Cardiac Contractility Modulation

State of the Heart 2024

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Nebraska Medicine

Disclosures

- Consultant- Biosense Webster
- Consultant - Medtronic

Case

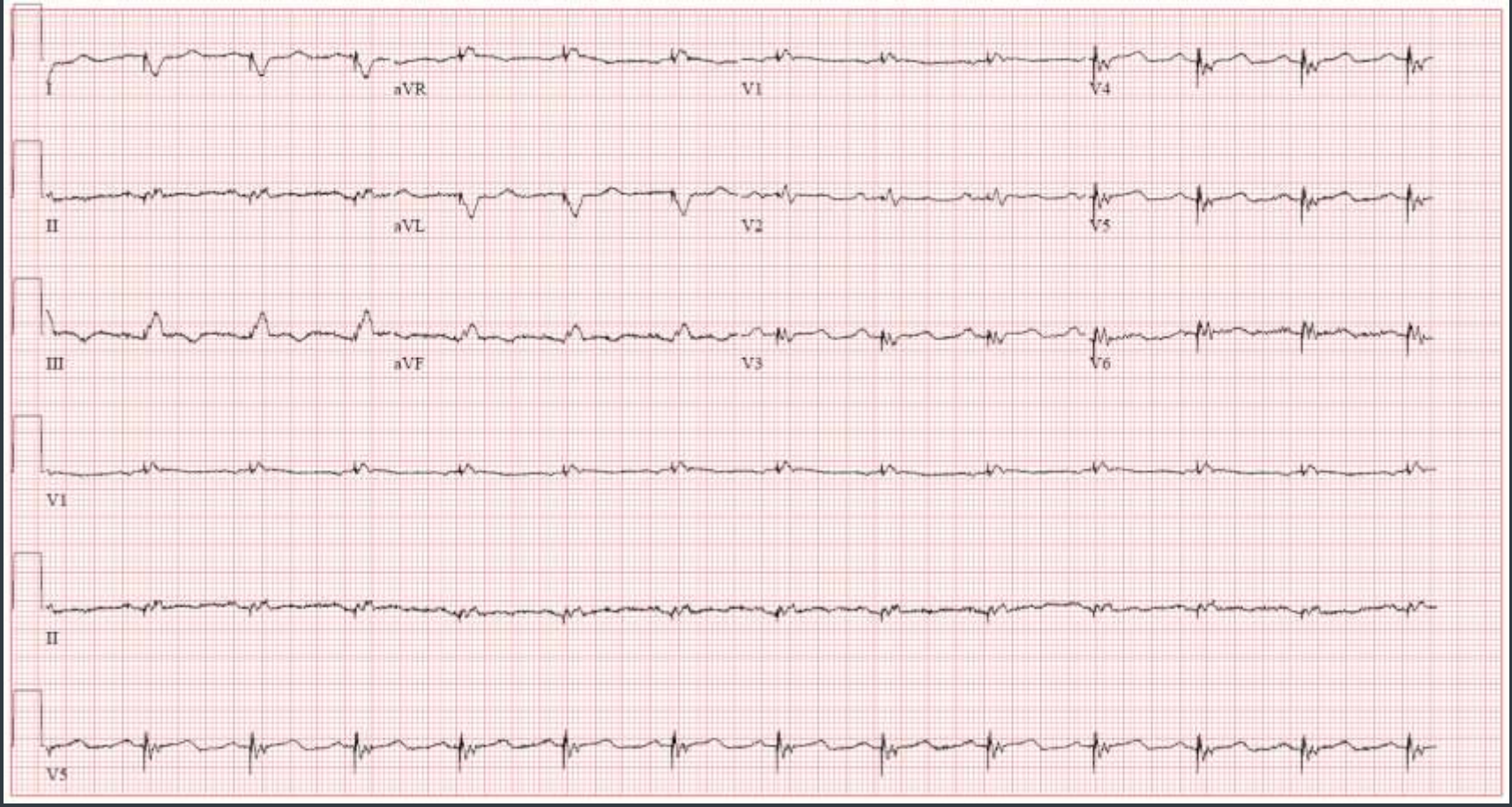
- 75 M with ischemic Cardiomyopathy, PAF, and a history of severe MR s/p MVR in 2015.

- Continues to have SOB at rest and DOE with minimal exertion and poor energy

- On GDMT including
  - **Beta-Blocker:** Bisoprolol 2.5mg daily
  - **ACEi/ARB/ARNI:** Entresto 12/13mg BID
  - **Aldosterone Antagonist:** Spironolactone 25mg
  - **SGLT2i:** dapagliflozin 10mg daily

- CRT-D

Adequate CRT



BiV Pacing 96%

Afib Burden 48%

Additional Testing

Echocardiogram
3/16/23

Left Ventricular ejection fraction = 30-35%; Severe hypokinesis of anteroseptal and inferior walls

The right ventricle is normal size with Mildly depressed right ventricular systolic function

The right atrium is moderately dilated.

Mild mitral regurgitation

Moderate tricuspid regurgitation:
Doppler-derived pulmonary artery systolic pressure = 30 mmHg +

CPET

Peak VO2 12.2 mL/kg per minute (50 % of predicted).
Peak RER was 1.21 suggesting a good effort.
Anaerobic threshold is 40 % of predicted (>40% normal).
The VE-VCO2 ratio at anaeorbic threshold was 35 (<34 normal).
Breathing reserve 66.3 % (>30% normal).

RHC

Arterial BP:	130/82 (98)		
RA:	6	RV:	44/3
PA:	44/15 (30)	PW:	15
TP Gradient:	15		
PA Sat:	61 %		
Aorta Sat:	97 %		

CO / CI (Fick): (4.21 L per min / 1.89 L per min per m^2)
CO / CI (Thermodiluaiton): (5.07 L per min / 2.27 L per min per m^2)
PVR: 285 Dynes.sec/cm^5 3.56Woods
SVR: 1748 Dynes.sec/$cm^5$21.85 Woods

Next Steps

Currently, he is a candidate for cardiac contractility modulation since he has not responded to cardiac resynchronization.

Indications for CCM:

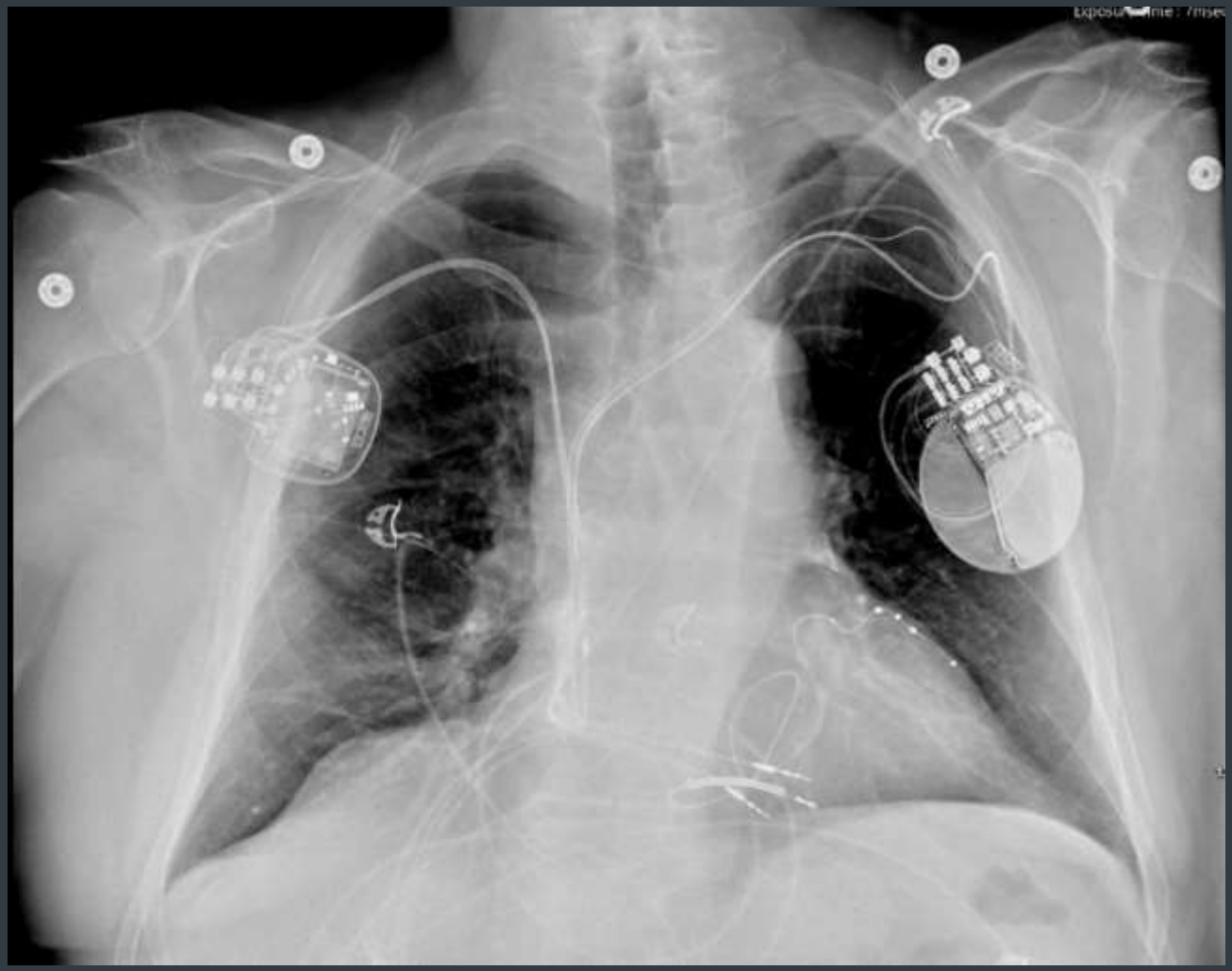
- LVEF 25–45%
- NYHA Class III
- Symptomatic despite guideline directed medical therapy
- In normal sinus rhythm
- Not responsive to Cardiac Resynchronization Therapy

Pre-Implant

The team of Dr. Jason Payne (far right): from left, Dr. Shane Tsai, Dr. John Schleifer, and Dr. Scott Lundgren were the first in Omaha to use cardiac contractility modulation or CCM therapy to help a patient, Steven Turner, with congestive heart failure. (Nebraska Medicine)

https://www.wowt.com/2024/01/02/new-device-changes-life-congestive-heart-failure-patient-nebraska-medicine/

Post Implant



Dr. Scott Lundgren and CCM therapy patient Steve Turner at Nebraska Medicine following Turner's procedure. (Erin Sullivan (WOWT))

Follow up

- Currently, Mr. Turner notes he is feeling great. He feels like he's a new person and can do so much more now than he could do a few months ago.

- This has been sustained for > 1 year

- No HF hospitalizations.

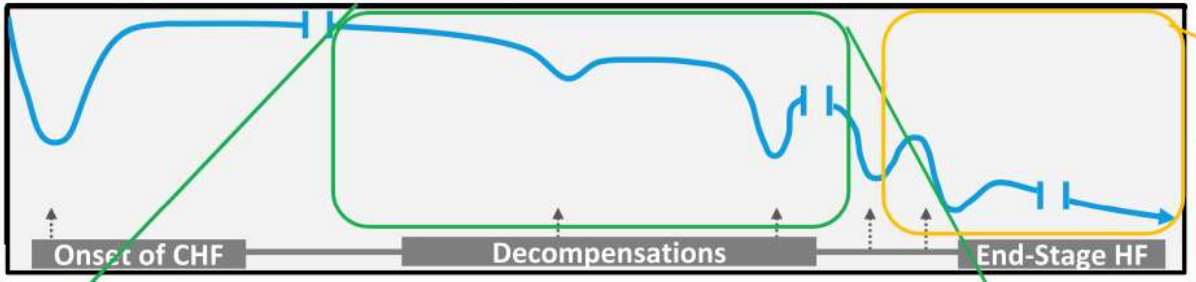
4 Pillars of GDMT

Four Pillars of Heart failure Therapy

Beyond Pharmacotherapy

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 patients)

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

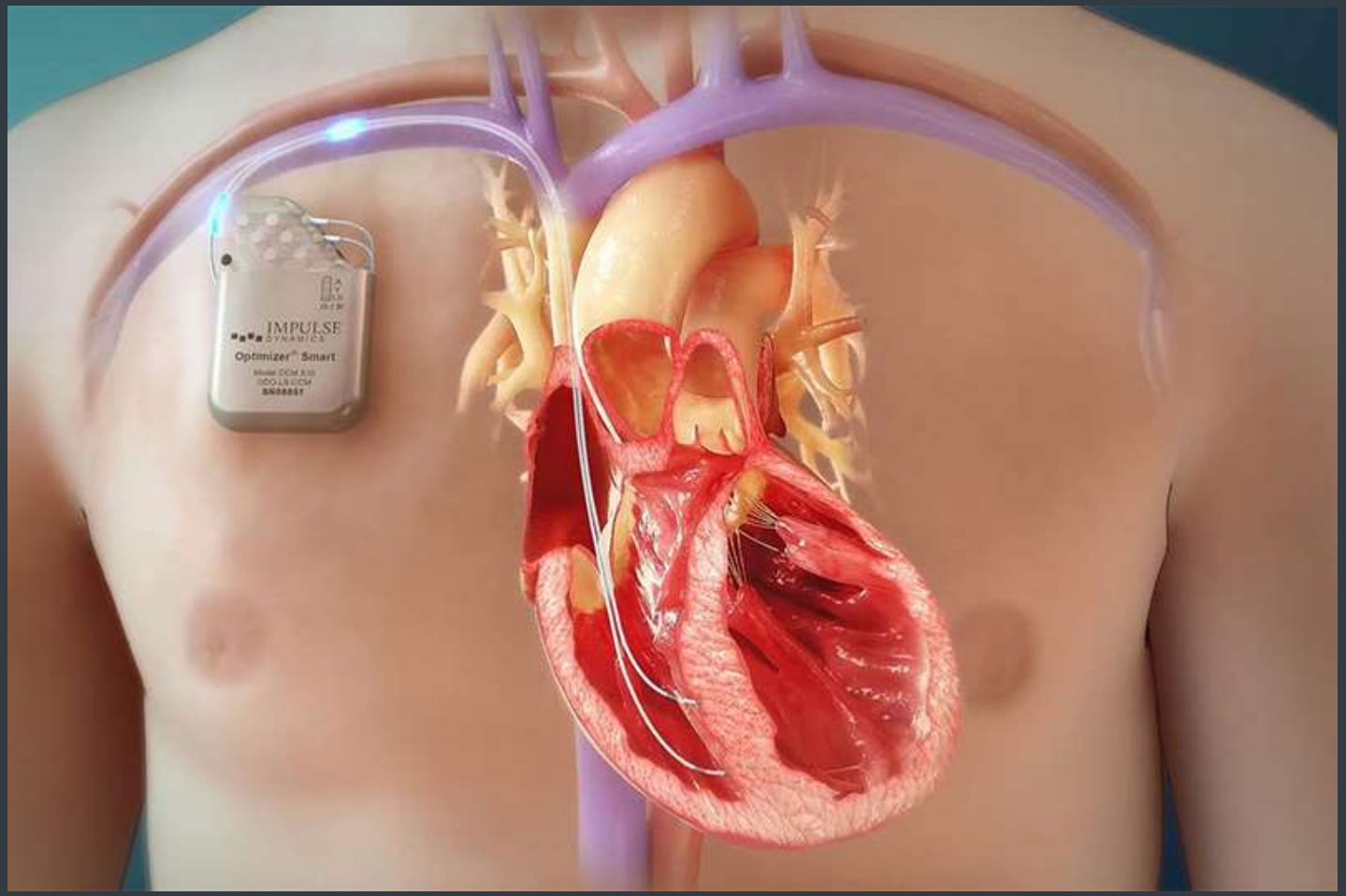
Baroreflex activation therapy (BAT)
-Persistent symptoms with NYHA III or II (with a recent history of Class III)
-LVEF ≤ 35%
- NT-proBNP <1600 pg/ml
-Excludes patients with a guideline indication for CRT

COR*: Not Provided

Cardiac Contractility Modulation (CCM)
-NYHA III
-LVEF 25-45%
-Excludes patients with a guideline indication for CRT

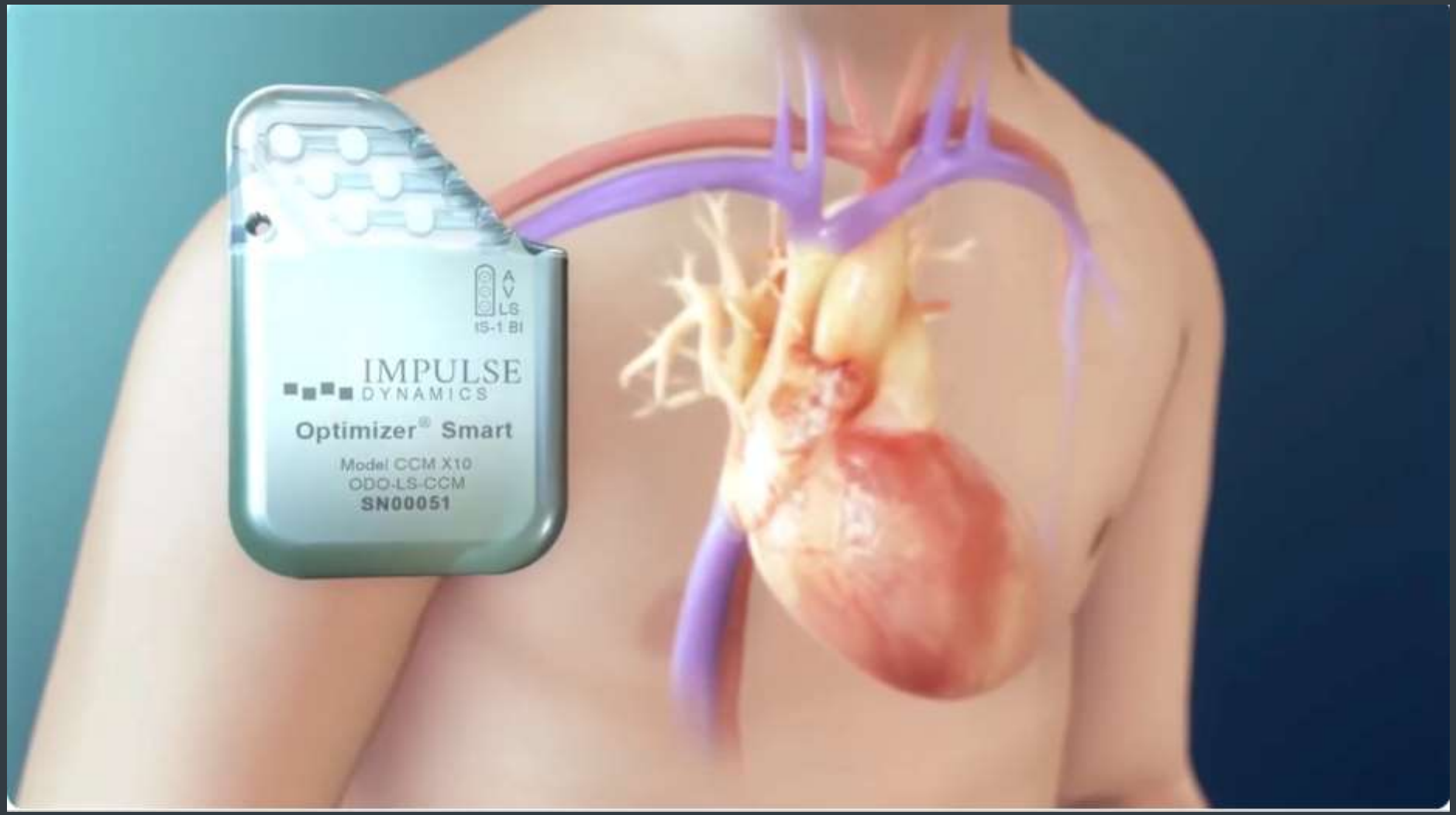
COR*: Not Provided

Novel Device based Therapy for Heart failure who are not candidates for or Non-responders to CRT

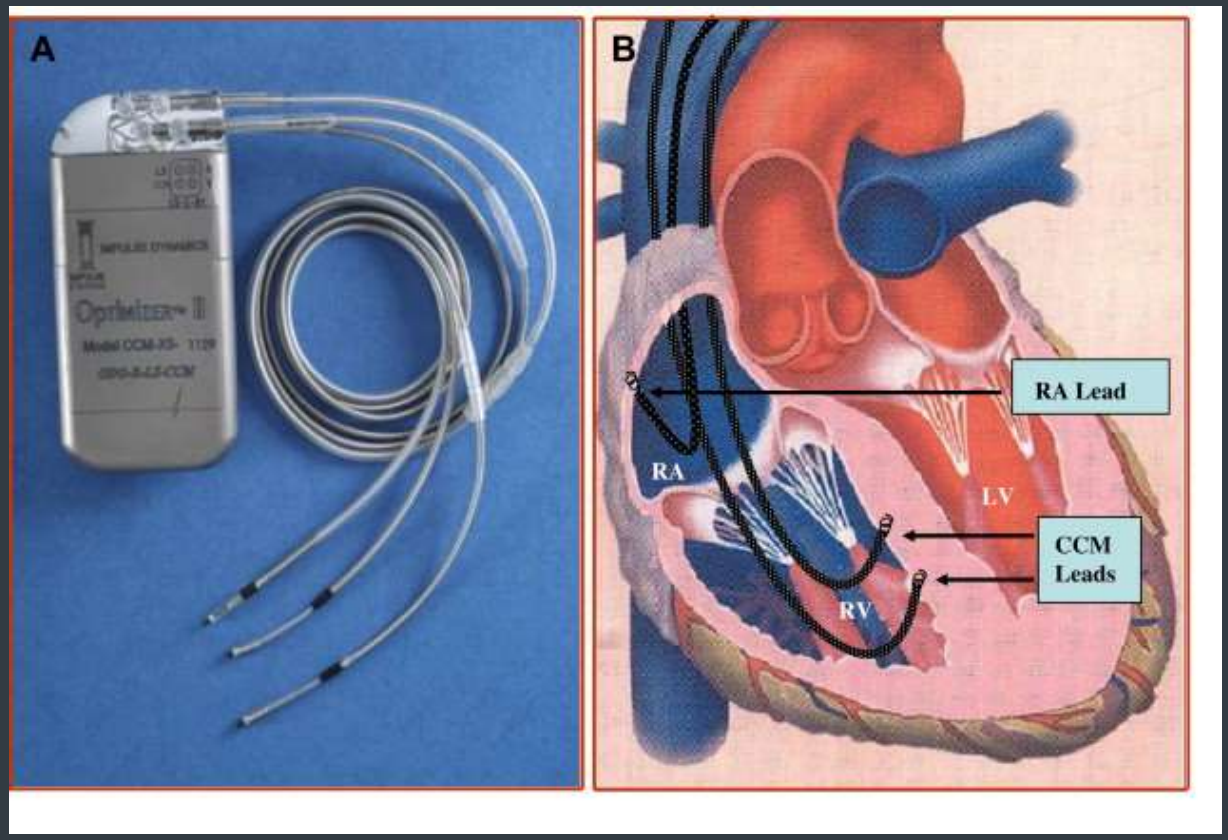


CRT remains the primary device-based therapy for HF

FDA approval 2019

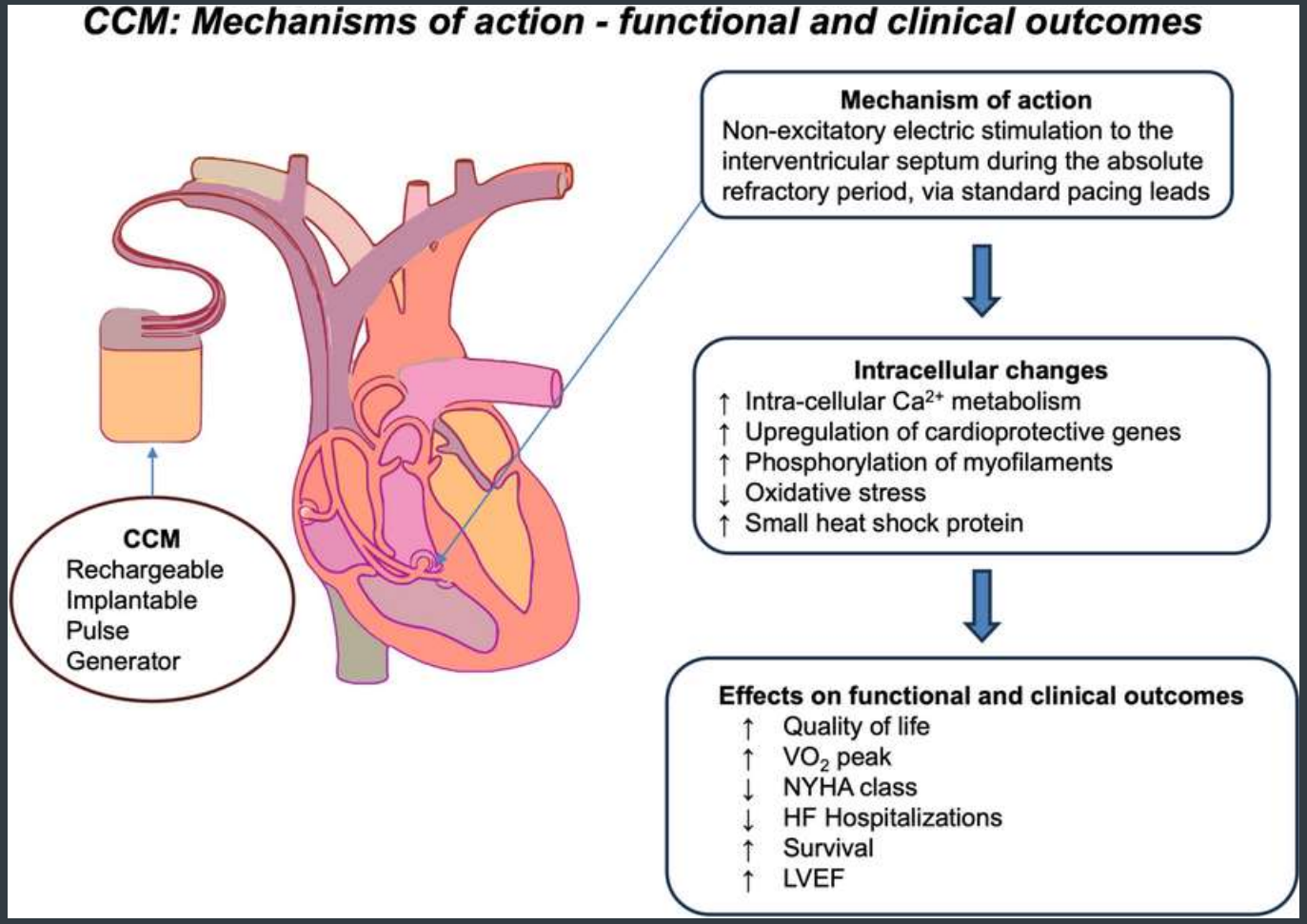

A
V
LS
IS-1 BI
IMPULSE
DYNAMICS
Optimizer® Smart
Model CCM X10
ODO-LS-CCM
SN00051

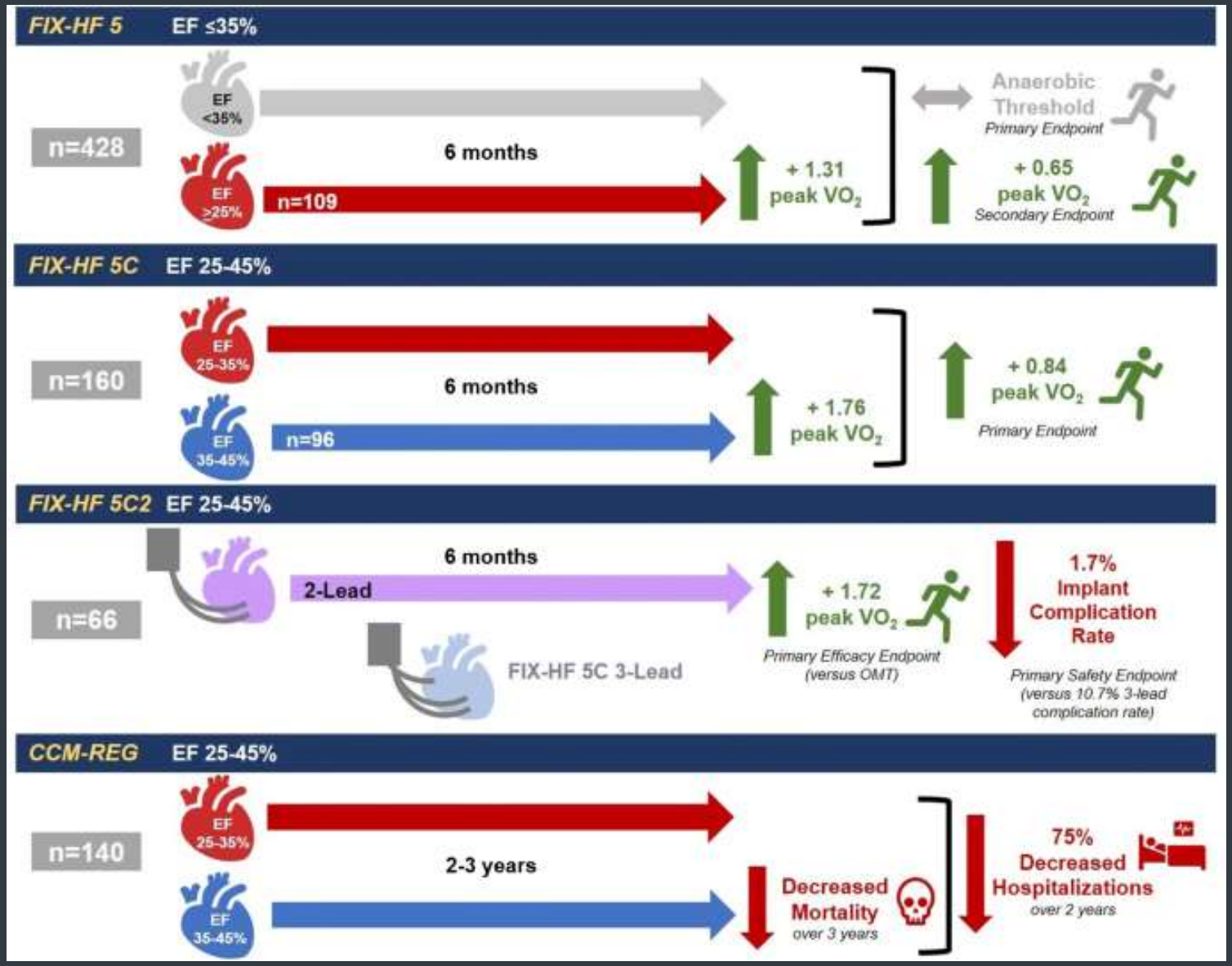
- Deviceimplantation resembles a traditional transvenous pace-maker system but uses 2 RV lead
- Delivers electrical impulse during the Absolute refractory period of the ventricle
- 4-7.5V in 4 biphasic pulses (20ms)



CCM therapy does not excite tissue but rather increases inotropy by prolonging the action potential

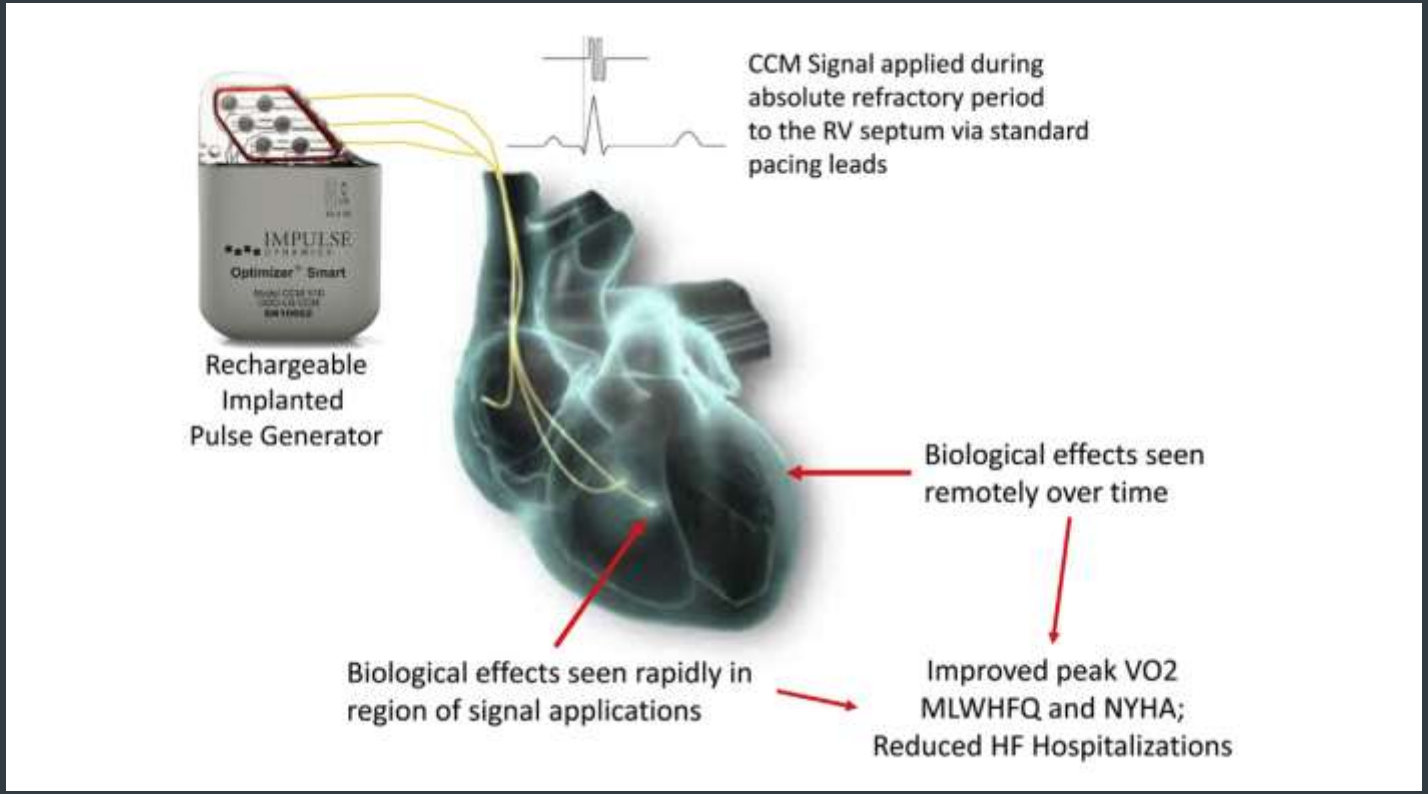
Mechanism of Action



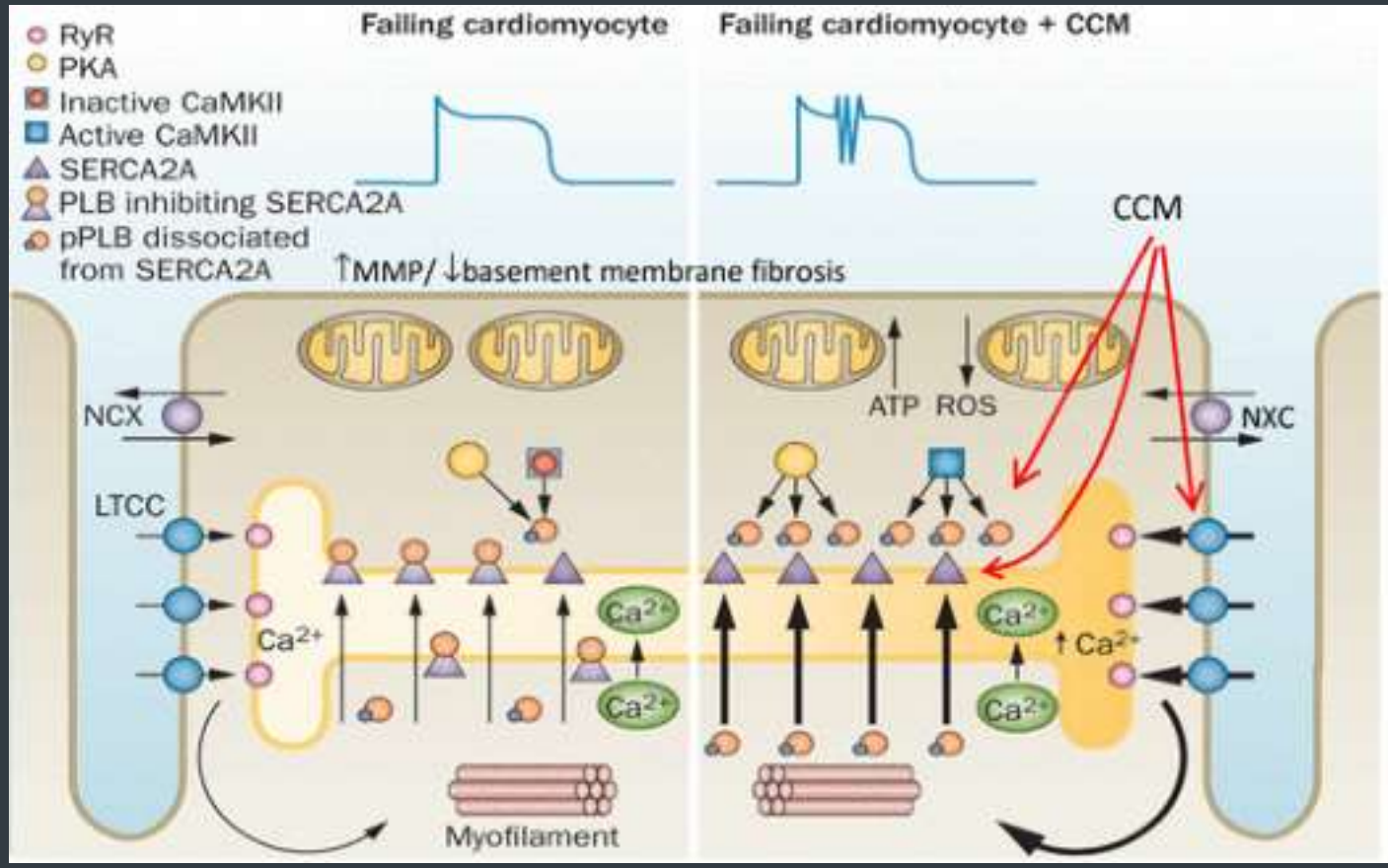

FIX-HF 5
EF ≤35%
n=428
EF <35%
EF >25%
6 months
n=109
+ 1.31 peak VO2
Anaerobic Threshold
Primary Endpoint
+ 0.65 peak VO2
Secondary Endpoint
FIX-HF 5C
EF 25-45%
n=160
EF 25-35%
EF 35-45%
6 months
n=96
+ 1.76 peak VO2
+ 0.84 peak VO2
Primary Endpoint
FIX-HF 5C2
EF 25-45%
n=66
6 months
2-Lead
FIX-HF 5C 3-Lead
+ 1.72 peak VO2
Primary Efficacy Endpoint (versus OMT)
1.7% Implant Complication Rate
Primary Safety Endpoint (versus 10.7% 3-lead complication rate)
CCM-REG
EF 25-45%
n=140
EF 25-35%
EF 35-45%
2-3 years
Decreased Mortality
over 3 years
75% Decreased Hospitalizations
over 2 years

	Study name/type	Study cohort	Study design	Clinical endpoints	Results	Adverse events
1.	FIX-HF-3 [17]Multicenter observational study (2004)Sample size = 25	Inclusion criteria:-Ischemic and nonischemic cardiomyopathy-HFrEF ≤ 35% on OMT ≥ 4 weeks-Sinus rhythm with QRS < 140 ms-NYHA class IIIExclusion criteria:-Sustained ventricular tachycardia-Coronary revascularization within 3 months-Patients eligible for CRT	Delivery of two biphasic, square-wave signals of up to 7.73 V during the absolute refractory period, 3 h/day between 7 p.m. and 10 p.m.CCM signal generator (optimizer II device)8-week follow-up	1. LVEF2. NYHA classification3. MLWHFQ4. 6MWT5. CCM-associated symptoms6. Ventricular ectopy	LVEF improved from 22 ± 7 to 28 ± 8% (P = 0.0002)Quality of life improved from 43 ± 22 to 25 ± 18% (P = 0.001)6MWT increased from 411 ± 86 to 465 ± 81 m (P = 0.02)	Two sudden deaths: Ventricular Fibrillation and Asystole. Neither during CCM therapyMild sensations in 35% of cohort. Lead repositioning required in 1 patient
2.	FIX-HF-4 [19]Multicenter, randomized, double blind, crossover study (2008)Sample size = 164	Inclusion criteria:-Ischemic and nonischemic cardiomyopathy-HFrEF ≤ 35% on OMT-NYHA class ≥ II-VO_2 peak: 10–20 ml O_2/kg/minExclusion criteria:-AFib-Frequent ectopy-MI (<3 months)-Clinically significant angina-HF requiring IV medication (<1 month)-Eligible for CRT	Randomized to 2 groups, 2–4 weeks after optimizer system implantGroup 1: CCM signals delivered for seven 1 h periods spaced equally over the dayGroup 2: device programmed to 'OFF'Phase 1: 12 weeksPhase 2: 12 weeks (participants crossed over to opposite treatment group)Data assessed with t-test	1. VO_2 peak2. MLWHFQ3. NYHA class4. 6MWT5. Safety	VO_2 peak increased significantly in the therapy group compared with the sham group; 0.52 ± 1.39 O_2/kg/min (t = 2.16, P = 0.032, 95% CI 0.04–0.99)MLWHFQ-score also improved significantly compared with sham; 2.93 ± 8.01 m (t = 2.20, P = 0.03, 95%CI 0.29–5.56)No change in LVEF in either groupSimilar improvement in NYHA class in both groups	No significant differences between the cohorts in the number or types of adverse events.No significant difference between the cohorts in arrhythmias or other Holter parameters
3.	FIX-HF-5 [20]Prospective randomized controlled trial (2011)Sample size = 428	Inclusion criteria:-Ischemic and nonischemic cardiomyopathy-Age ≥ 18 years-HFrEF ≤ 35% on OMT + ICD, if indicated-Sinus rhythm, QRS <130 ms-NYHA class III, IV-Baseline peak VO_2 ≥ 9 ml O_2/kg/minExclusion criteria:-Hospitalized within 30 days of enrollment-Inotrope dependence->8900 PVCs/day on Holter-Permanent AFib-MI or CABG within 90 days-PCI within 30 days	Randomized to OMT vs. OMT and CCMOptimizer system delivered CCM signals for five 1 h periodsspaced equally throughout the day12-month follow-up	Efficacy:1. Ventilatory anaerobic threshold (primary)2. VO_2 peak3. MLWHFQ (6 months)Safety:1. All-cause mortality and hospitalizations (12 months)2. Adverse events	No significant difference in ventilatory anaerobic threshold between the two groupsCCM significantly improved pVO_2 by 0.65 ml/kg/min (P = 0.024)CCM improved MLWHFQ by −9.7 points (P = 0.0001) compared with OMT	CCM was non inferior to OMT for safety endpoints
4.	FIX-HF-5C [22]Prospective randomized controlled trial (2018)Sample size = 160	Inclusion criteria:-Ischemic and nonischemic cardiomyopathy-Age ≥ 18 years-HFrEF ≥ 25% and ≤45% on OMT + ICD, if indicated-Sinus rhythm, QRS < 130 ms-NYHA class III, IV	Randomized to OMT vs. OMT and CCMOptimizer system delivered CCM signals for five 1-h periods spaced equally throughout the day2 Cardiopulmonary stress tests (averaged) were performed for each patient at baseline and at the 12- and 24-week follow-up visitsData assessed with Bayesian repeated measures linear modeling	Efficacy:1. VO_2 peak (primary)2. MLWHFQ3. NYHA class4. 6MWTSafety:1. All-cause mortality2. Cardiac mortality3. All-cause hospitalization4. Cardiac hospitalization5. HF hospitalization6. Adverse events	CCM significantlyimproved:1. VO_2 peak by 0.084 ml/kg/min (95% Bayesian credible interval: 0.123–1.552)2. MLWHFQ3. NYHA class	Composite of cardiovascular death and HF hospitalizations was reduced from 10.8 to 2.9% by CCM

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation (FIX-HF-5)



Abraham, W. T. *et al.* A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. *JACC: Hear. Fail.* **6**, 874–883 (2018).



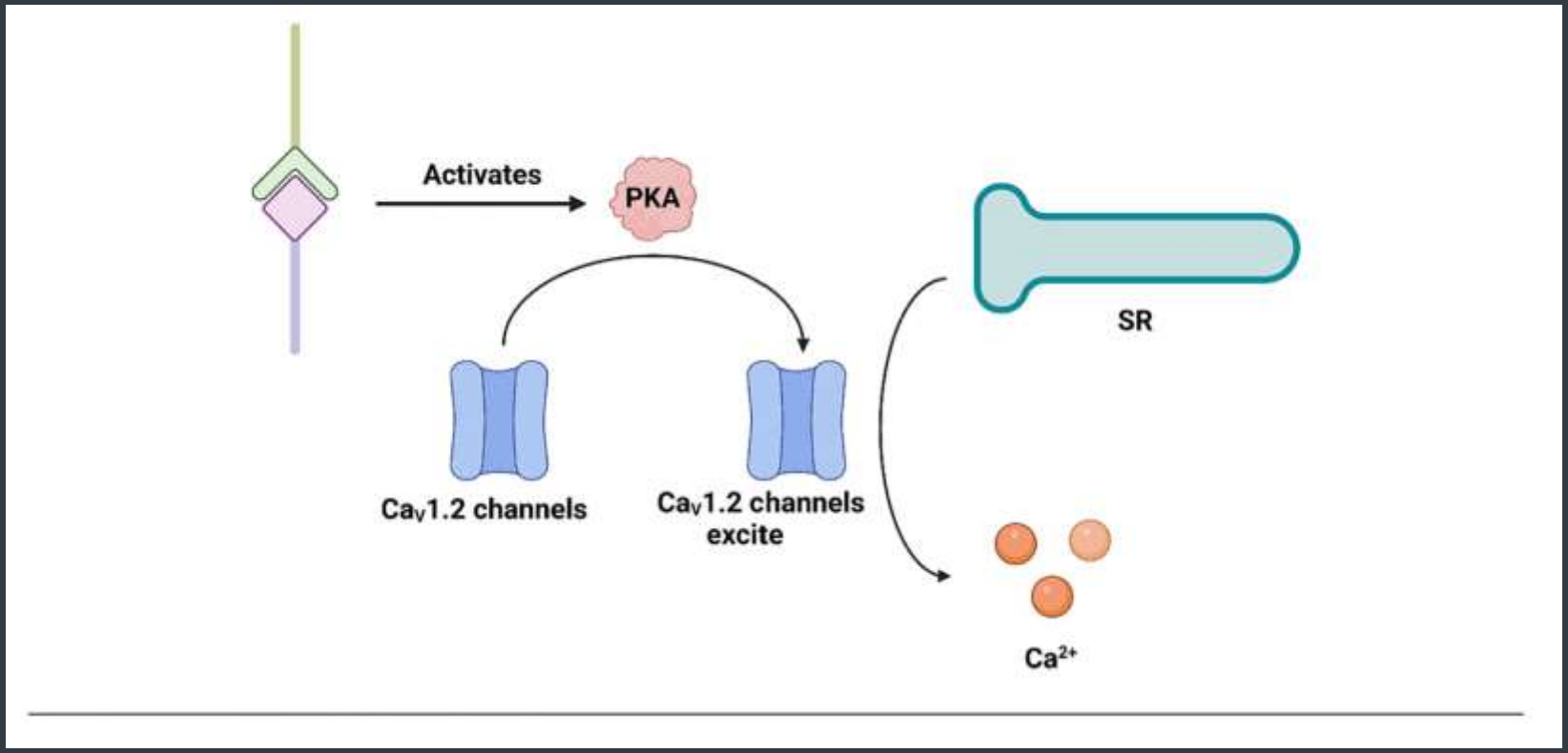
Upregulate SERCA Activity

Phosphorylate phospholamban, thereby detaching it from SERCA

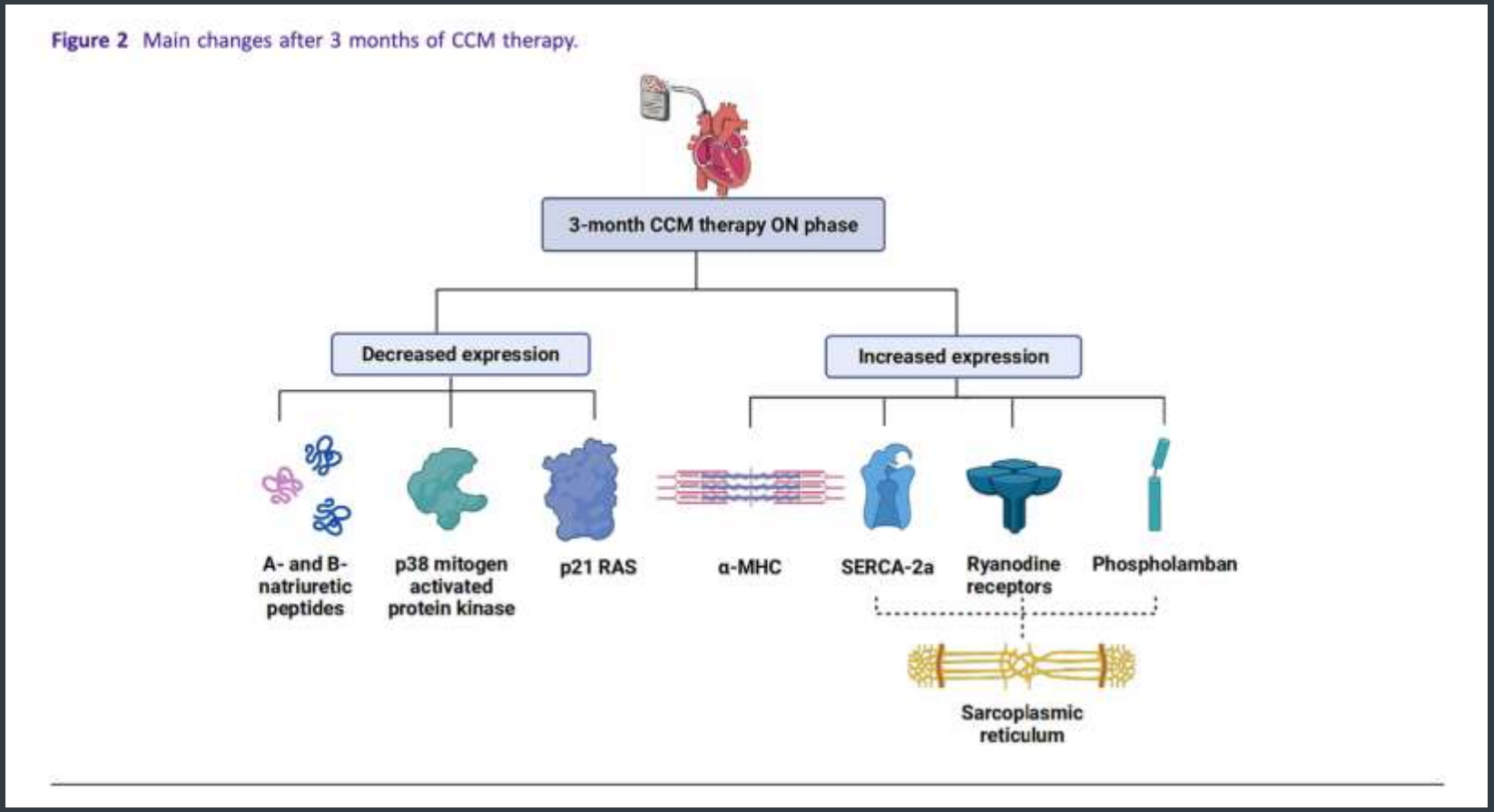
Activate LTCC currents

Normalize Na/Ca exchanger

Increase MMP; reverse pathological remodeling


Activates
PKA
SR
$Ca_V1.2$ channels
$Ca_V1.2$ channels excite
Ca^{2+}

Changes with CCM therapy



Indications

Impulse Dynamics received FDA approval in 2019

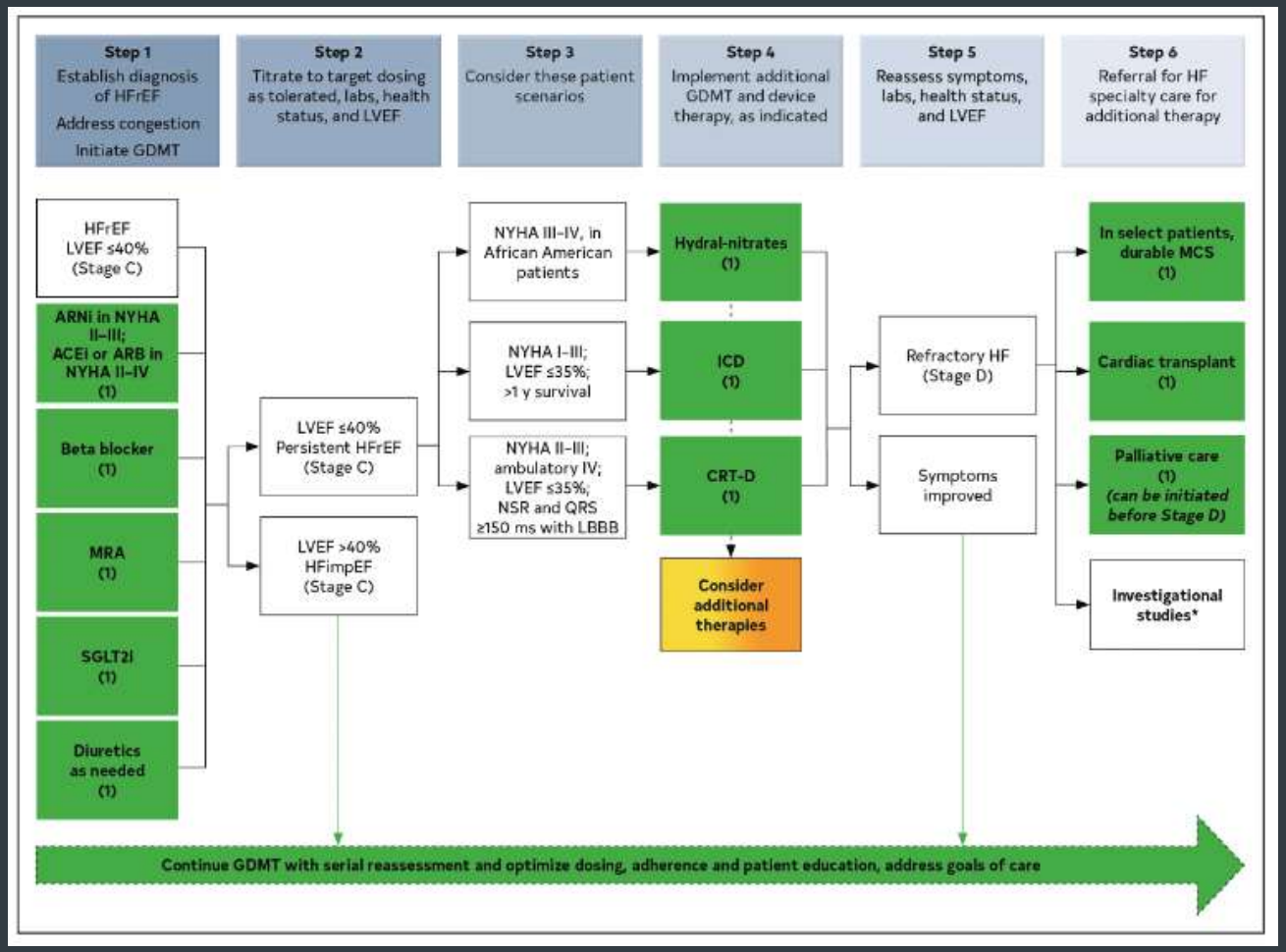
- NYHA class III symptoms, despite GDMT
- who do not have indications for CRT, including a narrow underlying QRS
- LVEF between 25% and 45%

The potential roles of CCM in the settings of HFmrEF and HFpEF populations (NCT05064709) and in combination with ICD therapy (NCT05855135) are currently under investigation.

Guidelines

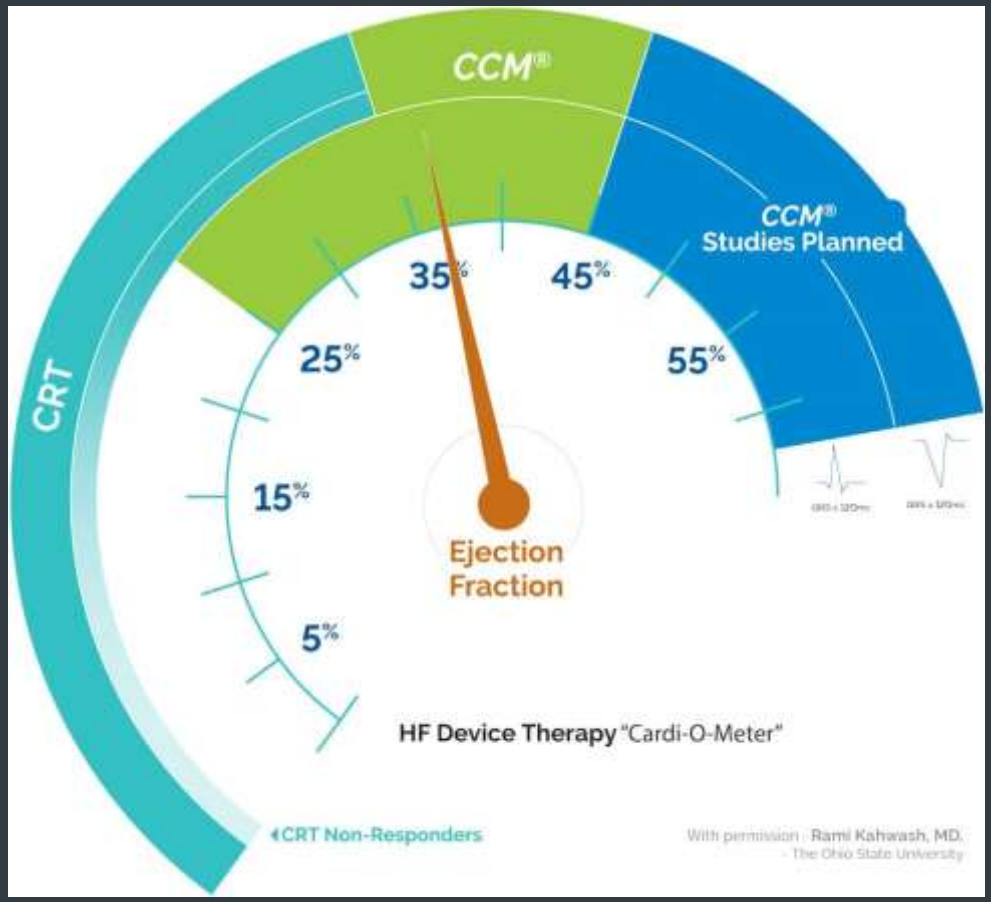
In the 2022 AHA/ACC/HFSA guidelines, it is stated, "Four RCTs have shown benefits in exercise capacity and quality of life (QOL) but, as of yet, no benefits in death or hospitalizations."

The 2021 ESC HF guideline states CCM use "was associated with a small improvement in exercise tolerance and QOL"; however, like the 2022 AHA/ACC/HFSA guideline document, a specific guideline recommendation was not provided.



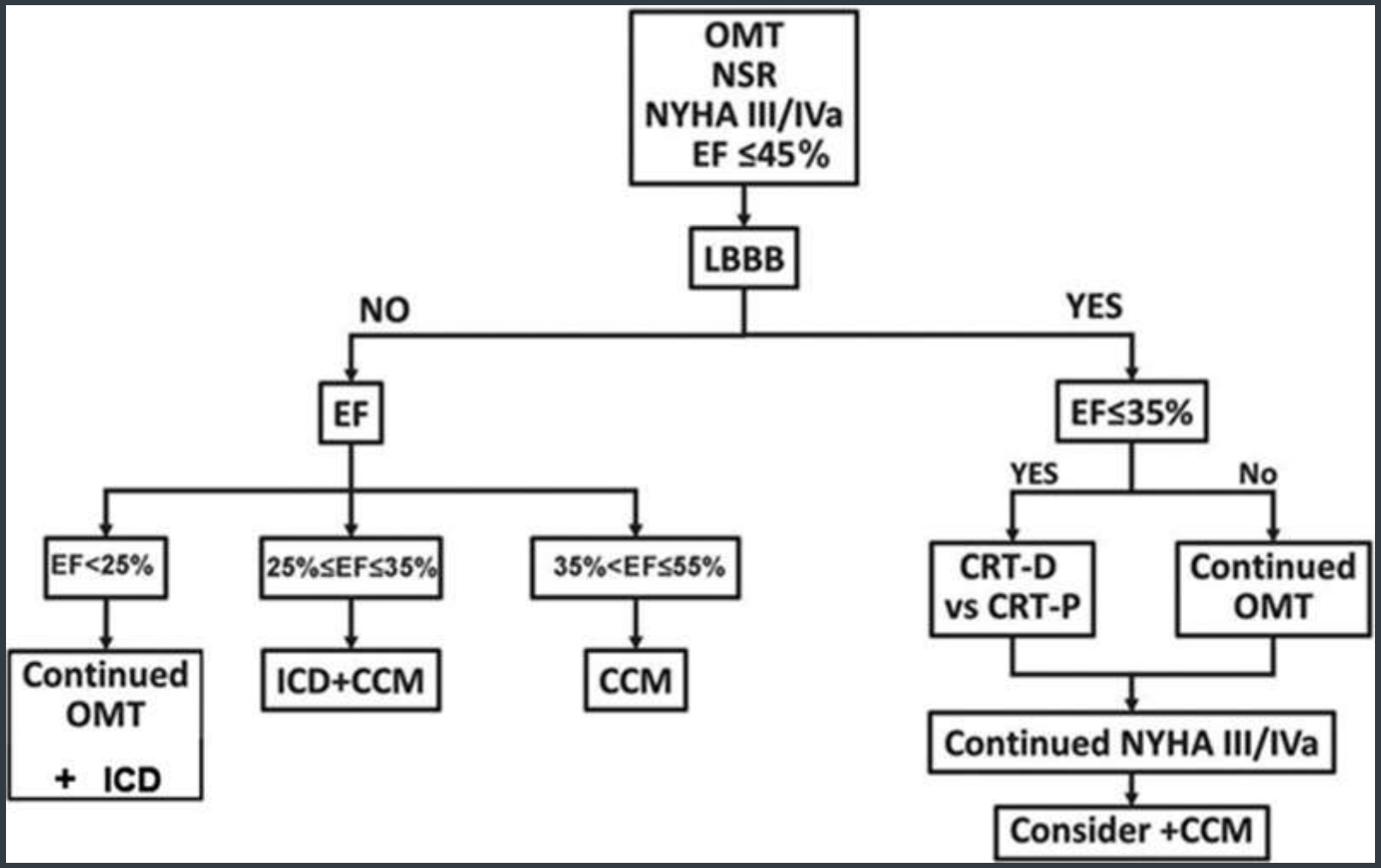
Heidenreich et al. 2022 AHA/ACC/HFSA HF Guidelines

Who is CCM for?



- CRT is only beneficial in 10-15% of the HF population
- CCM will potentially apply to another significant portion

Suggested pathway for how cardiac contractility modulation(CCM) fits, compared with cardiac resynchronization therapy (CRT), in the treatment of patients with heart failure



Borggrefe, M. & Mann, D. L. Cardiac Contractility Modulation in 2018. *Circulation* **138**, 2738–2740 (2018).

Relationship with other implantable Equipment

- CRT: 20-30% non-responders, and CCM can be used as an adjunct.
- 17 patients with significant HF despite CRT

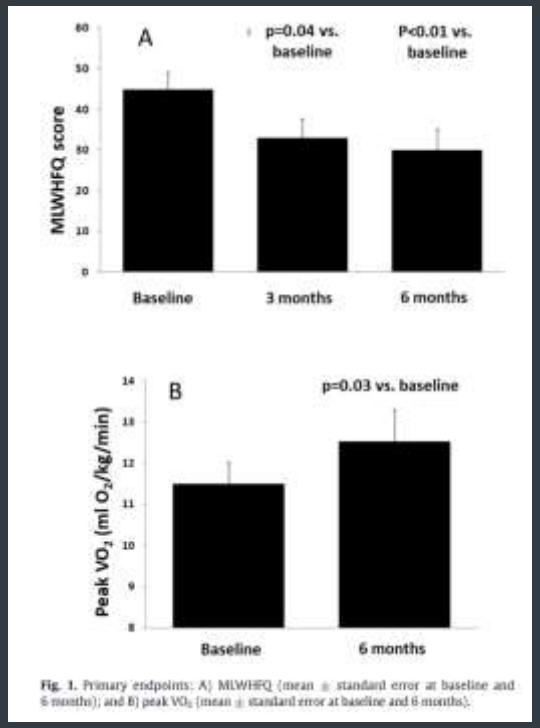


Fig. 1. Primary endpoints: A) MLWHFQ (mean ± standard error at baseline and 6 months); and B) peak VO_2 (mean ± standard error at baseline and 6 months).

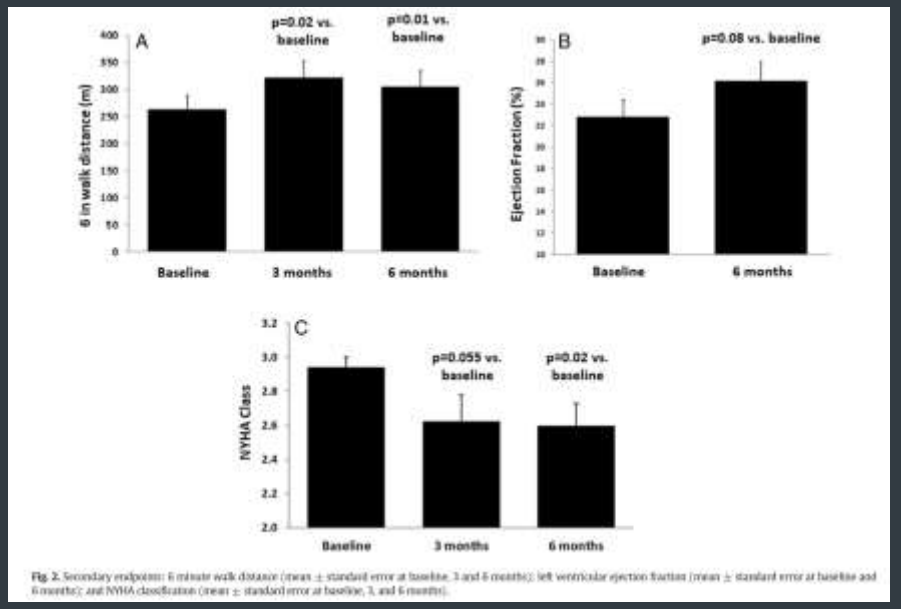
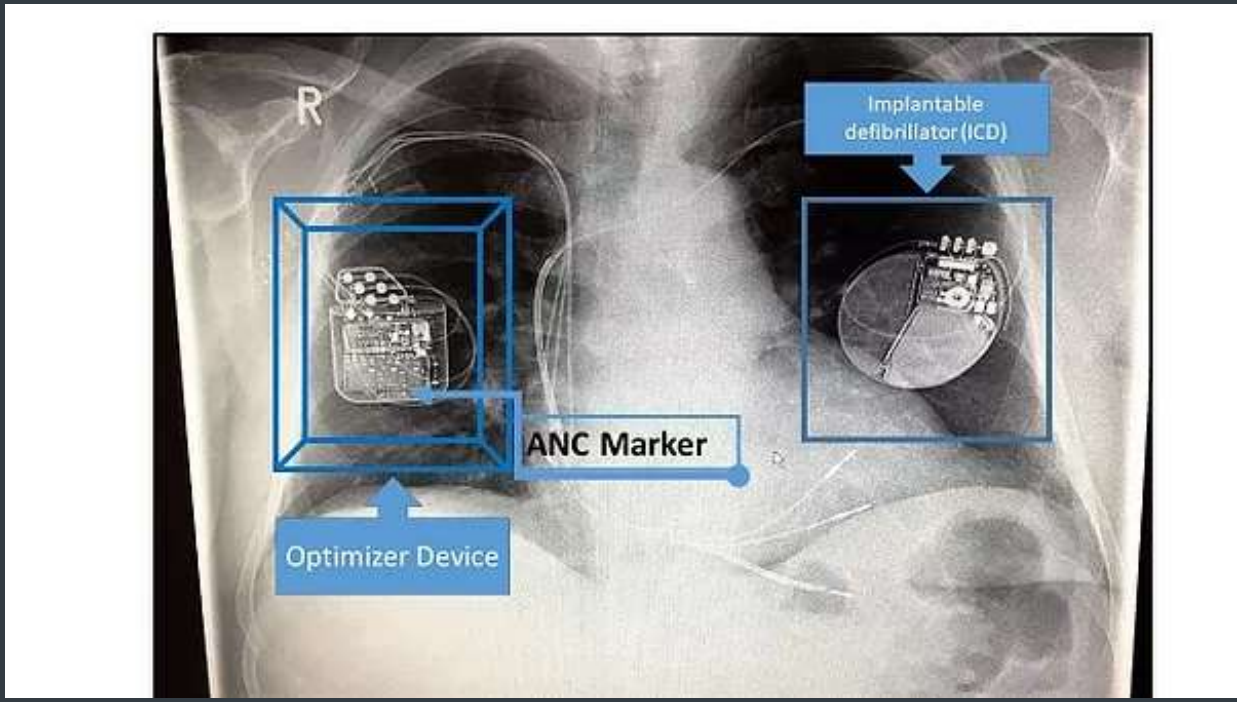


Fig. 2. Secondary endpoints: 6 minute walk distance (mean ± standard error at baseline, 3 and 6 months); left ventricular ejection fraction (mean ± standard error at baseline and 6 months); and NYHA classification (mean ± standard error at baseline, 3, and 6 months).

Kuschyk, J. *et al.* Cardiac contractility modulation treatment in patients with symptomatic heart failure despite optimal medical therapy and cardiac resynchronization therapy (CRT). *Int. J. Cardiol.* **277**, 173–177 (2019).

Relationship with other implantable Equipment

- CCM systems have not shown interactions with TV-ICD or S-ICD systems
- Many patients will have LVEF < 35%
- 20 patients
  - One inappropriate shock unrelated to CCM
  - 6 VT episodes all successfully treated
  - Improvement in HF class, EF, and MLWHFQ
- Integra-D



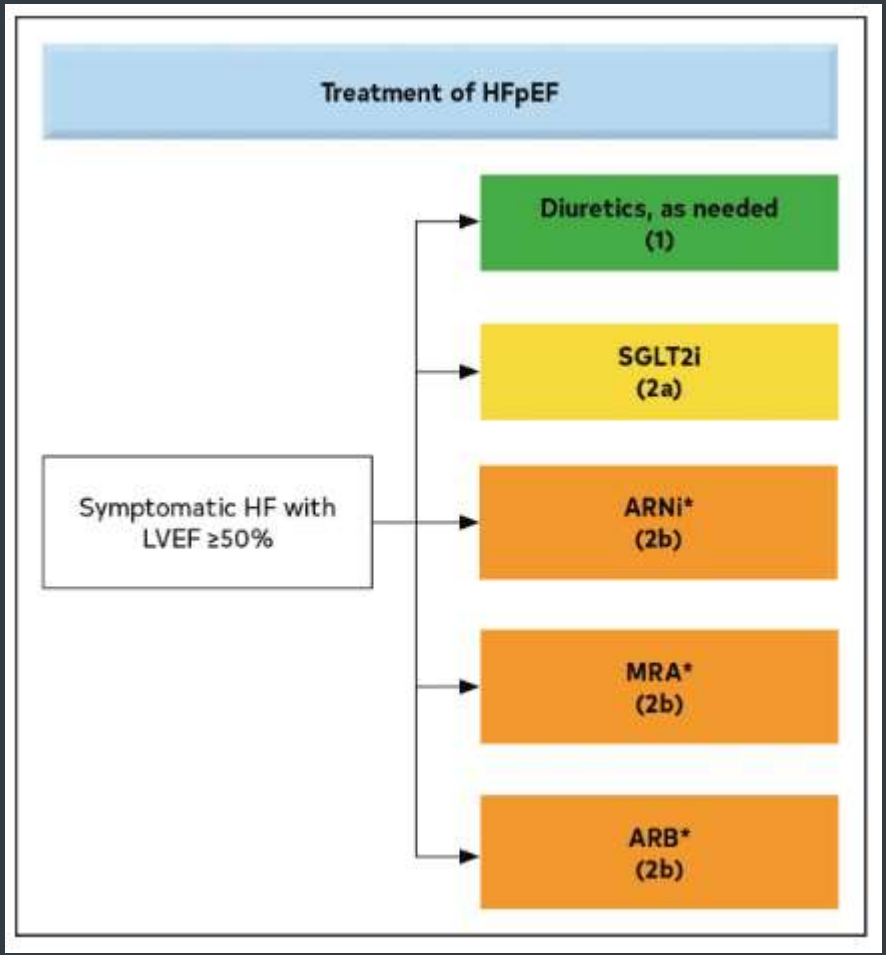
Röger, S. *et al.* Long-term results of combined cardiac contractility modulation and subcutaneous defibrillator therapy in patients with heart failure and reduced ejection fraction. *Clin. Cardiol.* **41**, 518–524 (2018)

Limitations

- Multiple Leads
    - Infection
    - Tricuspid Regurgitation
- CCM Non-response
- Device Interaction
- Category III CPT code
    - Paperwork Medicare

Integra-D

- Prospective Single Arm Trial to investigate safety and effectiveness of the CCM-D system
- Focus on the defibrillator function
- Includes DFT test
- If it functions as expected, it will be approved as an ICD



- HFpEF now affects as much as 50% of the population with heart failure (HF)
- There are limited therapeutic options
- **FIX-HF-5C2**, the upper range of EF was extended to 45%, suggesting the possibility of benefit for CCM in individuals with HFpEF

Aim Higher

The AIM HIGHer Clinical Trial is a prospective, multi-center, randomized, quadruple-blind, sham-controlled trial of the safety and efficacy of CCM therapy delivered via the OPTIMIZER Smart Mini System in subjects with heart failure and an LVEF =40% - 60%.

Subjects will be randomized in a 2:1 ratio to either CCM ON (CCM group) or to CCM OFF (Sham group).

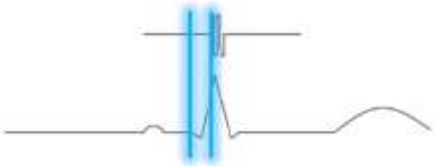
<u>Inclusion Criteria:</u>

- Diagnosed with symptomatic heart failure;
- LVEF =40 and =60%
- Heart failure hospitalization within 12 months AND elevated BNP

Cardiac Contractility Modulation

Optimizer Smart Mini

- Bipolar lead for pacing with active myocardial fixation
- Rechargeable battery, longevity 20+ years
- Size:
  - Height: 61.3mm
  - Width: 44 mm
  - Depth 11 mm



Clinical Benefits

- Improved six-minute walk test scores
- Improved NYHA Functional Class
- Increased peak VO2
- Fewer heart failure hospitalizations

Potential Mechanisms

- Increased intracellular Ca^{2+} metabolism
- More efficient Ca^{2+} induced Ca^{2+} release
- Reduction in fetal gene expression
- Decreased LV fibrosis and reverse remodeling

Indications

- LVEF 25-45% + NYHA III on GDMT + no indication for CRT

Future Applications

- CCM for HFpEF
- Combined CCM-ICD systems

Pipilas, D. C., Hanley, A., Singh, J. P. & Mela, T. Cardiac Contractility Modulation for Heart Failure: Current and Future Directions. *J. Soc.*

Nebraska Medicine