CONTRACTILITY REIMAGINED: THE EXPANDING ROLE OF CCM

April 16, 2026

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Cardiovascular Institute

NO DISCLOSURES

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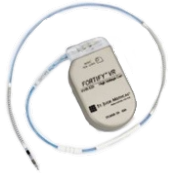
DEVICE THERAPY FOR HFREF – THE JOURNEY

1st AICD approved

ICD for 1° prevention



Transvenous leads

1985 1996 2021

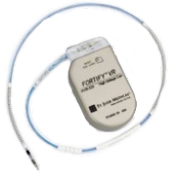
Protection from SCD

DEVICE THERAPY FOR HFREF –THE JOURNEY

New device options for HFrEF patients with narrow QRS

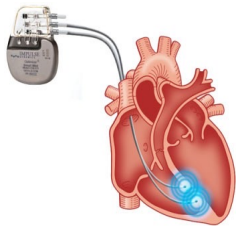
1st AICD approved

ICD for 1o prevention



Transvenous leads

1st CRT-D approved



BAT

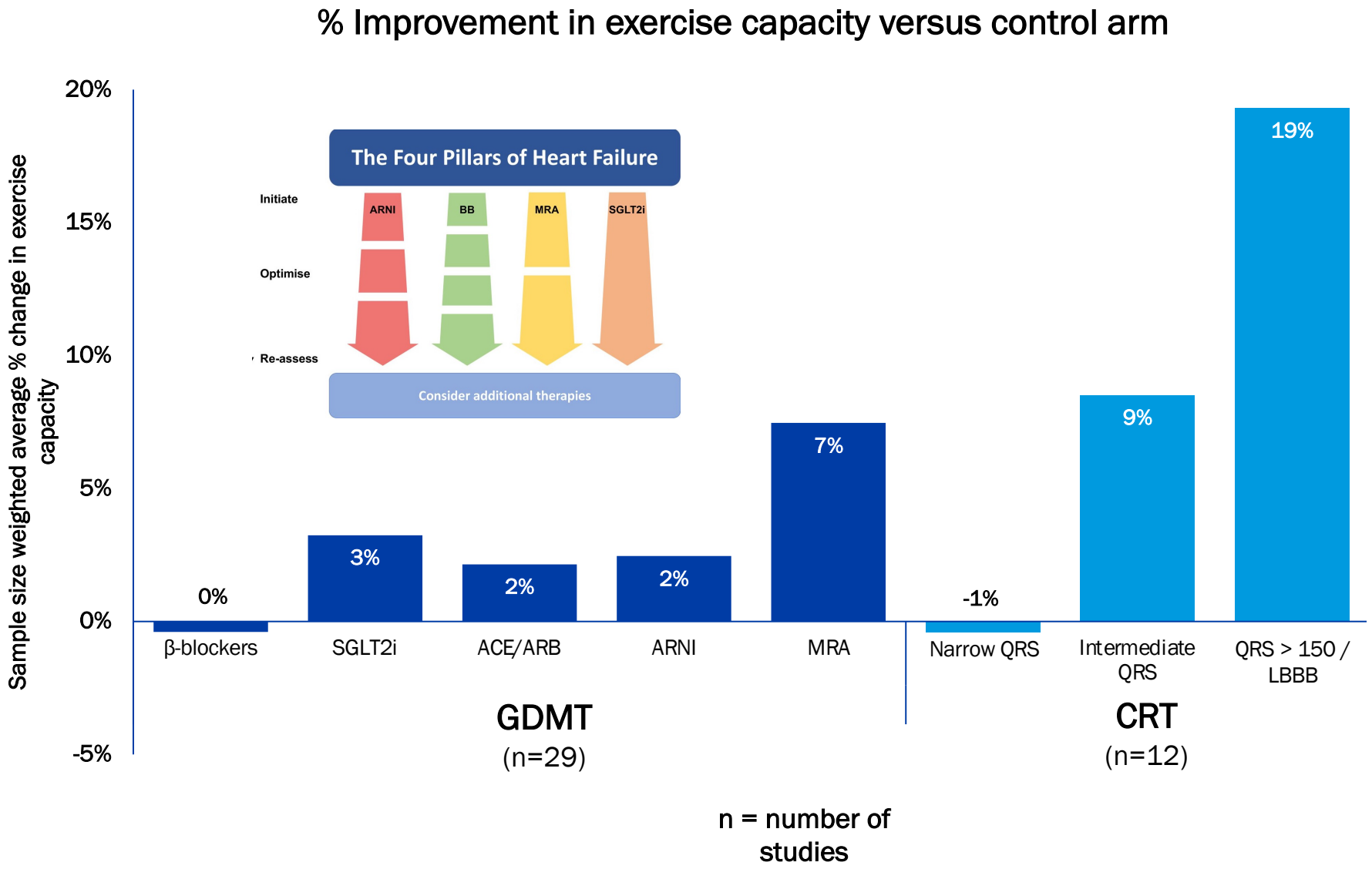
1985 1996 2002 2019 2021

Protection from SCD

Improve HF symptoms For wide QRS

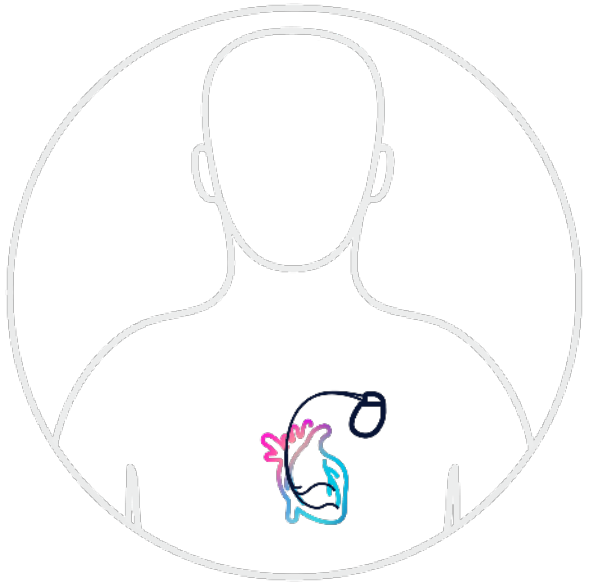
Improve HF symptoms For narrow QRS

GDMT PRODUCES MODEST IMPROVEMENTS IN EXERCISE CAPACITY



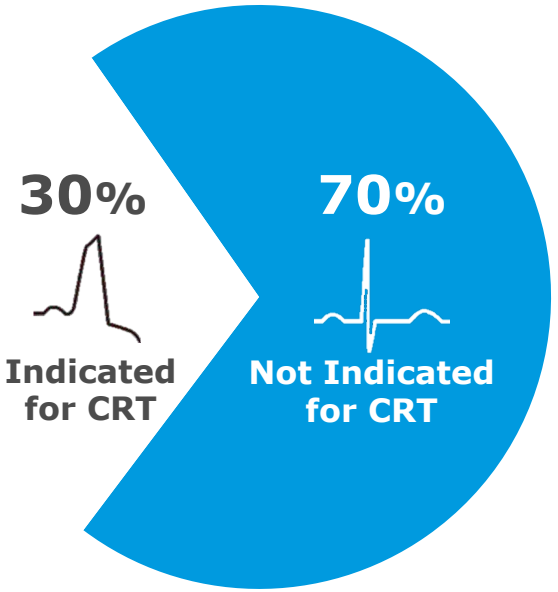
CRT IS INDICATED FOR ONLY 30% OF HFREF PATIENTS

CRT Indicated[1]
LBBB / QRS ≥ 150ms

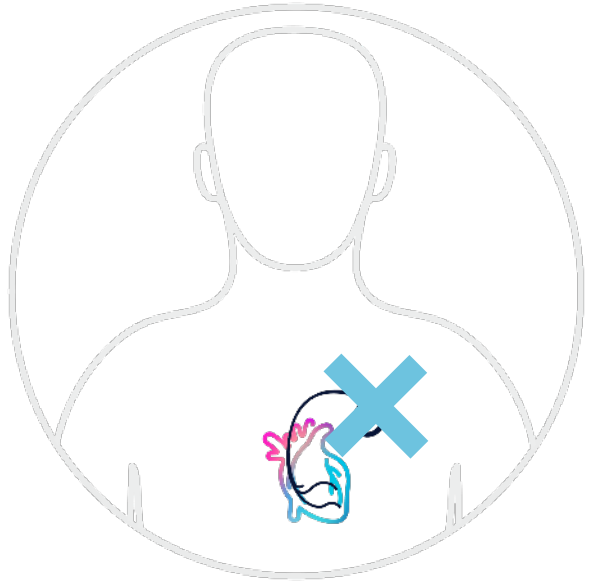


Approved in 2002

NYHA II & III
EF ≤ 35%
GDMT



Not CRT Indicated



Previous Attempts

- Empiric CRT
- Vagus Nerve and spinal cord stimulation

CARDIAC CONTRACTILITY MODULATION (CCM) THERAPY

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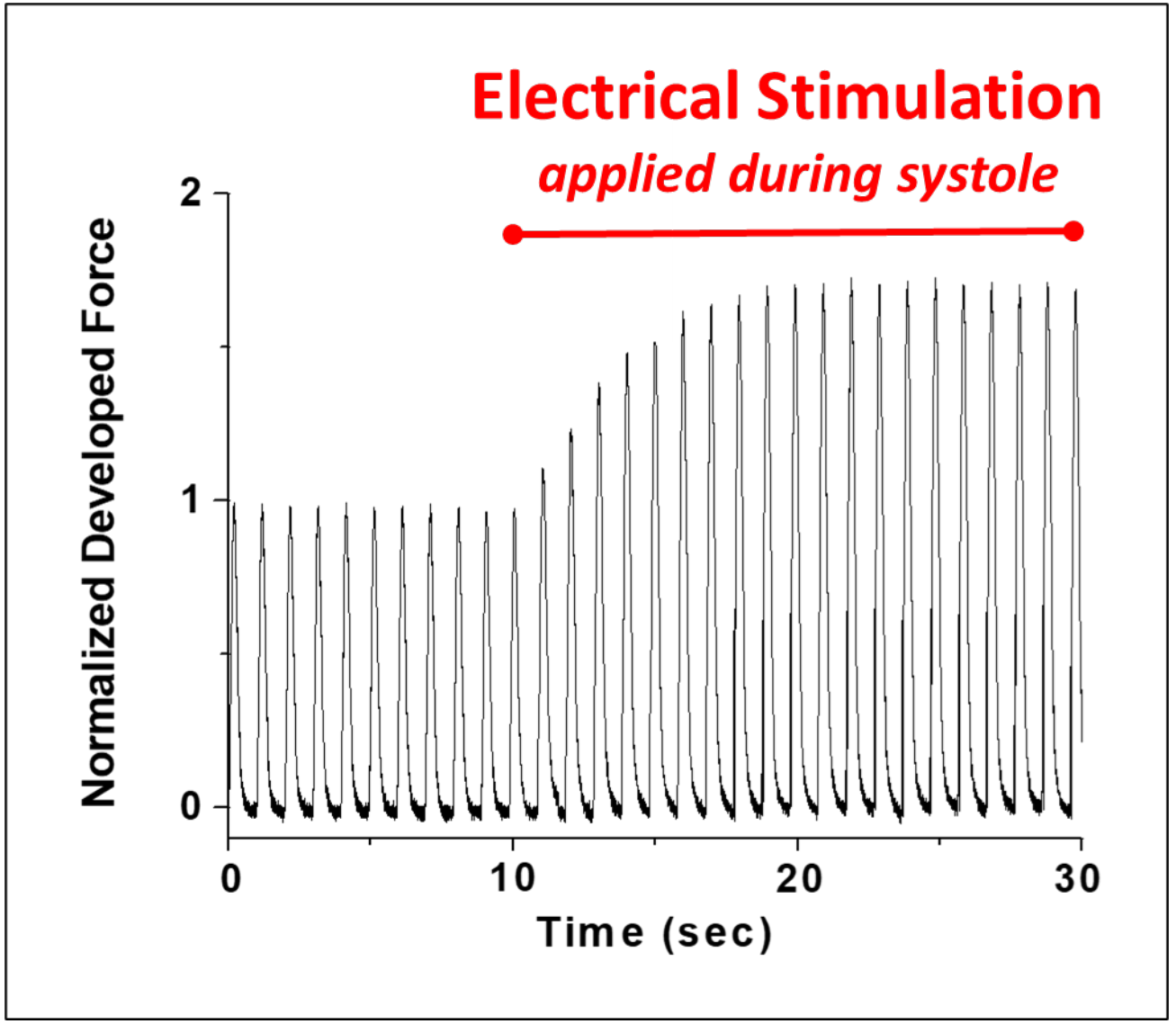
Physiology of CCM Therapy

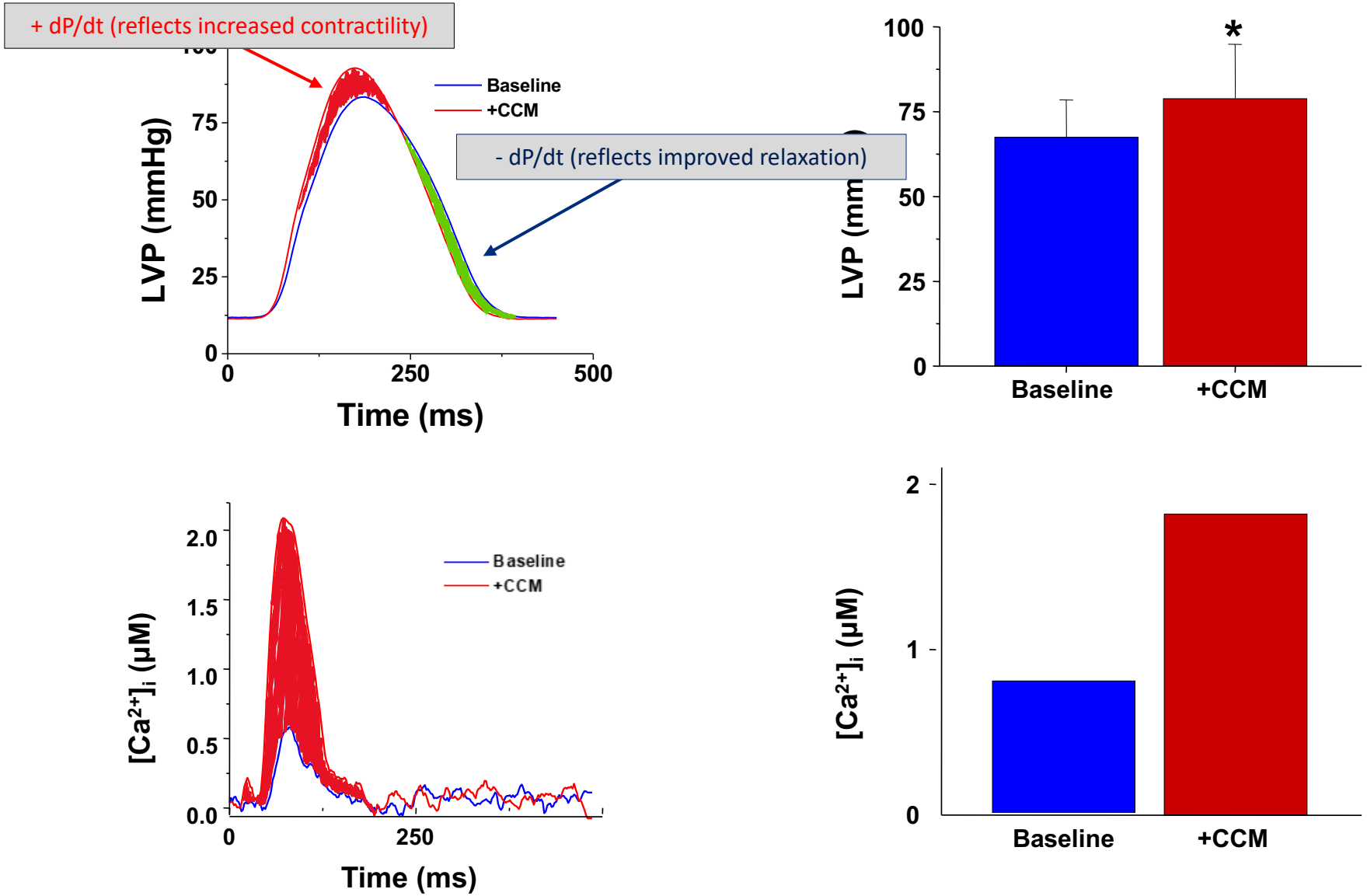
"Effects on End-Stage Failing Human Heart Muscle"



Burkhoff, Daniel, et al. "Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo." *Heart failure reviews* 6 (2001): 27-34.

Cardiac Contractility Modulation Therapy

Effects on Intracellular Calcium



Mohri, Satoshi, et al. "Electric currents applied during refractory period enhance contractility and systolic calcium in the ferret heart." *American Journal of Physiology-Heart and Circulatory Physiology* 284.4 (2003): H1119-H1123.

Physiology of CCM Therapy

Clinical effects of CCM signal on global LV function

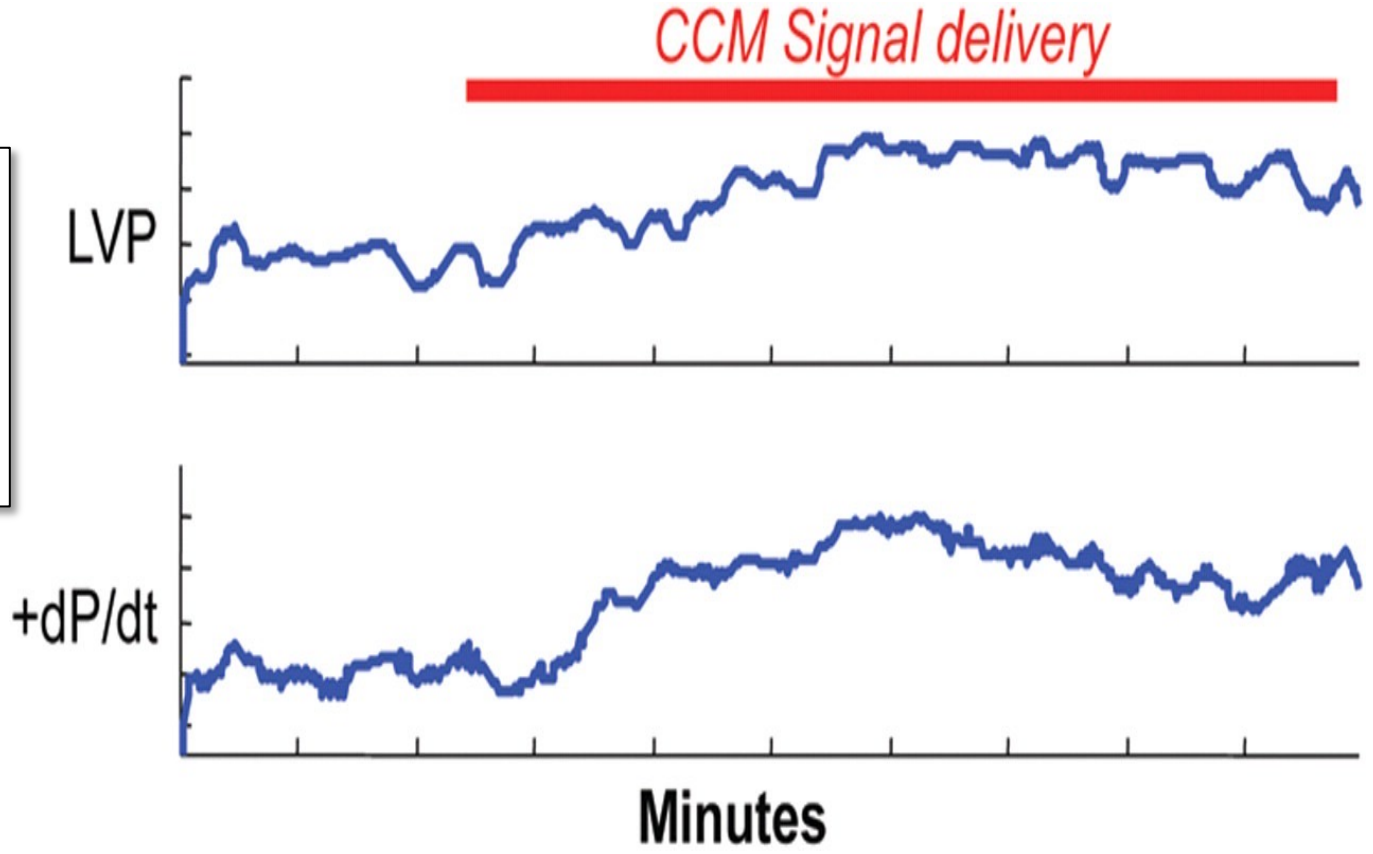
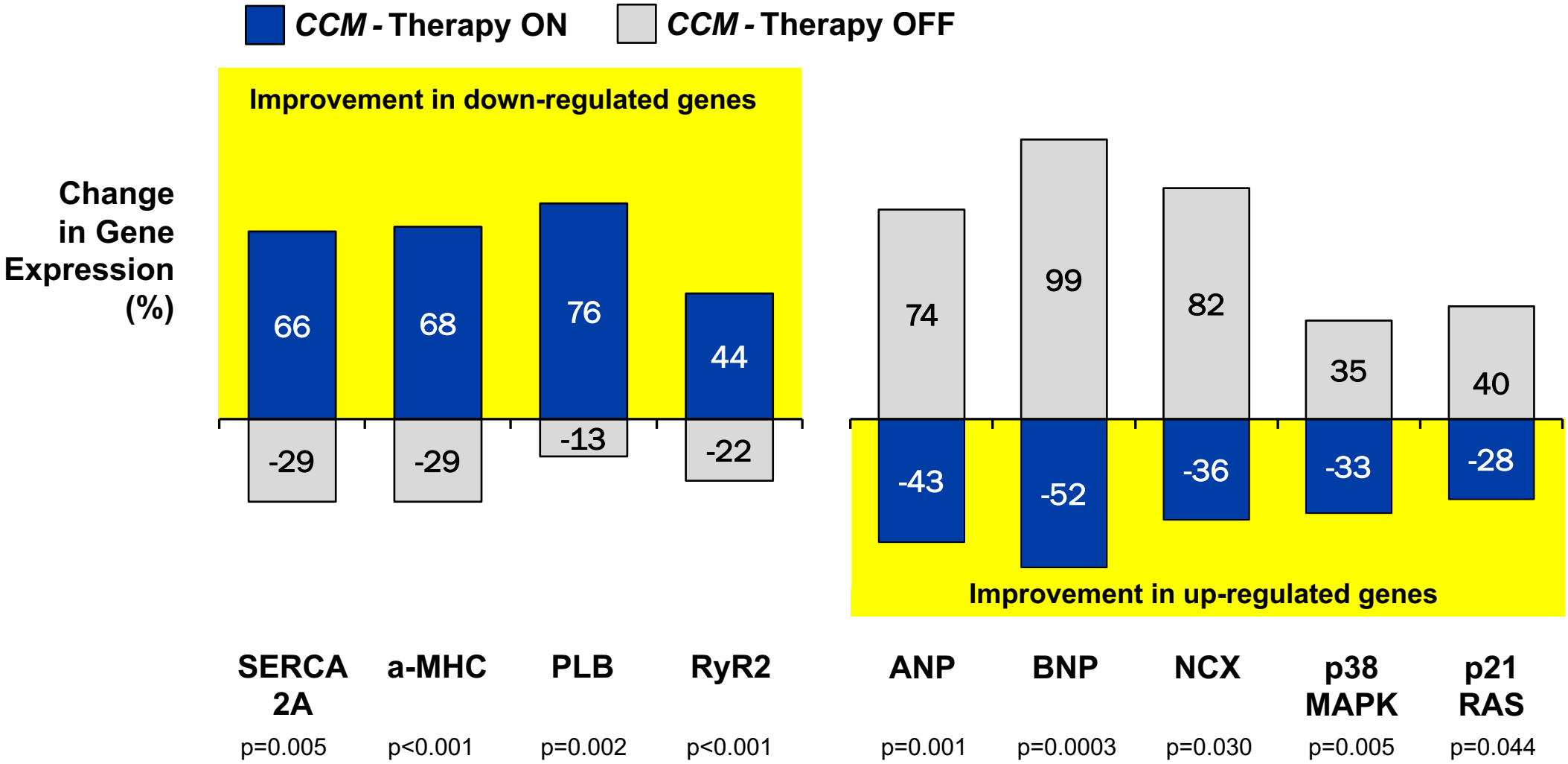


Figure 2. Effects of cardiac contractility modulation (CCM) signals on global function assessed by left ventricular pressure (LVP) and the rate of rise of LVP (+d*P*/d*t*) in a patient undergoing an acute OPTIMIZER III device implant

Borggrefe, M., & Burkhoff, D. (2012). Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. *European journal of heart failure*, *14*(7), 703-712.

MYOCARDIAL GENE EXPRESSION IN HF: THESE ARE GENES WITH ABNORMAL EXPRESSION IN HF

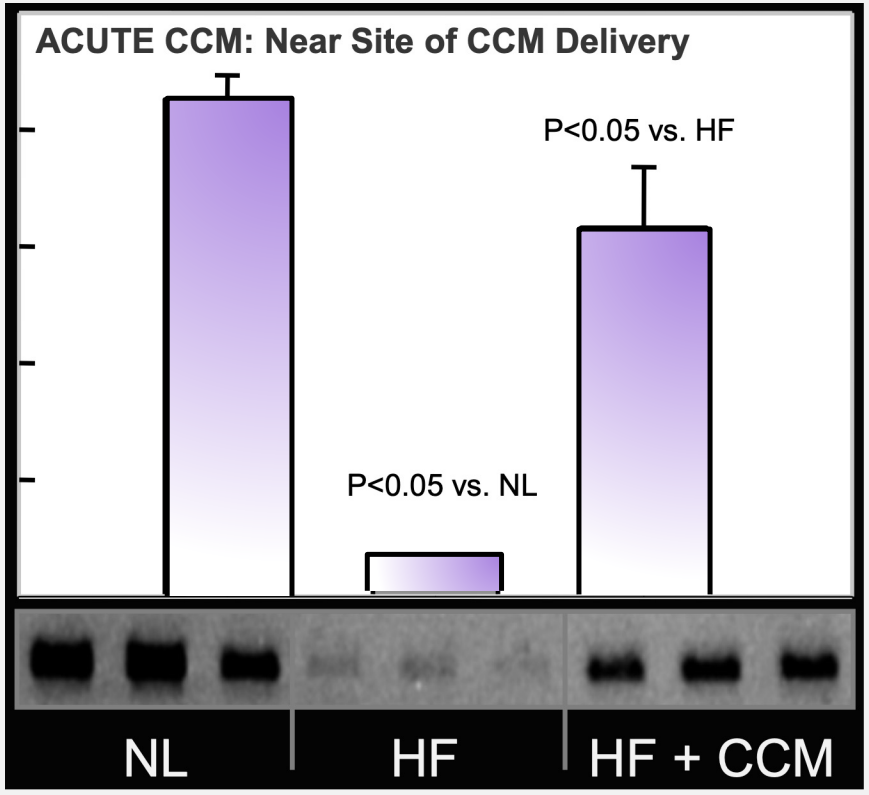
SIGNIFICANT IMPROVEMENT WITH CCM THERAPY

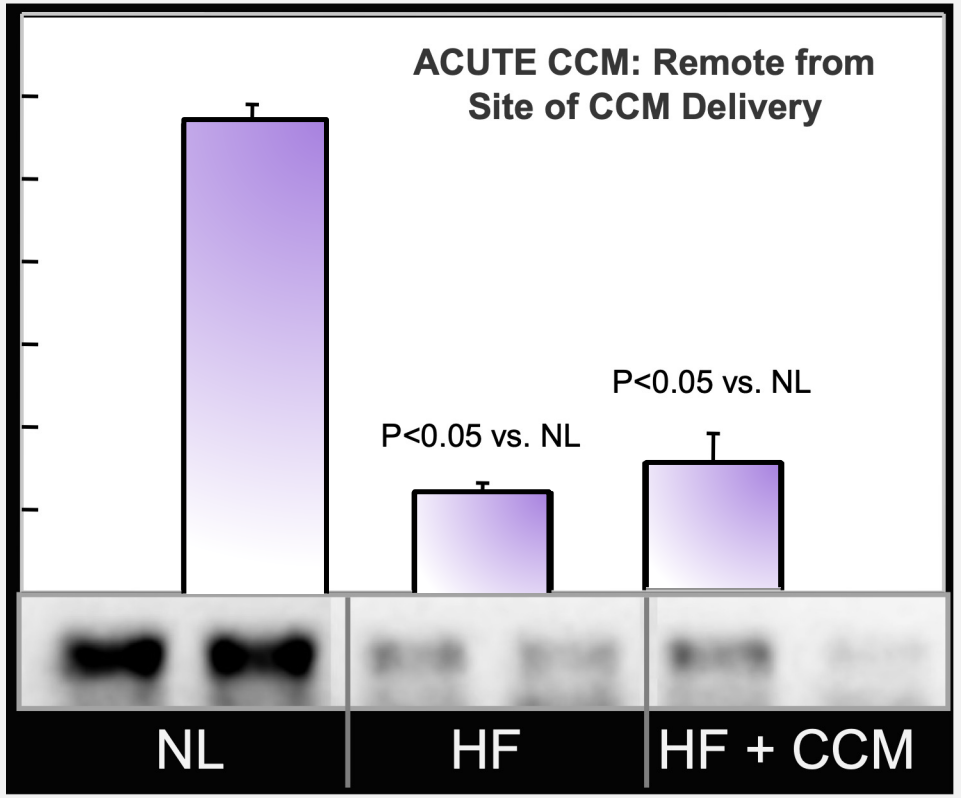


Adapted from Butter, JACC 2008 FIX-HF-4 (N=11 patients); Group 1: Therapy On > Off (n=7); Group 2: Therapy Off to On (n=4)

CCM® Therapy

Improved Regional Cardiac Function Induces Global Improvement and Reverse Remodeling



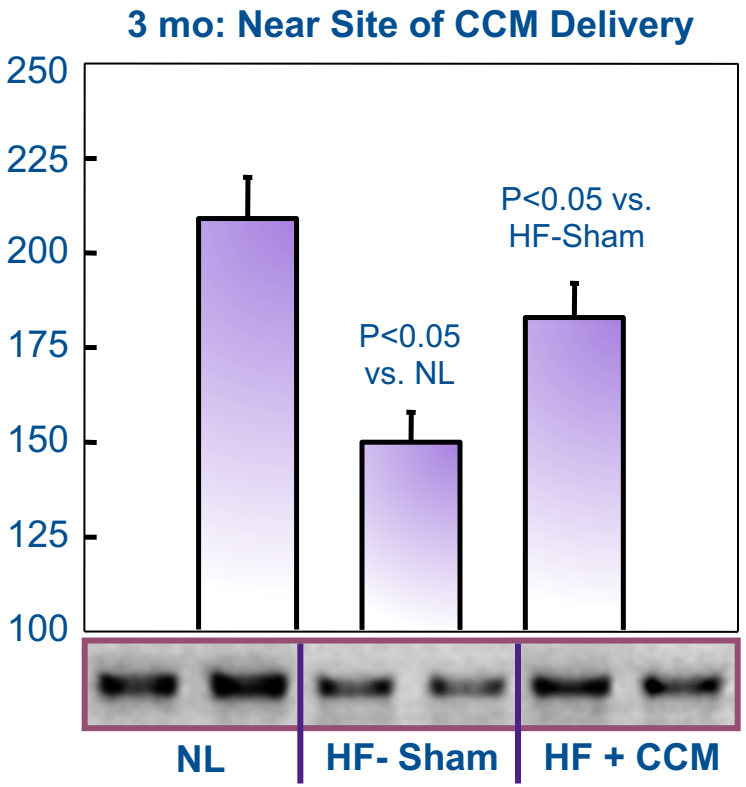


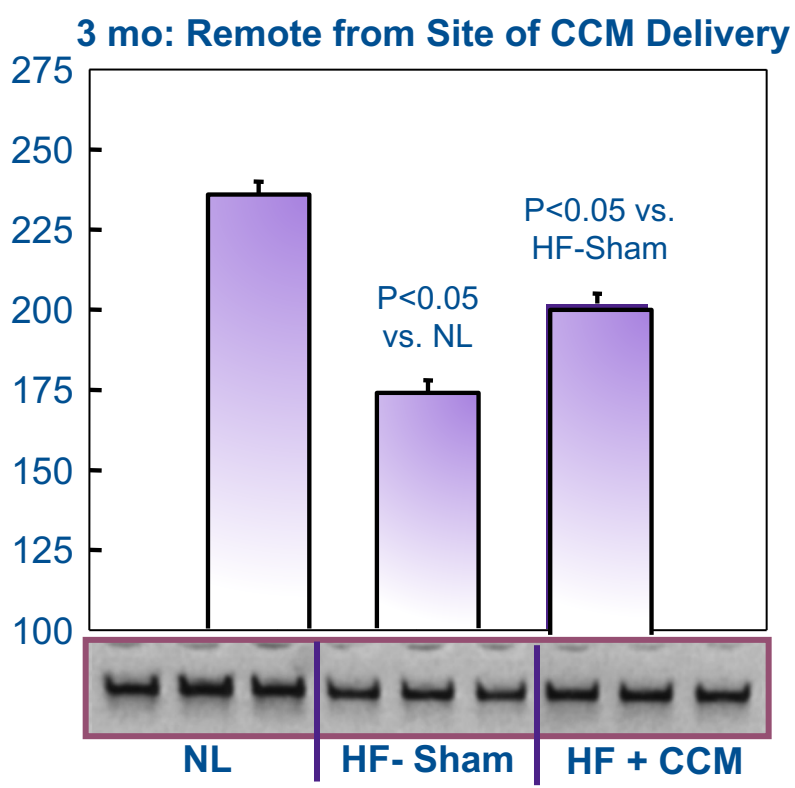
SERCa2a Expression is impacted <u>acutely</u> only in the region <u>near</u> where CCM signals are delivered

Source - Imai , et al., Therapy With Cardiac Contractility Modulation Electrical Signals Improves Left Ventricular Function and Remodeling in Dogs With Chronic Heart Failure JACC Volume 49, Issue 21, 29 May 2007, Pages 2120-2128

CCM® Therapy

Improved Regional Cardiac Function Induces Global Improvement and Reverse Remodeling

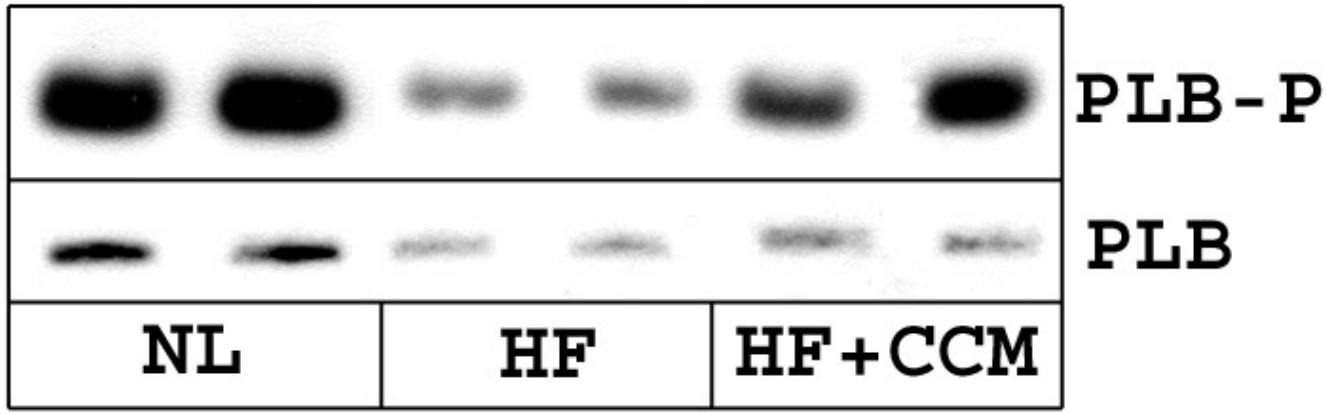




SERCa2a expression is normalized at sites both immediate to and remote from the site of CCM signal delivery by **3 months** of treatment

Physiology of CCM Therapy

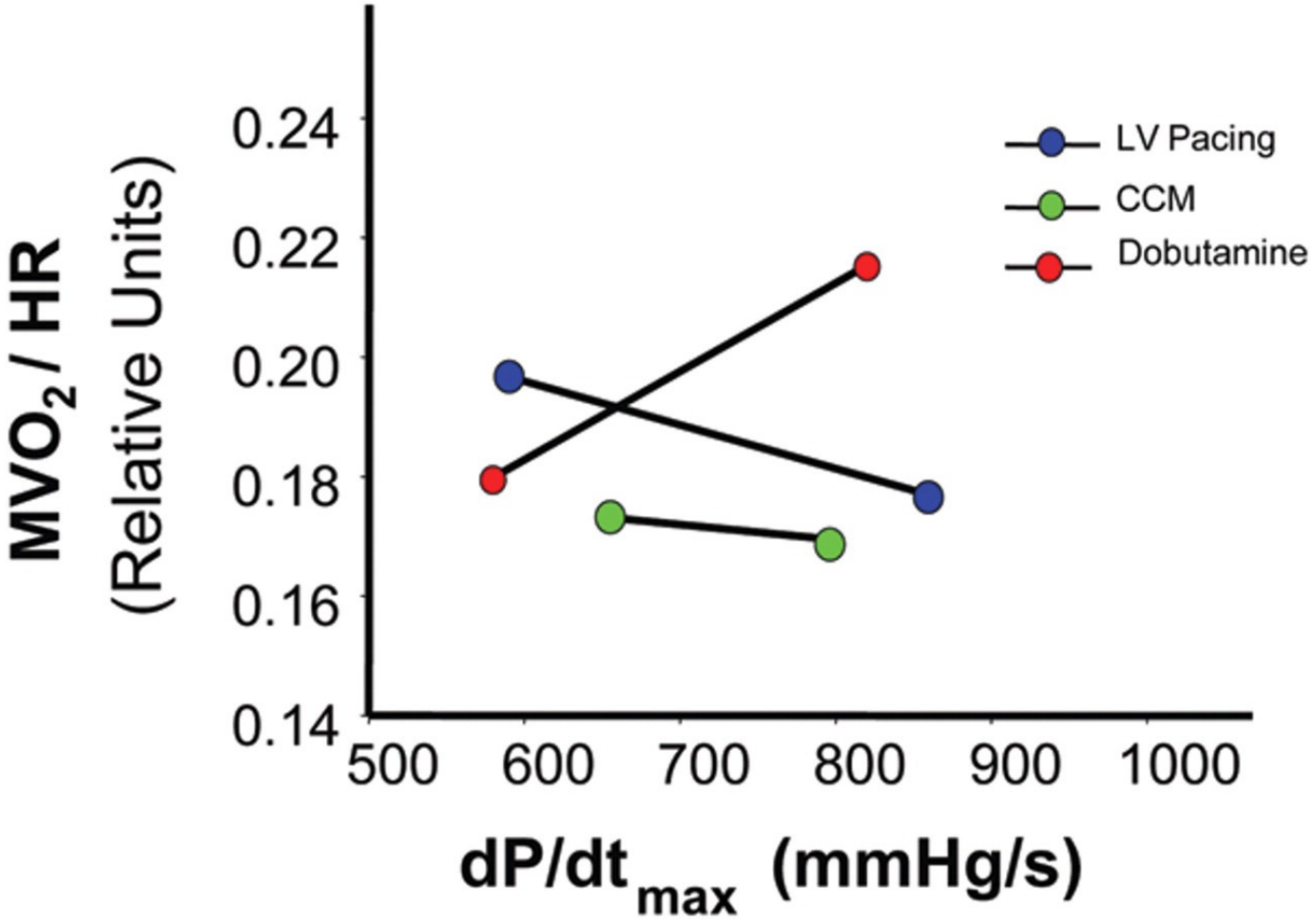
Western Blotting Demonstrates Improved Phosphorylation of Phospholamban in HF model with CCM Therapy



PLB-P = Phosphorylated Phospholamban
PLB = Total Phospholamban

Physiology of CCM Therapy

HUMAN STUDIES OF CCM AND MVO_2: NO INCREASE WITH CCM



When you compare LV. Pacing, CCM versus DBA

CARDIAC CONTRACTILITY MODULATION:

Delivers biphasic, high-voltage electrical signals to the RV septum during the absolute myocardial refractory period, which ***enhances myocardial contractility without increasing O2 demand.***

Improves calcium handling, reverses fetal myocyte gene programming associated with HF ***facilitating reverse remodeling.***

CLINICAL EXPERIENCE

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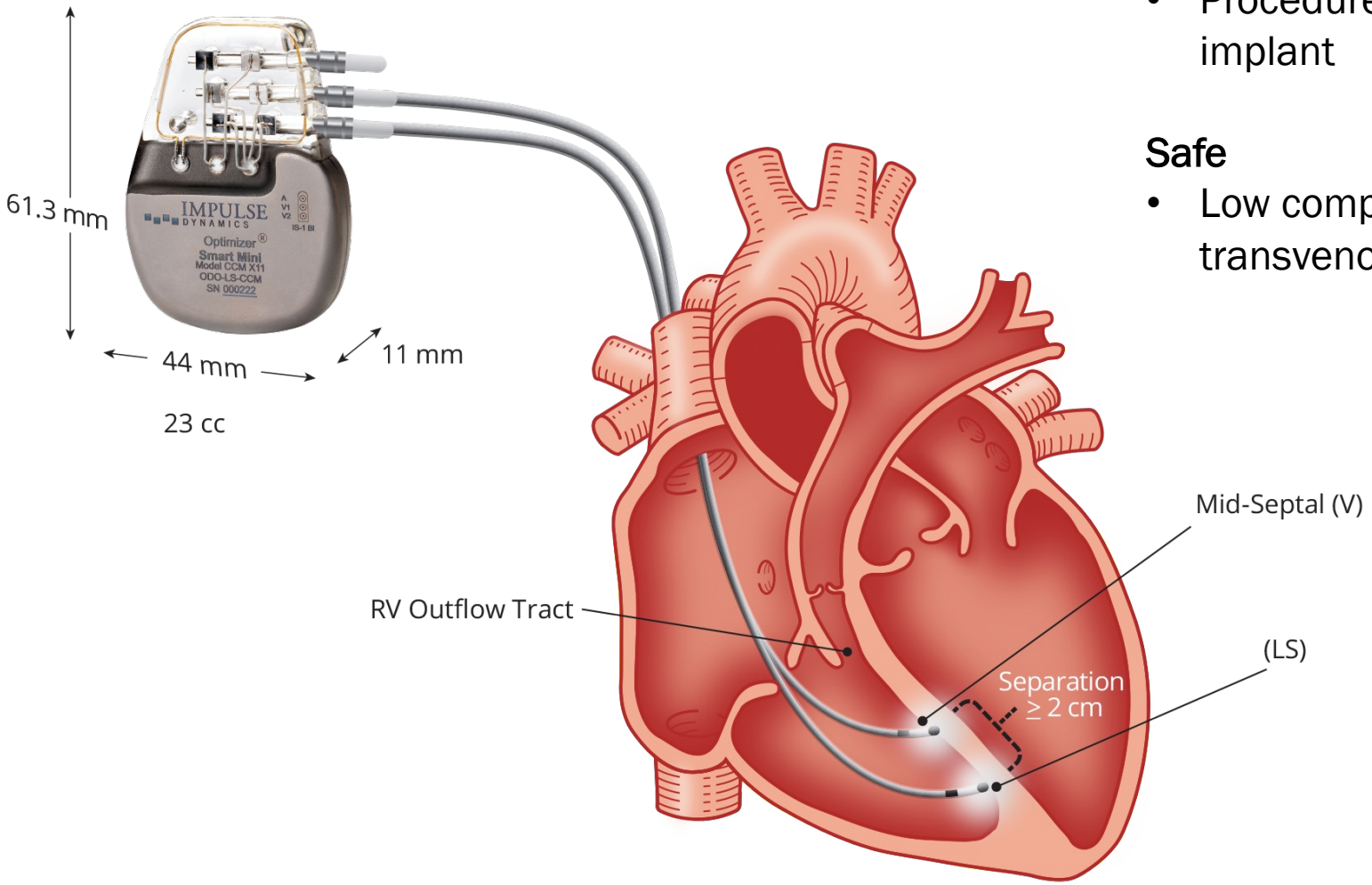
CCM Therapy Delivery



Simple

- Procedure is like a dual-chamber pacemaker implant

Safe

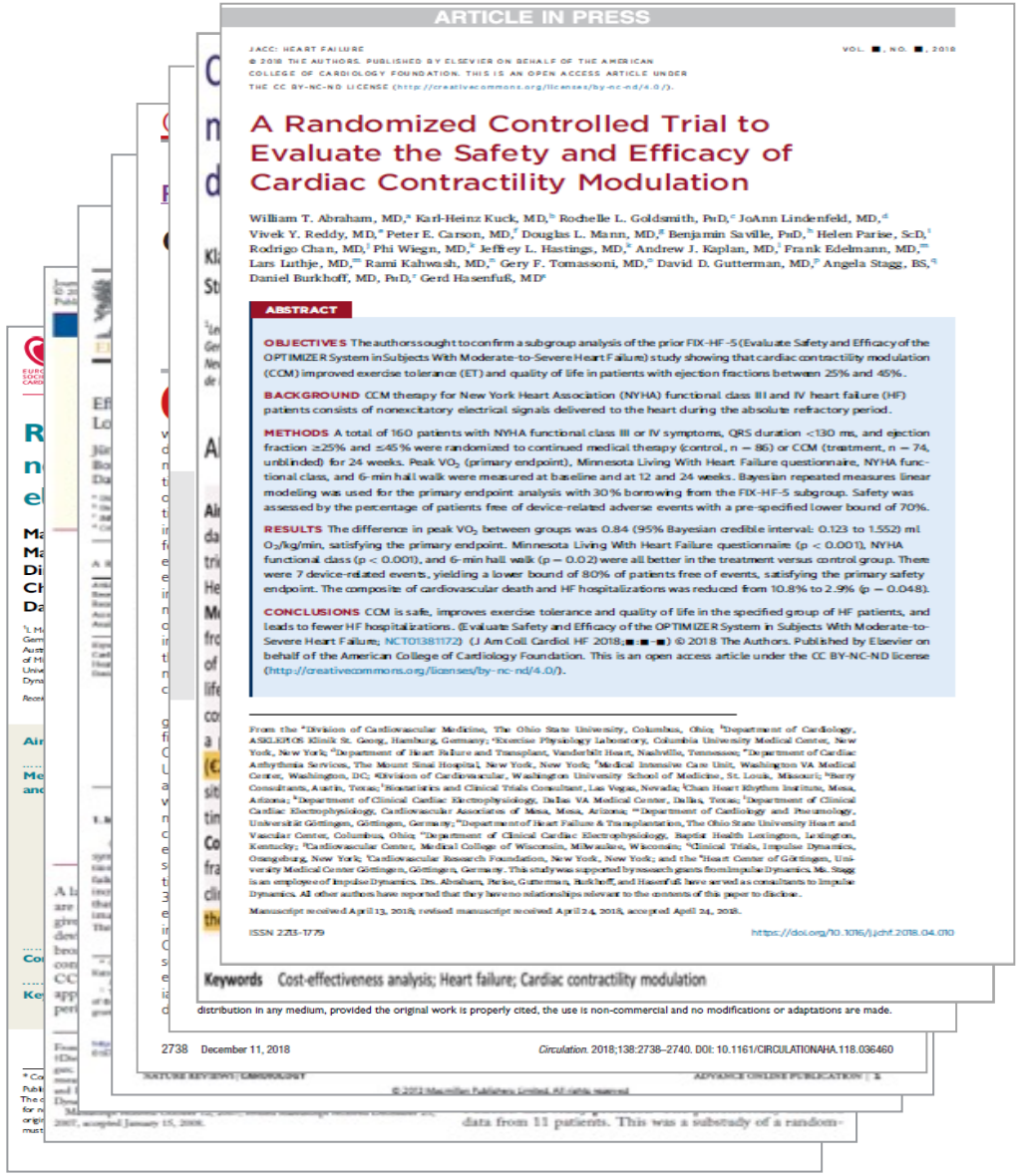
- Low complication rates – similar to a standard transvenous pacing system implantation

The Science Behind CCM

More Than 150 Publications in Peer-Reviewed Journals

Select Publications

- **Kuschyk et al:** “Long Term Clinical experience with cardiac contractility modulation delivered by the Optimizer Smart system” European Journal of Heart Failure, May 2021
- **Tschope -** Clinical effects of cardiac contractility modulation in heart failure with mildly reduced systolic function ESC Heart Failure December 2020
- **Abraham** et al: “A Randomized Control Trial to evaluate the safety and efficacy of Cardiac Contractility Modulation” JACC HF, May 2018
- **Tschope** et al: “Cardiac contractility modulation: mechanisms of action in heart failure with reduced ejection fraction and beyond” European Journal of Heart Failure, August 2018
- **Borggrefe** and **Mann**: “Cardiac Contractility Modulation in 2018” Circulation, December 2018
- **Butter** C: “Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients with heart failure” Journal of the American College of Cardiology, May 2008
- **Borggrefe** M.M. et al: “Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure” European Heart Journal, January 2008


ARTICLE IN PRESS

JACC: HEART FAILURE VOL. ■, NO. ■, 2018

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A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

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ABSTRACT

OBJECTIVES The authors sought 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 A total of 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; NCT01381172) (J Am Coll Cardiol HF 2018;■:■–■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Keywords Cost-effectiveness analysis; Heart failure; Cardiac contractility modulation

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data from 11 patients. This was a substudy of a random-

CCM CLINICAL TRIAL HISTORY

Study Name	Author, Journal (Year) of Pub	Comments	Randomized	Device	Countries	Total patients
FIX-HF-1	Pappone, Am J Cardiol (2002)	Acute study	No	SCEPTRE	IT	40
FIX-HF-2	Pappone, J Cardiovasc EP (2004)	First chronic study	No	Opt I	IT	6
FIX HF-3	Stix, European Heart J (2004)	CE study (EU)	No	Opt II	AUS, DE, IT	22
FIX-CHF-12	Nagele, Europace (2008)	CRT non-responder study	No	Opt III	DE	16
FIX-CHF-4	Borggrefe, Eur HJ (2008)	Crossover double-blind, 6 months	Yes	Opt II	IT, AUS, DE, FR, NL CZ	164
FIX-HF-5 Phase I	Neelagaru, Heart Rhythm (2006)	CCM vs OMT, 6 months	Yes	Opt II	USA	49
FIX-HF-5 Phase II	Abraham Am Heart J (2008) Kadish, Am Heart J (2011)	CCM vs. OMT	Yes	Opt III	USA	428
FIX-HF-9	Unpublished	CCM with and w/o dP/dt testing	Yes	Opt III	Hong Kong	38
FIX-CHF-13	Kloppe, Cardiol J (2016)	CCM dosage (5 vs. 12 hours)	Yes	Opt III	DE	19
CCM HF (FIX-HF-16)	Muller, Clin Res Cardiol. 2017	CCM Registry	No	Opt III	DE	143
FIX-CHF-18	Röger J Cardiol (2017)	Comparison 1 vs 2 leads	Yes	Opt III, Opt IVs	DE	48
FIX-HF-5C	Abraham JACC:HF (2018)	CCM vs. OMT confirmatory	Yes	Opt IVs	CZ, DE, US	160
CCM-REG	Kuschyk, Eu J of HF (2021)	CCM Registry	No	Opt III, Opt IVs, Smart	DE, 51 centers	503
FIX-HF-5C2	Wiegn, Circ HF (2020)	2-Lead CCM Device	No	Smart (2-lead)	DE, US	60
CCM HFpEF Pilot	Linde, Eu J of HF (2022)	CCM in EF ≥50% OUS	No	Smart (2-lead)	EU, AUS	47
					Total	**1,743**

Safety, Performance, and Efficacy of Cardiac Contractility Modulation Delivered by the 2-Lead Optimizer Smart System

The FIX-HF-5C2 Study

Circulation: Heart Failure
Volume 13, Issue 4, April 2020
https://doi.org/10.1161/CIRCHEARTFAILURE.119.006512

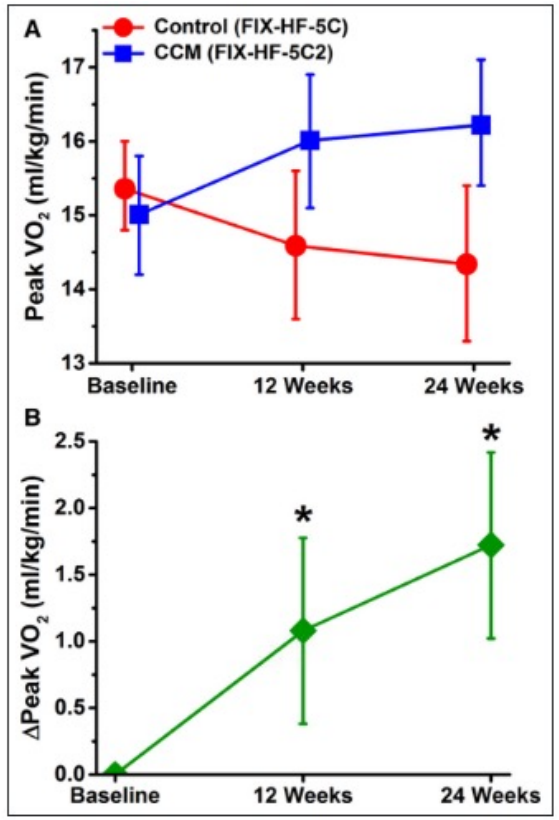

Figure 1. **A, Peak VO_2 over time comparing control group from FIX-HF-5C and the CCM treatment group from the FIX-HF-5C2 study.** Values represent mean±SD frequentist values at each timepoint. One side of error bars are shown for clarity. **B**, Between-group treatment effects (ie, difference between CCM treatment and control group and 95% CIs) over time as estimated by the primary Bayesian analysis. *Indicate statistically significant treatment effect. CCM indicates cardiac contractility modulation.

60 subjects, 88 % male, 66 ± 9 years, NYHA III/IV a, LVEF 25%-40% (34± 9) not eligible for CRT.

FIX-HF-5C2 (2-lead system, no RA lead)

Previous studies were performed with a 3-lead system (Fix HF-5C)

All patients received an Optimizer 2 lead system.

Primary end point was estimated difference in the change of peak VO2 from baseline to 24 weeks.

Additional efficacy end points include NYHA class and NT-pro BNP.

Primary safety end point was device-related adverse events

Safety, Performance, and Efficacy of Cardiac Contractility Modulation Delivered by the 2-Lead Optimizer Smart System

The FIX-HF-5C2 Study

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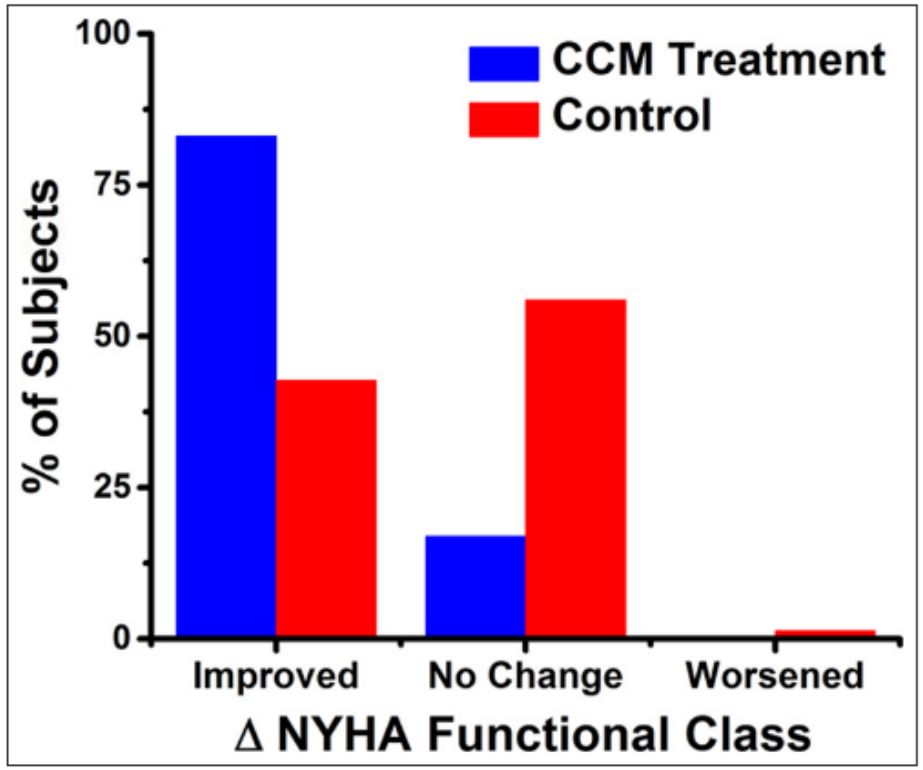
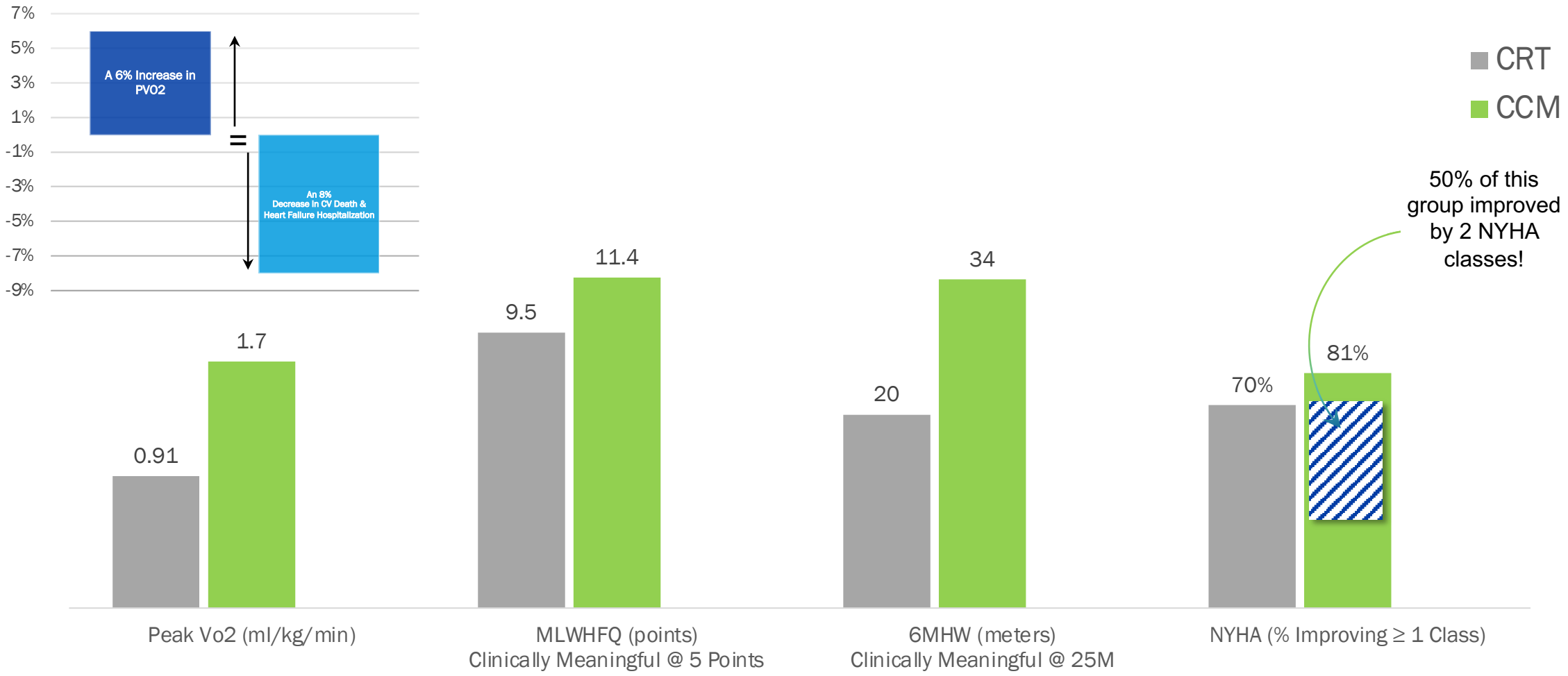


Figure 2. Distributions of changes of New York Heart Association (NYHA) class at 24 wks in control and CCM groups. The differences between these distributions were statisti [No Title] nificant (P<0.001). CCM indicates cardiac contractility modulation.

Table 6. Adjudicated Serious Adverse Events From Study Day 0 to 168 (Table view)

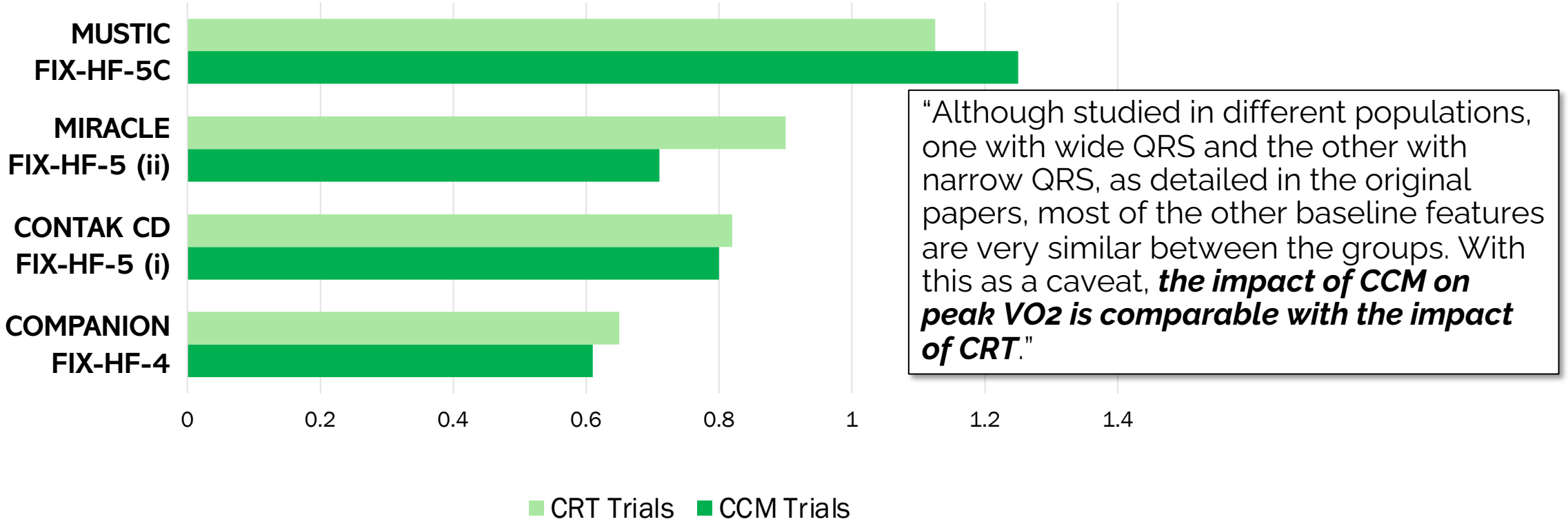
Variable	FIX-HF-5C2 Optimizer		FIX-HF-5C Optimizer			FIX-HF-5C Control		
	No. Events	No. and % of Subjects* (CI)	No. Events	No. and % of Subjects* (CI)	*P*Value†	No. Events	No. and % of Subjects* (CI)	*P*Value†
All	26	19 (31.7%) (20.3%–45.0%)	29	20 (27.0%) (17.4%, 38.6%)	0.572	27	19 (22.1%) (13.9%, 32.3%)	0.250
General Medical	8	7 (11.7%) (4.8%–22.6%)	7	7 (9.5%) (3.9%–18.5%)	0.779	8	7 (8.1%) (3.3%–16.1%)	0.571
Arrhythmia	3	2 (3.3%) (0.4%–11.5%)	3	3 (4.1%) (0.8%–11.4%)	1.000	2	2 (2.3%) (0.3%–8.1%)	1.000
Worsening heart failure	7	5 (8.3%) (2.8%–18.4%)	4	3 (4.1%) (0.8%–11.4%)	0.466	8	7 (8.1%) (3.3%–16.1%)	1.000
General cardiopulmonary	2	2 (3.3%) (0.4%–11.5%)	4	3 (4.1%) (0.8%–11.4%)	1.000	2	2 (2.3%) (0.3%–8.1%)	1.000
Bleeding	1	1 (1.7%) (0.0%–8.9%)	0	0 (0.0%) (0.0%–4.9%)	0.448	1	1 (1.2%) (0.0%–6.3%)	1.000
Neurological	1	1 (1.7%) (0.0%–8.9%)	0	0 (0.0%) (0.0%–4.9%)	0.448	0	0 (0.0%) (0.0%–4.2%)	0.411
Thromboembolism	1	1 (1.7%) (0.0%–8.9%)	1	1 (1.4%) (0.0%–7.3%)	1.000	1	1 (1.2%) (0.0%–6.3%)	1.000
Local infection	1	1 (1.7%) (0.0%–8.9%)	1	1 (1.4%) (0.0%–7.3%)	1.000	4	4 (4.7%) (1.3%–11.5%)	0.649
Sepsis	1	1 (1.7%) (0.0%–8.9%)	1	1 (1.4%) (0.0%–7.3%)	1.000	1	1 (1.2%) (0.0%–6.3%)	1.000
ICD or pacemaker system malfunction	1	1 (1.7%) (0.0%–8.9%)	2	2 (2.7%) (0.3%–9.4%)	1.000	0	0 (0.0%) (0.0%–4.2%)	0.411
Optimizer system malfunction	0	0 (0.0%) (0.0%–6.0%)	6	6 (8.1%) (3.0%–16.8%)	0.033		…	

CRT AND CCM LANDMARK TRIALS



CRT AND CCM® LANDMARK TRIALS

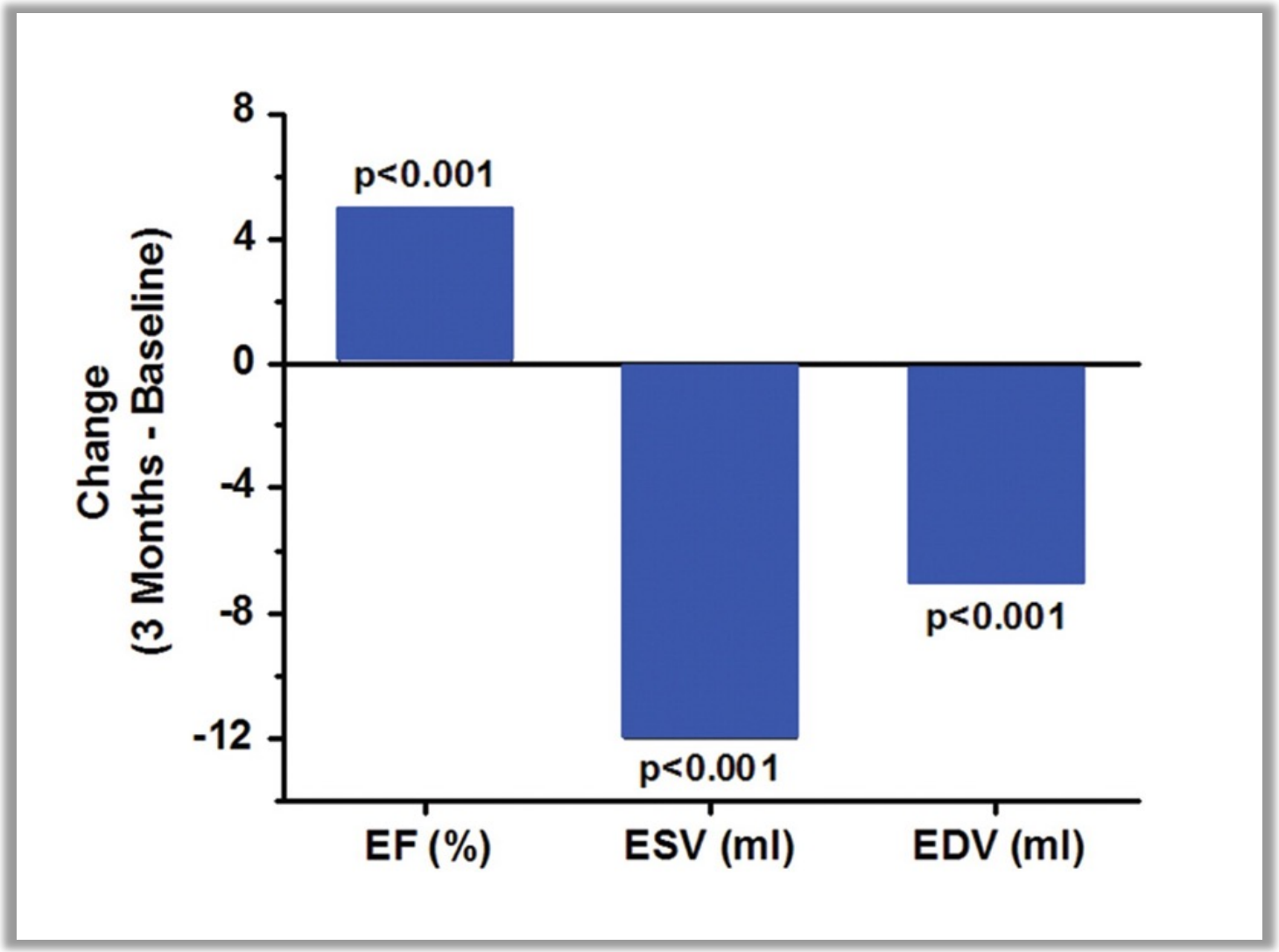
Comparison of the effects of CCM™ and CRT on peak oxygen consumption (VO_2) obtained from different clinical trials.



"Although studied in different populations, one with wide QRS and the other with narrow QRS, as detailed in the original papers, most of the other baseline features are very similar between the groups. With this as a caveat, ***the impact of CCM on peak VO2 is comparable with the impact of CRT***."

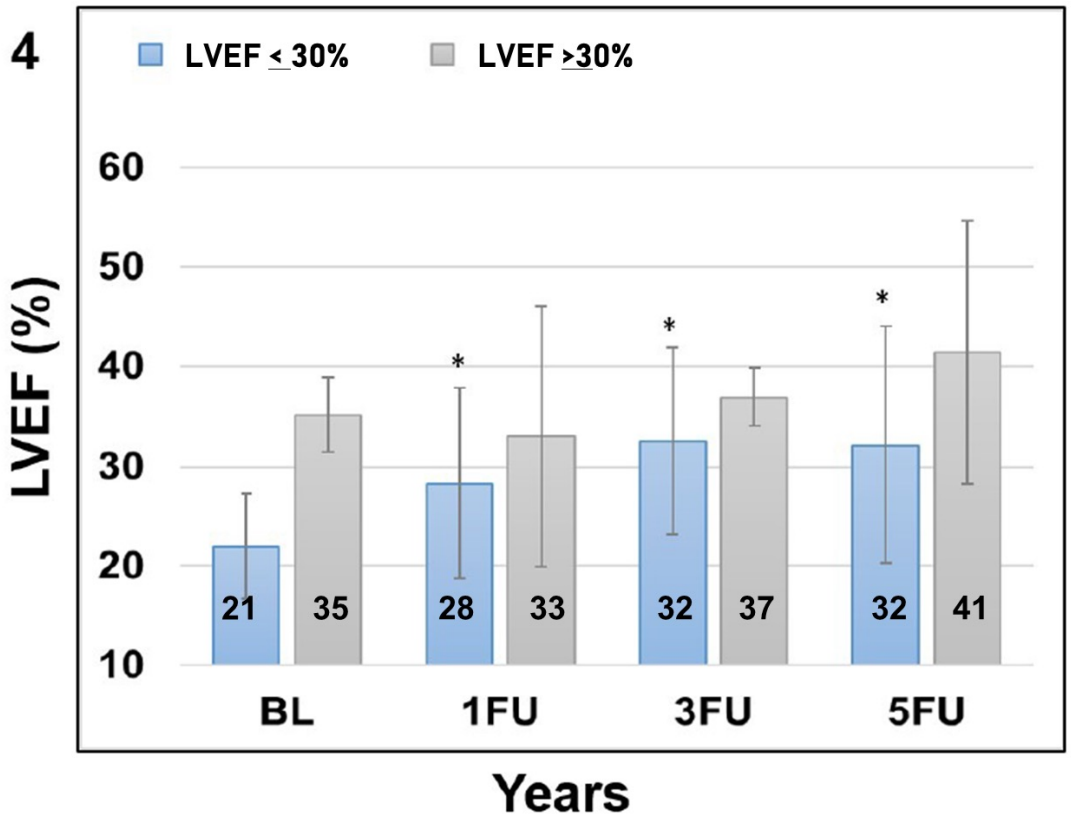
CCM Therapy

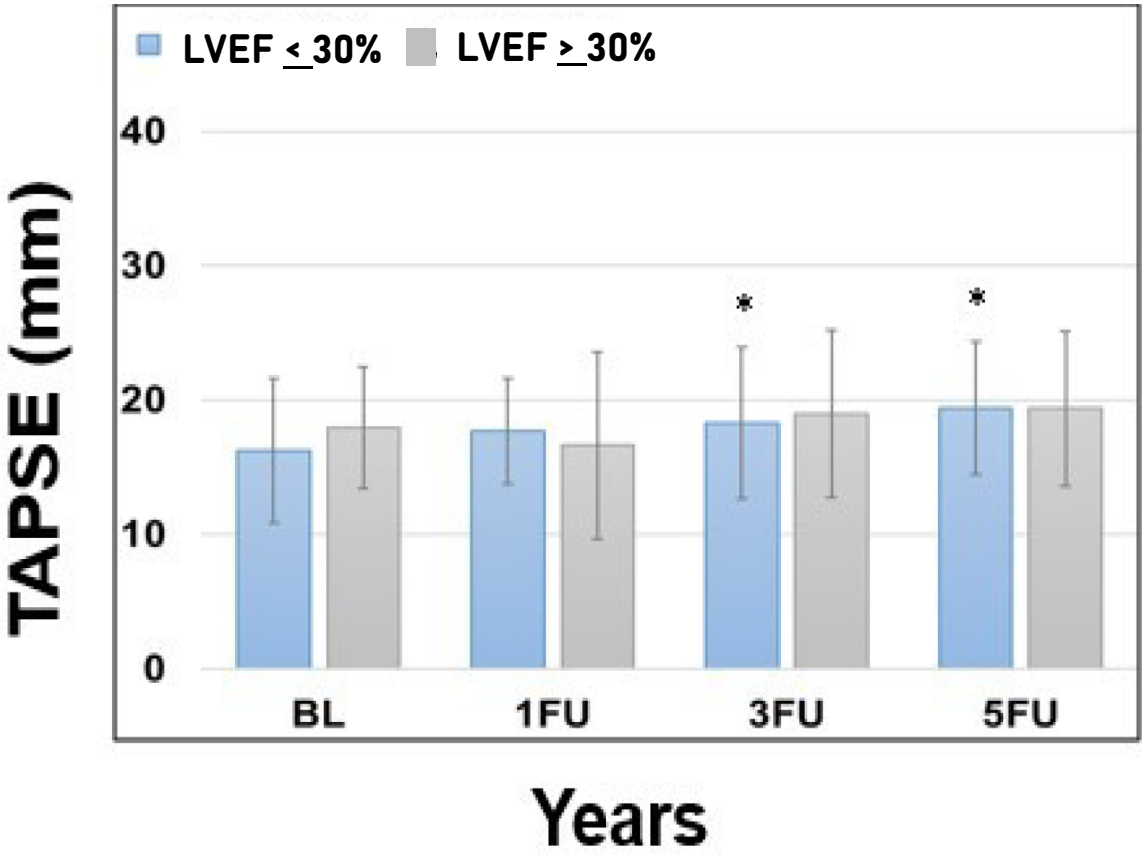
Improved Regional Cardiac Function Induces Global Improvement and Reverse Remodeling



Source - Yu, et al., Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. JACC Cardiovasc Imaging. 2009 Dec;2(12):1341-9. doi: 10.1016/j.jcmg.2009.07.011.

SUSTAINED EVIDENCE OF REMODELING





CCM VS. CRM DEVICE RELATED COMPLICATIONS

TABLE 1 Baseline Characteristics: Comparisons Between FIX-HF-5C and FIX-HF-5 Subgroup (With EF ≥25%) Cohorts by Group and Pooled

	Control Group			CCM Group					
	FIX-HF-5 Subgroup* (n = 112)	FIX-HF-5C* (n = 86)	p Value	FIX-HF-5 Subgroup* (n = 117)	FIX-HF-5C* (n = 74)	p Value	Control Merged (n = 198)	CCM Merged (n = 191)	p Value* (Control vs. CCM, Combined)
Age, yrs	60 ± 12	63 ± 11	0.08	59 ± 12	63 ± 11	**0.011**	61 ± 12	60 ± 12	0.51
Male	83/112 (74.1)	68/86 (79.1)	0.50	83/117 (71.0)	54/74 (73.0)	0.869	151/198 (76.3)	137/191 (71.3)	0.34
White ethnicity	81/112 (72.3)	61/74 (70.9)	0.87	88/117 (75.2)	55/74 (74.3)	1.0000	142/198 (71.72)	143/191 (74.87)	0.49
Ischemic CHF etiology	77/112 (68.8)	51/86 (59.3)	0.18	84/117 (71.8)	46/74 (62.2)	0.2026	128/198 (64.65)	130/191 (68.06)	0.52
Prior MI	66/112 (58.9)	51/86 (59.3)	1.00	78/117 (66.7)	36/74 (48.7)	**0.0157**	117/198 (59.09)	114/191 (59.69)	0.92
Prior PT/ICD	88/112 (78.6)	73/86 (84.9)	0.28	93/117 (79.5)	65/74 (87.8)	0.1702	161/198 (81.31)	158/191 (82.72)	0.79
Diabetes	58/112 (51.8)	42/86 (48.8)	0.77	57/117 (48.7)	38/74 (51.4)	0.7675	100/198 (50.51)	95/191 (49.74)	0.92
NYHA functional class IV	15/112 (13.4)	8/86 (9.3)	0.50	8/117 (6.8)	10/74 (13.50)	0.1350	23/198 (11.62)	18/191 (9.42)	0.51
QRS duration, ms	101.1 ± 13.8	103.6 ± 12.1	0.18	99 ± 14	103 ± 13	0.13	102 ± 13	101 ± 14	0.24
LVEF, % (core laboratory)	32 ± 4	33 ± 5	0.13	31 ± 4	33 ± 6	**0.012**	32 ± 5	32 ± 5	0.89
LVEDD, mm (core laboratory)	56 ± 11	60 ± 7	**0.003**	57 ± 10	58 ± 7	0.25	58 ± 9	58 ± 10	0.76
MLWHFQ	56 ± 24	57 ± 23	0.72	60 ± 23	56 ± 23	0.25	57 ± 23	59 ± 23	0.36
6MHW, m	324 ± 91	324 ± 90	0.97	326 ± 84	317 ± 88	0.48	324 ± 91	322 ± 86	0.08
CPX (core laboratory)									
Peak Vo_2, ml/kg/min	14.8 ± 3.2	15.4 ± 2.8	0.20	14.6 ± 3.0	15.5 ± 2.6	**0.036**	15.0 ± 3.0	15.0 ± 2.9	0.73
Exercise time, min	11.7 ± 3.5	10.6 ± 3.1	**0.025**	11.3 ± 3.2	11.4 ± 3.1	0.77	11.2 ± 3.3	11.3 ± 3.1	0.74
Physical examination									
Weight, kg	96 ± 23	100 ± 23	0.23	92 ± 22	100 ± 21	**0.027**	98 ± 23	95 ± 22	0.20
Height, cm	173 ± 10	174 ± 9	0.44	173 ± 9	175 ± 102	0.24	174 ± 10	174 ± 9	0.98
BMI, kg/m^2	32 ± 7	33 ± 7	0.36	31 ± 7	32 ± 6	0.05	32 ± 7	31 ± 7	0.15
Resting HR, beats/min	73 ± 12	76 ± 14	0.09	71 ± 12	74 ± 11	**0.039**	75 ± 13	72 ± 12	0.07
Blood pressure									
Systolic	117 ± 18	126 ± 19	**0.0007**	119 ± 18	123 ± 18	0.12	121 ± 19	120 ± 18	0.71
Diastolic	71 ± 11	74 ± 11	**0.023**	70 ± 11	74 ± 11	0.058	72 ± 11	72 ± 11	0.65

Values are mean ± SD or n/N (%). **Bold** values indicate statistical significance. *p value from 2-sample Student's *t*-test or Fisher exact test as appropriate.

6MHW = 6-min hall walk test; BMI = body mass index; CHF = chronic heart failure; CPX = cardiopulmonary exercise stress test; HR = heart rate; ICD = implanted cardiac-defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; PT = pacing therapy.

Fix HF-5 & 5C:

Concomitant ICD in 8% of pts

no inappropriate shocks due to CCM® therapy reported to date

SAEs: 6 in 6 subjects (8.8%)

	Acute (0-1 Months)		
	Single-Chamber (n = 8,956)	Dual-Chamber (n = 60,902)	Both (n = 69,858)
All	7.68 (688)	9.13 (5,559)	8.94 (6,247)
Infection	1.23 (110)	1.14 (694)	1.15 (804)
Endocarditis	0.84 (75)	0.78 (475)	0.79 (550)
Other (device related)	0.42 (38)	0.44 (269)	0.44 (307)
Thoracic trauma	3.51 (314)	3.74 (2,278)	3.71 (2,592)
Pneumothorax	2.53 (227)	3.01 (1,832)	2.95 (2,059)
Hemothorax	1.45 (130)	1.41 (858)	1.41 (988)
Pocket complication	0.27 (24)	0.26 (160)	0.26 (184)
Hematoma	0.15 (13)	0.08 (47)	0.09 (60)
Pocket revision	0.16 (14)	0.19 (114)	0.18 (128)
Generator complication	0.09 (8)	0.06 (37)	0.06 (45)
Lead complication requiring revision	2.51 (225)	3.66 (2,226)	3.51 (2,451)
Venous embolism/thrombosis	0.35 (31)	0.51 (312)	0.49 (343)
Cardiac perforation	0.25 (22)	0.60 (367)	0.56 (389)

CCM® AND RIGHT HEART FUNCTION

Small (n=**21**), single-center study prospective study analyzed the effects of CCM on RV systolic function and RV–pulmonary artery (PA) coupling using echocardiography:

tricuspid annular systolic excursion (TAPSE)
myocardial systolic excursion velocity (RVs)
RV free-wall strain
PA systolic pressure (PASP) - estimated from TR + CVP
RV-PA coupling calculated as TAPSE/PASP ratio

Conclusions: At six months, CCM increases RV reverse remodeling and performance, reducing RV size and improving RV systolic function, PASP, and RV-PA coupling.

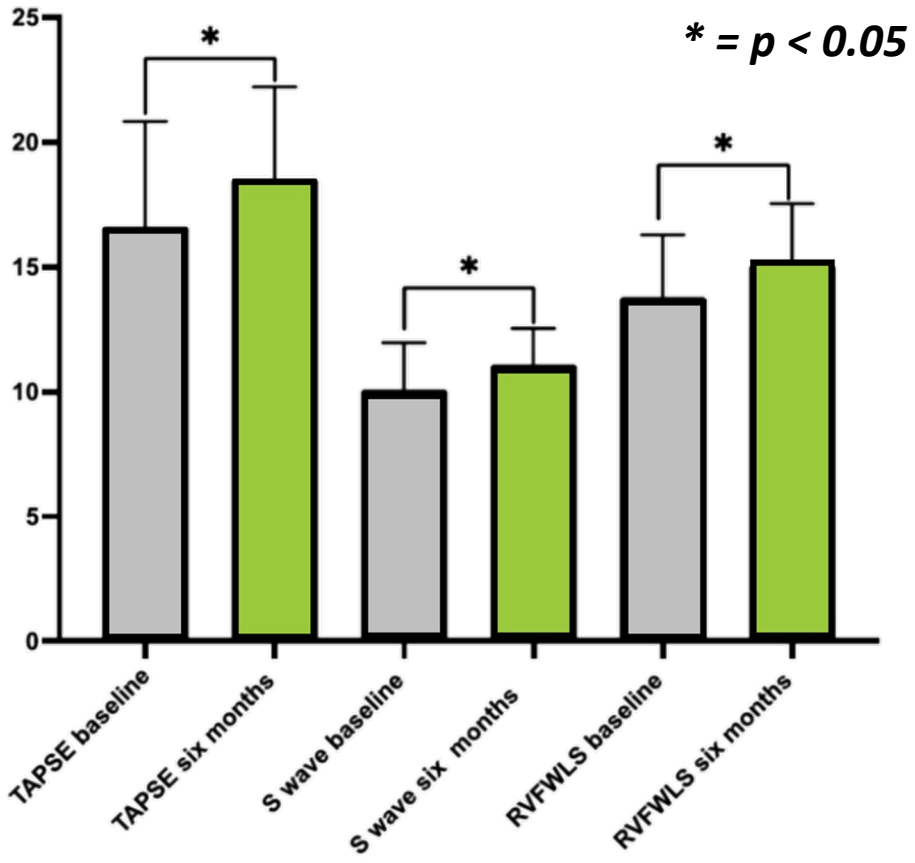


Figure 2. Effects of CCM therapy of right
contractility indexes.

CCM® AND RIGHT HEART FUNCTION

No evidence to date that CCM significantly worsens TR

There was a significant reduction in RV end-diastolic transversal diameters ($p < 0.05$) (Table 3), while the severity of tricuspid regurgitation remained stable (Table 3).

Table 3. Effects of CCM on LV and RV echocardiographic variables at six months follow up.

Variable	Baseline	6 Months Follow Up	*p*-Value
LVEDV (mL)	224.2 ± 69.8	198.3 ± 45.7	<0.05
LVESV (mL)	154.8 ± 53.6	122.6 ± 66.3	<0.05
LVEF (%)	30.2 ± 6.1	35.4 ± 7.3	<0.05
TAPSE (mm)	16.6 ± 4.2	18.5 ± 3.6	<0.05
S wave (cm/s)	10.1 ± 1.8	11.3 ± 1.4	<0.05
PASP (mmHg)	34.2 ± 9.6	28.1 ± 6.9	<0.05
RVFWLS (%)	−13.7 ± 2.5	−15.1 ± 2.8	<0.05
TAPSE/PASP (mm/mmHg)	0.52 ± 0.22	0.66 ± 0.21	<0.05
RVOT PLAX (mm)	28.2 ± 3.1	27.1 ± 4.2	0.062
RVD 1	26.8 ± 5.3	25.7 ± 4.1	<0.05
RVD 2	28.1 ± 4.3	26.2 ± 3.2	<0.05
TI mild (n, %)	16 (76%)	18 (85%)	NA
TI moderate (n, %)	3 (14%)	2 (9%)	NA
TI severe (n, %)	2 (10%)	1 (4%)	NA

Contaldi, C., De Vivo, S., Martucci, M. L., D'Onofrio, A., Ammendola, E., Nigro, G., ... & Masarone, D. (2022). Effects of Cardiac Contractility Modulation Therapy on Right Ventricular Function: An Echocardiographic Study. *Applied Sciences*, *12*(15), 7917.

Tricuspid Regurgitation?

Fix HF-5/5C/EU REG:

no reports of worsening TR in 651 patients

Abraham, William T., et al. "A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation." *Heart Failure* 6.10 (2018): 874-883.

Kadish, Alan, et al. "A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure." *American heart journal* 161.2 (2011): 329-337.

Kuschyk, Jürgen, et al. "Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer Smart system." *European Journal of Heart Failure* 23.7 (2021): 1160-1169.

Growing Body of Clinical Evidence that CCM therapy can:

- **treat LV HF**
- **reduce RV pressure**
- **improve RV dimensions**
- *potentially* **stabilize or even improve pre-existing TR**

Cardiac Contractility Modulation in Symptomatic Heart Failure With Reduced Ejection Fraction: A Systematic Review and Single-Arm Meta-Analysis

Journal of Cardiovascular Electrophysiology, 2025

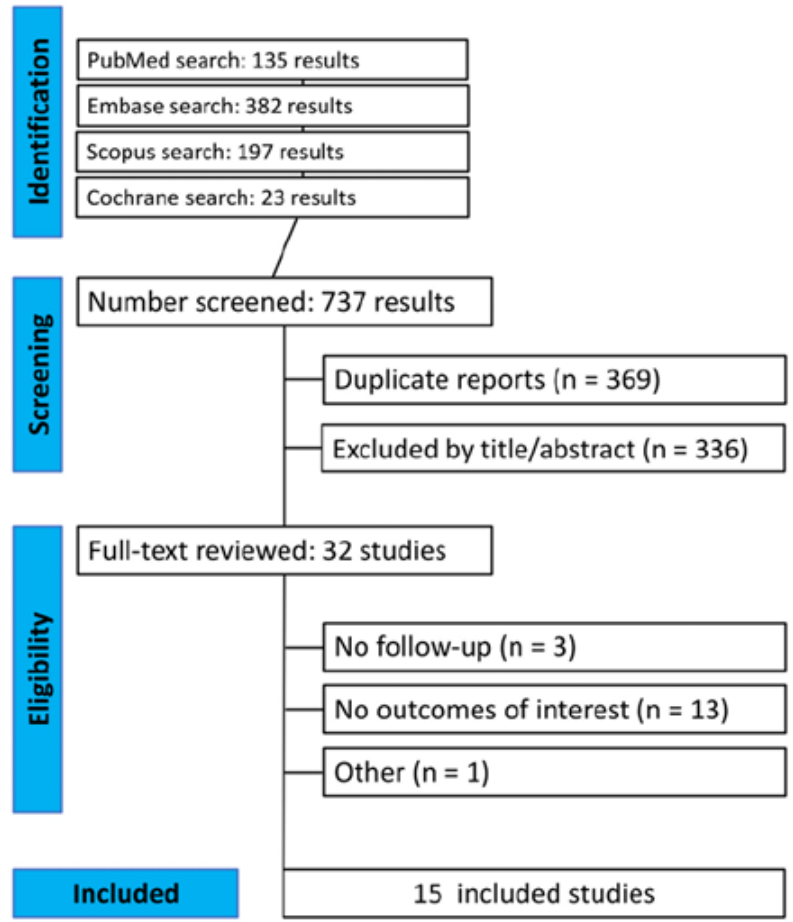
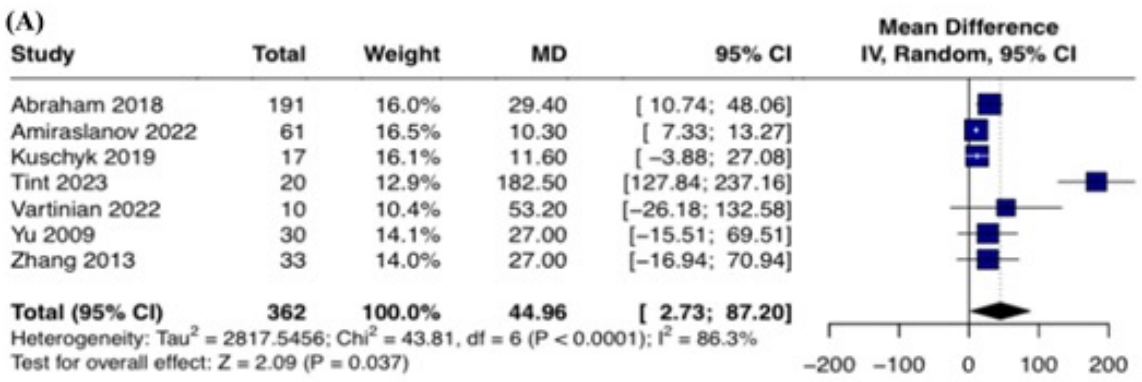


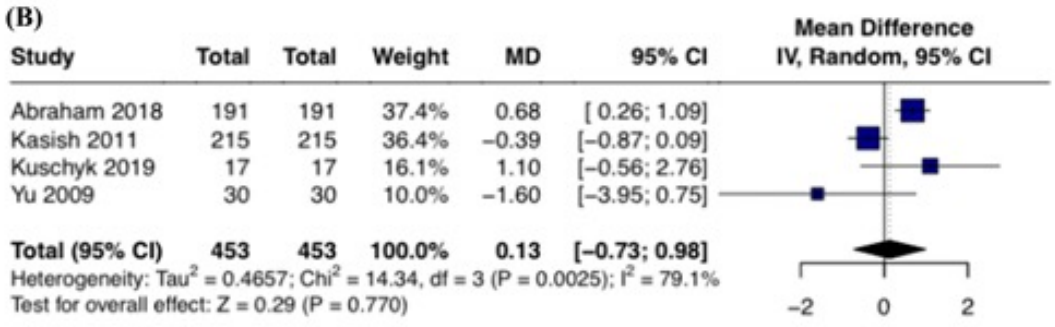
FIGURE 1 | PRISMA flowchart.

Cardiac Contractility Modulation in Symptomatic Heart Failure With Reduced Ejection Fraction: A Systematic Review and Single-Arm Meta-Analysis

Journal of Cardiovascular Electrophysiology, 2025

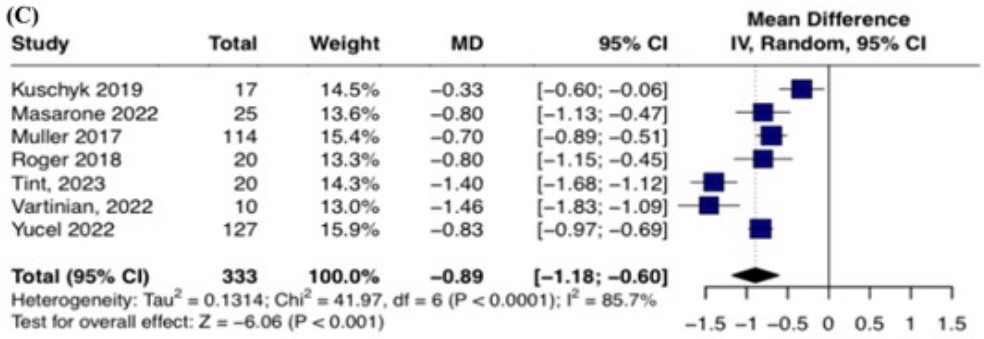
6 MWT
Increase 44.96 M (95% CI: 2.73-87.2; p=0.037)

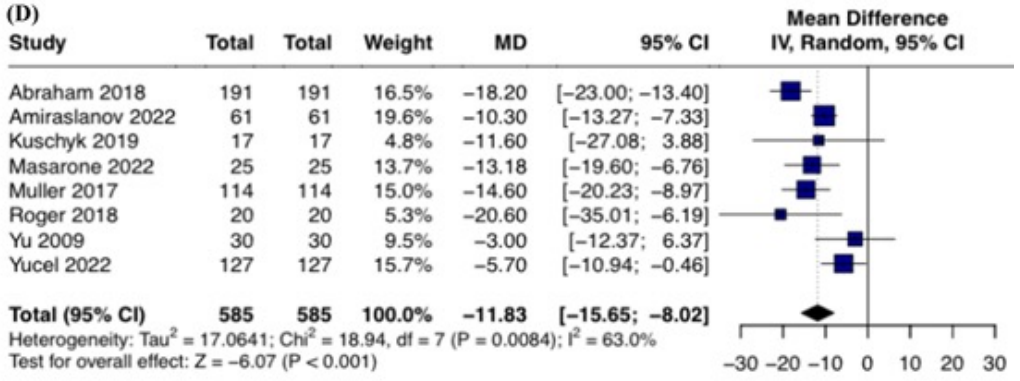




Peak VO2
0.13 mlO2/kg/min (95% CI: -0.73-0.98, p=0.770)

NYHA
Decrease 0.89 (95% CI: -1.18—0.60; p<0.001)





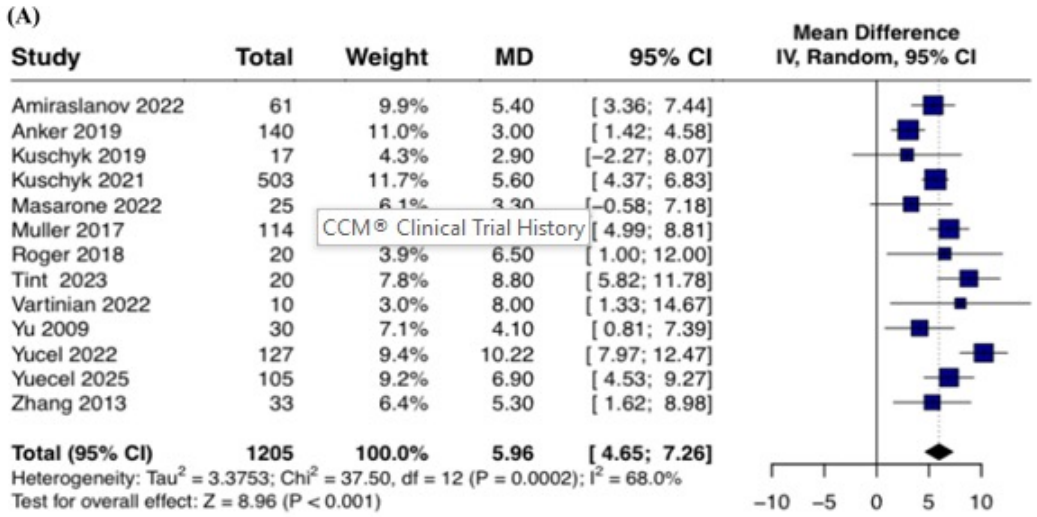
MLHFA
Reduction of 11.83 (95% CI: -15.65—8.02, p<0.001)

Cardiac Contractility Modulation in Symptomatic Heart Failure With Reduced Ejection Fraction: A Systematic Review and Single-Arm Meta-Analysis

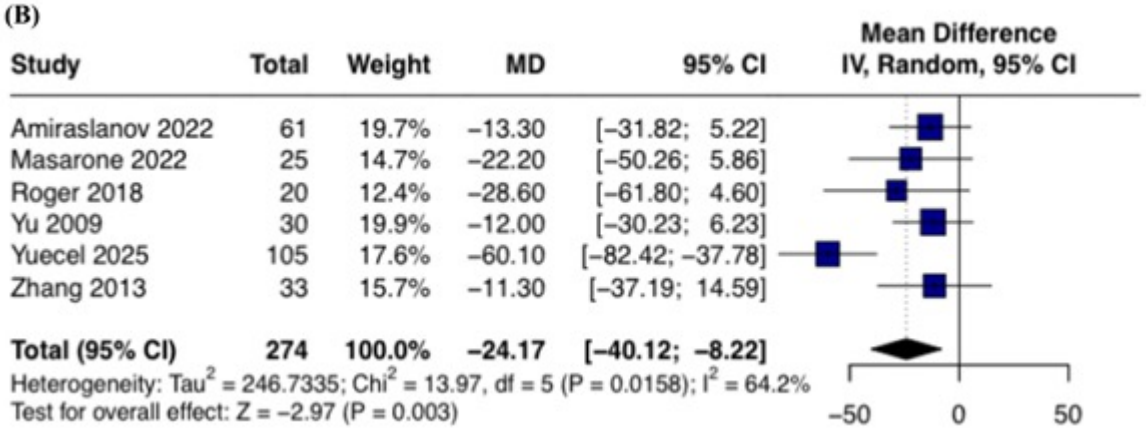
Journal of Cardiovascular Electrophysiology, 2025

LVEF

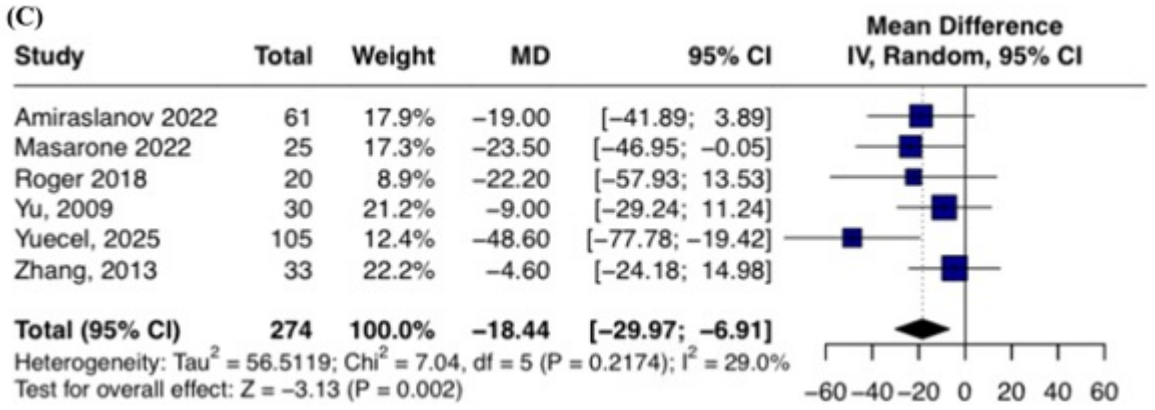
Increase by 5.96% (95% CI 4.65-7.26, p < 0.001)



LV ESV



LV EDV



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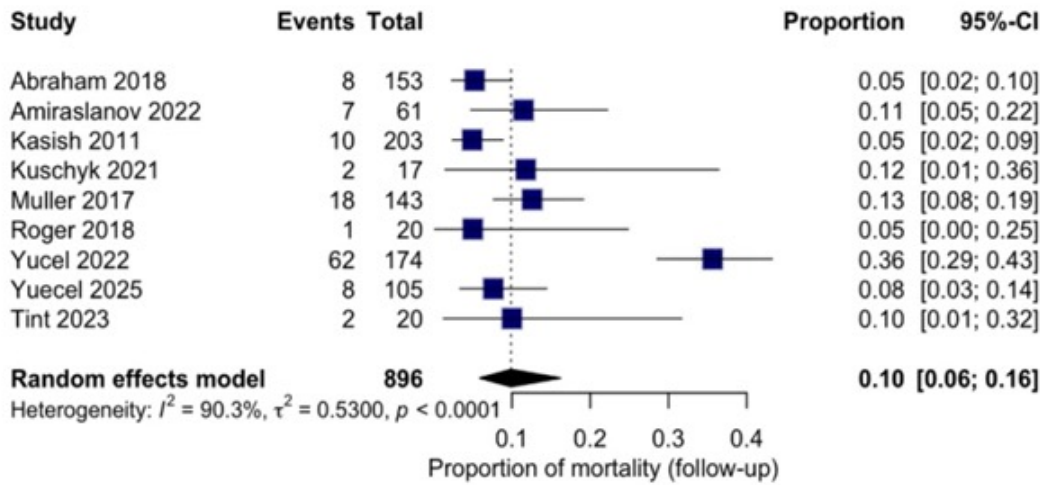


FIGURE 4 | Forest plot for the outcome of mortality rates. The analysis shows the mortality rates, analyzing the efficiency of cardiac contractility modulation across all included studies. CI, confidence interval.

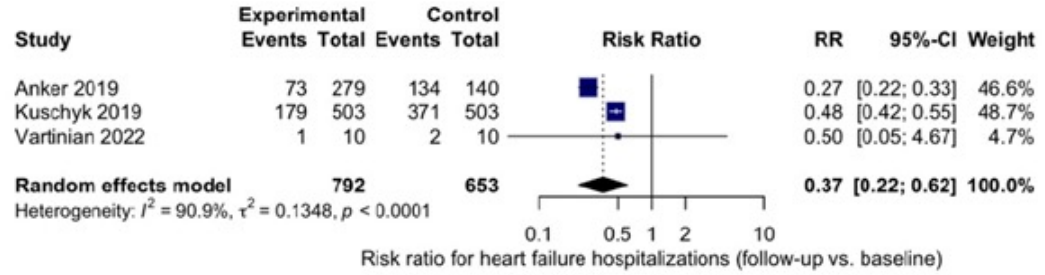


FIGURE 5 | Forest plot for the outcome of hospitalization for heart failure rates. The analysis shows the hospitalizations for heart failure, analyzing the efficiency of cardiac contractility modulation across all included studies. CI, confidence interval; RR, risk ratio.

Mortality rates

- 10% (95% CI: 6%-16%,; p <0.0001)

Heart Failure Hospitalization

- 0.37 (95% CI: 0.22-0.62; p=0.0001)
- Reflecting a 63% reduction in HF hospitalization.

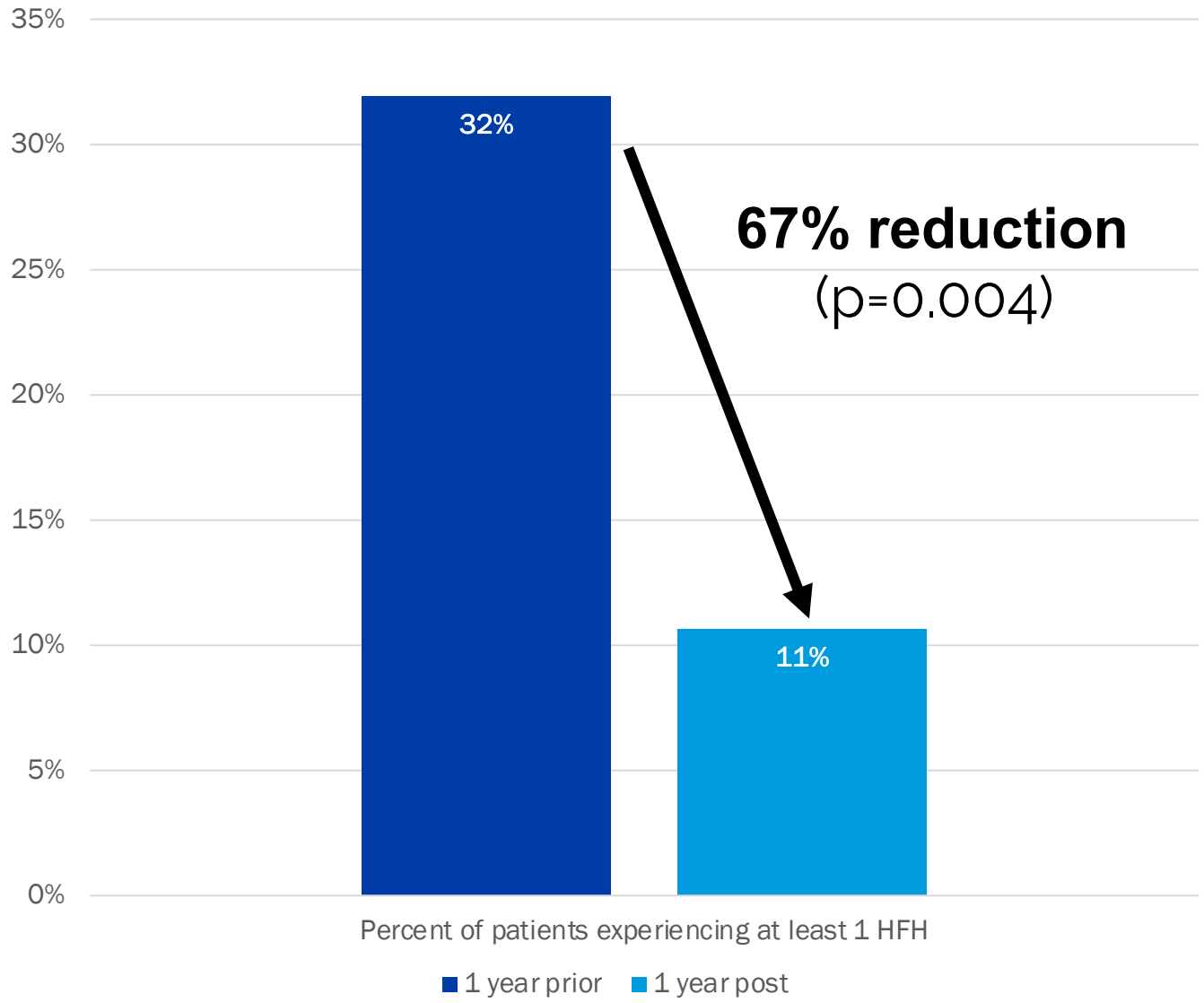
FEWER HOSPITALIZATIONS FOR PATIENTS RECEIVING CCM

"Fewer patients required HF hospitalization in the 1-year period after CCM therapy device implant compared to the 1-year period prior."

15 of 47 patients (**32%**) required at least one HFH in the year prior to device implantation.

5 of 47 patients (**11%**) required at least one HFH in the year after device implantation

represents a **67% reduction** in the number of patients experiencing a HFH (**p=0.004**)



Linde, C., Grabowski, M., Ponikowski, P., Rao, I., Stagg, A., & Tschöpe, C. (2022). Cardiac contractility modulation therapy improves health status in patients with heart failure with preserved ejection fraction: a pilot study (CCM-HFpEF). *European Journal of Heart Failure*.

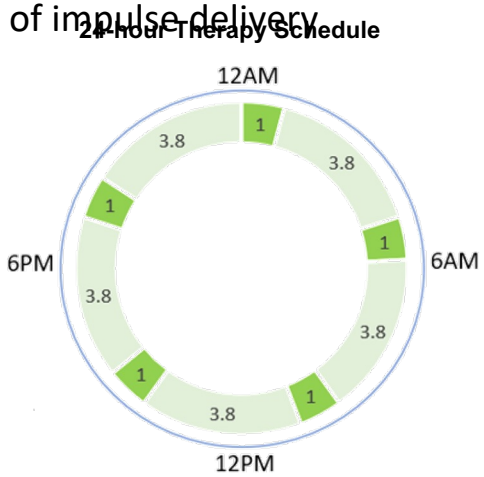
CARDIAC CONTRACTILITY MODULATION: MECHANISMS AND CLINICAL EVIDENCE

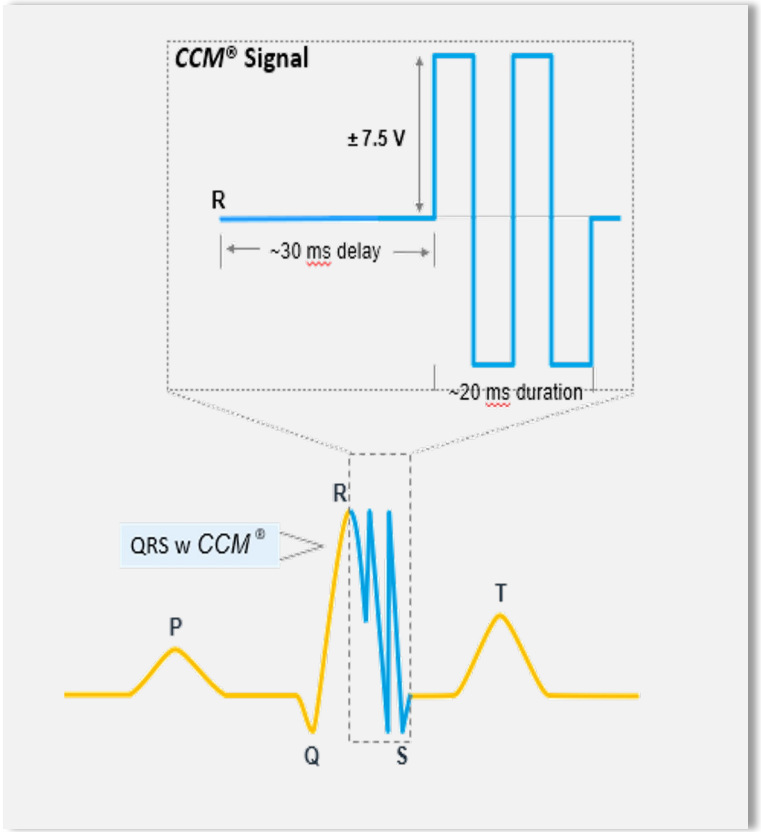
Cardiac contractility modulation (CCM) therapy has demonstrated benefits in symptomatic heart failure patients with reduced ejection fraction (HFrEF)who have narrow QRS complex and are not candidates for CRT.

THE TECHNOLOGY

CCM® Therapy Delivery

- CCM impulses are 300-400 X the output of typical pacing capture threshold for ventricular tissue
- therapy is non-excitatory given the timing of impulse delivery



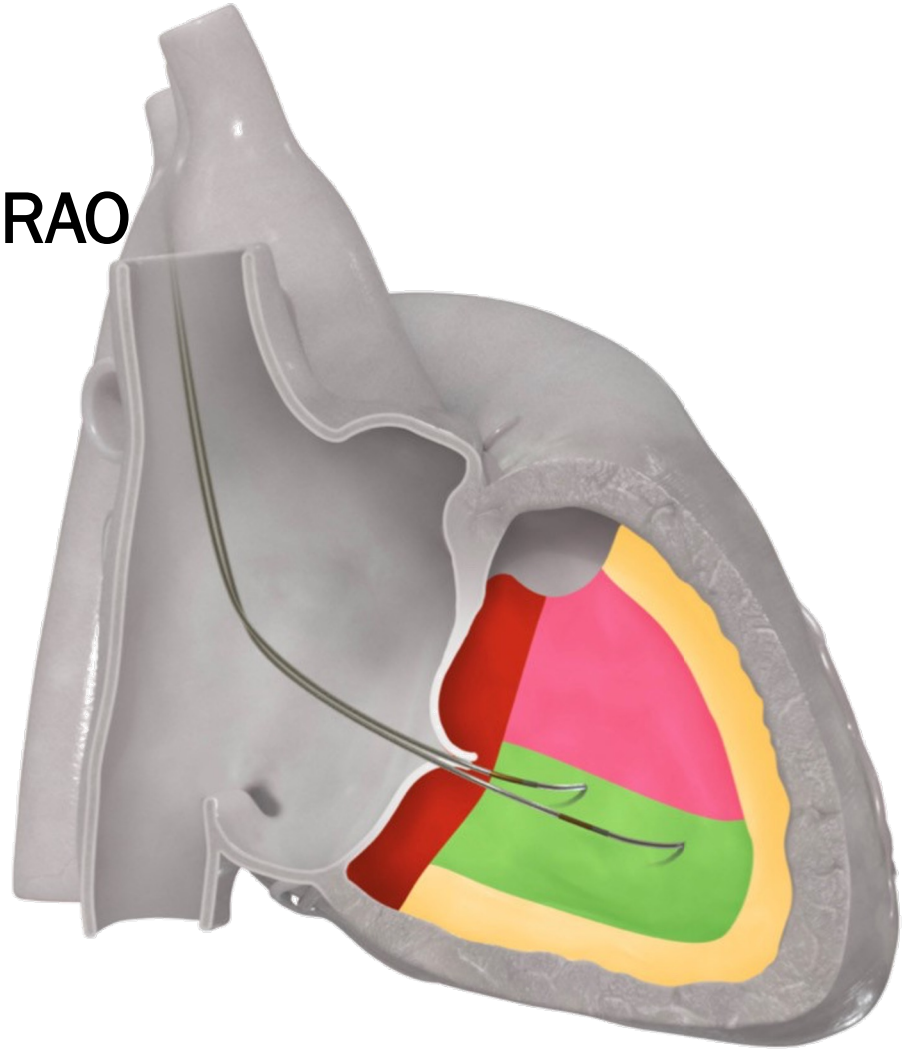


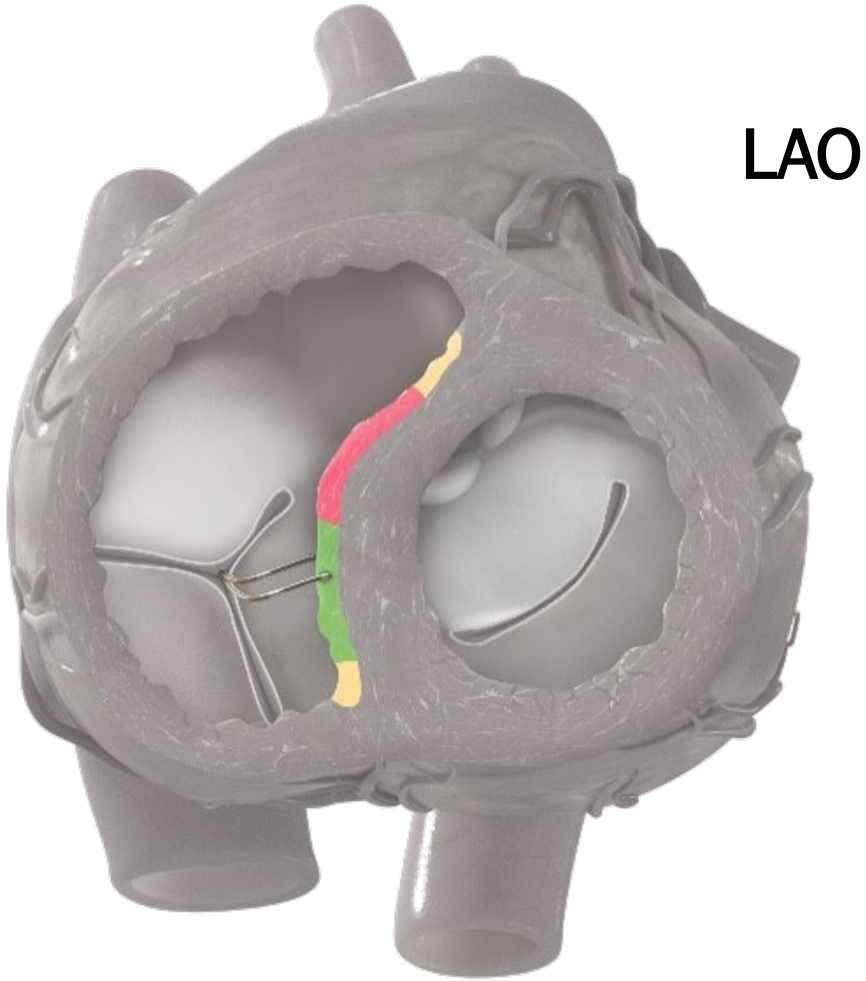
CCM® Therapy Schedule

- Seven (7) one-hour therapy delivery phases equally spaced over 24-hour period
- Device is recharged for 1 hour weekly
- Rechargeable battery warranted for 20 years

OPTIMIZER® IDEAL LEAD PLACEMENT

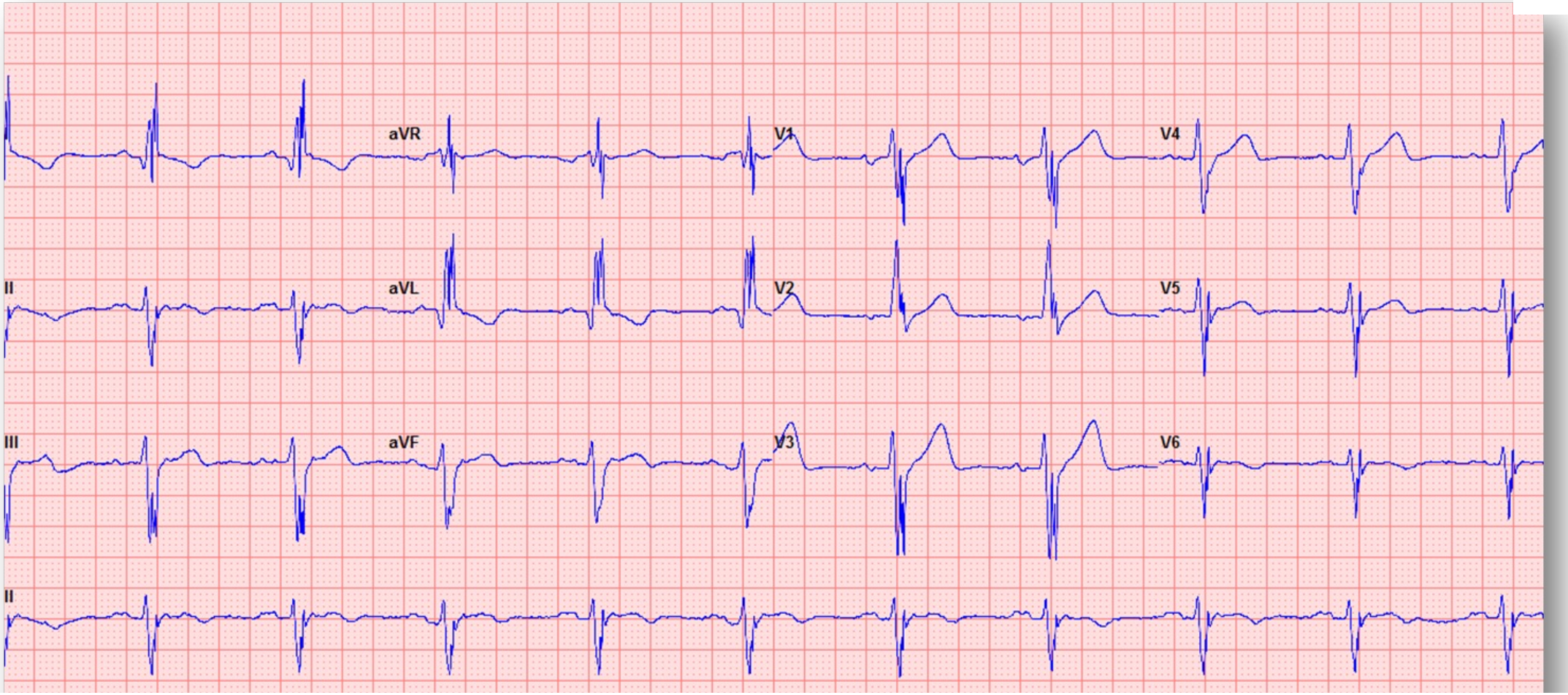
RAO



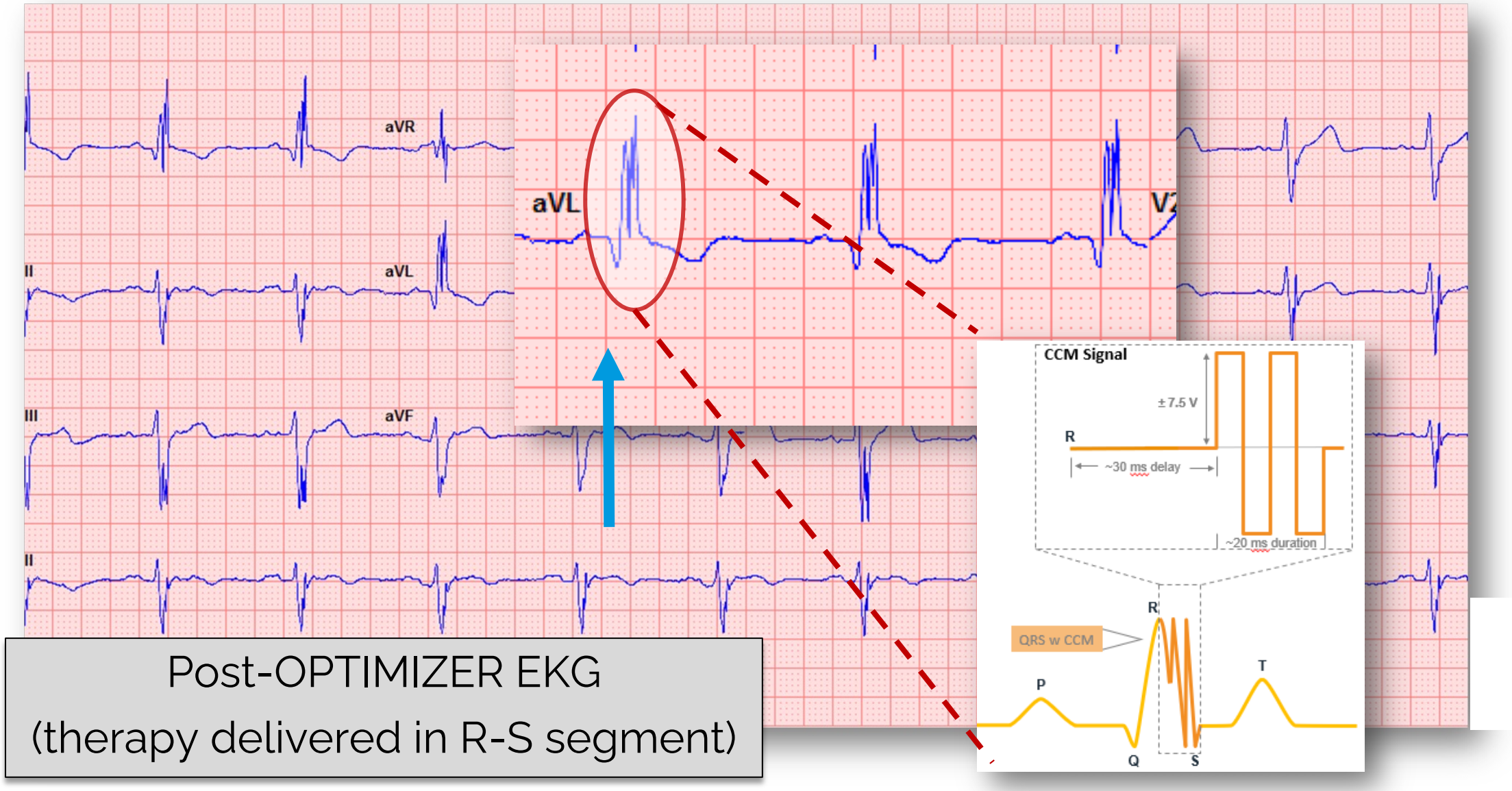


LAO

THERAPY DELIVERY – EXAMPLE ECG



THERAPY DELIVERY – EXAMPLE ECG



Post-OPTIMIZER EKG
(therapy delivered in R-S segment)

FUTURE DIRECTIONS

Optimizer® Smart

Optimizer® Smart Mini

Optimizer® Integra CCM-D

Clinical Portfolio

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

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

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

Current FDA Approved Indications

NYHA Class III heart failure patients who:

Have an LVEF (left ventricular ejection fraction) **from 45 % to 25 %**

Remain **symptomatic despite GDMT** (guideline directed medical therapy)

Have no current **indication for CRT** (Cardiac Resynchronization Therapy)

Northwell[SM]
Cardiovascular Institute

Northwell Intermediate Heart Failure Device Algorithm

***Symptomatic* HF, LVEF < 45%, on optimal GDMT**

↓

Not a CRT candidate OR CRT non-responder

No clinical improvement > 3-6 months post implant despite:
Bi-V pacing > 90%, appropriate LV lead placement, maintenance of sinus rhythm, and device optimization by EP team

↓

HF Risk Stratification
6MWT, CPET, Right Heart Catheterization

No high-risk features...evaluate EF

LVEF <25% | **LVEF 25-35%** | **LVEF 35-40%**

Consider BAT (Barostim)
If NT pro BNP < 1600, NYHA III or recent II, and no sub-cutaneous ICD

Consider CCM
if NYHA III
Evaluate risk of device related TR, especially if existing transvenous device (e.g PPM/ICD)

HIGH RISK FEATURES:
CI < 2.2
< 350 m on 6MWT
VO2 max < 14 mg/kg/min
or < 12 (on beta blocker)
VE/VCO2 slope > 34
NYHA class IV

Referral for LVAD or Heart Transplant Evaluation
(if life expectancy > 1 yr)

CCM = Cardiac Contractility Modulation
BAT = Baroreflex Activation Therapy