QUANDO L'ELETTROFISIOLOGO AIUTA LO SCOMPENSOLOGO: DEVICE DI MONITORAGGIO E DEVICE TERAPEUTICI

Dott. Gaetano Senatore
SC CARDIOLOGIA
OSPEDALE DI CIRIE'

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Recommendations for RM considerations			
COR	LOE	Recommendations	References
1	A	1. In patients with CIEDs, RM is recommended as part of the standard of care.	1,11,30-38
1	B-R	2. In patients with CIEDs on RM, routine surveillance of lead function and battery status is recommended to ensure device integrity.	30,39,40
1	C-EO	3. In patients with CIEDs on RM with a device capable of continuous connectivity, connectivity should be maintained.	

2023 HRS/EHRA/APHRS/LAHRS expert consensus statement on practical management of the remote device clinic

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Figure 1. Benefits of Remote Monitoring.

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Table 1
Device diagnostics and algorithms for management of patients with heart failure.
A more extensive version of the table including the name of related clinical studies and the related references in shown in the supplemental material as Supplemental Table S1.
AF, atrial fibrillation; AT, atrial tachycardia; biv, biventricular; HR, heart rate; HRV, heart rate variability; PVC, premature ventricular complex; RM, remote monitoring; S1, first heart sound; S3, third heart sound.

HF diagnostics available at RM (Name of the RM system)	ST Jude/ Abbott Yes (Merlin)	Biotronik Yes (Home Monitoring)	Boston Yes (Latitude)	Medtronic Yes (Carelink)
Monitored patient parameters				
Night heart rate	+	+	+	+
24 h heart rate	+	+	+	+
Heart rate variability		+	+	+
Intrathoracic impedance	+	+	+	+
Heart sounds (S1, S3)			+	
Respiratory rate			+	
Relative tidal volume			+	
Rapid shallow breathing index			+	
Respiratory disturbance index			+	
Activity response	+	+	+	+
AT/AF (burden)	+	+	+	+
Ventricular rate during AT/AF	+	+	+	+
Ventricular arrhythmias	+	+	+	+
PVC per day		+		
% Pacing (biv)	+	+	+	+
Defibrillator therapies	+	+	+	+
Sleep incline			+	
Combined score name	CorVue	HeartInsight	HeartLogic	TriageHF
Parameters included in the combined score	Intrathoracic impedance	Night HR, 24 h HR, HRV, intrathoracic impedance, activity response, AT/ AF, PVC per day	Night HR, intrathoracic impedance, heart sounds, respiratory rate, relative tidal volume, activity response	Night HR, HRV, intrathoracic impedance, activity response, AT/ AF, ventricular rate during AT/AF,% pacing (biv), defibrillator therapies

Contents lists available at ScienceDirect
European Journal of Internal Medicine
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ELSEVIER

Review Article

Remote multiparametric monitoring and management of heart failure patients through cardiac implantable electronic devices

Giuseppe Boriani [a,*], Jacopo F. Imberti [a,b], Niccolò Bonini [a], Cosimo Carriere [c], Davide A. Mei [a], Massimo Zecchin [c], Francesca Piccinin [c], Marco Vitolo [a,b], Gianfranco Sinagra [c]

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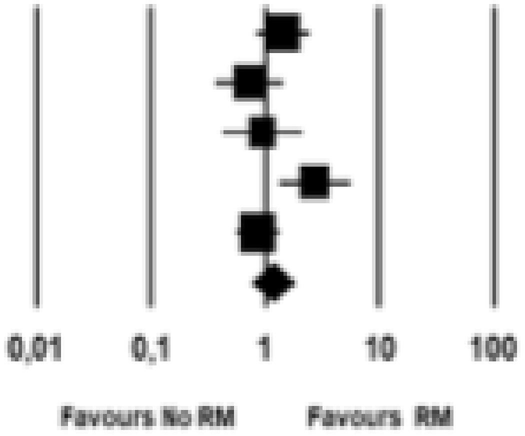
MORTALITY

Death	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
TRUST	1,427	0,830	2,454	1,286	0,198
COMPAS	0,728	0,365	1,453	-0,900	0,368
ECOST	0,956	0,431	2,118	-0,112	0,911
IN TIME	2,716	1,336	5,522	2,761	0,006
MORE CARE	0,868	0,560	1,344	-0,635	0,525
	1,169	0,761	1,796	0,715	0,475

Risk ratio and 95% CI

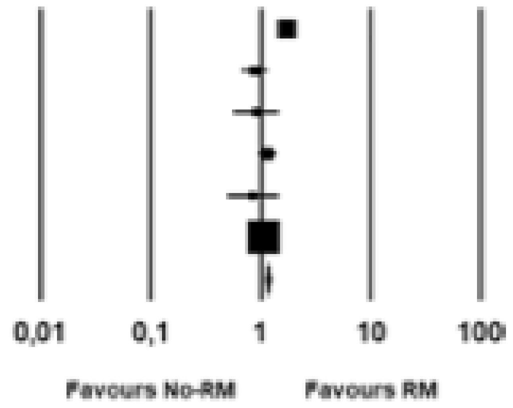


HOSPITALIZATIONS

F. Lucà et al. / IJC Heart & Vasculature 24 (2019) 100380

Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
TRUST	1,713	1,492	1,965	7,665	0,000
EVOLVO	0,877	0,674	1,140	-0,979	0,327
COMPAS	0,906	0,565	1,455	-0,408	0,683
EVATEL	1,133	0,934	1,375	1,267	0,205
IN TIME	0,847	0,496	1,446	-0,610	0,542
MORE CARE	1,058	0,979	1,143	1,430	0,153
	1,152	1,084	1,225	4,568	0,000

Risk ratio and 95% CI



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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Remote monitoring (RM) of cardiac implantable electronic devices (CIEDs) is the standard of care. While this improves management of these devices, how this contributes to the management of heart failure (HF) is unclear.

WHAT THIS STUDY ADDS

⇒ RM of CIEDs does not improve the management of patients with HF.

⇒ In patients with HF who have a CIED, the utility of RM and its role with respect to HF is poorly defined.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ RM requires further refinement and investigation before it can be recommended routinely for patients with HF and CIED.

Remote monitoring in patients with heart failure with cardiac implantable electronic devices: a systematic review and meta-analysis

Michael J McGee [1,2] Max Ray,[2] Stepehn C Brienesse,[2] Shanathan Sritharan,[2] Andrew J Boyle,[2,3] Nicholas Jackson,[2] James W Leitch,[2] Aaron L Sverdlov [2,3]

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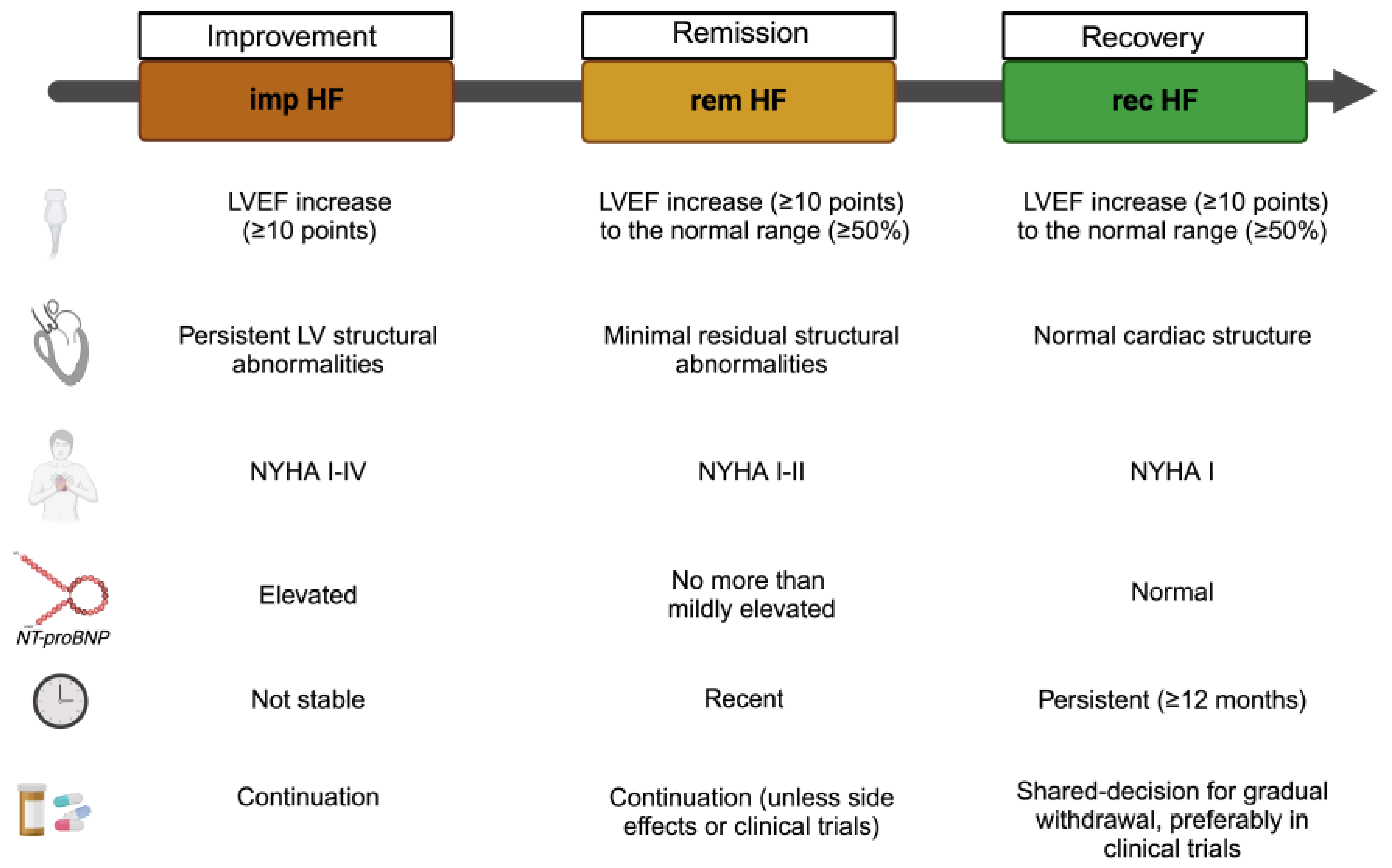

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ESC European Society of Cardiology
European Journal of Heart Failure (2025)
doi:10.1002/ejhf.3732
POSITION PAPER

Heart failure improvement, remission, and recovery: A *European Journal of Heart Failure* expert consensus document

Jean-Sébastien Hulot[1,2], Jozine M. Ter Maaten[3], Antoni Bayes-Genis[4], Brian P. Halliday[5], Marco Metra[6], Brenda Moura[7], Mark C. Petrie[8], Gianluigi Savarese[9], Michele Senni[10], Sophie Van Linhout[11,12], Lynne Warner Stevenson[13], and Wilfried Mullens[14,15]*

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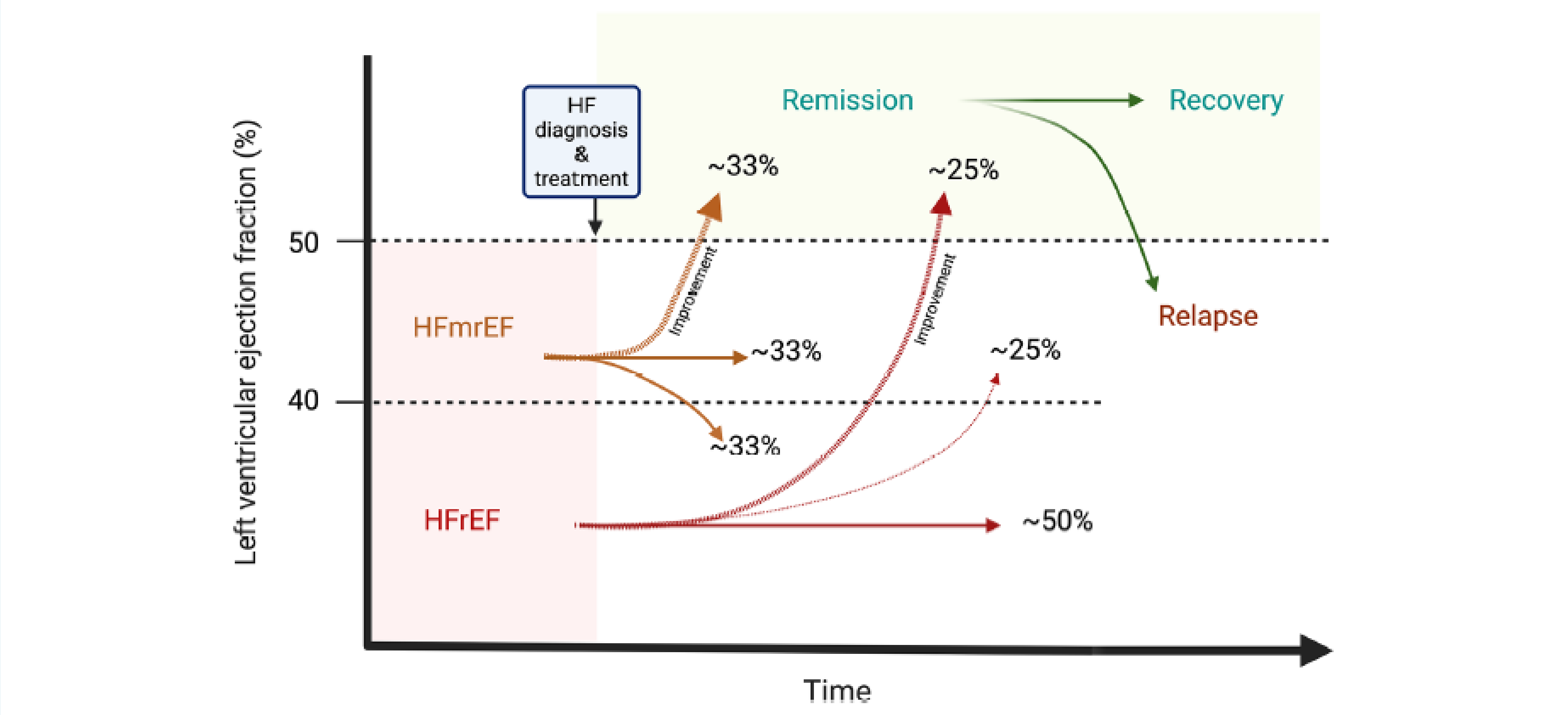
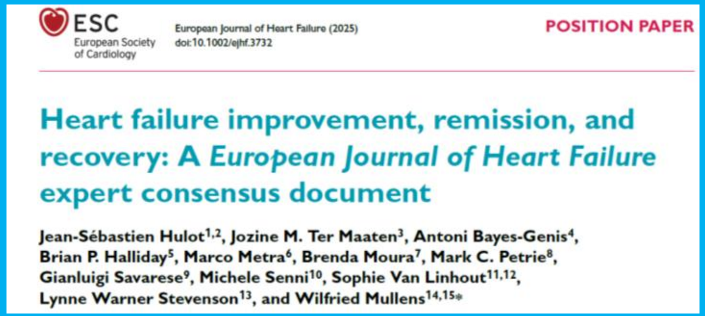


Figure 1 Improvement, remission and recovery of heart failure (HF) as a continuum. Progressive normalization of key HF markers and persistence over time incrementally separate the three subtypes. HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.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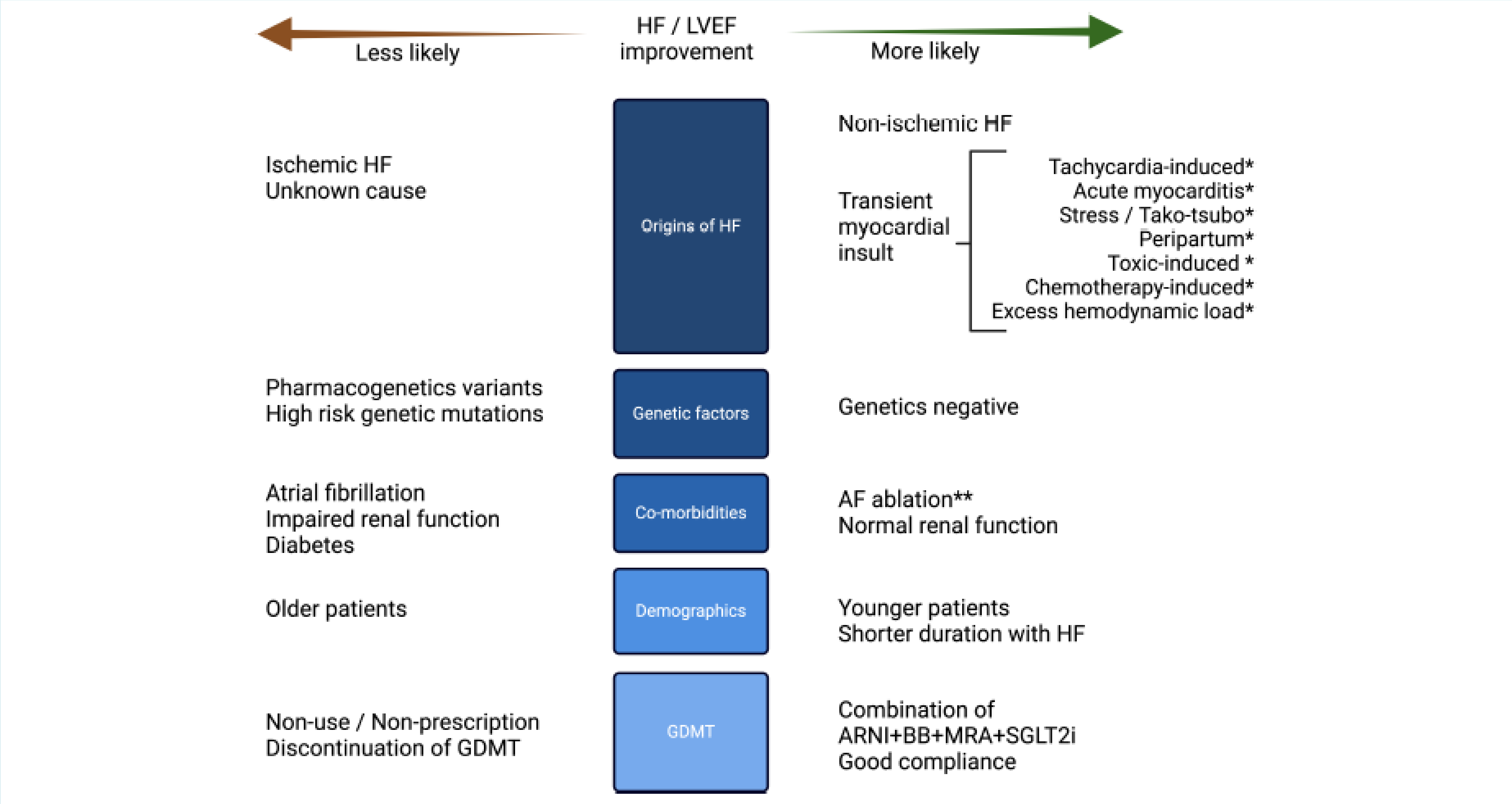

Figure 2 Factors influencing the probability of left ventricular ejection fraction (LVEF) improvement. AF, atrial fibrillation; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; GDMT, guideline-directed medical therapy; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor. *With the assumption that the myocardial insult is discontinued (i.e. weaning of alcohol consumption, withdrawal of damaging chemotherapies, etc.). **In HF patients with AF, as compared to a rhythm control with antiarrhythmics drugs.

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

JACC SCIENTIFIC STATEMENT

Remote Monitoring for Heart Failure Management at Home

JACC Scientific Statement

Lynne Warner Stevenson, MD,[a] Heather J. Ross, MD,[b] Lisa D. Rathman, MSN, CRNP,[c] John P. Boehmer, MD[d]

TABLE 1 Examples of Signal Types for Remote Monitoring

Type of Signal	Specific Product	Patient Site	Representative Trials (Year)	Impact on Heart Failure Hospitalizations
Weights, vital signs, and other				
Traditional telemonitoring with combinations of weights, vital signs, reported symptoms + rhythm strips	Various	Home	TELE-HF (2010)[4] BEAT-HF (2016)[6] TIM-HF I (2010)[5] TIM-HF II (2018)[79]	No benefit No benefit, small signal for better quality of life No benefit Benefit for mortality with 24/7 emergency medical HF phone access
Fluid in the lung				
Thoracic impedance with impedance cardiography	BioZ	Clinic Hospital	PREDICT (2006)[43] BIG substudy of ESCAPE (2009)[44]	Predictive of outcomes in clinic outpatients Poor correlation with hemodynamics or outcomes for inpatients
Thoracic impedance with ICD	OptiVol OptiVol or CorVue	Home	DOT HF (2011)[41] OptiLink-HF (2016)[119] MORE-CARE (2017)[120] LIMIT-CHF (2016)[121]	Alerts increased patient visits with no decrease in HF hospitalizations More HF hospitalizations with intervention than in control No benefit
Thoracic impedance and other measures from ICD		Home	IN TIME (2014)[122]	No benefit
Thoracic impedance with ICD		Home	EVOLVO (2012)[123]	No benefit
Remote dielectric sensing of lung water (ReDS)	Sensivest	Home Hospital before discharge	SMILE trial (2016)[49] ReDS-pilot SAFE-HF (2021)[47]	Validated against CT measured lung water content Preliminary results in discharged patients showed reduction in HFH with ReDS when managed per protocol Pilot trial before discharge showing 32% needed further diuresis
Radiofrequency sensor: wearable patch on chest	Microcor	Home	BMAD Trial (2023)[60]	Pair of single-arm trials suggesting decreased HFH using patch to guide therapy
Hemodynamic pressure monitoring				
PA pressure monitor	CardioMEMS	Home	CHAMPION (2011)[22] GUIDE-HF (2021)[20,33] Nonrandomized 2,000 Medicare patients (2017)[27] 234 Europe-MEMS (2020)[28] FDA Postapproval U.S. 1,200 patients (2023)[29]	Benefit for HFH and total hospitalizations, QOL Benefit in prespecified pre-Covid 19 analysis Compared with preimplantation: Benefit to reduce PA pressures and HF hospitalizations at 6 months Benefit to reduce PA pressures and HF hospitalizations at 1 year Sustained reduction in PA pressures and HF hospitalizations over 2 years
LA lead for pressure monitoring enabled for self-management with personalized algorithm	HeartPOD monitor alone or with CRTD	Home	LAPTOP (2016)[34,124]	Benefit to reduce HFH was comparable to CHAMPION trial discontinued because of complications of device insertion across septum
LA pressure monitoring tube anchored across atrial septum	V-LAP	Home	VECTOR-HF(2022)[36]	Correlates with pulmonary wedge pressure at 3 months
PA pressure data integrated with HF package of vital signs and symptoms	Cordella with Heart Failure System	Home	PROACTIVE-HF III[35]	450 patients in PROACTIVE class III—ongoing follow-up
Multiparameter scores with rhythm devices				
ICD with impedance,[a] heart rate and variability, activity		Home	Cowie (2013)[53] REM-HF (2017)[54]	High risk score conferred 10X risk for events compared with low risk Remote monitoring to guide therapy had no impact to decrease HFH or death
ICD with impedance,[a] minute ventilation, activity		Home	CLEPSYDRA (2014)[125]	Alert score with 34% sensitivity False-positive rate of 2.4 alerts per patient-year
CRTD with impedance, HR, RR, activity, and heart sounds	HeartLogic	Home	MultiSENSE Trial (2017)[56] (2018)[57]	Alert score validated with 70% sensitivity, specificity 85.7% Alert zone conferred 10X risk of HF event.
CRTD or ICD with impedance, HR + HRV, atrial arrhythmias and PVCs, activity		Home	SELENE-HF (2022)[58]	Alert score with sensitivity of 65.5%; false-positive rate of 0.7/patient-year Improved by adding Seattle HF Model score before device implantation
CRTD and ICD with impedance, HR, HRV, arrhythmias, pacing		Home Early after discharge	TRIAGE-HF (2018)[126] (2023)[16]	Risk metric became predictive 60 days before HF event, continued rising until discharge Fell by a week after discharge in patients with low risk of readmission
Example of multiparameter wearable technology				
LINK HF	Multisensor Health Patch	Hospital to Home	LINK-HF (2020)[127]	Multivariate physiological telemetry from a wearable sensor can provide early detection of impending rehospitalization

[a]Impedance refers to thoracic impedance.

CRTD = cardiac resynchronization therapy defibrillator; HF = heart failure; HFH = heart failure hospitalizations; HR = heart rate; HRV = heart rate variability; ICD = implantable cardioverter-defibrillator; LA = left atrium; PA = pulmonary artery; PAD = pulmonary artery diastolic pressure; PVC = premature ventricular complexes; ReDS = remote dielectric sensing; RR = respiratory rate.

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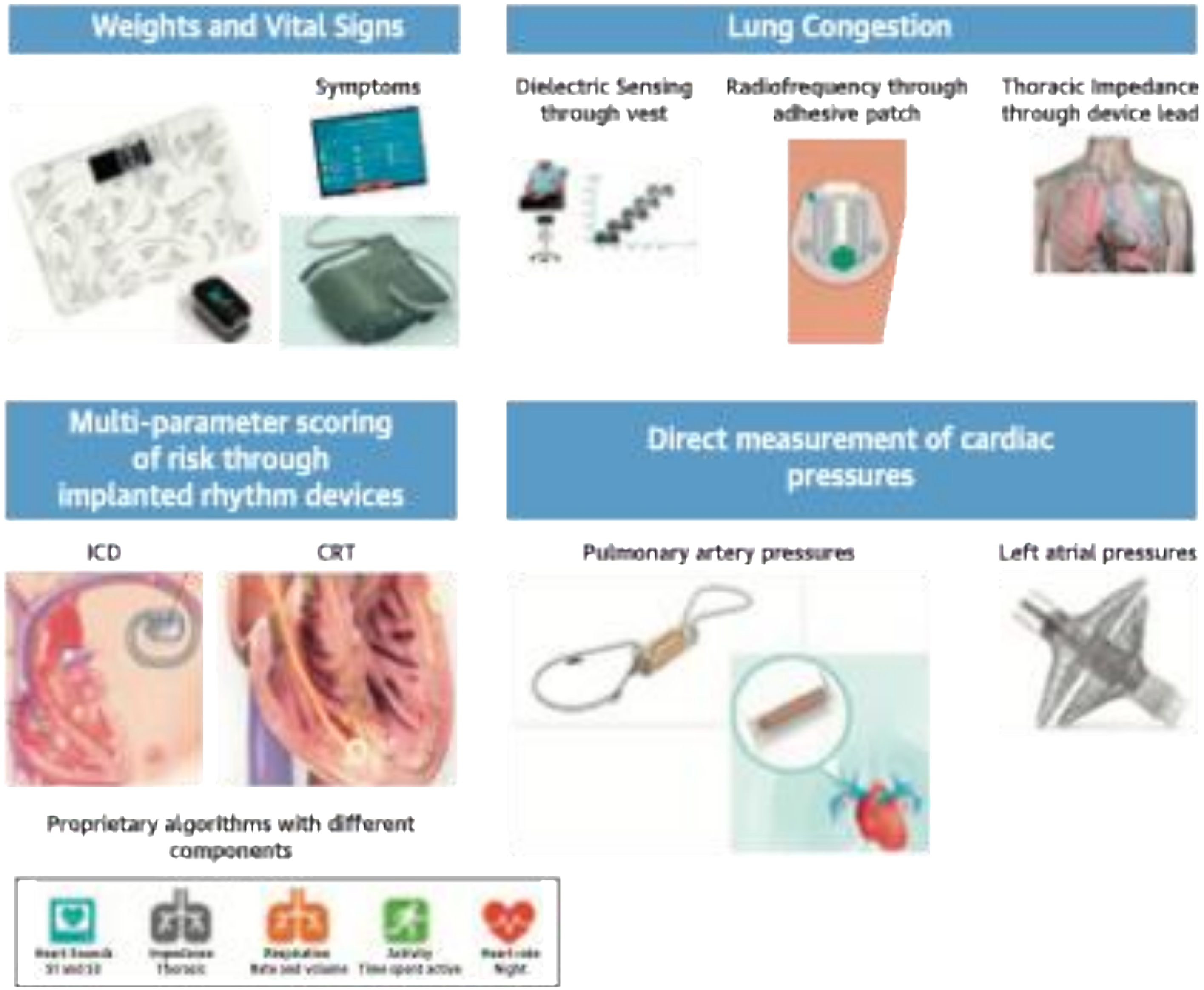
FIGURE 3 Examples of Device Technologies for Remote Monitoring of Heart Failure



The authors have adapted the organizing structure from the excellent review by Mohebali and Kittleson.[84] CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

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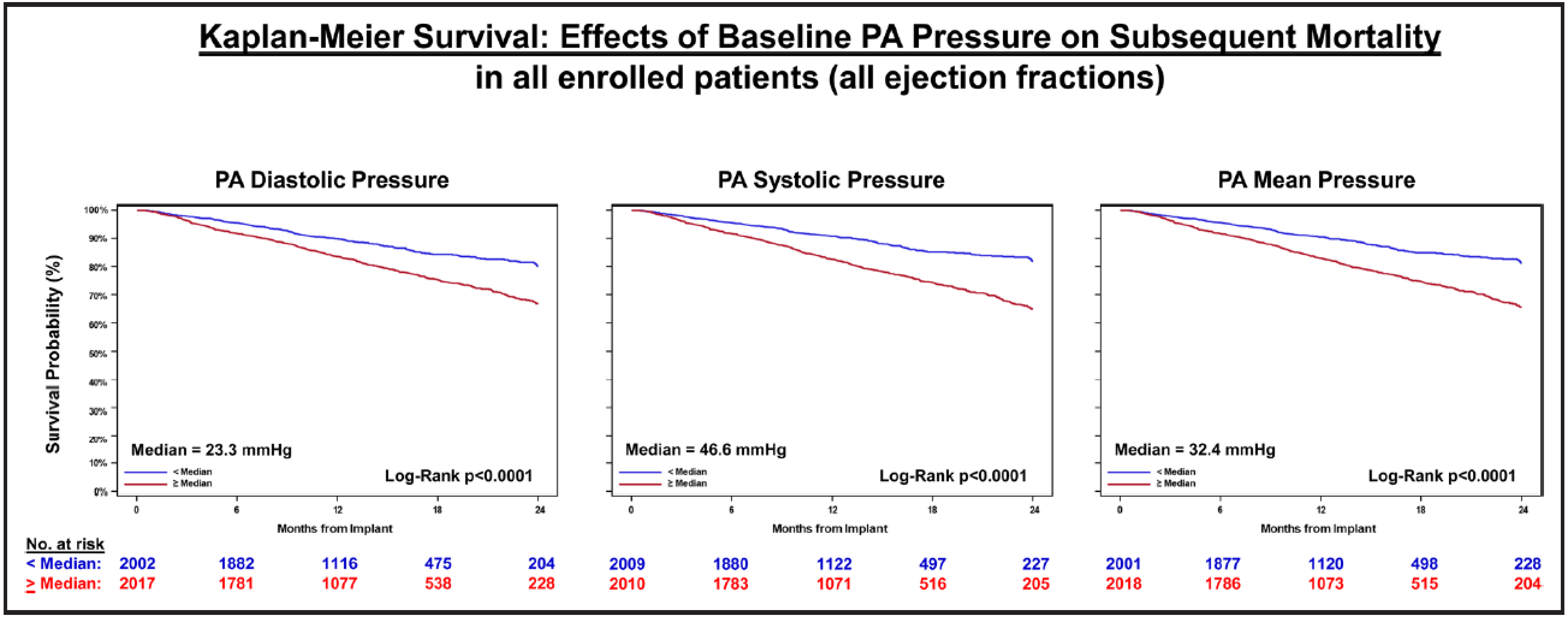

Figure 1. Kaplan-Meier survival: effects of baseline pulmonary artery (PA) pressure on subsequent mortality in all enrolled patients (all ejection fractions).

Circulation: Heart Failure

ORIGINAL ARTICLE

Relationship Between Remote, Ambulatory Pulmonary Artery Pressures, and All-Cause Mortality in Patients With Chronic Heart Failure

Michael R. Zile, MD; William T. Abraham, MD; Lynne W. Stevenson, MD; Maria Rosa Costanzo, MD; Christiane E. Angermann, MD; Mandeep R. Mehra, MD, MSc; Akshay S. Desai, MD, MPH; Anique Ducharme, MD, MSc; Nessa Johnson, PhD; John Henderson, MS; JoAnn Lindenfeld, MD

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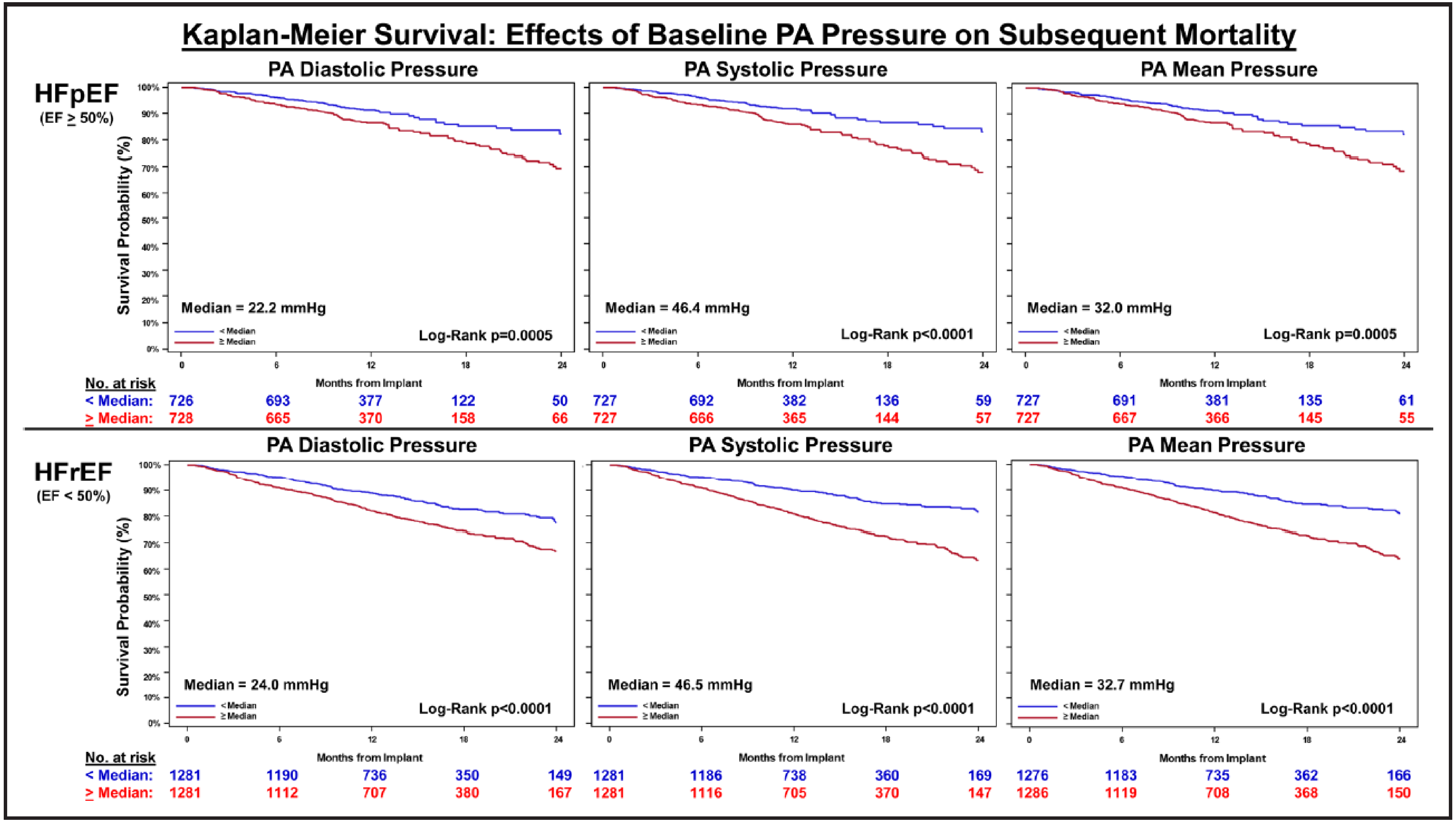
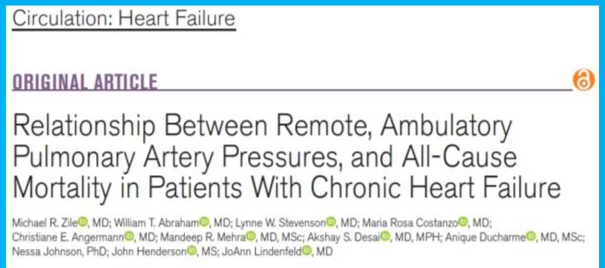


Figure 3. Kaplan-Meier survival: effects of baseline pulmonary artery (PA) pressure on subsequent mortality.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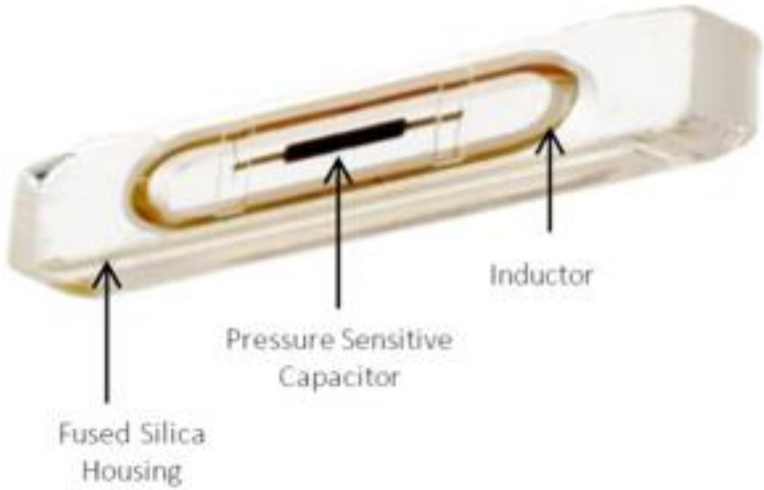
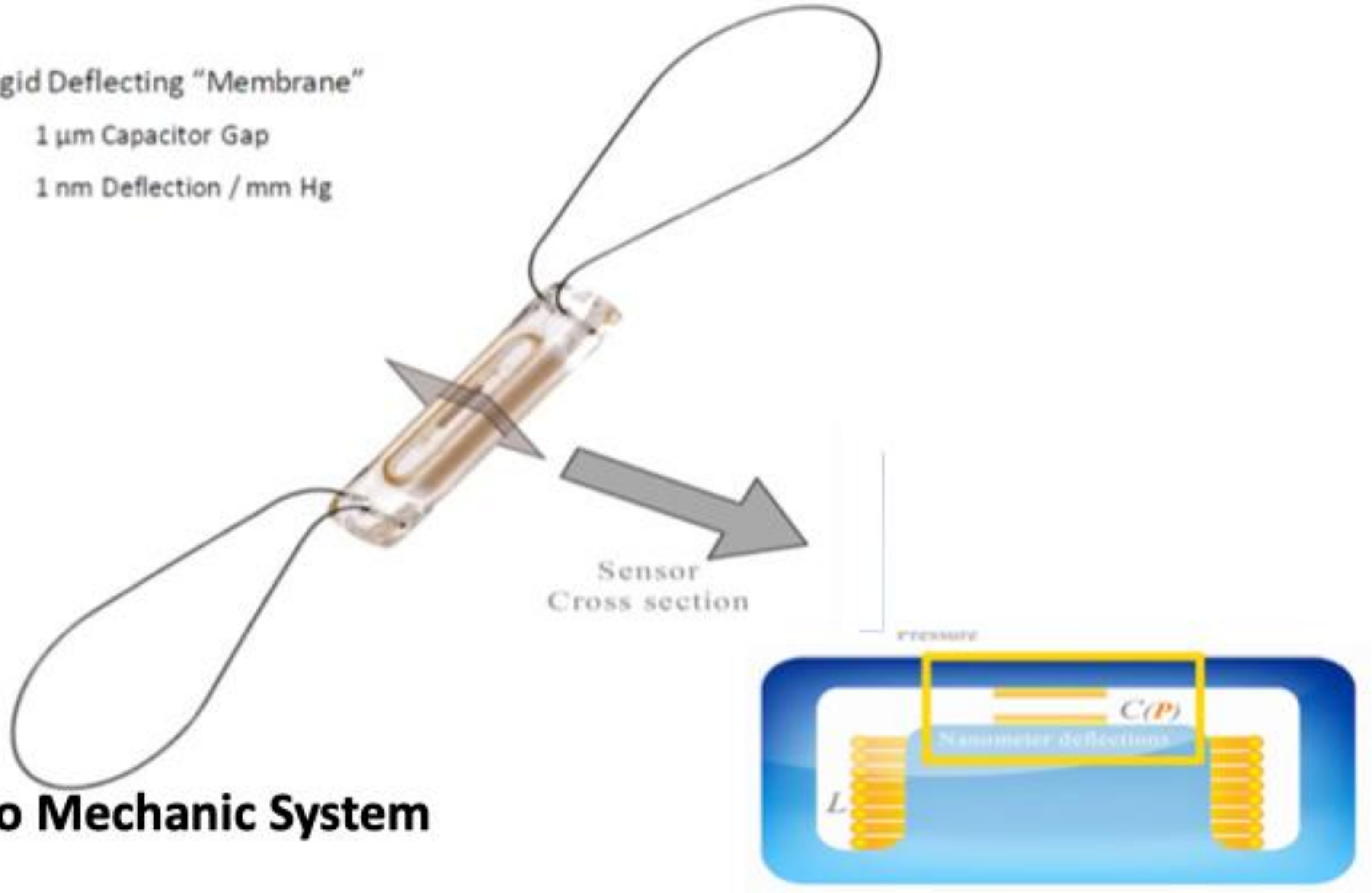
Invasive PA pressure monitoring system, the CardioMEMS device.

Rigid Deflecting "Membrane"

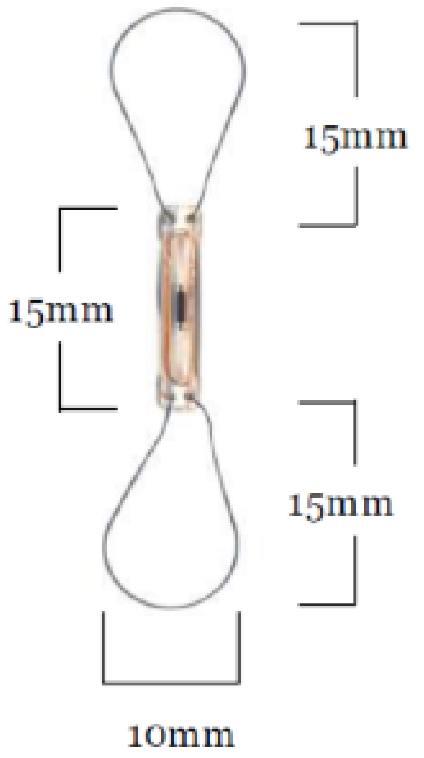
- 1 µm Capacitor Gap
- 1 nm Deflection / mm Hg

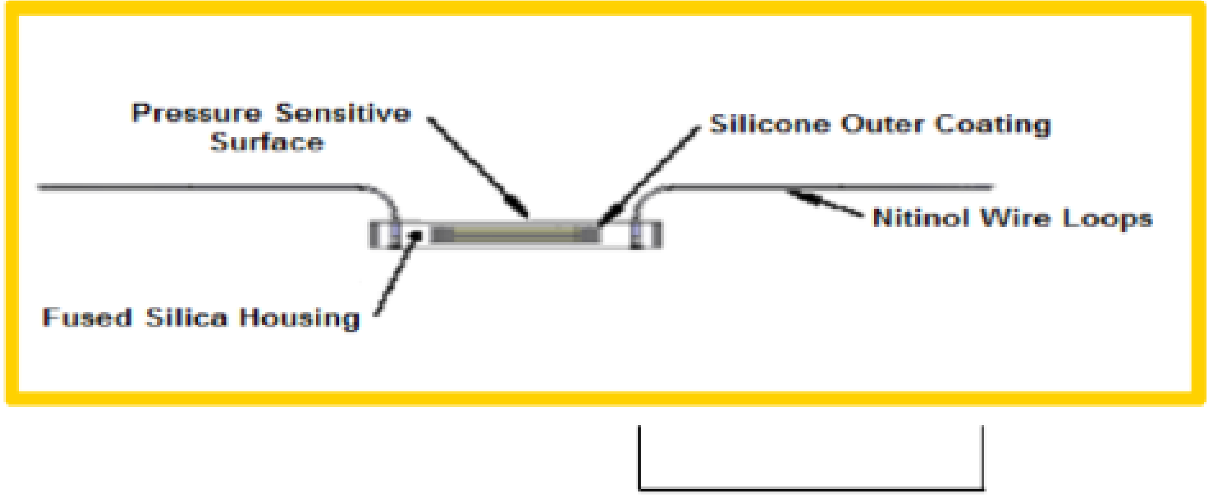




CardioMEMS= Cardio Micro Electro Mechanic System

Invasive PA pressure monitoring system, the CardioMEMS device.





Length	15 mm
Width	3.5 mm
Height	2.0 mm
Wire Loops	10 mm diameter, 15 mm length
Total Length with Loops	4.5 cm

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Invasive PA pressure monitoring system, the CardioMEMS device.

CardioMEMS™ PA Sensor Delivery System

Sensor loaded on catheter shaft

Delivery System Specifications

Shaft Configuration	Over-the-wire
Guidewire compatibility	0.018"x260 cm
Usable length	120 cm

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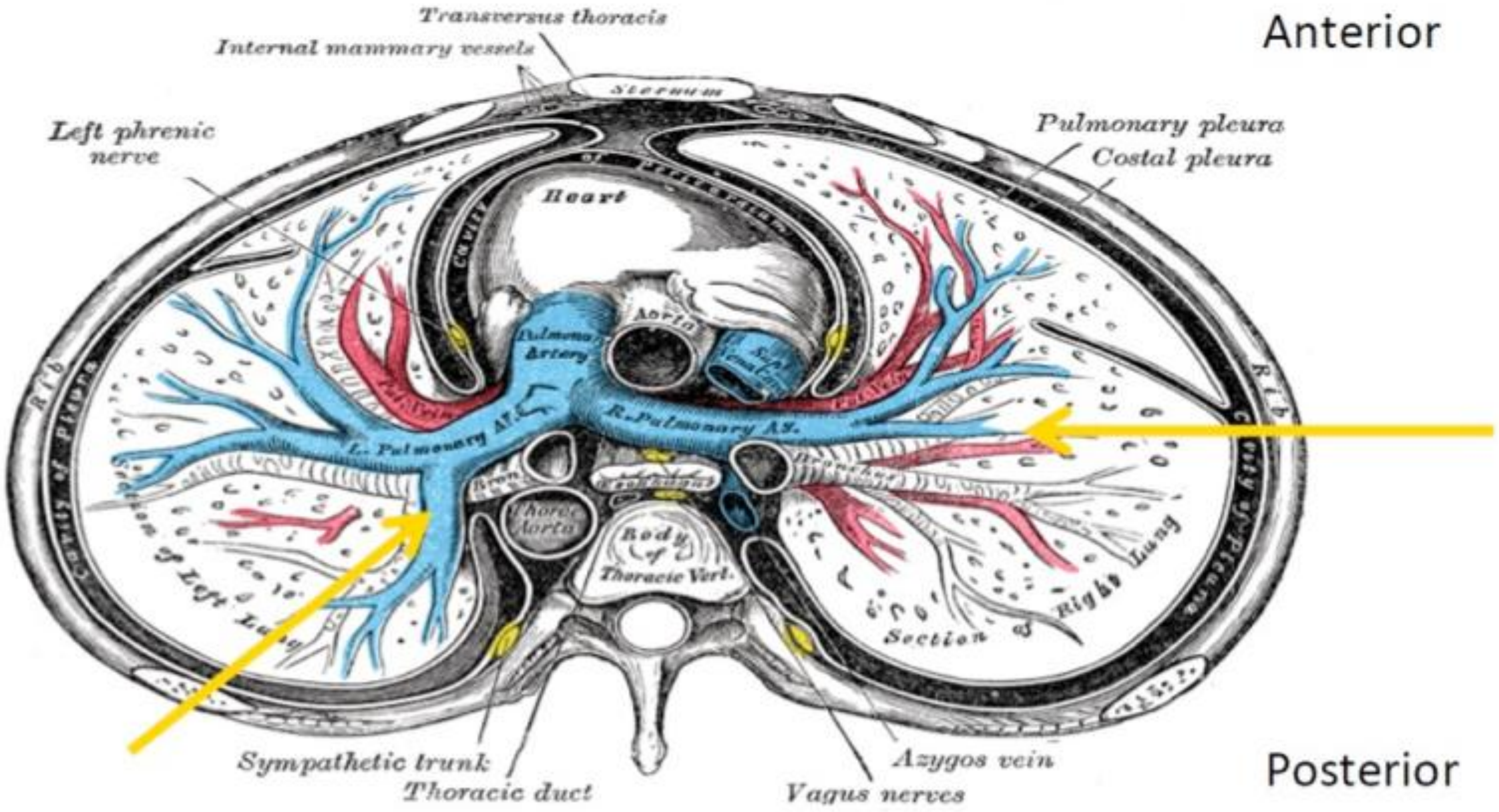

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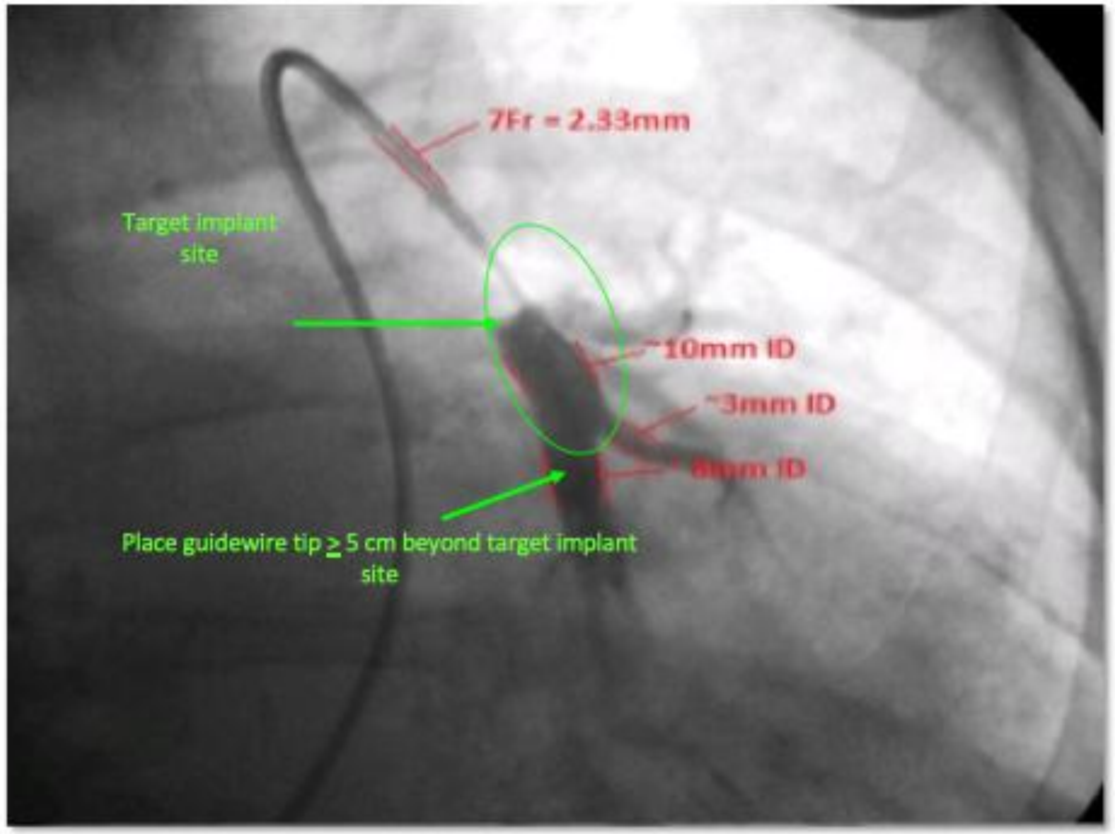
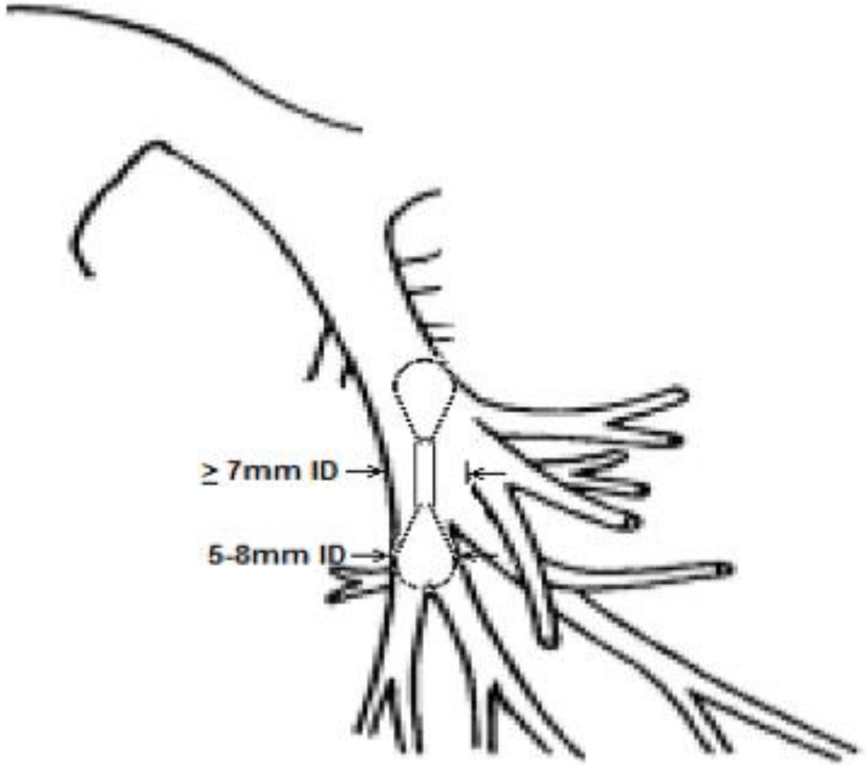
Implant procedure CardioMEMS device





Diametro vaso target

7 – 10mm per il **corpo** del sensore
5-8 mm per il **loop** distale

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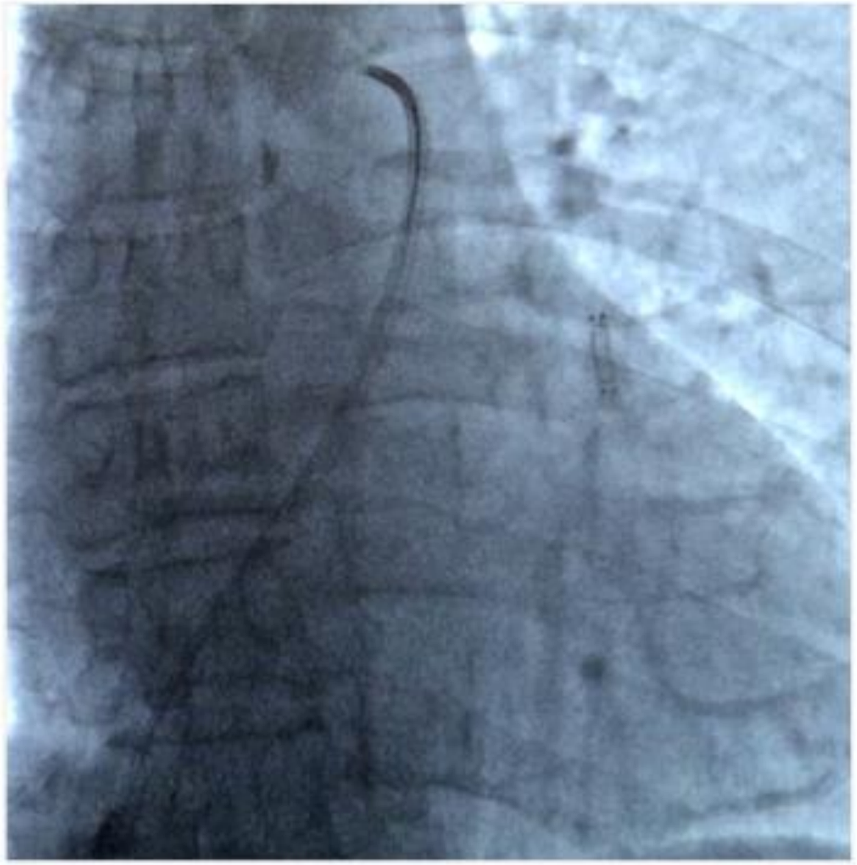
Implant procedure CardioMEMS device



8. Careful wire removal (risk of dislocation). Reposition the wire in a PA branch, remove delivery and advance MPA1 (or Swan Ganz cath)

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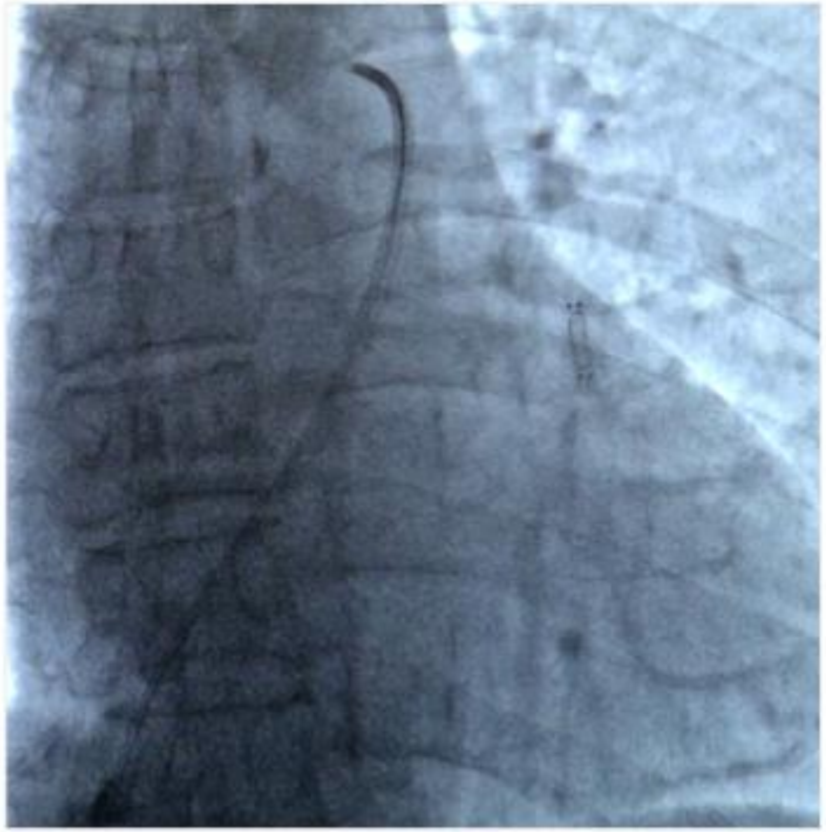
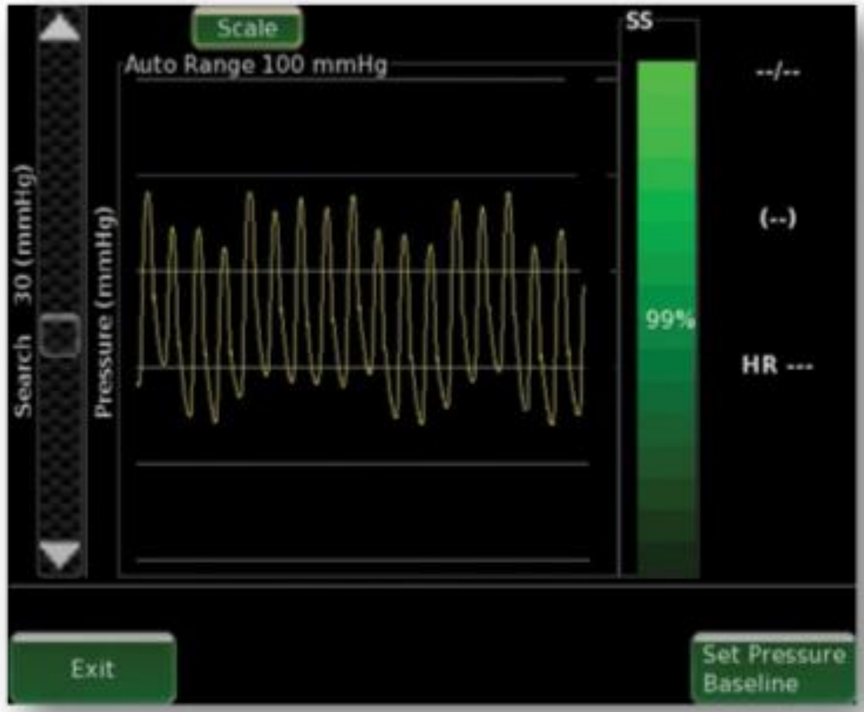
Implant CardioMEMS device





9. Sensor calibration

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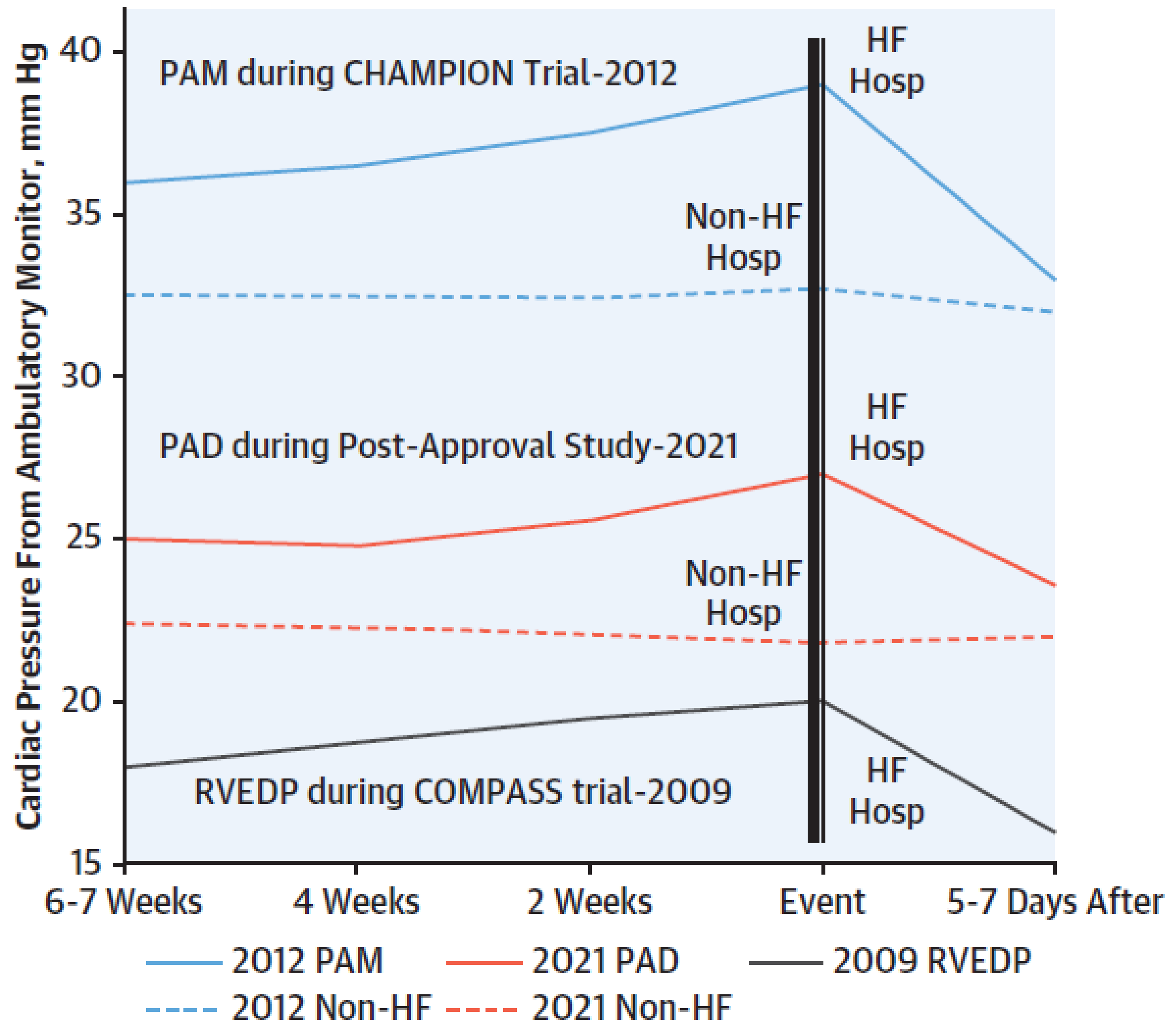
FIGURE 1 Consistent Patterns of Increasing Cardiac Pressures Before Heart Failure Events



Averaged cardiac pressures obtained from indwelling monitors in ambulatory populations with histories of heart failure (HF) hospitalization. Pressures show gradual increase before hospitalizations due to HF but not to other causes (Non-HF). Data provided courtesy of RC Bourge, PB Adamson, TD Bennett, V Manda, WT Abraham, MR Zile, A Desai. CHAMPION = CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients; COMPASS-HF = Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; PAD = pulmonary artery diastolic pressure; PAM = pulmonary artery mean pressure; RVEDP = right ventricular diastolic pressure.

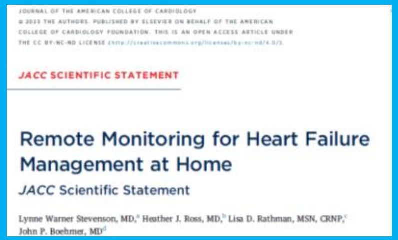

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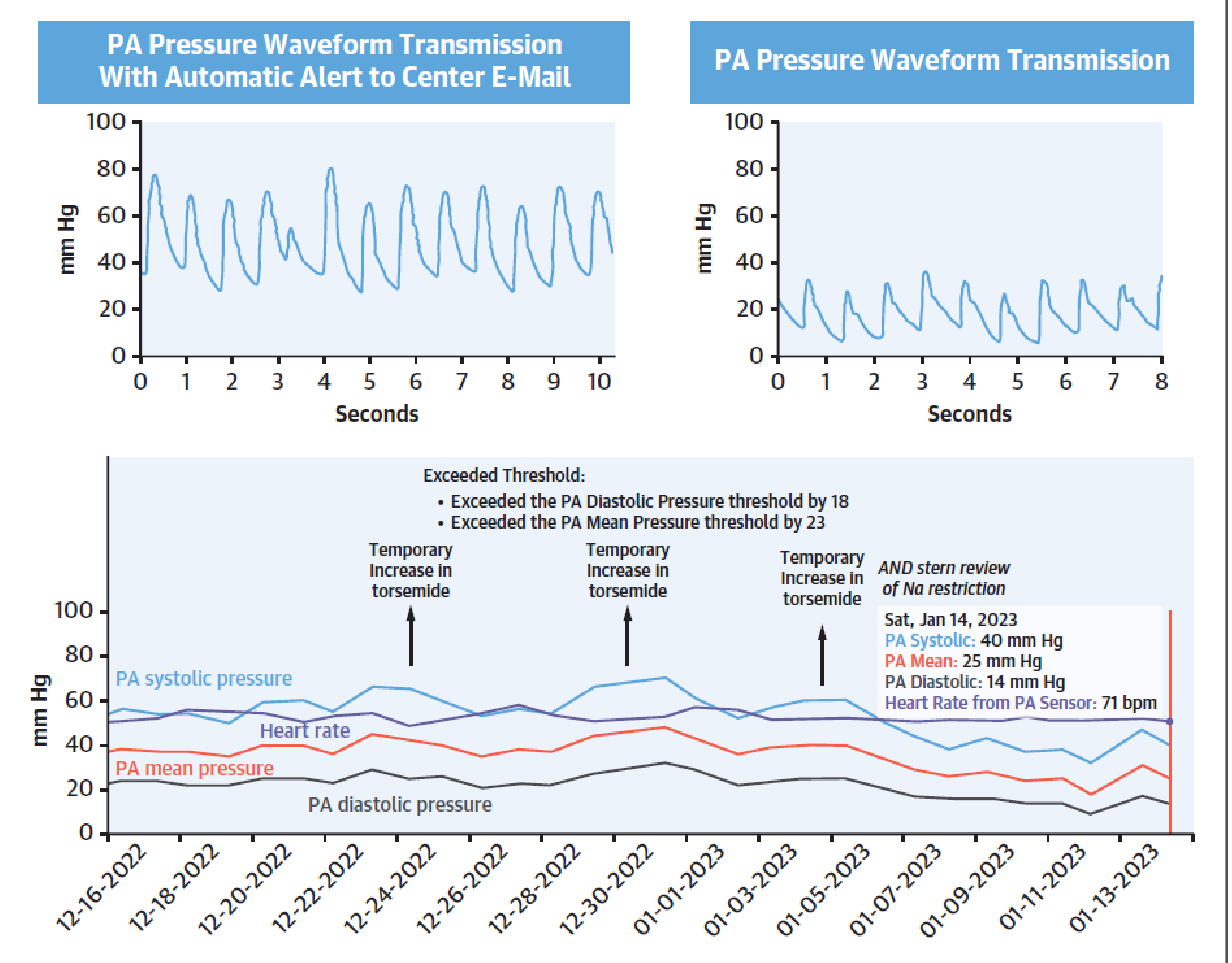
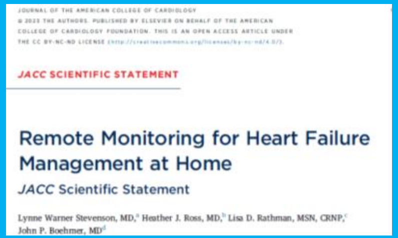
FIGURE 2 Holiday Monitoring of Pulmonary Artery Pressures



Ambulatory monitoring in a 64-year-old man 4 years after implantation of a pulmonary artery (PA) pressure monitor for pulmonary hypertension with left ventricular failure from valvular heart disease. During the winter holidays, each PA pressure elevation episode decreased briefly after increased diuretic agents, but the reduction was sustained after the dedicated program nurse delivered a stern re-education about salt restriction.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Evidenze Cliniche

2011
CHAMPION Trial[1,2]

2014
Proven Benefits in HFpEF Patients[3]

2017
Synergistic Impact With GDMT[4]

2017
First Commercial Implants[5]

2017
Economic Impact[6]

2019
Propensity-matched Outcomes[7]

2020
MEMS-HF European Study[8]

2020
U.S. Post-approval Study[9]

2021
GUIDE-HF Study[10]

2023
MONITOR-HF[11]

1.Abraham WT, et al. *Lancet*. 2011.
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VOL. 83, NO. 6, 2024

Implantable Hemodynamic Monitors Improve Survival in Patients With Heart Failure and Reduced Ejection Fraction

JoAnn Lindenfeld, MD, Maria Rosa Costanzo, MD, Michael R. Zile, MD, Anique Ducharme, MD, Richard Troughton, MD, Alan Maisel, MD, Mandeep R. Mehra, MD, MSc, Sara Paul, DNP, Samuel F. Sears, PhD, Frank Smart, MD, Nessa Johnson, PhD, John Henderson, MS, Philip B. Adamson, MD, Akshay S. Desai, MD, William T. Abraham, MD, on behalf of the GUIDE-HF, CHAMPION, and LAPTOP-HF Investigators

TABLE 1 Summary of Studies

	GUIDE-HF Randomized Arm	CHAMPION	LAPTOP-HF
Design	Prospective, multicenter, randomized, controlled, single-blinded evaluation of the CardioMEMS HF System	Prospective, multicenter, randomized, controlled, single-blinded evaluation of the CardioMEMS HF System	Prospective, multicenter, randomized, controlled evaluation of the LAP Monitoring System (HeartPOD and PAM)
Pressure sensor	Hemodynamic management using PAP via implanted sensor	Hemodynamic management using PAP via implanted sensor	Hemodynamic management using LAP via a transeptal lead
Patient engagement	• Blinded to treatment group, implanted control group • Daily PAP measurements • Interventions communicated by phone through blinded caller, minimum contact frequency for both groups	• Blinded to treatment group, implanted control group • Daily PAP measurements • Interventions communicated by phone, matched contact frequency between groups	• Unblinded to treatment group, unimplanted control group • Twice daily recording of symptoms, weights, and blood pressure, continuous measurement of LAP • Interventions communicated through handheld PAM
Trial dates	March 2018 to January 2021	September 2007 to December 2014	June 2010 to April 2015
Duration of follow-up HFrEF, mo	12 mo Median 8.2 mo (Q1, Q3: 4.6, 11.4 mo) (pre-COVID-19)	Continued until last subject reached 6 mo Median 17.0 mo (Q1, Q3: 11.5, 23.0 mo)	Continued until last subject reached 12 months Median 22.8 mo (Q1, Q3: 14.6, 34.8 mo)
Primary endpoint	Composite of HF hospitalizations, urgent HF visits, and all-cause mortality at 12 mo	HF hospitalizations at 6 mo	HF major acute cardiovascular and neurological events at overall follow-up
Major inclusion	NYHA functional class II/III/IV with prior HF hospitalization or elevated BNP/NT-proBNP	NYHA functional class III with prior HF hospitalization	NYHA functional class III with prior HF hospitalization or persistently elevated BNP
Sample size (HFrEF)	Baseline: 531 12 mo: 63 24 mo: not applicable	Baseline: 456 12 mo: 332 24 mo: 104	Baseline: 363 12 mo: 305 24 mo: 169
Safety outcomes	DSRCs: 0.8% (8/1,022)	DSRCs: 1.4% (8/575) Sensor Failures: 0% (0/575)	Not reported previously (see Supplemental Table 1)
Notes	Study affected by COVID-19 pandemic; pre-COVID-19 follow-up utilized (before March 13, 2020).		Study stopped because of implant-related complications, follow-up continued in therapy-initiated patients.

BNP = brain natriuretic peptide; DSRC = device or system-related complication; HFrEF = heart failure with reduced ejection fraction; LAP = left atrial pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAM = Patient Advisory Module; PAP = pulmonary artery pressure.

FIGURE 3 Heart Failure Hospitalizations for Implantable Hemodynamic Monitoring and Medical Therapy in Pooled Population

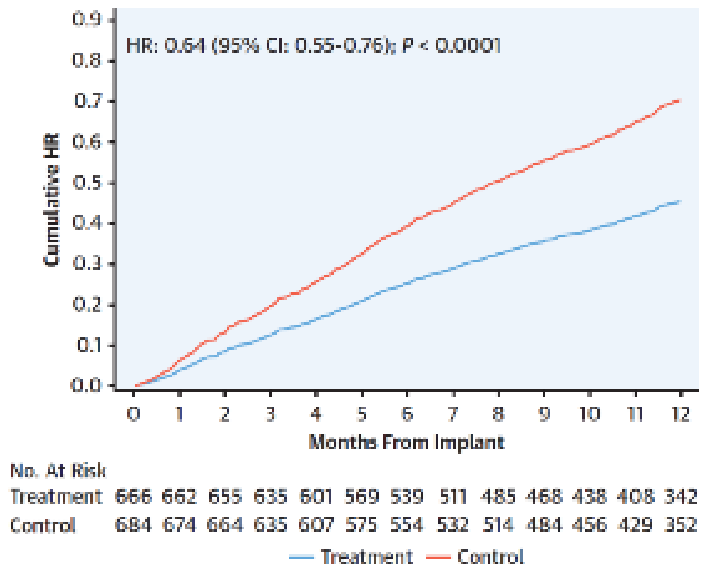

FIGURE 4 Survival for Implantable Hemodynamic Monitoring and Medical Therapy in Pooled Population

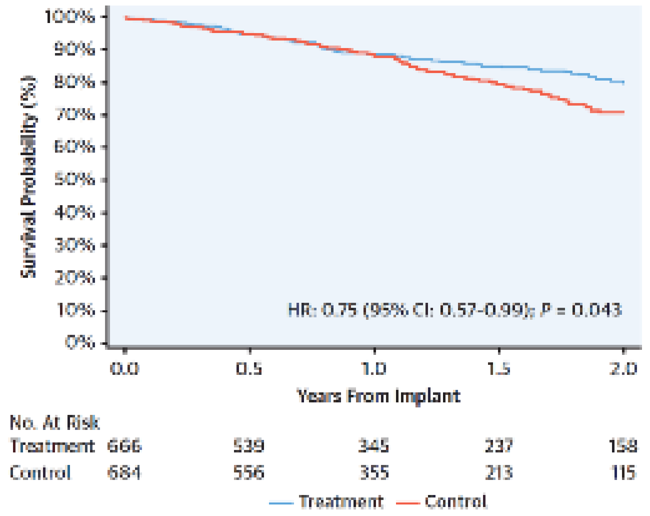

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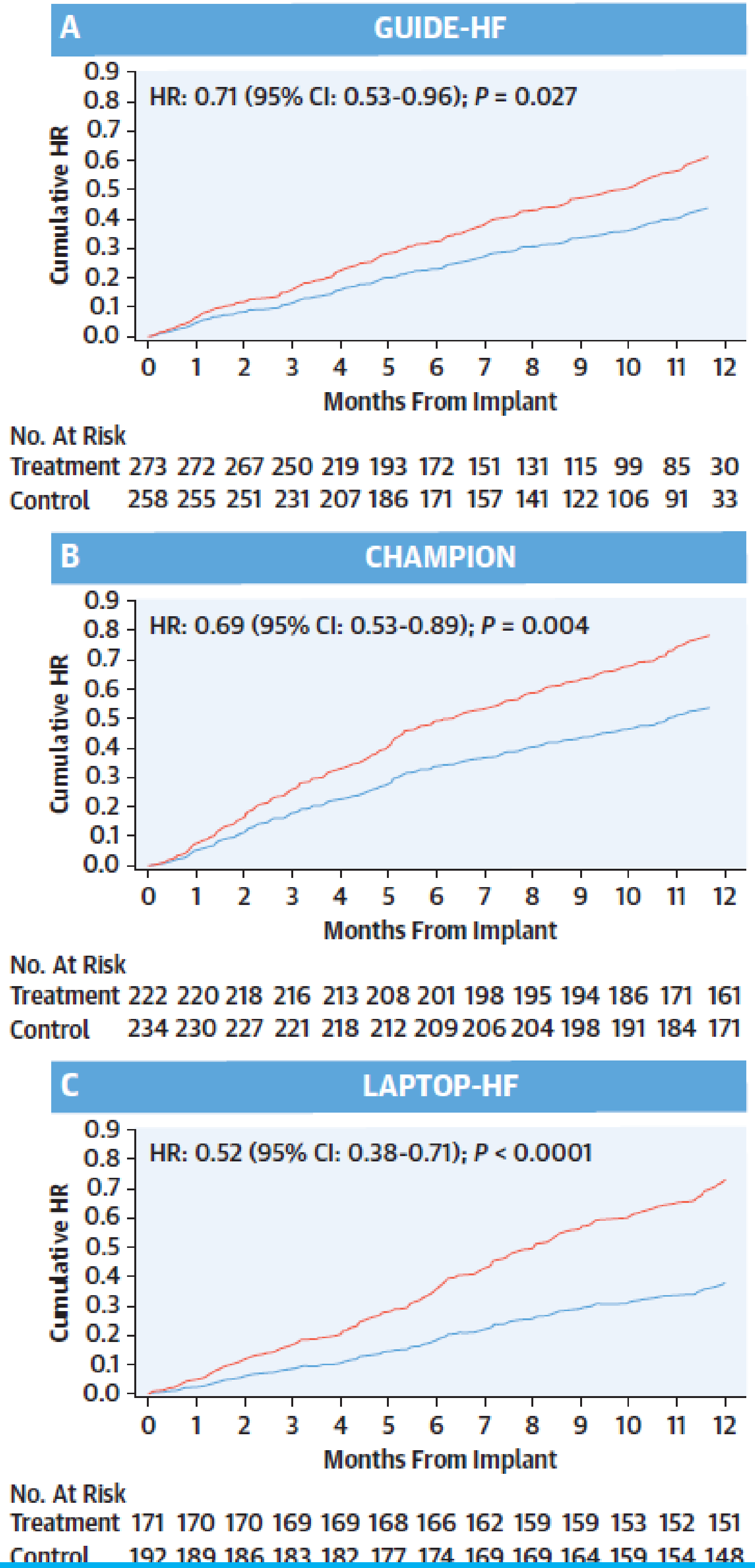
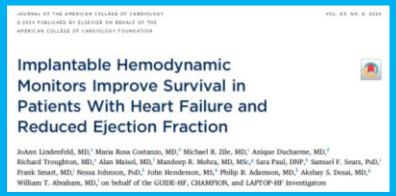
FIGURE 1 Heart Failure Hospitalizations for Implantable Hemodynamic Monitoring and Medical Therapy by Study




Implantable Hemodynamic Monitors Improve Survival in Patients With Heart Failure and Reduced Ejection Fraction

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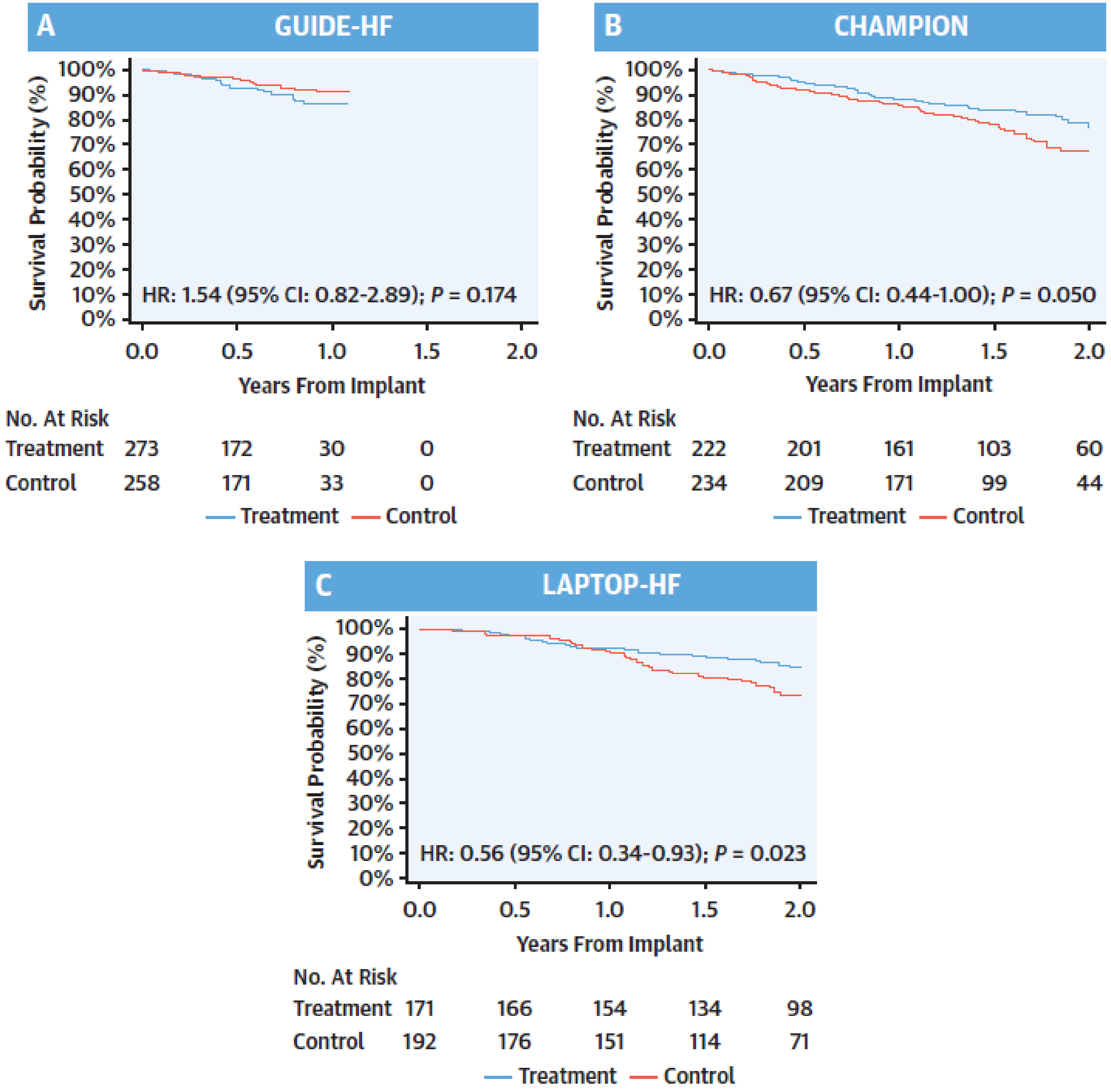
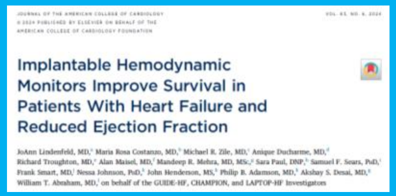
Cardiologia Cirié

FIGURE 3 Survival for Implantable Hemodynamic Monitoring and Medical Therapy by Study



Survival through 24 months for (A) GUIDE-HF, (B) CHAMPION, and (C) LAPTOP-HF, with implantable hemodynamic monitoring (treatment) in blue and medical therapy (control) in red. Outcomes varied by study, with no reduction in mortality in GUIDE-HF (A), a trend toward reduced mortality in CHAMPION (B), and a significant 44% reduction in mortality in LAPTOP-HF (C) at 24 months. Survival estimated using Kaplan-Meier estimates; HR, 95% CI, and *P* values estimated using Cox Proportional Hazards model. Abbreviations as in Figure 1.



Implantable Hemodynamic Monitors Improve Survival in Patients With Heart Failure and Reduced Ejection Fraction

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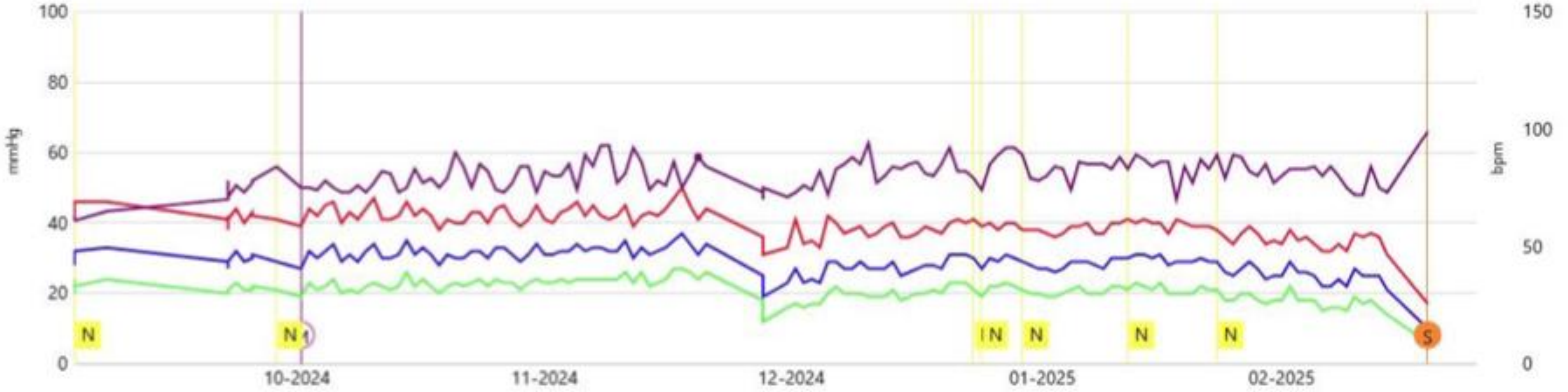

100
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02-2025

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CARDIAC CONTRACTILITY MODULATION

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Cardiologia Ciriè

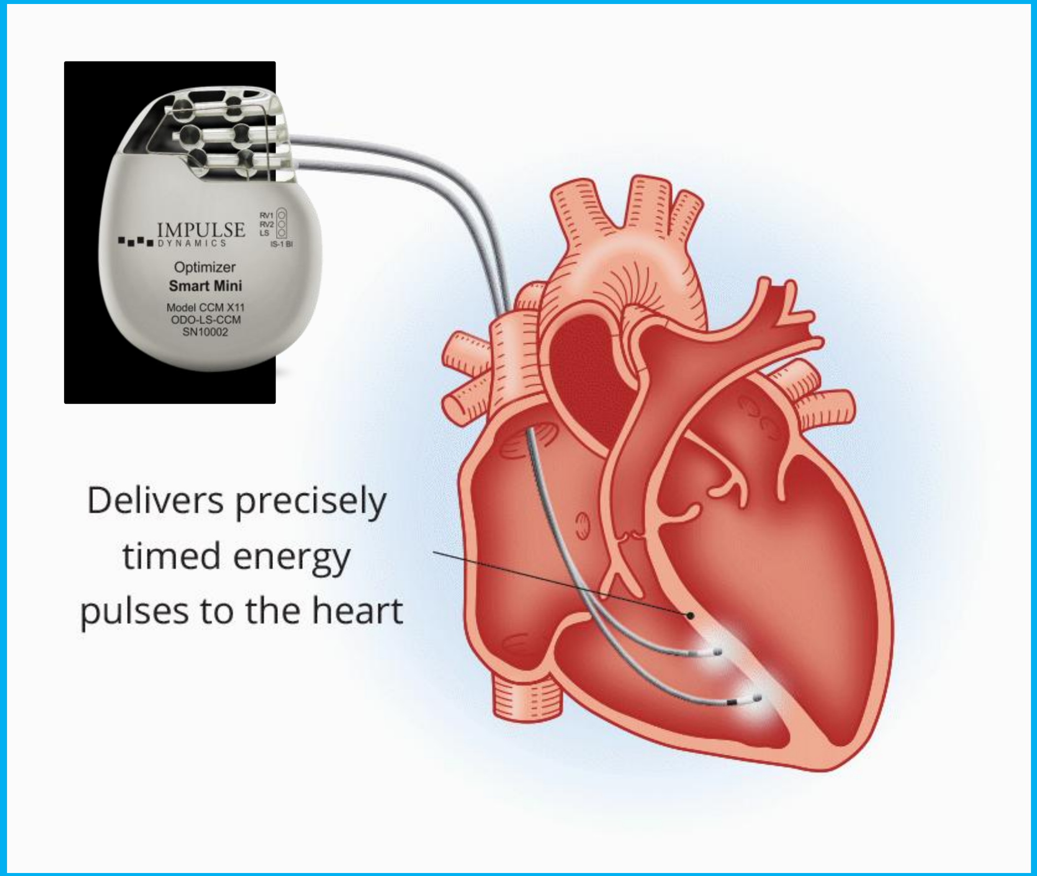
OPTIMIZER SMART MINI AND CCM™ SIGNAL

- **Cardiac Contractility Modulation** is a unique and innovative **therapy for patients with reduced and moderately reduced left ventricular systolic function and normal QRS duration**.

- CCM therapy is delivered by the Optimizer® Smart, an implantable pulse generator, that delivers the **non-excitatory impulses to the right ventricular septum during the absolute refractory period**

IPG

Charger



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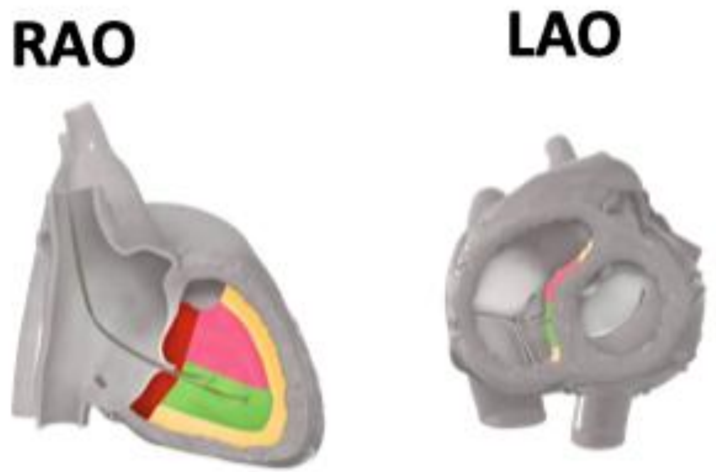
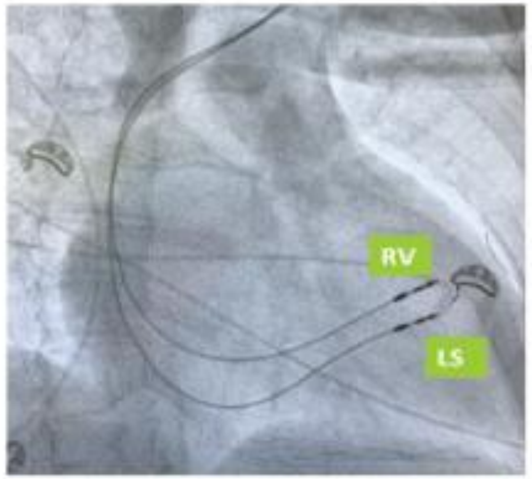
OPTIMIZER Smart system details

- **Implant with 2 usual pacemaker screw-in leads in right ventricle** (atrium not necessary with the latest algorithm)
- Rechargeable battery: **expected life 20 years**
- **Charging suggested once per week / ~ 60-90 min**
- Battery has "0V tolerance", means if battery is not being recharged:
  - Battery is not getting damaged by being discharged
  - Patient can recharge his Optimizer himself
  - CCM Therapy starts automatically after reaching a certain recharge level
- **Optimizer (all Generations) can be disabled by MAGNET application**





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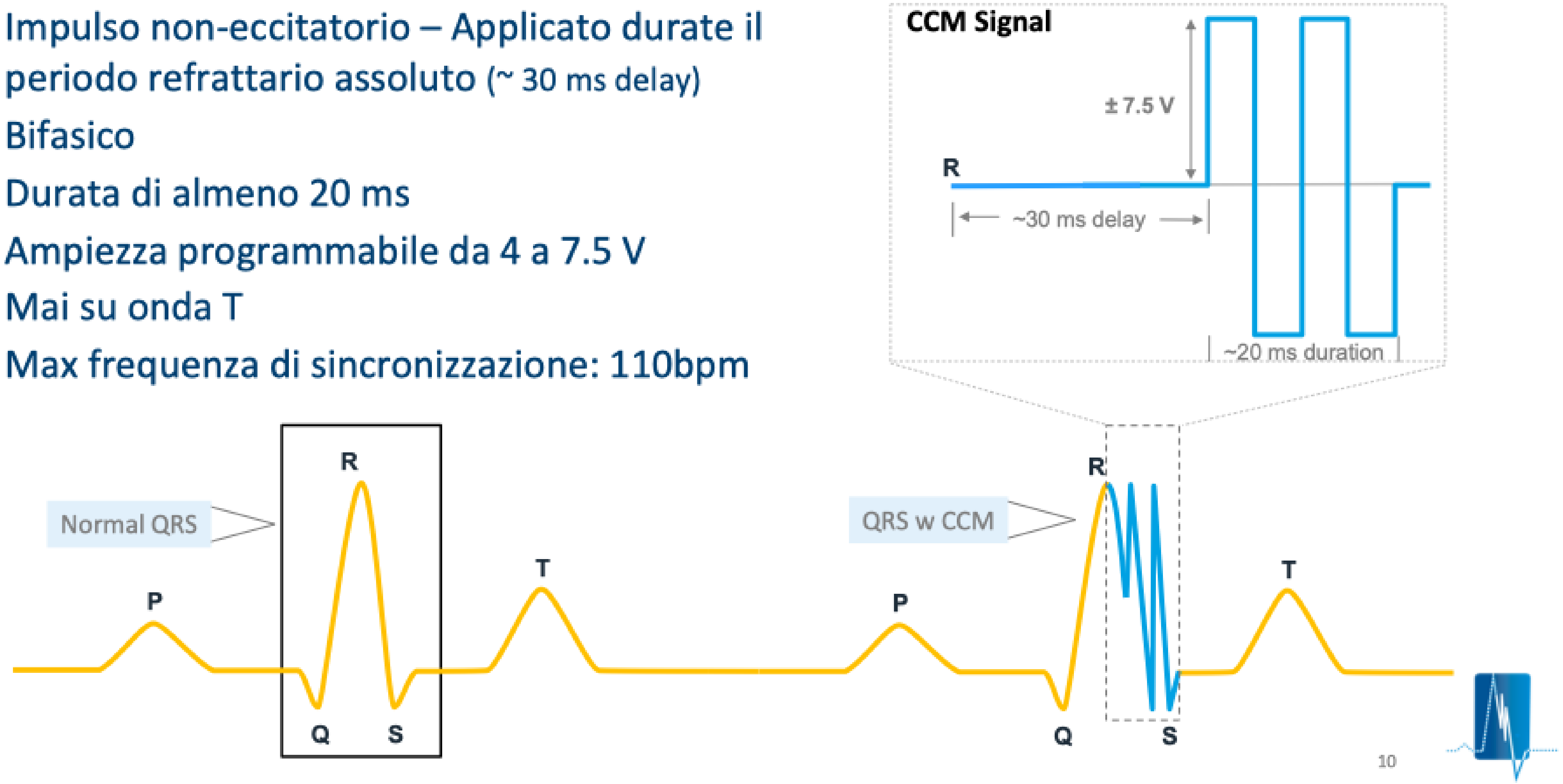
Cardiologia Ciriè

Terapia Modulazione della Contrattilità Cardiaca

- Impulso non-eccitatorio – Applicato durate il periodo refrattario assoluto (~ 30 ms delay)
- Bifasico
- Durata di almeno 20 ms
- Ampiezza programmabile da 4 a 7.5 V
- Mai su onda T
- Max frequenza di sincronizzazione: 110bpm



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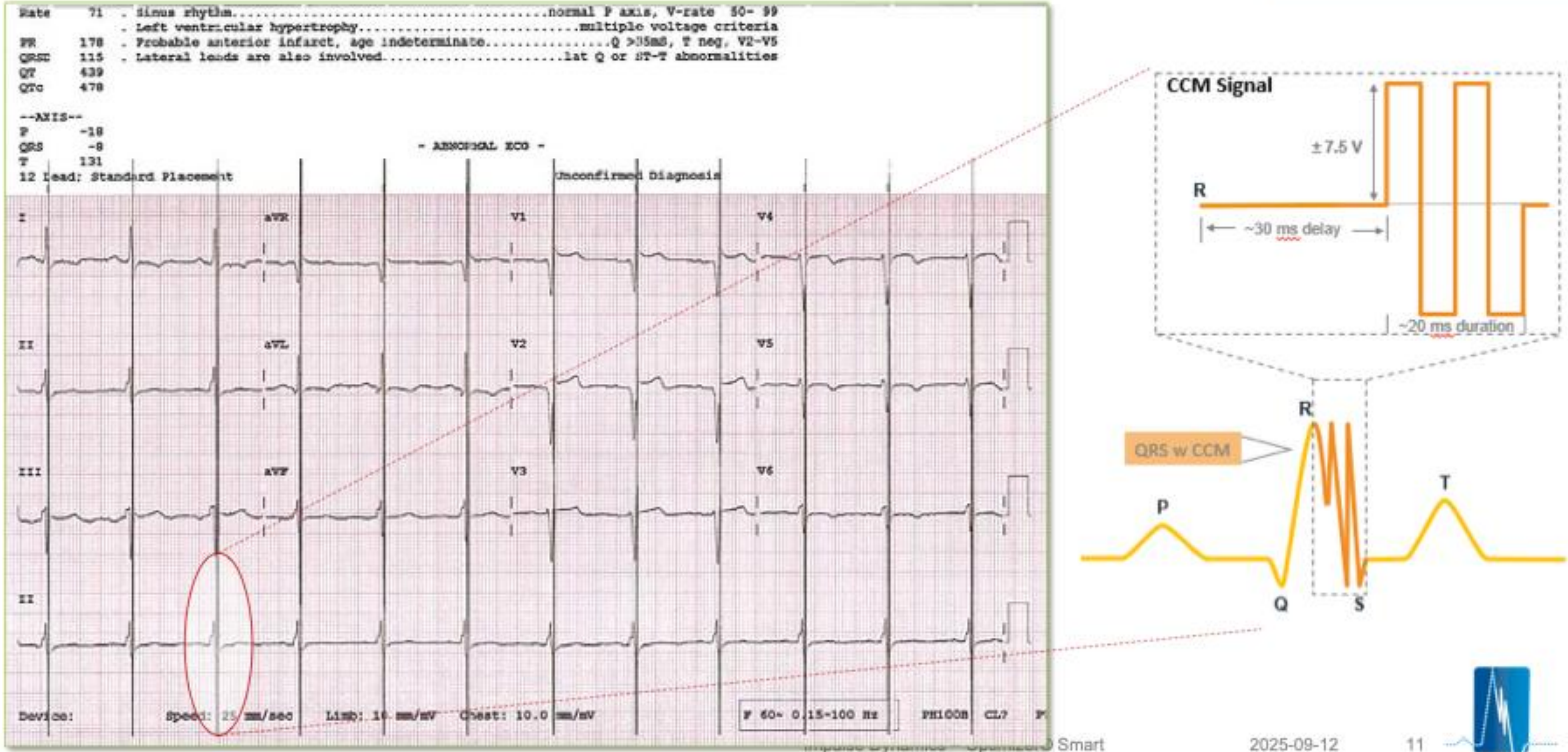
Cardiologia Cirié

Terapia Modulazione della Contrattilità Cardiaca



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Il Sistema Optimizer Smart & Smart Mini

- Five one-hour therapy delivery phases
- Separated by 3.8-hour rest periods
- CCM impulses are 300-400 X the output of typical pacing capture threshold for ventricular tissue
- Device Recharged Weekly
- One Hour Charging Period
- Device longevity ≥ 20years

Meccanismo di azione

Evidenze da modelli pre-clinici ex-vivo

Nel 2001, il gruppo della Columbia University guidato da Daniel Burkhoff produsse evidenze su tessuti miocardici ex-vivo che **l'erogazione di stimoli elettrici extracellulari fosse in grado di determinare un prolungamento del potenziale d'azione, una modifica del ciclo del calcio e un miglioramento della contrattilità** paragonabili a quelli ottenuti con tecnica di "voltage clamping", permettendo quindi al percorso sperimentale di avanzare verso studi meccanicistici e modelli in vivo con alla base una stimolazione elettrica di tipo cellulare

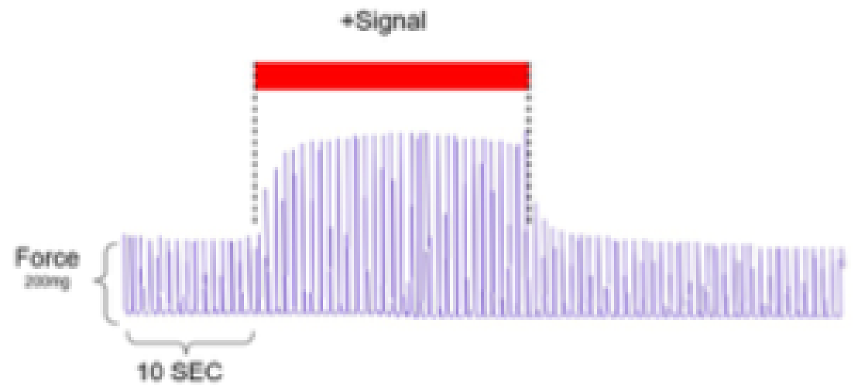

Tabella 2. Principali effetti mediati dalla modulazione della contrattilità cardiaca e rispettiva latenza d'azione.

Meccanismo	Tempistica
Allungamento della durata del potenziale d'azione[17,18]	Secondi
Aumento del calcio intracellulare[17-19]	Secondi
Potenziamento del reticolo sarcoplasmatico[17,18]	Secondi-minuti
Aumento dello stato inotropo[17-21,25]	Minuti-ore
Variazione dell'espressione genica[21,27,28,30]	Settimane-mesi

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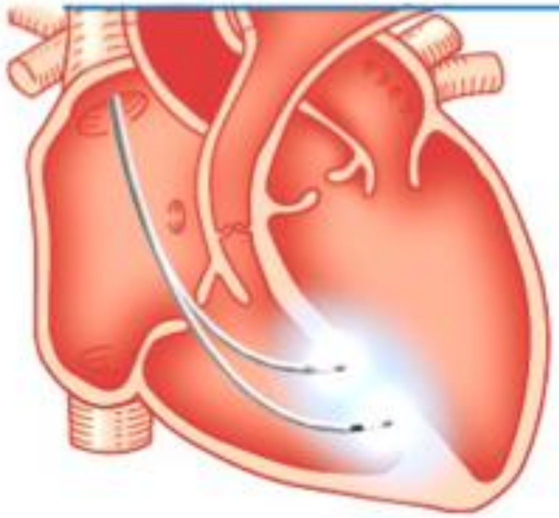
Meccanismo di azione

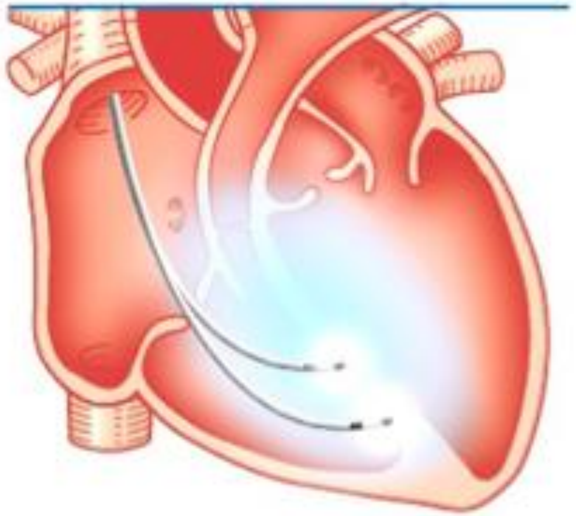
Rapidi
DA MINUTI A ORE



Miglioramento del ciclo del calcio e della forza contrattile

- Propagazione elettrotonica locale del segnale
- Rapida fosforilazione delle principali proteine
- Nessun aumento del consumo di ossigeno da parte del miocardio

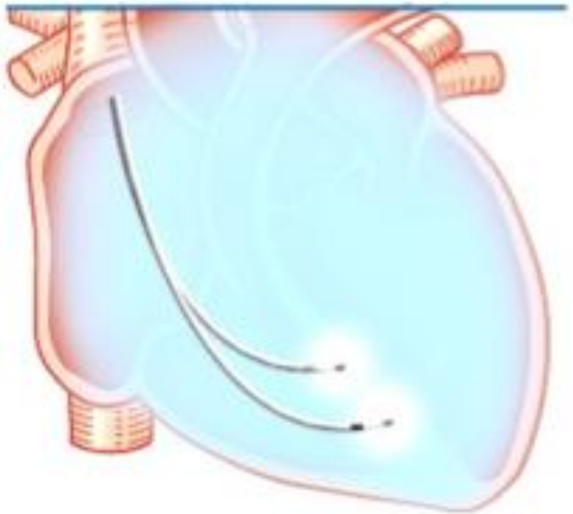
Intermedi
DA ORE A SETTIMANE



Cambiamento del programma genico da insufficienza cardiaca a normale

- Gli effetti locali migliorano la contrazione a livello globale

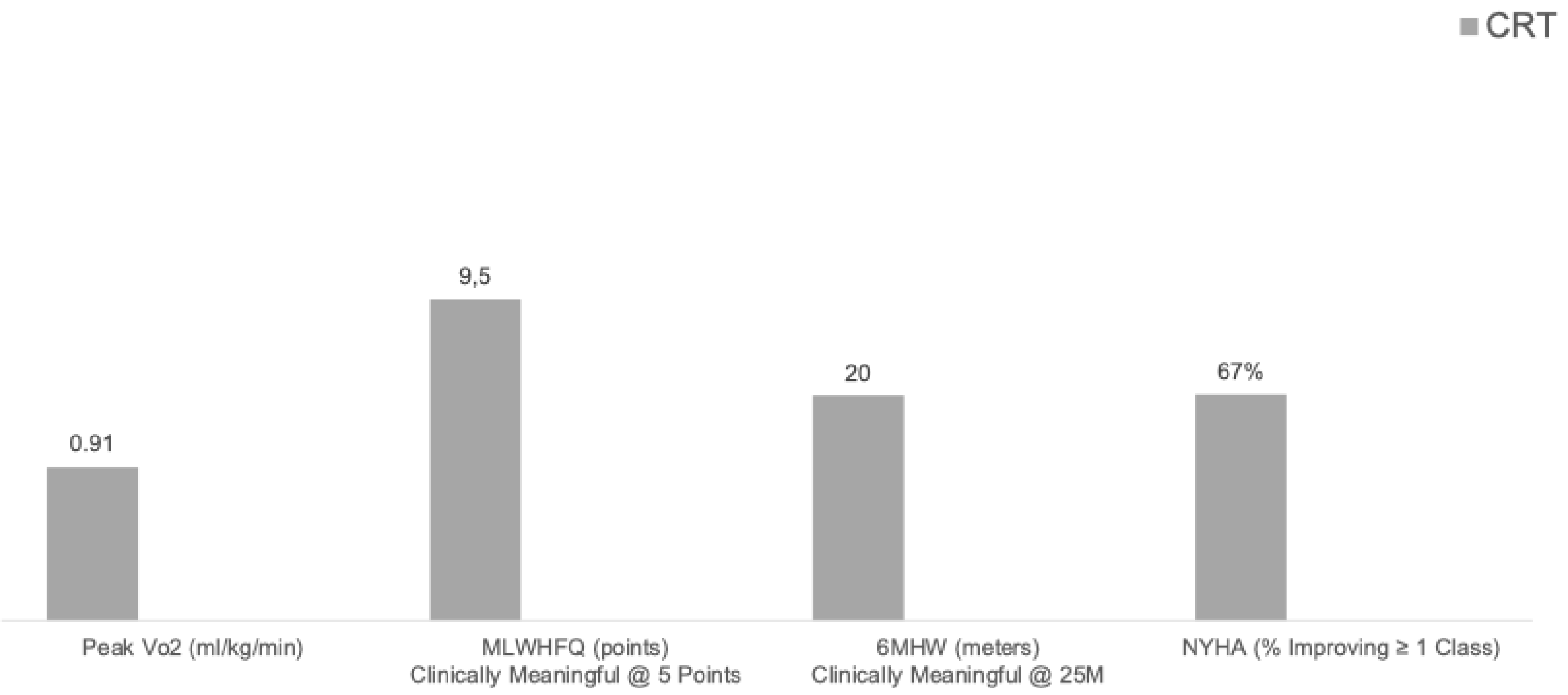
A lungo termine
DA SETTIMANE A MESI



Effetto benefico sulle proprietà ventricolari globali e sul **rimodellamento inverso**

CRT Landmark Trials

Now a Class 1 Indication



[10] For CRT: Higgins JACC 2003, Abraham NEJM 2002, Abraham Circulation 2004, Young JAMA 2003, Cazeau NEJM 2001, Leclercq EHJ 2002
[11] For CCM 25-45% - 2020 - Wiegn, et al, Circulation Heart Failure - doi.org/10.1161/CIRCHEARTFAILURE.119.006512
[12] For CCM 35-45% - 2018 - Abraham, et al, JACC Heart Failure - doi.org/10.1016/j.jchf.2018.04.010
Note - data weighted by patient numbers and provided only as a comparison

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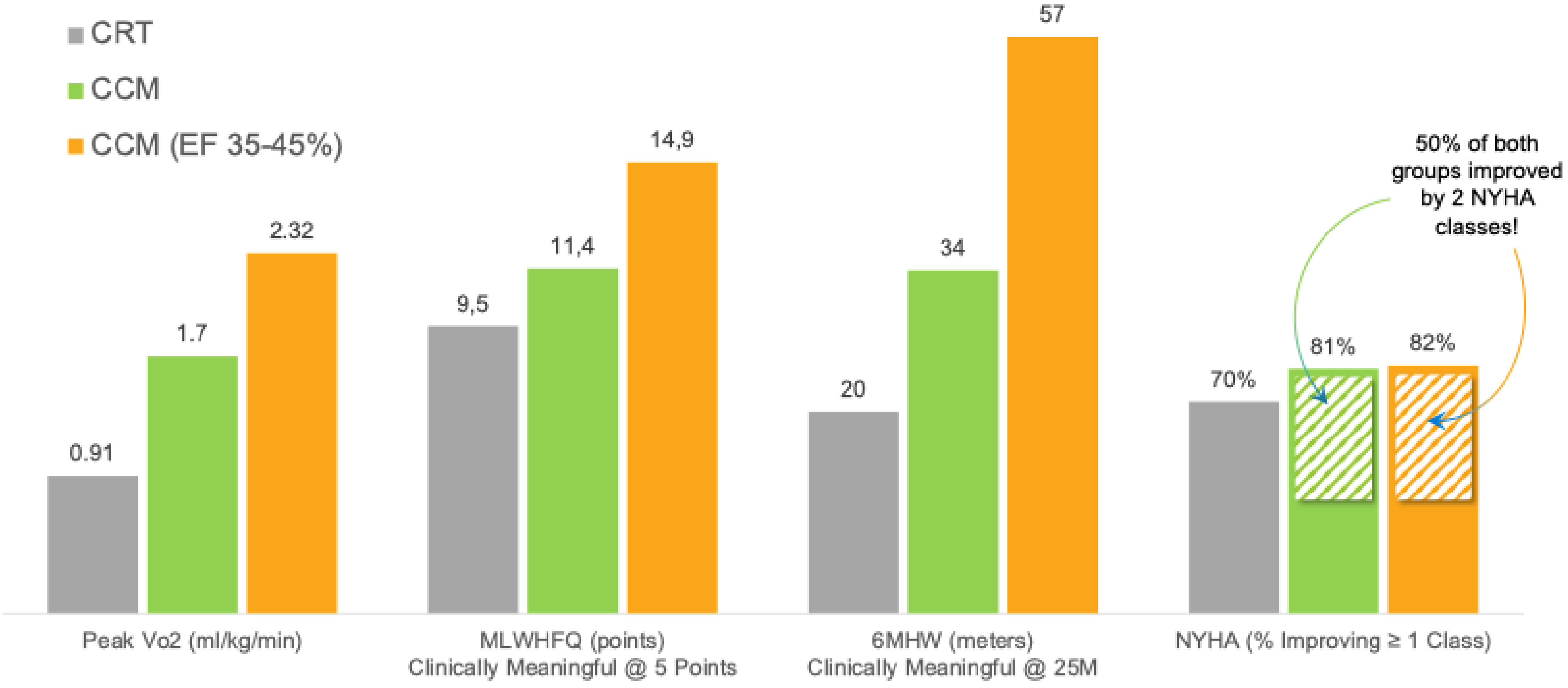
Cardiologia Cirié

CRT and *CCM*® Landmark Trials

Outcomes Comparison

IMPULSE DYNAMICS



For CRT: Higgins JACC 2003, Abraham NEJM 2002, Abraham Circulation 2004, Young JAMA 2003, Caseau NEJM 2001, Leclercq EHJ 2002
For CCM 25-45% - 2020 - Wiegn, et al, Circulation Heart Failure - doi.org/10.1161/CIRCHEARTFAILURE.119.006512
For CCM 35-45% - 2018 - Abraham, et al, JACC Heart Failure - doi.org/10.1016/j.jchf.2018.04.010
Note - data weighted by patient numbers and provided only as a comparison

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CCM – Principali studi e registri

Study Name	Comments	Rand.	Device	Countries	Total patients
FIX-HF-1	Acute study		Opt I	Italy	40
FIX-HF-2	First chronic study		Opt I	Italy	6
FIX HF-3	CE study (EU)		Opt II	Italy, Germany, Austria	22
FIX-CHF-4	Crossover double-blind, 6 months	Yes	Opt II	Italy, Austria, Germany, France, The Netherlands and Czech	164
FIX-HF-5 Phase I	CCM vs OMT, 6 months	Yes	Opt II	USA	49
FIX-HF-5 Phase II	CCM vs. OMT	Yes	Opt III	USA	428
FIX-HF-9	CCM vs. OMT	Yes	Opt III	Hong Kong	42
FIX-CHF-12	CRT non-responder study		Opt III	Germany	19
FIX-CHF-13	CCM dosage (5 vs. 12 hours)		Opt III	Germany	20
CCM HF	CCM Registry		Opt III	Germany	143
FIX-CHF-18	Comparison 1 vs 2 leads		Opt III, Opt IVs	Germany	48
FIX-HF-5C	CCM vs. OMT confirmatory	Yes	Opt IVs	USA, Germany, Czech	160
CCM-REG	CCM Registry		Opt IVs, Smart	Germany, Russia, France, Italy	503
FIX-HF-5C2	2-Lead CCM Device		Opt Smart (2-lead)	US, Germany	60
CCM-HFpEF Phase I*	CCM in HF with preserved EF		Opt Smart (2-lead)	Italy, Poland Germany, Spain, Australia	50
Total					1.754

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Cardiologia Cirié

CCM: metananalisys

IMPULSE DYNAMICS

4 Randomized Trials:

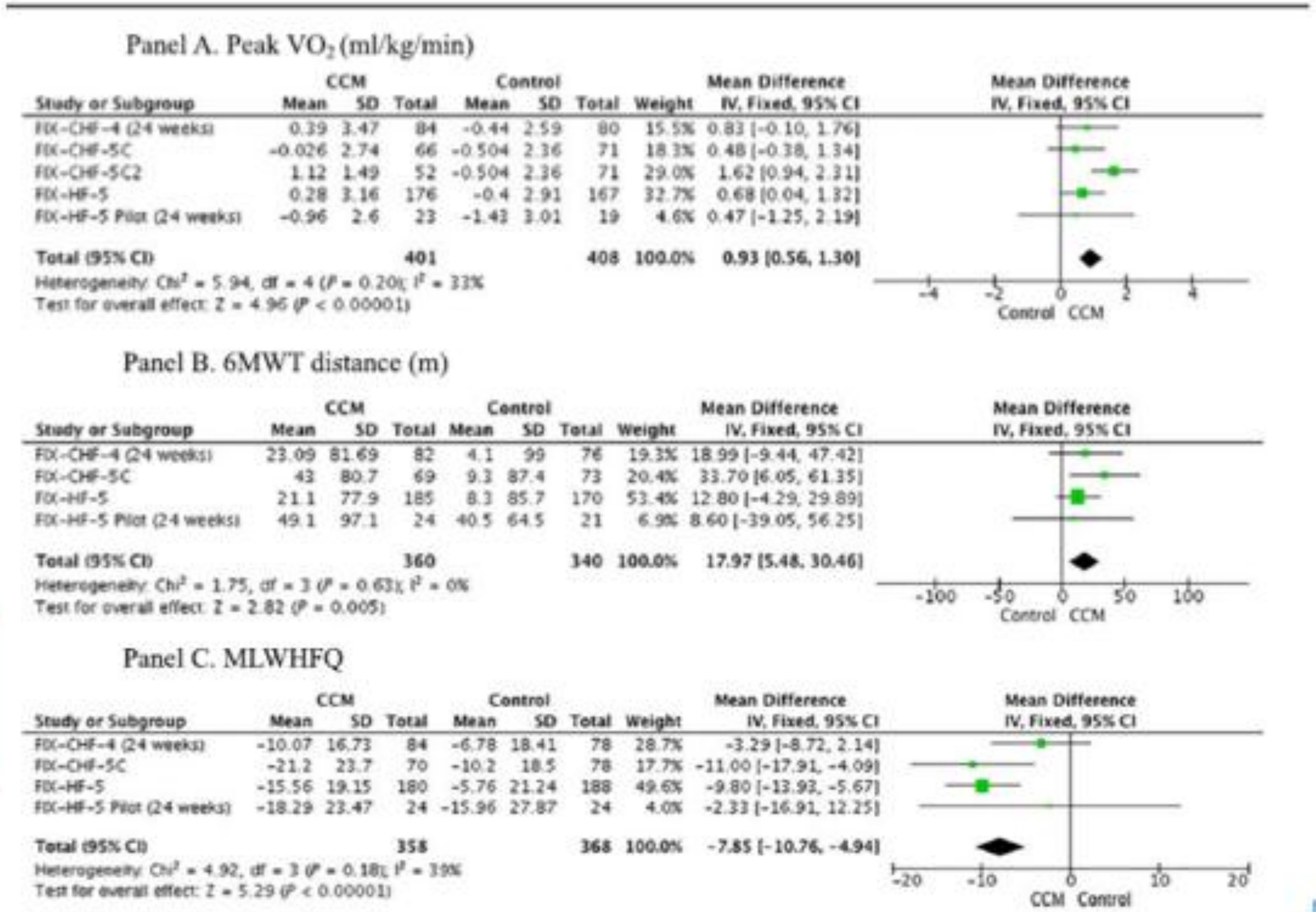
- FIX-HF-4
- FIX-HF-5 pilot
- FIX-HF-5
- FIX-HF-5C

1 single arm Trial:

- FIX-HF-5C2

801 pts

The overall impact of CCM on functional capacity and quality of life is similar to that reported in prior studies of CRT



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: $Z = 5.29$ ($P < 0.00001$)

Giallauria F et al. ESC Heart Failure 2020; 7(5): 2922-2932

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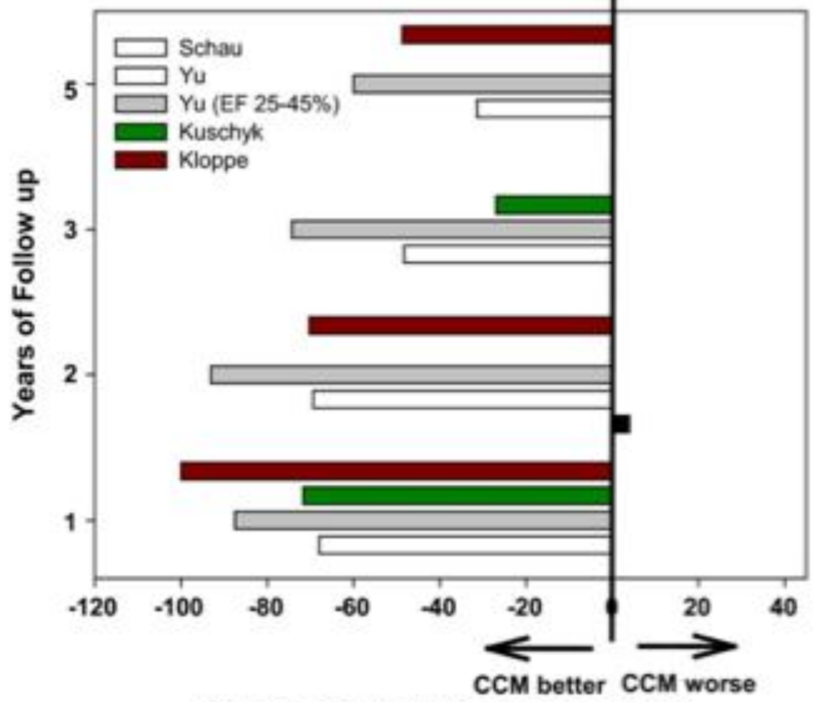
Cardiologia Cirié

CCM: meta analysis on mortality rates over 5 studies

IMPULSE DYNAMICS

Mortality rates for CCM versus OMT or comparator groups after long-term follow up



Difference in mortality between CCM and predicted/control (%)

- At the longest follow-up time point for each study, mortality rates were the same or lower in the CCM group compared to the medically treated comparator (in one study mortality with CCM was higher in year 2).
- The benefit was consistent across a broad spectrum of severity of disease
  - Schau et al. enrolled **54** patients with more severe heart failure—NYHA III–IV, EF = 23 %
  - Kloppe et al. followed **68** patients with NYHA II–III, mean EF = 26 %
  - Kuyschyk et al. studied **81** patients NYHA II–IV, EF = 23 %, 14 % of patients had prolonged QRS duration
  - Liu et al. tracked **41** subjects with NYHA III and EF = 27 %

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Cardiologia Cirié

Terapia CCM: Italian Position Paper

Modulazione della contrattilità cardiaca nello scompenso cardiaco a frazione di eiezione ridotta: revisione critica delle evidenze ed aspetti decisionali pratici

Mauro Biffi[1], Nadia Aspromonte[2], Maria Grazia Bongiorni[3], Francesco Clemenza[4], Antonio D'Onofrio[5], Gaetano Maria De Ferrari[6], Francesco Giallauria[7], Massimo Grimaldi[8], Fabrizio Oliva[9], Michele Senni[10], Claudio Tondo[11], Massimo Zecchin[12], Luigi Cappannoli[2], Mario Giannotti Santoro[3], Matteo Ziacchi[1], Aldostefano Porcari[12], Gianfranco Sinagra[12]

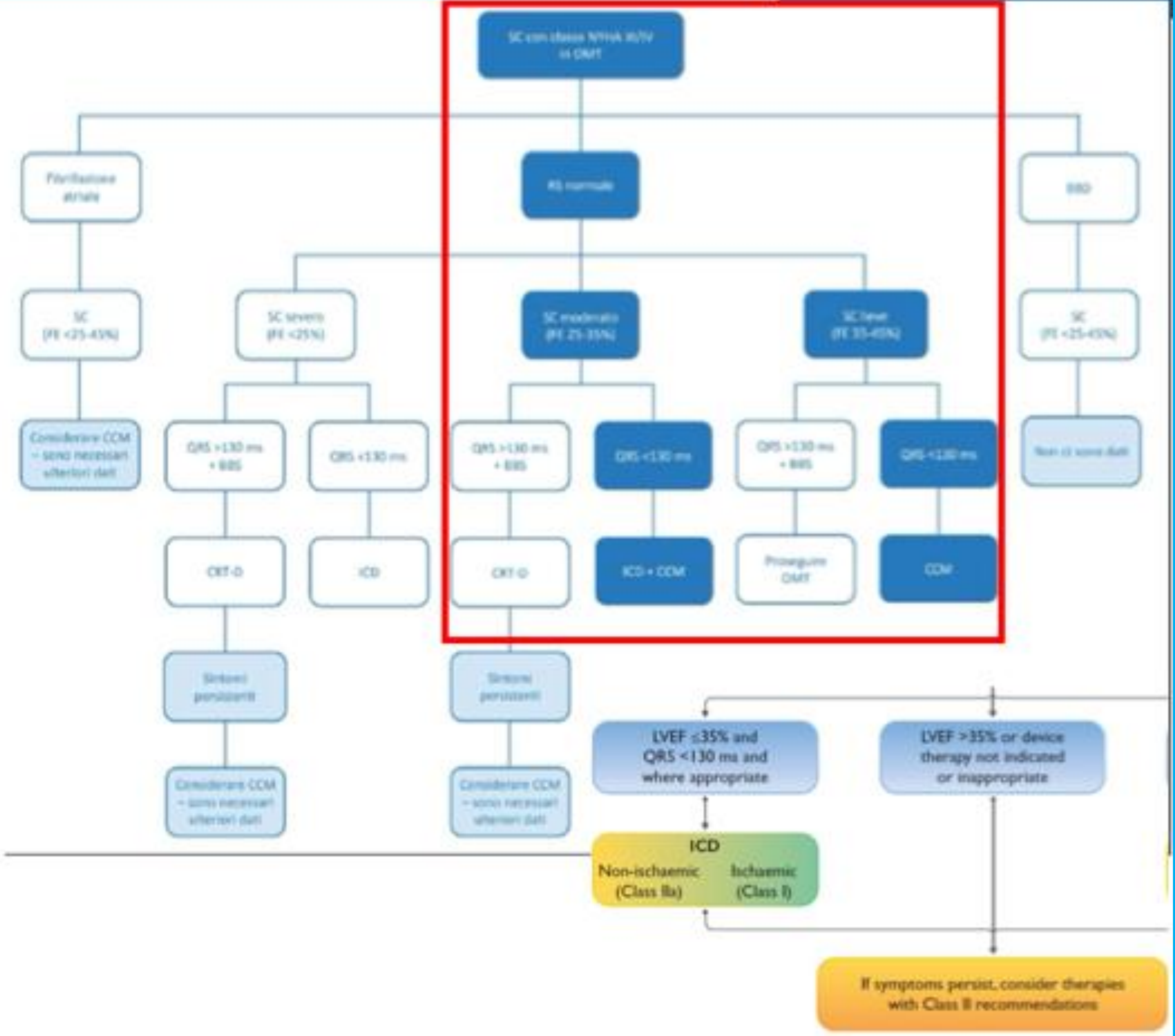
[1]Policlinico Sant'Orsola, Azienda Ospedaliero-Universitaria di Bologna, Bologna
[2]Dipartimento di Scienze Cardiovascolari, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Roma
[3]U.O. Cardiologia 2 SSN, Dipartimento Cardiovascolare, Ospedale Cisanello, Azienda Ospedaliero-Universitaria, Pisa
[4]Dipartimento Cardiotoracico, IRCCS ISMETT, Palermo
[5]Dipartimento Cardiovascolare, Ospedale Monaldi, Napoli
[6]Dipartimento Cardiovascolare, Ospedale Le Molinette, Torino
[7]U.O. Medicina Interna ad Indirizzo Metabolico e Riabilitativo, Dipartimento di Scienze Mediche Traslazionali, Università degli Studi di Napoli "Federico II", Napoli
[8]U.O.C. Cardiologia, Ospedale "F. Miulli", Acquaviva delle Fonti (BA)
[9]Dipartimento Cardiovascolare, ASST Grande Ospedale Metropolitano Niguarda, Milano
[10]Dipartimento Cardiovascolare, ASST Papa Giovanni XXIII, Bergamo
[11]Centro Cardiologico Monzino, IRCCS, Dipartimento di Scienze Biochimiche, Chirurgiche e Odontoiatriche, Università degli Studi, Milano
[12]Dipartimento Cardiovascolare, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI) e Università degli Studi di Trieste, Trieste

This critical review illustrates the pathophysiological aspects and available scientific evidence about cardiac contractility modulation therapy. A useful algorithm dealing with the essential decisional knots to consider for device implantation in patients with heart failure in NYHA class ≥II and ejection fraction ≤45% is presented. The present review paves the way for the development of an Italian registry aiming at analyzing the characteristics of implanted patients based on a multiparametric approach, including cardiac biomarkers, to identify clinical profiles and predictors of response to therapy. The "Answers and Questions" section provides useful insights into pathophysiology, technical specifications, clinically relevant scenarios and future perspectives.

Key words. Cardiac contractility modulation; Ejection fraction; Electrical therapy; Heart failure; Prognosis.

G Ital Cardiol 2021;22

G Ital Cardiol 2021;22



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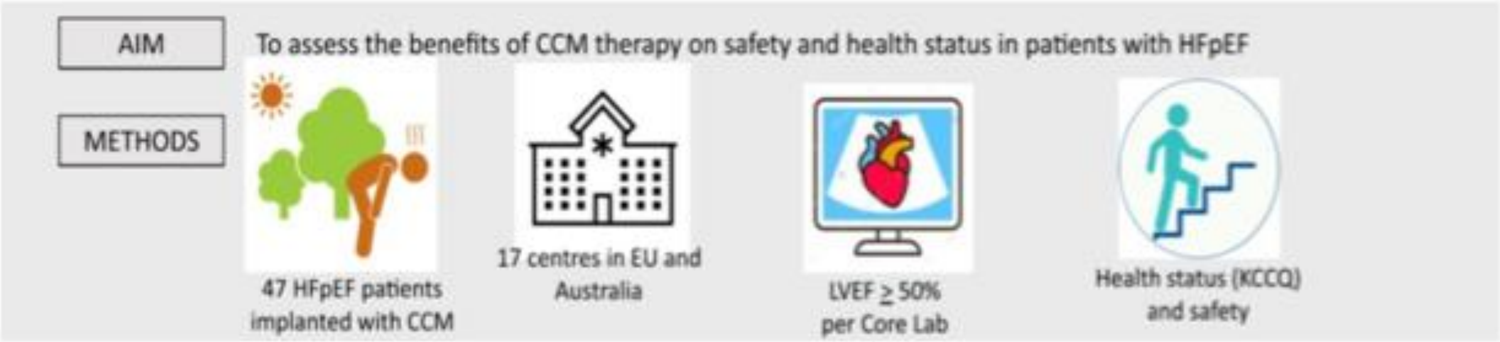
Cardiologia Cirié

Terapia CCM e pazienti HFpEF

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

Cecilia Linde[1*], Marcin Grabowski[2], Piotr Ponikowski[3], Ishu Rao[4], Angela Stagg[5], and Carsten Tschöpe[6]

Altri criteri di inclusione:
- Classe NYHA II o III;
- OMT per HF stable da 3 mesi;
- NT-proBNP > 220 pg/ml in RS o > 600 pg/ml in AF
- Età >40 anni e <80 anni



End-point primario di sicurezza:
Tasso di libertà da eventi: 93,6%

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Cardiologia Cirié

CCMT
Mechanism of Action

HFpEF

- Reduction of cardiac fibrosis
- Increase in titin phosphorylation

HFrEF

- Increase in peak cytosolic calcium concentrations
- Metabolic remodelling
- Reverse of fetal gene programs
- Rebalancing Cardiac Autonomic Tone
- Reduction of cardiac fibrosis
- Electrophysiological remodeling

Masarone D. Heart Rhytm 2023

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Cardiologia Cirié

Future Directions

Optimizer® Smart & Smart Mini | Optimizer® Smart Mini | Optimizer® Integra CCM-D

Clinical Portfolio

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

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

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

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Cardiologia Ciriè

Terapia CCM: Italian Position Paper

IMPULSE DYNAMICS

Modulazione della contrattilità cardiaca nello scompenso cardiaco a frazione di eiezione ridotta: revisione critica delle evidenze ed aspetti decisionali pratici

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This critical review illustrates the pathophysiological aspects and available scientific evidence about cardiac contractility modulation therapy. A useful algorithm dealing with the essential decisional knots to consider for device implantation in patients with heart failure in NYHA class >II and ejection fraction ≤45% is presented. The present review paves the way for the development of an Italian registry aiming at analyzing the characteristics of implanted patients based on a multiparametric approach, including cardiac biomarkers, to identify clinical profiles and predictors of response to therapy. The "Answers and Questions" section provides useful insights into pathophysiology, technical specifications, clinically relevant scenarios and future perspectives.

Key words. Cardiac contractility modulation; Ejection fraction; Electrical therapy; Heart failure; Prognosis.

G Ital Cardiol 2021;22

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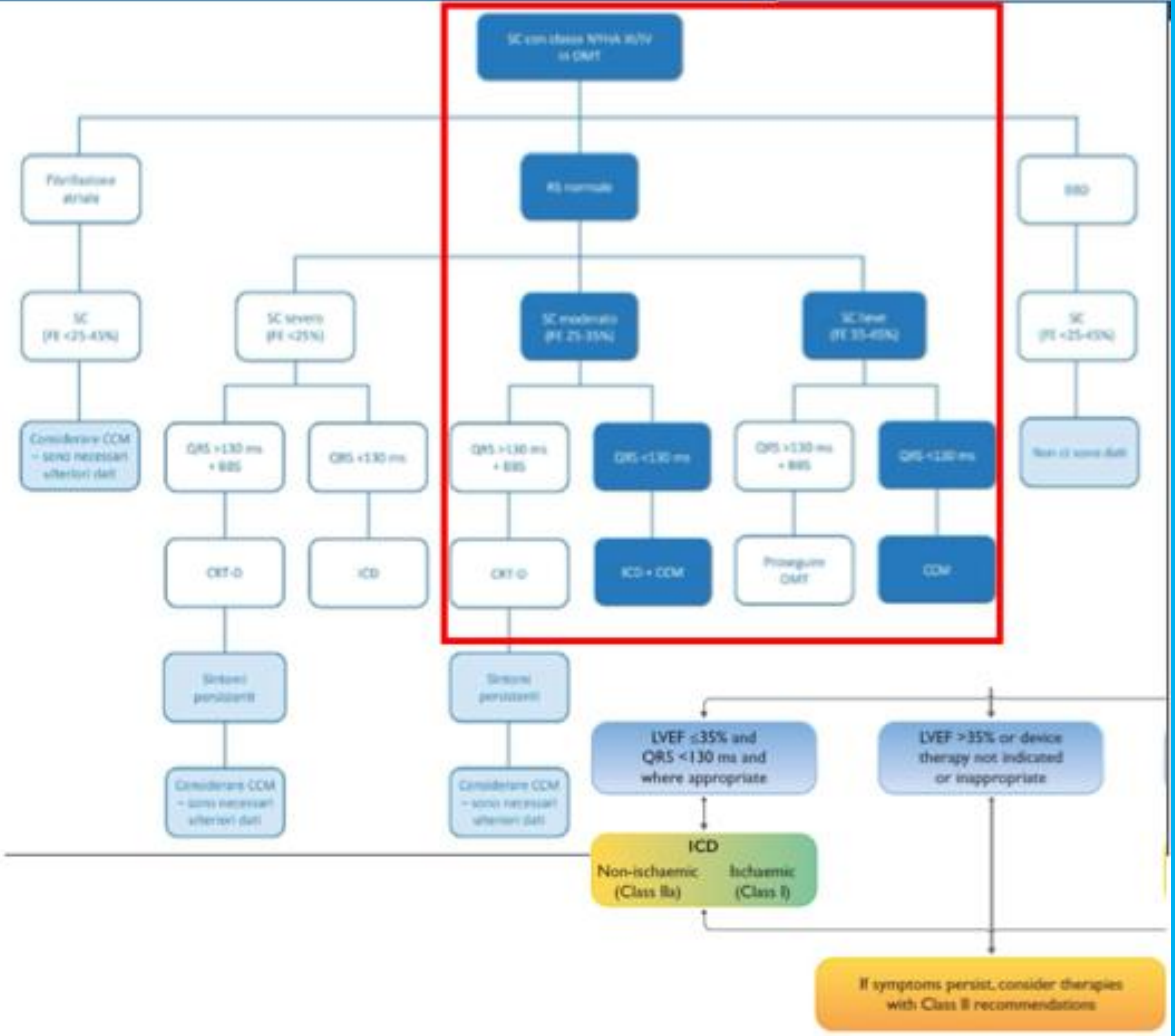

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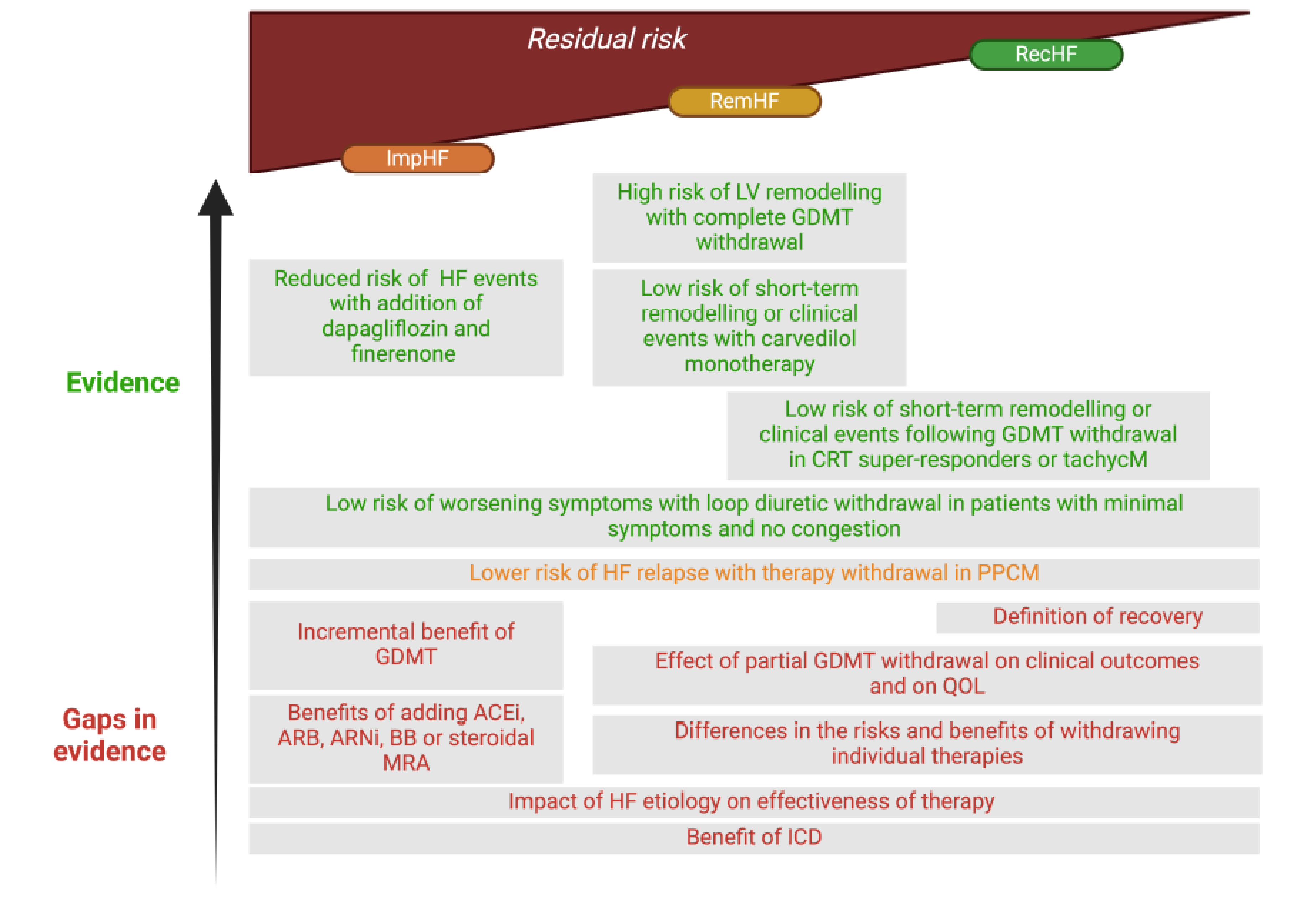

Figure 3 Summary of the evidence and gaps in evidence for the management of patients with improved (ImpHF), remission (RemHF) and recovered heart failure (RecHF). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; PPCM, peripartum cardiomyopathy; QOL, quality of life, tachycM, tachycardia-induced cardiomyopathy.

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POSITION PAPER

Heart failure improvement, remission, and recovery: A *European Journal of Heart Failure* expert consensus document

Jean-Sébastien Hulot[1,2], Jozine M. Ter Maaten[3], Antoni Bayes-Genis[4], Brian P. Halliday[5], Marco Metra[6], Brenda Moura[7], Mark C. Petrie[8], Gianluigi Savarese[9], Michele Senni[10], Sophie Van Linhout[11,12], Lynne Warner Stevenson[13], and Wilfried Mullens[14,15*]

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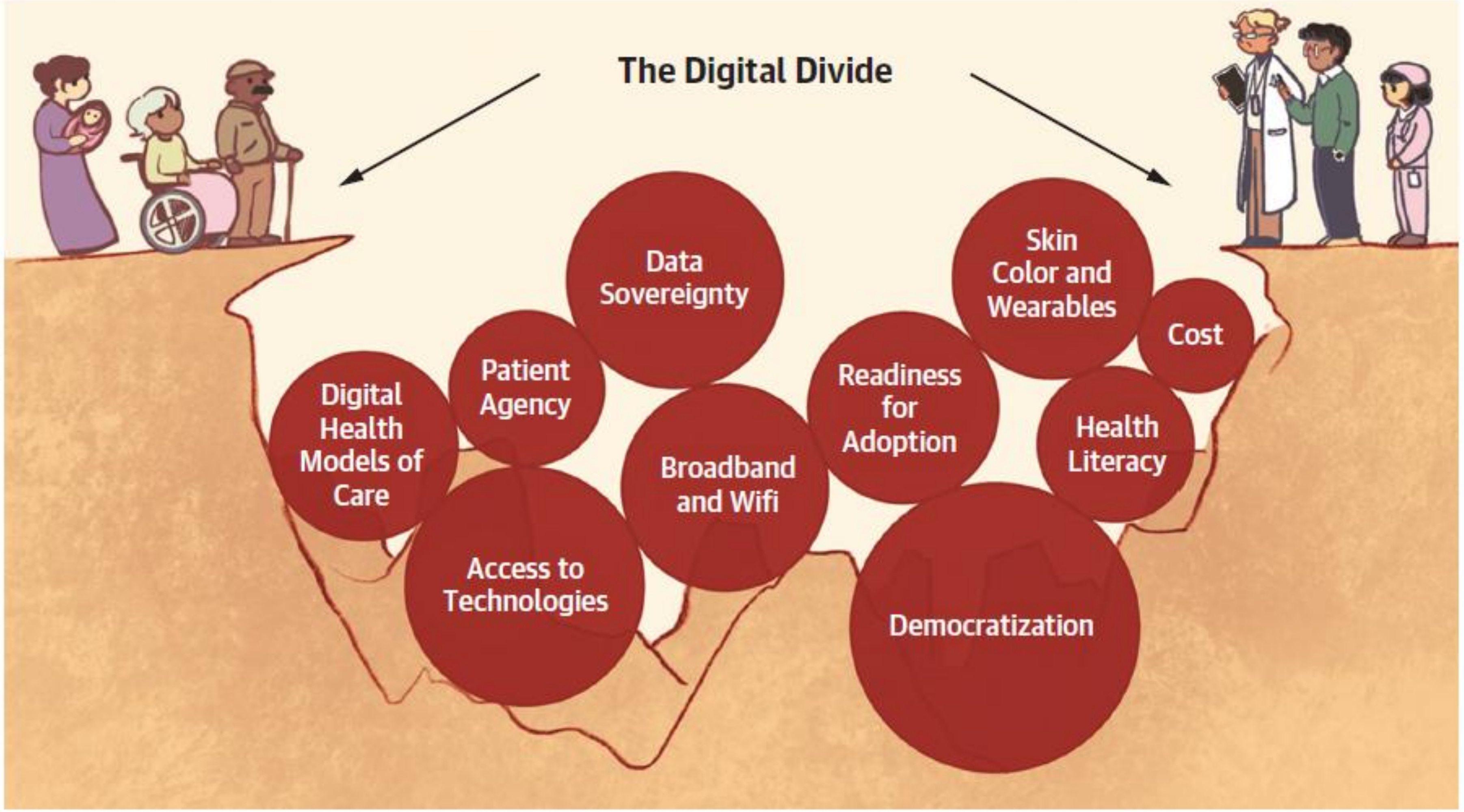
FIGURE 6 The Digital Divide



Examples of challenges that need to be bridged to enable equitable access to care through digital health care platforms.

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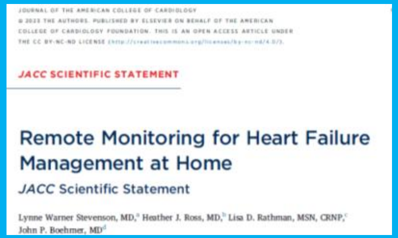

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JACC SCIENTIFIC STATEMENT

Remote Monitoring for Heart Failure Management at Home

JACC Scientific Statement

Lynne Warner Stevenson, MD,[a] Heather J. Ross, MD,[b] Lisa D. Rathman, MSN, CRNP,[c] John P. Boehmer, MD[d]

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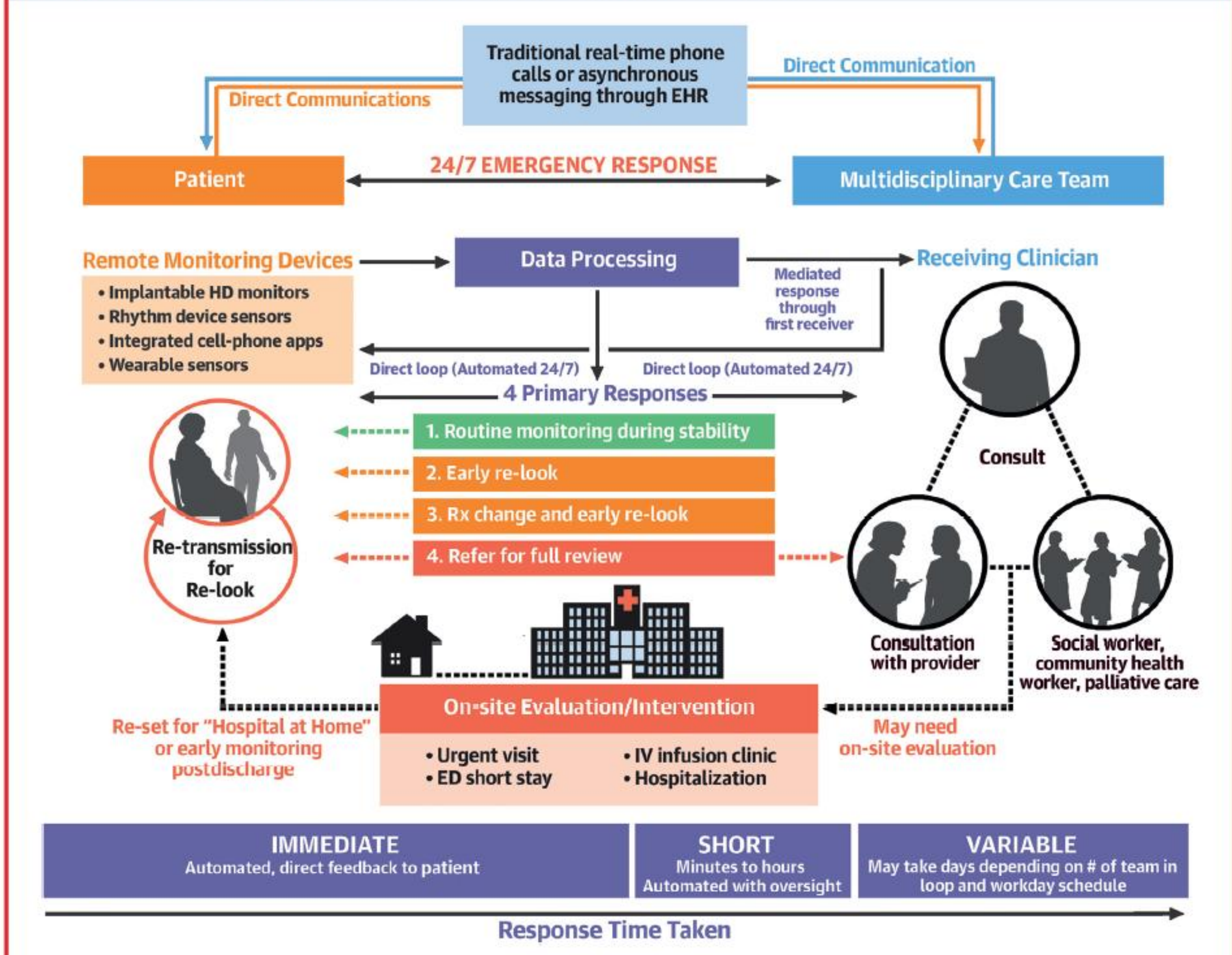
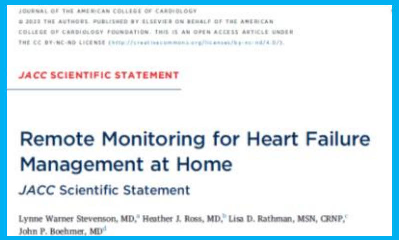
CENTRAL ILLUSTRATION Connecting the Circles Between Clinic and Home



Stevenson LW, et al. J Am Coll Cardiol. 2023;81(23):2272-2291.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