Evolving Cardiac Electrical Therapies for Advanced Heart Failure Patients

Babak Kazemi, M.D

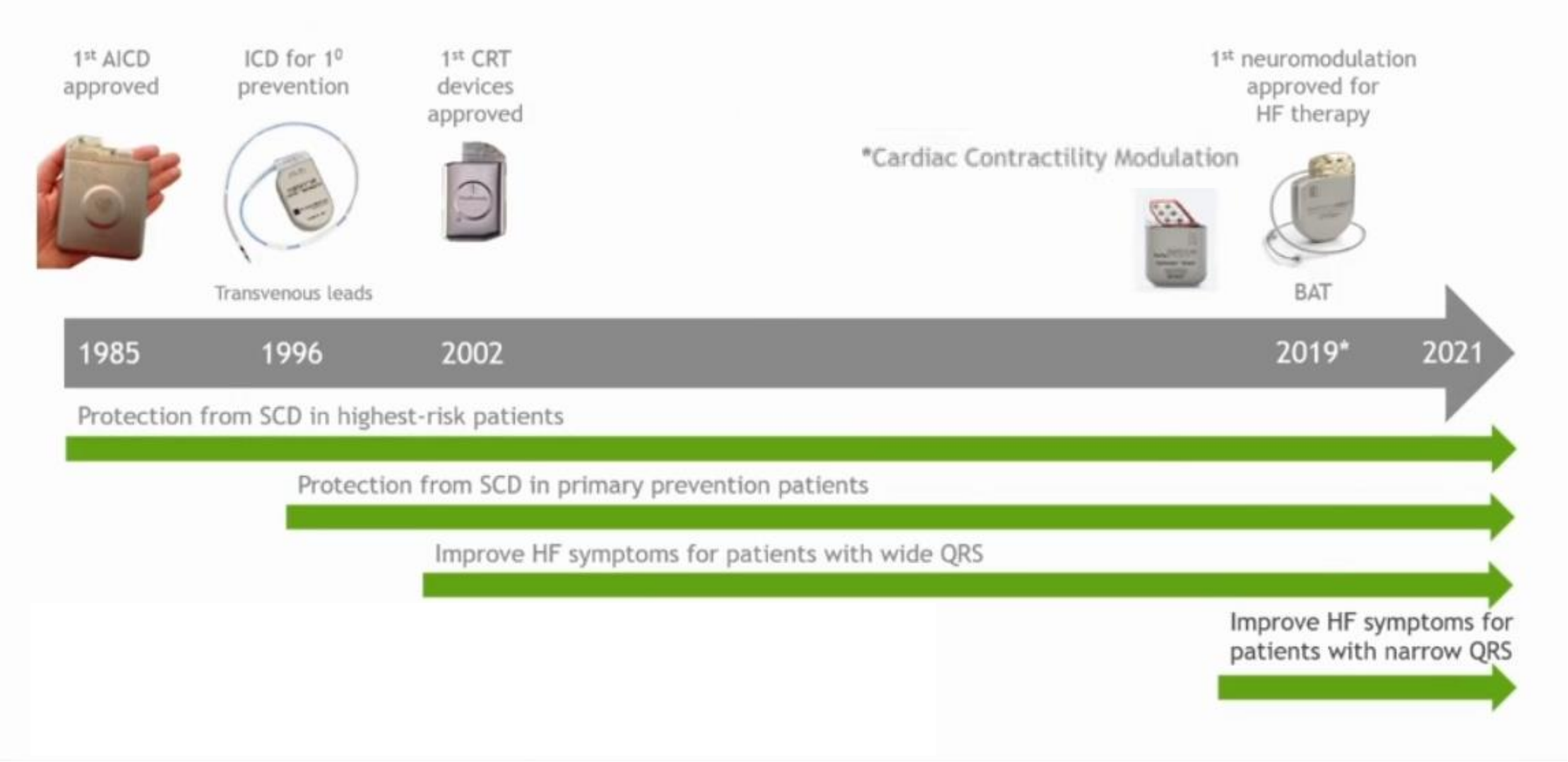
Professor of Cardiology,

Fellowship in Interventional Electrophysiology

Department of Cardiology

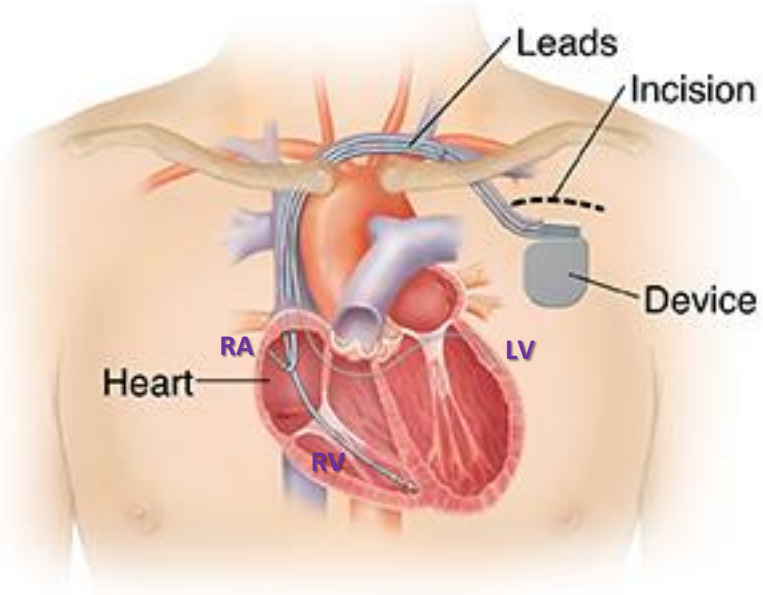
Shahid Madani Cardiovascular Center

Evolution of Device Therapy for HFrEF



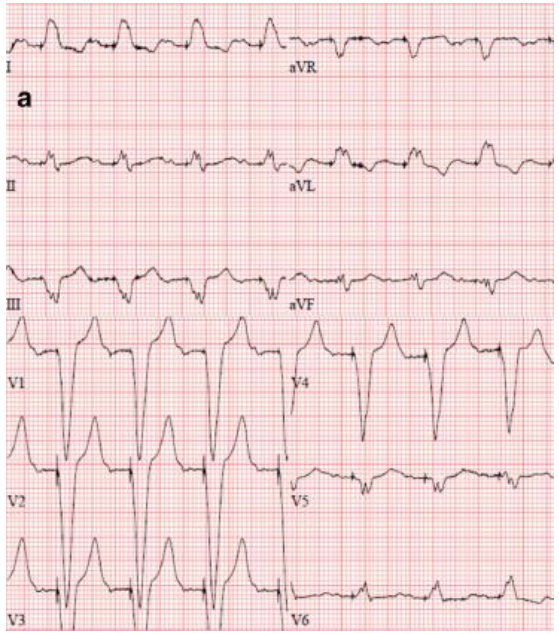
LVEF ≤35%

QRS morphology	QRS duration (ms)	NYHA functional class	Level of recommendation
LBBB	≥150	II, III, ambulatory IV	Class I
	130-149	II, III, ambulatory IV	Class IIa
	≥150	I + LVEF **≤35%** + ischemic heart disease	Class IIb
Non-LBBB	≥150	III, ambulatory IV	Class IIa
	130-149	III, ambulatory IV	Class IIb
	≥150	II	Class IIb
	130-149	I, II	Class III (no CRT)
Significant (>40%) ventricular pacing	Any QRS	I, II, III, ambulatory IV	Class IIa

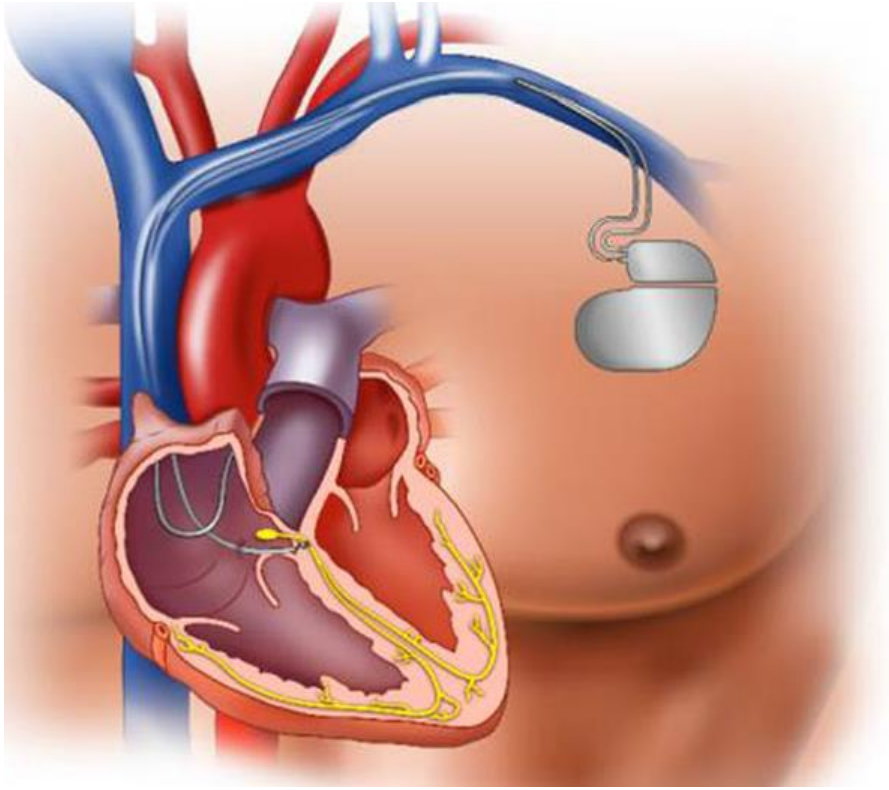


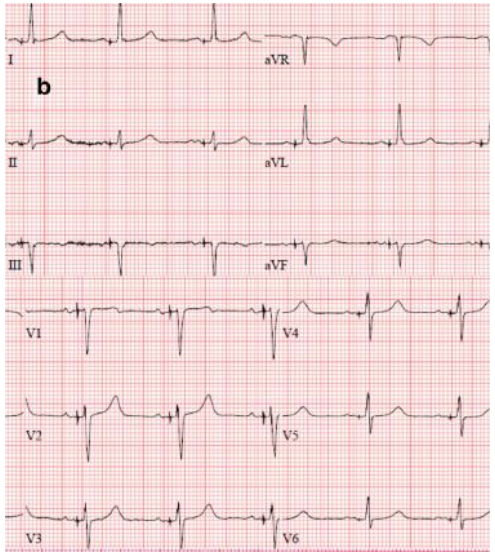
Innovations in CRT

RV pacing

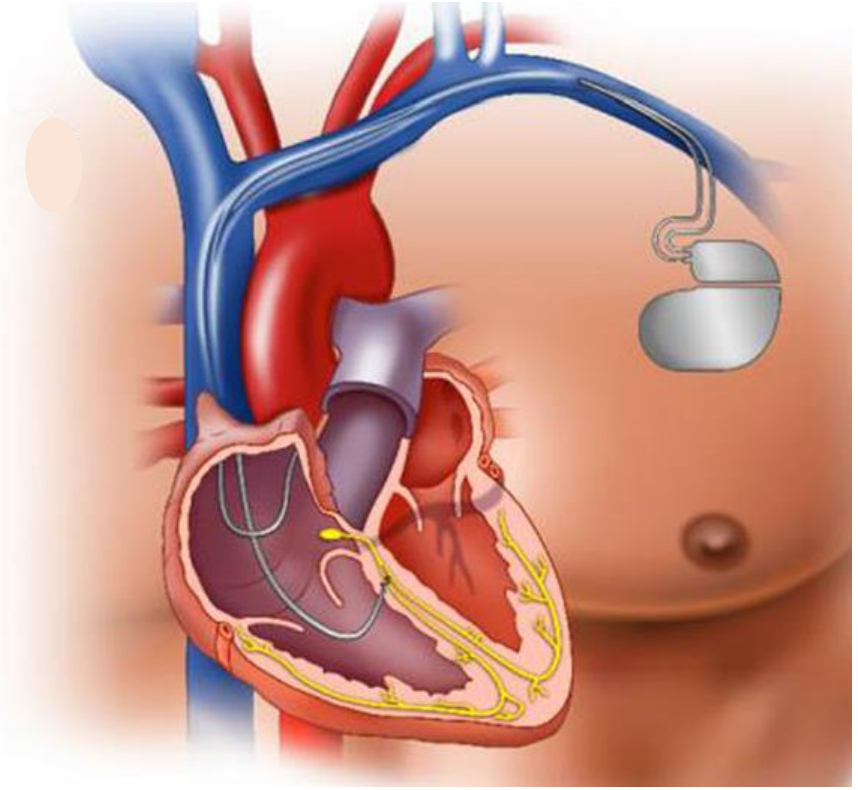


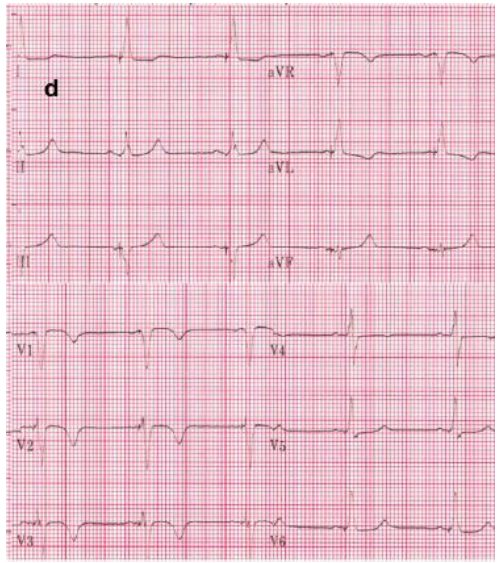
His-bundle pacing



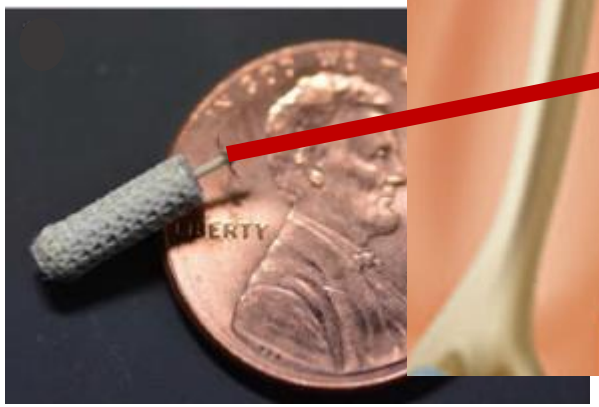


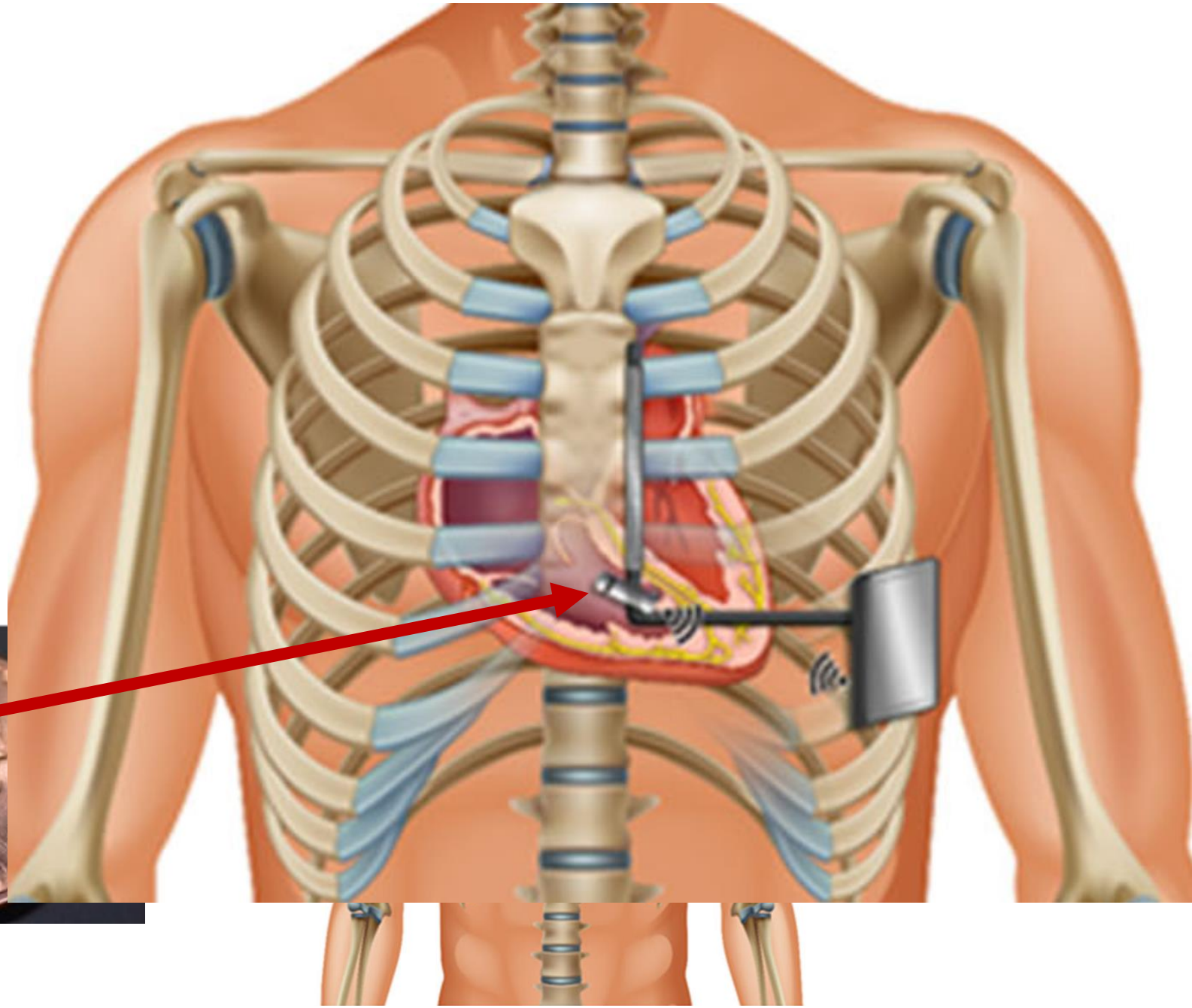
LBB pacing





Innovations in ICDs





In the largest cohort with ≈15 000 patients with HF, only 9.1% of the population was eligible for CRT.

QRS duration		
CRT is not indicated in patients with HF and QRS duration <130 ms without an indication for RV pacing.	III	A

CRT = cardiac resynchronization therapy; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; SR = sinus rhythm.

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab364)

FDA-Approved Therapies

Cardiac contractility modulation (CCM)

- QRS duration <130 ms
- LVEF 25%-45%
- Currently contraindicated with longstanding or permanent atrial fibrillation

Baroreflex activation therapy (BAT)

- LVEF ≤35%
- Excludes patients with a guideline indication for cardiac resynchronization therapy (CRT)

Phrenic nerve stimulation

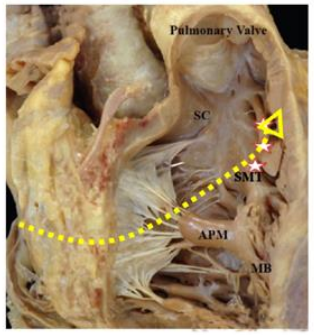
- Moderate to severe central sleep apnea
- Independent of heart failure

Vagus nerve stimulation

cardiac contractility modulation

Currently qualified ventricular lead

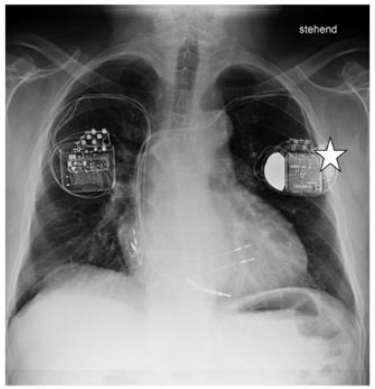
Manufacturers	Leads
Biotronik	Setrox : S45; S53; S60
Boston Scientific	Dextrus = 4135; 4136; 4137
Abbott	Tendril DX = 1688T; 1788T; 1088 or 2088



☆ Septo-marginal trabeculations = the target implantation site

⇩

Excellent RV sensing and high Impedance are preferred

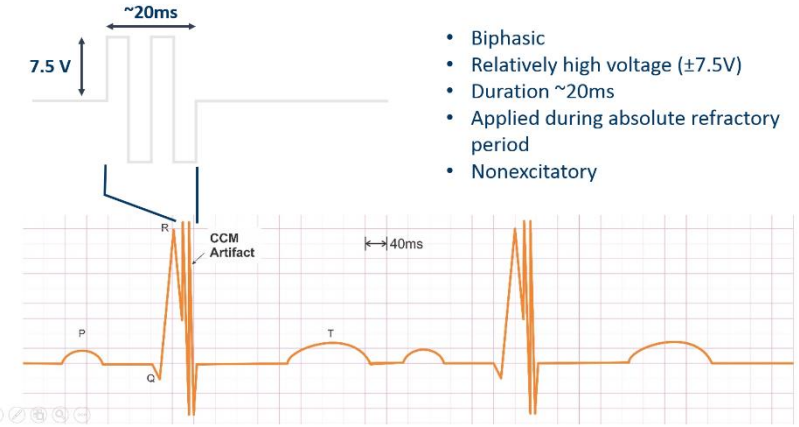


☆ Concomitant implantable cardiac device

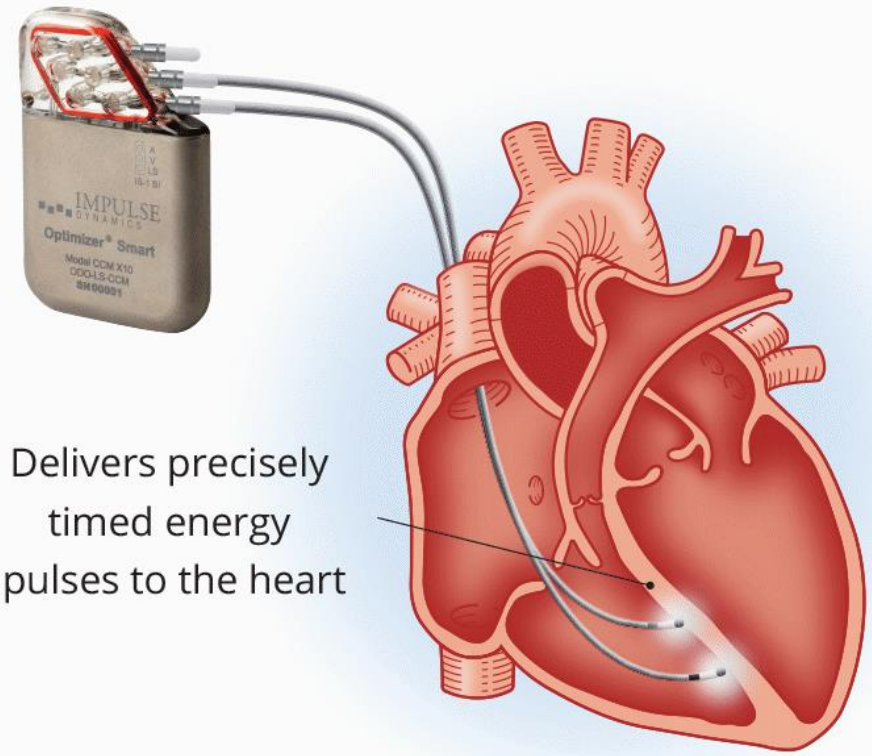
⇩

Per-procedural testing to detect device-device interaction

Cardiac Contractility Modulation (CCM) Signals



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



Delivers precisely timed energy pulses to the heart

BENEFIT

METABOLISM

Intra-cellular CA^{2+} metabolism ⇧

calcium induced calcium release ⇧
- Up regulation of SERCA
- Phospholamban Phosphorylation
- RyR2 Phosphorylation

Reverse remodeling of the fetal gene expression

CLINICAL

NYHA class status ⇩

Quality of life ⇧

VO2 peak ⇧

Trend towards fewer HF hospitalization

Mechanism of Action

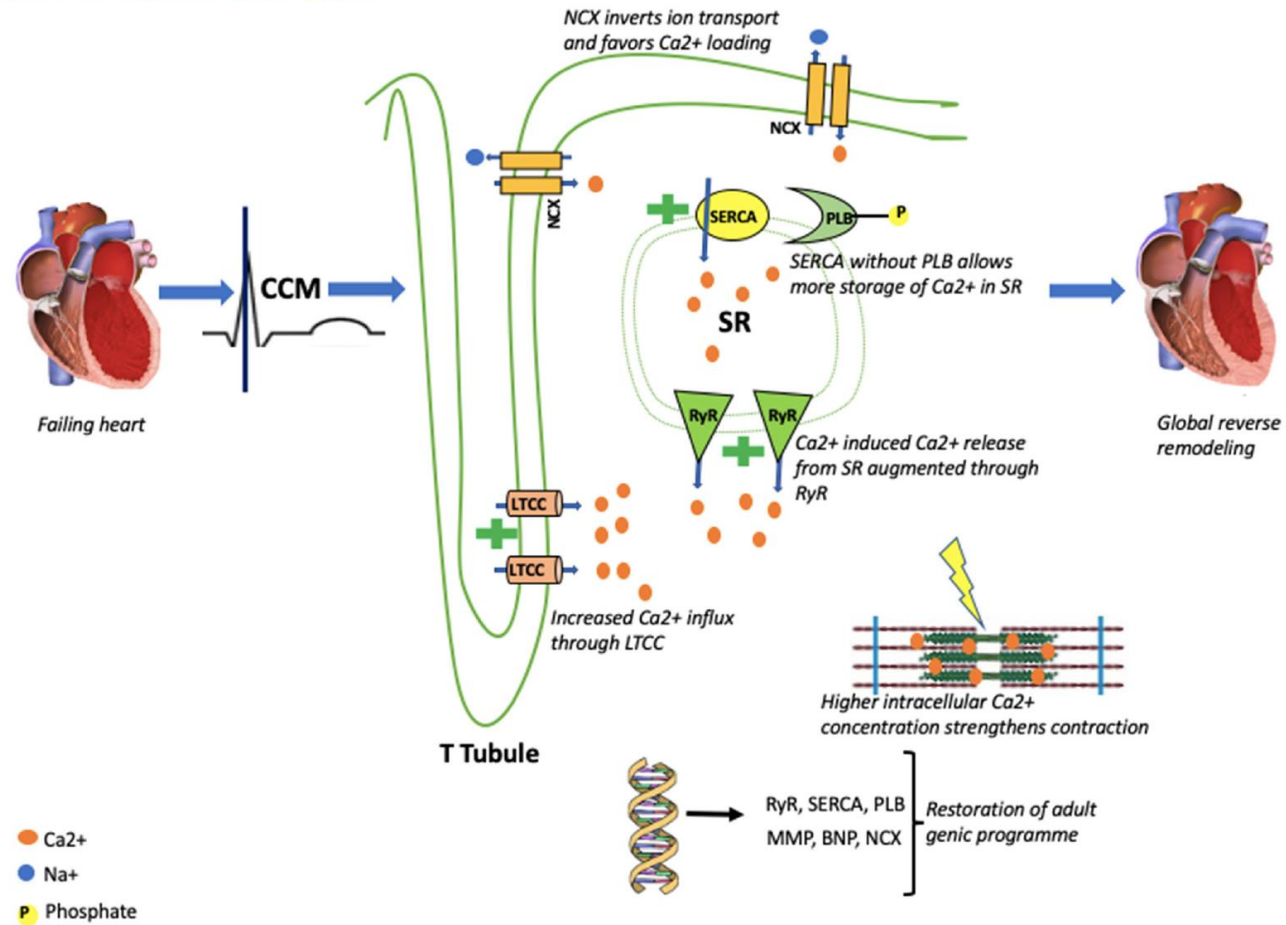
CCM therapy is UNIQUE affecting ALL six components of chronic heart failure:

1. Calcium distribution within cardiomyocytes
2. Titin phosphorylation
3. Cardiac fibrosis
4. Autonomic nervous system control
5. Energy balance
6. Cardiac tissue remodeling

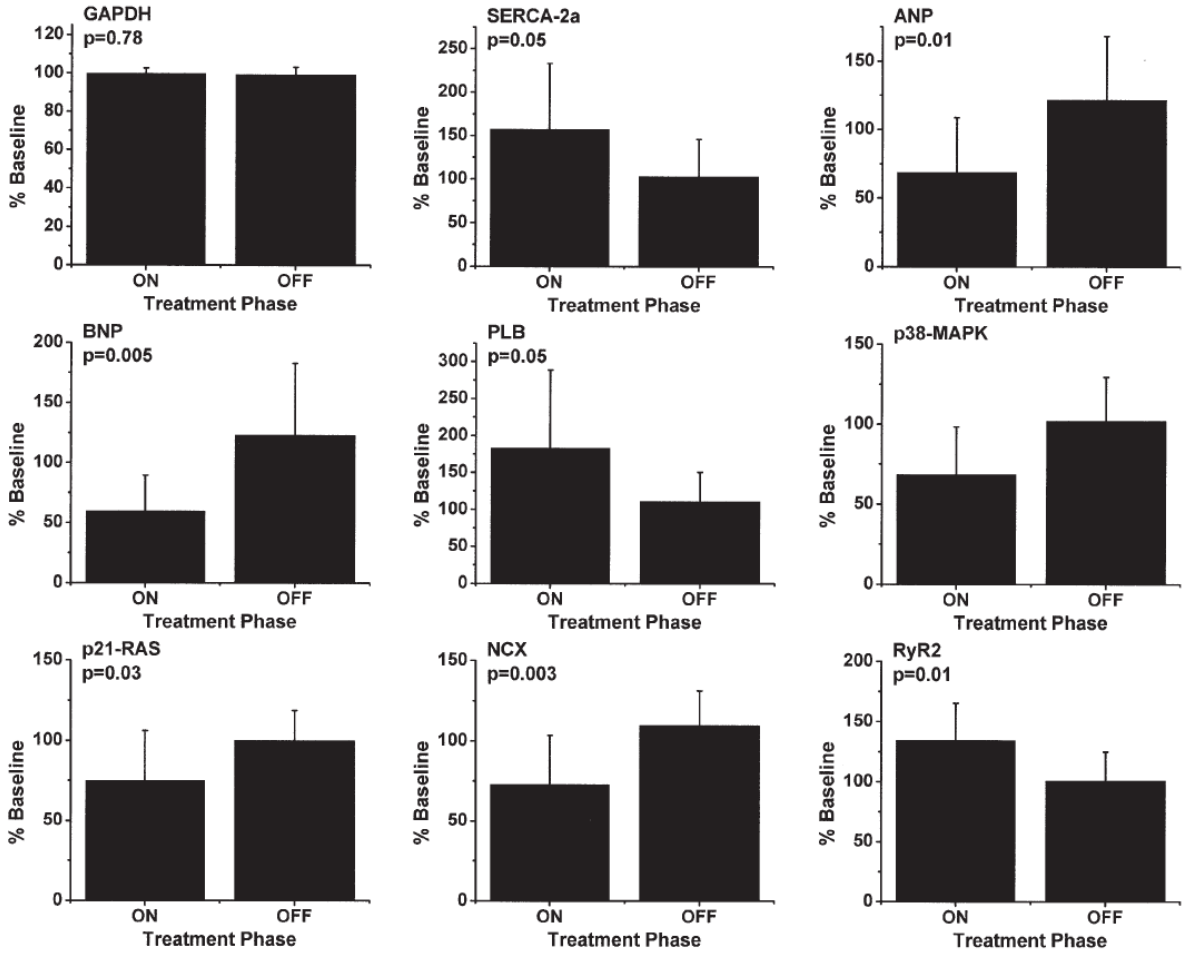
} Increased contractility ↑ **30%**

Restoring Normal Calcium Handling

- Upregulation of SERCA
- Greater phosphorylation of phospholamban
- Increase of SR uptake of calcium resulting in greater release of calcium during the next depolarization
- Greater contractility



CCM Improves Myocardial Gene Expression in the Failing Human Heart



- Expression of multiple HF related genes improves with CCM
- Findings in human myocardial samples from a double-blind randomized controlled study

N=11

Butter C, et al. J Am Coll Cardiol 2008;51:1784–1789.

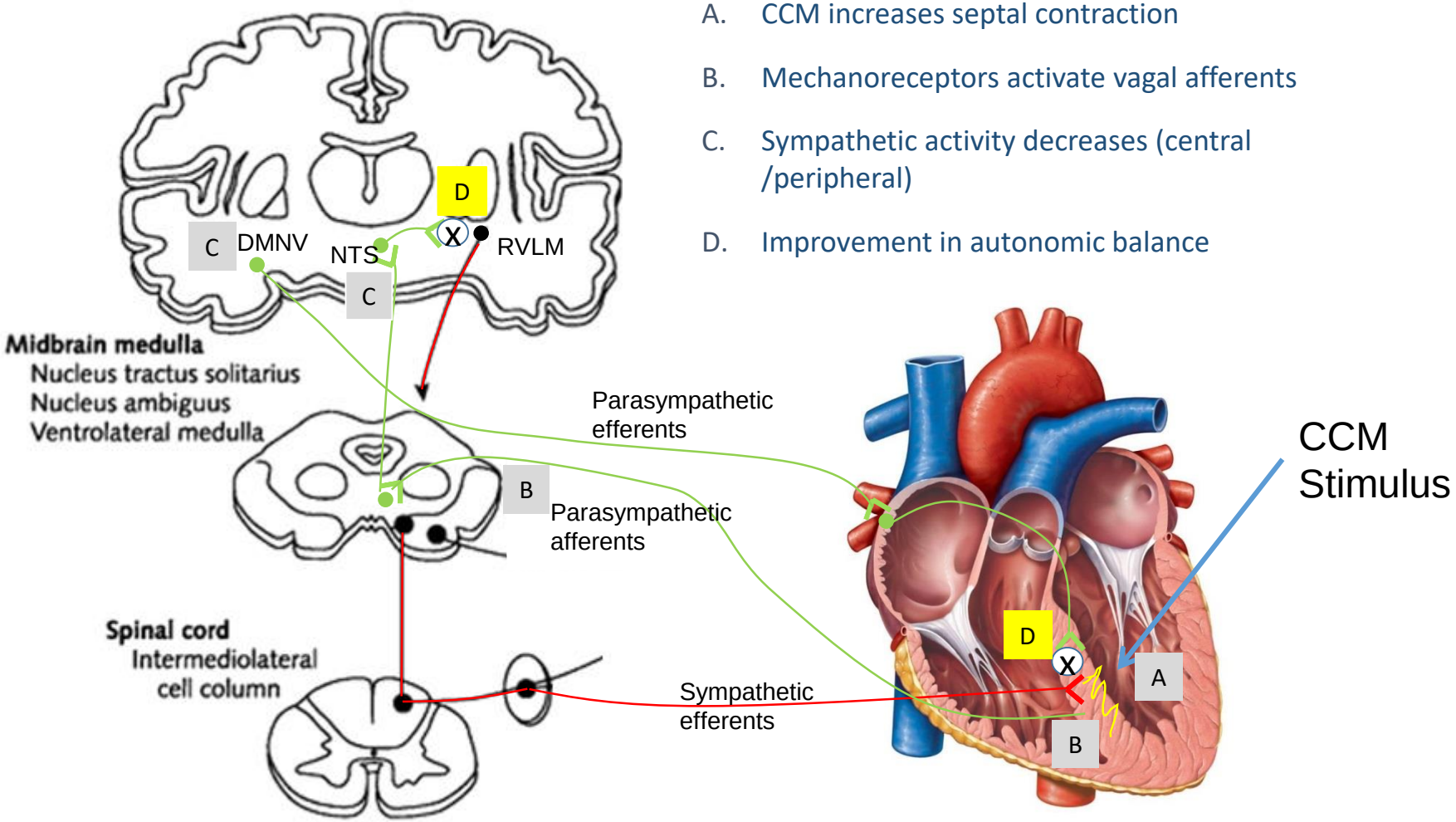
CCM and Its Suggested Influences on the Sympathetic Activity

A. CCM increases septal contraction

B. Mechanoreceptors activate vagal afferents

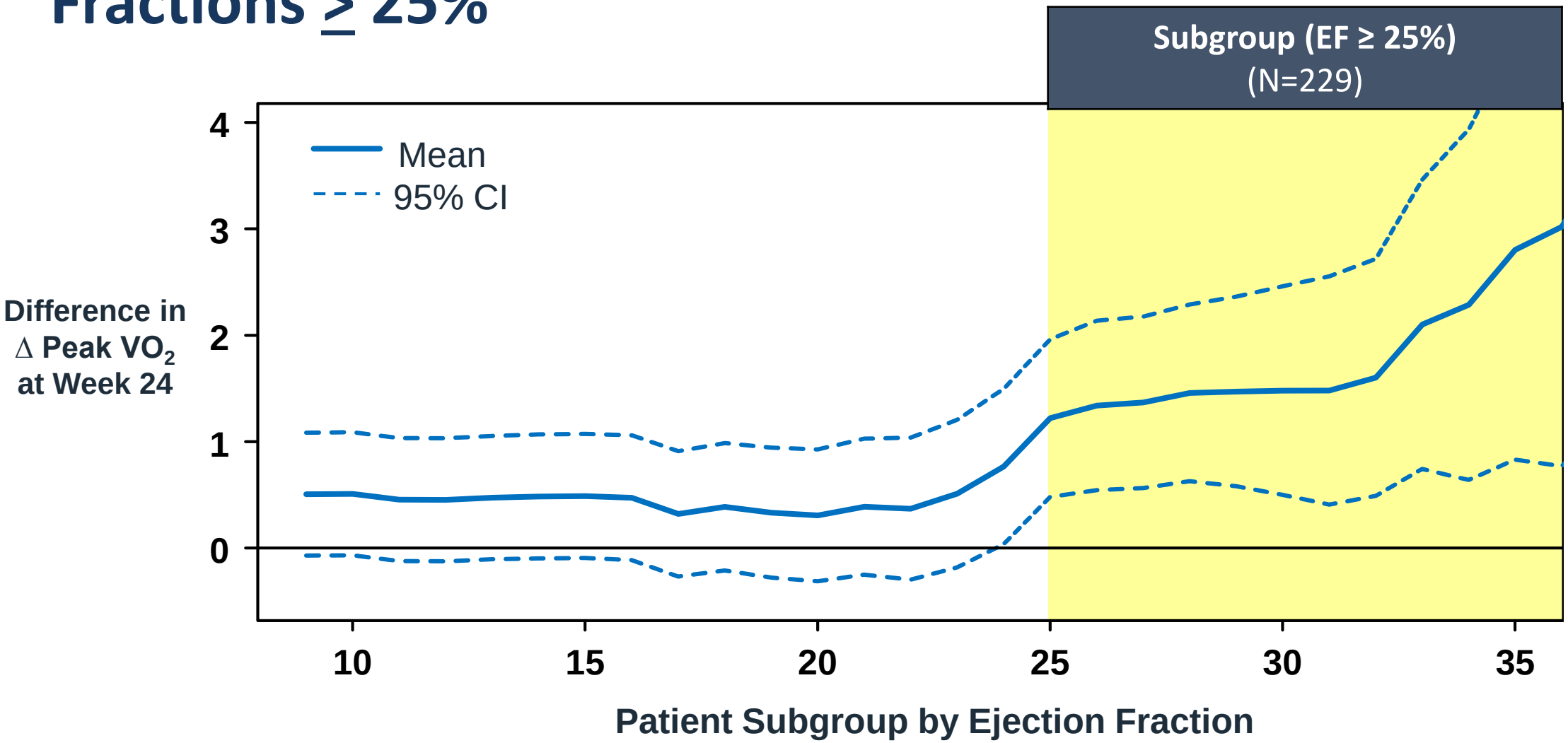
C. Sympathetic activity decreases (central /peripheral)

D. Improvement in autonomic balance



Adapted from Tschöpe et al. Eur J of Heart Fail 2019;21:14–22.

FIX-HF-5: Greater Benefit in Patients with Ejection Fractions ≥ 25%



Abraham WT, et al. J Card Fail 2011; 17:710-717.

CCM: Improvement in Cardiac Energy *Efficiency*

Studies in animals and humans show that CCM does not increase myocardial oxygen consumption

Dogs - Chronic CHF

Table 2. Hemodynamic and Ventriculographic Findings in Dogs with Heart Failure Obtained at Baseline and 2 hours After Initiating CCM Therapy (n = 6)

	Baseline	2 Hours of CCM	*P* value
HR (beats/min)	79 ± 3	75 ± 3	.26
Peak LVP (mm Hg)	101 ± 5	107 ± 8	.23
LV EDP (mm Hg)	14 ± 1	9 ± 1	.005
Stroke volume (mL)	18 ± 1	21 ± 1	.004
LV EDV (mL)	71 ± 8	68 ± 7	.001
LV ESV (mL)	53 ± 7	47 ± 6	.001
LV EF (%)	26 ± 1	31 ± 2	.001
LV CBF (mL/min)	35 ± 4	27 ± 3	.017
LV Power (watts)	0.32 ± 0.02	0.37 ± 0.03	.040
MVO_2 (μmol/min)	257 ± 41	180 ± 34	.12

Abbreviations are same as in Table 1. CCM, cardiac contractility modulation; *P* value = probability value of baseline versus CCM.

- Burkhoff et al., Heart Failure Reviews, 2001.

Humans - Chronic CHF (PET scan)

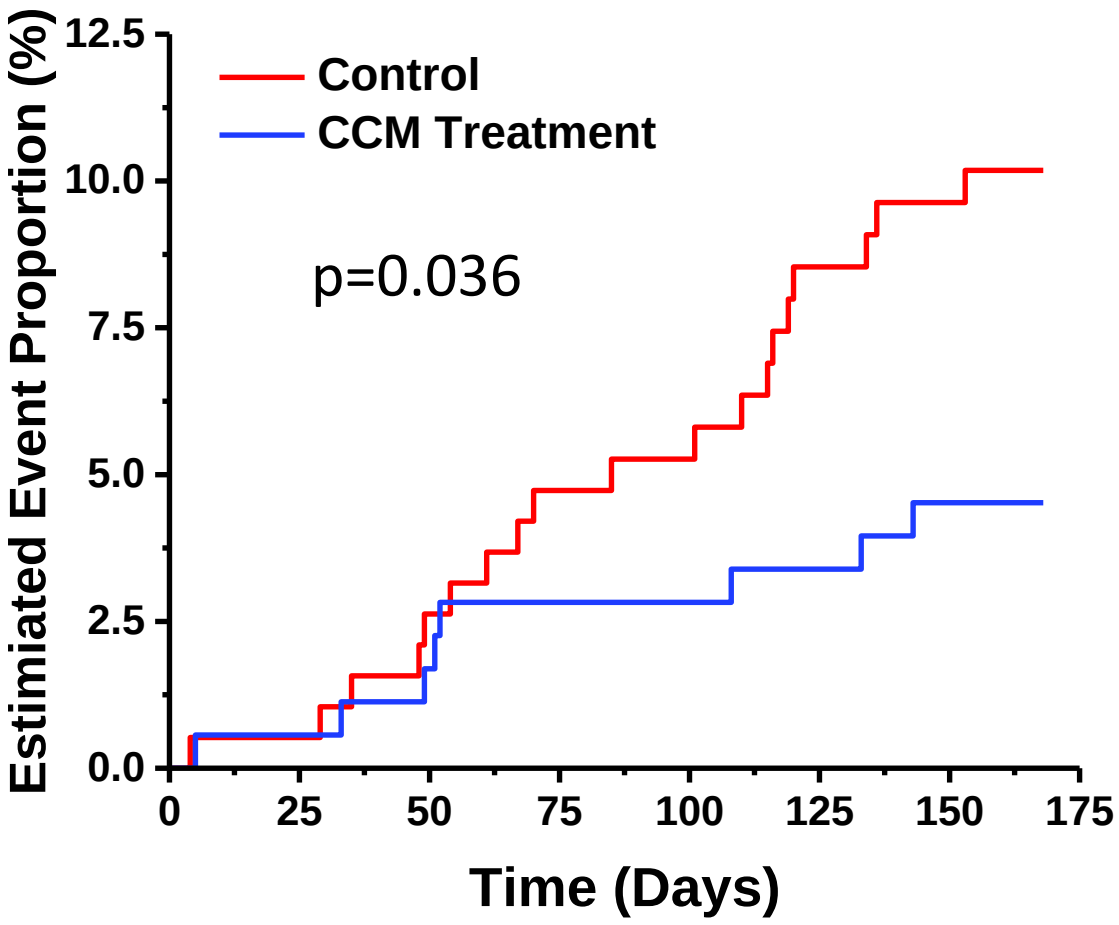
Table 2 Comparison of cardiac parameters under resting conditions with the CCM device deactivated and activated (values are means± SD, n=21; p-values were calculated using the paired t-test)

Parameter	CCM deactivated	CCM activated	p-value
Systolic blood pressure (mmHg)	112.62±15.78	113.10±20.28	0.858
Heart rate (bpm)	65.71±10.47	70.81±12.82	0.001
Rate–pressure product	7,382±1,439	7,967±7,128	0.047
MBF (ml min^{-1} g^{-1})	0.81±0.18	0.80±0.15	0.818
k_{mono}	0.053±0.01	0.055±0.01	0.239
MVO_2 (ml/min/100 g)	6.81±1.69	7.15±1.62	0.241
WMI (mmHg ml/m^2)	4.94±1.14	5.21±1.36	0.344
LVEF (%)	28.37±5.53	28.43±6.48	0.928

- Goliasch et al., Eur J Nucl Med Mol Imaging, 2011.

CCM increases contractility but not oxygen consumption

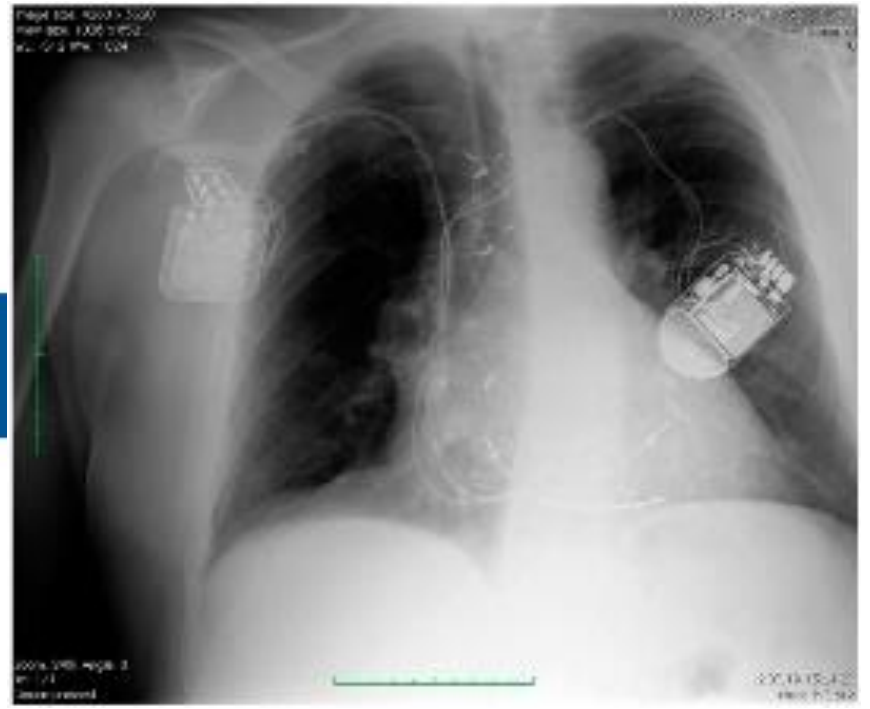
CCM Effect on Cardiovascular Death and HF Hospitalizations: FIX-HF-5 + FIX-HF-5C

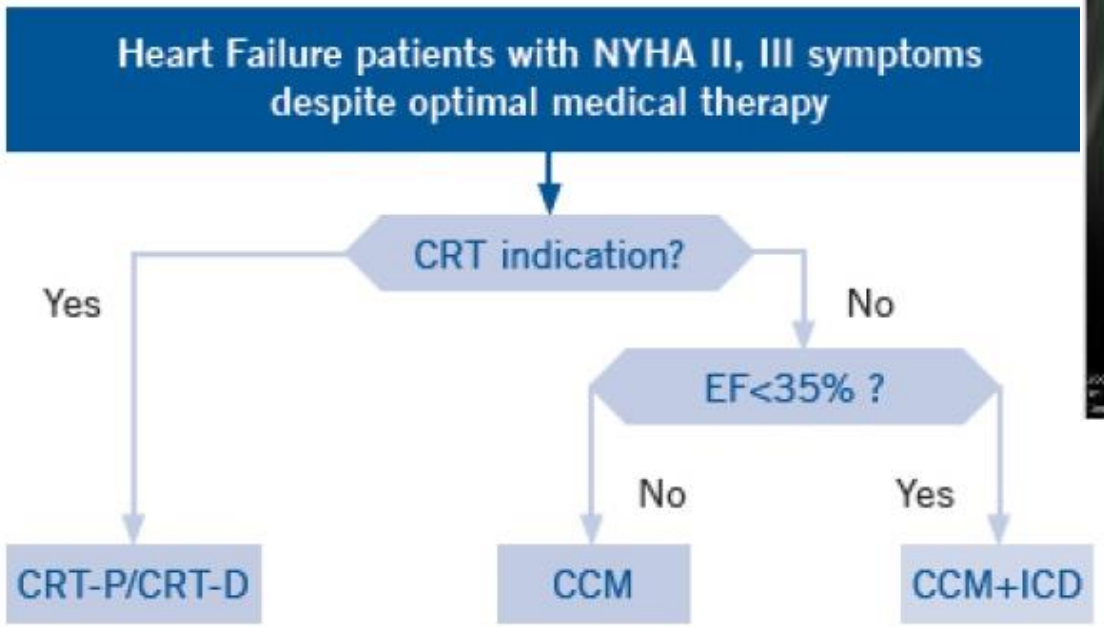


FDA approval in patients with HF ineligible for CRT (March 2019)

Abraham WT, et al. JACC Heart Failure 2018; 6:874-883.

Cardiac Contractility Modulation: Who Should Receive This Therapy?





More than 17m patients globally with NYHA II/III

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

Current Ongoing Large-Scale Studies for CCM in Narrow Complex Heart Failure

Primary Investigator	Title	Study start date	Research question	Design	Estimated n	Outcome measure
Burkhoff et al[45]	FIX-HF-5CA Continued Access Protocol	July 2017	Safety and effectiveness of CCM in HFrEF population	Multicenter, prospective, single-arm continued access study of the Optimizer Smart System with CCM therapy.	200	Primary: serious adverse device events Secondary: (1) Kansas City Cardiomyopathy Questionnaire; (2) NYHA class
Tschoepe et al[46]	CCM-HFpEF	May 2018	Efficacy and safety of CCM therapy in patients with HFpEF	Single group assignment of the Optimizer Smart system in HFpEF.	60	Primary: mean KCCQ change, baseline to 24 wk Secondary: (1) echocardiography, 24 wk (LAVi and diastolic function: septal E′ velocity, septal E/E′ ratio); (2) NT-proBNP mean change at 24 wk; (3) NYHA class mean change at 24 wk
Kahwash, Weiss et al[47]	Post Approval Study (PAS) of the OPTIMIZER Smart and CCM Therapy	January 2020	Long-term safety and efficacy of the the OPTIMIZER Smart system in real-world setting	Prospective, multicenter, nonrandomized, single-arm open-label study.	620	Primary: (1) incidence of procedure-related complications (30 d) and device-related complications (1 y); (2) all-cause mortality; observed mortality to be compared with predicted mortality according to the Seattle Heart Failure Model at 1 and 3 y post-implant
Matta, Rametta et al[48]	CCM Italian Registry	September 2019	Long-term safety and efficacy of the OPTIMIZER Smart system in real-world setting	Prospective observational cohort study.	200	Primary at 24 mo: (1) exercise tolerance as measured by 6MWT; (2) QOL as per MLWHFQ; (3) NYHA class Secondary at 24 mo: (1) LVEF; (2) hospitalization for worsening HF; (3) LV volume

ELECTRICAL DEVICE–BASED MODULATION of the AUTONOMIC NERVOUS SYSTEM (ANS)

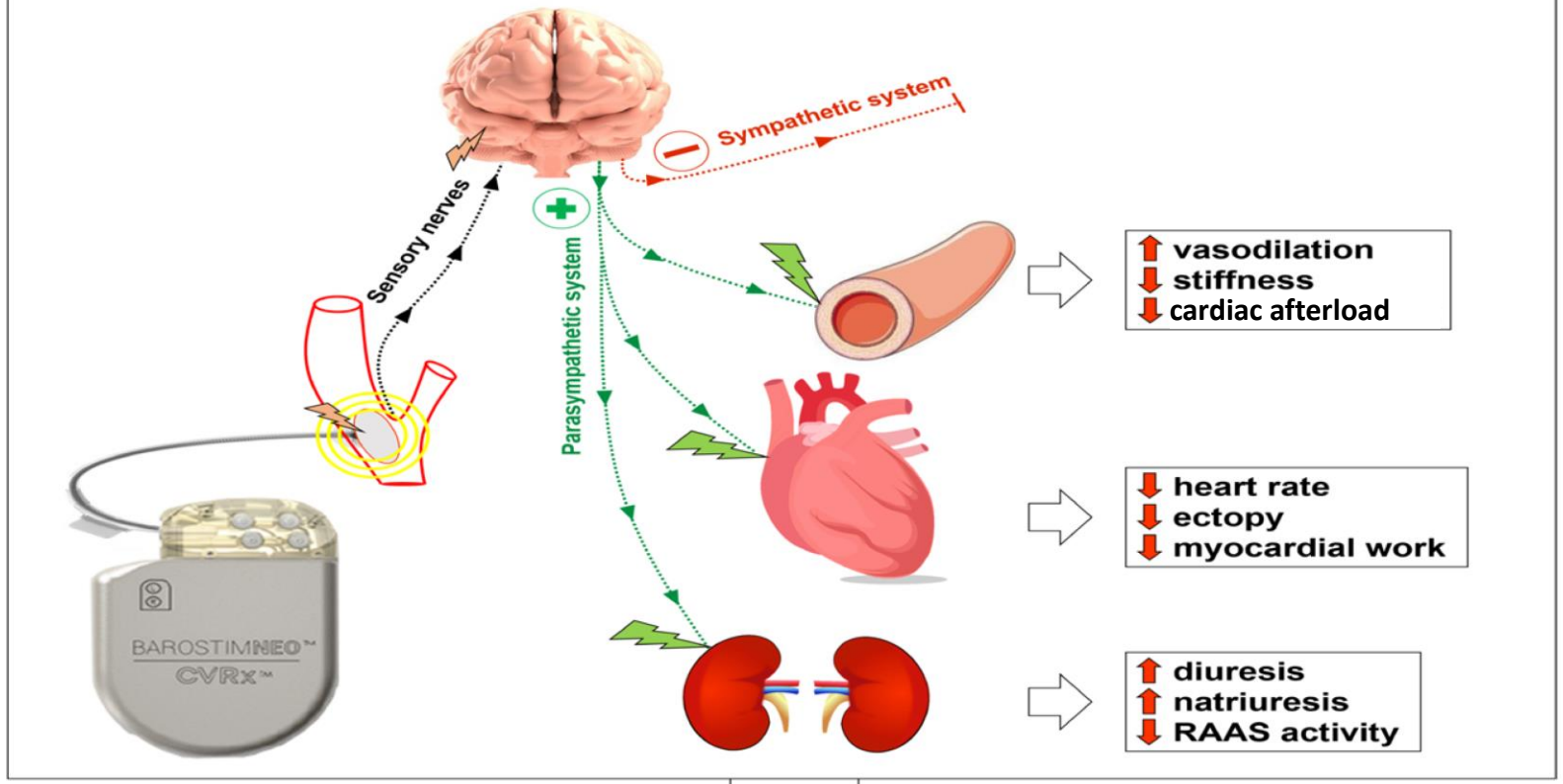
(1)carotid baroreceptor activation therapy (BAT)

(2) vagal nerve stimulation (VNS)

Device-based Modulation of the ANS

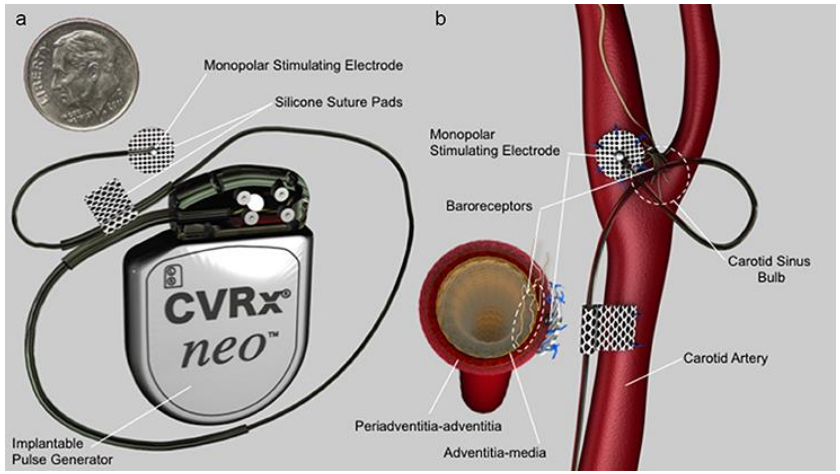
- HF is associated with autonomic imbalance with increased sympathetic activity and withdrawal of parasympathetic activity.
- This leads to subcellular myocardial dysfunction (including abnormal calcium handing and apoptosis), increase in interstitial fibrosis, a higher susceptibility of arrhythmia, and increased peripheral vascular resistance.
- Autonomic dysfunction is also a strong contributor to HF progression and mortality.
- Consequently, manipulating the ANS to restore sympathovagal balance may be an attractive therapeutic option for HF patients.

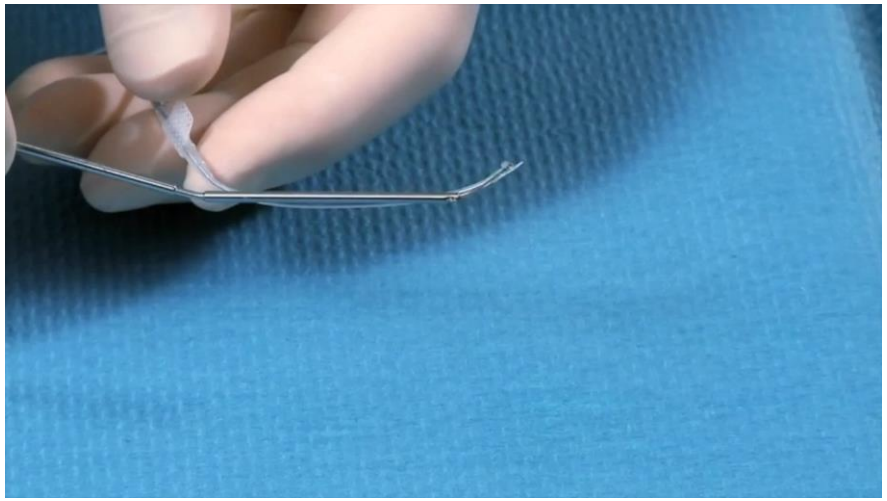
MECHANISM OF BAT



BENEFIT IN CLINICAL TRIALS

- NYHA class status ⇩
- NT-pro BNP level ⇩
- Cardiovascular events ⇩
- Quality of life ⇧
- VO2 peak ⇧

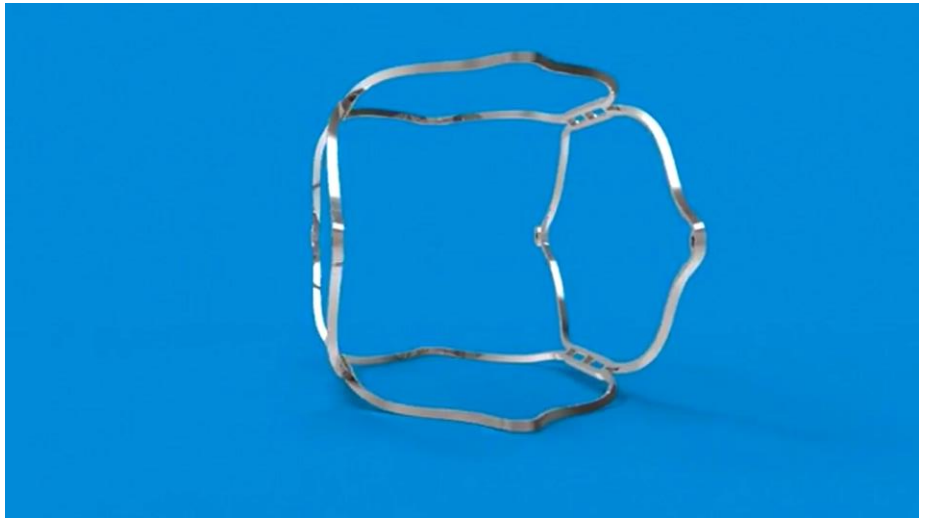


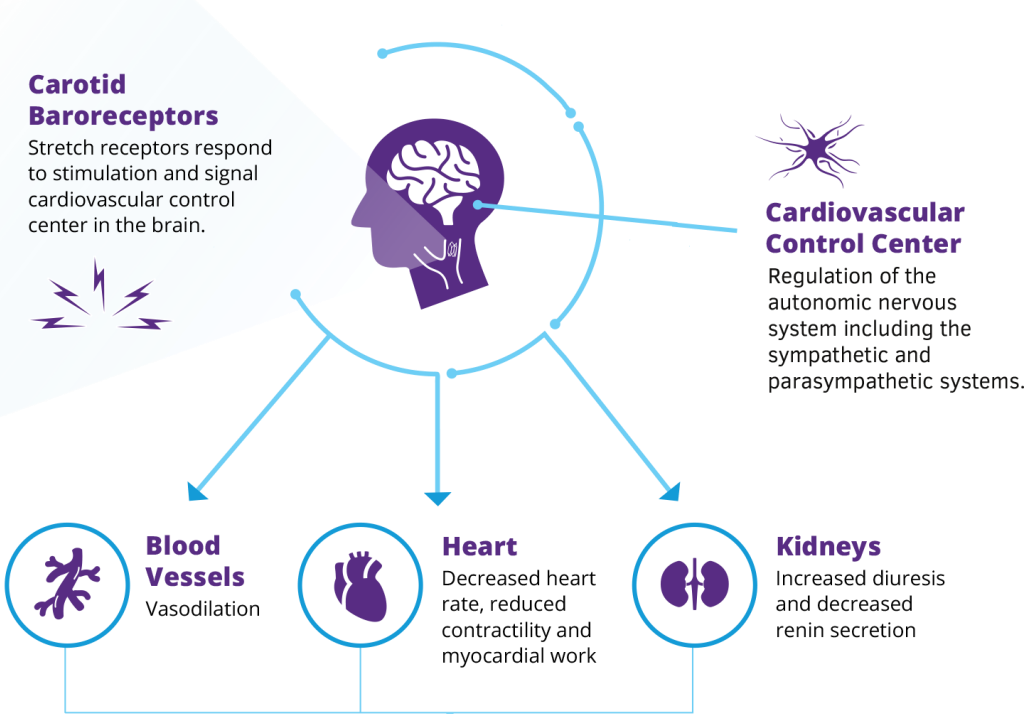


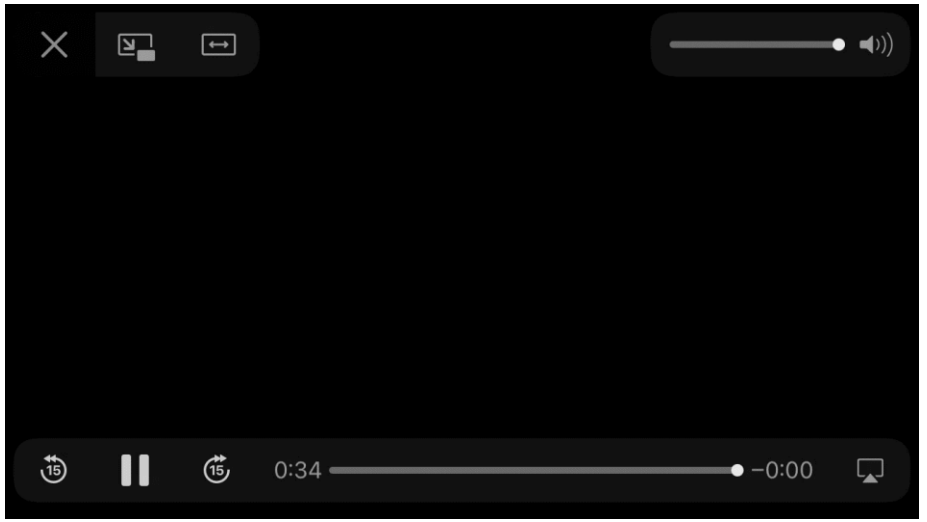
Reshaping Neuromodulation With the MobiusHD Device

The catheter-delivered MobiusHD device is a four-sided implant that reshapes the carotid sinus following its endovascular implantation. The implant-induced arterial stretch is intended to improve functional outcomes for heart failure patients by creating a sustainable amplification of the baroreflex while maintaining normal blood flow and pulsatility.

- Self-expanding, rectangular nitinol implant
- Reshapes the carotid artery without expansion
- Retains pulsatility
- Increases carotid artery strain/stretch
- Amplifies baroreceptor signals to CNS







Baroreflex Activation Therapy for the Treatment of Heart Failure With a Reduced Ejection Fraction

ABSTRACT

OBJECTIVES The objective of this clinical trial was to assess the safety and efficacy of carotid BAT in advanced HF.

BACKGROUND Increased sympathetic and decreased parasympathetic activity contribute to heart failure (HF) symptoms and disease progression. Baroreflex activation therapy (BAT) results in centrally mediated reduction of sympathetic outflow and increased parasympathetic activity.

METHODS Patients with New York Heart Association (NYHA) functional class III HF and ejection fractions ≤35% on chronic stable guideline-directed medical therapy (GDMT) were enrolled at 45 centers in the United States, Canada, and Europe. They were randomly assigned to receive ongoing GDMT alone (control group) or ongoing GDMT plus BAT (treatment group) for 6 months. The primary safety end point was system- and procedure-related major adverse neurological and cardiovascular events. The primary efficacy end points were changes in NYHA functional class, quality-of-life score, and 6-minute hall walk distance.

RESULTS One hundred forty-six patients were randomized, 70 to control and 76 to treatment. The major adverse neurological and cardiovascular event-free rate was 97.2% (lower 95% confidence bound 91.4%). Patients assigned to BAT, compared with control group patients, experienced improvements in the distance walked in 6 min (59.6 ± 14 m vs. 1.5 ± 13.2 m; $p = 0.004$), quality-of-life score (-17.4 ± 2.8 points vs. 2.1 ± 3.1 points; $p < 0.001$), and NYHA functional class ranking ($p = 0.002$ for change in distribution). BAT significantly reduced N-terminal pro-brain natriuretic peptide ($p = 0.02$) and was associated with a trend toward fewer days hospitalized for HF ($p = 0.08$).

CONCLUSIONS BAT is safe and improves functional status, quality of life, exercise capacity, N-terminal pro-brain natriuretic peptide, and possibly the burden of heart failure hospitalizations in patients with GDMT-treated NYHA functional class III HF. (Barostim Neo System in the Treatment of Heart Failure; NCT01471860; Barostim HOPE4HF [Hope for Heart Failure] Study; NCT01720160) (J Am Coll Cardiol HF 2015;3:487-96)

JACC: HEART FAILURE VOL. 3, NO. 6, 2015; JUNE 2015: 487–96

BAROSTIM HOPE4HF Trial

Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction

Michael R. Zile, MD,[a,b] JoAnn Lindenfeld, MD,[c] Fred A. Weaver, MD,[d] Faiez Zannad, MD,[e] Elizabeth Galle, MPH,[f] Tyson Rogers, MS,[g] William T. Abraham, MD[h]

ABSTRACT

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

OBJECTIVES The BeAT-HF (Baroreflex Activation Therapy for Heart Failure) trial was a multicenter, prospective, randomized, controlled trial; subjects were randomized 1:1 to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group).

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. (Baroreflex Activation Therapy for Heart Failure [BeAT-HF]; NCT02627196) (J Am Coll Cardiol 2020;76:1-13)

FDA approval in patients with advanced HF ineligible for CRT (August 2019)

Zile et al., J A C C VOL . 7 6 , N O . 1 , 2 0 2 0 J U L Y 7 , 2 0 2 0 : 1 – 1 3

BeAT-HF Trial

Who should receive BAT?

- Neither HOPE4HF nor BeAT-HF was adequately powered or had follow-up long enough to determine whether BAT reduced death or HF hospitalizations.

- On the basis of the results of the BeAT-HF trial, the FDA approved the Barostim neo system in 2019 for the improvement of symptoms of HF in patients in NYHA functional class III (or class II with a recent history of class III), LVEF ≤35%, and NT-proBNP <1,600 pg/mL who are not CRT candidates.

- The extended phase of BeAT-HF is ongoing, and the presentation of the morbidity and mortality results is expected in 2022.

Phrenic nerve stimulation (PNS)

Prevalence of Sleep Disordered Breathing in Cardiovascular Disease

- **30% of cardiac disease patients**

  Schafer et al, Cardiology 1999

- **50% of heart failure patients** (40% CSA; 11% OSA)

  Javaheri, Circulation 1998

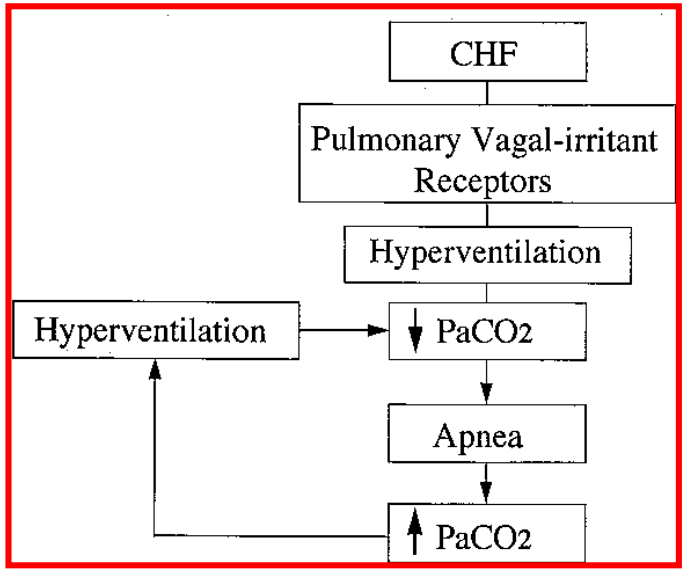
  - **40%** pts with systolic HF
  - **50%** pts with diastolic HF

- **30% of hypertensive patients**

  – **83%** of refractory hypertension

  Logan et al, J Hypertension 2001

Central Sleep Apnea/Cheyne-Stokes respiration: *mechanism*



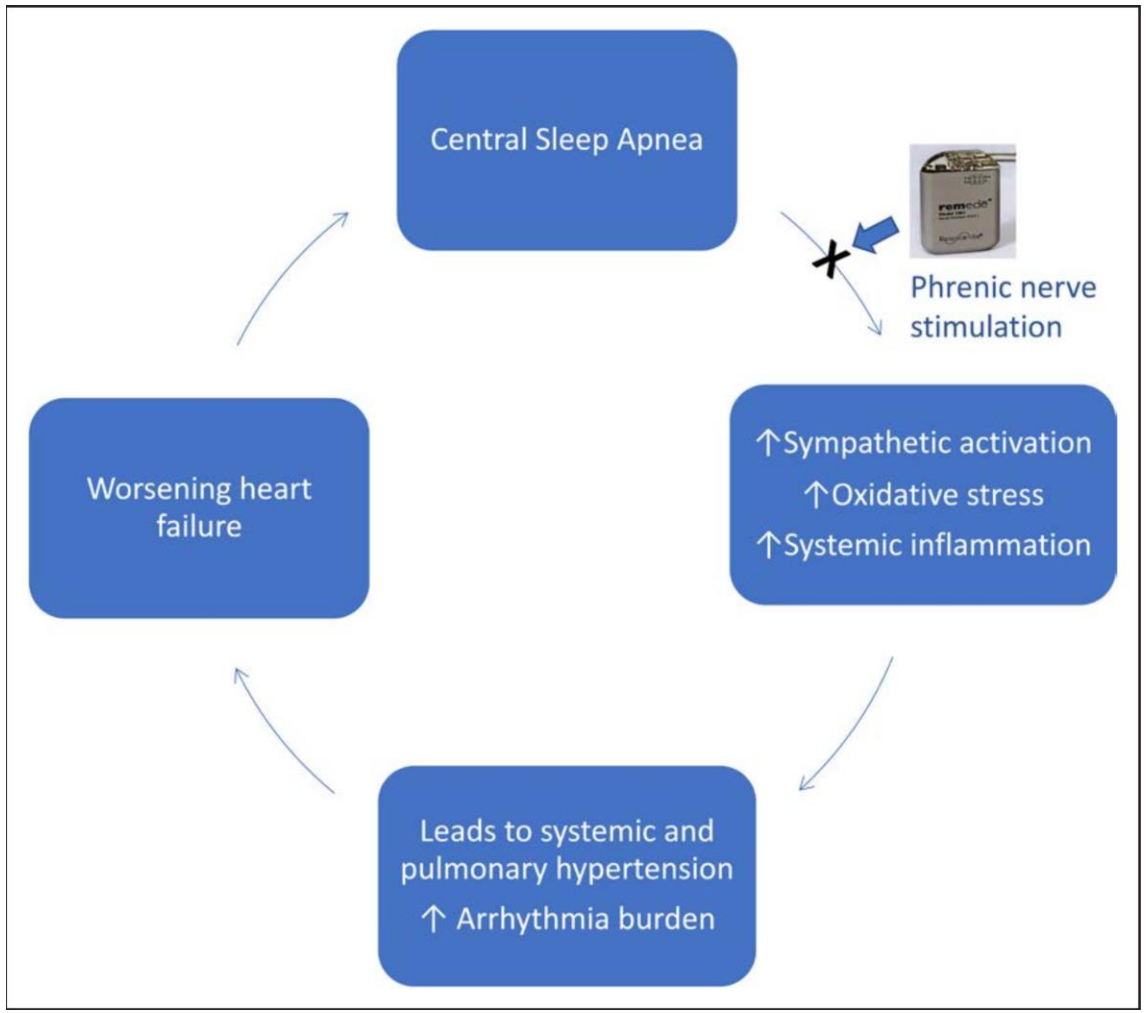
- CSA-CSR reflects derangements in ventilatory control mechanisms because of irritant receptor stimulation by pulmonary microvascular congestion (left atrial hypertension and decreased cardiac output), heart failure patients chronically hyperventilate, resulting in ***low blood carbon dioxide tensions during wakefulness***.

- The relative hypocapnia, together with a heightened chemoreflex response to carbon dioxid and prolonged circulation time, destabilize the ventilator control system during sleep and result in CSA-CSR.

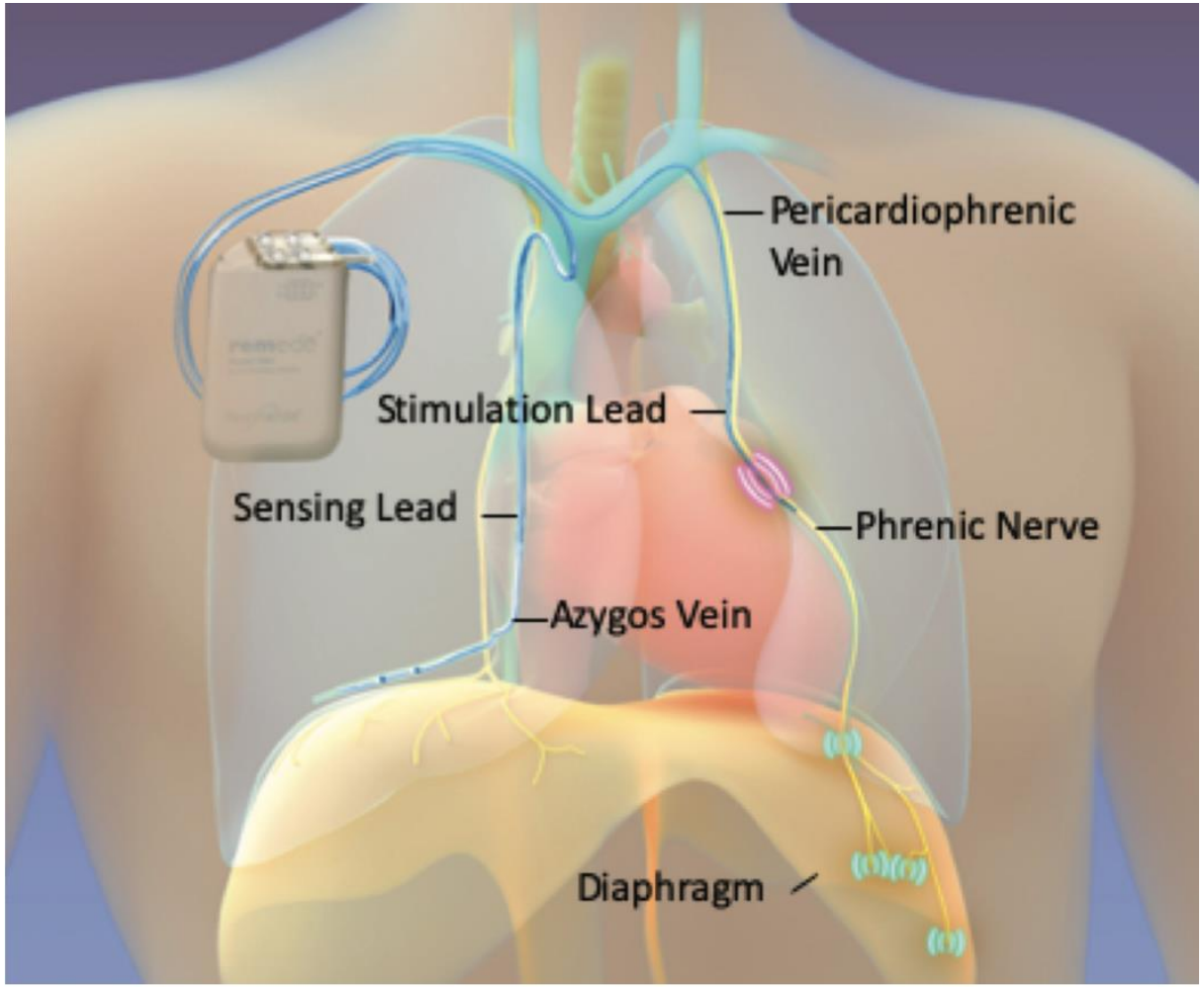
- As would be expected by these mechanisms, inhalation of a carbon dioxide– enriched gas abolishes CSA.

phrenic nerve stimulation

pathophysiology



Vein targets: left pericardiophrenic or right brachiocephalic



96 (64%) enrolled patients had previous heart failure

FDA approval in 2017 for CSA

- ***Apnea***: cessation of airflow that lasted at least 10 seconds,
- ***CSA:*** absence of airflow and thoracoabdominal movements
- ***OSA:*** absence of airflow in the presence of thoracoabdominal movements.
- ***Hypopnea***: ≥50% decrease in the sum of thoracoabdominal movements lasting ≥10 seconds, followed by a reduction in Sao_2 of at least 4%.
- ***Apnea-hypopnea index (AHI)*** is an assessment of sleep apnea severity based on the number of apnea and hypopnea events per hour of sleep

Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial

*Maria Rosa Costanzo, Piotr Ponikowski, Shahrokh Javaheri, Ralph Augostini, Lee Goldberg, Richard Holcomb, Andrew Kao, Rami N Khayat, Olaf Oldenburg, Christoph Stellbrink, William T Abraham, for the remedé System Pivotal Trial Study Group**

Lancet 2016; 388: 974–82

See Comment page 938

*Members of the remedé System Pivotal Trial Study Group are listed in the appendix

Advocate Heart Institute, Naperville, IL, USA (M R Costanzo MD); **Department of Heart Diseases, Medical University, Military Hospital, Wroclaw, Poland** (Prof P Ponikowski MD); **Bethesda North Hospital, Cincinnati, OH, USA** (Prof S Javaheri MD); **Ohio State University, Columbus, OH, USA** (R Augostini MD, R N Khayat MD, Prof W T Abraham MD); **University of Pennsylvania, Philadelphia, PA, USA** (L Goldberg MD); **Independent Biostatistician, Minneapolis, MN, USA** (R Holcomb PhD); **Mid America Heart Institute, Kansas City, MO, USA** (A Kao MD); **Bad Oeynhausen Heart and Diabetes Centre, Bad Oeynhausen, Germany** (Prof O Oldenburg MD); **and Bielefeld Medical Centre, Bielefeld, Germany** (Prof C Stellbrink MD)

Correspondence to Dr Maria Rosa Costanzo, Advocate Medical Group Midwest Heart Specialists, Edward Heart Hospital, Naperville, IL 60566, USA **mariarosa.costanzo@advocatehealth.com**

See Online for appendix

Summary

Background Central sleep apnoea is a serious breathing disorder associated with poor outcomes. The remedé system (Respicardia Inc, Minnetonka, MN, USA) is an implantable device which transvenously stimulates a nerve causing diaphragmatic contraction similar to normal breathing. We evaluated the safety and effectiveness of unilateral neurostimulation in patients with central sleep apnoea.

Methods We recruited patients from 31 hospital-based centres in Germany, Poland, and the USA in this prospective, multicentre, randomised trial. Participants had to have been medically stable for at least 30 days and have received appropriate guideline recommended therapy, be aged at least 18 years, be expected to tolerate study procedures, and willing and able to comply with study requirements. Eligible patients with an apnoea-hypopnoea index (AHI) of at least 20 events per h, tested by a polysomnography, underwent device implantation and were randomly assigned (1:1) by a computer-generated method stratified by site to either stimulation (treatment) or no stimulation (control) for 6 months. The primary effectiveness endpoint in the intention-to-treat population was the comparison of the proportions of patients in the treatment versus control groups achieving a 50% or greater AHI reduction from baseline to 6 months, measured by a full-night polysomnography assessed by masked investigators in a core laboratory. The primary safety endpoint of 12-month freedom from serious adverse events related to the procedure, system, or therapy was evaluated in all patients. This trial is active, but not recruiting, and is registered with ClinicalTrials.gov (NCT01816776).

Findings Between April 17, 2013, and May 28, 2015, we randomly assigned 151 eligible patients to the treatment (n=73) or control (n=78) groups. In the analysis of the intention-to-treat population, significantly more patients in the treatment group (35 [51%] of 68) had an AHI reduction from baseline of 50% or greater at 6 months than had those in the control group (eight [11%] of 73; difference between groups 41%, 95% CI 25–54, p<0·0001). 138 (91%) of 151 patients had no serious-related adverse events at 12 months. Seven (9%) cases of related-serious adverse events occurred in the control group and six (8%) cases were reported in the treatment group. Seven patients died (unrelated to implant, system, or therapy), four deaths (two in treatment group and two in control group) during the 6-month randomisation period when neurostimulation was delivered to only the treatment group and was off in the control group, and three deaths between 6 months and 12 months of follow-up when all patients received neurostimulation. 27 (37%) of 73 patients in the treatment group reported non-serious therapy-related discomfort that was resolved with simple system reprogramming in 26 (36%) patients, but was unresolved in one (1%) patient.

Interpretation Transvenous neurostimulation significantly reduced the severity of central sleep apnoea, including improvements in sleep metrics, and was well tolerated. The clinically meaningful effects of the therapy are supported by the concordant improvements in oxygenation and quality of life, making transvenous neurostimulation a promising therapeutic approach for central sleep apnoea.

ESC European Society of Cardiology

European Journal of Heart Failure (2018) **20**, 1746–1754
doi:10.1002/ejhf.1312

RESEARCH ARTICLE

Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure

Maria Rosa Costanzo[1]*, Piotr Ponikowski[2], Andrew Coats[3], Shahrokh Javaheri[4], Ralph Augostini[5], Lee R. Goldberg[6], Richard Holcomb[7], Andrew Kao[8], Rami N. Khayat[5], Olaf Oldenburg[9], Christoph Stellbrink[10], Scott McKane[11], and William T. Abraham[5], for the remedē® System Pivotal Trial Study Group

[1]Advocate Heart Institute, Naperville, IL, USA; [2]Medical University, Military Hospital, Wroclaw, Poland; [3]University of Warwick, Coventry, UK; [4]Bethesda North Hospital, Cincinnati, OH, USA; [5]The Ohio State University, Columbus, OH, USA; [6]University of Pennsylvania, Philadelphia, PA, USA; [7]Independent Biostatistician, Minneapolis, MN, USA; [8]Mid America Heart Institute, Kansas City, MO, USA; [9]Bad Oeynhausen Heart and Diabetes Center, Bad Oeynhausen, Germany; [10]Bielefeld Medical Center, Bielefeld, Germany; and [11]Respicardia, Inc., Minnetonka, MN, USA

Received 20 March 2018; revised 7 August 2018; accepted 9 August 2018; online publish-ahead-of-print 10 October 2018

Aims The presence of central sleep apnoea (CSA) is associated with poor prognosis in patients with heart failure (HF). The aim of this analysis was to evaluate if using phrenic nerve stimulation to treat CSA in patients with CSA and HF was associated with changes in HF-specific metrics.

Methods and results All patients randomized in the **rem**edē System Pivotal Trial and identified at baseline with HF were included ($n = 96$). Effectiveness data from treatment and former control groups were pooled based on months since therapy activation. Changes from baseline to 6 and 12 months in sleep metrics, Epworth Sleepiness Scale, patient global assessment health-related quality of life, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and echocardiographic parameters are reported. HF hospitalization, cardiovascular death, and the composite of HF hospitalization or cardiovascular death within 6 months are reported by the original randomized group assignment for safety assessment. Sleep metrics and quality of life improved from baseline to 6 and 12 months. At 12 months, MLHFQ scores changed by -6.8 ± 20.0 ($P = 0.005$). The 6-month rate of HF hospitalization was 4.7% in treatment patients (standard error = 3.3) and 17.0% in control patients (standard error = 5.5) ($P = 0.065$). Reported adverse events were as expected for a transvenous implantable system.

Conclusions Phrenic nerve stimulation reduces CSA severity in patients with HF. In parallel, this CSA treatment was associated with benefits on HF quality of life.

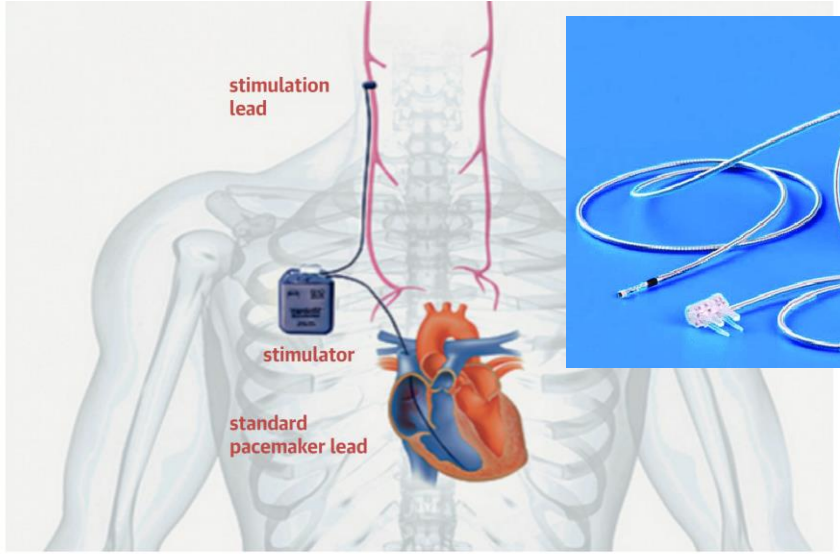
- improvement in sleep metrics
- reduction in the severity of CSA
- improvement in both sleep and HF-specific quality of life measures
- Small increase in LV systolic function
- **No difference in cardiovascular mortality or time-to-first HF hospitalization**

Current Ongoing Large-Scale Studies in PNS With Outcomes Being Evaluated in HF Patients

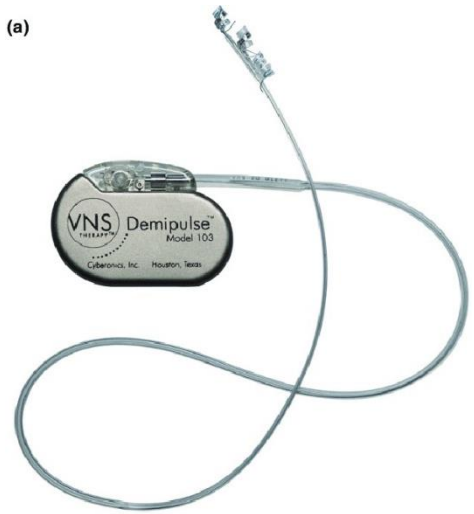
Primary investigator	Title	Study start date	Research question	Design	Estimated n	Outcome measure
13 at multiple centers[92]	Remedē System Therapy Study	June 2019	Postmarket registry of safety and effectiveness of PNS in patients with central sleep apnea; selected outcomes evaluate effectiveness in HF patients	Observational cohort, prospective study	500	Primary: (1) serious adverse device events; (2) change in Apnea-Hypopnea Index; (3) change in ESS, PGA, and PROMIS-29 at 6 mo; (4) change in KCCQ at 6 mo; (5) change in LVEF in patients with HF

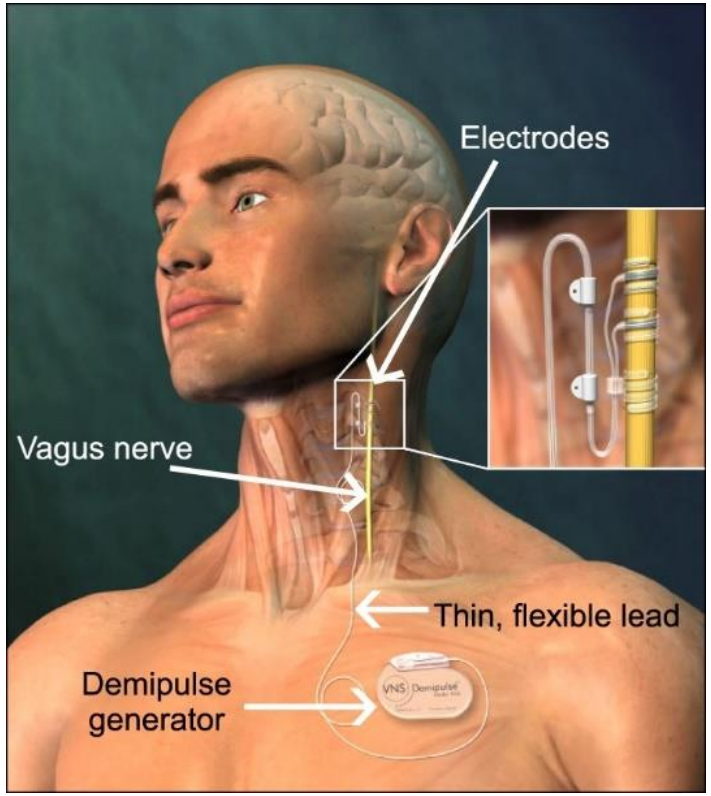
Estimated Study Completion Date : April 15, 2027

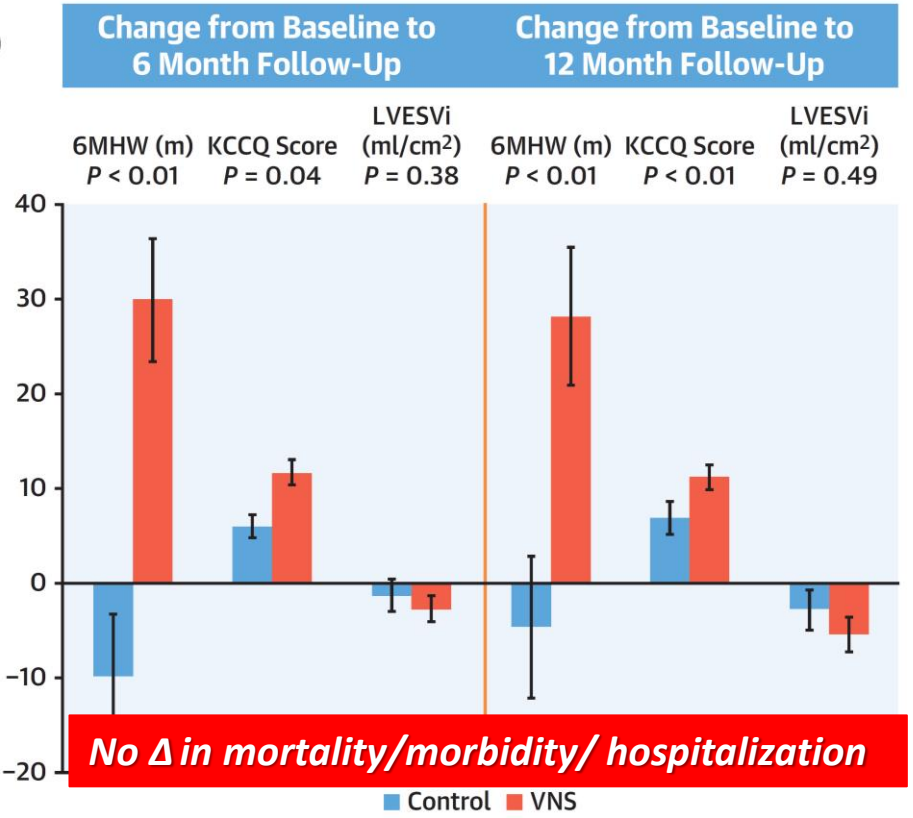
vagal nerve stimulation (VNS)



VNS





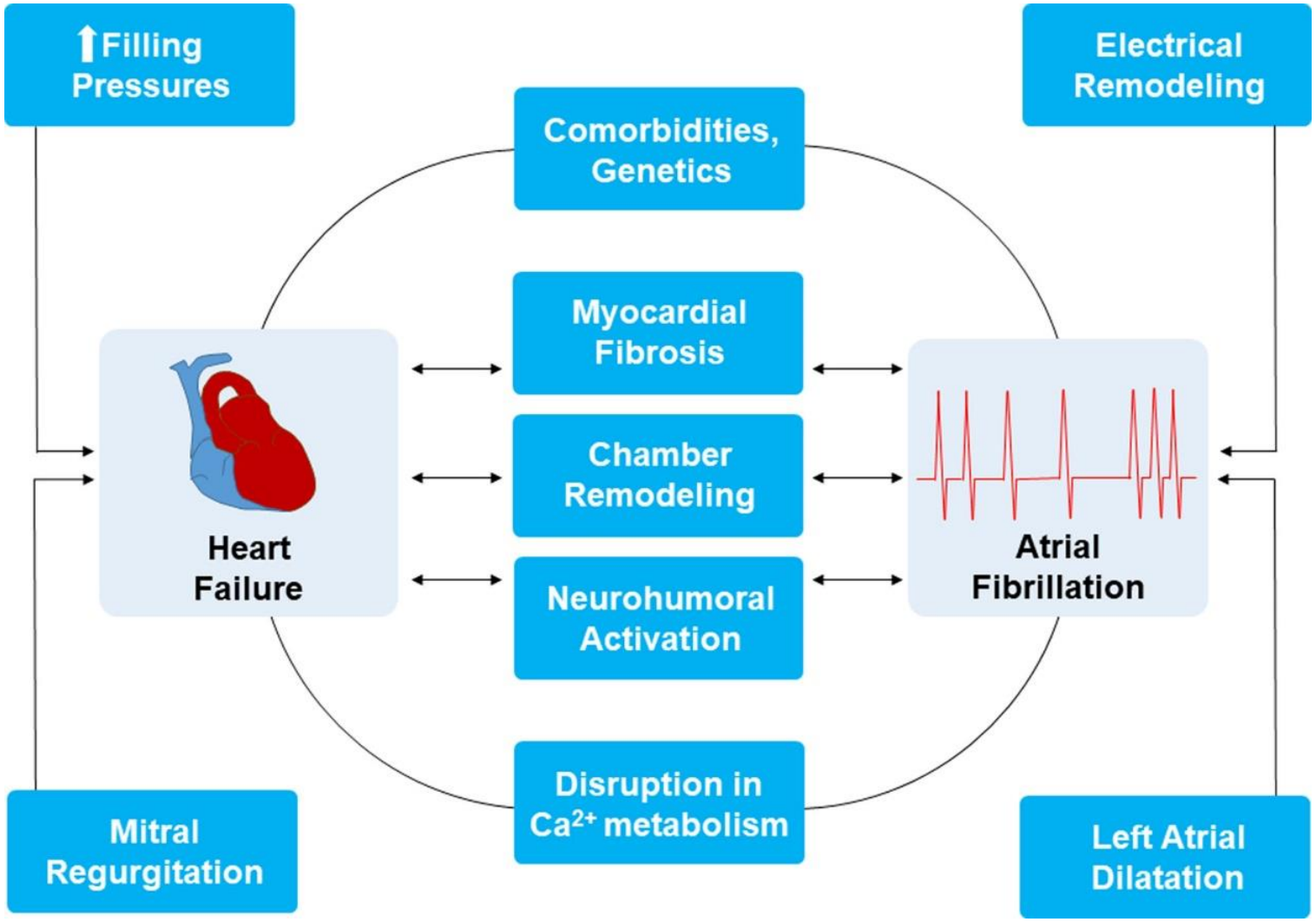


- **ANTHEM-HF** (Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure) study-completed
- **INOVATE-HF** (Increase of Vagal Tone in Heart Failure) study-completed
- **NECTAR-HF** (Neural Cardiac Therapy for Heart Failure) study-completed

- **ANTHEM-HFrEF** (Autonomic Regulation Therapy to Enhance Myocardial Function and Reduce Progression of Heart Failure with Reduced Ejection Fraction)-ongoing
- **ANTHEMHFpEF** (Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Patients with Heart Failure and Preserved Ejection Fraction)-ongoing

Thank You!

Additional slides



Rakesh Gopinathannair. Circulation: Arrhythmia and Electrophysiology. Managing Atrial Fibrillation in Patients With Heart Failure and Reduced Ejection Fraction: A Scientific Statement From the American Heart Association, Volume: 14, Issue: 7, DOI: (10.1161/HAE.0000000000000078)

Summary of AF Ablation Trials in HFrEF (Completed)

Study	Sample size, n	Population characteristics			Comparison arm	Follow-up, mo	Primary end point	Primary results
		LVEF, %	NYHA class	AF/device				
PABA-CHF[56]	81	≤40	II–III	Persistent/ paroxysmal	Ablation vs AVN ablation with bi-ventricular pacing	6	Composite of LVEF, 6MWD, and MLWHF score	CA was superior to AVN ablation with biventricular pacing.
MacDonald et al[57]	41	<35	II–IV	Persistent	CA vs rate control	6	LVEF change with CMR	No significant differences between treatment groups.
ARC-HF[58]	52	≤35	II–IV	Persistent	CA vs rate control	12	Peak VO_2	CA improved peak VO_2.
CAMTAF[10]	50	<50	II–IV	Persistent	CA vs rate control	12	LVEF change	CA improved LV function compared with rate control.
AATAC[8]	203	≤40	II–III	Persistent ICD/CRT-D	CA vs amioda-rone	36	AF recurrence	Ablation was superior to amiodarone in terms of rhythm control and im-provement in LV dysfunction.
CAMERA-MRI[11]	68	≤45	II–IV	Persistent	CA vs rate control	6	LVEF change	Ablation resulted in improvement in LVEF.
CASTLE-AF[9]	363	≤35	II–IV	Persistent; ICD/CRT-D	CA vs medical therapy (rate control or AADs)	60	Composite of all-cause mortality and HF hospital-ization	CA was superior to conventional medical treatment of either rate or rhythm control.
AMICA[59]	202	≤35	II–III	Persistent/ long-standing persistent	CA vs medical treatment	12	LVEF change	No significant differences between treatment groups.

AlTurki et al. BMC Cardiovascular Disorders (2019) 19:18
https://doi.org/10.1186/s12872-019-0998-2

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials

Ahmed AlTurki[1], Riccardo Proietti[2], Ahmed Dawas[1], Hasan Alturki[3], Thao Huynh[1] and Vidal Essebag[1,4*]

Abstract

Background: Previous randomized controlled trials (RCT)s showed similar outcomes in patients with atrial fibrillation (AF) and heart failure with reduced ejection fraction (HFrEF) treated with anti-arrhythmic drugs (AAD) compared to rate control therapy. We sought to evaluate whether catheter ablation is superior to medical therapy in patients with AF and HFrEF.

Methods: We searched electronic databases for all RCTs that compared catheter ablation and medical therapy (with or without use of AAD). We used random-effects models to summarize the studies. The primary end-point was all-cause mortality. Secondary outcomes included heart failure-related hospitalizations and change in left ventricular ejection fraction (LVEF).

Results: We retrieved and summarized 7 randomized controlled trials, enrolling 856 patients (429 in the catheter ablation arm and 427 in the medical therapy arm). Compared with medical therapy (including use of AAD), AF catheter ablation was associated with a significant reduction in mortality (risk ratio 0.50; 95% confidence interval [CI]: 0.34 to 0.74; $P = 0.0005$) and heart failure-related hospitalizations (risk ratio 0.56; 95% CI: 0.44 to 0.71; $P < 0.0001$). Furthermore, catheter ablation led to significant improvements in LVEF (weighted mean difference, 7.48; 95% CI: 3.71 to 11.26; $P < 0.0001$).

Conclusions: Compared to medical therapy, including use of AAD, catheter ablation for AF was associated with a significant reduction in mortality and heart failure-related hospitalizations as well as an improvement in LVEF in patients with HFrEF. Larger trials are needed to confirm whether rhythm control with ablation is superior to rate control in patients with AF and heart failure.

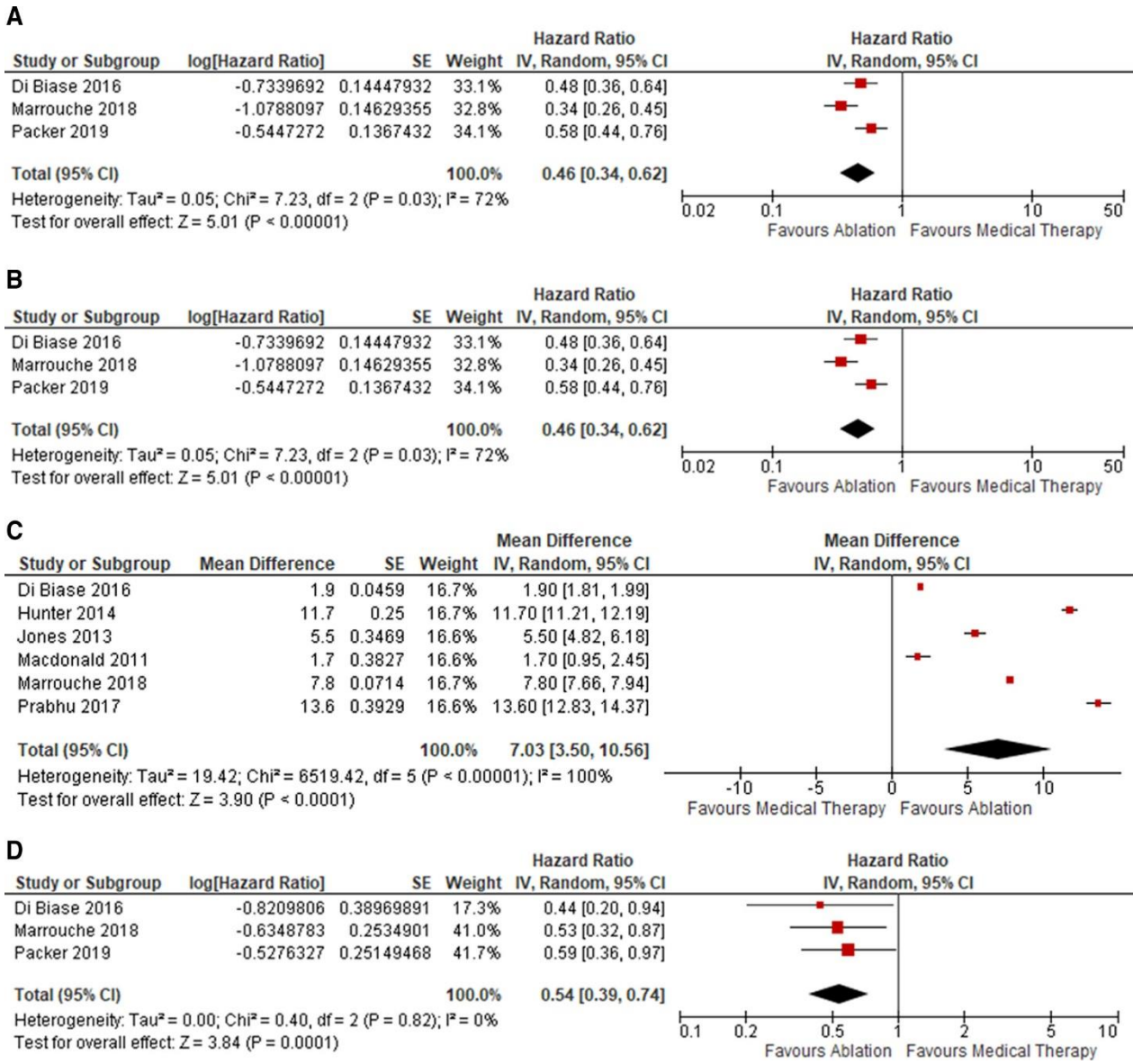
Keywords: Catheter ablation, Atrial fibrillation, Heart failure

AF recurrence

HF hospitalization

Change in LVEF

All cause mortality

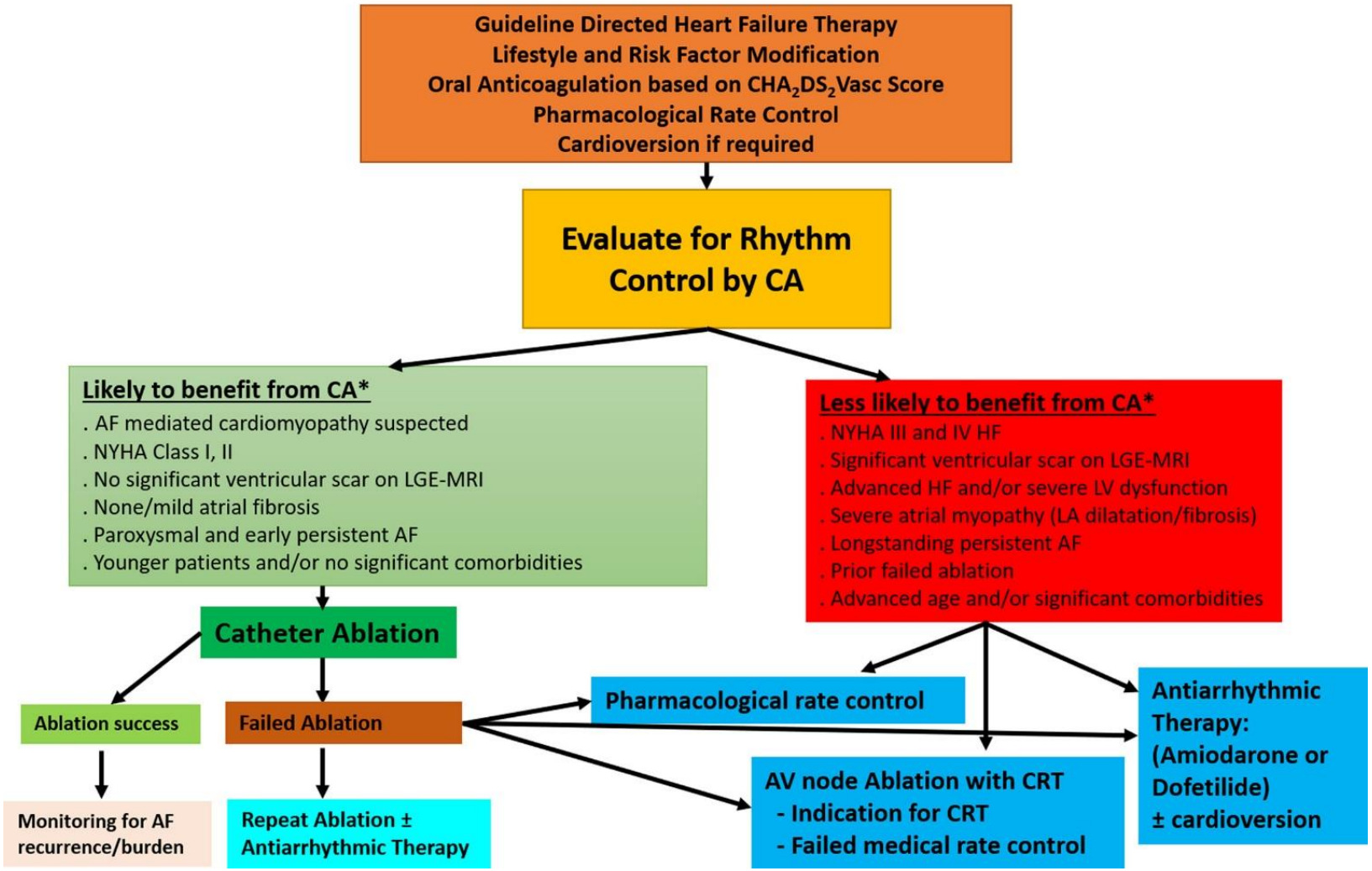


Rakesh Gopinathannair. Circulation: Arrhythmia and Electrophysiology. Managing Atrial Fibrillation in Patients With Heart Failure and Reduced Ejection Fraction: A Scientific Statement From the American Heart Association, Volume: 14, Issue: 7, DOI: (10.1161/HAE.0000000000000078)

Ongoing Clinical Trials Assessing Utility of Ablation in Patients With AF and HFrEF

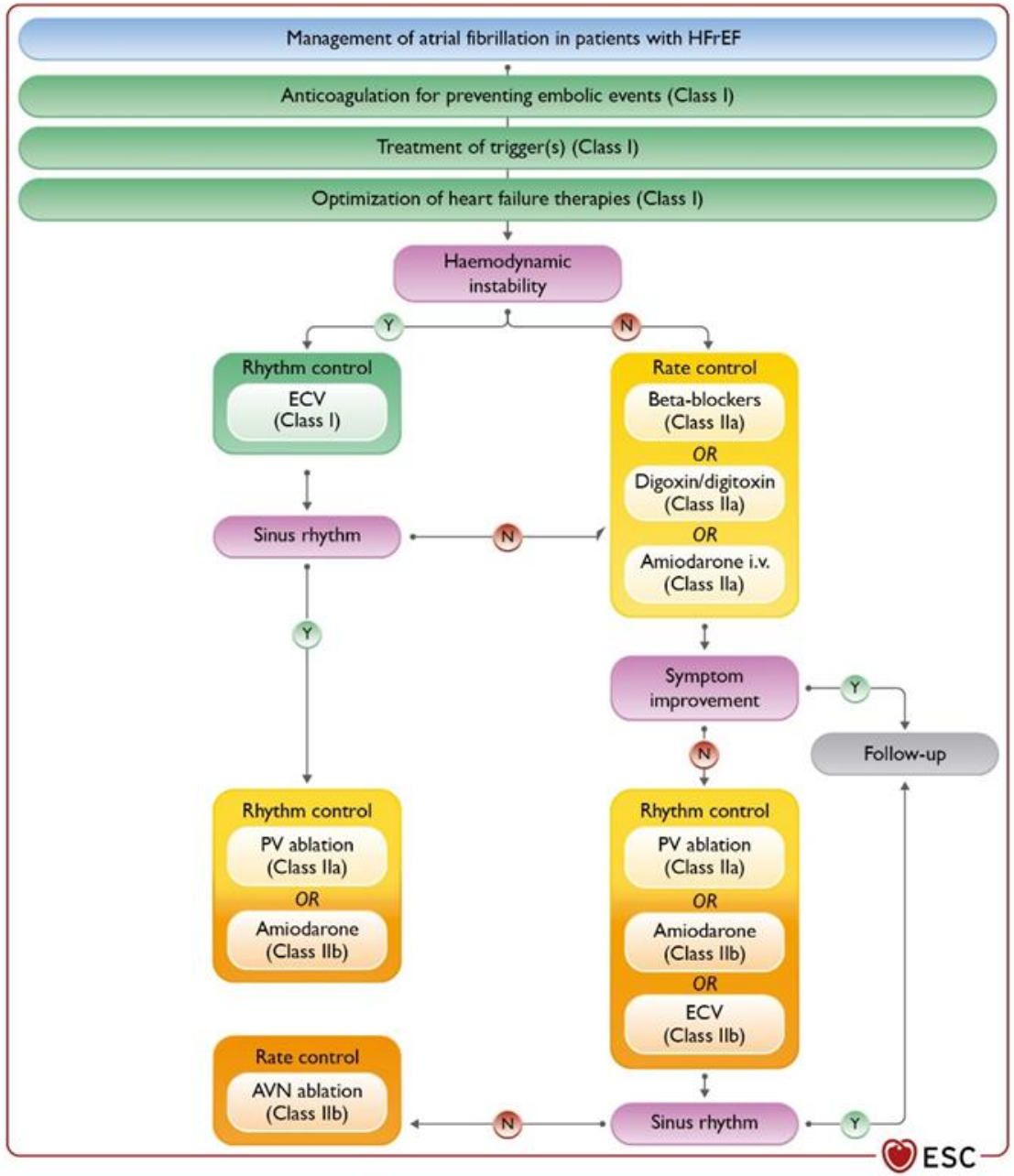
Study	ClinicalTrial.gov identifier	Status	Description	Primary outcome
CONTRA-HF	NCT03062241	Recruiting	Cryoablation vs pharmacological therapy in patients with AF and HF with implanted ICD or CRT-D	Composite of hospitalization for worsening HF, mortality, use of mechanical LV support, and heart transplantation
RAFT-AF	NCT01420393	Active, not recruiting	CA vs rate control to achieve a resting HR <80 bpm and 6-min walk HR <110 bpm	Composite of all-cause mortality and HF hospitalization
AFARC-LVF	NCT02509754	Not yet recruiting	CA vs rate control with device implantation±AVN ablation in patients with AF and HF	Composite of the improvement of LVEF >35% and concomitant NYHA class lower than II
RACE-8-HF	NCT04342832	Recruiting	Cryoablation vs standard medical care in patients with paroxysmal or persistent AF and HF (LVEF <40%)	Composite of all-cause mortality, unplanned cardiovascular hospitalizations, and stroke

Management of AF in HFrEF



Rakesh Gopinathannair. Circulation: Arrhythmia and Electrophysiology. Managing Atrial Fibrillation in Patients With Heart Failure and Reduced Ejection Fraction: A Scientific Statement From the American Heart Association, Volume: 14, Issue: 7, DOI: (10.1161/HAE.0000000000000078)

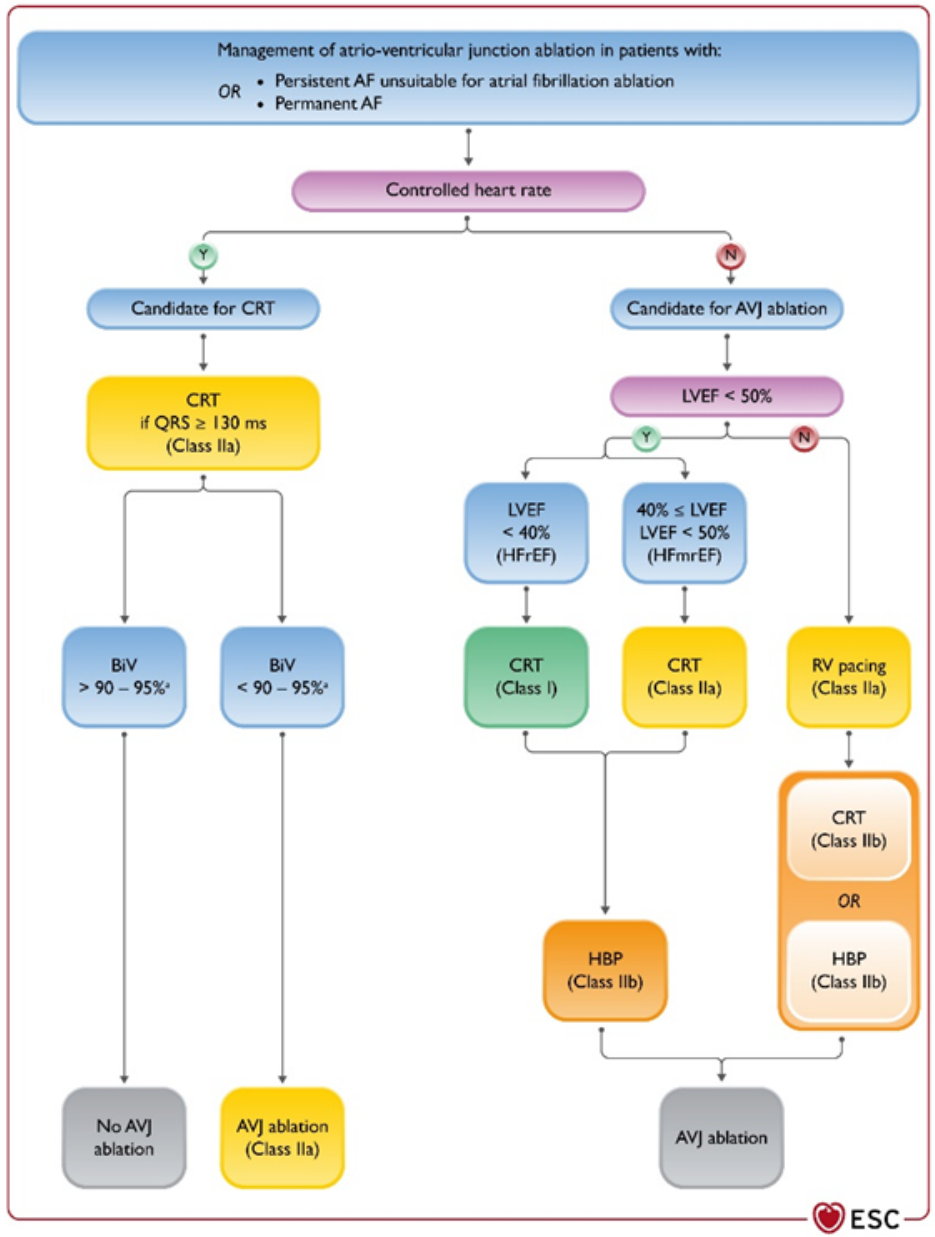
Management of atrial fibrillation in patients with heart failure



AF = atrial fibrillation; AVN = atrioventricular node; ECV = electrical cardioversion; HF = heart failure; i.v. = intravenous; PV = pulmonary vein.
Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa; Orange for Class of recommendation IIb; Red for Class of recommendation III (see Table 1 for further details on classes of recommendation).

www.escardio.org/guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)



Indication for atrioventricular junction ablation in patients with symptomatic permanent atrial fibrillation or persistent atrial fibrillation unsuitable for atrial fibrillation ablation

AF = atrial fibrillation; AVJ = atrioventricular junction; BiV = biventricular; CRT = cardiac resynchronization therapy; ESC = European Society of Cardiology; HBP = His bundle pacing; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; QRS = Q,R, and S waves; RV = right ventricular/right ventricle.

[a] Due to a rapid ventricular response.

Note: Figure based on the recommendations in the ESC guidelines on AF.

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab364)

Recommendations for using His bundle pacing (1)

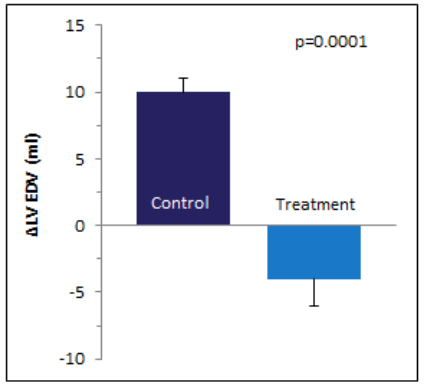
Recommendations	Class	Level
In patients treated with HBP, device programming tailored to specific requirements of HBP is recommended.	I	C
In CRT candidates in whom coronary sinus lead implantation is unsuccessful, HBP should be considered as a treatment option along with other techniques such as surgical epicardial lead.	IIa	B
In patients treated with HBP, implantation of a RV lead used as "backup" for pacing should be considered in specific situations (e.g. pacemaker-dependency, high-grade AVB, infra-nodal block, high pacing threshold, planned AVJ ablation) or for sensing in case of issues with detection (e.g. risk of ventricular undersensing or oversensing of atrial/His potentials).	IIa	C

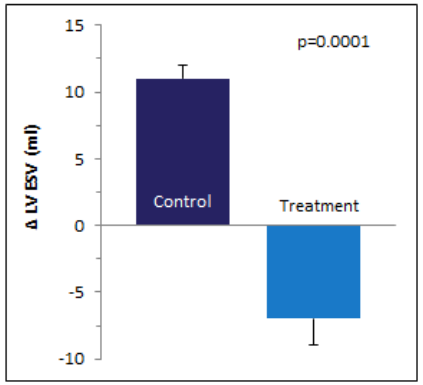
AVB = atrioventricular block; AVJ = atrioventricular junction; CRT = cardiac resynchronization therapy; HBP = His bundle pacing; LVEF = left ventricular ejection fraction; RV = right ventricular.

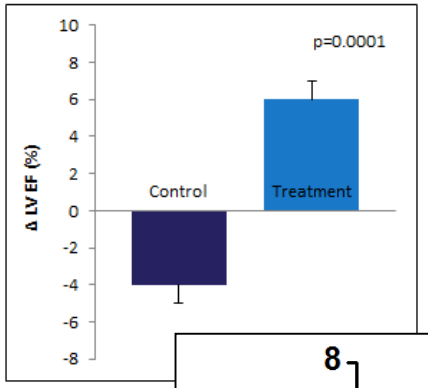
2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab364)

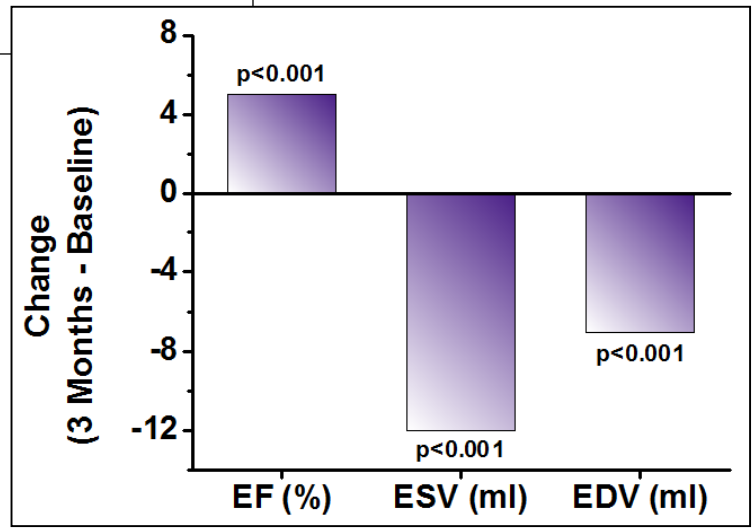
Cardiac Contractility Modulation Produces LV Reverse Remodeling

3D Echo studies in humans and ventriculography studies in animals demonstrate reverse remodeling within 3 months of initiating CCM therapy





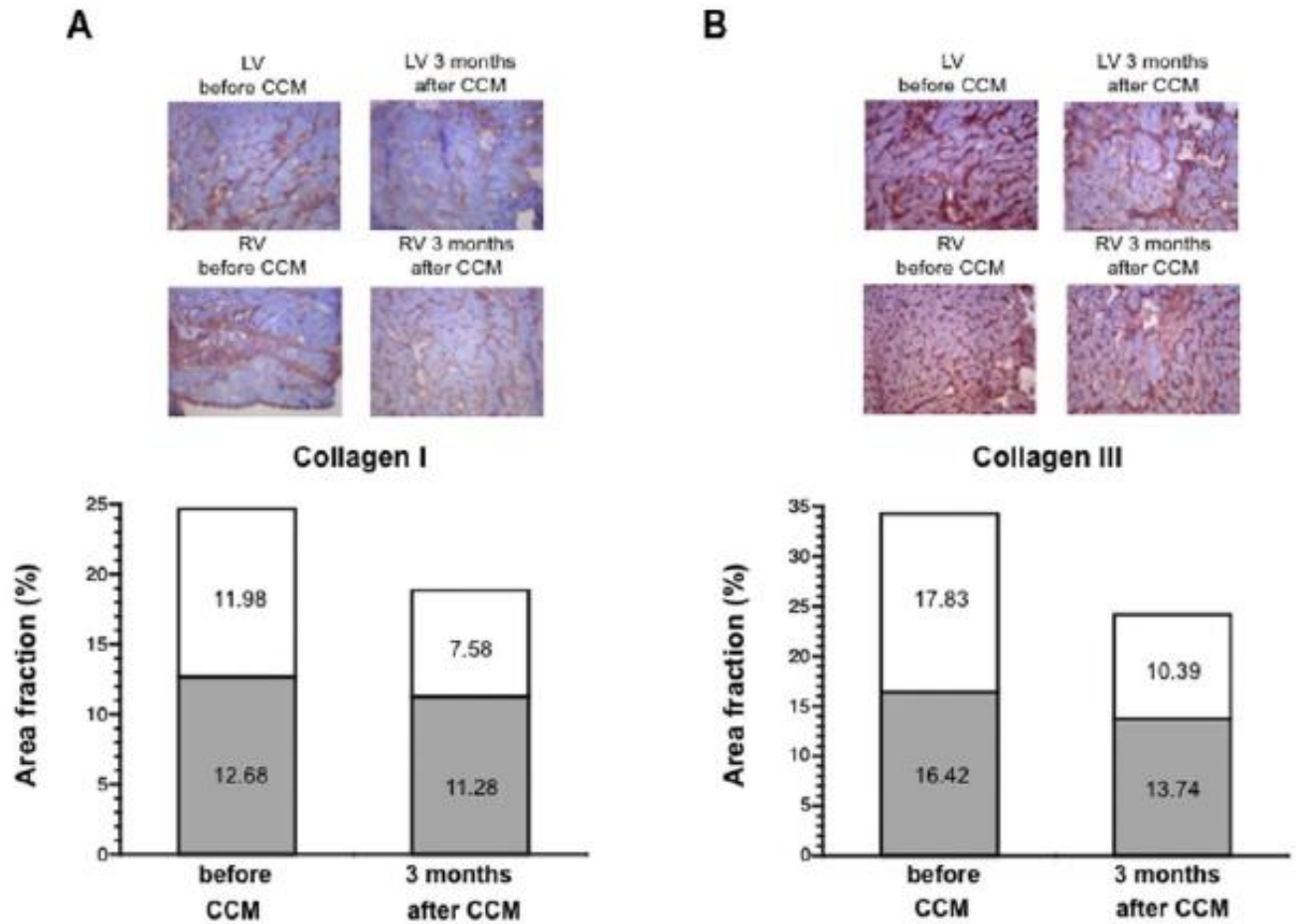




Yu et al. JACC Cardiovascular Imaging 2009

Imai et al. JACC 2007

CCM Reduces Cardiac Fibrosis



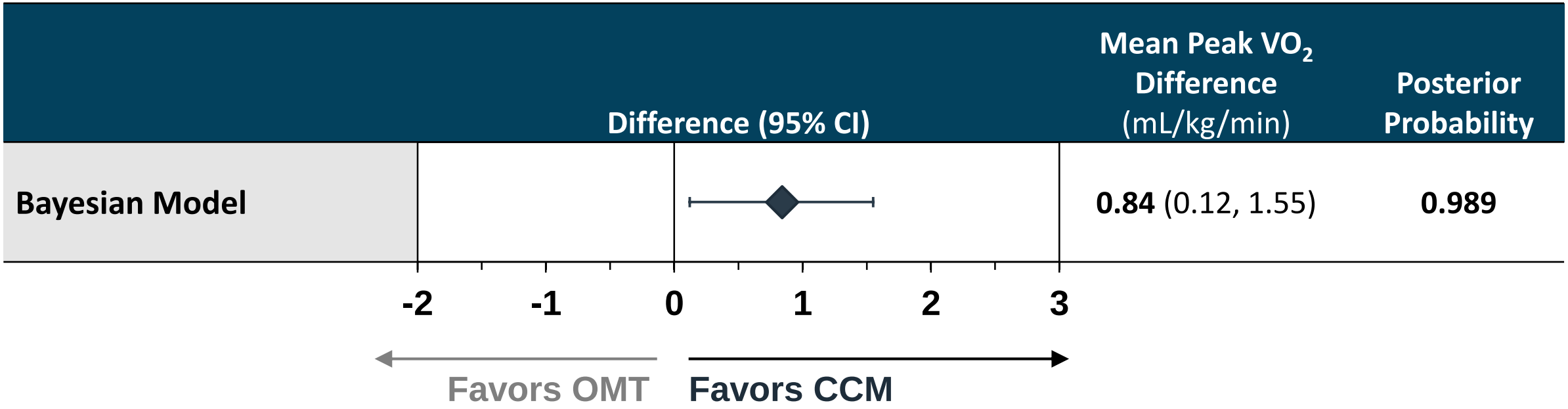
Tschöpe C, et al. J Cardiol. 203 2016

Randomized Controlled CCM Trials Prior to FIX-HF-5C

- Three randomized studies showed significant impact on exercise tolerance and quality of life:
  - FIX-CHF-4 (n=164; randomized, double-blinded; EU)
  - FIX-HF-5 Feasibility (n=50; randomized, double-blinded; US)
  - FIX-HF-5 (n=428; randomized; US)
- Peak VO2 endpoint consistently positive across trials
- Pre-specified subgroup analyses of FIX-HF-5 demonstrated greatest benefits in patients with heart failure and mildly to moderately reduced ejection fractions ranging from 25% to 45%[1]

[1]Abraham WT, et al. J Card Fail 2011; 17:710-717.

Cardiac Contractility Modulation Significantly Improves Peak VO_2

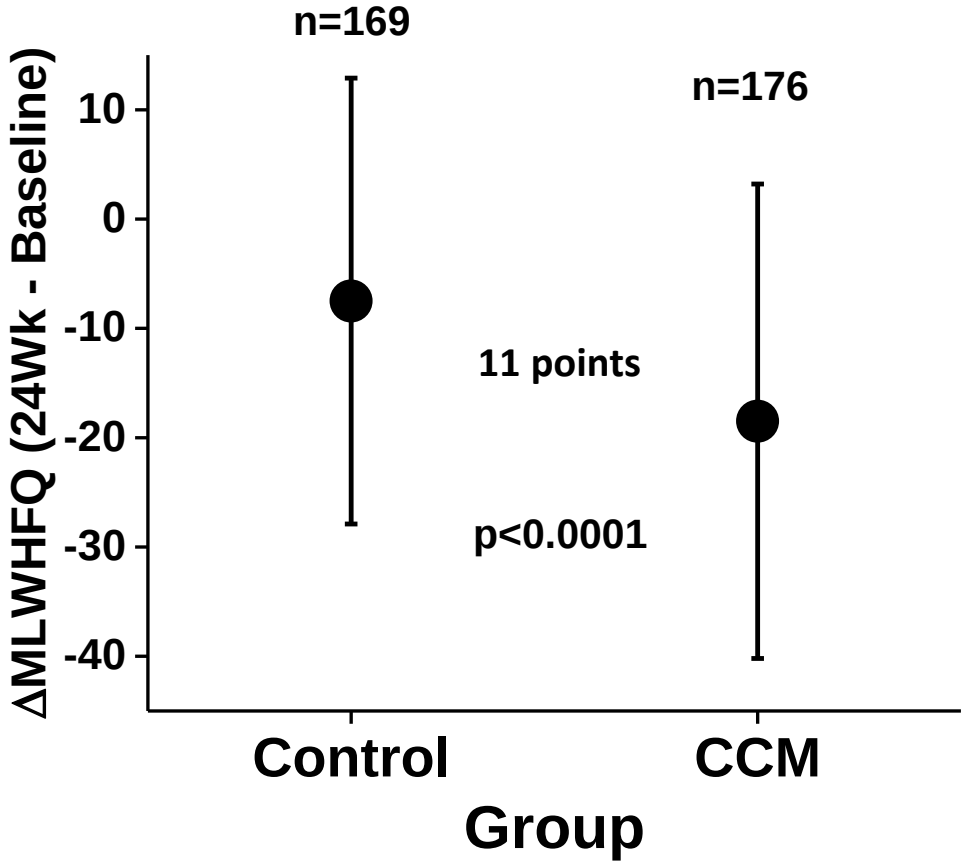


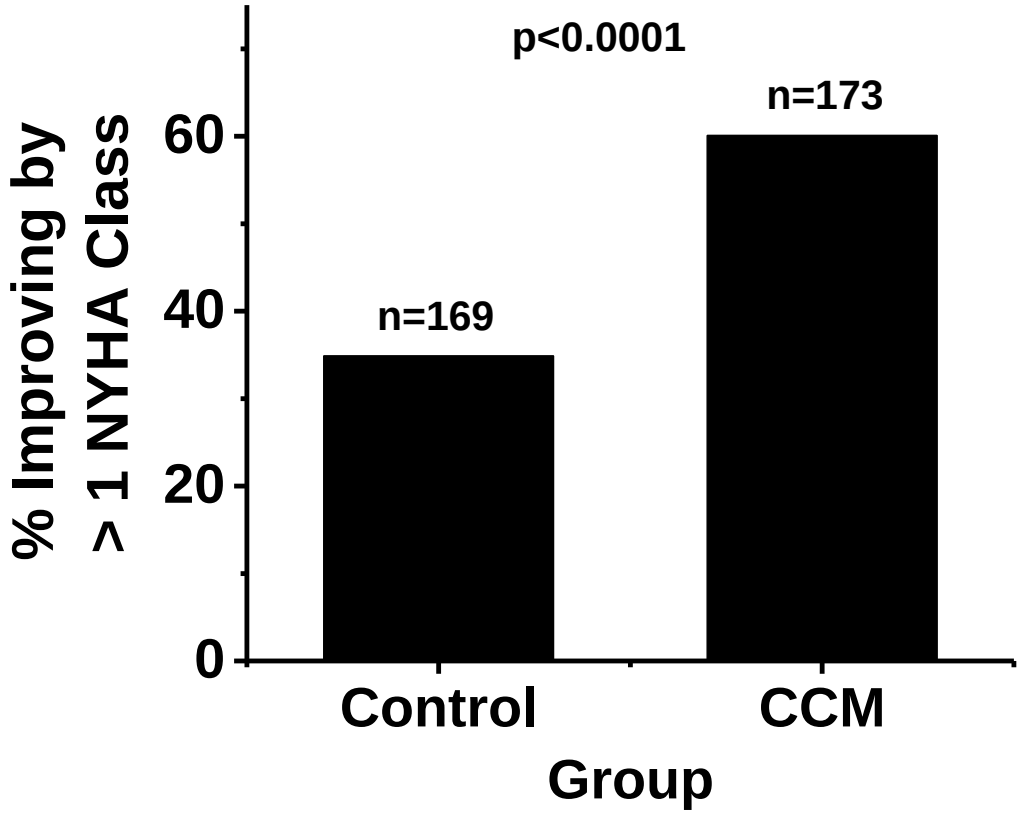
- Success = Posterior Probability > 0.975

Abraham WT, et al. JACC Heart Failure 2018; 6:874-883.

FIX-HF-5C Secondary Efficacy Endpoints

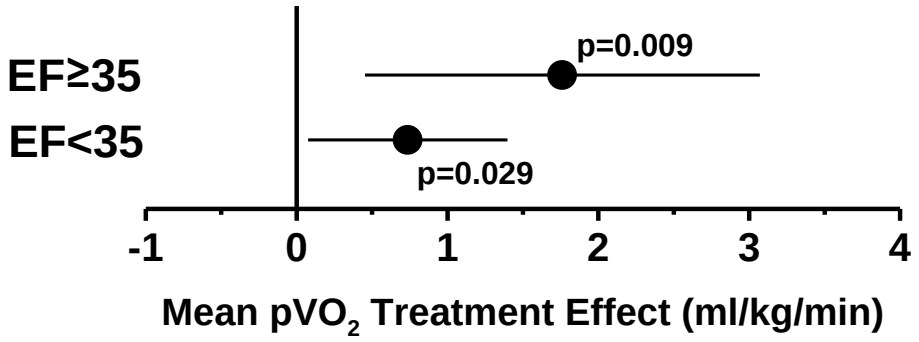
CCM Significantly Improves QoL and Functional Status

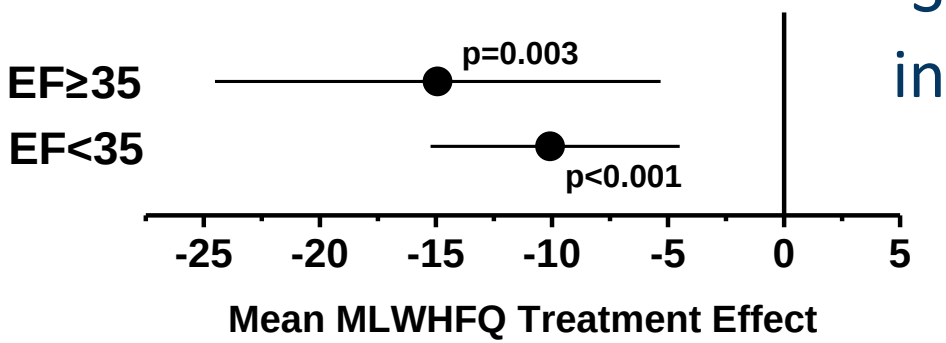


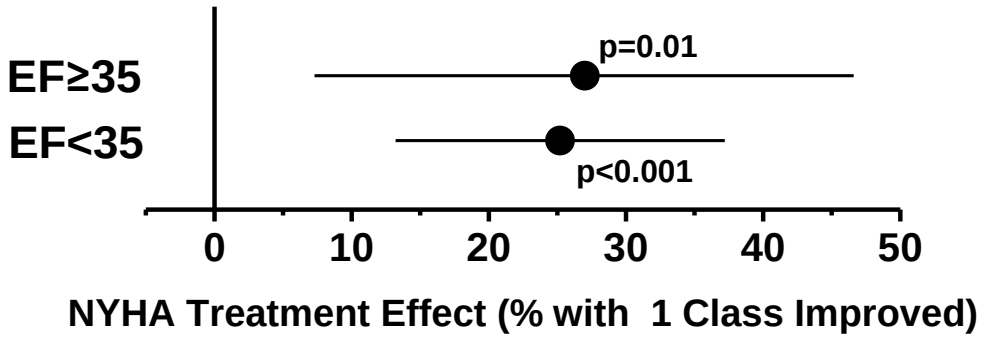


Abraham WT, et al. JACC Heart Failure 2018; 6:874-883.

Pre-specified Subgroup Analysis by LVEF







Significant clinical effects in both HFrEF and HFmrEF patients

Abraham WT, et al. JACC Heart Failure 2018; 6:874-883.

Conclusions: Cardiac Contractility Modulation

- Based on the totality of clinical data in NYHA Class III heart failure patients with HFrEF and HFmrEF (LVEF ranging from 25% to 45%), CCM:
  - Improves exercise capacity, quality of life, and functional status
  - Shows strong trends toward improved morbidity and mortality, especially reduction in heart failure hospitalizations
  - Has an acceptable rate of device/procedure-related complications, similar to CRT
- Effects are seen in both HFrEF and HFmrEF groups
- CCM is a valuable addition to our armamentarium for the treatment of heart failure, especially in HFmrEF where no effective drug or device therapies exist

Cardiac Contractility Modulation
Current Regulatory Status

- CE Marked and commercially available in many countries around the world
  - Extensive post-market experience in European Union
- FDA approved CCM on March 21, 2019
  - “The OPTIMIZER Smart System, which delivers CCM therapy, is indicated to improve 6-minute hall walk distance, quality of life, and functional status of NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for CRT, and have an LVEF ranging from 25% to 45%”

Cardiac Contractility Modulation: Frequently Asked Questions

- Who prescribes the therapy?:
  - Anyone who takes care of NYHA Class III heart failure patients
- Who implants the device/performs the procedure?
  - Electrophysiologists and those skilled in cardiac implantable electronic device implantation
- What is next for this therapy?
  - Development of a combined CCM-ICD device
  - Expansion of indication to other heart failure populations
- Who should really receive this device?
  - Heart failure patients with NYHA Class III symptoms despite optimally-tolerated guideline directed medical therapy, who are not candidates for CRT