HOT TOPICS
IN CARDIOLOGIA
2024
Università degli studi di Napoli Parthenope
Villa Doria D'Angri - Via F. Petrarca 80, Napoli
Presidente del congresso: Dr. Ciro Mauro

CCM nello scompenso cardiaco: quando pensarci e quali aspettative nutrire?

Daniele Masarone MD; PhD

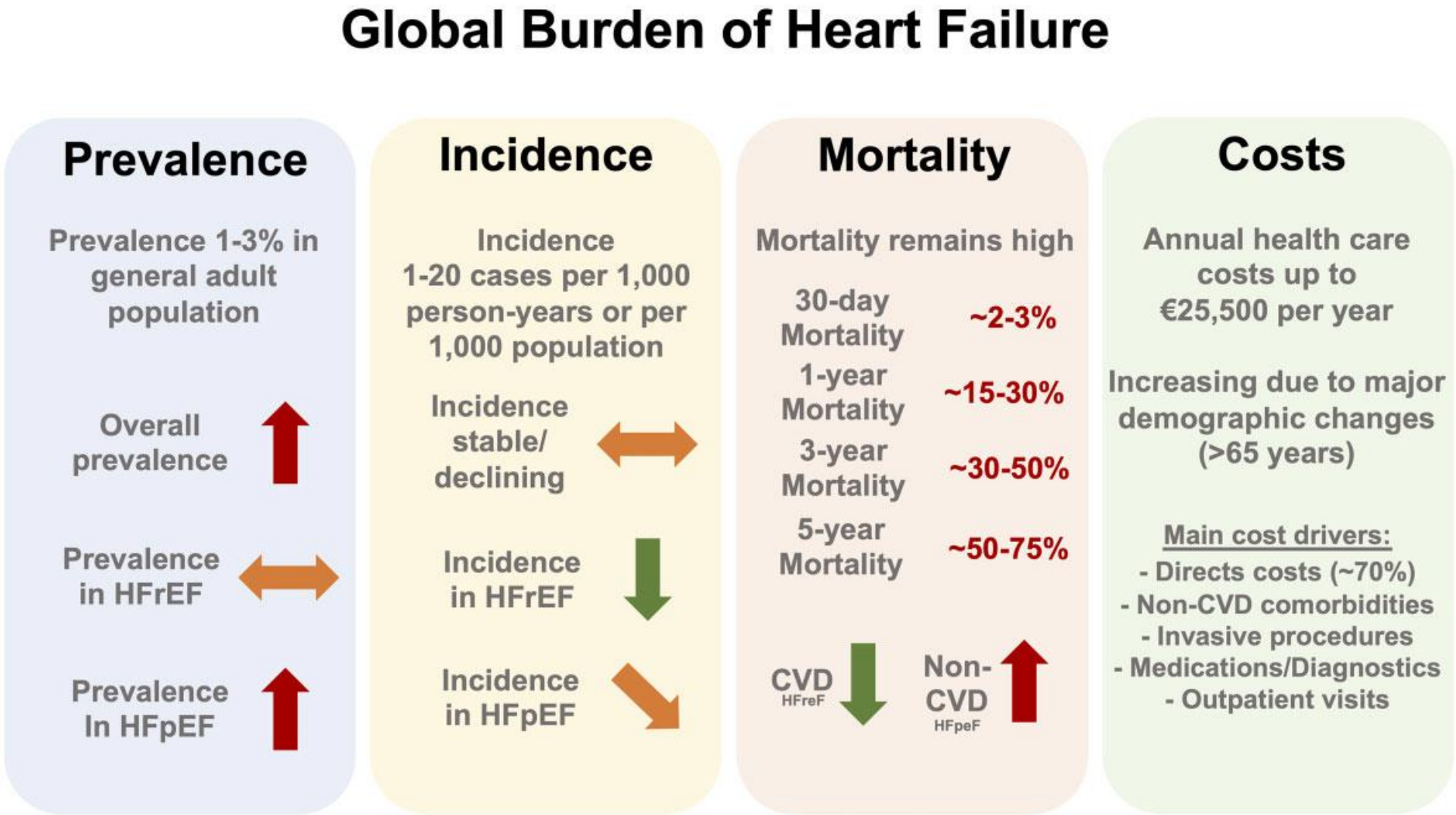
Dipartimento di Cardiologia

AOS dei Colli

Ospedale Monaldi

Global burden of heart failure: a comprehensive and updated review of epidemiology

Gianluigi Savarese [1,2†], Peter Moritz Becher[1,3†], Lars H. Lund[1,2], Petar Seferovic[4,5], Giuseppe M.C. Rosano[6], and Andrew J.S. Coats[7*]

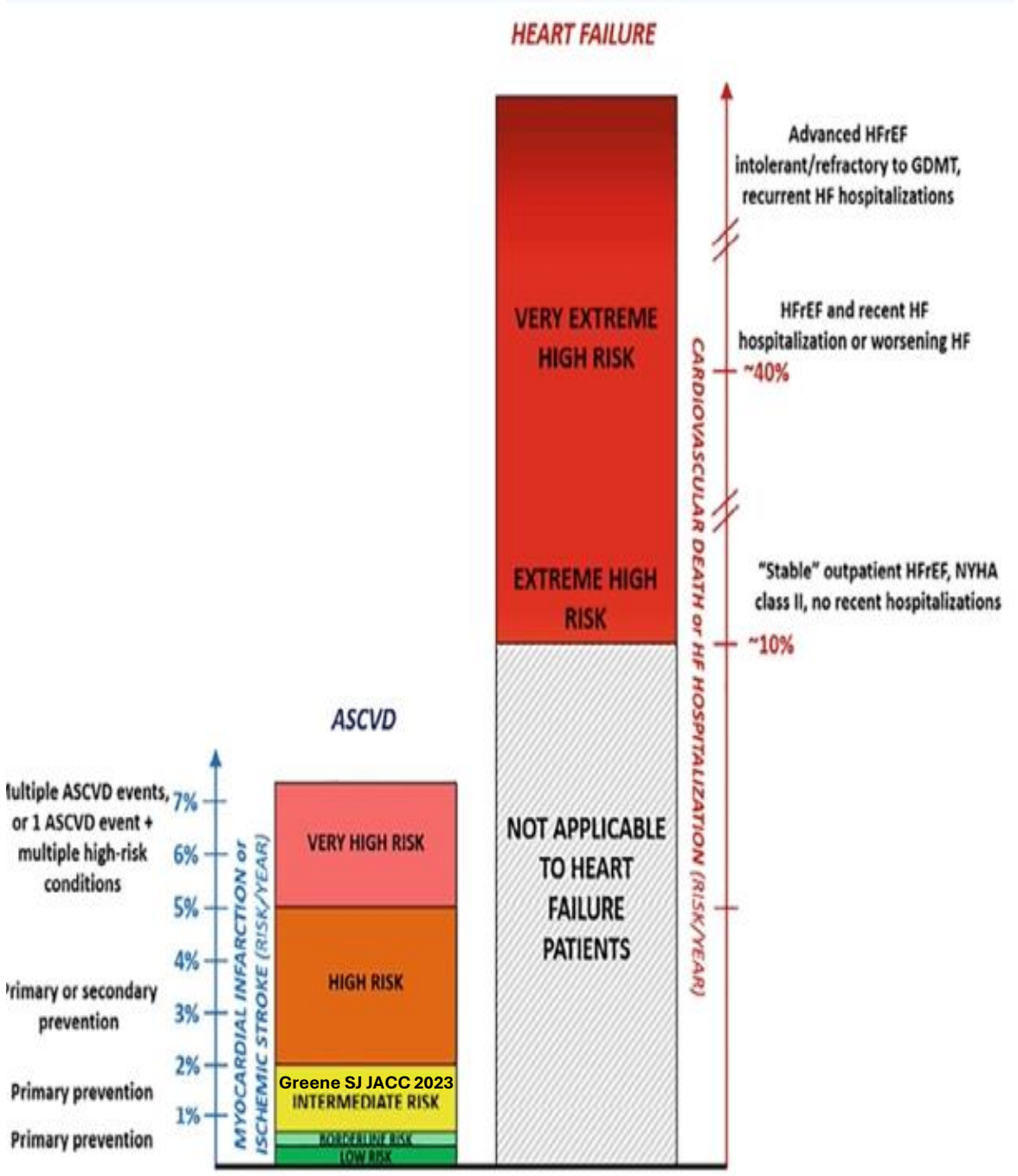


Savarese GL Card Res 2023

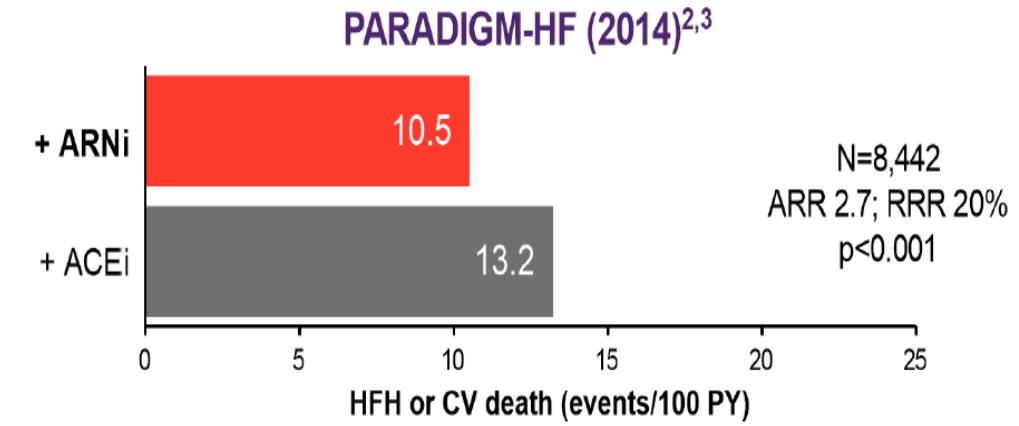
The war against heart failure: the *Lancet* lecture

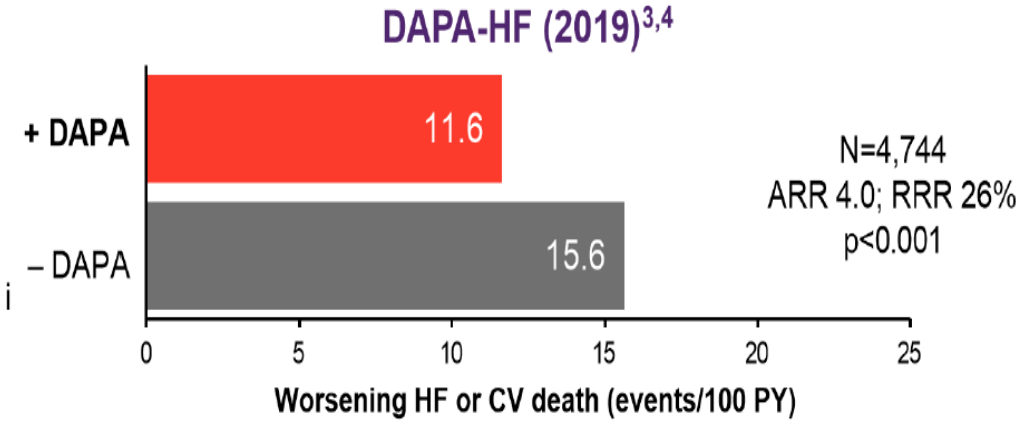
Eugene Braunwald

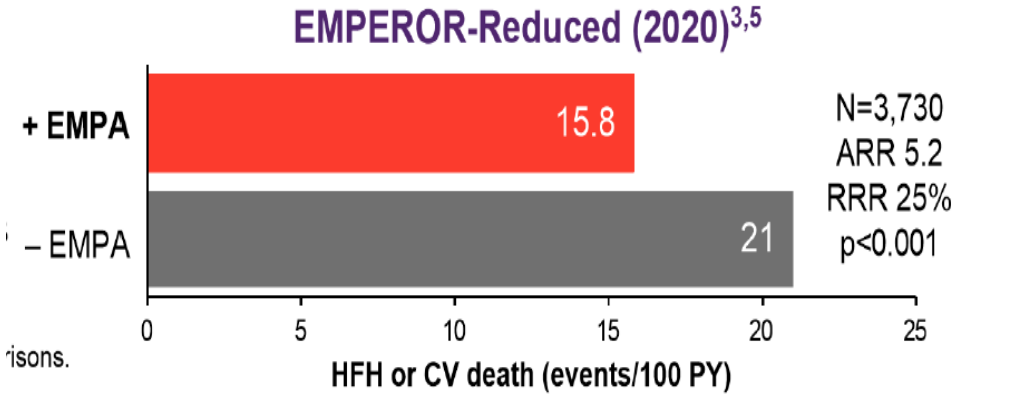
Braunwald E Lancet 2015



Greene SJ JACC 2023



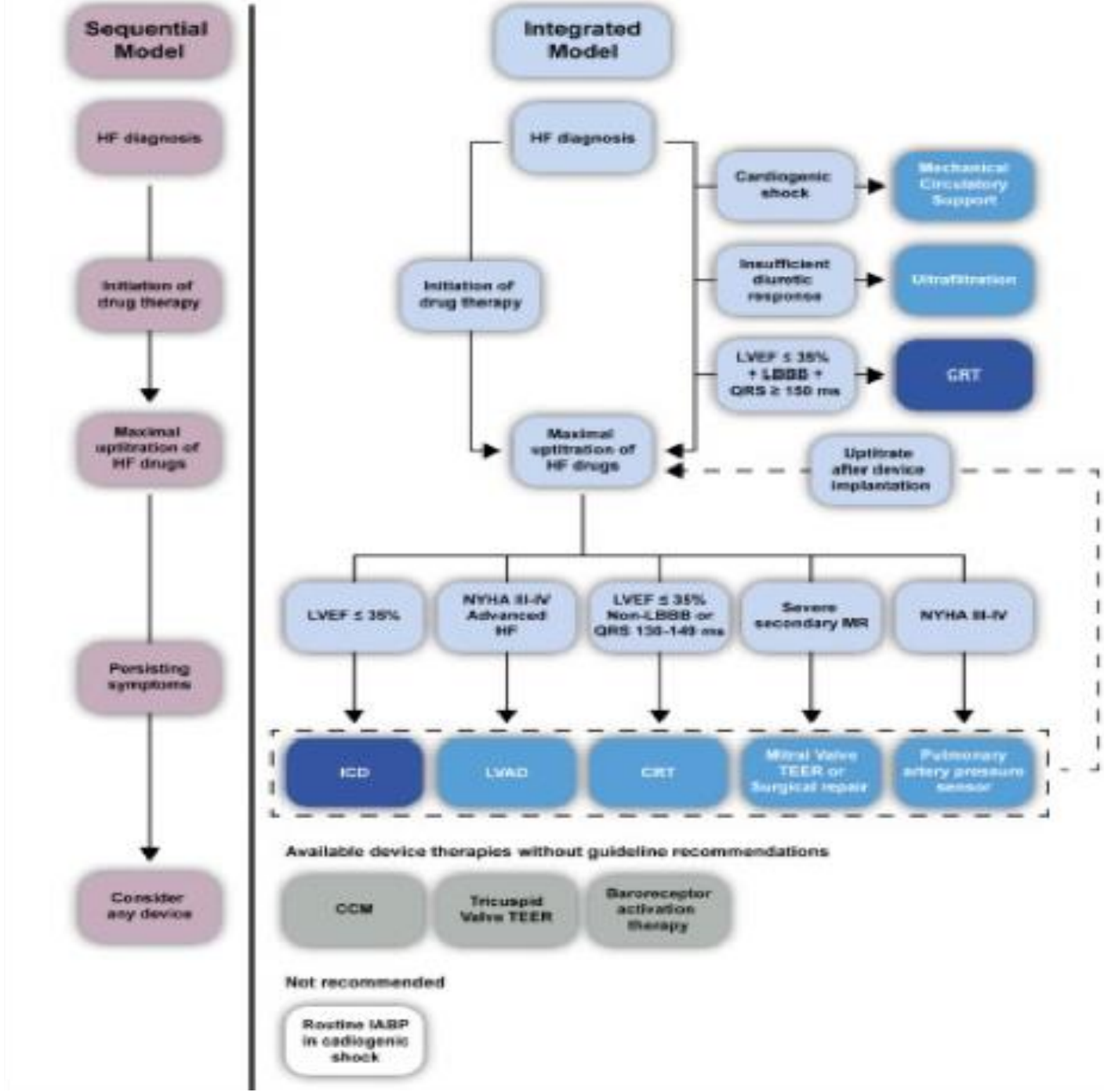




ESC European Society of Cardiology
European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3168
POSITION PAPER

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[1,2], Finn Gustafsson[3], Alexandre Mebazaa[4], Jan Stoffel[5], Klaus K. Witte[6], Victoria Delgado[7,8], Cecilia Linde[9], Kevin Vernooy[10], Stefan D. Anker[11], Ovidiu Chioncel[12], Davor Milicic[13], Gerd Hasenfuß[11], Piotr Ponikowski[14], Ralph Stephan von Bardeleben[15], Friedrich Koehler[16], Frank Ruschitzka[17], Kevin Damman[18], Ehud Schwammenthal[21], Jeffrey M. Testani[22], Faiez Zannad[23], Michael Böhm[24], Martin R. Cowie[25], Kenneth Dickstein[26], Tiny Jaarsma[27], Gerasimos Filippatos[28], Maurizio Volterrani[29], Thomas Thum[30], Stamatis Adamopoulos[31], Alain Cohen-Solal[32], Brenda Moura[33], Amina Rakisheva[34], Arsen Ristic[35], Antoni Bayes-Genis[36], Sophie Van Linthout[37], Carlo Gabriele Tocchetti[38], Gianluigi Savarese[39], Hadi Skouri[40], Marianna Adamo[41], Offer Amir[42], Mehmet Birhan Yilmaz[43], Maggie Simpson[44], Mariya Tokmakova[45], Arantxa González[46], Massimo Piepoli[47], Petar Seferovic[35], Marco Metra[41], Andrew J.S. Coats[48], and Giuseppe M.C. Rosano[49]



JCF
Journal of Cardiac Failure

Review Article

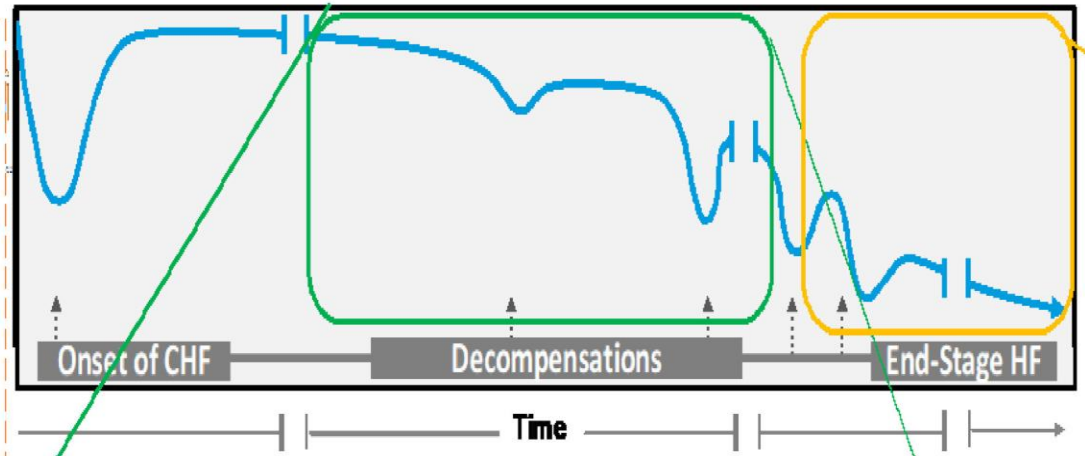
HFSA Scientific Statement: Update on Device Based Therapies in Heart Failure

JERRY D. ESTEP, MD[1] HUSAM M. SALAH, MD[2] SAMIR R. KAPADIA, MD[3]
DANIEL BURKHOFF, MD, PhD[4] ANURADHA LALA, MD[5] JAVED BUTLER, MD, MPH, MBA[6,7]
SHELLEY HALL, MD[8] and MARAT FUDIM, MD, MHS[2,9]

Weston, FL; Durham, NC; Cleveland, OH; New York, NY; Dallas, TX; and Jackson, MI

Approved Devices for Stage C and D Chronic Heart Failure

An interdisciplinary team that consists of a general cardiologist, HF cardiologist, interventional cardiologist, structural cardiologist, multimodality imaging cardiologist, electrophysiologist, and cardiothoracic surgeon is crucial for the successful implantation and delivery of device-based therapies in heart failure



Implantable cardioverter-defibrillator (ICD)
-NYHA I-III
-LVEF ≤ 35%
-Projected survival > 1 year

COR*: 1

Cardiac resynchronization therapy (CRT-D)
-NYHA II-III; ambulatory IV
-LVEF ≤ 35%
-Normal sinus
-QRS ≥ 150 msec with a LBBB

COR*: 1

LVAD (HM3)
-NYHA IV
-LVEF ≤ 25%
-inotrope dependent or Cardiac Index (CI) < 2.2 L/min/m2
- Failing to respond to GDMT for at least 45 out of the last 60 days

COR*: 1 (inotrope dependent)
COR*: 2a (Select NYHA IV patient

Transcatheter edge-to-edge mitral valve repair (M-TEER)
-NYHA II-Ambulatory IV
-LVEF 20-50%
-Moderate-severe (grade 3+) or severe (grade 4+) secondary MR
-LVESD ≤ 7cm
-Excludes RHF and/or severe PHTN (RVSP > 70 mmHg)

COR*: 2a

AVR (TAVI or SAVR)
-NYHA I-IV
-Asymptomatic patients with severe AS and LVEF < 50%
-Severe high-gradient AS with symptoms (independent of LVEF)
-Symptomatic patients with low-flow, low gradient severe AS with reduced LVEF
-Symptomatic patients with low-flow, low gradient with normal LVEF if AS is the most likely cause of symptoms

COR**: 1

Transcatheter tricuspid valve replacement system OR transcatheter edge-to-edge mitral valve repair (T-TEER)
-NYHA I-IV
-Signs/symptoms of TR or prior hospitalization for HF
- Severe TR

COR*: Not Provided

Remote Hemodynamic Monitoring (CardioMEMs)
-NYHA II-III
-Independent of LVEF
- Hospitalized for HF in the previous year and/or have elevated natriuretic peptides

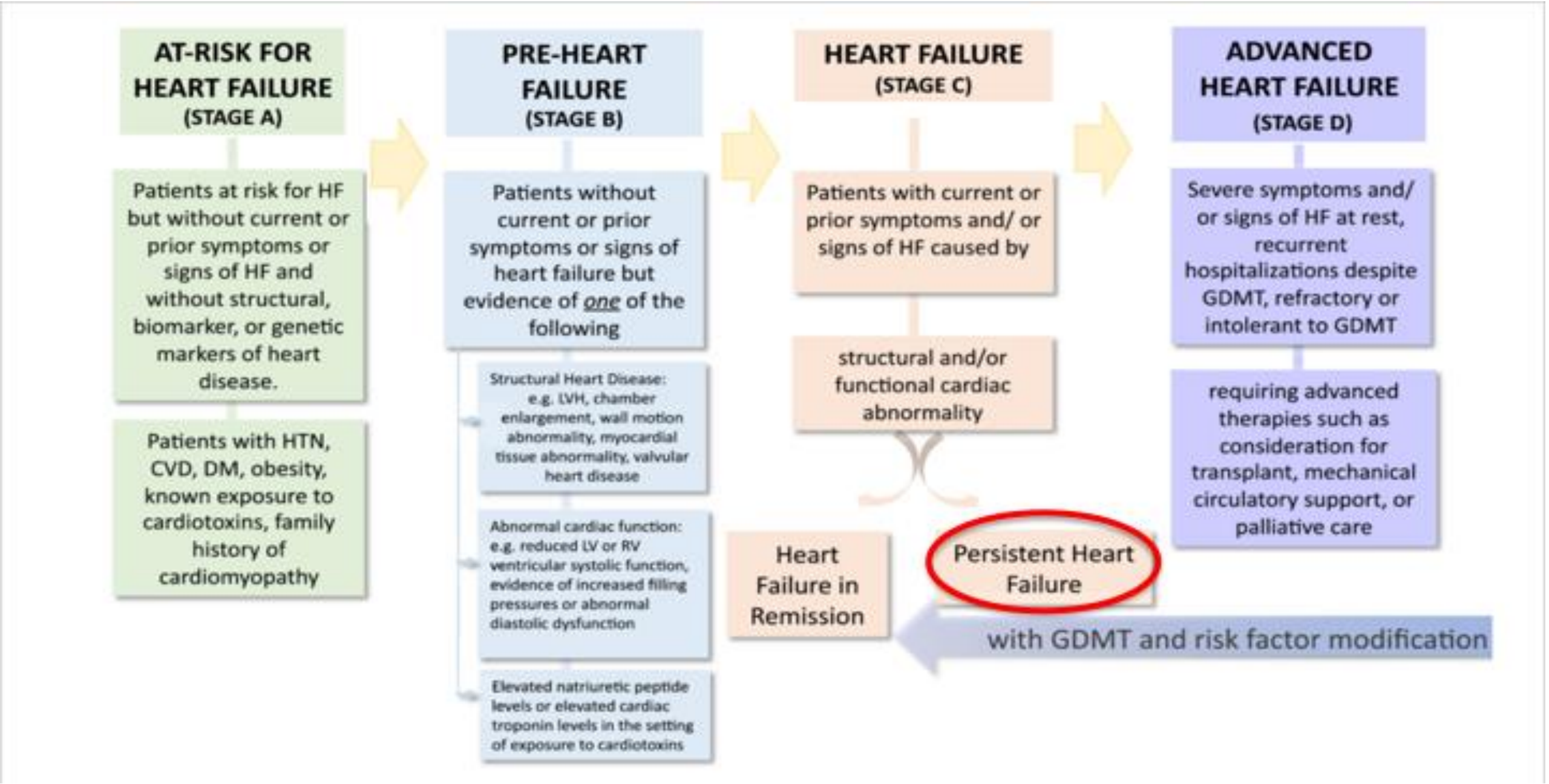
COR*: 2b

Baroreflex activation therapy (BAT)
-Persistent symptoms with NYHA III or II (with a recent history of Class III)
-LVEF ≤ 35%
- NT-proBNP <1600 pg/ml
-Excludes patients with a guideline indication for CRT

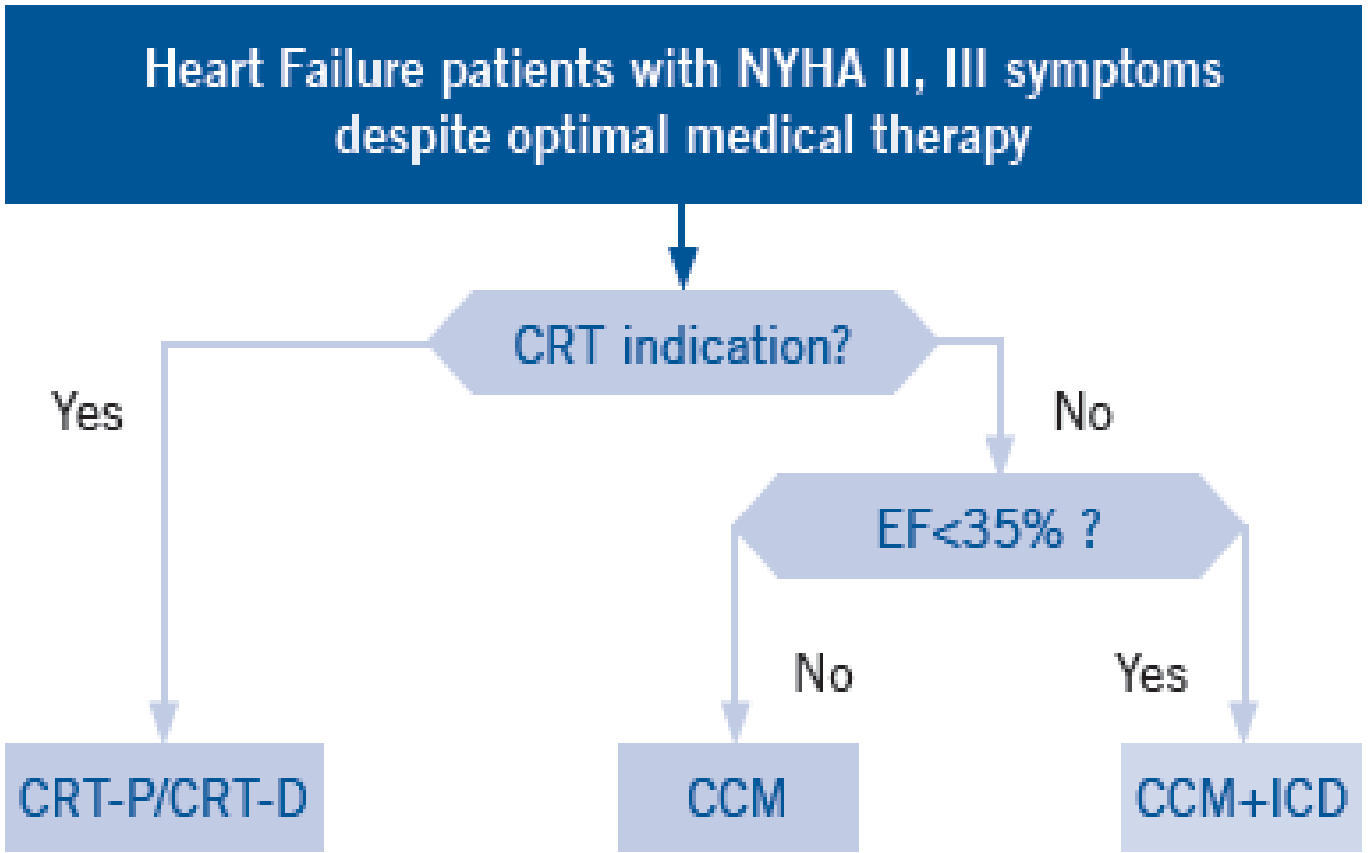
COR*: Not Provided

Cardiac Contractility Modulation (CCM)
-NYHA III
-LVEF 25-45%
-QRS duration < 130 ms
-Contraindicated with permanent atrial fibrillation

COR*: Not Provided


AT-RISK FOR HEART FAILURE (STAGE A)
Patients at risk for HF but without current or prior symptoms or signs of HF and without structural, biomarker, or genetic markers of heart disease.
Patients with HTN, CVD, DM, obesity, known exposure to cardiotoxins, family history of cardiomyopathy
PRE-HEART FAILURE (STAGE B)
Patients without current or prior symptoms or signs of heart failure but evidence of one of the following
Structural Heart Disease: e.g. LVH, chamber enlargement, wall motion abnormality, myocardial tissue abnormality, valvular heart disease
Abnormal cardiac function: e.g. reduced LV or RV ventricular systolic function, evidence of increased filling pressures or abnormal diastolic dysfunction
Elevated natriuretic peptide levels or elevated cardiac troponin levels in the setting of exposure to cardiotoxins
HEART FAILURE (STAGE C)
Patients with current or prior symptoms and/ or signs of HF caused by
structural and/or functional cardiac abnormality
ADVANCED HEART FAILURE (STAGE D)
Severe symptoms and/ or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT
requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care
Heart Failure in Remission
Persistent Heart Failure
with GDMT and risk factor modification

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

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

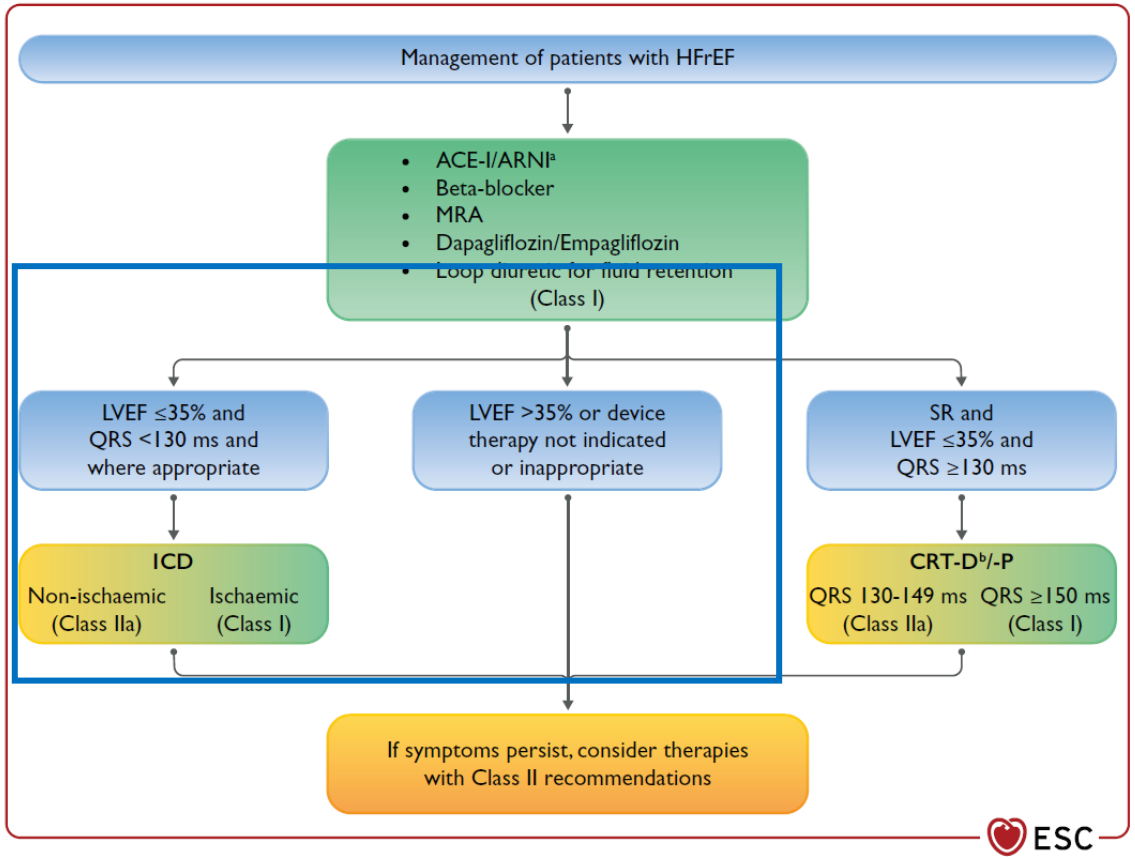
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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]

Supplementary Table 9 Interventions aiming to improve quality of life and/or exercise capacity in symptomatic patient with heart failure with reduced ejection fraction

	Intervention	Additional criteria beyond the presence of symptomatic HFrEF (if any)
DRUGS	Sacubitril/valsartan[17,18]	
	Dapagliflozin[19]	
	Diuretics[20]	Fluid overload
	Ferric carboxymaltose i.v.[21–23]	Iron deficiency
	Ivabradine[24–26]	SR >70 b.p.m.
	Trimetazidine[27–29]	
DEVICES AND INVASIVE PROCEDURES	CRT[30,31]	Eligibility for CRT
	Pulmonary vein isolation[32–34]	AF
	Percutaneous correction of severe functional mitral regurgitation[35–38]	Severe functional mitral regurgitation
	Cardiac contractility modulation[39–41]	QRS <130 ms, LVEF 25–45%
	Baroreflex activation therapy[42–44]	
	Phrenic nerve stimulation[45–47]	Central sleep apnoea



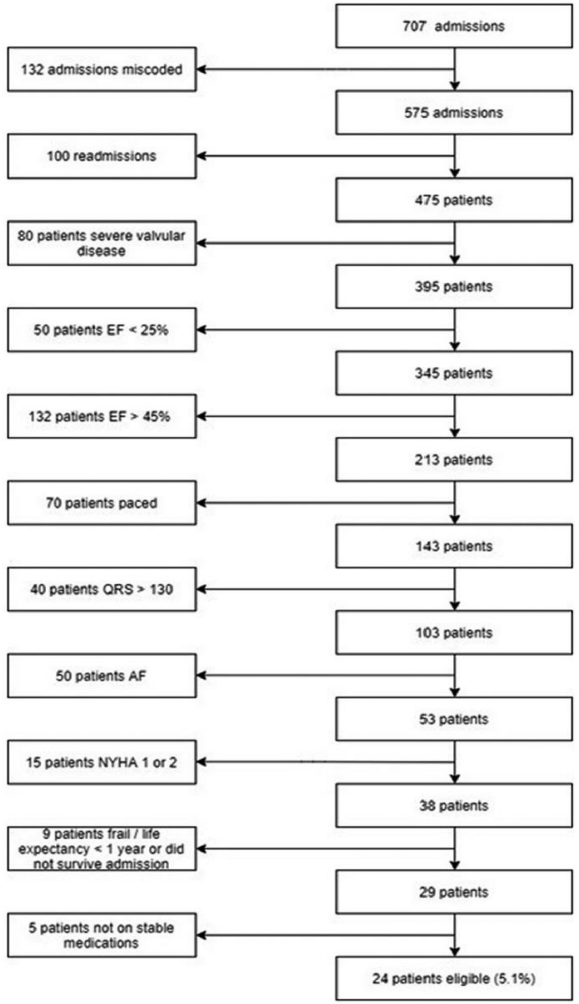
CCMT in which patients?

- NYHA II with 2 or more WHF episodes in the last 12 months
- NYHA III with at least 1 WHF episodes in the last 12 months
- 25%≤EF ≤45%
- QRS ≤130 ms (in some selected cases also in CRT-D non responder)
- GDMT
- BEV < 10.000; AF with VR < 110 b/min
- 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

Received: 20 June 2020 | Accepted: 24 July 2020
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.

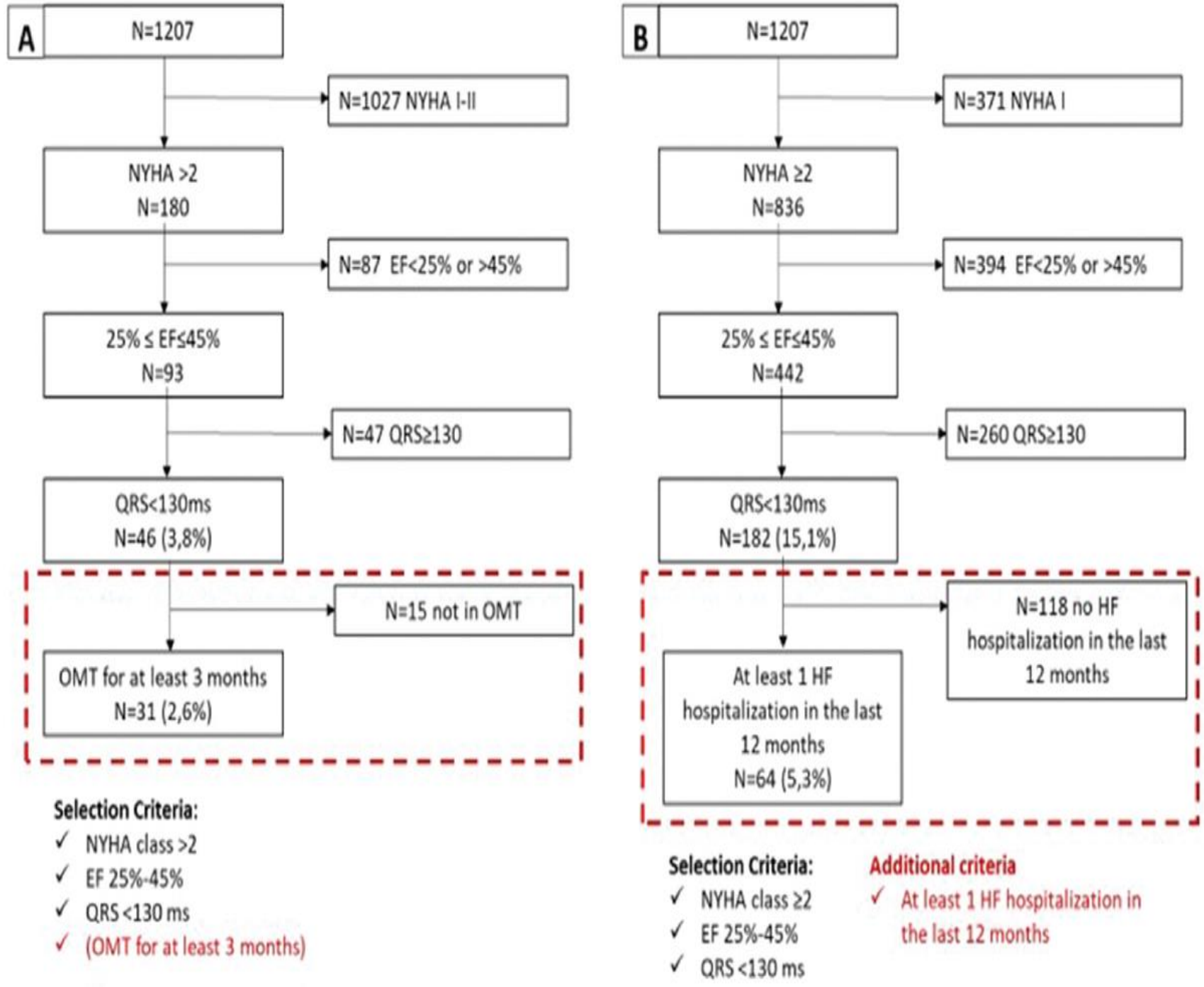
Dulai R et al. IJCP 2020

Expert Review of Medical Devices

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

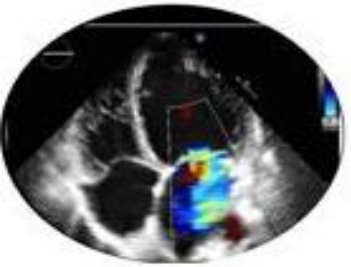
Bridging the gap in the symptomatic heart failure patient journey: insights from the Italian scenario

Matteo Ziacchi, Alberto Spadotto, Stefano Ghio, Marta Pellegrino, Luciano Potena, Daniele Masarone, Marco Merlo, Davide Stolfo, Maria Michela Caracciolo, Corinna Inserra, Fabrizio Ammirati, Michele Ciccarelli, Furio Colivicchi, Stefano Bianchi, Giuseppe Patti, Fabrizio Oliva, Giuseppe Arcidiacono, Roberto Rordorf, Daniela Pini, Giuseppe Pacileo, Antonio D'Onofrio, Giovanni Battista Forleo, Matteo Mariani, Francesco Adamo, Alessandro Alonzo, Matteo Ruzzolini, Chiara Ghiglieno, Manlio Cipriani, Giorgio Firetto, Nadia Aspromonte, Francesco Clemenza, Gaetano Maria De Ferrari, Michele Senni, Maria Grazia Bongiorni, Claudio Tondo, Massimo Grimaldi, Francesco Giallauria, Francesco Rametta, Procolo Marchese, Mauro Biffi & Gianfranco Sinagra



Ziacchi M et al. Ex Rev Med Dev 2023

CCMT
Biological Effects



Minutes

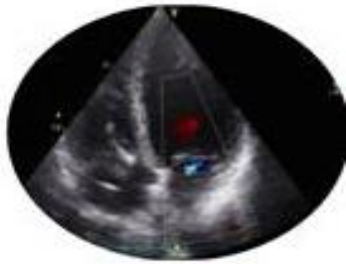
- Upregulation of SERCA2a
- Increased phosphorylation of titin
- Increased phosphorylation of PLB
- Increased phosphorylation of PKA and PKG

Hours

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

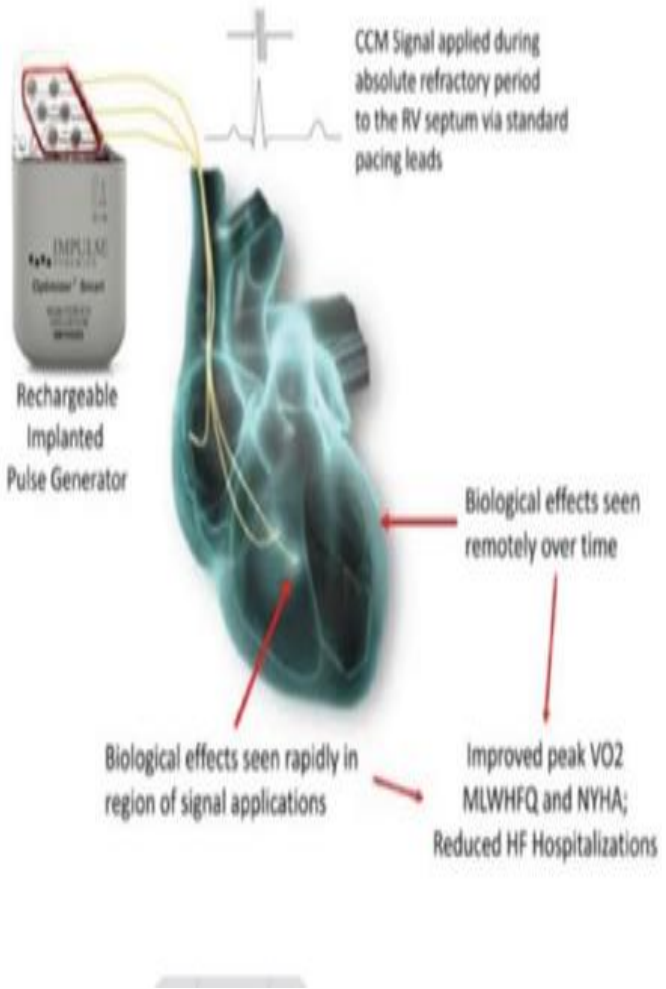
Months

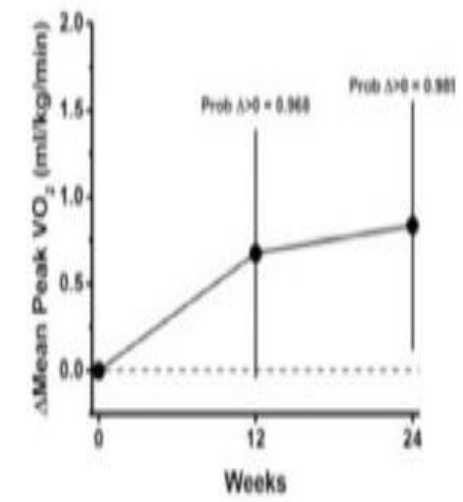
- Improved ejection fraction reserve
- Improved diastolic filling index

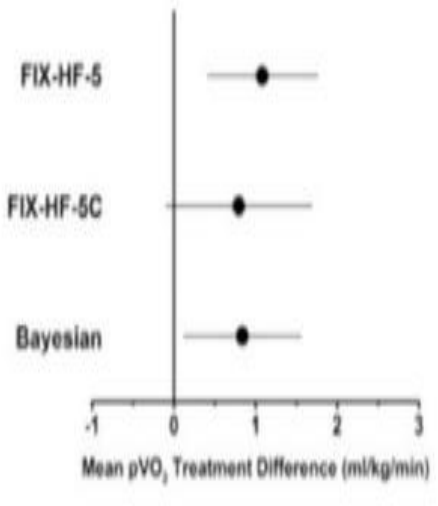


Masarone D . Heart Rhythm 2023

CCMT
Clinical Effects







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

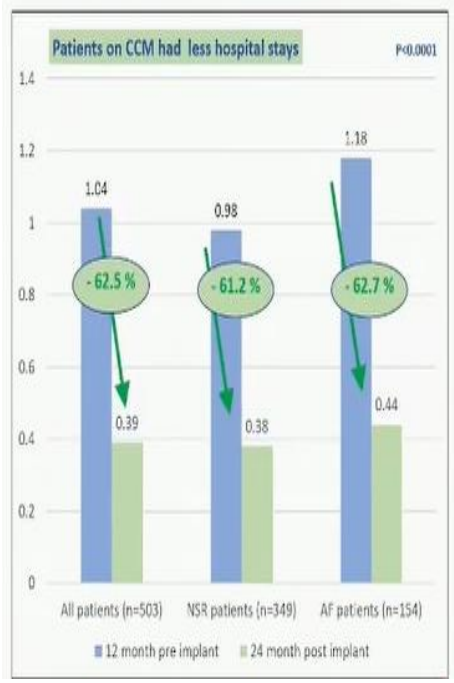
Jürgen Kuschyk[1], Peter Falk[2], Thomas Demming[3], Oliver Marx[3], Deborah Morley[4], Ishu Rao[4], and Daniel Burkhoff[5]*

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

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

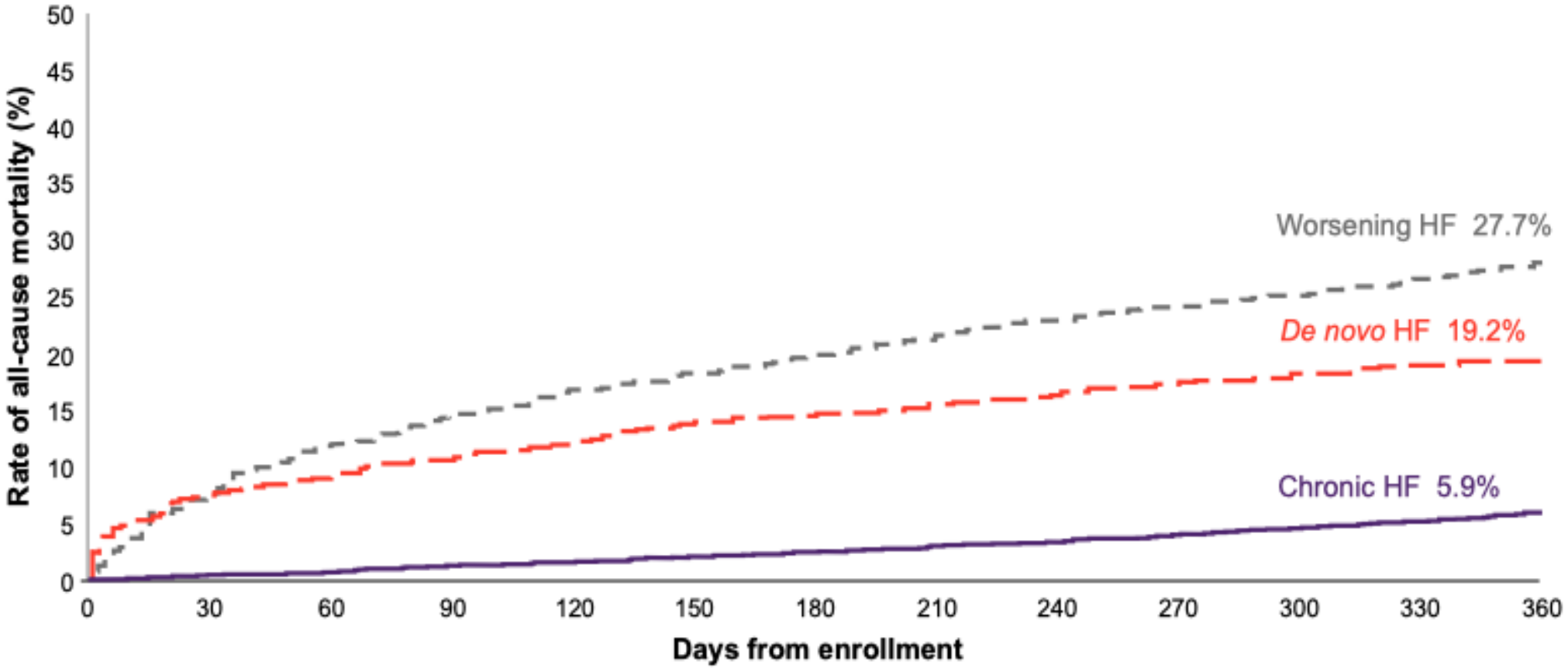
Subgroup	Pre-treatment (1 year prior)				Post-treatment (0–730 days)				
	Patients	Patient-years	Events	Event rate	Patients	Patient-years	Events	Event rate	*P*-value
All patients									
All cardiovascular events	503	503	523	1.04	503	729	287	0.39	<0.0001
Heart failure events			371	0.74			179	0.25	<0.0001
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	98	0.38	<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.



Worsening HF is associated with a four-fold increase in 1-year mortality risk compared with chronic HF

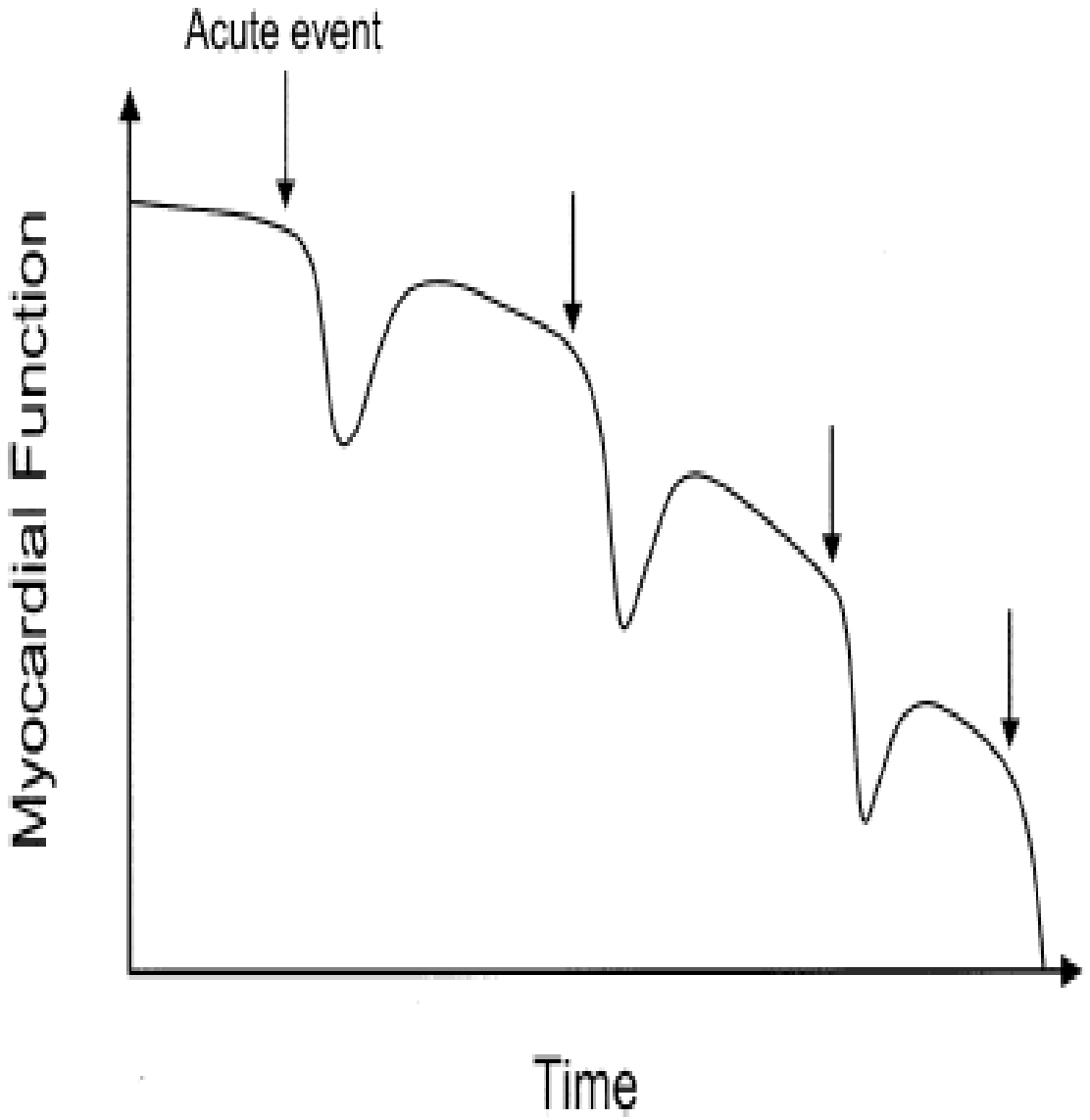
One-year all-cause mortality rate in patients hospitalized with acute HF or outpatients with chronic HF, prospectively enrolled in the IN-HF outcome registry (N=5,610)[1]



Tavazzi L Circ HF 2013

Pathophysiologic Targets in the Early Phase of Acute Heart Failure Syndromes

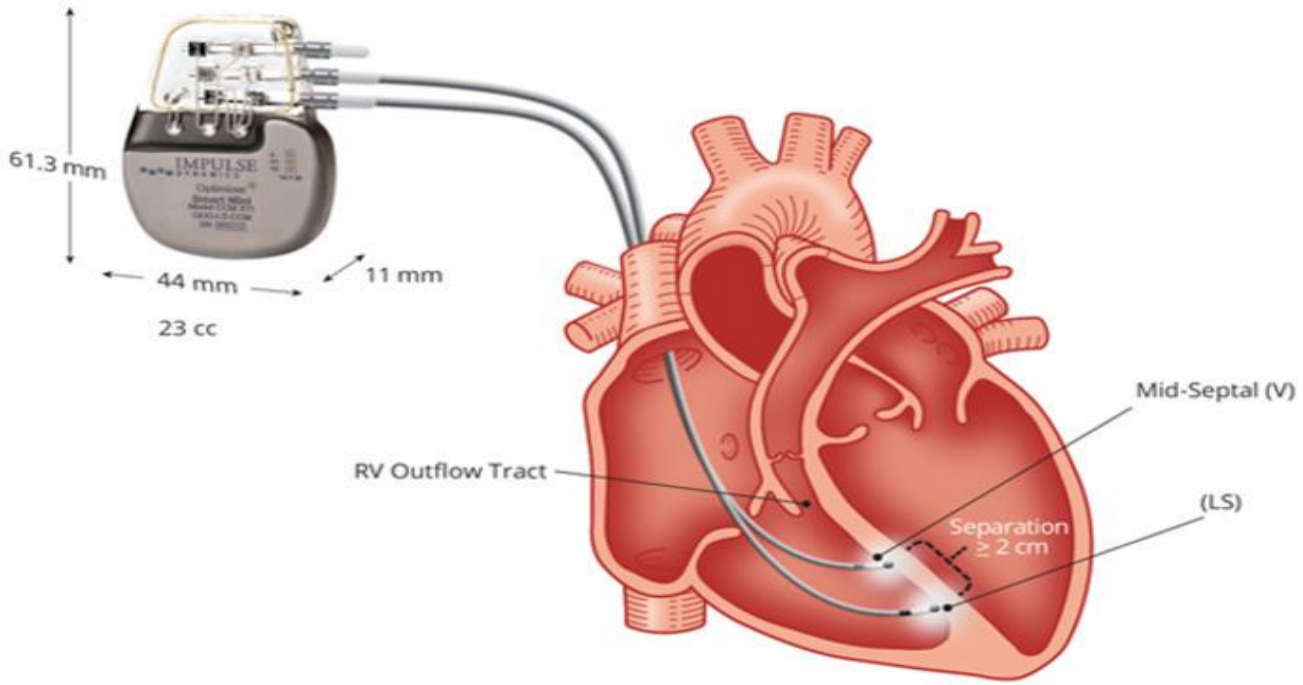
Mihai Gheorghiade, MD,[a,*] Leonardo De Luca, MD,[b] Gregg C. Fonarow, MD,[c] Gerasimos Filippatos, MD,[d] Marco Metra, MD,[e] and Gary S. Francis, MD[f]



Gheorgiade M et al. Am Heart J.2005

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

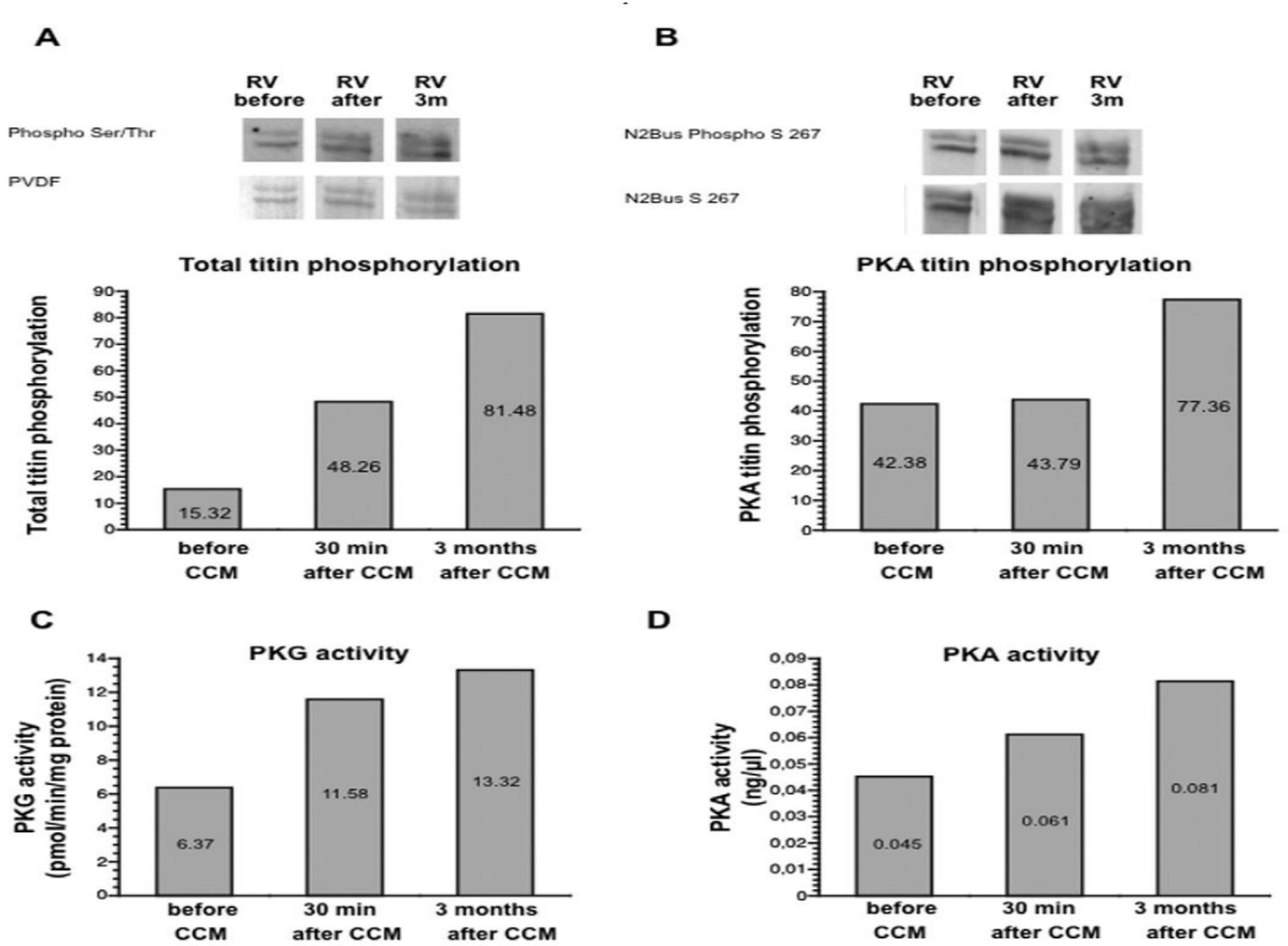
- Lusitropic effect with improved diastolic recoil
- Increased left ventricular contractility

Effect on functional and clinical outcomes

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

Talha K JCF 2022

CCM Increase Titin Phosphorylation



Tschöpe C. J Cardiol. 2016

Available online at www.sciencedirect.com
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www.elsevier.com/locate/tcm

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

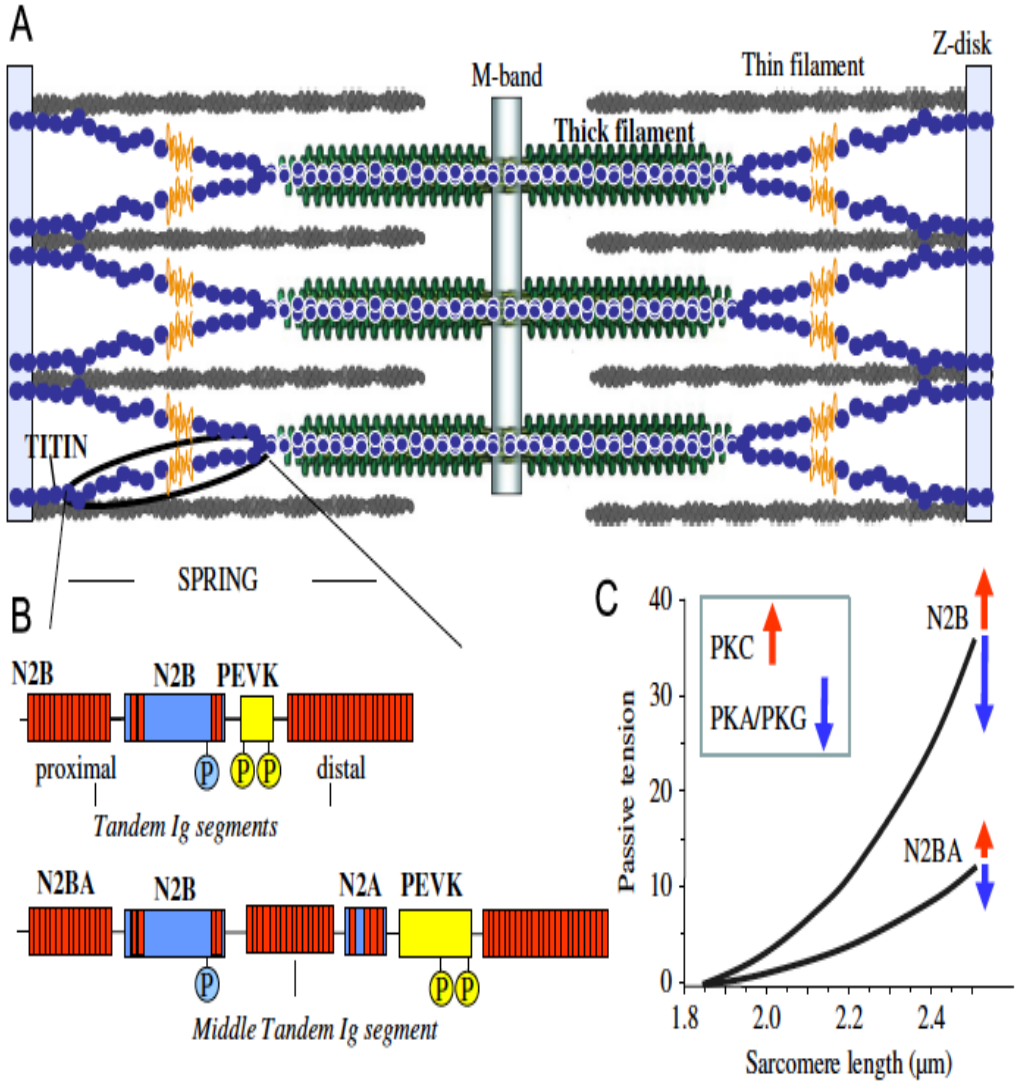
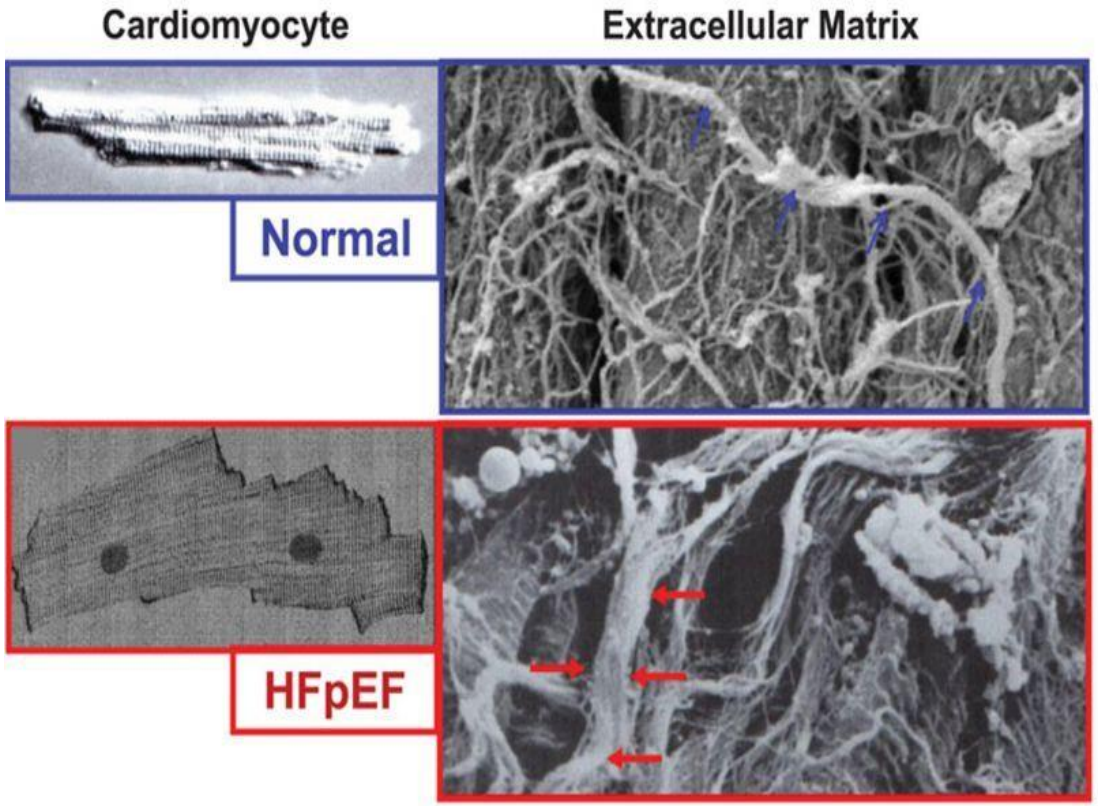
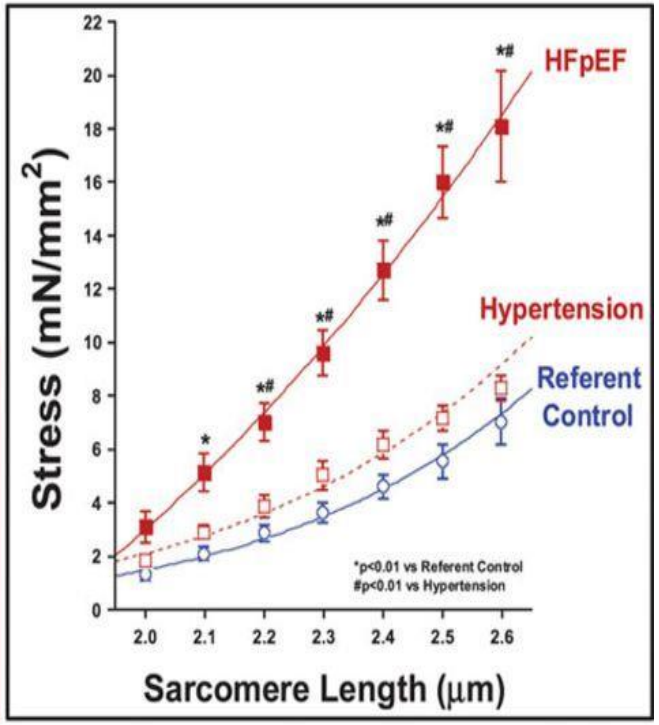
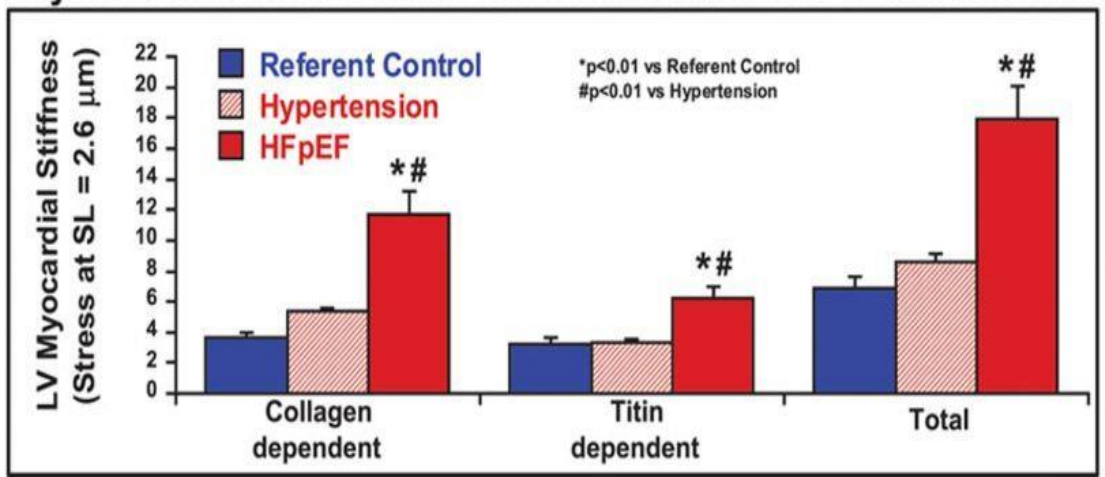


Fig. 1 – (A) Schematic of titin in the cardiac sarcomere. Single titin molecules (shown in blue and yellow) span from Z-disk (N-terminus) to M-band (C-terminus). (B) Composition of extensible I-band region of the N2B and N2BA titin isoforms (found in adults). Red blocks denote Ig-like domains, blue is 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.

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







LeWinter M, Circulation 2016

frontiers in Physiology

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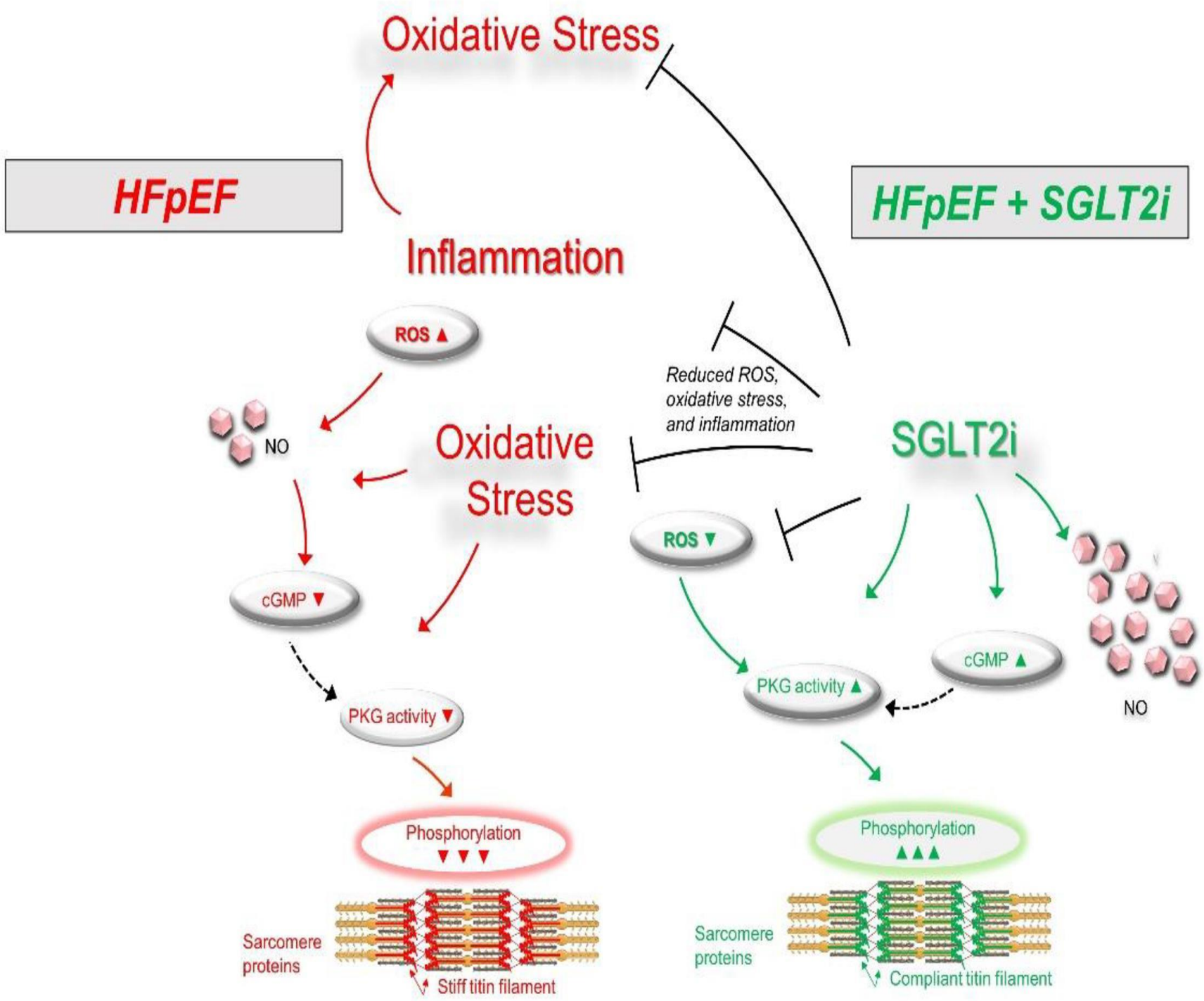
Potential Mechanisms of SGLT2 Inhibitors for the Treatment of Heart Failure With Preserved Ejection Fraction

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



Pabel S Front. Phi. 2021

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

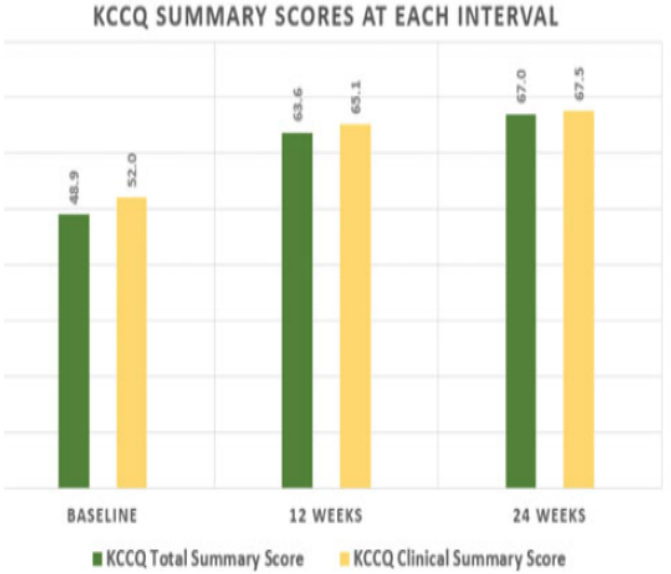
47 HFpEF patients implanted with CCM

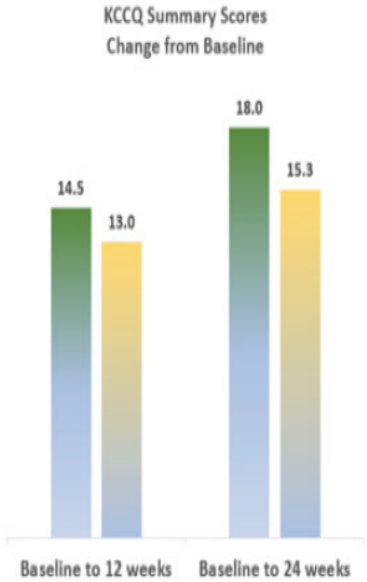
17 centres in EU and Australia

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

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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 HIGHer trial

https://clinicaltrials.gov/ct2/show/NCT05064709

AIM HIGH*er* trial

Studio multicentrico randomizzato, doppio cieco, sham-controlled per la valutazione dell'efficacia della terapia CCM in 1500 pazienti HF con F**E 40%-60%.**

- Endpoint parte 1: 6MWTD e KCCQ a 6 mesi di Fu;
- Endpoint parte 2: Outcome composito di esiti di mortalità, morbilità e QoL (KCCQ CSS) al FU a 18 mesi.

La terapia CCM per HFpEF ha già ricevuto la ***breakthrough device designation*** della FDA

Future Directions

Optimizer® Smart

Optimizer® Smart Mini

Optimizer® Integra CCM-D

Clinical Portfolio

Post Approval Study
620 subjects
3-year follow-up
MLWHFQ, Mortality vs SHFM, Safety

AIM HIGHer Trial *(Opened 2022)*
~1,500 subjects, LVEF 40-60%
Randomized, double blinded,
CCM ON:CCM OFF 2:1, 6- and 18-month endpoints

INTEGRA-D Trial *(Opened 2023)*
300 Subjects
FDA Breakthrough Designation
6-month and 2-year endpoints


thank you
danke
謝謝
gracias
merci
obrigado
dziękuję
bedankt
teşekkür ederim
go raibh maith agat
sukriya
kop khun krap
terima kasih
grazie
arigatô
dakujem
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tapadh leat
mochchakkeram
mauruuru
hvala
sagolun
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спасибо
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