DEVICES IN HEART FAILURE

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Conflict of interest

- None

OUTLINE

- Introduction
- PA sensors
- Autonomic modulators: Barostim (BAT)
- Cardiac contractility modulators (CCM)
- Conclusion

INTRODUCTION

- Heart failure is a complex chronic illness.
- Variability of hemodynamics, frequent hospitalizations.
- High events rates.
- Monitoring strategies needed to improve outcomes.
- Variable trials results.

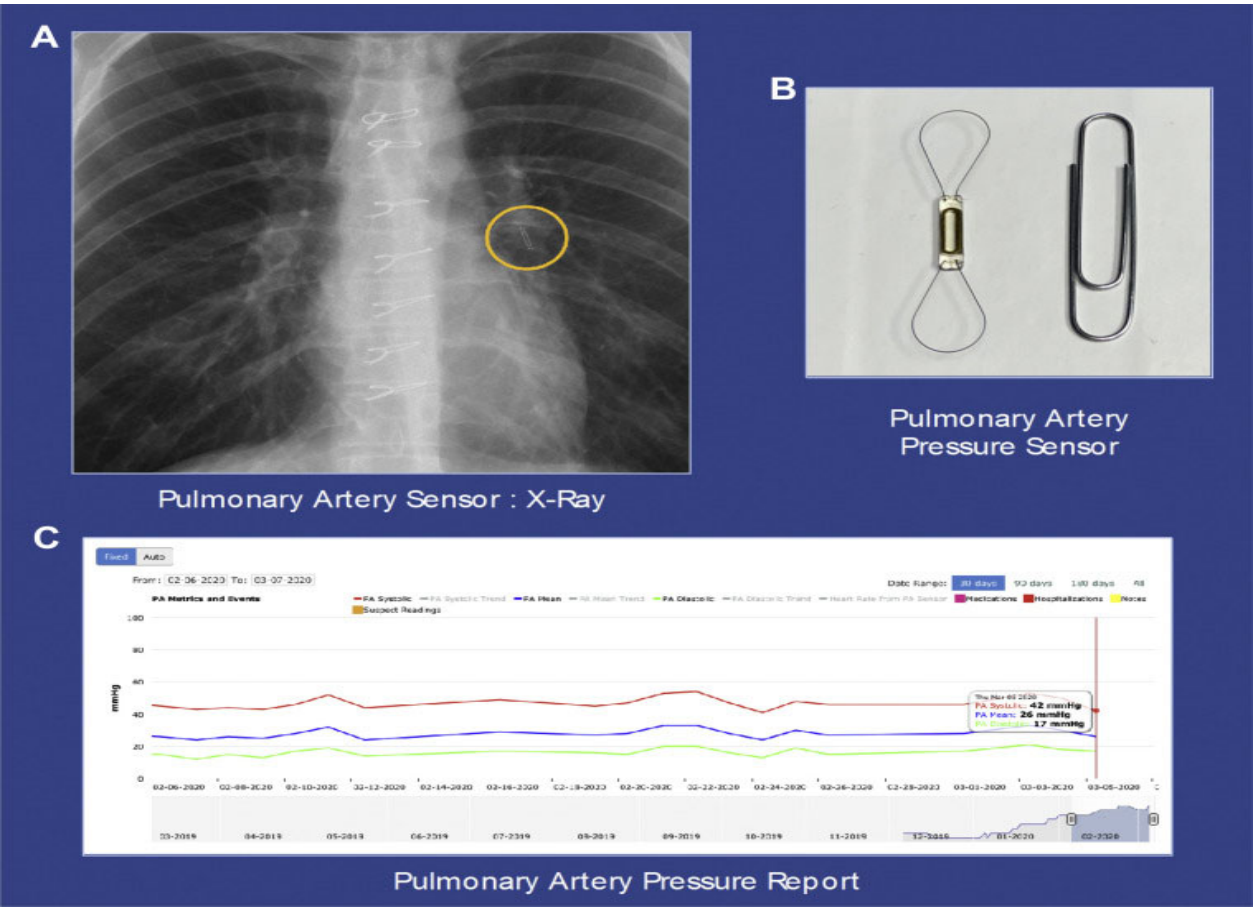
Types of heart failure devices

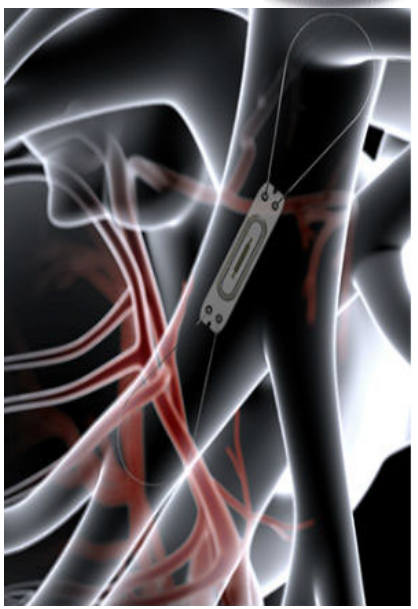
- Remote Patient Monitoring devices
  - implantable PA pressure sensor (CardioMEMS).

- Cardiac implantable electronic devices (CIEDs)
  - ICDs, CRTs
  - Baroreflex Activation Therapy (BAT)
  - Cardiac contractility modulators (CCM)
  - Chronicle

- Wearables and Telehealth interventions.

Implantable PA pressure sensor (CardioMEMS).





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The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure patients) trial

- Reported a **significant 28% reduction of HF-related hospitalizations after 6 months in patients randomized to an implanted PA pressure monitor** compared with a control group.

- Caveat: Patients had to have a **HF hospitalization in the previous year and be on stable doses of a beta blocker and angiotensin-converting enzyme inhibitor (ACEi) (or angiotensin (II) receptor blocker [ARB])** if tolerated.

- The clinical benefit persisted after longer term follow up and was seen in both subjects with **reduced and preserved LVEF**.

- Limitation:
  - Single blinded trial.
  - Clinicians contacted patients in the treatment arm, raising methodological concerns about the possibility of bias.

GUIDE-HF TRIAL

- **Description:**
  - The goal of the trial was to assess the **safety and efficacy of management** based on pulmonary artery (PA) pressures measured by the CardioMEMS heart failure (HF) system **compared with usual care across the spectrum of symptom severity (NYHA functional class II-IV), including those with elevated natriuretic peptides but without a recent heart failure hospitalization.**

- Study Design
  - **All patients had a CardioMEMS monitor** implanted. Patients were then **randomized in a single-blind 1:1** fashion to either hemodynamic monitoring and titration based on PA pressures (n = 497) or standard of care HF management (n = 503).
  - Total screened: 1,484
  - Total number of **enrollees: 1,000**
  - Duration of follow-up: 12 months
  - Mean patient age: 71 years
  - Percentage female: 38%

- Inclusion criteria:
  - New York Heart Association (NYHA) class II-IV HF patients
  - Elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) or BNP, and/or prior HF hospitalization

- Exclusion criteria:
  - Patients likely to receive a heart transplant or left ventricular assist device in the next 12 months
  - Patients with stage D HF
  - Those who required inotropes within the past 6 months

GUIDE-HF

- Other salient features/characteristics:
  - NYHA class III: 65%
  - Atrial fibrillation/flutter: 59%
  - Baseline PA pressures: 45/22 mm Hg
  - Left ventricular ejection fraction (LVEF): 39%
  - Baseline cardiac index: 2.1 L/min/m^2

- Principal Findings:
  - The primary endpoint of all-cause mortality, HF hospitalization, or urgent HF visits, for hemodynamic monitoring vs. usual care, was: 0.56 events/person-year (PY) vs. 0.64/PY (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.74-1.05, p = 0.16).

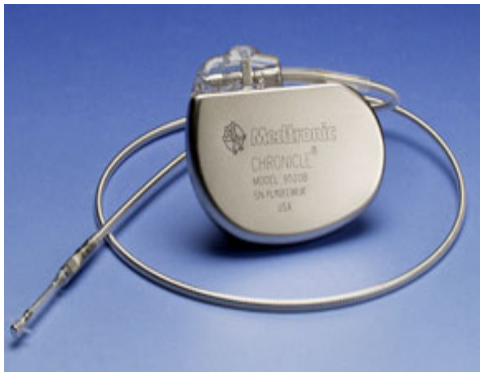
GUIDE-HF trial

- Hemodynamic-guided management of patients with NYHA class II to IV heart failure did not significantly reduce the composite endpoint rate of mortality and total HF events.
- There was no difference in cardiovascular outcomes among stable outpatients with chronic HF when comparing hemodynamic-guided management (monitored by CardioMEMS HF system) to optimal GDMT.
- Analysis of patients enrolled pre-COVID 19 pandemic showed possible benefit.
- PA parameters were lower in the CardioMEMS group.
- Results were similar in HFrEF and HFpEF patients.

Chronicle

- An implantable hemodynamic monitoring device that is like a single lead pacemaker that is placed in **the right ventricular outflow tract** that helps to transmit data to a subcutaneously placed device and can transmit a real-time report on cardiac hemodynamics.

- The COMPASS (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) trial did not show any benefit over optimal medical management.



https://www.medgadget.com/img/chronicle.jpg

Optivol

- Implantable hemodynamic **monitoring system** that detects **increased left ventricular filling pressures via a reduction in impedance within a right ventricular defibrillator coil of an ICD device,** which **occurs due to increases in the intrathoracic fluid.**

- FAST (Fluid Accumulation Status Trial): limited study.
  - Goal: To assess the sensitivity and unexplained detection rate of Optivol, associated with changes in intrathoracic impedance and with changes in daily weight. To compare the intrathoracic impedance and the weight.

- DOT-HF (Diagnostic Outcome Trial in Heart Failure):
  Terminated early due to increased ambulatory visits and hospitalizations without clinical benefit.

HF Guideline statement

- “The usefulness of noninvasive telemonitoring or remote monitoring of physiological parameters (e.g., patient activity, thoracic impedance, heart rate) via implanted electrical devices (ICDs or CRT-Ds) to improve clinical outcomes **remains uncertain.** Further study of these approaches is needed before they can be recommended for routine clinical care.

- Results from previous clinical trials do not support the alternative remote monitoring strategies (e.g., noninvasive telemonitoring or remote monitoring of physiological parameters such as patient activity, thoracic impedance, heart rate) for this purpose”.

HEART FAILURE GUIDELINES

4.6. Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)

Recommendation for Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATION
2b	B-R	1. In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of GDMT with optimal device therapy, the usefulness of wireless monitoring of PA pressure by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain (1-4).
Value Statement: Uncertain Value (B-NR)		2. In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PA pressure by an implanted hemodynamic monitor provides uncertain value (4-7).

Economic impact of CardioMEMs

- CardioMEMS implantation and monitoring increased survival and quality-adjusted life year (QALY) while increasing costs.

- High vs intermediate value based on different models (the model duration, QOL data, cost estimates, and assumptions regarding mortality).

Autonomic Modulators: Barostim

- **Changes in heart failure results in increased sympathetic response and a decreased parasympathetic response.**
- Barostim applies Autonomic nervous system modulation.
- An implantable device that electrically **stimulates the baroreceptors of the carotid artery**.
- **FDA approved** symptom improvement in patients with **advanced HF who are unsuited for treatment with other HF devices including CRT.**
- There are no mortality or hospitalization rates results available with this device.
- Although early trials of vagus nerve stimulation were positive, the largest and latest trial did not show a reduction in mortality and HF hospitalization

Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction (BeAT-HF)

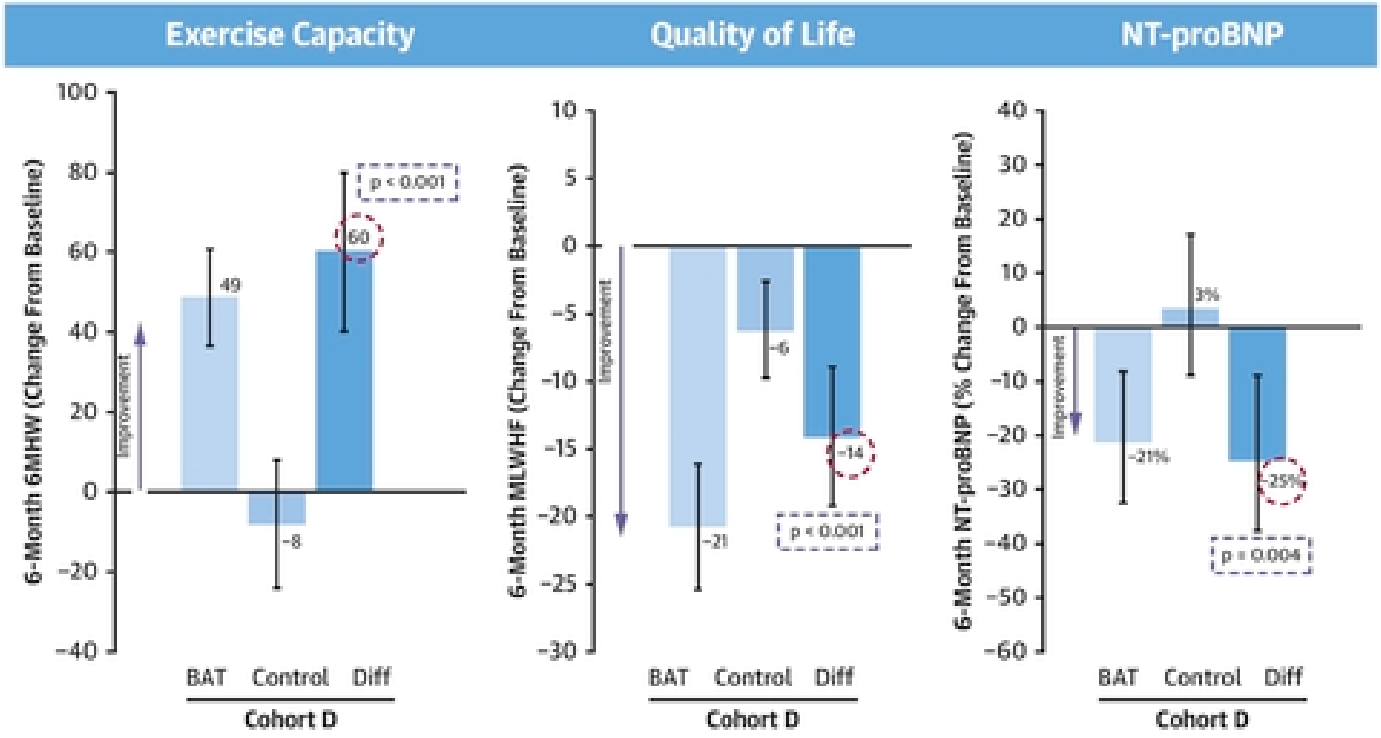
- **Background:**
  - This study demonstrated the safety and effectiveness of baroreflex activation therapy (BAT) in patients with heart failure with reduced ejection fraction (HFrEF).

- **Methods**
  - Four patient cohorts were created from **408 randomized** patients with HFrEF using the following enrollment criteria: current New York Heart Association (NYHA) functional **class III or functional class II (patients who had a recent history of NYHA functional class III); ejection fraction ≤35%; stable medical management for ≥4 weeks; and no Class I indication for cardiac resynchronization therapy**. **Effectiveness endpoints were the change from baseline to 6 months in 6-min hall walk distance (6MHW), Minnesota Living with HF Questionnaire quality-of-life (QOL) score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The safety endpoint included the major adverse neurological or cardiovascular system or procedure-related event rate (MANCE).**

- **Results**
  - Results from, timeline and rationale for, cohorts A, B, and C are presented in detail in the text. Cohort D, which represented the intended use population that reflected the U.S. Food and Drug Administration–approved instructions for use (enrollment criteria plus NT-proBNP <1,600 pg/ml), consisted of 245 patients followed-up for 6 months (120 in the BAT group and 125 in the control group). **BAT was safe and significantly improved QOL, 6MHW, and NT-proBNP.** In the BAT group versus the control group, QOL score decreased ($\Delta = -14.1$; 95% confidence interval [CI]: −19 to −9; $p < 0.001$), 6MHW distance increased ($\Delta = 60$ m; 95% CI: 40 to 80 m; $p < 0.001$), NT-proBNP decreased ($\Delta = -25\%$; 95% CI: −38% to −9%; $p = 0.004$), and the MANCE free rate was 97% (95% CI: 93% to 100%; $p < 0.001$).

- **Conclusions**
  - BAT was safe and significantly improved QOL, exercise capacity, and NT-proBNP.

CENTRAL ILLUSTRATION: Phase III, Baroreflex Activation Therapy for Heart Failure Trial Top-Line Results



Zile, M.R. et al. J Am Coll Cardiol. 2020;76(1):1-13.

https://orlandocvi.com/wp-content/uploads/2021/09/CVRx_IPG.jpg

Physiological mechanism of action in heart failure

1. BAROSTIM NEO™

- A single electrode, powered by one of the most powerful implantable batteries in the world.
- Activates the baroreflex.

2. Baroreceptors

- Sensors that provide information to the central nervous system, which are used in autonomic reflexes and act as part of the baroreflex.
- Are stimulated by BAROSTIM THERAPY™.

3. Brain

- Control board for autonomic nervous system.
- Achieves autonomic balance by reducing sympathetic activity while increasing parasympathetic activity.

4. Heart

↓ HR ↓Remodeling

- Reduces myocardial work
- Reduces oxygen consumption

5. Blood Vessels

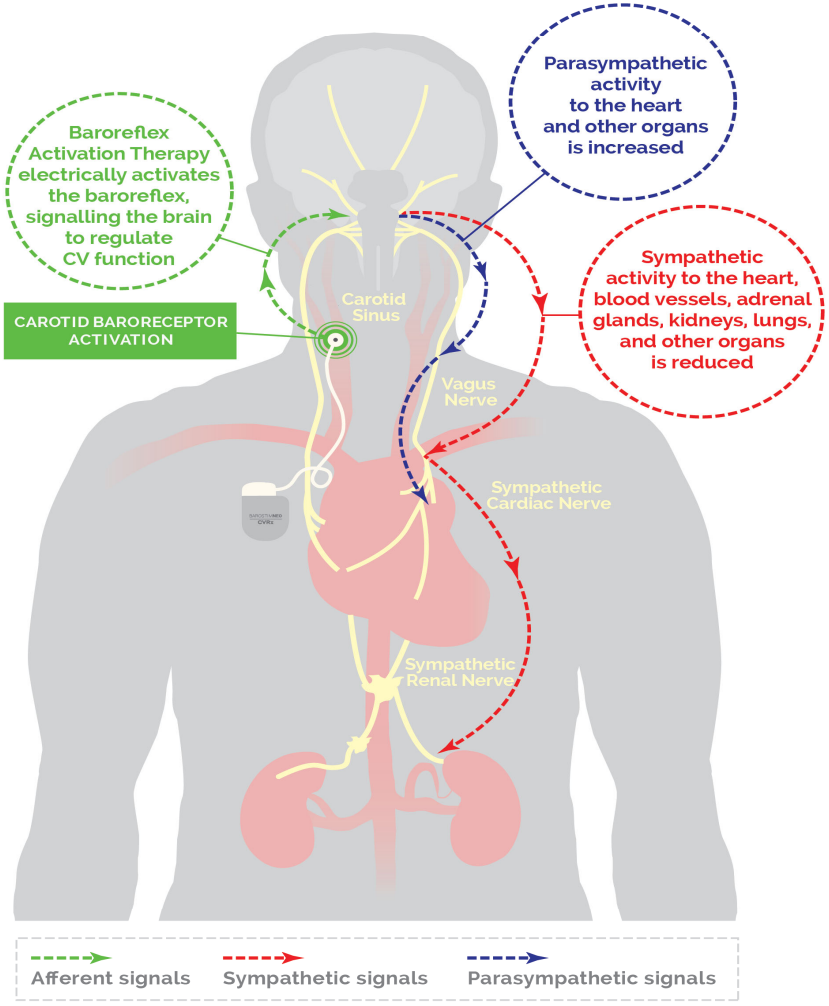
↑Vasodilation ↑ Venous capacitance

- Reduces cardiac afterload
- Reduces pulmonary congestion

6. Kidneys

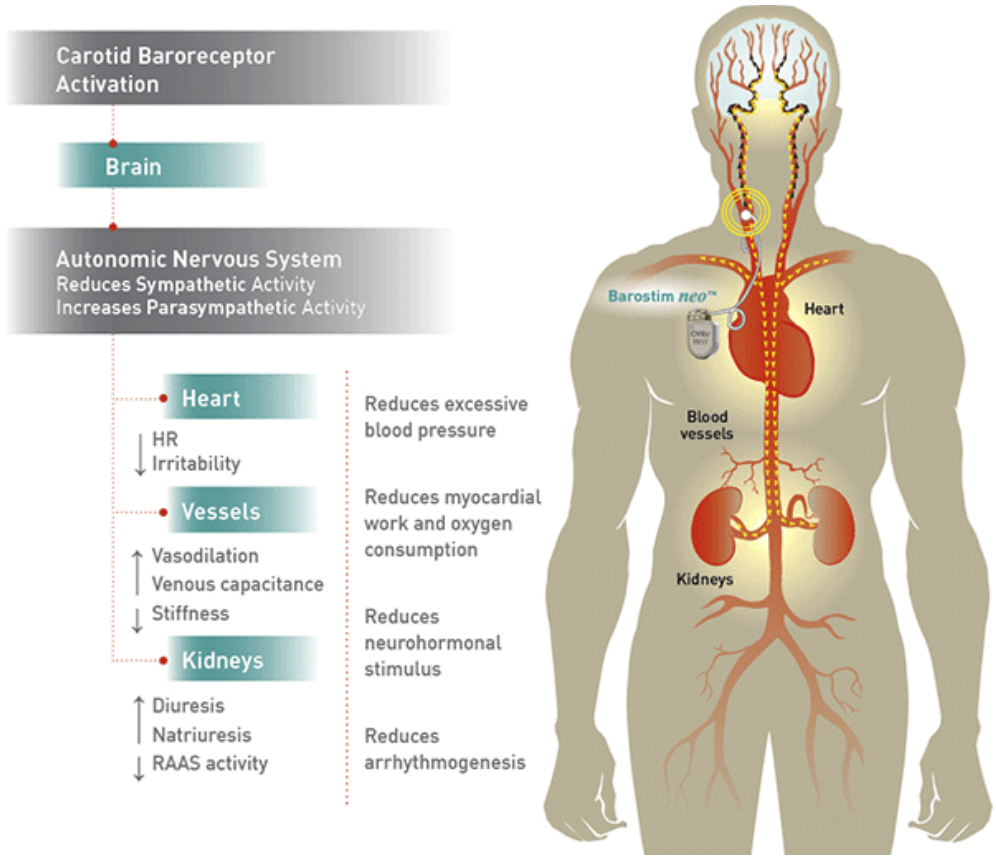
↑ Diuresis ↓ Renin secretion

- Reduces neurohormonal stimulus
- Reduces fluid retention



https://legacymedsearch.com/wp-content/uploads/2019/08/barostimneo-process.png

https://capitalcardiology.com/patient-education/barostim



https://www.medaxs.com.au/2014/12/17/cvrx-barostim-neo-now-cleared-for-mri-use-in-europe/

Cardiac Contractility Modulation (CCM)

- A device that applies **relatively high-voltage, non-excitatory, long duration electric signals to the right ventricular septum during the absolute myocardial refractory period**.

- Results in the augmentation of LV contractile performance.

- **FDA-approved** for heart failure patients with **functional class NYHA class III with LVEF of 25% to 45% who are not candidates for CRT.**

FIX-HF 5C Trial

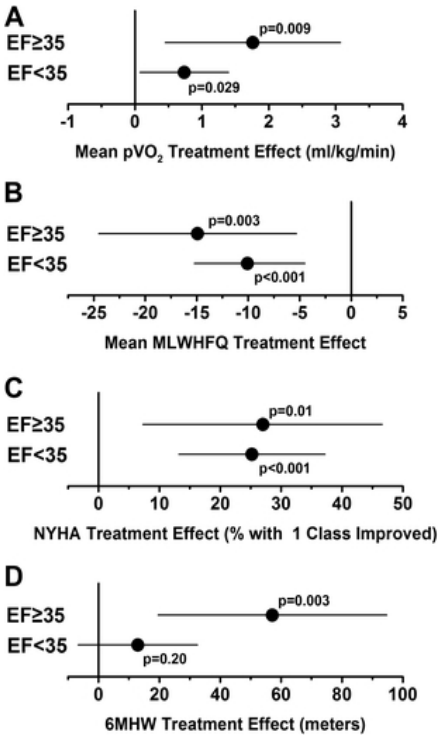
- A Randomized Controlled Trial to Evaluate the Safety and Efficacy of CCM
- **Aim:**
  - to confirm a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) study showing that cardiac contractility modulation (CCM)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

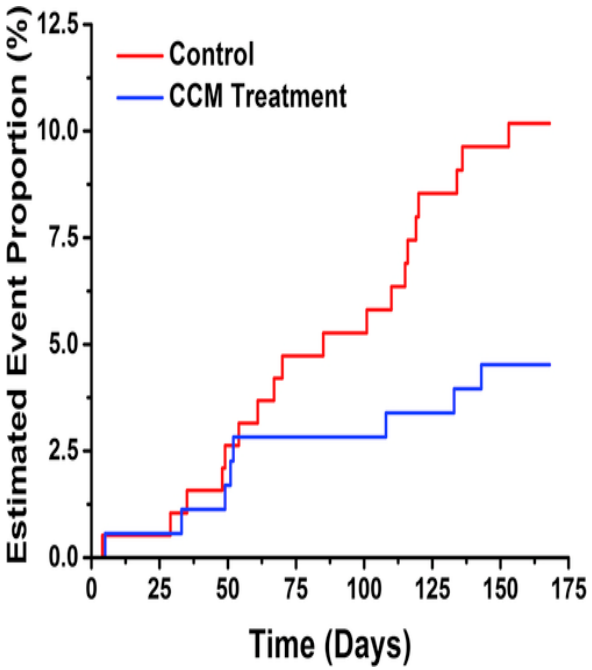
- **Background:**
  - CCM therapy for New York Heart Association (NYHA) functional class III and IV heart failure (HF) patients consists of nonexcitatory electrical signals delivered to the heart during the absolute refractory period.

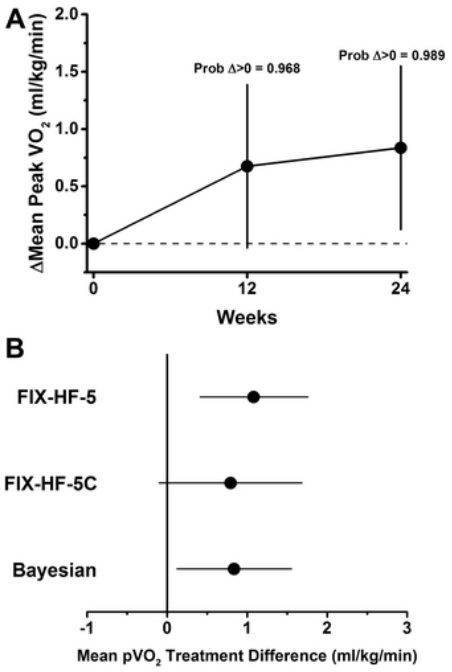
- **Methods:**
  - **160 patients with NYHA functional class III or IV symptoms, QRS duration <130 ms, and ejection fraction ≥25% and ≤45%** were randomized to continued medical therapy (control, n = 86) or CCM (treatment, n = 74, unblinded) **for 24 weeks**.
  - **Peak Vo_2 (primary endpoint), Minnesota Living With Heart Failure questionnaire, NYHA functional class, and 6-min hall walk were measured at baseline and at 12 and 24 weeks.** Bayesian repeated measures linear modeling was used for the primary endpoint analysis with 30% borrowing from the FIX-HF-5 subgroup. Safety was assessed by the percentage of patients free of device-related adverse events with a pre-specified lower bound of 70%.

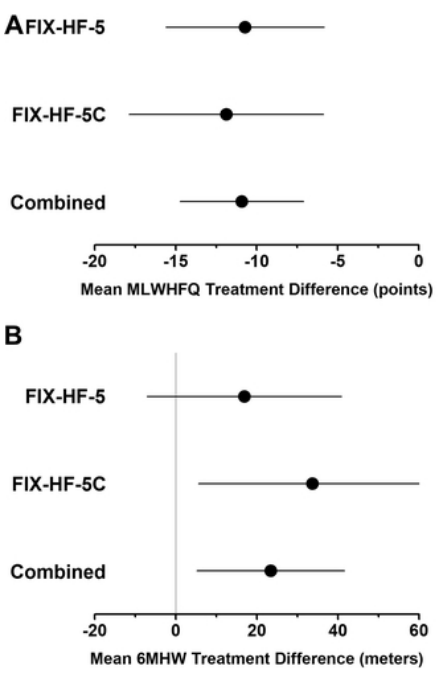
- **Results:**
  - The difference in peak Vo_2 between groups was 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml O_2/kg/min, satisfying the primary endpoint. Minnesota Living With Heart Failure questionnaire ($p < 0.001$), NYHA functional class ($p < 0.001$), and 6-min hall walk ($p = 0.02$) were all better in the treatment versus control group. There were 7 device-related events, yielding a lower bound of 80% of patients free of events, satisfying the primary safety endpoint. The composite of cardiovascular death and HF hospitalizations was reduced from 10.8% to 2.9% ($p = 0.048$).

- **Conclusions:**
  - CCM is safe, improves exercise tolerance and quality of life in the specified group of HF patients, and leads to fewer HF hospitalizations. (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure.



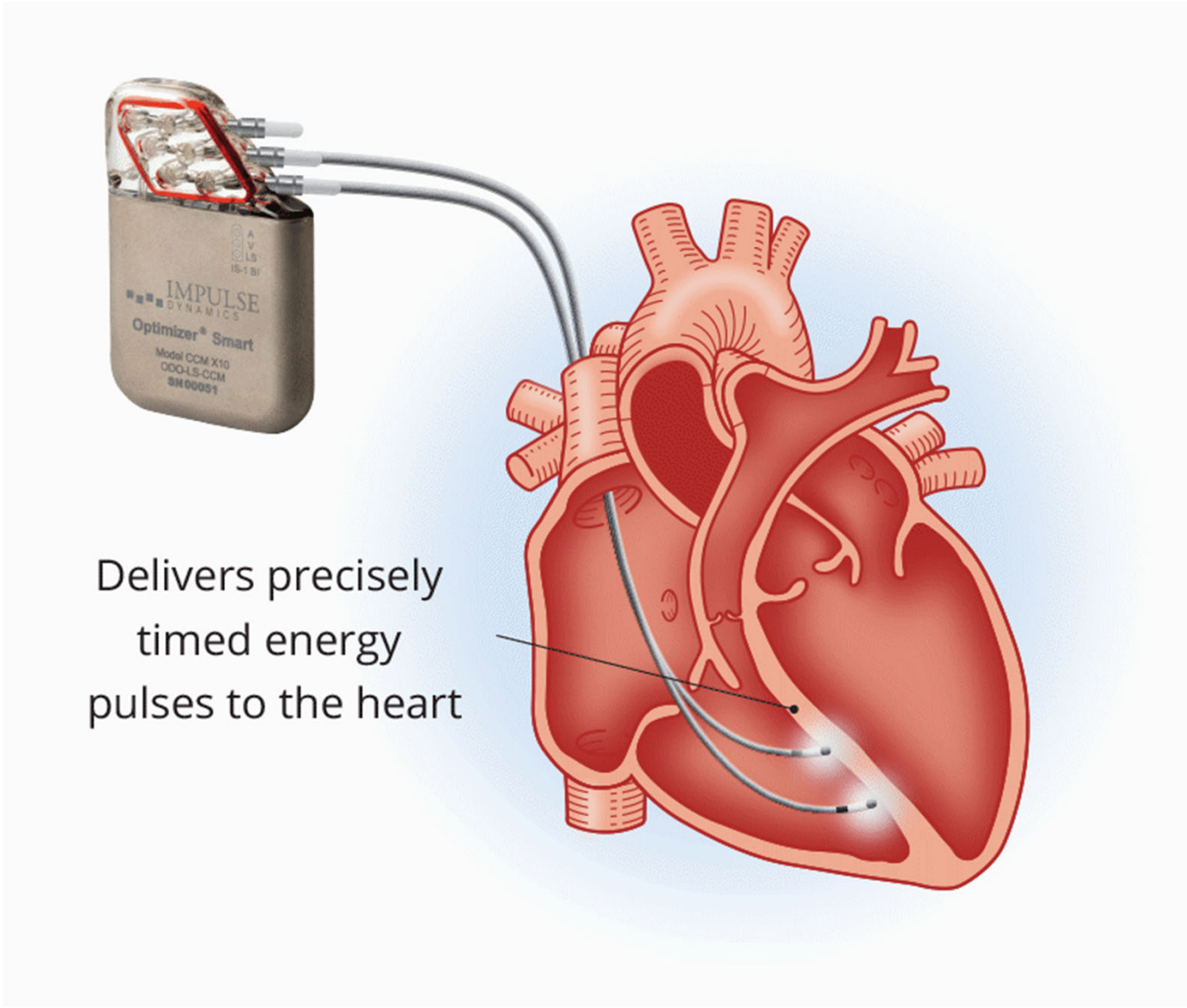






William T. Abraham et al. *J Am Coll Cardiol HF* 2018; 6:874-883.

JACC Heart Failure



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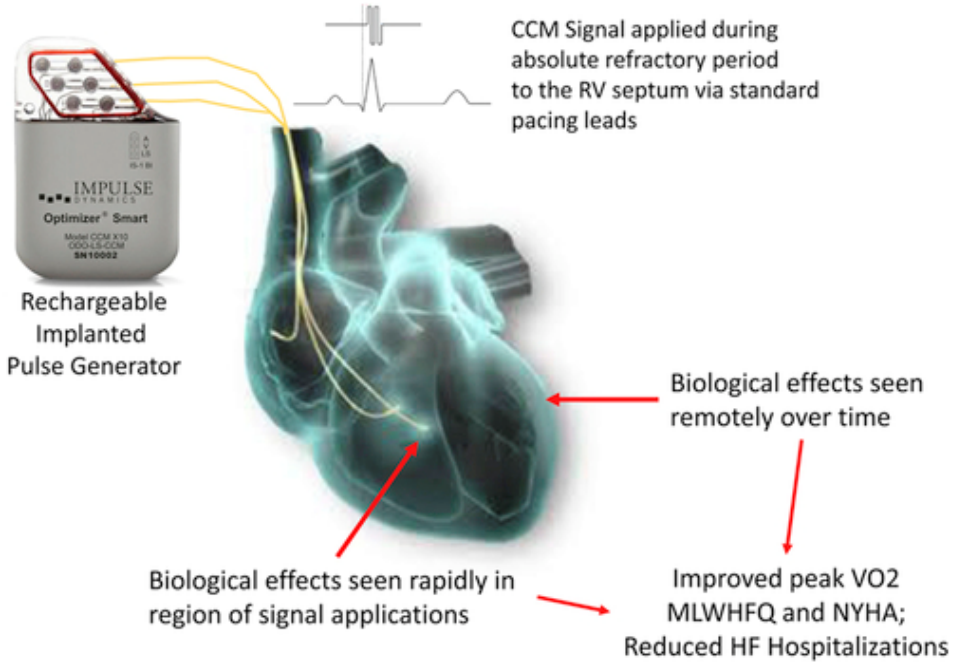
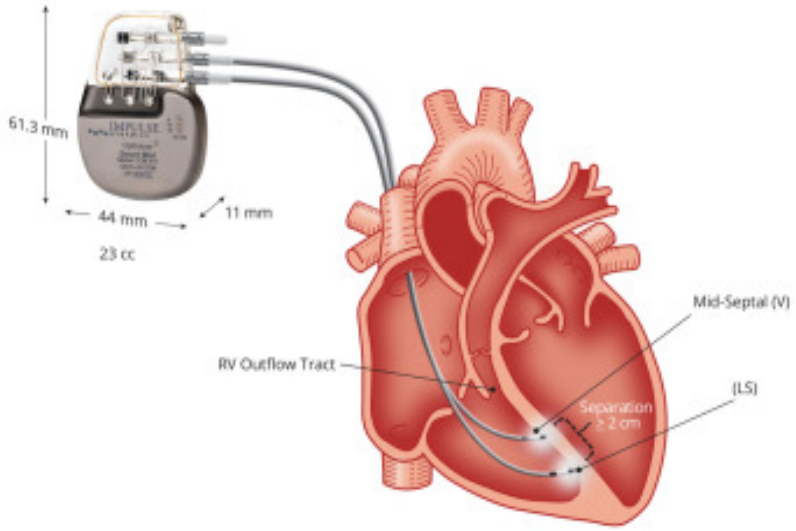


William T. Abraham et al. *J Am Coll Cardiol HF* 2018; 6:874-883.

JACC Heart Failure

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

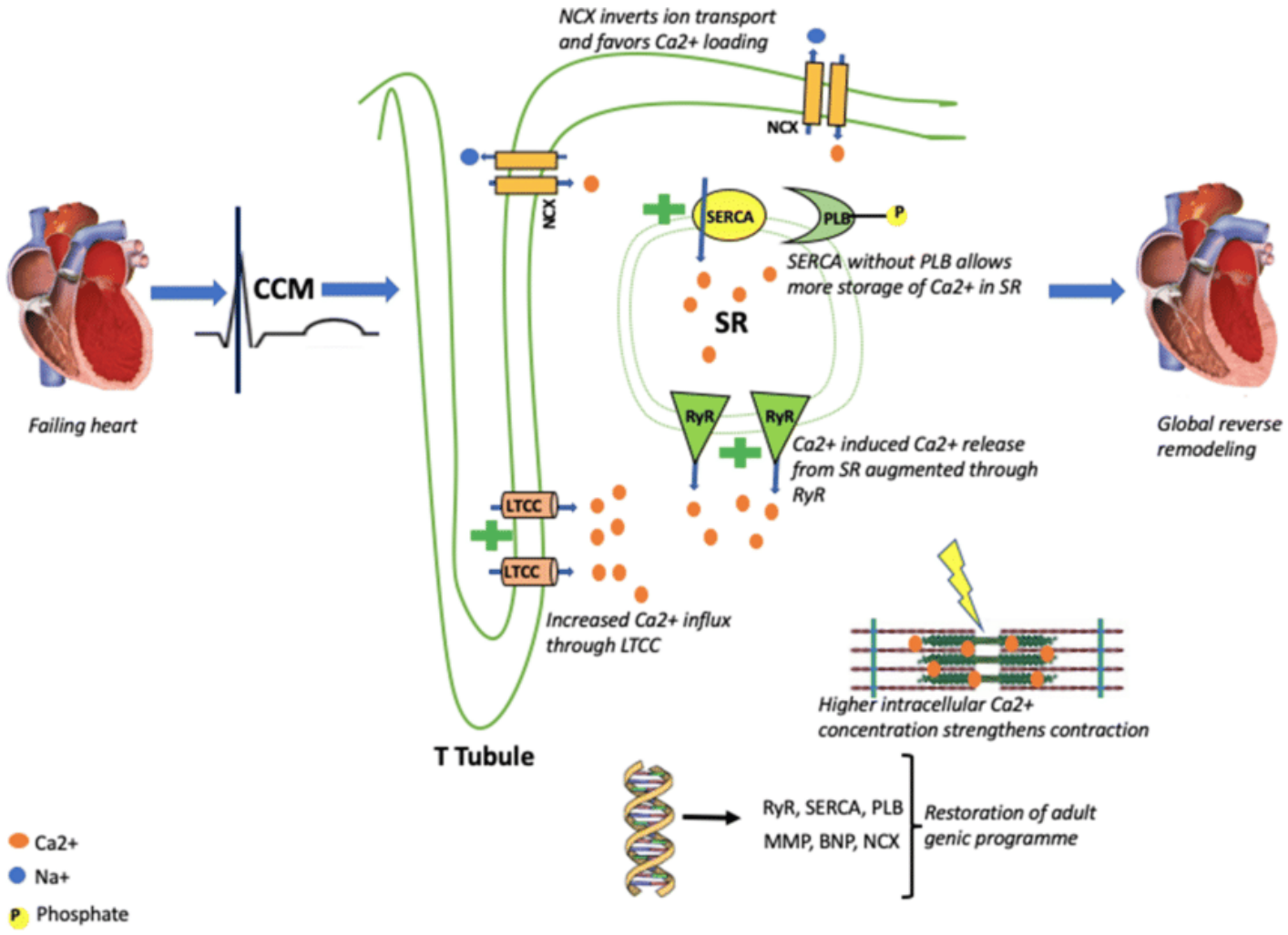
Alteration in myocardial properties

- 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

KHAWAJA M. TALHA, STEFAN D. ANKER, DANIEL BURKHOFF, GERASIMOS FILIPPATOS, CAROLYN S.P. LAM, GREGG W. STONE, OUSSAMA WAZNI, JAVED BUTLER, Role of Cardiac Contractility Modulation in Heart Failure With a Higher Ejection Fraction, Journal of Cardiac Failure, Volume 28, Issue 12, 2022, Pages 1717-1726, ISSN 1071-9164, https://doi.org/10.1016/j.cardfail.2022.08.013.



Cappannoli, L. (2021). Cardiac contractility modulation for patient with refractory heart failure: an updated evidence-based review. Heart failure reviews. 26. 10.1007/s10741-020-10030-4.

Conclusion

- Management of heart failure is complex and medical devices have mechanisms that appear to simplify the nuances of care. However, for most devices, available clinical trials are insufficient to prove superiority over the usual guideline directed medical therapies.

- More evidence is needed to justify the clinical utility of some HF devices in the face of the rising healthcare cost and safety concerns.

Thank You