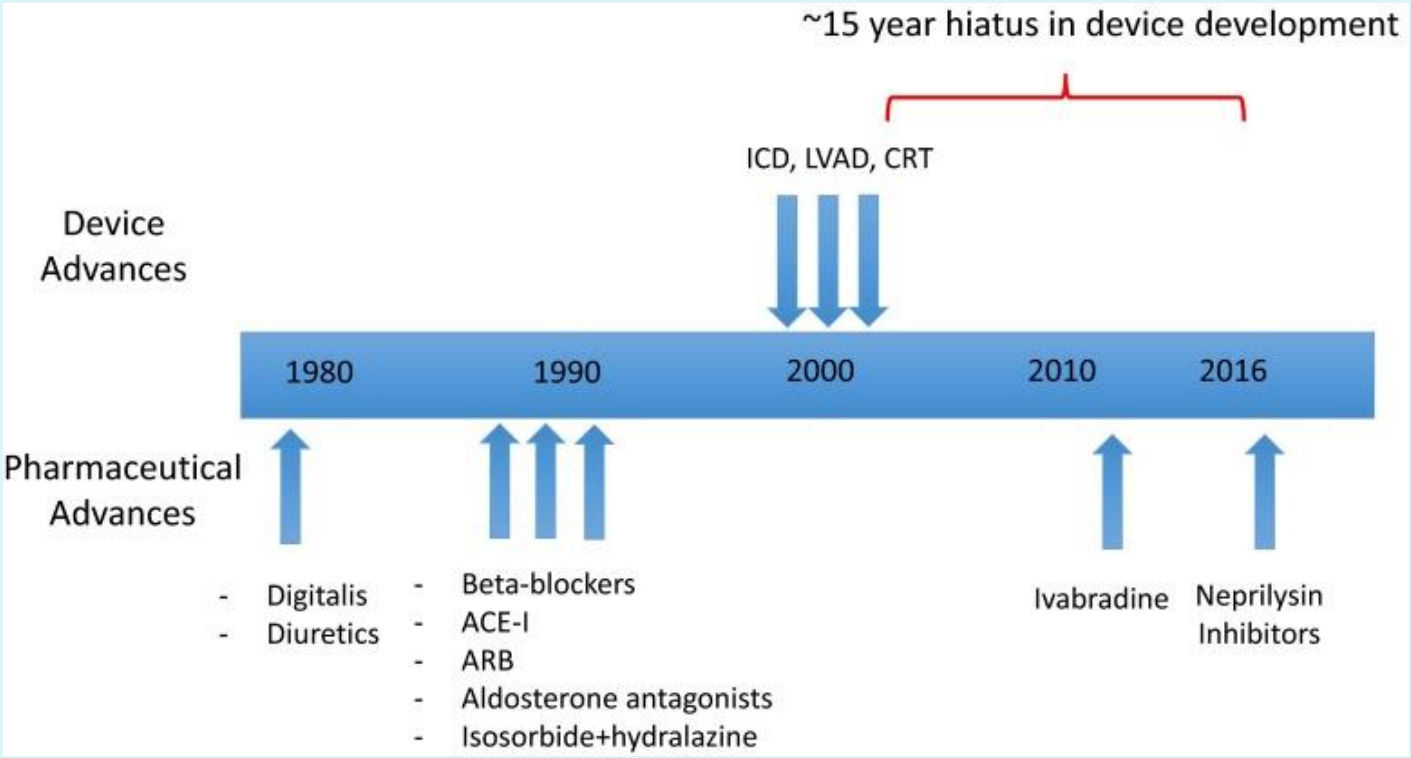
A.S.L. TO4

Azienda Sanitaria Locale
di Ciriè, Chivasso e Ivrea

LA STIMOLAZIONE INOTROPA NON FARMACOLOGICA NEL VENTRICOLO SINISTRO: UN NUOVO TRATTAMENTO PER L'INSUFFICIENZA VENTRICOLARE SINISTRA

Dr. Gaetano Senatore. Asl TO4, Cirié - Ivrea

CARDIAC CONTRACTILITY MODULATION: *PRIMI STUDI*



PAZIENTI CON QRS STRETTO E SCOMPENSO CARDIACO

The NEW ENGLAND JOURNAL of MEDICINE

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Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex

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RESULTS

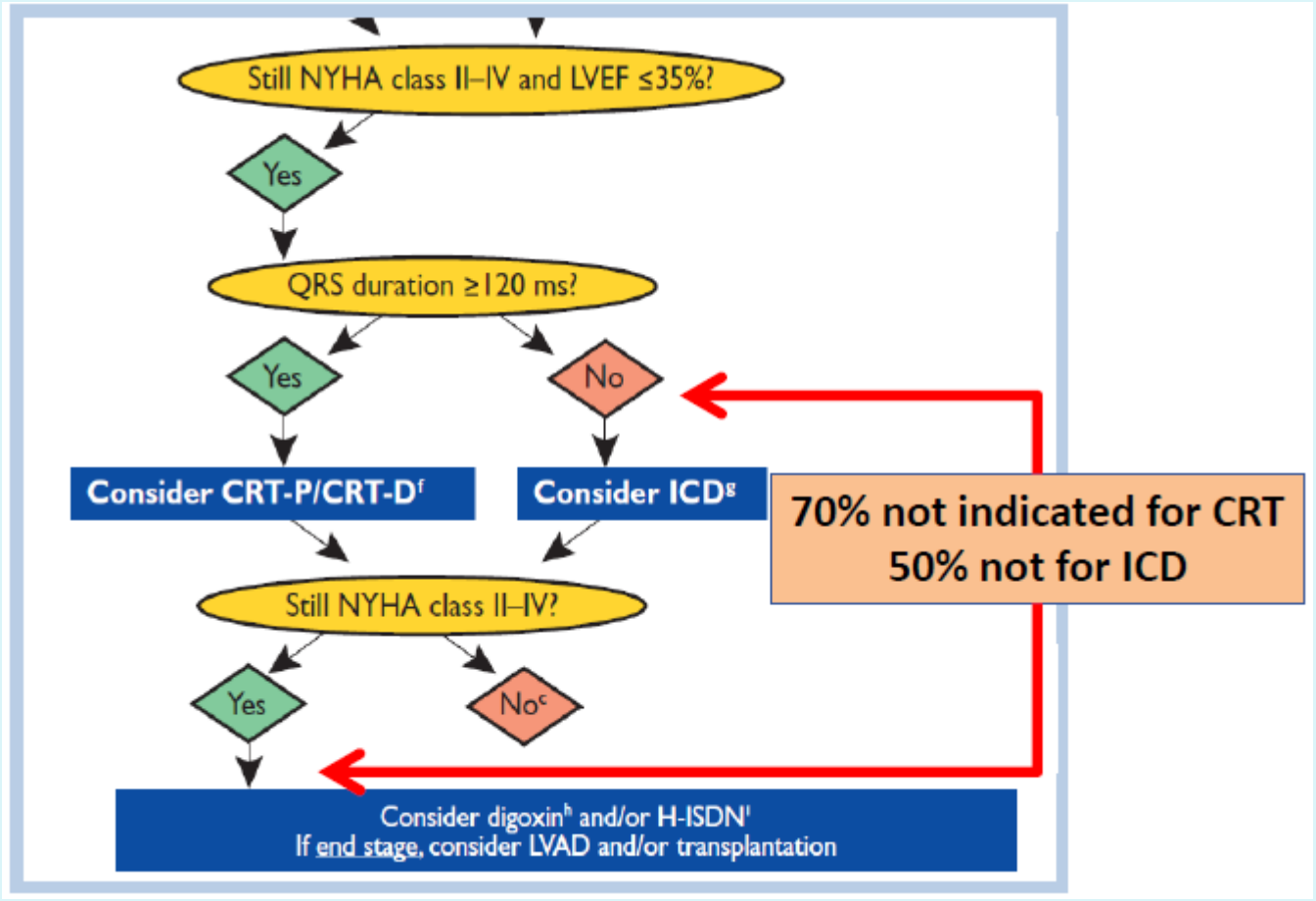
On March 13, 2013, the study was stopped for futility on the recommendation of the data and safety monitoring board. At study closure, the 809 patients who had undergone randomization had been followed for a mean of 19.4 months. The primary outcome occurred in 116 of 404 patients in the CRT group, as compared with 102 of 405 in the control group (28.7% vs. 25.2%; hazard ratio, 1.20; 95% confidence interval [CI], 0.92 to 1.57; P=0.15). There were 45 deaths in the CRT group and 26 in the control group (11.1% vs. 6.4%; hazard ratio, 1.81; 95% CI, 1.11 to 2.93; P=0.02).

CONCLUSIONS

In patients with systolic heart failure and a QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality. (Funded by Biotronik and GE Healthcare; EchoCRT ClinicalTrials.gov number, NCT00683696.)

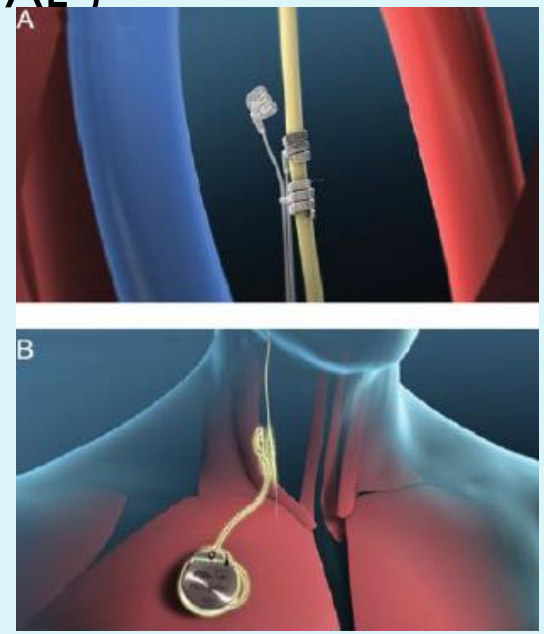
- LA CRT È DUNQUE CONTROINDICATA IN PAZIENTI CON QRS INFERIORE A 130 MS.

PAZIENTI CON QRS STRETTO E SCOMPENSO CARDIACO



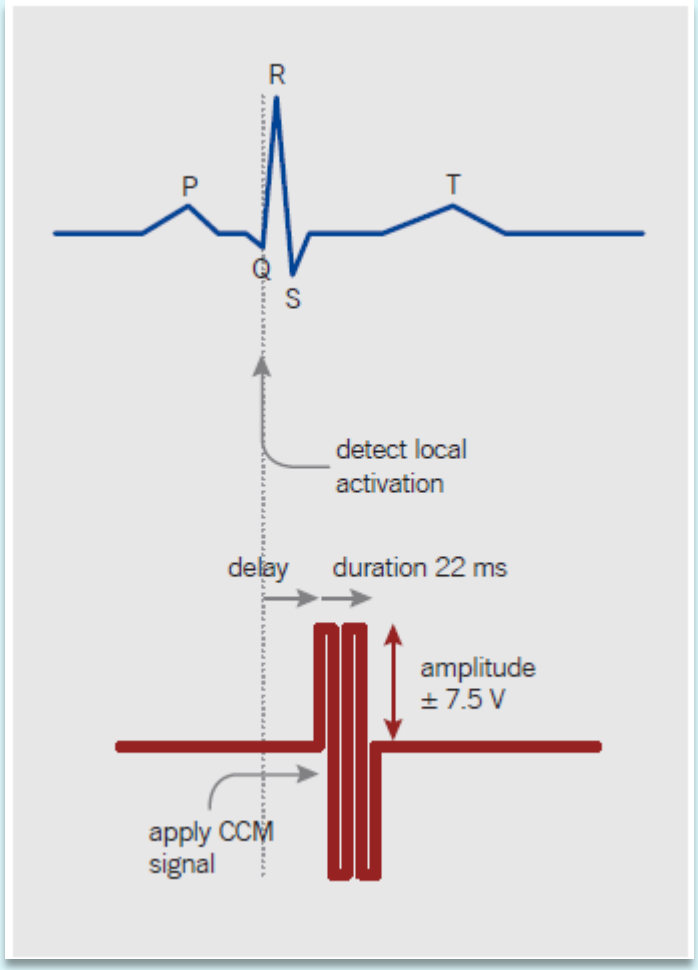
OPZIONI TERAPEUTICHE NEI MD PER PAZIENTI CON QRS STRETTO E CHF

- SPINAL CORD STIMULATION (SCS AND DEFEAT STUDY)
- VAGAL STIMULATION (NECTAR TRIAL)
- BARORECEPTOR-STIMULATORS (BEATHF TRIAL)

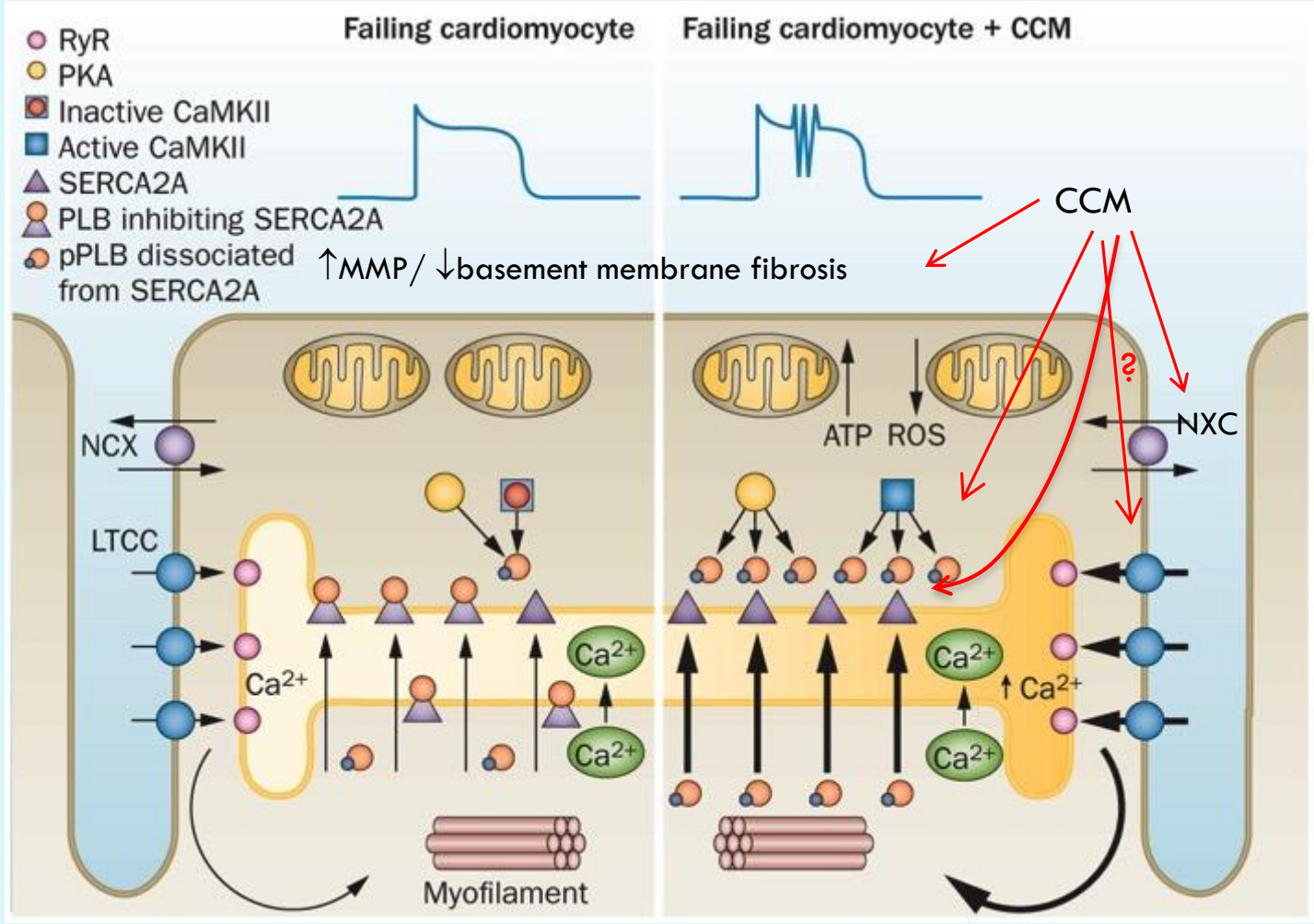


OPZIONI TERAPEUTICHE NEI MD PER PAZIENTI CON QRS STRETTO E CHF: CCM

- CCM – CARDIAC CONTRACTILITY MODULATION.
- I SEGNALI CCM SONO DI NATURA NON ECCITATORIA.
- TALI SEGNALI VENGONO EROGATI DURANTE IL PERIODO REFRATTARIO ASSOLUTO DELLA CELLULA CARDIACA.
- LA CCM ESERCITA UNA ATTIVITA' IN PRIMA BATTUTA LOCALIZZATA IN PROSSIMITA' DEGLI ELETTRODI.



CARDIAC CONTRACTILITY MODULATION: MECCANISMO D'AZIONE



Lyon et al. 2013 Nat. Rev. Cardiol.

Upregulate SERCA Activity

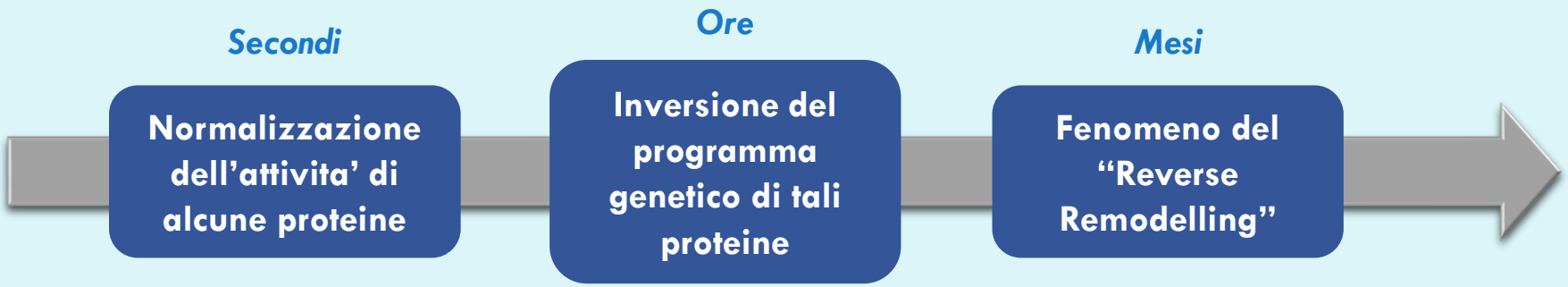
Phosphorylate phospholamban, thereby detaching it from SERCA

Activate LTCC currents

Normalize Na/Ca exchanger

Increase MMP; revert pathological remodeling

CARDIAC CONTRACTILITY MODULATION: MECCANISMO D'AZIONE



La Terapia CCM interessa tutti e 6 i componenti dello scompenso cardiaco

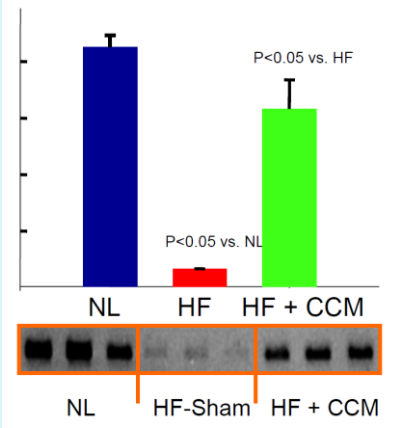
1. Distribuzione del Calcio nei Cardiomiociti
2. Fosforilazione della Tititna

} Incremento Contrattilita'

3. Fibrosi Cardiaca
4. Controllo sistema nervoso autonomico
5. Bilancio dell'energia
6. Rimodellamento tessuto cardiaco

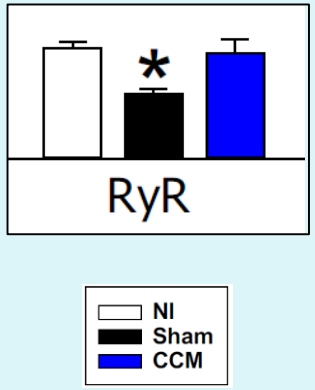
CARDIAC CONTRACTILITY MODULATION: MECCANISMO D'AZIONE

Normalizes SERCA mRNA expression



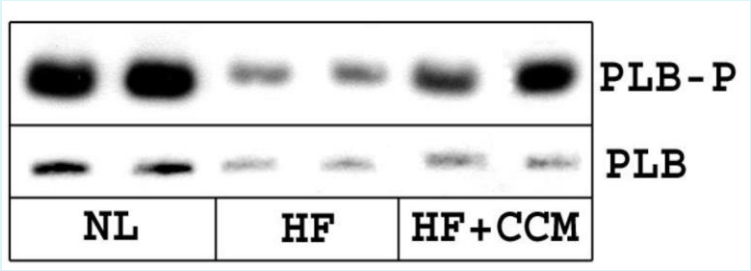
Sabbah et. al. Curr Heart Fail Rep. 2006;

Normalizes ryanodine receptor (RyR2)



Imai et al. JACC, 2007

Restores normal level of PLB



Imai JACC, 2007

CARDIAC CONTRACTILITY MODULATION: MECCANISMO D'AZIONE

METHODS:
Thirty patients (60 + or - 11 years, 80% male) with New York Heart Association (NYHA) functional class III heart failure, ejection fraction <35%, and QRS <120 ms were assessed at baseline and 3 months. LV reverse remodeling was measured by real-time 3-dimensional echocardiography.

RESULTS:
LV reverse remodeling was evident, with a reduction in LV end-systolic volume by -11.5 + or - 10.5% and a gain in ejection fraction by 4.8 + or - 3.6% (both $p < 0.001$). Myocardial contraction was improved in all LV walls, including sites remote from CCM delivery (all $p < 0.05$) (…) Clinically, there was improvement of NYHA functional class ($p < 0.001$) and 6-min hall walk distance ($p = 0.015$).

CONCLUSIONS:
CCM improves both global and regional LV contractility, including regions remote from the impulse delivery, and may contribute to LV reverse remodeling and gain in systolic function. Such improvement is unrelated to diastolic function or mechanical dyssynchrony.
Similar results in long term follow up (Mannheim data)

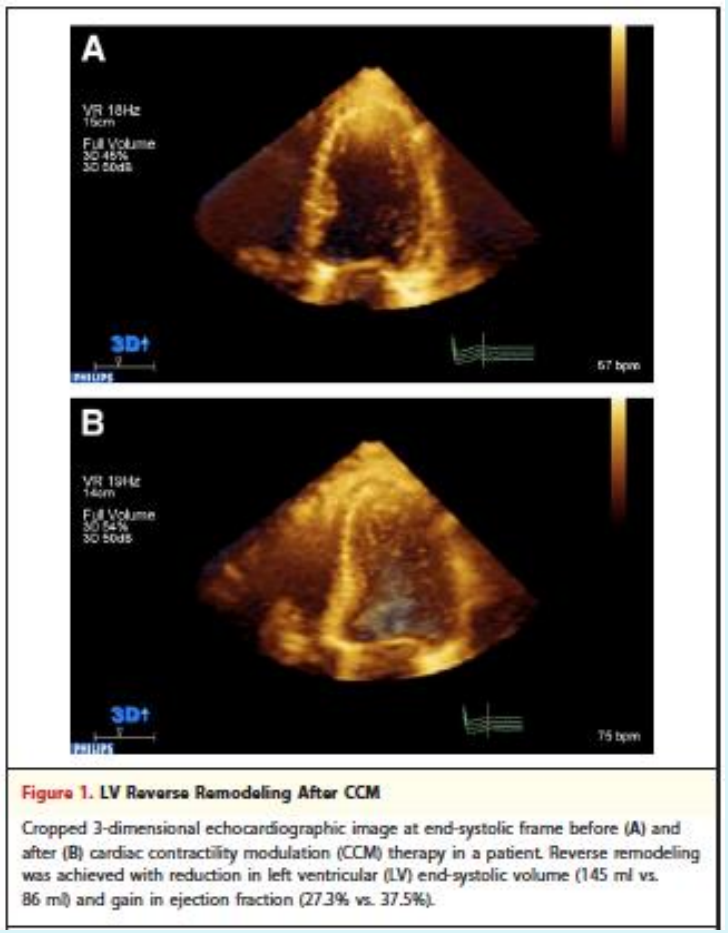


Figure 1. **LV Reverse Remodeling After CCM**

Cropped 3-dimensional echocardiographic image at end-systolic frame before (A) and after (B) cardiac contractility modulation (CCM) therapy in a patient. Reverse remodeling was achieved with reduction in left ventricular (LV) end-systolic volume (145 ml vs. 86 ml) and gain in ejection fraction (27.3% vs. 37.5%).

Yu et al. JACC Cardiovascular Imaging, July 2000

CCM: PRECEDENTI DEVICES & OPTIMIZER SMART

- Device estremamente piú piccolo rispetto alle precedenti generazioni (**31 CC, 48 Gr**)
- **Batteria ricaricabile** dall'esterno;
- Non neccessariamente associato all'impianto di un ICD;
- Disponibile per pazienti **con FA**;

CCM: PRECEDENTI DEVICES & OPTIMIZER SMART

Cassa

Caricatore portatile

Programmatore

OPTIMIZER SMART: LINEE GUIDA ESC

8.3 Other implantable electrical devices

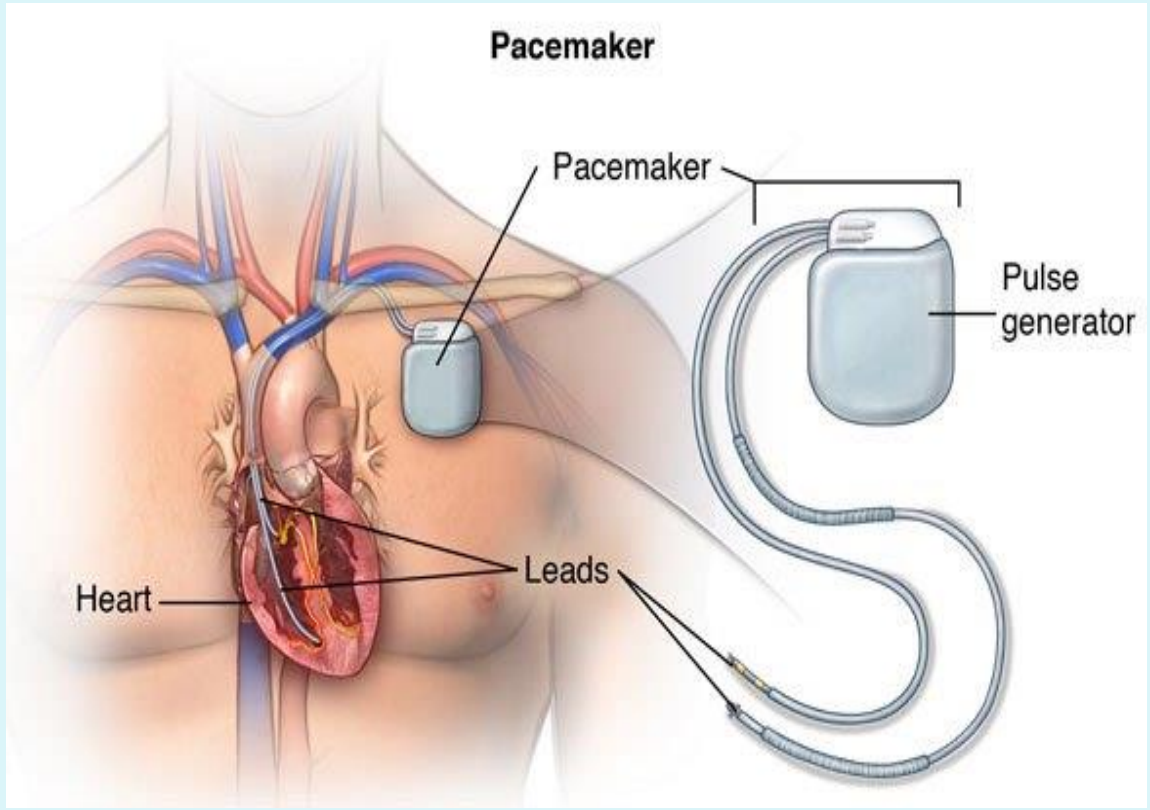
For patients with HFrEF who remain symptomatic despite OMT and do not have an indication for CRT, new device therapies have been proposed and in some cases are approved for clinical use in several European Union (EU) countries but remain under trial evaluation.

Cardiac contractility modulation (CCM) is similar in its mode of insertion to CRT, but it involves non-excitatory electrical stimulation of the ventricle during the absolute refractory period to enhance contractile performance without activating extra systolic contractions. CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (< 120 ms).[221,222] An individual patient data meta-analysis demonstrated an improvement in exercise tolerance (peak VO_2) and quality of life (Minnesota Living with Heart Failure questionnaire). Thus CCM may be considered in selected patients with HF. The effect of CCM on HF morbidity and mortality remains to be established.

Most other devices under evaluation involve some modification of the activity of the autonomic nervous system (ANS) by targeted electrical stimulation.[298,299] These include vagal nerve stimulation, spinal cord stimulation, carotid body ablation and renal denervation, but so far none of the devices has improved symptoms or outcomes in RCTs.

- LINEE GUIDA ESC SU HF (OTTOBRE 2016)
- COSA FARE QUANDO OMT NON GENERA MIGLIORAMENTI SIGNIFICATIVI
- PRIMA VOLTA MENTION SU CCM
- ALTRE TERAPIE DIMOSTRATE NON EFFICACI!

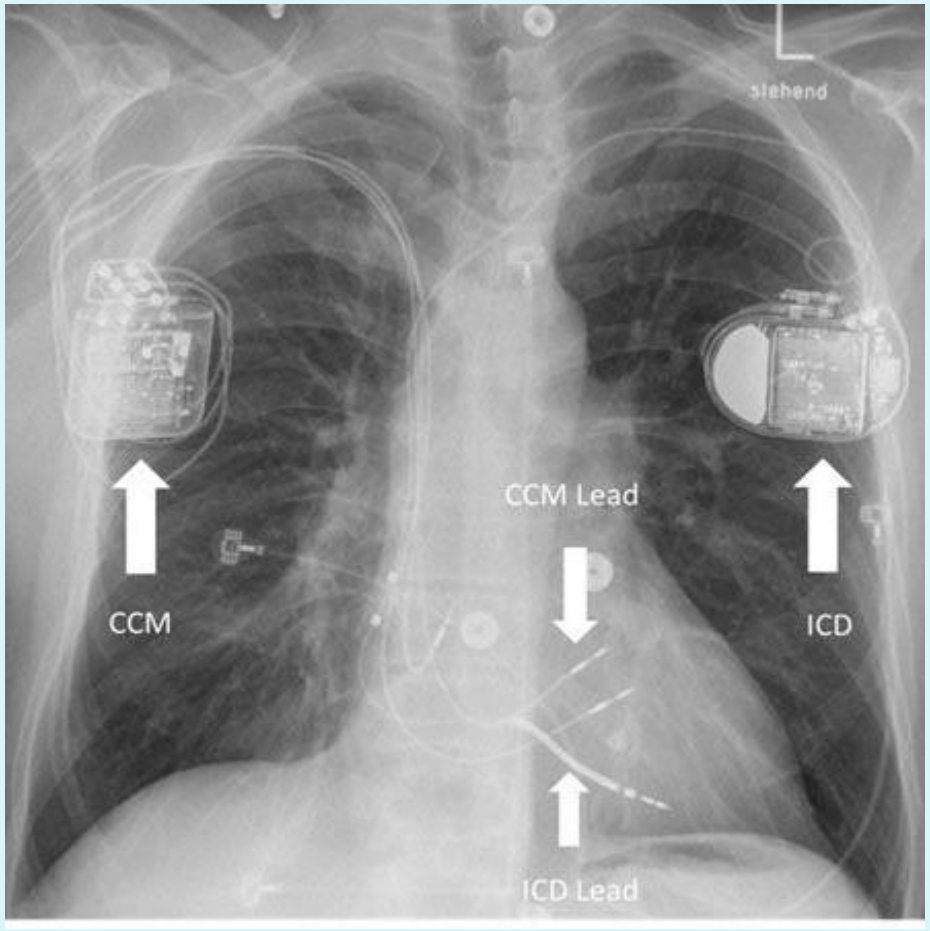
OPTIMIZER SMART: DEVICE PER ELETTROFISIOLOGI?



OPTIMIZER SMART: PROCEDURA DI IMPIANTO

- PROCEDURA SEMPLICE E LINEARE
- IDENTICA A PROCEDURA PM CON DUE LEADS IN POSIZIONE RV SEPTUM
- LEAD ATRIALE RICHIESTO SOLO SE SENSING VENTRICOLARE DEL SETTO < 2.5MV
- POSIZIONAMENTO DEVICE CON SISTEMA INDUZIONE RICARICA VERSO L'ALTO

OPTIMIZER SMART: PROCEDURA DI IMPIANTO



- DEVICE COMPATIBILE CON BRADY LEADS ATTUALMENTE IN COMMERCIO CON ALCUNE CARATTERISTICHE (RIVESTIMENTO E SUPERFICIE PUNTA);
- POSIZIONAMENTO DEI 2 LEADS CCM SU RV SEPTUM CON DISTANZA DI ALMENO 1 CM ;
- DEVICE IN GRADO DI FUNZIONARE PER PAZIENTI CON FE <35% CON ICD. MANTENERE DISTANZA DA LEAD TACHY DI ALMENO 1.5 CM PER EVITARE CROSSTALK SU ICD LEAD CHANNEL;
- FUNZIONAMENTO ANCHE CON S-ICD;
- POSIZIONAMENTO DEVICE CON SISTEMA INDUZIONE RICARICA VERSO L'ALTO

OPTIMIZER SMART: PROCEDURA DI IMPIANTO

- PROCEDURA DI RICARICA DEL DEVICE 1 VOLTA A SETTIMANA PER CIRCA 40-45 MIN;
- MINICHARGER GARANTISCE UNA SERIE DI “SEMPLICI COMUNICAZIONI” SENZA AUSILIO DEL PROGRAMMATORE;
- TROUBLESHOOTING CON MAGNETE: DISATTIVAZIONE TOTALE DEL DEVICE
- GESTIONE FOLLOW UP IDENTICA A PAZIENTI PORTATORI DI PM O ICD

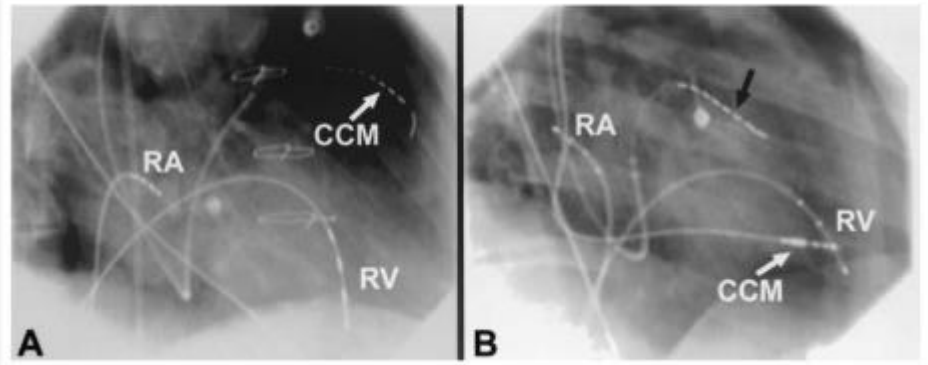
CARDIAC CONTRACTILITY MODULATION: *PRIMI STUDI*

Cardiac Contractility Modulation by Electric Currents Applied During the Refractory Period in Patients With Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy

Carlo Pappone, MD, PhD, Salvatore Rosanio, MD, PhD, Daniel Burkhoff, MD, PhD, Yuval Mika, DSc, Gabriele Vicedomini, MD, Giuseppe Augello, MS, Itzhak Shemer, MD, David Prutchi, DSc, Walid Haddad, PhD, Ricardo Aviv, DSc, Yehuda Snir, DSc, Itzhak Kronzon, MD, Ottavio Alfieri, MD, and Shlomo A. Ben-Haim, MD, PhD

We assessed the feasibility of cardiac contractility modulation (CCM) by electric currents applied during the refractory period in patients with heart failure (HF). Extracellular electric currents modulating action potential and calcium transients have been shown to potentiate myocardial contractility in vitro and in animal models of chronic HF. CCM signals were biphasic square-wave pulses with adjustable amplitude, duration, and time delay from sensing of local electric activity. Signals were applied to the left ventricle through an epicardial vein (in 12 patients) or to the right ventricular (RV) aspect of the septum endocardially (in 6 patients). Simultaneous left ventricular (LV) and aortic pressure measurements were performed using a Millar catheter (Millar Instruments, Houston, Texas). Hemodynamics during RV temporary dual-chamber pacing was regarded as the control condition. Both LV and RV CCM stimulation increased dP/dt_{max} to a similar degree (9.1 ± 4.5% and 7.1 ± 0.8%, respectively; $p < 0.01$ vs controls), with associated aortic pulse pressure changes of 10.3 ± 7.2% and 10.8 ± 1.1% ($p < 0.01$ vs controls). Regional systolic wall motion assessed quantitatively by color kinesis echocardiography was markedly enhanced near the CCM electrode, and the area of increased contractility involved 4.6 ± 1.2 segments per patient. In 6 patients with HF with left bundle branch block, CCM signals delivered during biventricular pacing (BVP) produced an additional 16.1 ± 3.7% increase in dP/dt_{max} and a 17.0 ± 7.5% increase in pulse pressure compared with BVP alone ($p < 0.01$). CCM stimulation in patients with HF enhanced regional and global measures of LV systolic function, regardless of the varied delivery chamber or whether modulation was performed during RV pacing or BVP.

(Am J Cardiol 2002;90:1307–1313)



- **Primo Studio**: Am.J.CARDIOLOGY, Pappone (2002);
- *Applicazione su RV Septum (6 patient) e LV (12 Patient)*
- ***Variazioni significative Dp/Dt***

CARDIAC CONTRACTILITY MODULATION: *PRIMI STUDI*

First Human Chronic Experience with Cardiac Contractility Modulation by Nonexcitatory Electrical Currents for Treating Systolic Heart Failure: Mid-Term Safety and Efficacy Results from a Multicenter Study

CARLO PAPPONE, M.D., PH.D., GIUSEPPE AUGELLO, M.D., SALVATORE ROSANIO, M.D., PH.D., GABRIELE VICEDOMINI, M.D., VINCENZO SANTINELLI, M.D., MASSIMO ROMANO, M.D., EUSTACHIO AGRICOLA, M.D., FRANCESCO MAGGI, D.SC., GERHARD BUCHMAYR, D.SC.,‡ GIOVANNI MORETTI,‡ YUVAL MIKA, D.SC.,* SHLOMO A. BEN-HAIM, M.D., PH.D.,† MICHAEL WOLZT, M.D.,‡ GUENTER STIX, M.D.,‡ and HERWIG SCHMIDINGER, M.D.‡

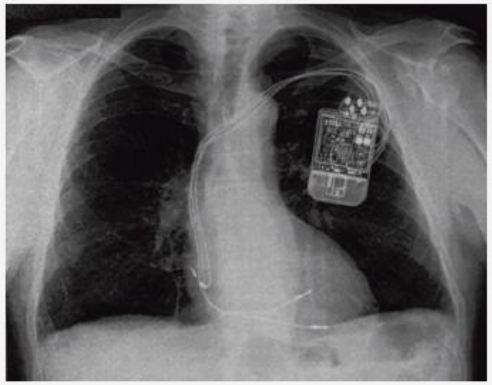
From the Department of Cardiology, Electrophysiology and Cardiac Pacing Unit, San Raffaele University Hospital, Milan, Italy; *Department of Physiology and Biophysics, Technion-Israel Institute of Technology, Haifa, Israel; †Division of Cardiology, New York University Medical Center, New York, New York, USA; and ‡Department of Cardiology, University of Vienna, Vienna, Austria

Electrical Modulation of the Failing Contractility. *Introduction:* Conventional electrical therapies for heart failure (HF) encompass defibrillation and ventricular resynchronization for patients at high risk for lethal arrhythmias and/or with inhomogeneous ventricular contraction. Cardiac contractility modulation (CCM) by means of nonexcitatory electrical currents delivered during the action potential plateau has been shown to acutely enhance systolic function in humans with HF. The aim of this multicenter study was to assess the chronic safety and preliminary efficacy of an implantable device delivering this novel form of electrical therapy.

Methods and Results: Thirteen patients with drug-resistant HF (New York Heart Association [NYHA] class III) were consecutively implanted with a device (OPTIMIZER™ II) delivering CCM biphasic square-wave pulses (20 ms, 5.8–7.7 V, 30 ms after detection of local activation) through two right ventricular leads screwed into the right aspect of the interventricular septum. CCM signals were delivered 3 hours daily over 8 weeks (3-hour phase) and 7 hours daily over the next 24 weeks (7-hour phase). Safety and feasibility of this novel therapy were regarded as primary endpoints. Preliminary clinical efficacy, -as expressed by changes in ejection fraction (EF), NYHA class, 6-minute walking test (6-MWT), peak O_2 uptake (peak VO_2), and Minnesota Living with HF Questionnaire (MLWHFQ), was assessed at baseline and at the end of each phase. At the end of follow-up (8.8 ± 0.2 months), all patients were alive, without heart transplantation or need for left ventricular assist device. Serial 24-hour Holter analysis revealed no proarrhythmic effect. No devices malfunctioned or failed for any reason other than end-of-battery life. Throughout the two study phases, EF improved from 22.7 ± 7% to 28.7 ± 7% and 37 ± 13% ($P = 0.004$), 6-MWT from 418 ± 99 m to 477 ± 96 m and 510 ± 107 m ($P = 0.002$), MLWHFQ from 36 ± 21 to 18 ± 12 and 7 ± 6 ($P = 0.002$), peak VO_2 from 13.7 ± 1.1 to 14.9 ± 1.9 to 16.2 ± 2.4 ($P = 0.037$), and NYHA class from 3 to 1.8 ± 0.4 to 1.5 ± 0.7 ($P < 0.001$).

Conclusion: CCM therapy appears to be safe and feasible. Proarrhythmic effects of this novel therapy seem unlikely. Preliminary data indicate that CCM gradually and significantly improves systolic performance, symptoms, and functional status. CCM therapy for 7 hours per day is associated with greater dispersion near the mean, emphasizing the need to individually tailor CCM delivery duration. The technique appears to be attractive as an additive treatment for severe HF. Controlled randomized studies are needed to validate this novel concept. *(J Cardiovasc Electrophysiol, Vol. 15, pp. 418-427, April 2004)*

cardiac contractility modulation, heart failure



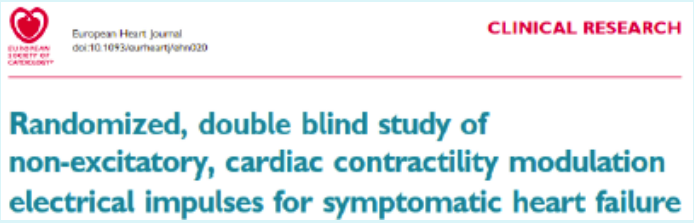
Pappone et al. J Cardiovasc Electrophysiol, Vol. 15, pp. 418-427, April 2004

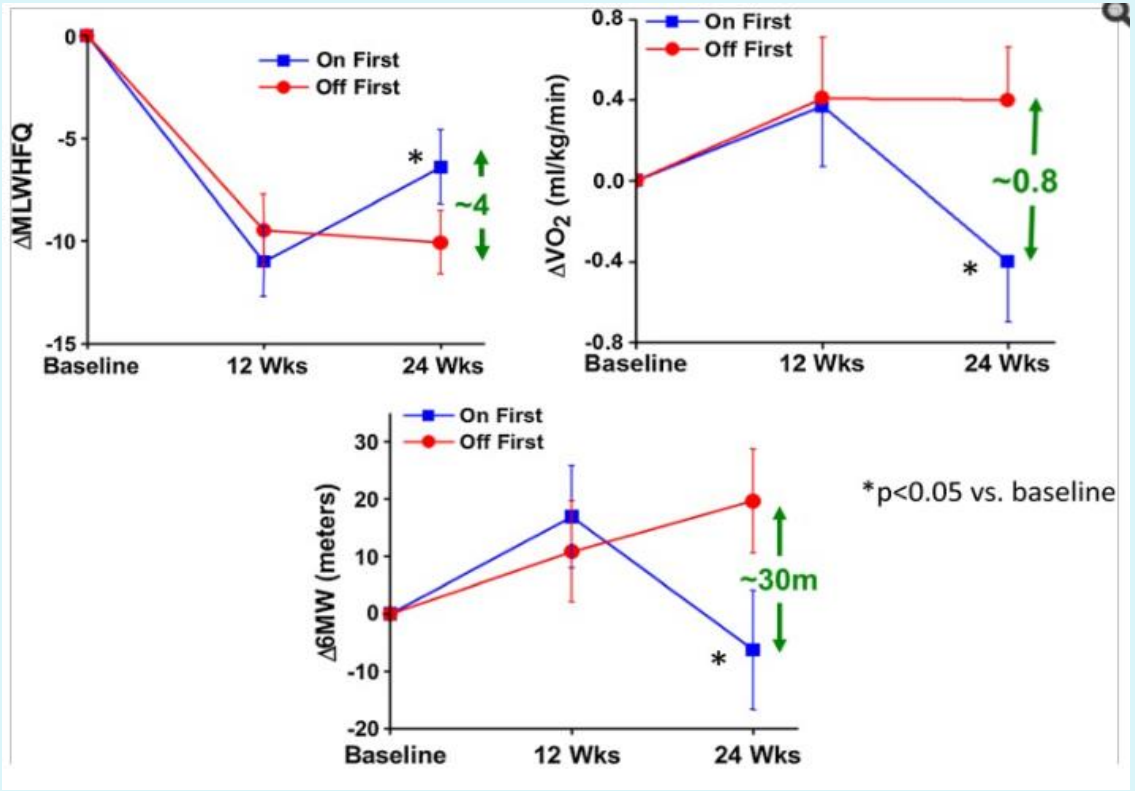
- **Primo Studio Cronico**: Pappone et al. J.Cardiovasc Electrophysiol (2002);
- *13 Pazienti , 2 leads RV Sept (OPT II) ;*
- *Variazioni significative su **EF, NYHA Class, 6-MWT, Peak Vo2, MLWHFQ***

CARDIAC CONTRACTILITY MODULATION: *RCT*

Study Designation	Comments	Randomized	Device	Countries	Total patients
FIX-HF-1	Acute study		Opt I	Italy	40
FIX-HF-2	First chronic study		Opt I	Italy	6
FIX HF-3	CE study (EU)		Opt II	Italy, Germany, Austria	22
FIX-CHF-4	Crossover double-blind, 6 months	Yes	Opt II	Italy, Austria, Germany, France, The Netherlands and Czech Republic.	164
FIX-HF-5 Phase I	5 CCM hrs/day vs OMT, 6 months	Yes	Opt II	USA	49
FIX-HF-5 Phase II	5 CCM hrs/day vs OMT	Yes	Opt III	USA	428
FIX-HF-9	5 CCM hrs/day vs OMT	Yes	Opt III	Hong Kong	40
FIX-CHF-12	CRT Non-responder Study		Opt III	Germany	19
FIX-CHF-13	5 vs. 12 CCM hours		Opt III	Germany	20
CCM HF	Registry		Opt III	Germany	139
FIX-CHF-18	Comparison 1 vs 2 leads		Opt III, Opt IVs	Germany	48
Total					**975**

CARDIAC CONTRACTILITY MODULATION: *RCT FIX-HF-4*



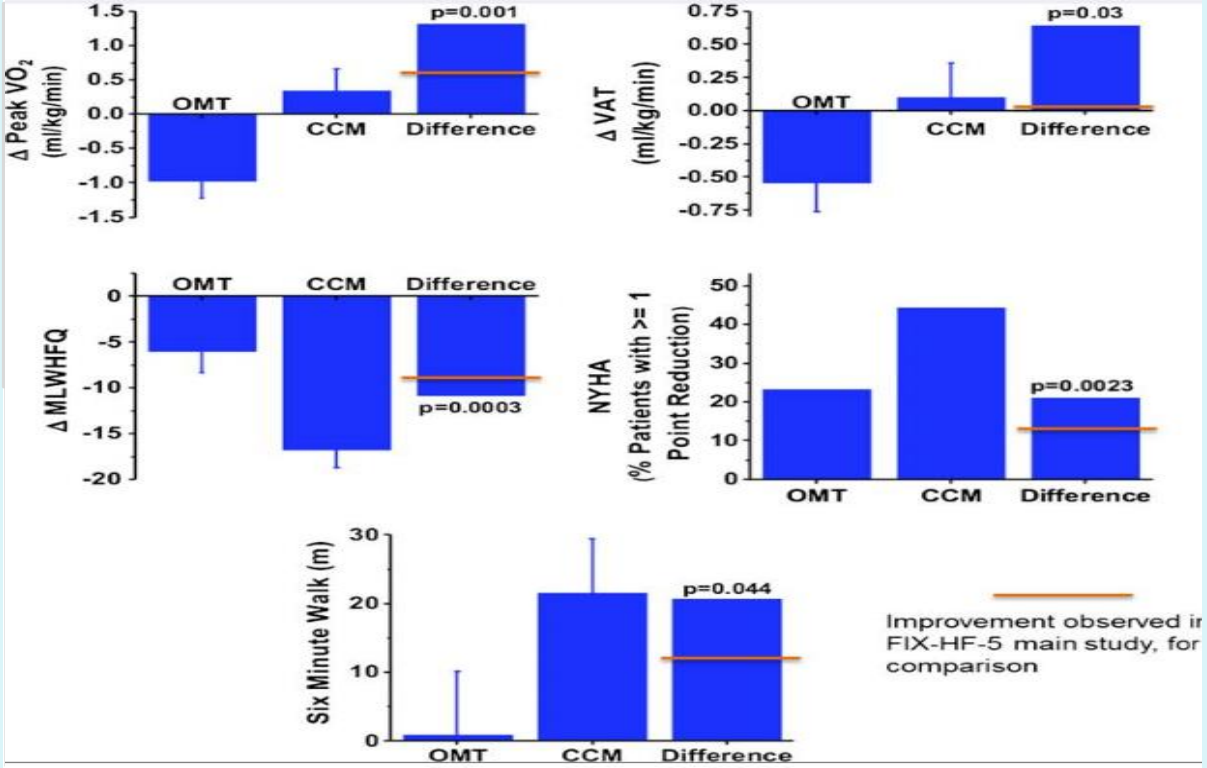


- Due Gruppi: OMT e OMT+CCM;
- **164 Pazienti**;
- Trial **Multicentrico**, **Randomizzato**, doppio cieco con Crossover;
- **Primary Endpoint**: Delta pVO2, **Secondary Endpoint**: QoL (After 12 and 24 weeks);
- Effetto Placebo presente ma NON SOSTENUTO;
- Risultati simili al **MUSTIC** (stesso periodo storico)

CARDIAC CONTRACTILITY MODULATION: *RCT FIX-HF-5*

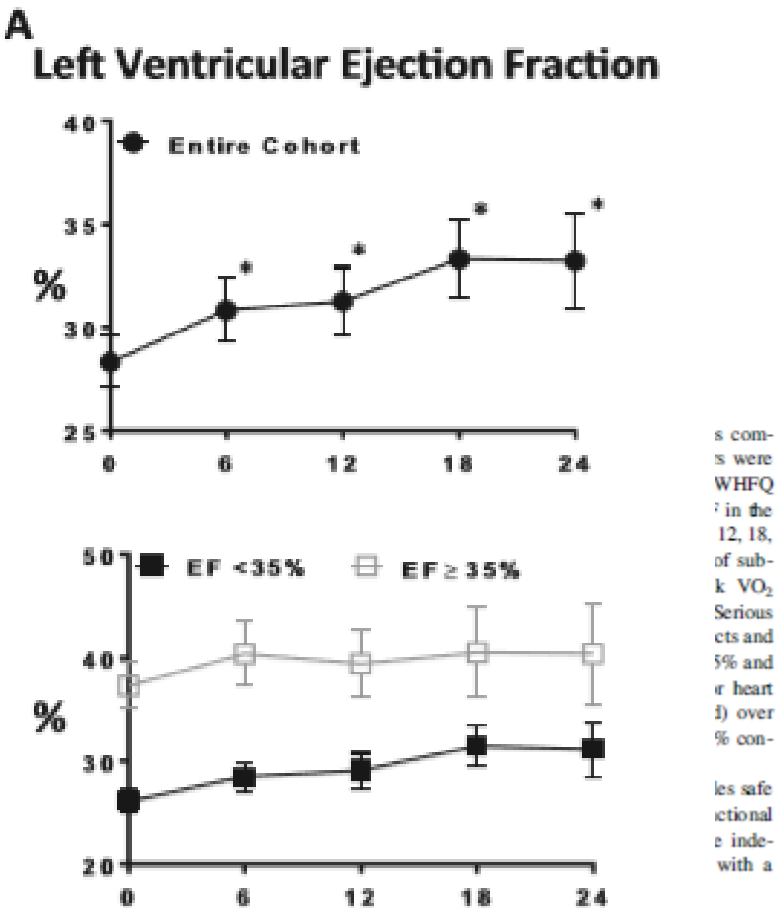
AHJ American Heart Journal

A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure



- Due Gruppi OMT e OMT+CCM
- **428 Pazienti**, **50 centri** (US) ;
- **Multicentrico**, **Randomizzato**, unblinded
- **Primary Endpoint**: Ventilatory anaerobic threshold (VAT), **Secondary Endpoint**: pVO2 and MLHFQ
- Pazienti con NYHA III-IV; EF <35%; QRS <130ms; OMT
- **Sottogruppo pazienti con EF >25%**
- Scelta della VAT con endpoint primario;

CARDIAC CONTRACTILITY MODULATION: *REVERSE REMODELING*



Clin Res Cardiol

Table 2 Impact of CCM on NYHA, MLWHFQ, and LV ejection fraction over time and by EF class

	EF group	NYHA	MLWHFQ		LV ejection fraction	
		Mean (*n*)	Value (*n*)	Δ from baseline	% (*n*)	Δ from baseline
Baseline	EF <35%	2.9 ± 0.5 (114)	45.4 ± 19.6 (104)	–	26.1 ± 5.0 (114)	–
	*EF ≥35%	2.8 ± 0.4 (28)	44.6 ± 17.3 (25)	–	37.3 ± 3.1 (28)	–
	Total	2.9 ± 0.5 (143)	45.0 ± 19.2 (130)	–	28.3 ± 6.4 (142)	–
6 Months	EF <35%	2.3 ± 0.8* (87)	30.0 ± 19.8 (66)	−16.4 ± 20.8*	28.2 ± 8.3 (68)	2.6 ± 7.2*
	EF ≥35%	1.9 ± 0.8* (21)	37.3 ± 18.8 (18)	−9.7 ± 17.9	40.5 ± 6.2 (15)	3.2 ± 6.6
	Total	2.2 ± 0.8* (109)	31.4 ± 19.7 (22)	−15.1 ± 20.3*	30.5 ± 9.2 (83)	2.7 ± 7.1*
12 Months	EF <35%	2.2 ± 0.8* (79)	32.2 ± 21.9 (61)	−12.3 ± 22.8*	28.9 ± 8.8 (62)	3.3 ± 7.8*
	EF ≥35%	2.4 ± 0.8* (19)	35.3 ± 14.5 (15)	−8.9 ± 9.9	39.1 ± 4.3 (17)	2.4 ± 4.7
	Total	2.2 ± 0.8* (99)	32.8 ± 20.6 (76)	−11.6 ± 20.9*	31.7 ± 13.1 (79)	3.1 ± 7.3*
18 Months	EF <35%	2.2 ± 0.7* (70)	32.5 ± 24.3 (59)	−13.0 ± 25.6*	31.1 ± 10.3 (55)	5.3 ± 9.8*
	EF ≥35%	2.1 ± 0.6* (15)	35.0 ± 16.0 (11)	−4.8 ± 15.9	39.3 ± 4.9 (11)	2.4 ± 5.7
	Total	2.2 ± 0.7* (86)	32.9 ± 23.1 (70)	−11.7 ± 24.5*	32.0 ± 10.5 (66)	4.8 ± 9.3*
24 Months	EF <35%	2.2 ± 0.9* (52)	30.8 ± 23.6 (44)	−15.0 ± 21.6*	33.0 ± 9.1 (37)	7.5 ± 9.3*
	EF ≥35%	2.3 ± 0.7* (15)	34.5 ± 18.7 (14)	−9.4 ± 18	40.2 ± 5.6 (13)	3.5 ± 6.0
	Total	2.2 ± 0.8* (68)	31.2 ± 22.5 (59)	−13.6 ± 20.6*	34.9 ± 8.8 (51)	6.5 ± 8.7*

All data are presented as mean ± SD; n's reflect numbers of subjects with available data. LV ejection fraction (EF; mean±SD). Means and standard deviations of available raw data are shown. *P* values at individual time points were determined by the mixed model using Sidaks method for multiple comparisons. *$p < 0.05$ vs. corresponding baseline

CARDIAC CONTRACTILITY MODULATION: *LONG TERM*

Mortality	CCM-KM (+/- std err)	SHFM (+/- std err)	Z	P
1 year	0.0% (+/- 0.0%)	6.1% (+/- 0.4%)	14.492	<0.001
2 years	3.5% (+/- 2.6%)	11.8% (+/- 0.8%)	3.089	0.002
5 years	14.2% (+/- 6.4%)	27.7% (+/- 1.5%)	2.045	0.041

Log Rank Result P = 0.045

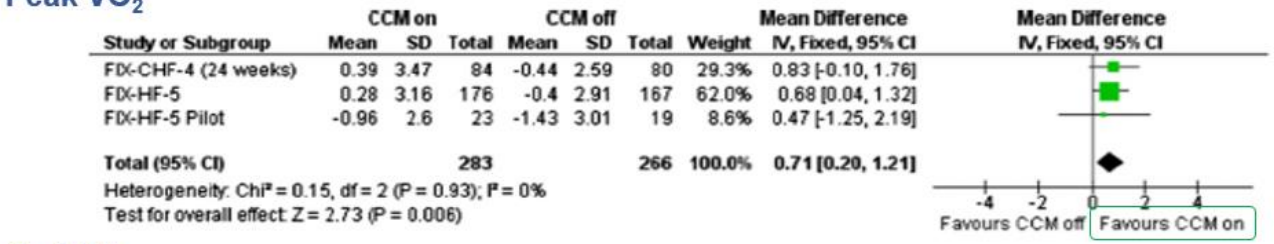
Months	0	12	24	60
N at risk	68	59	50	29

Data from 68 patients NYHA II-III with narrow QRS treated with CCM in two implanting centers (Bochum, Ludenscheid) with average follow up of 4.5 years (range: 3 months to 10 years)

CARDIAC CONTRACTILITY MODULATION: *ANALISI RCT*

Meta-Analysis by Individual Patient Data Based on Data from 641Participants in 3 RCTS

Peak VO_2

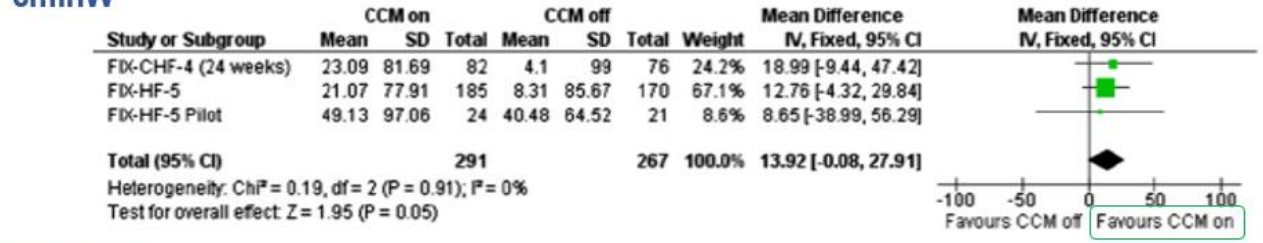


Study or Subgroup	CCM on Mean	CCM on SD	CCM on Total	CCM off Mean	CCM off SD	CCM off Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	0.39	3.47	84	-0.44	2.59	80	29.3%	0.83 [-0.10, 1.76]
FIX-HF-5	0.28	3.16	176	-0.4	2.91	167	62.0%	0.68 [0.04, 1.32]
FIX-HF-5 Pilot	-0.96	2.6	23	-1.43	3.01	19	8.6%	0.47 [-1.25, 2.19]
Total (95% CI)			**283**			**266**	**100.0%**	**0.71 [0.20, 1.21]**

Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)

Mean Difference IV, Fixed, 95% CI
-4 -2 0 2 4
Favours CCM off | Favours CCM on

6minW

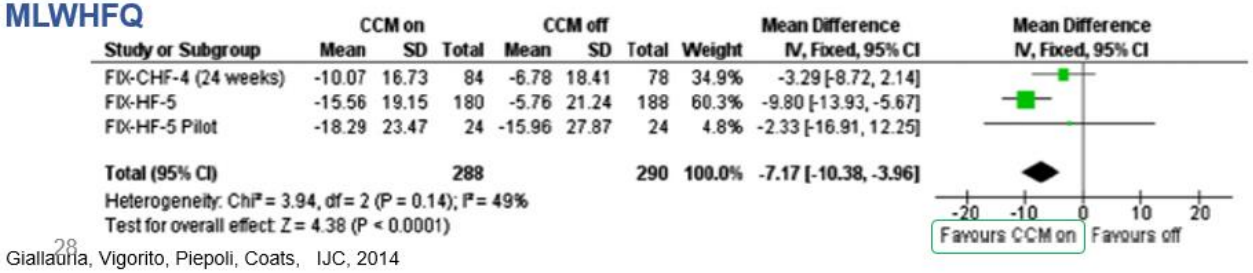


Study or Subgroup	CCM on Mean	CCM on SD	CCM on Total	CCM off Mean	CCM off SD	CCM off Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	23.09	81.69	82	4.1	99	76	24.2%	18.99 [-9.44, 47.42]
FIX-HF-5	21.07	77.91	185	8.31	85.67	170	67.1%	12.76 [-4.32, 29.84]
FIX-HF-5 Pilot	49.13	97.06	24	40.48	64.52	21	8.6%	8.65 [-38.99, 56.29]
Total (95% CI)			**291**			**267**	**100.0%**	**13.92 [-0.08, 27.91]**

Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)

Mean Difference IV, Fixed, 95% CI
-100 -50 0 50 100
Favours CCM off | Favours CCM on

MLWHFQ



Study or Subgroup	CCM on Mean	CCM on SD	CCM on Total	CCM off Mean	CCM off SD	CCM off Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	-10.07	16.73	84	-6.78	18.41	78	34.9%	-3.29 [-8.72, 2.14]
FIX-HF-5	-15.56	19.15	180	-5.76	21.24	188	60.3%	-9.80 [-13.93, -5.67]
FIX-HF-5 Pilot	-18.29	23.47	24	-15.96	27.87	24	4.8%	-2.33 [-16.91, 12.25]
Total (95% CI)			**288**			**290**	**100.0%**	**-7.17 [-10.38, -3.96]**

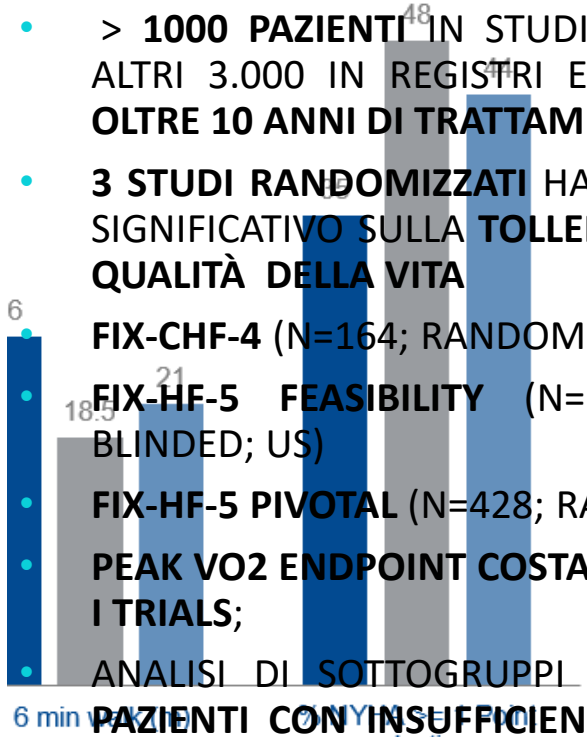
Heterogeneity: Chi² = 3.94, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 4.38 (P < 0.0001)

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favours CCM on | Favours off

28

Giallauria, Vigorito, Piepoli, Coats, IJC, 2014

- > **1000 PAZIENTI** IN STUDI CLINICI RANDOMIZZATI, CON ALTRI 3.000 IN REGISTRI E CONTESTI COMMERCIALI DA **OLTRE 10 ANNI DI TRATTAMENTO**;
- **3 STUDI RANDOMIZZATI** HANNO MOSTRATO UN IMPATTO SIGNIFICATIVO SULLA **TOLLERANZA ALL'ESERCIZIO E SULLA QUALITÀ DELLA VITA**
- **FIX-CHF-4** (N=164; RANDOMIZED, DOUBLE-BLINDED; EU)
- **FIX-HF-5 FEASIBILITY** (N=50; RANDOMIZED, DOUBLE-BLINDED; US)
- **FIX-HF-5 PIVOTAL** (N=428; RANDOMIZED; US)
- **PEAK VO2 ENDPOINT COSTANTEMENTE POSITIVO IN TUTTI I TRIALS**;
- ANALISI DI SOTTOGRUPPI **SUGGERISCONO BENEFICI IN PAZIENTI CON INSUFFICIENZA CARDIACA E FRAZIONE DI EIEZIONE LIEVEMENTE RIDOTTA**;



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al. American Heart Journal, February

CARDIAC CONTRACTILITY MODULATION: *FUTURE DATA*

- FIX-HF-5C, 230 pazienti, **FDA Approval study**
- **Analisi pazienti con FE tra 25 e 45%**
- Primary endpoint : **Delta peak VO2**
- **CCM Registry** (Registro monitorizzato)
- Analisi **Ospedalizzazioni,** Quality of Life, Tolleranza esercizio

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

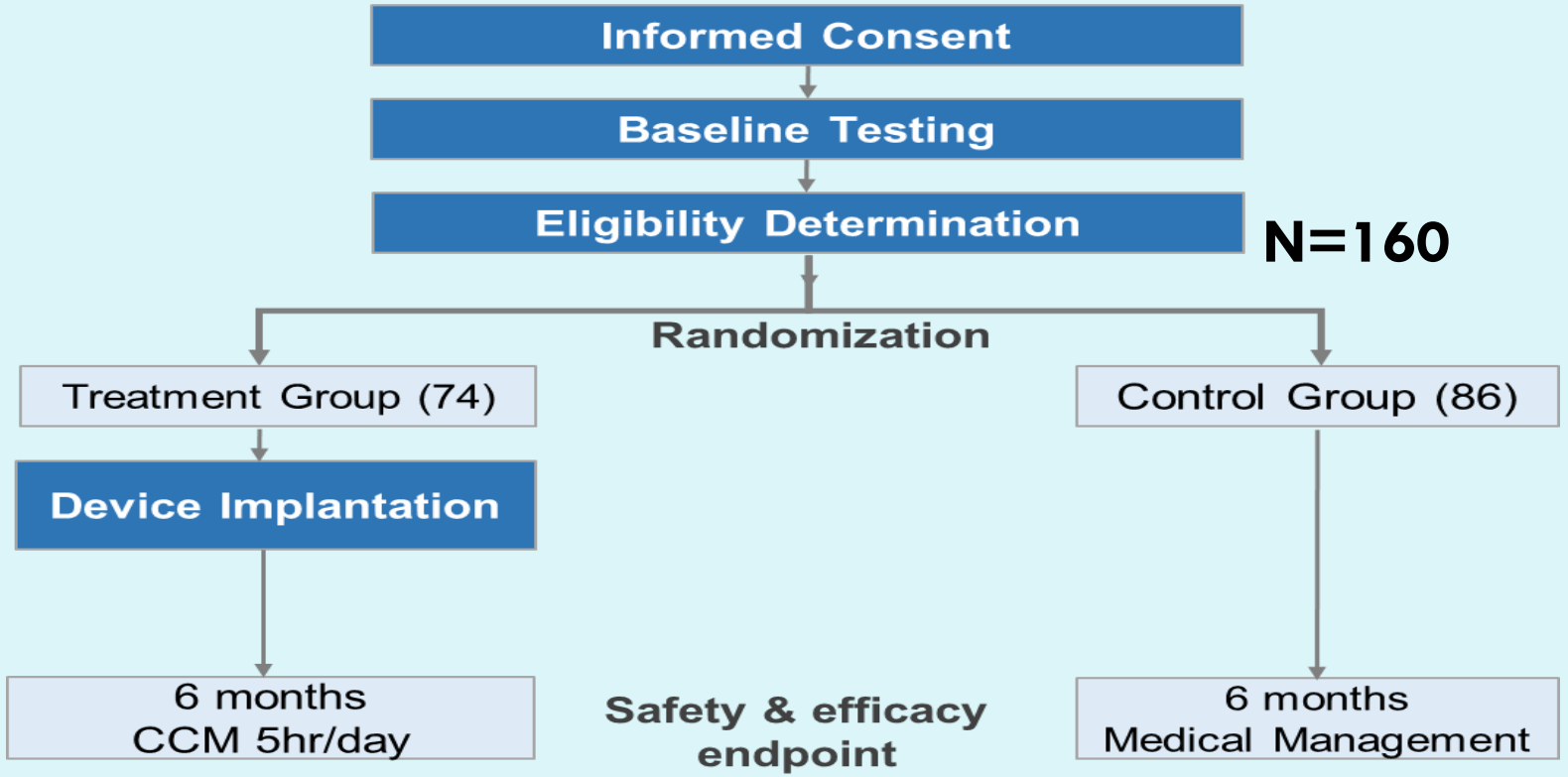
A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PhD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PhD,[h] Helen Parise, ScD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PhD,[r] Gerd Hasenfuß, MD[s]

FIX-HF-5C "CONFIRMATORY" STUDY

- **160 patients** randomized 1:1: at 20 US sites and 8 EU sites
- **Target population:** Heart failure patients with **EF 25% to 45%**
- **Primary Efficacy Endpoint:** Improvement in **peak VO_2**
- **Primary Safety Endpoint:** Proportion of Treatment group that did not experience an Optimizer device or Optimizer procedure related complication through 24-weeks greater than 70% (OPC)
- **Major Secondary Efficacy Endpoint**
  - Minnesota Living with Heart Failure Quality of Life (QoL) Score
- **Granted Expedited Access Pathway by the FDA qualifying for priority review**

FIX-HF-5C “CONFIRMATORY” STUDY SCHEMATIC



FIX-HF-5C ANALYSIS PLAN

Efficacy:

- Between group differences in **peak VO2** at 24 weeks
- Bayesian repeated measures model-estimated treatment effects
- Fixed, 30% borrowing of information from the prior FIX-HF-5 subgroup with 25% ≤ EF ≤ 45%
- MLWHFQ and NYHA as secondary endpoints

Safety:

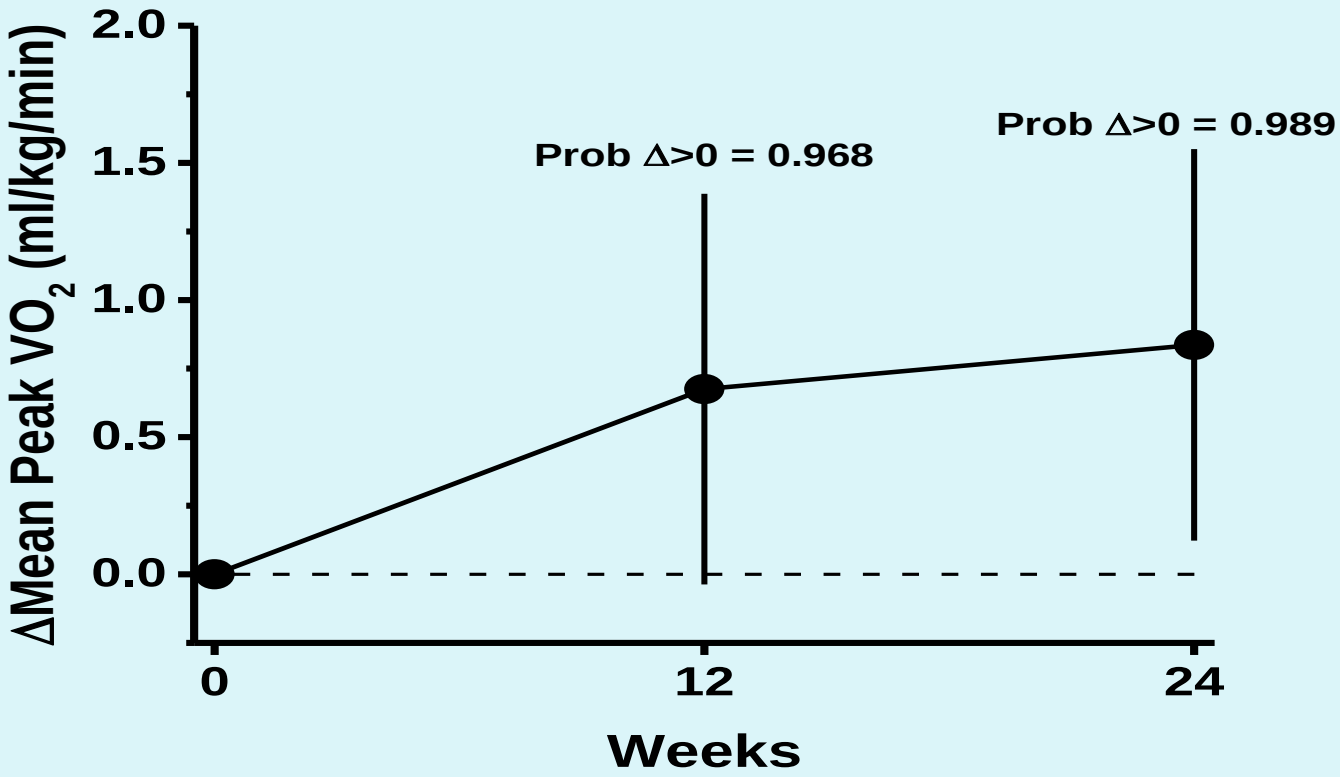
- Objective Performance Criterion (OPC)
  - Optimizer procedure- or device-related complication rates through 24-weeks
  - Superiority based on exact binomial 95% confidence interval with complication-free proportion of patients higher than 70%

PATIENT BASELINE DEMOGRAPHICS*

Variable	Control	CCM	P-value
	86+112 (198)*	n=74+117 (191)*	
Age (yrs)	61±12	60±12	0.51
Male	76.3%	71.3%	0.34
Ethnicity (White)	71.7%	74.9%	0.49
CHF Etiology (Ischemic)	64.7%	68.1%	0.52
Prior MI	59.1%	59.7%	0.92
Prior ICD	81.3%	82.7%	0.79
Diabetes	50.5%	49.7%	0.92
NYHA (%IV)	11.6%	9.4%	0.51
QRS Duration (ms)	102±13	101±14	0.24
LVEF (%) (core lab)	32±5	32±5	0.89
LVEDD (mm) (core lab)	58±9	58±10	0.76
MLWHFQ	57±23	59±23	0.36
6MHW (meters)	324±91	322±86	0.08
CPX (core lab)			
Peak VO2 (ml/kg/min)	15.0±3.0	15.0±2.9	0.73
Exercise Time (minutes)	11.2±3.3	11.3±3.1	0.74

***Primary analysis cohort from FIX-HF-5C + FIX-HF-5 25≤EF≤45 Subgroup**

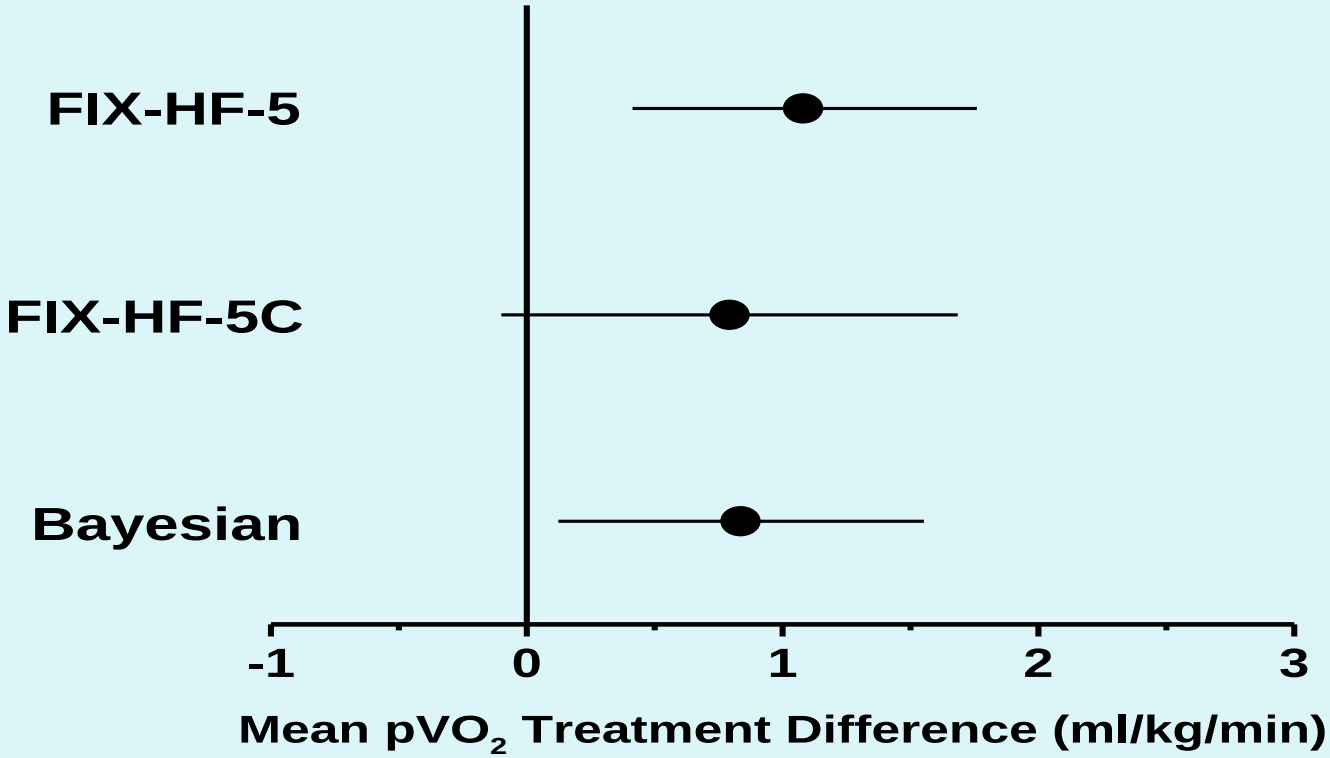
FIX-HF-5C PRIMARY EFFICACY ENDPOINT MET
CCM SIGNIFICANTLY IMPROVES EXERCISE CAPACITY



Statistically significant between group difference At 24 weeks: 0.84 mlO2/kg/min

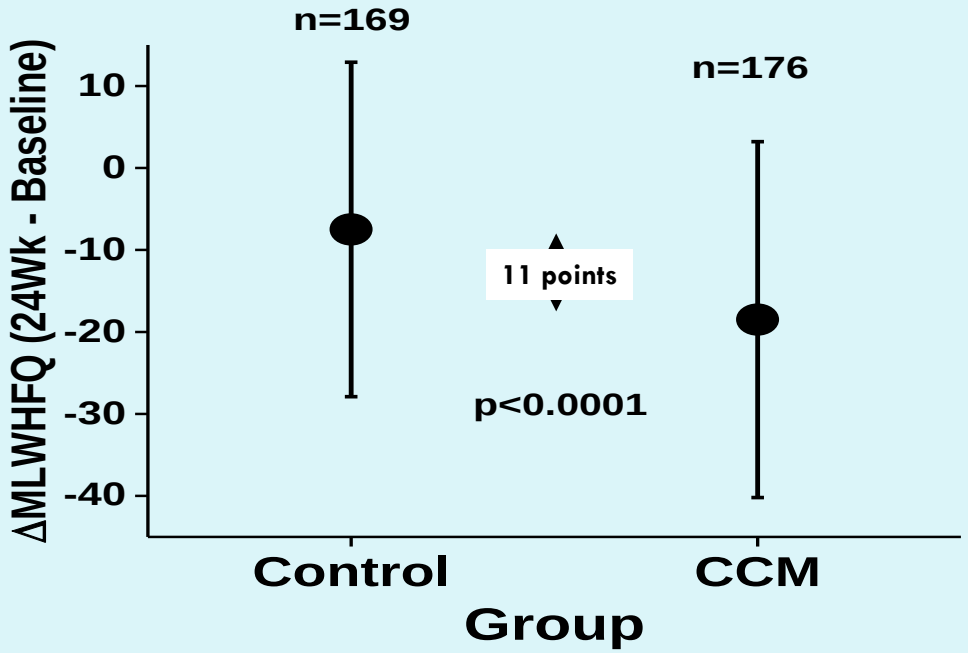
FIX-HF-5C: PRIMARY EFFICACY ENDPOINT

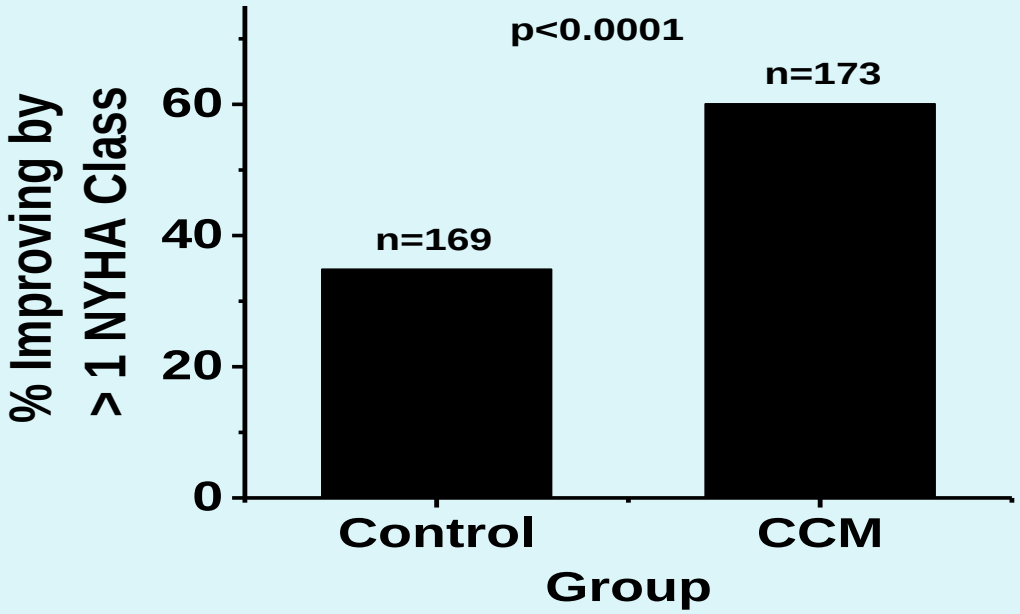
EFFECTS IN FIX-HF-5 SUBGROUP, FIX-HF-5C ALONE, AND BAYESIAN RESULT



FIX-HF-5C SECONDARY EFFICACY ENDPOINTS MET

CCM SIGNIFICANTLY IMPROVES QOL AND FUNCTIONAL STATUS





FIX-HF-5C PRIMARY SAFETY ENDPOINT MET

7 protocol-specified device/procedure-related events (n=68)

5 - lead dislodgements

1 - deep vein thrombosis

1 - generator erosion/ pocket stimulation with pocket revision/lead exchanges

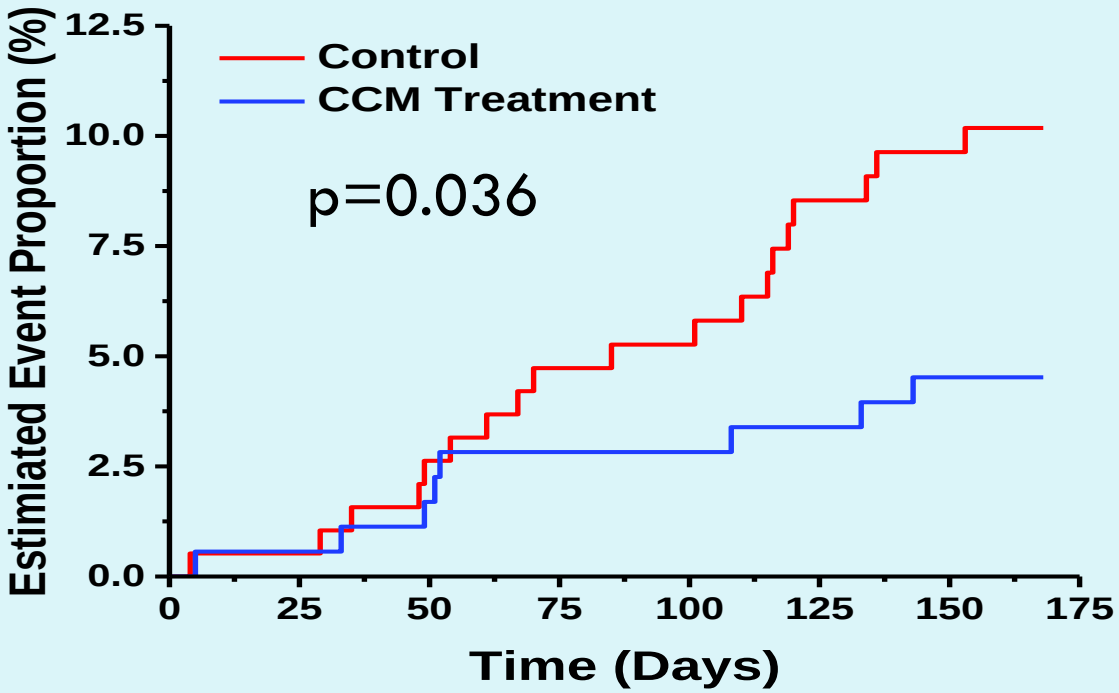
- **Event Rate 10.3% [95% CL 4.2-20.1]**
- **Complication-free rate: 89.7% [95% CL 79.9-95.8]**
  - OPC required 95% LCL > 70%

FIX-HF-5C OVERALL MORTALITY

GROUP	GENDER	AGE	DAYS*	Adjudicated Cause of Death
CONTROL	M	61.6	70	Cardiac Procedure-VT Ablation
	M	69	36	Cardiac-Pump failure
	F	70.6	117	Non-CV - Pulmonary: Complication of a non-cardiac procedure
	M	51.8	4	Cardiac-Pump failure
ACTIVE	F	69.6	-2	Cardiac-Sudden **prior to implant**
	F	73.6	164	Non-CV: Sepsis post cholecystectomy

***Days following Randomization**

CARDIOVASCULAR DEATH + HF HOSPITALIZATIONS



HOSPITALIZATIONS AND DAYS ALIVE OUT OF HOSPITAL

Greater Days alive not hospitalized for HF
CCM: 165.8 (hosp. days 2.5)
Control: 162.0 (hosp. days 6)
(Δ=3.8; p=0.035)

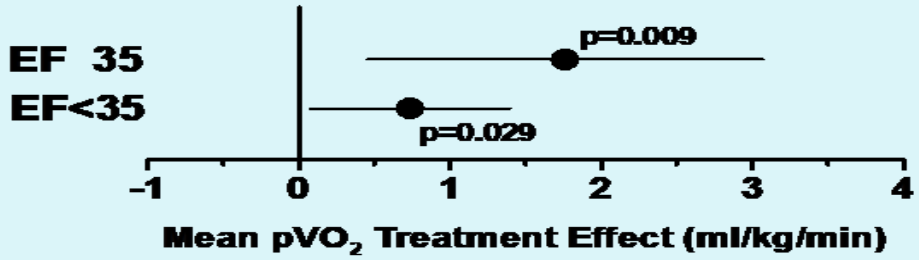
Greater Total Days Alive Out of Hospital*
CCM: 164.3 (hosp. days 3.7)
Control: 160.4 (hosp. days 7.6)
(Δ=3.9; p=0.035)

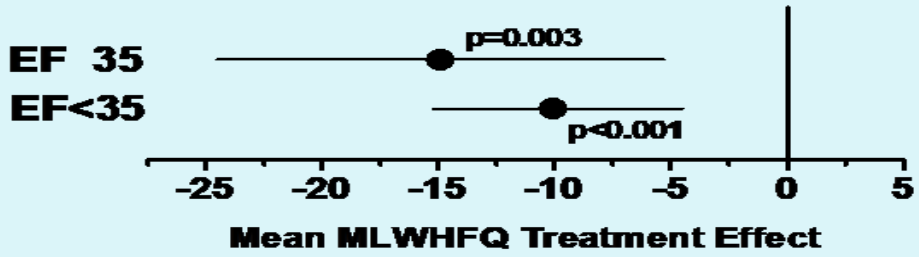
Reduced Rate of HF hospitalizations compared to year prior to CCM (table)

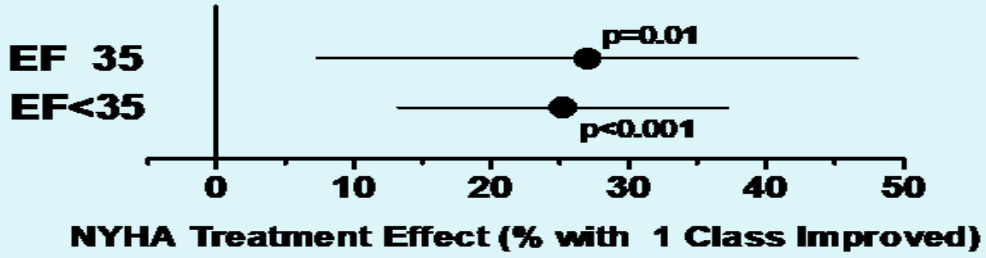
		Events/Patient Year		
		1 yr Prior	24 Wk Study Period	p
All CV	CCM	1.11	0.44	**0.004**
	Control	0.65	0.39	0.126
HF	CCM	0.81	0.13	**0.001**
	Control	0.37	0.31	0.616

PRE-SPECIFIED SUBGROUP ANALYSIS: EF 35%-45%

Variable	Value	P	Notes
pVO_2 in 5/5c	1.35	0.0050	Bayes - repeated measures model
pVO_2 in 5/5c	1.45	0.0440	Pooled
MLWHF in 5c	13.8	0.0257	0.0031 for pooled
NYHA in 5c	82%	0.0031	% with at least 1 point reduction
6MW in 5c	59.3	0.0167	0.0036 for pooled







SUMMARY OF NEW FIX-HF 5C STUDY

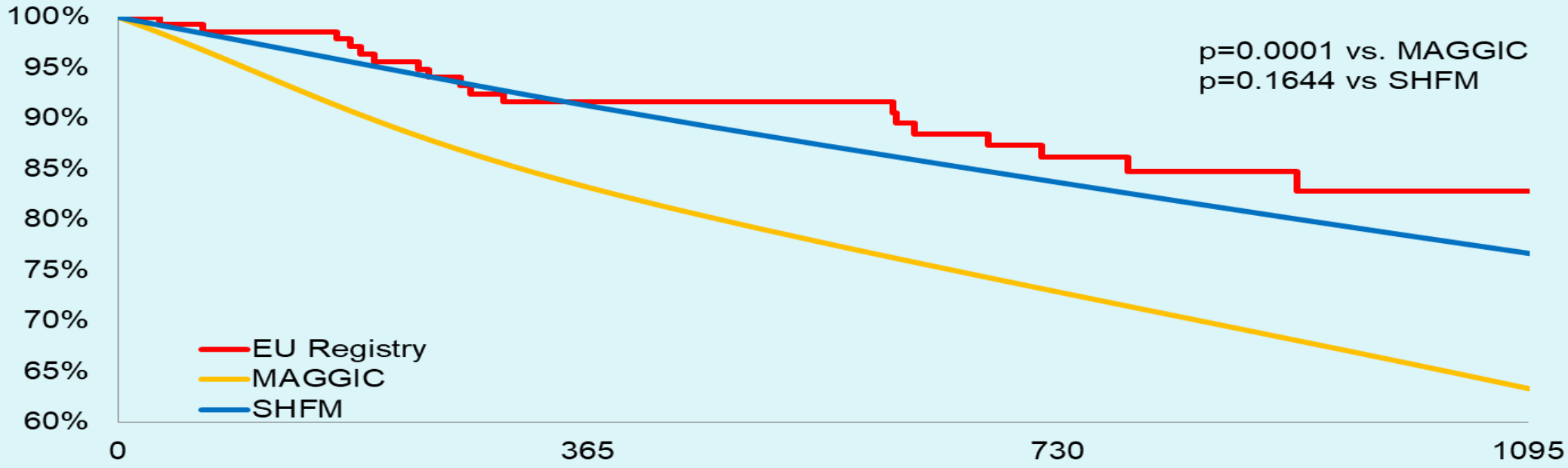
- Study met all endpoints
- In patients with EF 25%-45%, QRS<130ms, on guideline-directed medical therapy with persistent NYHA III/IVa symptoms;
  - CCM Reduce Cardiovascular Death/HF Hospitalizations
  - CCM improves: Peak VO2, MLWHFQ, NYHA
  - CCM treatment is safe
  - Even stronger clinical effects noted in patients with EF 35-45%

CONTENTS

CCM-REG-5C REGISTRY STUDY

- 140 PATIENTS AT 31 EU SITES
- TARGET POPULATION-HEART FAILURE PATIENTS:
  - WITH EF 25% TO 45% (CCM-REG-5C COHORT)
    - SUBPOPULATION WITH EF 35% TO 45% (CCM-REG-5C≥35 COHORT)
  - NYHA CLASS III AND IVA
  - VIRTUALLY IDENTICAL WITH FIX 5C STUDY POPULATION
- FOLLOW UP - 3 YEARS
- PRIMARY EFFICACY ENDPOINT: COMPARISON OF OBSERVED SURVIVAL (BASED ON KAPLAN-MEIER ANALYSIS) TO THAT PREDICTED BY THE SEATTLE HEART FAILURE MODEL (SHFM)
- MAJOR SECONDARY EFFICACY ENDPOINTS: RATE OF HEART FAILURE AND CARDIOVASCULAR HOSPITALIZATIONS, MINNESOTA LIVING WITH HEART FAILURE QUALITY OF LIFE (QOL) SCORE, NYHA CLASS, EF%

CCM-REG-5C; LONG TERM SURVIVAL: POPULATION UNDER THE FIX-5C CRITERIA



N=140 patients, NYHA: III/IV, EF: 25-45, QRS: <130

	DAY			
	0	365	730	1095
Survival Estimate (%)	100.0	91.6	86.2	82.8
Patients at Risk	140	104	71	29
Cumulative Deaths	0	11	16	18

All data monitored

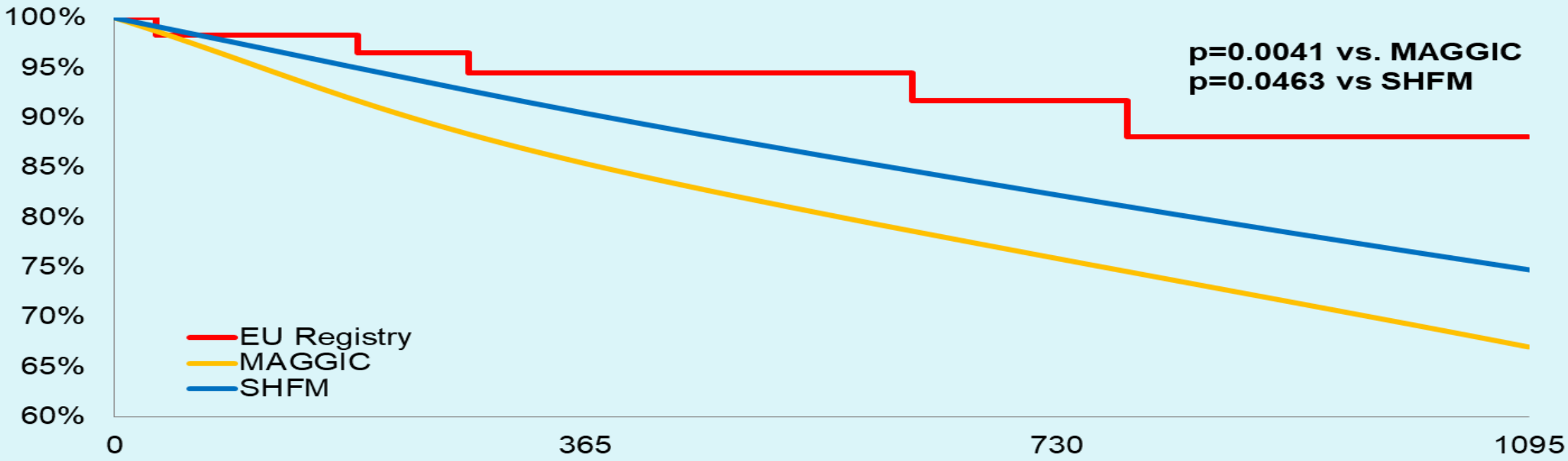
CCM- 5C- REG: MARKED HOSPITALIZATION REDUCTION

SUBGROUP	EVENT	Pre-Enrollment			Post-Enrollment			p-value
		Patient-Yrs	Events	Event-Rate	Patient-Yrs	Events	Event-Rate	
EF 25-45	HF	140.0	134	0.96	279.6	73	0.26	<0.0001
	CV		34	0.24		24	0.09	<0.0001
	HF/CV		168	1.20		97	0.35	<0.0001
EF 35-45	HF	57.0	47	0.82	113.5	18	0.16	<0.0001
	CV		23	0.40		9	0.08	<0.0001
	HF/CV		70	1.23		27	0.24	<0.0001

P-value: Hospitalization events are based on a Poisson distribution. Establishing event-rates (events per patient-year) allows for standardized comparisons between time periods (pre-enrollment vs. post-enrollment). The p-value is derived from a chi-square test on the difference between event-rates.

All data monitored

CCM-REG-5C; LONG TERM SURVIVAL: POPULATION UNDER THE FIX-5C CRITERIA, 35%+)

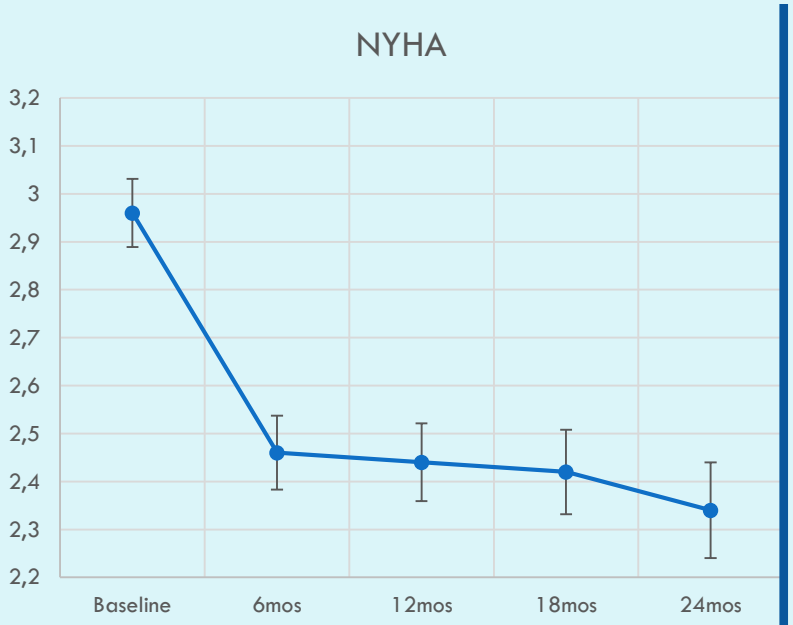


N=57 patients, NYHA: III/IV, EF: 35-45, QRS:<130

	DAY			
	0	365	730	1095
Survival Estimate (%)	100.0	94.5	91.7	88.0
Patients at Risk	57	43	30	12
Cumulative Deaths	0	3	4	5

All data monitored

CCM-REG-5C; IMPROVEMENT OF QOL & EF



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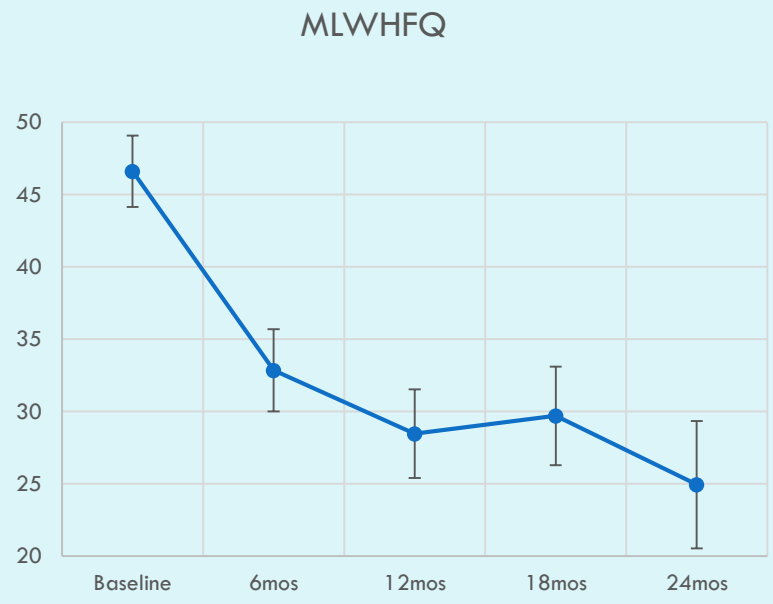

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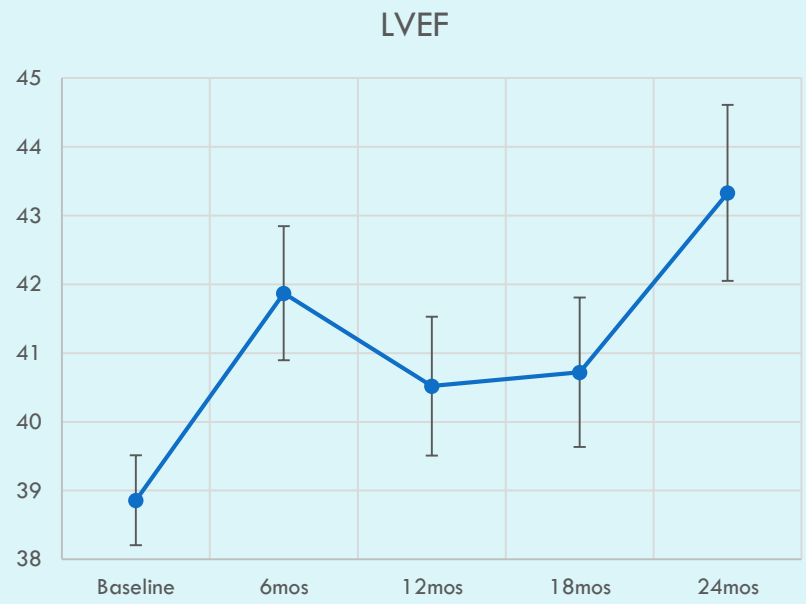
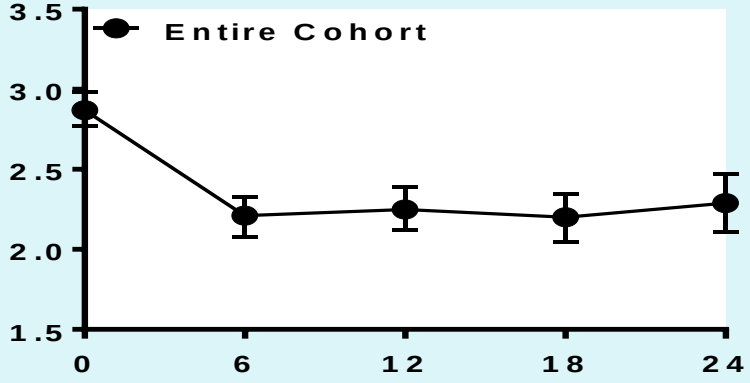


P: 0.0167

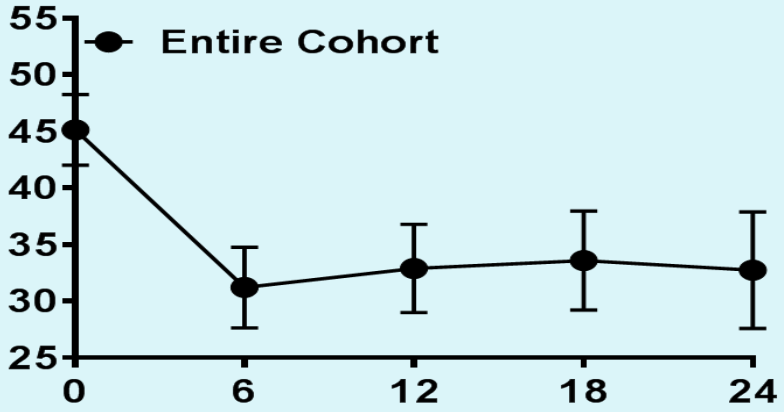
Change from baseline analyses at 6, 12, 18, and 24 months for left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) Class, and the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) were assessed with a paired t-test. The influence of time (Baseline, 6 months, 12 months, 18 months, and 24 months) for LVEF, NYHA Class, and MLWHFQ was also assessed using a mixed linear model (PROC MIXED) with a repeated measures approach.

All data monitored; publication under preparation

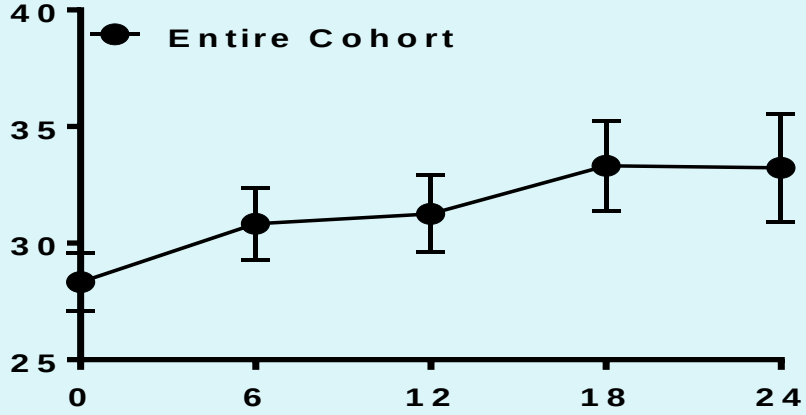
LONG TERM DATA: 1ST GERMAN CLINICAL REGISTRY



Functional Status (NYHA)



Quality of Life (MLWHFQ)



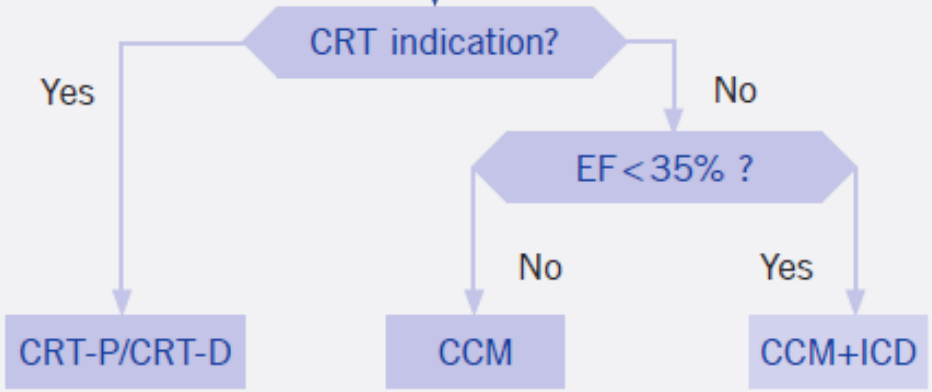
Performance (Ejection Fraction)

- N=143, NYHA II-IV IN 28 CENTERS
- EF UP TO 45%, MEAN 28.3 ± 6.4 (20% HAD EF≥35%)
- 95% OF CASES WITH EF ≥ 35% MAINTAINED THIS EF LEVEL, A THIRD OF EF 30-35% BECAME EF≥35% (MAY CONSIDER AVOIDING THE NEED FOR AN ICD)
- DATA COMPARABLE TO SINGLE SITE EXPERIENCE (*KUSHYK ET AL*) PREVIOUSLY PUBLISHED

Muller et al. Clin Res Cardiol 2017

OPTIMIZER SMART: CANDIDATO TIPO

Heart Failure patients with symptoms despite optimal medical therapy



Common patient profile	Common Contraindications
• NYHA II / III • Normal QRS • EF ≥ 20% • Peak VO_2 ≥ 10 ml/kg/min	• Mechanical tricuspid valve • No venous access

Ci sono tanti cuori
troppo sani per morire
ed alcuni cuori
troppo malati per vivere