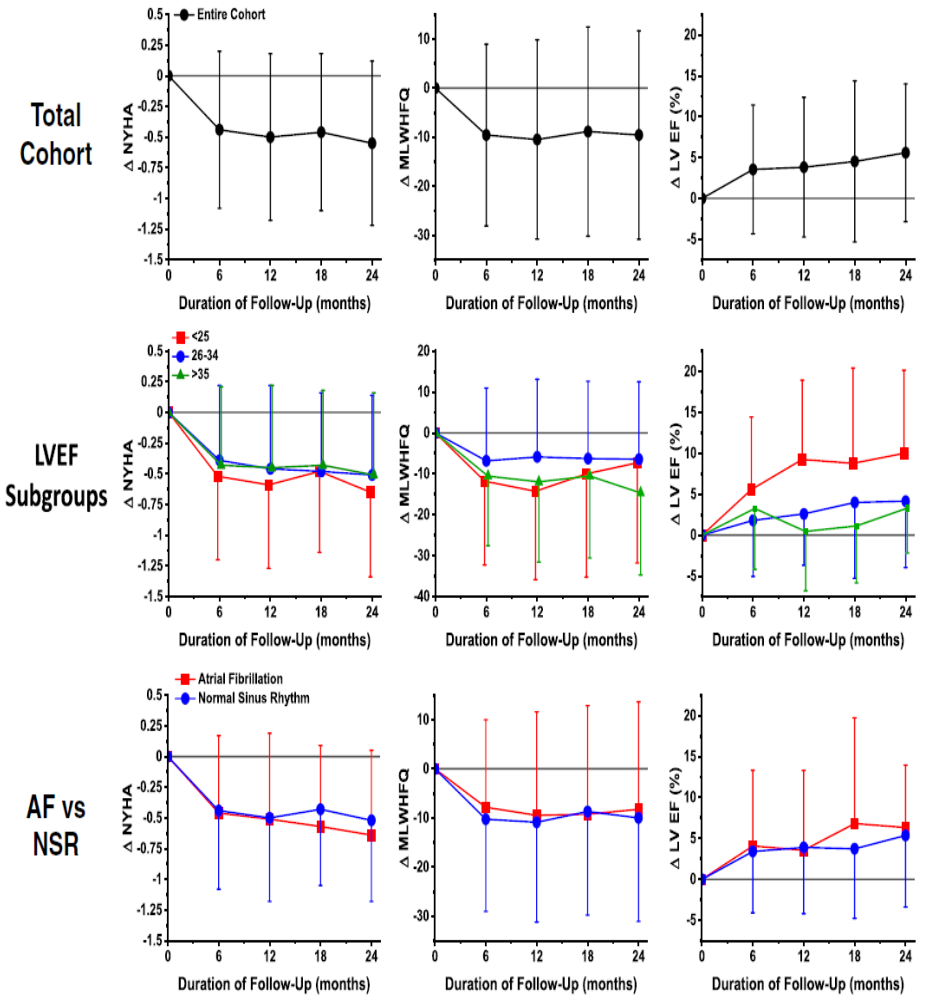
ESC European Society of Cardiology

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

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

CCM-REG Registry Study N=503

- **LVEF ≤25%** *n*= 178
- **LVEF 26–34%** *n*= 164
- **LVEF ≥35%** *n*= 161



- Effects of CCM on NYHA class, MLWHFQ and LVEF maintained over 2 years across range of LVEF.
- 3-year survival of patients treated with CCM better than predicted by the MAGGIC score.

Kuschyck J. EJHF 2021

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]*

ESC European Society of Cardiology

European Journal of Heart Failure (2021)
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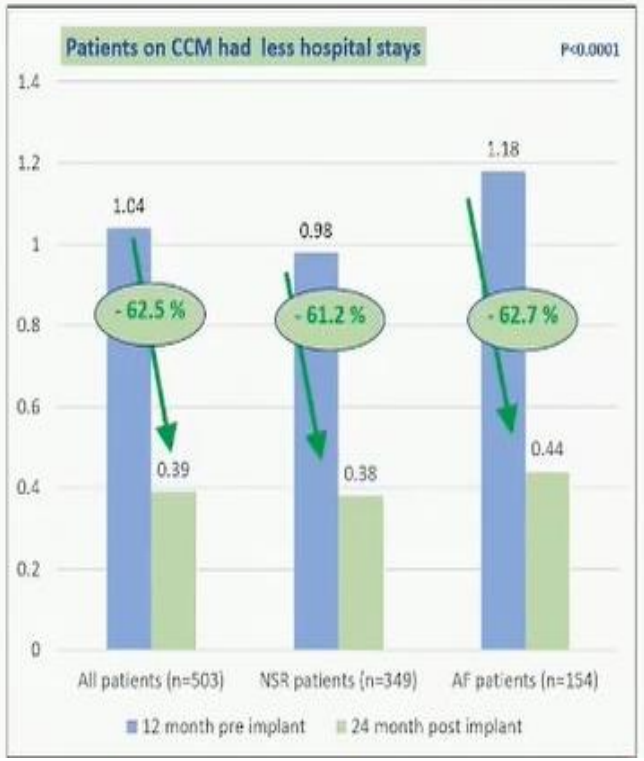
Table 3 Hospitalization rates the year prior to Optimizer implant compared to the 2 years following Optimizer implant in the entire cohort and in the five subgroups of interest

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	0.38	<0.0001
Heart failure events			229	0.66			130	0.25	<0.0001
Non-heart failure cardiovascular events			113	0.32			70	0.13	<0.0001
Atrial fibrillation									
All cardiovascular events	154	154	181	1.18	154	198	87	0.44	<0.0001
Heart failure events			142	0.92			49	0.25	<0.0001
Non-heart failure cardiovascular events			39	0.25			38	0.19	0.2189

LVEF, left ventricular ejection fraction.



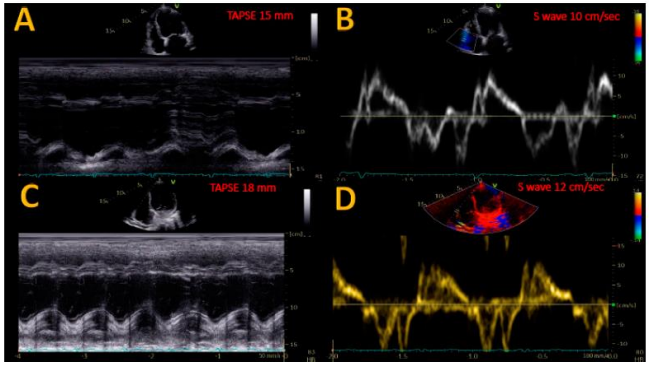
applied sciences

MDPI

Article

Effects of Cardiac Contractility Modulation Therapy on Right Ventricular Function: An Echocardiographic Study

Carla Contaldi [1,*], Stefano De Vivo [2], Maria L. Martucci [1], Antonio D'Onofrio [2], Ernesto Ammendola [1], Gerardo Nigro [3], Vittoria Errigo [1], Giuseppe Pacileo [1] and Daniele Masarone [1]



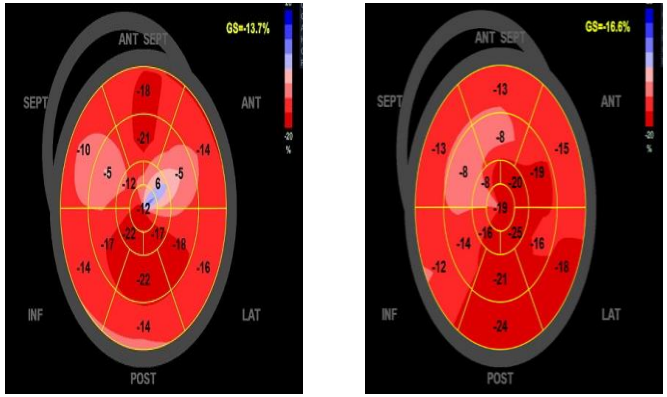
Journal of Clinical Medicine

MDPI

Article

The Effects of Device-Based Cardiac Contractility Modulation Therapy on Left Ventricle Global Longitudinal Strain and Myocardial Mechano-Energetic Efficiency in Patients with Heart Failure with Reduced Ejection Fraction

Daniele Masarone [1,*], Michelle M. Kittleson [2], Stefano De Vivo [3], Antonio D'Onofrio [3], Ernesto Ammendola [1], Gerardo Nigro [4], Carla Contaldi [1], Maria L. Martucci [1], Vittoria Errigo [1] and Giuseppe Pacileo [1]



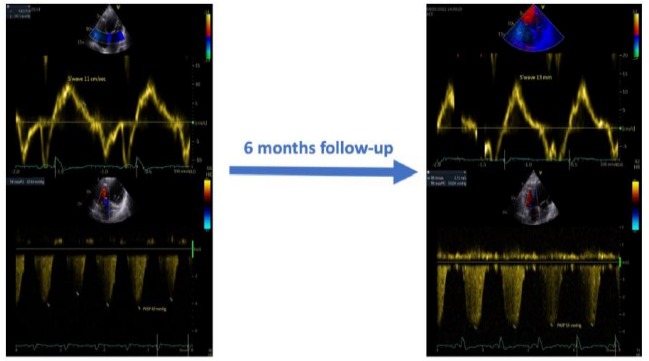
Journal of Clinical Medicine

MDPI

Article

Effects of Cardiac Contractility Modulation Electrodes on Tricuspid Regurgitation in Patients with Heart Failure with Reduced Ejection Fraction: A Pilot Study

Daniele Masarone [1,*], Michelle M. Kittleson [2], Stefano De Vivo [3], Antonio D'Onofrio [3], Ishu Rao [4], Ernesto Ammendola [1], Vittoria Errigo [1], Maria L. Martucci [1], Gerardo Nigro [5] and Giuseppe Pacileo [1]



Monaldi Experience

Monaldi Experience (Nov 2019- Sep2023)

	Totale pazienti impiantati (n= 45)
Età	66 [51-74]
Maschi	89 (39/44)
Ischemici	59% (n 26)
Altro device impiantato - ICD - CRTD	95% (42/44) 59,5% (25/42) 40,5% (17/42)
NYHA III	86% (n 38/44)
NYHA II	14% (n 6/44)
Lista Trapianto	9% (n 4/44)
FA permanente	50% (n 21/44)
QRS (ms)	120 [100-146]
FE (%)	30 [25-33]
MLWHFQ	50 [41-64]
NT-ProBNP	2462,5 [1124-3842]

Monaldi Experience (Nov 2019- Sep2023)

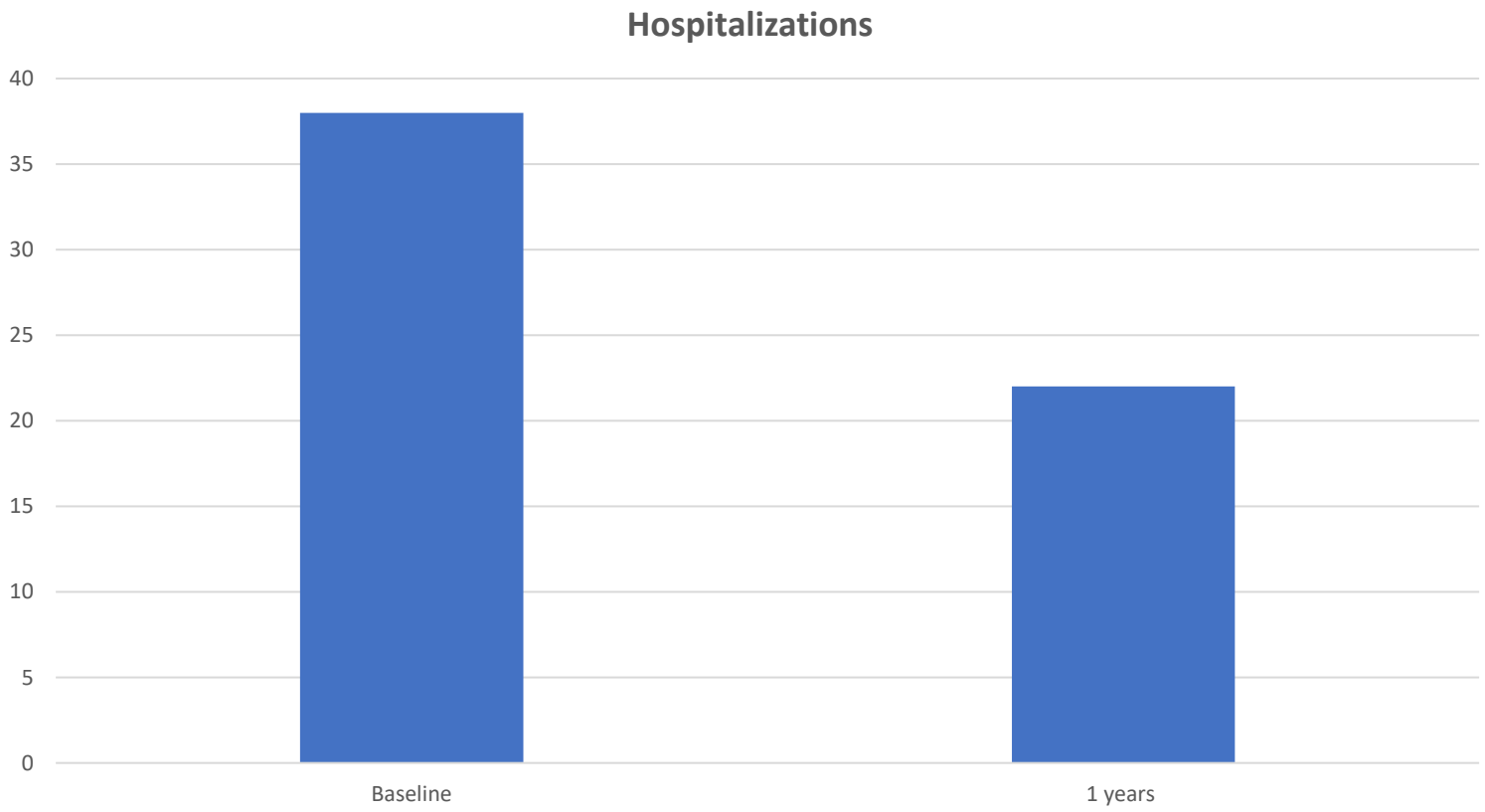
Terapia Farmacologica basale	Totale pazienti impiantati (n= 44)
Ace Inibitori	23% (10/44)
Beta-Bloccanti	82% (36/44)
Glifozine*	25% (11/44)
Allopurinolo	34% (15/44)
Sacubritil/Valsartan	68% (30/44)
Antagonisti Aldosterone	61% (27/44)
Diuretici Ansa	91% (40/44)

***introdotti dal 1/2022**

6 Months Follow-Up (38 patients)

Parameters	Baseline	3-Mo	6-Mo
MLWHFQ scroe	50,5 [41,25-63,75]	46 [14,75-59,25]	33 [24,51-59,67]
EF (%)	30 [25-33]	33 [30-38]	39 [33,5-44]
NT-proBNP (pg/ml)	2462,5 [1124-3842]	1906 [989-7880,5]	1842 [1013,5-2496,625]

12 Months Follow-Up (20 patients)



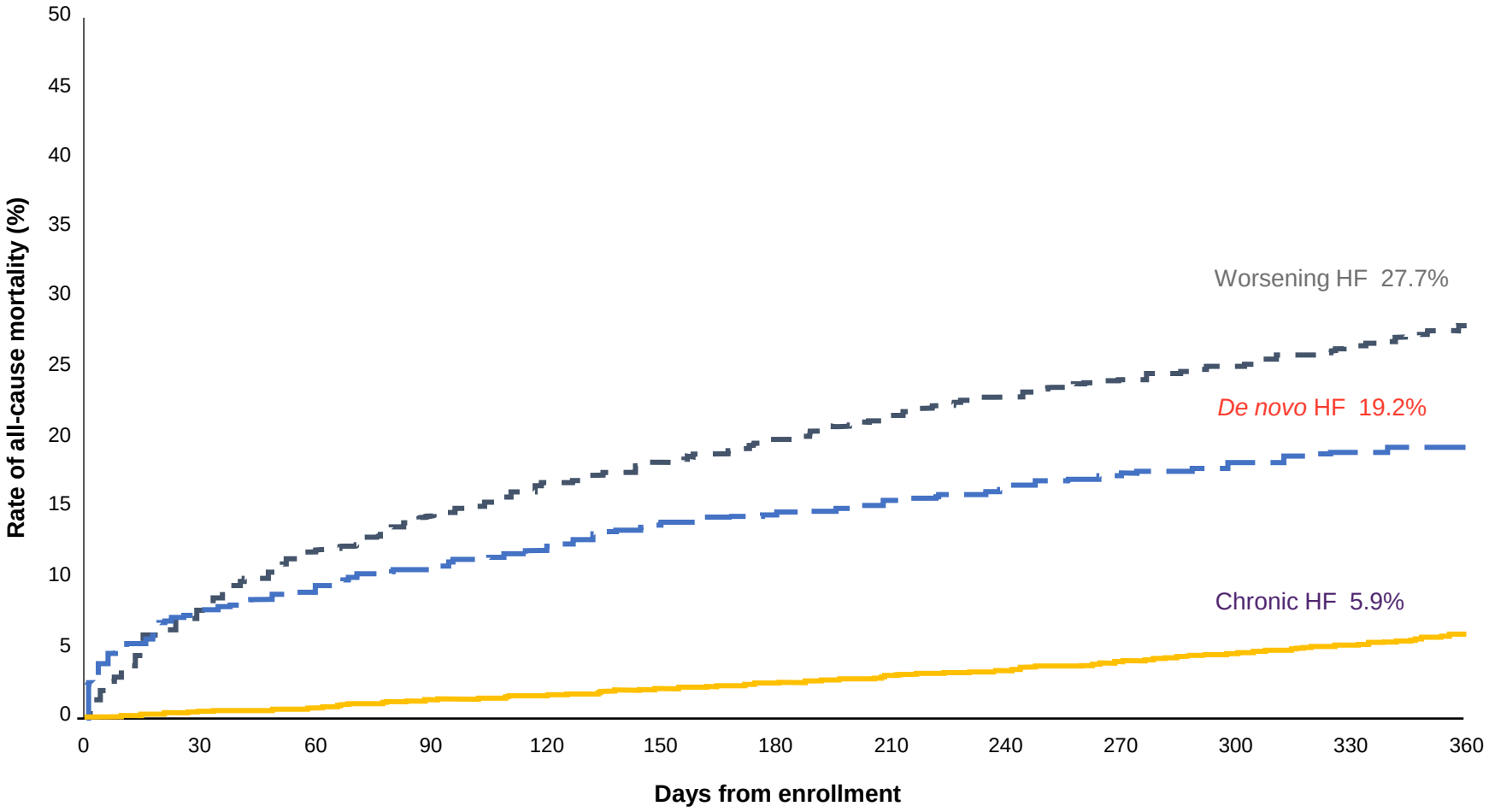
ESC European Society of Cardiology
European Journal of Heart Failure (2023)
doi:10.1002/ejhf.2874
POSITION PAPER

Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology

Marco Metra[1,#], Daniela Tomasoni[1,#], Marianna Adamo[1*], Antoni Bayes-Genis[2], Gerasimos Filippatos[3], Magdy Abdelhamid[4], Stamatis Adamopoulos[5], Stefan D. Anker[6], Laura Antohi[7,8], Michael Böhm[9], Frieder Braunschweig[10], Tuvia Ben Gal[11], Javed Butler[12], John G.F. Cleland[13], Alain Cohen-Solal[14], Kevin Damman[15], Finn Gustafsson[16], Loreena Hill[17], Ewa A. Jankowska[18], Mitja Lainscak[19], Lars H. Lund[9], Theresa McDonagh[20], Alexandre Mebazaa[21], Brenda Moura[22,23], Wilfried Mullens[24], Massimo Piepoli[25,26], Piotr Ponikowski[18], Amina Rakisheva[27], Arsen Ristic[28], Gianluigi Savarese[9], Petar Seferovic[28], Rajan Sharma[29], Carlo Gabriele Tocchetti[30], Mehmet Birhan Yılmaz[31], Cristiana Vitale[32], Maurizio Volterrani[32], Stephan von Haehling[33,34], Ovidiu Chioncel[6,7], Andrew J.S. Coats[35], and Giuseppe Rosano[32]

The clinical course of heart failure (HF) is characterized by episodes of worsening symptoms and signs.[1–3] These episodes of worsening HF (WHF) are followed by an increased risk of hospitalizations and death and are a major burden on the health-care system, because of their frequency, urgency and prognostic impact.[1,3–5] Their prevention is a major target of current treatment of HF. The aim of the present clinical consensus statement by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) is to provide an update on the definition and clinical characteristics of WHF and summarize recent findings for the management and prevention of WHF in clinical practice.

One-year all-cause mortality rate in patients hospitalized with acute HF or outpatients with chronic HF, prospectively enrolled in the IN-HF outcome registry (N=5,610)



Tavazzi L et al. Circ Heart Fail 2013

Pathophysiologic Targets in the Early Phase of Acute Heart Failure Syndromes

Mihai Gheorghiade, MD,[a,*] Leonardo De Luca, MD,[b] Gregg C. Fonarow, MD,[c] Gerasimos Filippatos, MD,[d] Marco Metra, MD,[e] and Gary S. Francis, MD[f]

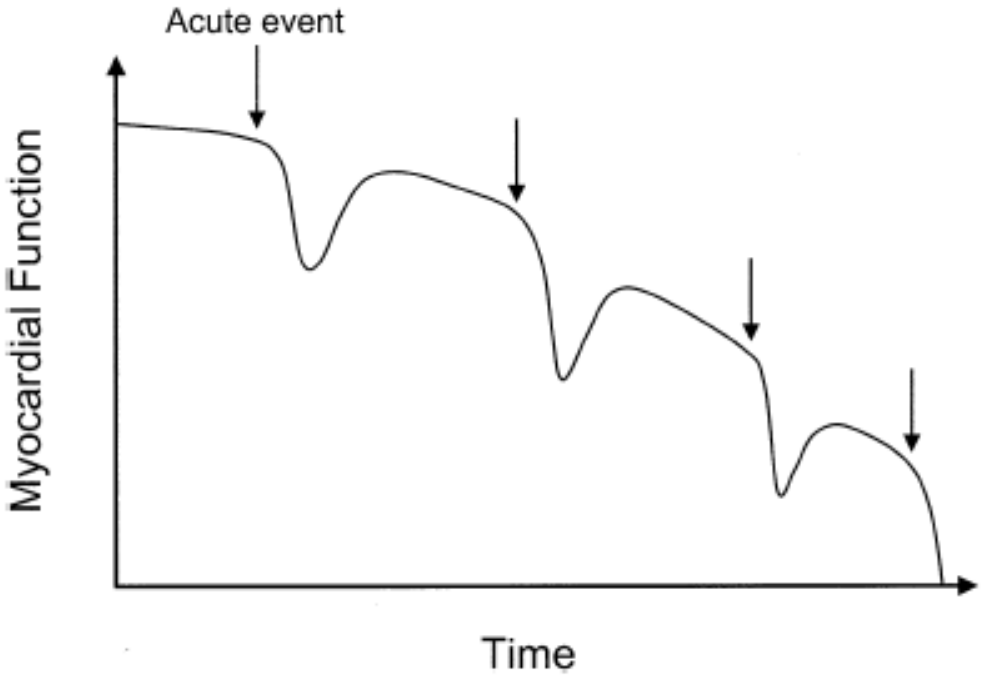


Figure 2. Contribution of acute events to the progression of heart failure. With each admission for acute heart failure syndromes, there is a short-term improvement; however, the patient leaves the hospital with a further decrease in cardiac function.

CCMT in which patients?

- NYHA II with frequent AHF episodes
- NYHA III-V
- 25%≤EF ≤45%
- QRS ≤130 ms
- OMT
- VO2 peak > 9ml/kg/min < 20 ml/kg/min
- BEV < 8.900 BEV
- No severe tricuspid, aortic or disproportionate mitral valve regurgitation

How many patients with heart failure are eligible for cardiac contractility modulation therapy?

Rajdip Dulai | Ahmed Chilmeran | Mazin Hassan | Rick A. Veasey | Stephen Furniss | Nikhil R. Patel | Neil Sulke

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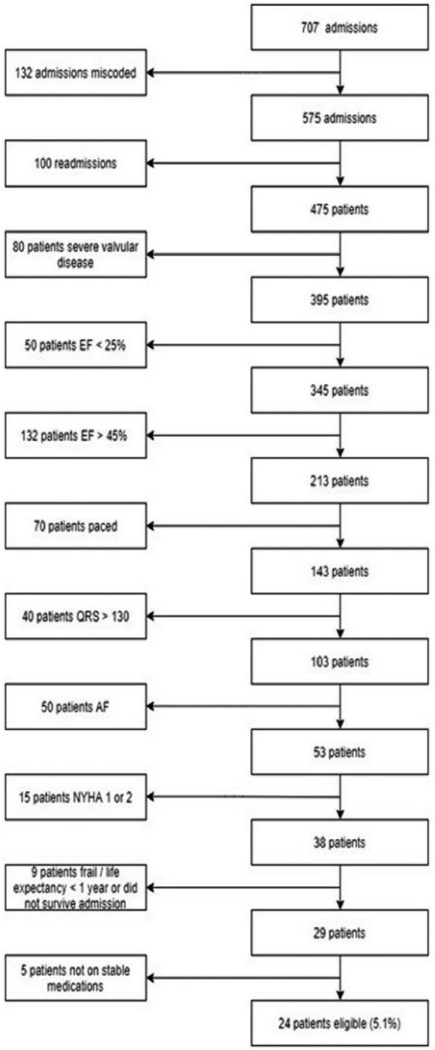
DOI: 10.1111/ijcp.13646

ORIGINAL PAPER
CARDIOVASCULAR MEDICINE

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY



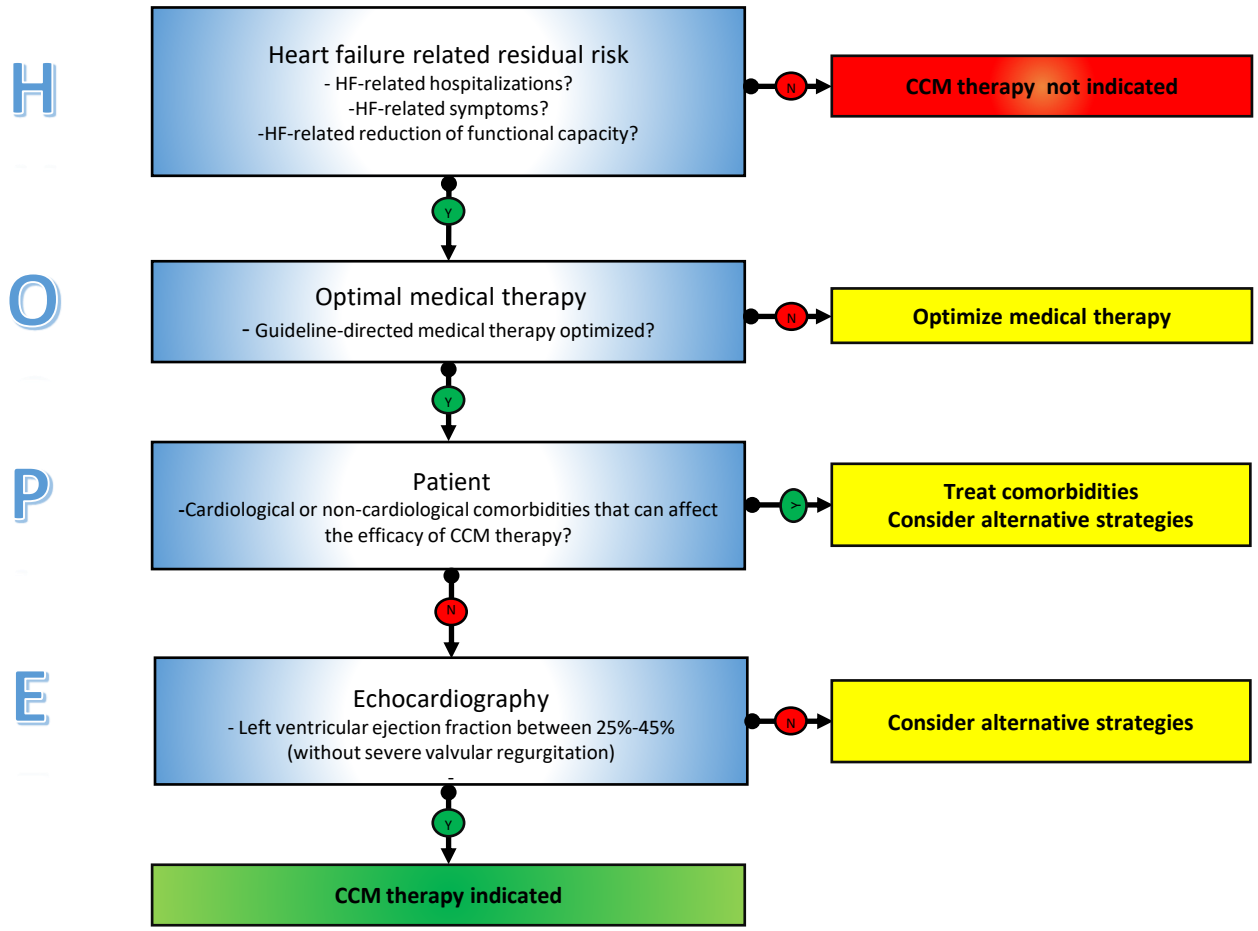
Results: A total of 475 patients were admitted with heart failure during the study period. From this group, 24 (5.1%) patients fulfilled the criteria for CCM therapy. The mean age and ejection fraction were 70.8 ± 10.2 and 32.5% ± 7.4%. The majority of patients were men (71%) and had an ischaemic cardiomyopathy (75%). If patients with atrial fibrillation were included, an additional 18 (3.8%) patients potentially may be eligible for CCM.

Conclusion: Only 5.1% of all patients presenting with heart failure might benefit from cardiac CCM. This is a small proportion of the overall heart failure population. However, this population has no other current option for device therapy of their condition.

TABLE 3 Comparison of baseline characteristics of patients eligible for CCM therapy (Sinus rhythm patients vs atrial fibrillation patients)

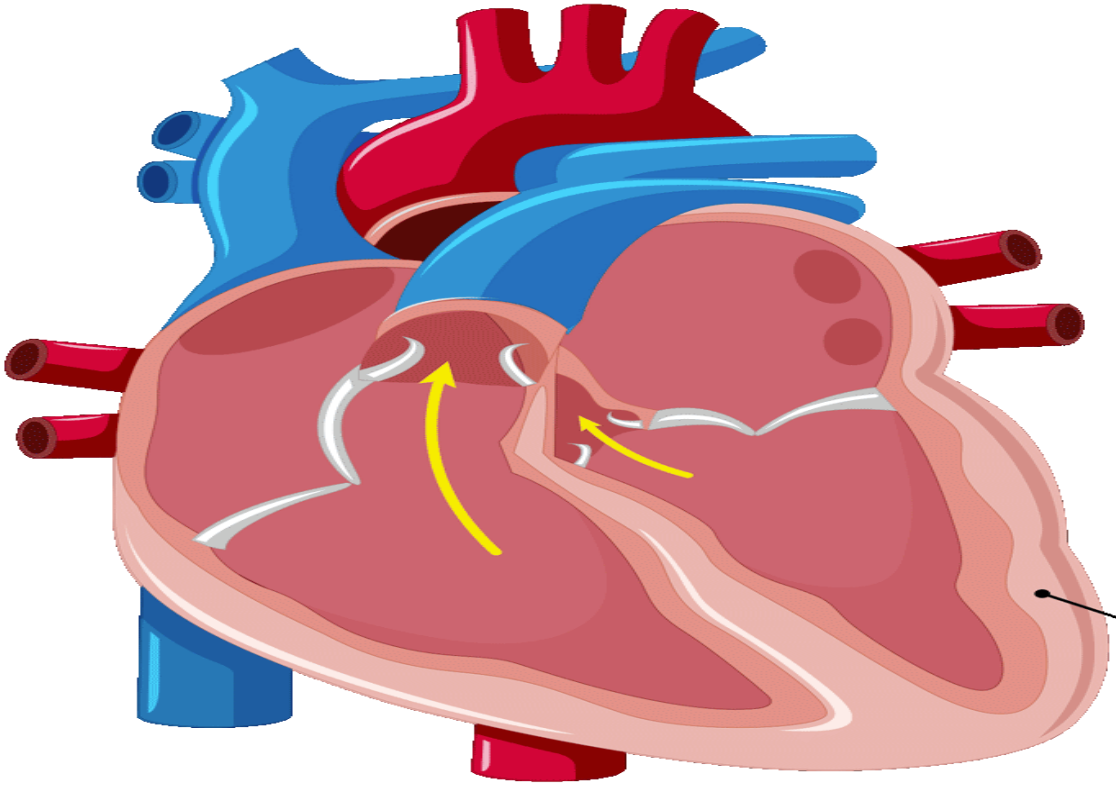
	Sinus Rhythm patients (N = 24)	Atrial fibrillation patients (N = 18)	P value
Age	70.9 ± 10.2	77.2 ± 7.7	.03
Male Gender (%)	17 (70.8)	11 (61.1)	.53
Ejection fraction (%)	32.5 ± 7.4	35.7 ± 8.4	.20
QRS duration (msec)	106.0 ± 13.0	102.3 ± 12.4	.36
Ischaemic aetiology (%)	21 (87.5)	12 (66.7)	.14
Hypertension (%)	11 (45.8)	13 (72.2)	.12
Diabetes (%)	9 (37.5)	4 (22.2)	.33
COPD (%)	3 (12.5)	2 (11.1)	1.00
CKD (%)	18 (75.0)	10 (55.6)	.20
MRA (%)	15 (62.5)	7 (38.9)	.21
NYHA class			
3	14 (58.3)	7 (38.9)	.35
4	10 (41.7)	11 (61.1)	.35

Abbreviations: CCM, contractility modulation; CKD chronic kidney disease; COPD Chronic obstructive pulmonary disease; EF, ejection fraction; MRA mineralocorticoid receptor antagonist; NYHA, New York Heart Association.



Masarone D. Exp Rev Med Dev 2023

Preserved Ejection Fraction



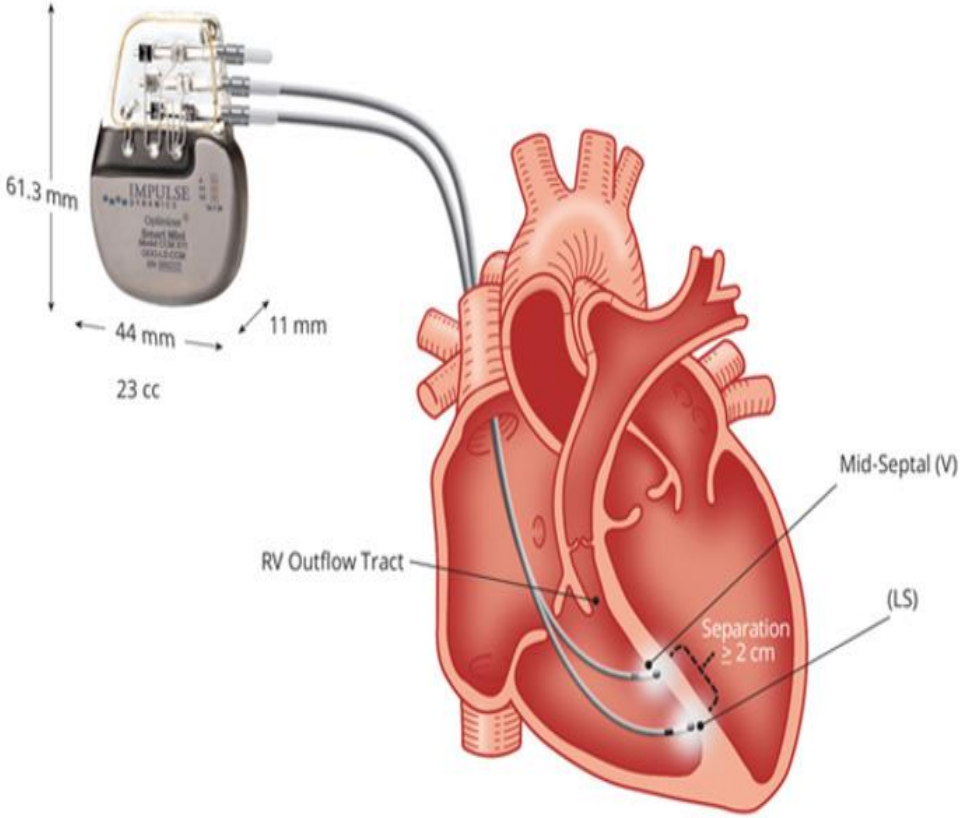
Left ventricle does not fill enough blood.

Heart pumping function is preserved

Heart muscle is stiff and not able to relax

CARDIAC CONTRACTILITY MODULATION IN HEART FAILURE WITH HIGHER EJECTION FRACTION

CCM DEVICE AND ANATOMICAL LOCATION OF PACING WIRES



Mechanism of action

Application of non-excitatory electric stimulation to the interventricular septum during the absolute refractory period

Biomolecular changes

- Optimization of intra-cellular calcium homeostasis
- ↑ titin phosphorylation
- Upregulation of pivotal cardioprotective genes
- Amplification of downstream proteomic signaling

Alteration in myocardial properties

- Lusitropic effect with improved diastolic recoil
- Increased left ventricular contractility

Effect on functional and clinical outcomes

↑ ejection fraction reserve
↑ diastolic filling index
↑ exercise capacity
↑ functional status
↑ survival

Talha K JCF 2022

Available online at www.sciencedirect.com
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Review article

Tuning the molecular giant titin through phosphorylation: Role in health and disease

*Carlos Hidalgo, and Henk Granzier**
Sarver Molecular Cardiovascular Research Program and the Department of Physiology, University of Arizona, Tucson, AZ, USA

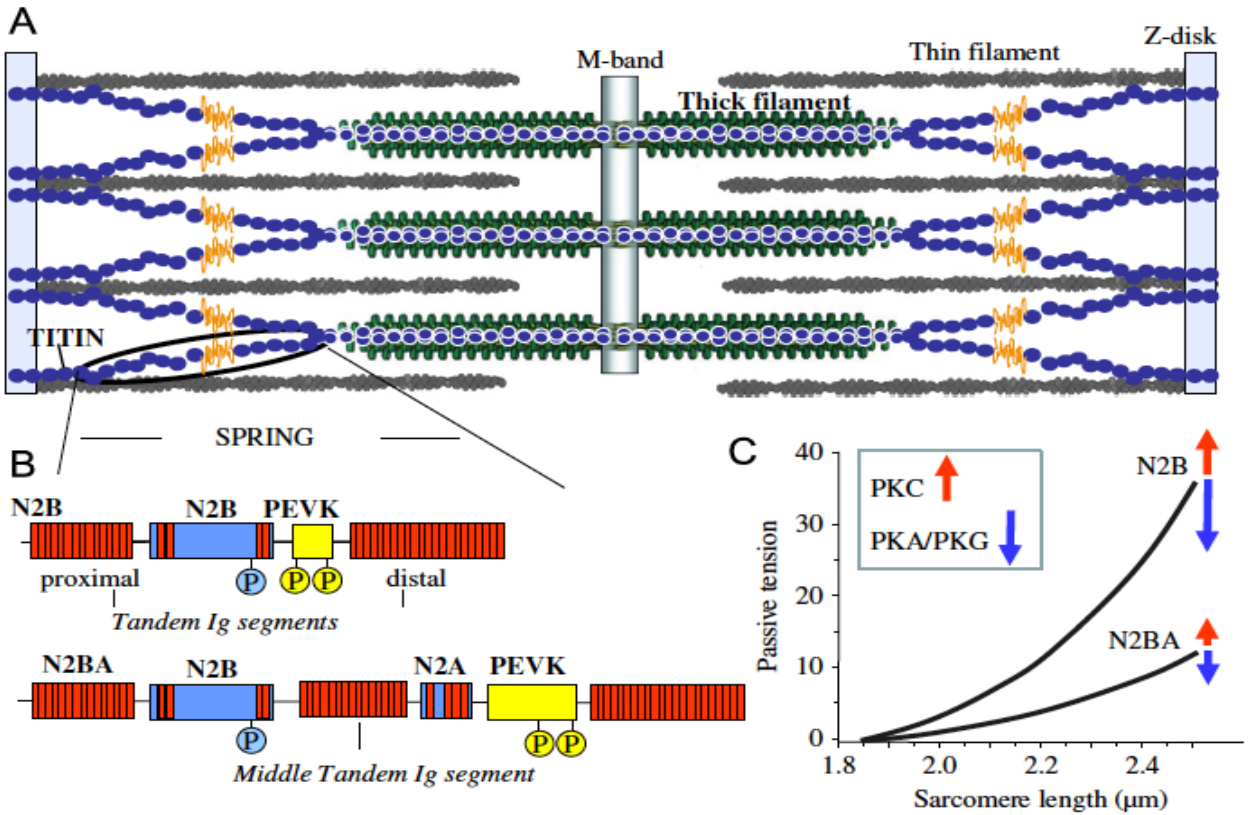
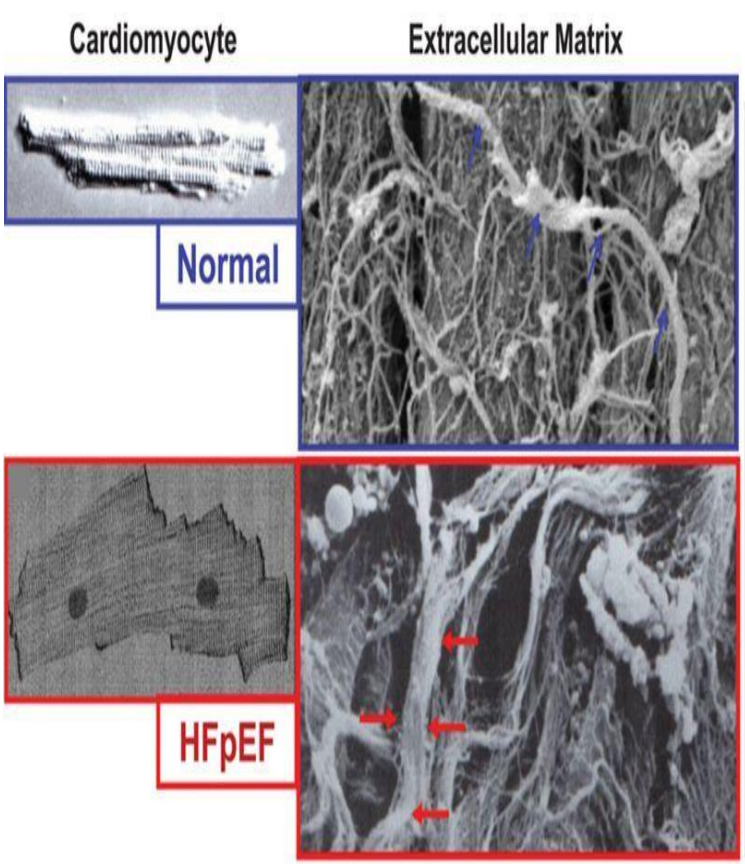
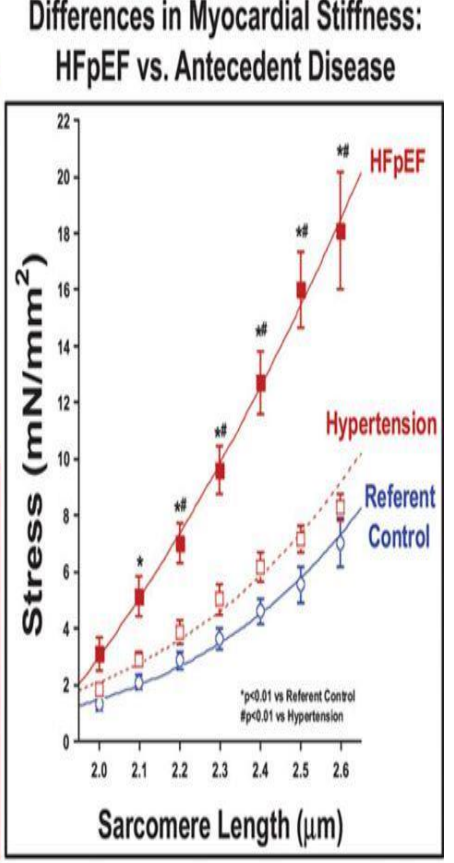


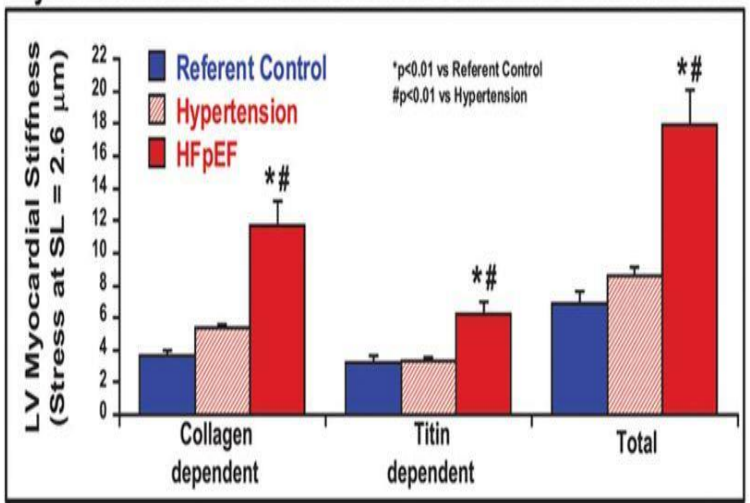
Fig. 1 – (A) Schematic of titin in the cardiac sarcomere. Single titin molecules (shown in blue and yellow) span from Z-disk (N-terminus) to M-band (C-terminus). (B) Composition of extensible I-band region of the N2B and N2BA titin isoforms (found in adults). Red blocks denote Ig-like domains, blue is unique sequence and yellow is PEVK sequence. Also indicated are known phosphorylation sites for PKA/PKG (blue) and PKCα (yellow). (C) Schematic of force–extension curves of titin isoforms and the effects of phosphorylation on passive tension.

EDITORIAL

Could Modification of Titin Contribute to an Answer for Heart Failure With Preserved Ejection Fraction?





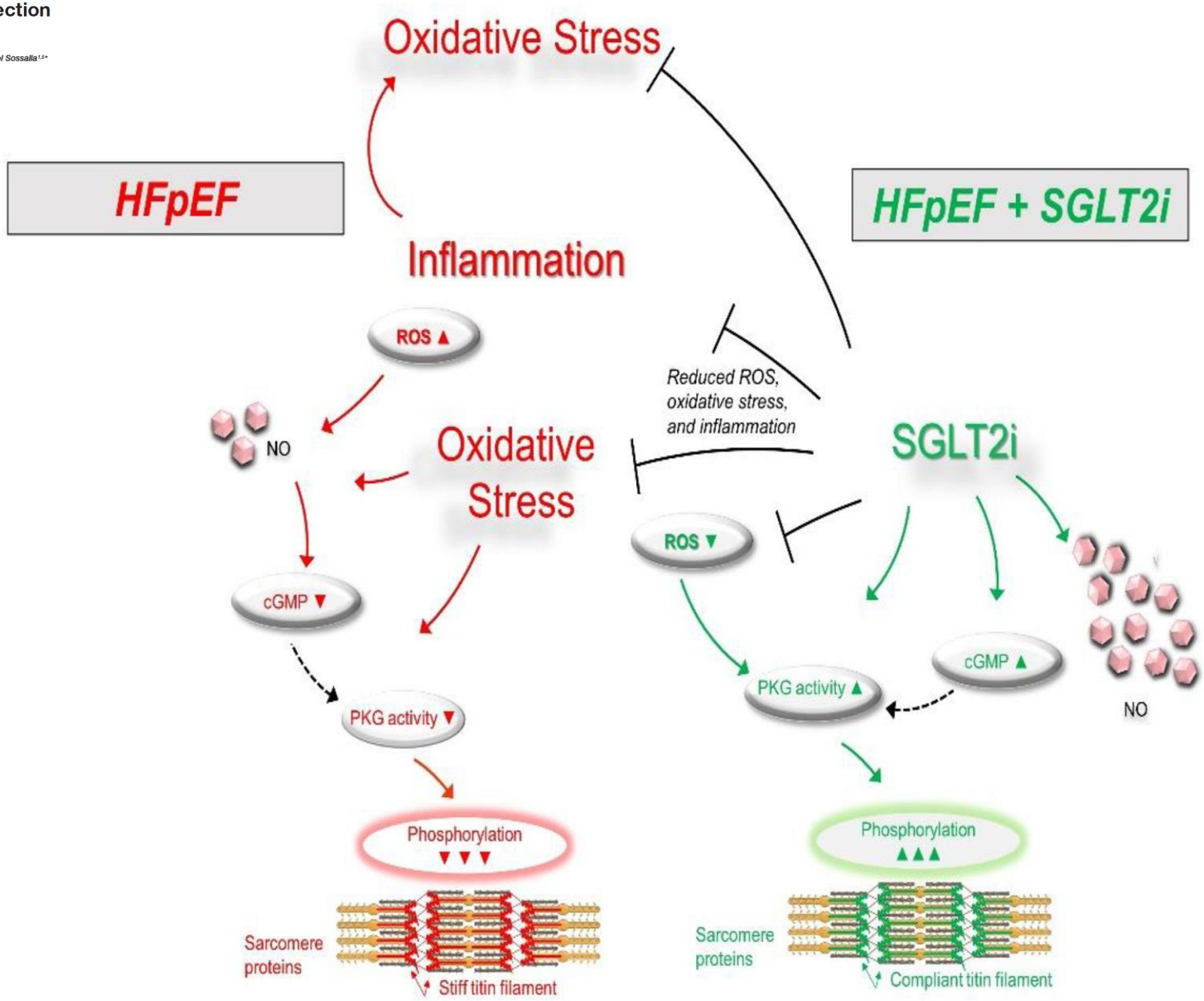


LeWinter M, Circulation 2016

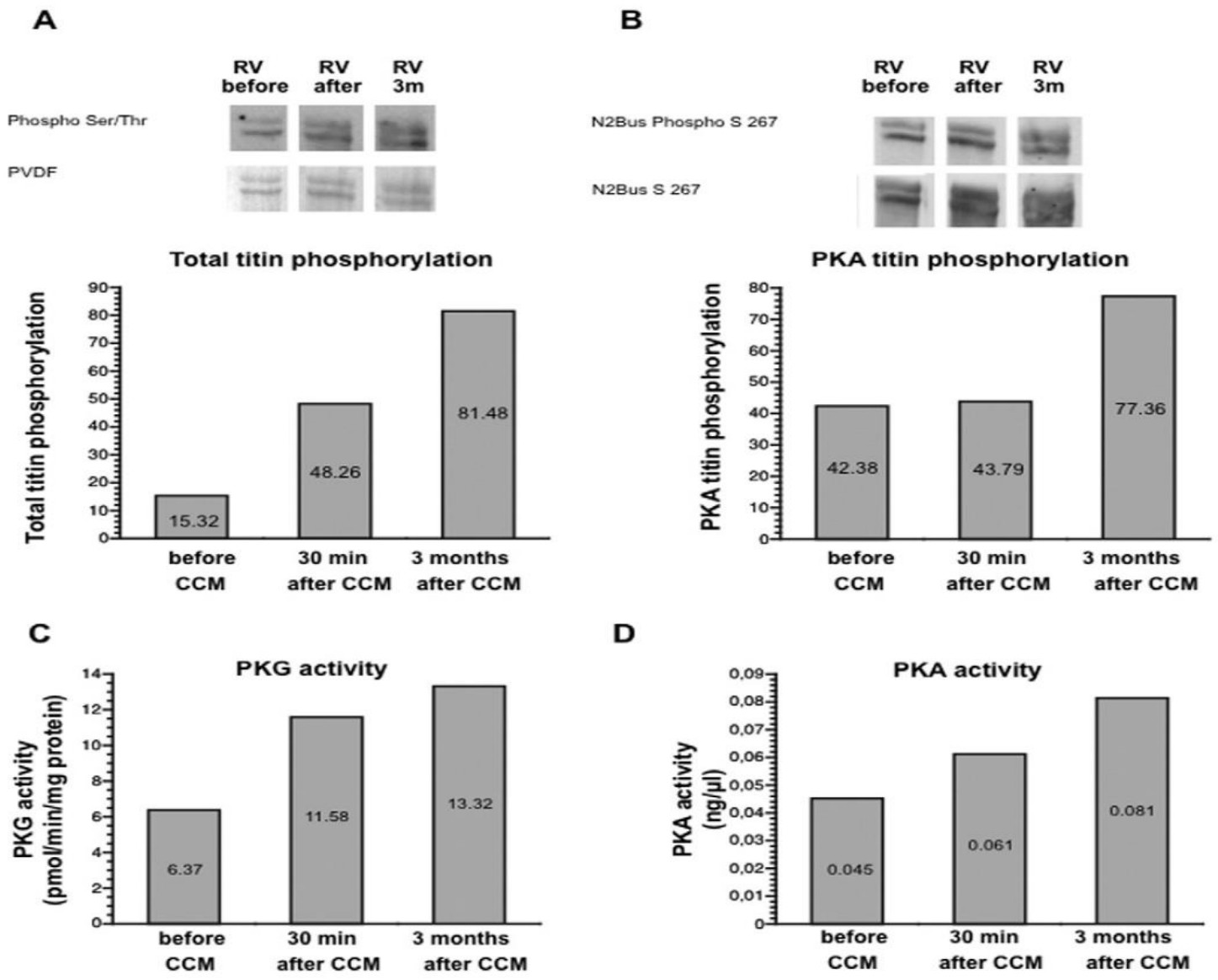
frontiers in Physiology
REVIEW
published: 05 November 2021
doi: 10.3389/fphys.2021.752370

Potential Mechanisms of SGLT2 Inhibitors for the Treatment of Heart Failure With Preserved Ejection Fraction

*Steffen Pabel[1], Nazha Hamdani[2,3], Jagdeep Singh[4] and Samuel Sossalla[1,5]**



CCMT Increase Titin Phosphorylation



Tschöpe C. J Cardiol. 2016

ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 2275–2284
doi:10.1002/ejhf.2619
RESEARCH ARTICLE

Cardiac contractility modulation therapy improves health status in patients with heart failure with preserved ejection fraction: a pilot study (CCM-HFpEF)

Cardiac Contractility Modulation Therapy Improves Health Status in Patients with Heart Failure with Preserved Ejection Fraction; A Pilot Study (CCM-HFpEF)

AIM

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

METHODS

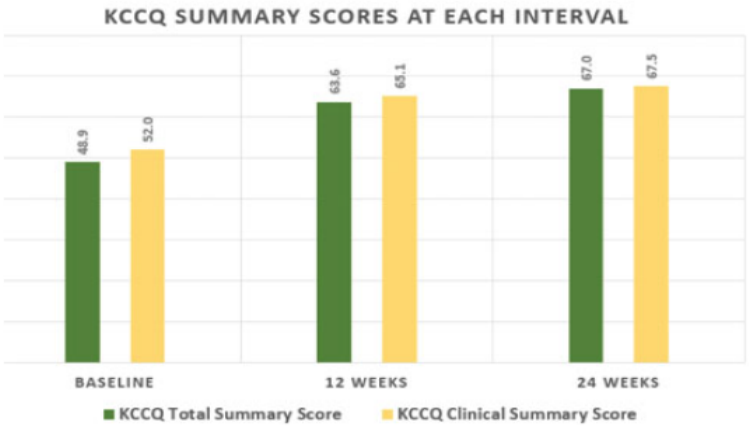
47 HFpEF patients implanted with CCM

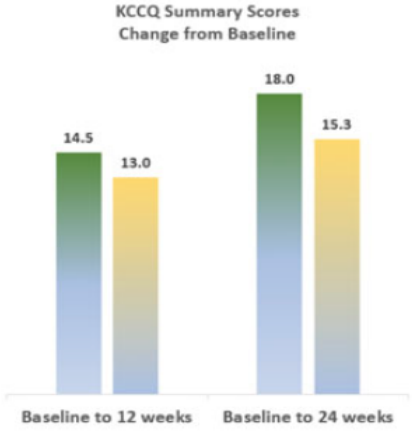
17 centres in EU and Australia

LVEF ≥ 50% per Core Lab

Health status (KCCQ) and safety

KCCQ RESULTS





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

Linde C. EHJ 2022

ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 2275–2284
doi:10.1002/ejhf.2619

RESEARCH ARTICLE

Cardiac contractility modulation therapy improves health status in patients with heart failure with preserved ejection fraction: a pilot study (CCM-HFpEF)

Table 3 Primary and additional efficacy endpoints: Kansas City Cardiomyopathy Questionnaire summary scores (with last observation carried forward)

Parameter	Baseline	12 weeks	Baseline–12 weeks	24 weeks	Baselin–24 weeks	*p*-values for baseline–24 weeks: t-test	Wilcoxon signed-rank test	Normality test
KCCQ overall summary score	48.9 ± 21.7 (47)	63.6 ± 21.2 (46)	14.5 ± 18.6 (46) (9.0–20.1)	67.0 ± 21.1 (46)	18.0 ± 16.6 (46) (13.1–22.9)	<0.001	<0.001	0.219
KCCQ clinical summary score	52.0 ± 21.9 (47)	65.1 ± 21.5 (46)	13.0 ± 19.8 (46) (7.1–18.8)	67.5 ± 21.9 (46)	15.3 ± 19.4 (46) (9.6–21.1)	<0.001	<0.001	<0.001

Values are given as mean ± standard deviation (*N*), and 95% confidence interval.
KCCQ, Kansas City Cardiomyopathy Questionnaire; SD, standard deviation.
Patients missing a 24-week value with an available 12-week value had that last observation carried forward for this analysis; this included one patient with KCCQ missing at 24 weeks.

Table 4 Secondary efficacy endpoints (with last observation carried forward)

Parameter	Baseline	24 weeks	Baseline–24 weeks	*p*-values for baseline–24 weeks: t-test	Wilcoxon signed-rank test	Normality test
Echocardiography						
LAVi (ml/m^2)	48.2 ± 14.0 (47)	45.9 ± 14.4 (44)	−2.8 ± 8.2 (44) (−5.3 to −0.3)	0.014	0.034	0.046
Septal E/e′	15.3 ± 4.4 (47)	14.5 ± 5.2 (42)	−0.9 ± 4.7 (42) (−2.4 to 0.6)	0.111	0.038	0.022
Septal e′	5.7 ± 1.2 (47)	5.6 ± 1.6 (43)	−0.0 ± 1.5 (43) (−0.5 to 0.4)	0.417	0.336	0.008
NT-proBNP (pg/ml)[a]	702.0 (470–1005) (46) (230.0–6814)	730.0 (394–1140) (42) (152.0–4720)	23.0 (43) (−85.0 to −283.1) (−2399 to 1710)	NA	0.077	NA
NYHA class	2.6 ± 0.5 (47)	2.2 ± 0.6 (46)	−0.5 ± 0.6 (46) (−0.6 to −0.3)	<0.001	<0.001	<0.001

Values are given as mean ± standard deviation (*N*), and 95% confidence interval.
LAVi, left atrial volume index; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]One was an outlier and removed from this analysis. For NT-proBNP we present median (interquartile range) and minimum – maximum values.


AIM
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News

Impulse Dynamics achieves first implantation in INTEGRA-D study

The trial will assess the world's first cardiac device combining CCM therapy with an ICD in a single implant.

May 19, 2023

Share

The first-ever implantation of the company's dual cardiac device took place at Cleveland Clinic. Credit: Cleveland Clinic.


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