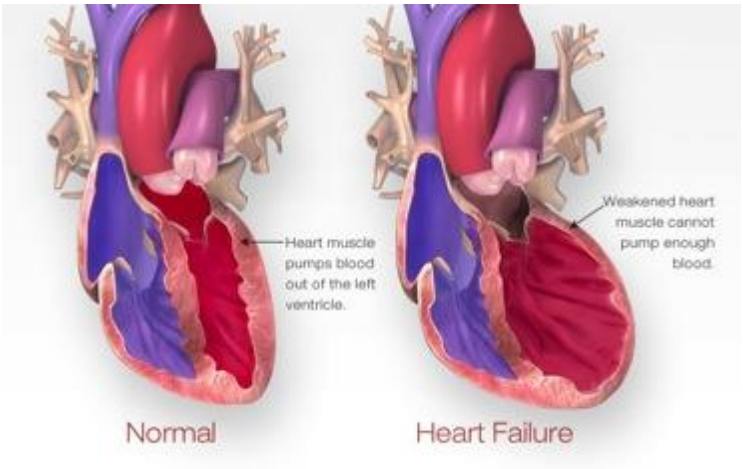
TRATTAMENTO INTERVENTISTICO

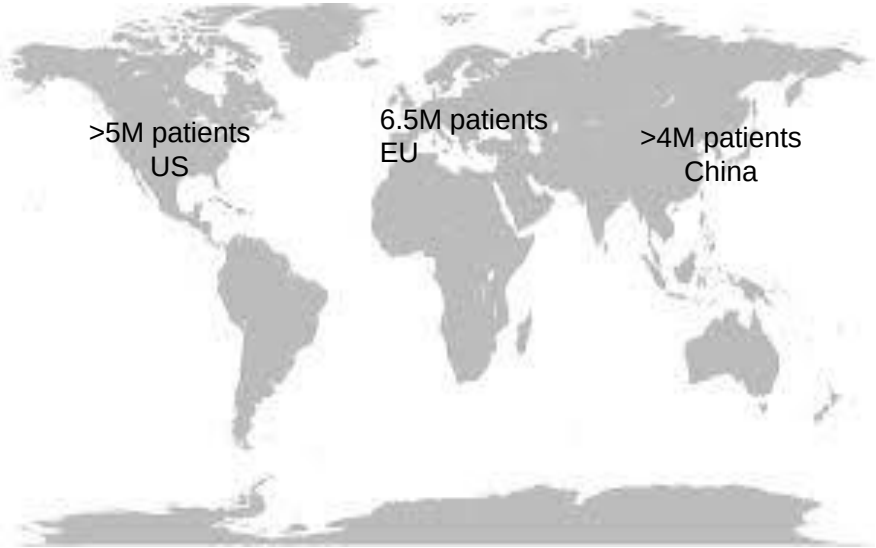
- Dr. Antonio Sagone

Heart Failure – Prevalence & Prognosis

Over 26 million people worldwide suffer from heart failure, a chronic, progressive condition in which the heart muscle is unable to pump enough blood through the heart to meet the body's needs for blood and oxygen

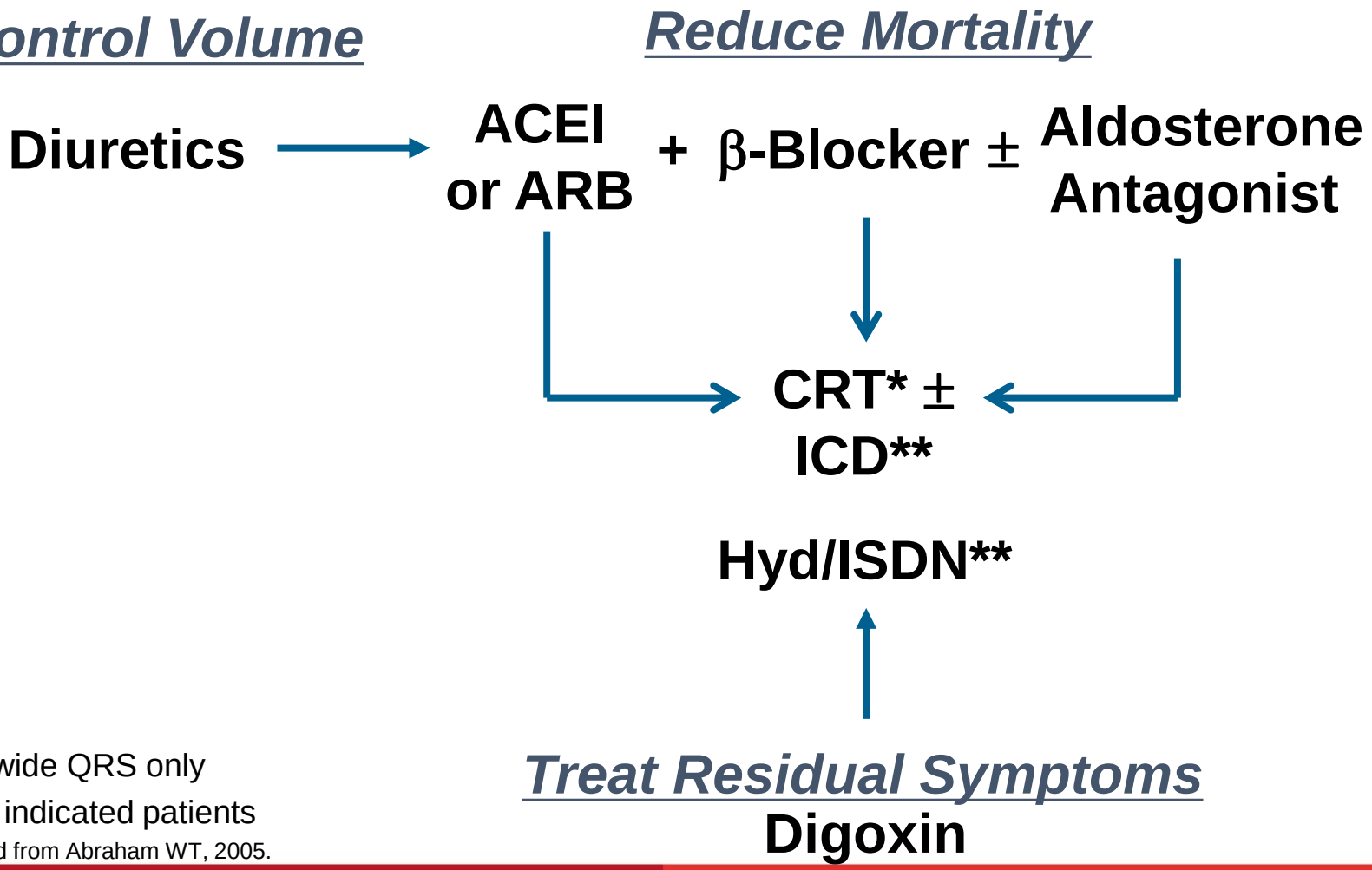
- Worst Quality Of Life amongst all chronic diseases
- Worse prognosis than most cancers





American Heart Association
Medicographia. 2011;33:363-369

Evidence-based, Guidelines-directed Treatment of Heart Failure

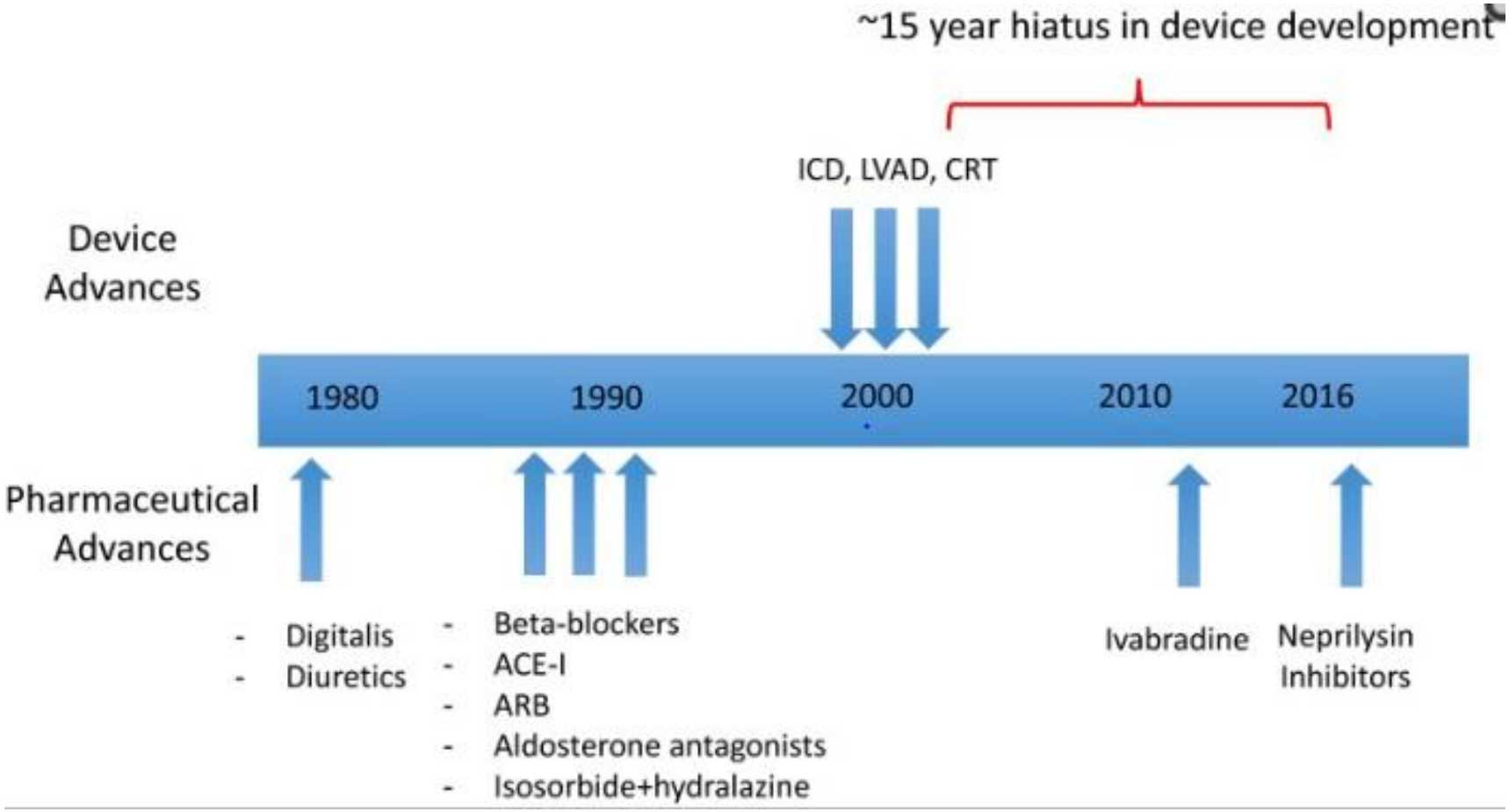


*For wide QRS only

**For indicated patients

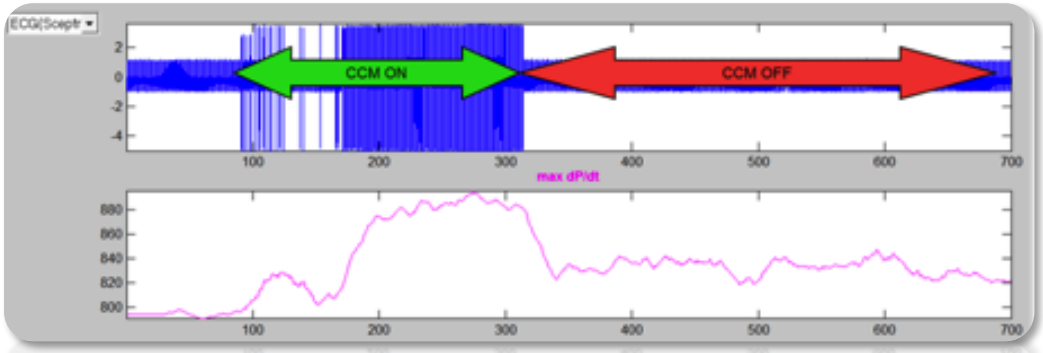
Adapted from Abraham WT, 2005.

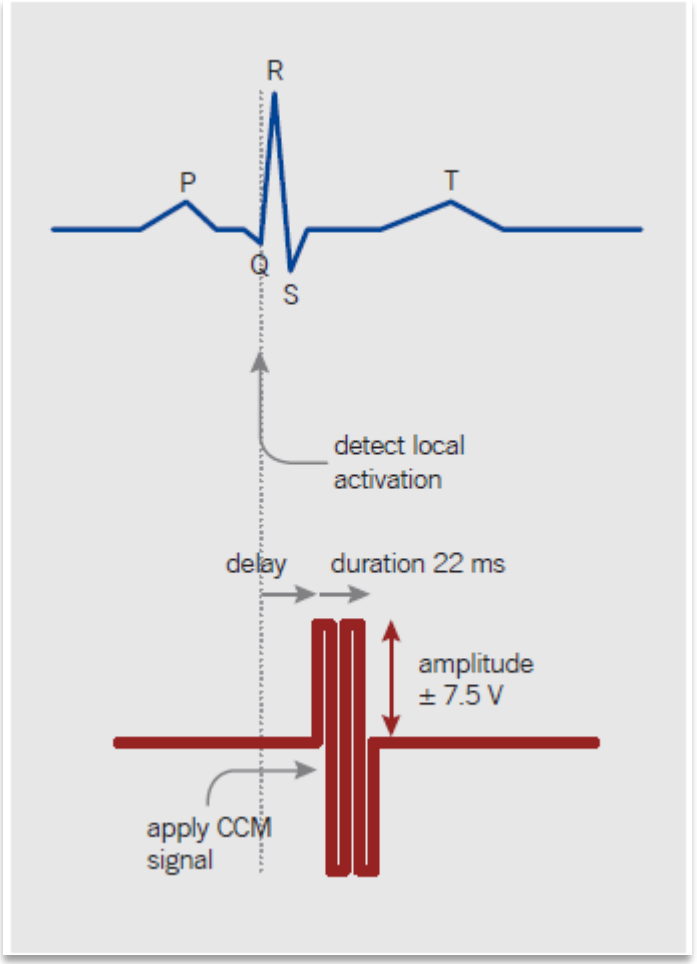
Evidence-based, Guidelines-directed Treatment of Heart Failure



CCM – Innovative Heart Failure Treatment

- CCM – Cardiac Contractility Modulation
- CCM signals are non-excitatory
- Applied during the absolute refractory period of the heart contraction
- CCM exert a predominantly localized effect





Cardiac Contractility Modulation: Overview

- A treatment for a **major disease, heart failure** where patients lack any other solution once they fail drug treatment
- A **novel mechanism** of action acting at the cellular level as an electroceutical, improving the central cause of heart failure (*i.e.*, decreased contractility)
- A well researched concept with **over 60 publications** in leading medical journals
- A novel, **state of the art device** with a small size (31cc) and proven reliability (up to 10 years of *in vivo* performance data)
- An **abundance of clinical data** (>1,000 patients in randomized trials) showing improved functional status, quality of life, and exercise capacity

OPTIMIZER Generation – The Past and Present Devices

- **Smaller than the previous generations (31 CC, 48 Gr)**
- **Rechargeable battery**
- **Not necessary associated an ICD**
- **Also for AF Patient**

OPTIMIZER Smart – Delivers CCM Signals to Heart

IPG

Small,
Rechargeable battery,
Flexible positioning

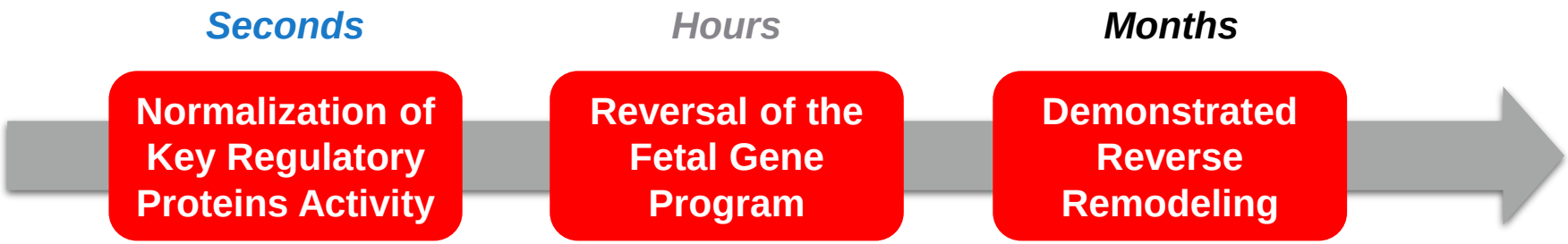
Charger

Portable,
Battery driven,
Integrity testing

Programmer

Intuitive user interface,
Remote support

Mechanism of Action

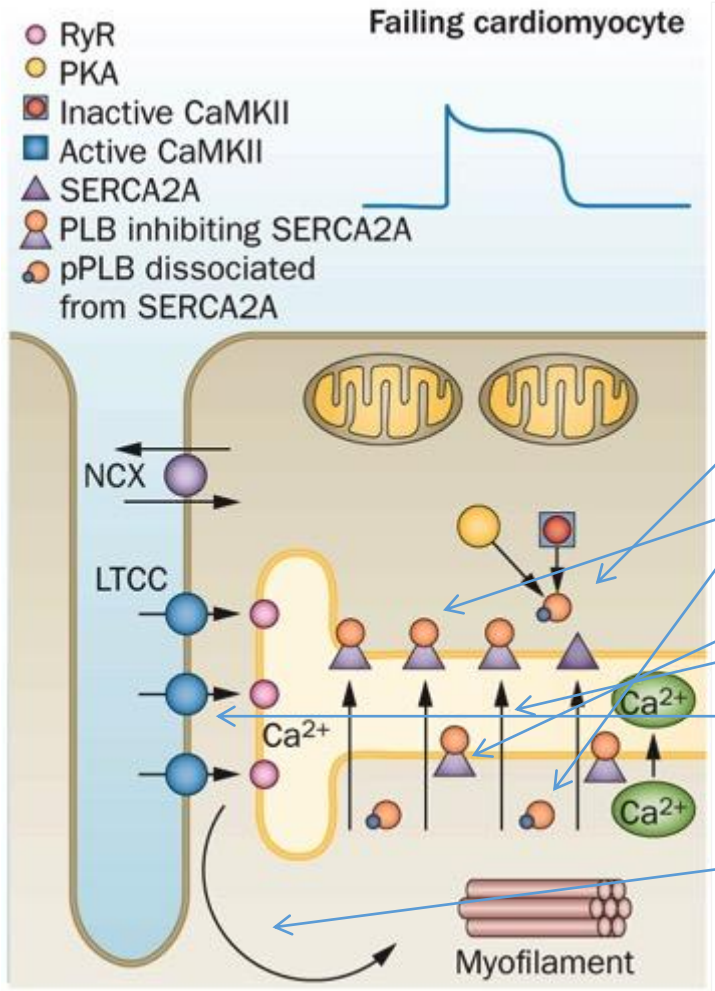


CCM therapy is affecting all six components of chronic heart failure:

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

1. Abnormal Calcium Handling in CHF



Less phosphorylation of phospholamban

Greater binding to, and inhibition of SERCA by phospholamban

Reduced SERCA expression

Less Ca reuptake into SR

Reduced calcium entry through LTCC

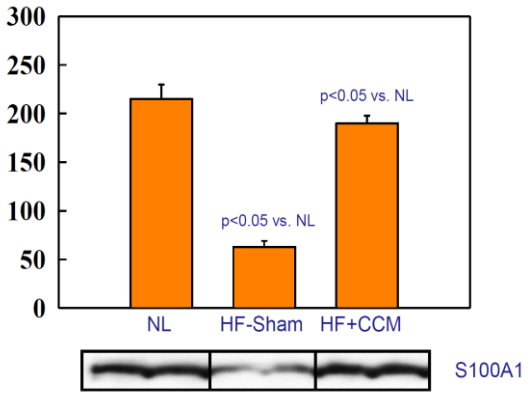
Less calcium release from RyR during depolarization

Attenuated contractility

- Lyon et al. 2013 *Nat. Rev. Cardiol.*

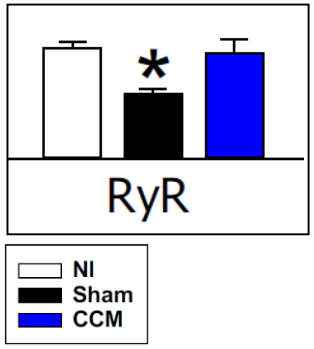
1. CCM Effect on Calcium Distribution

1. Restores AS100A1 - S100 calcium-binding protein A1



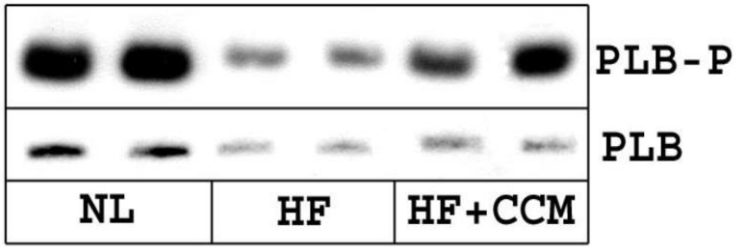
Sabbah et. al. Curr Heart Fail Rep. 2006

2. Normalizes ryanodine receptor (RyR2)



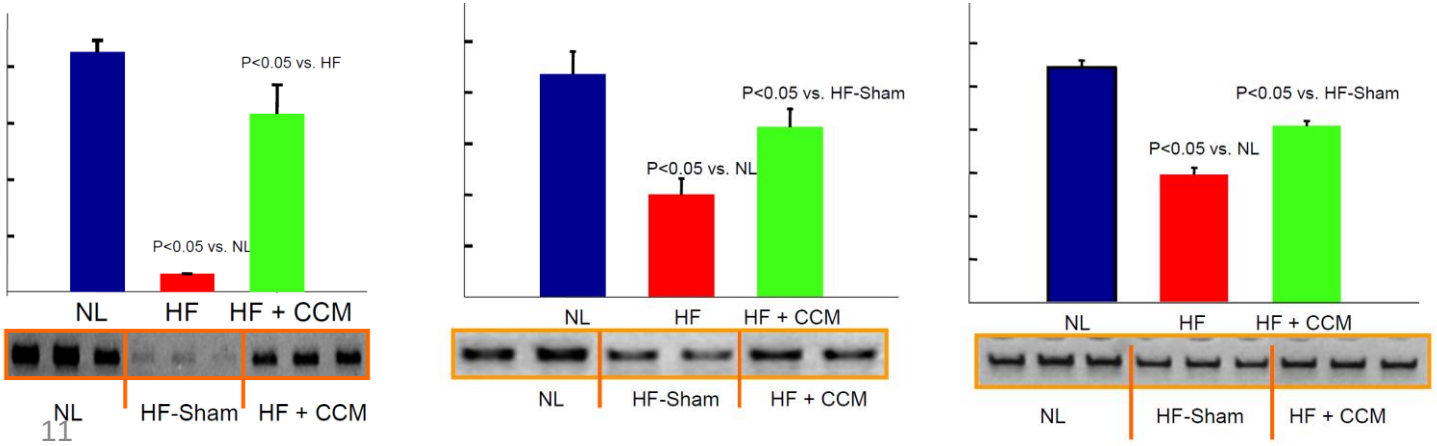
Imai et al. JACC, 2007

3. Restores normal level of PLB



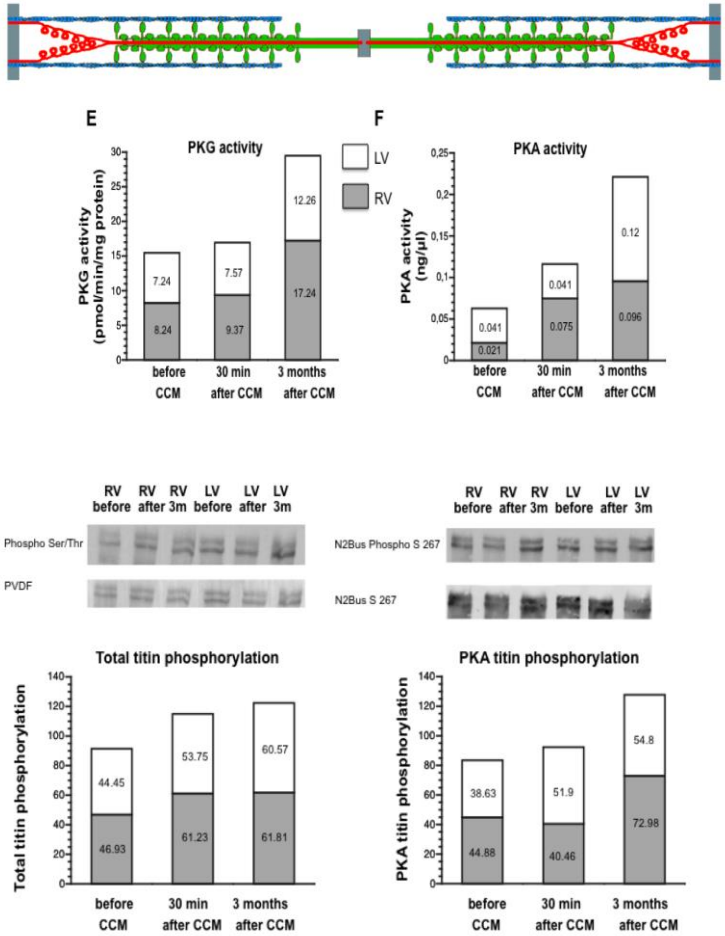
Imai JACC, 2007

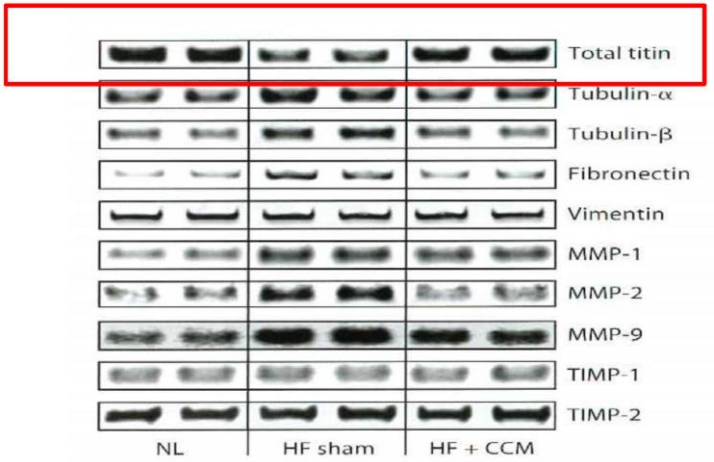
4. Normalizes SERCA mRNA expression



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

2. Titin Total Level and Phosphorylation

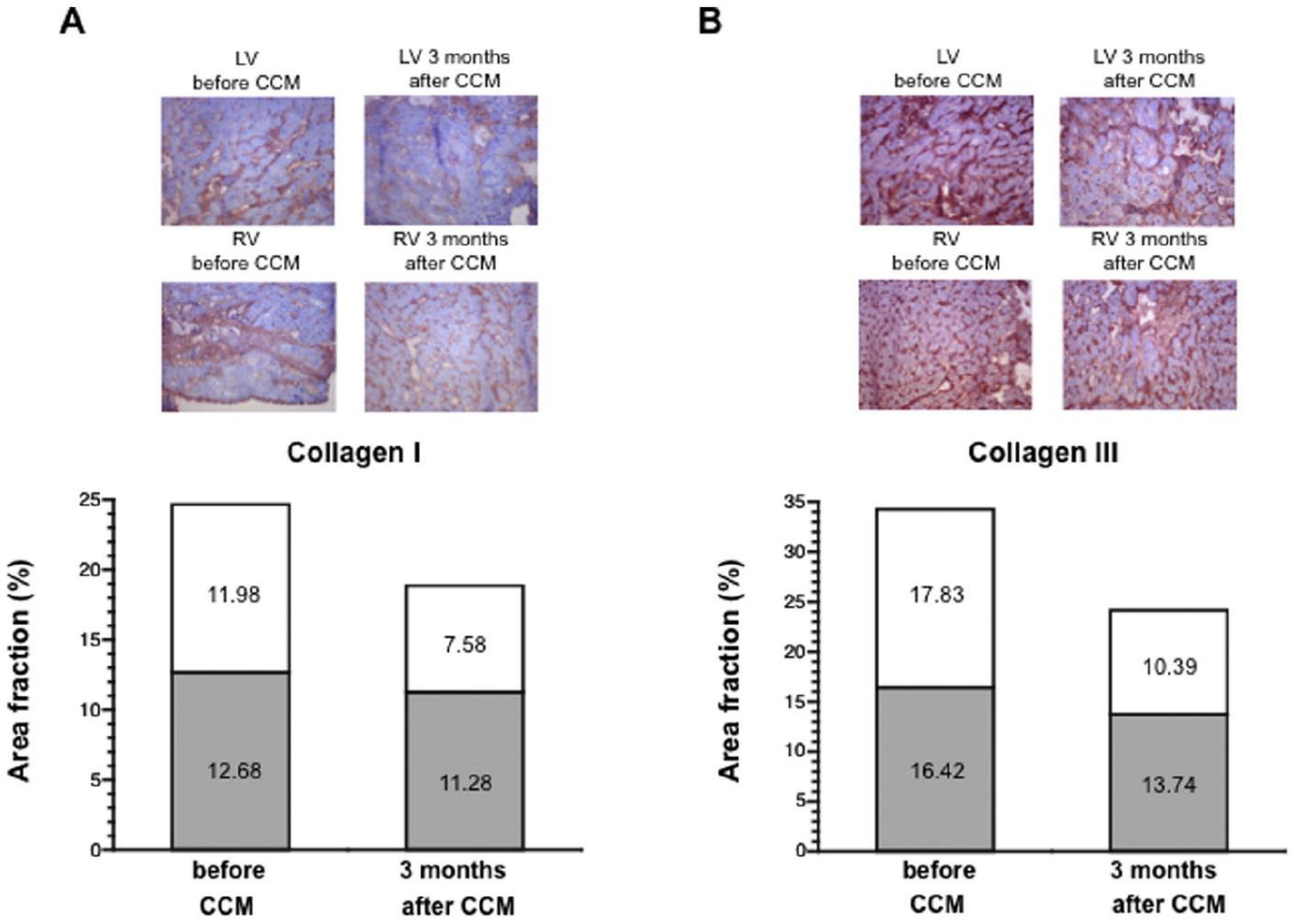




Rastogi S et.al. Cardilogy 2008. J Cardiol. 203 2016

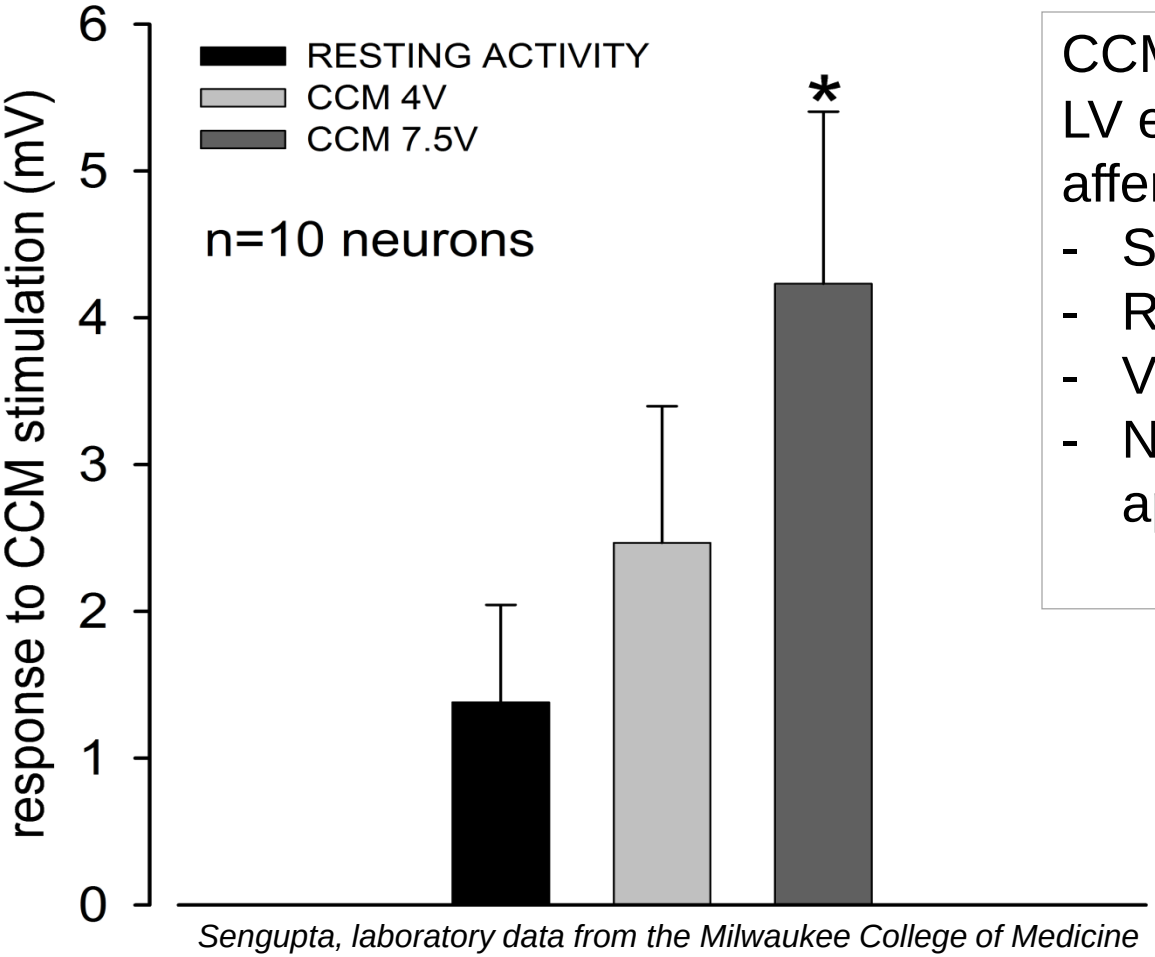
Tschöpe C, et al. J Cardiol. 203 2016

3. CCM Reduces Cardiac Fibrosis



Tschöpe C, et al. J Cardiol. 203 2016

4. Autonomic Nervous System
Summary of 10 Vagal Afferent Single Fiber Recordings



Sengupta, laboratory data from the Milwaukee College of Medicine

CCM applied to the base of the LV elicits a prominent vagal afferent response that is:

- Sustained
- Reversible
- Voltage-dependent
- Not observed when stimuli are applied outside the heart

5. 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 Review 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

6. Cardiac Remodeling
Remodeling in 3D Clinical Echo

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)

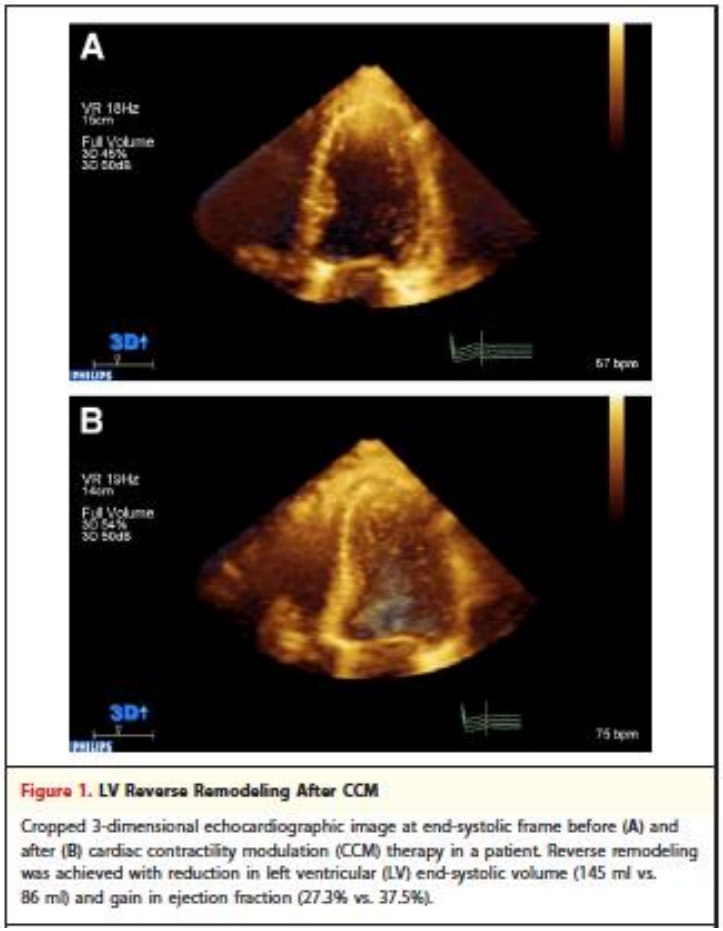


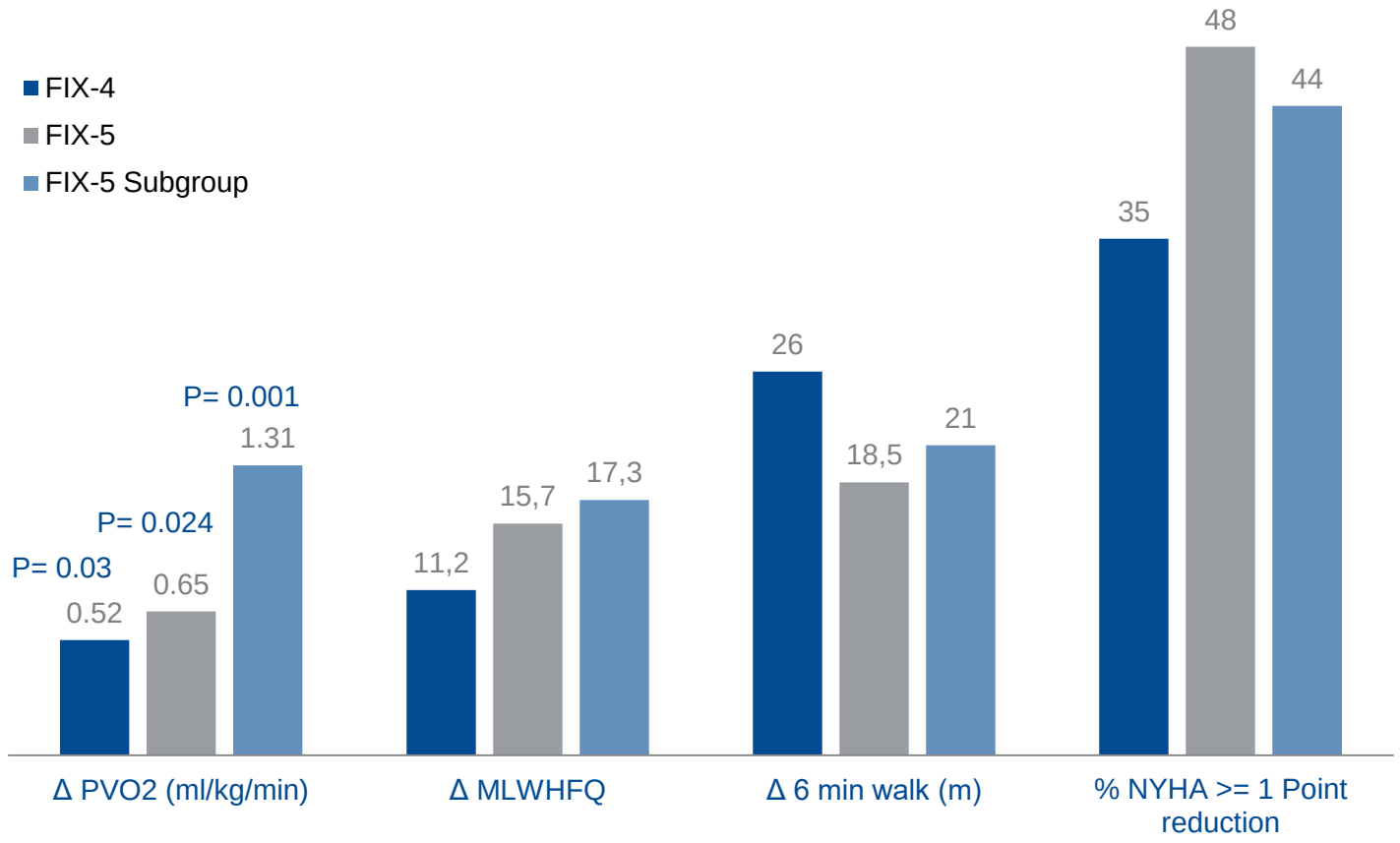
Figure 1. LV Reverse Remodeling After CCM
Cropped 3-dimensional echocardiographic image at end-systolic frame before (**A**) and after (**B**) cardiac contractility modulation (CCM) therapy in a patient. Reverse remodeling was achieved with reduction in left ventricular (LV) end-systolic volume (145 ml vs. 86 ml) and gain in ejection fraction (27.3% vs. 37.5%).

Yu et al. JACC Cardiovascular Imaging, July 2000

Clinical Trial History

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**

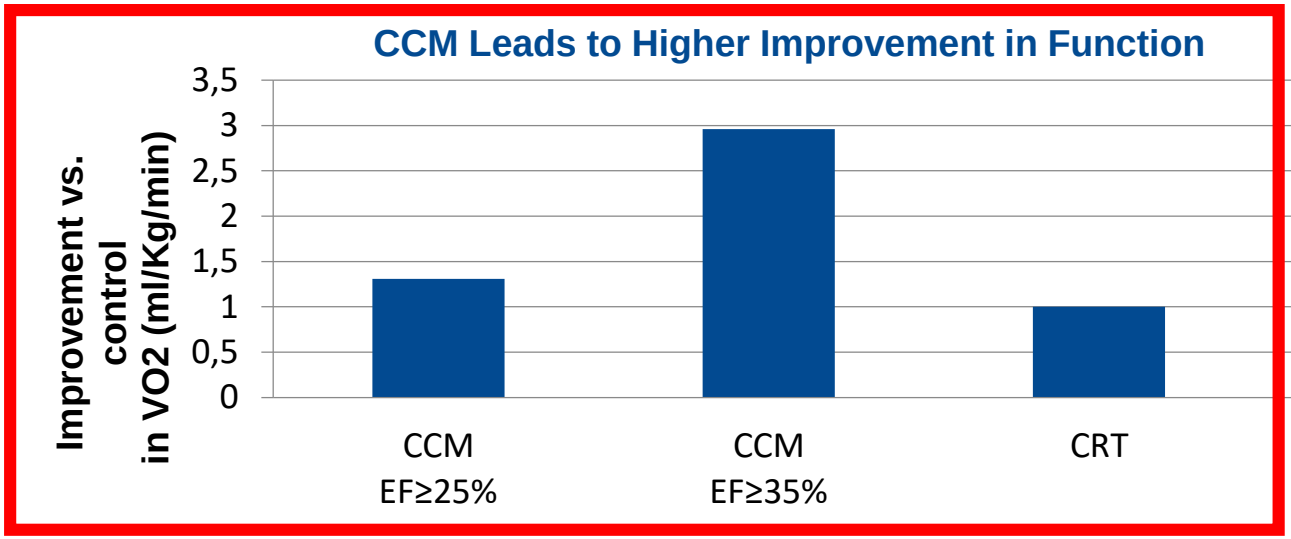
Clinical Data Review

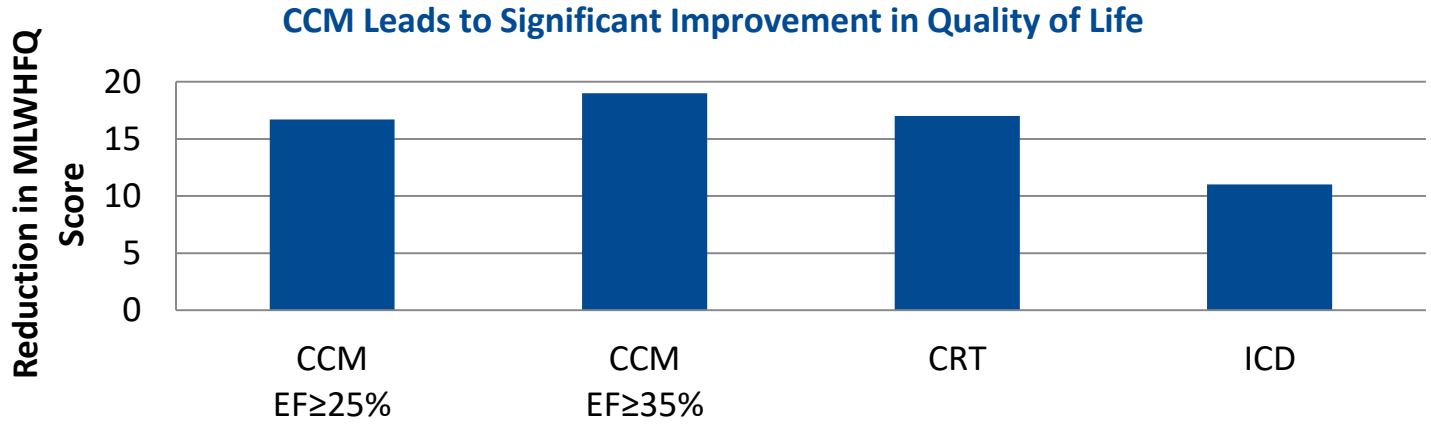


* PVO2 compared to control, all other parameters compared to baseline

Borggrefe et al. European Heart Journal, February 2008; Kadish et al. American Heart Journal, February 2011; Abraham et al, Journal of Cardiac Failure 2011

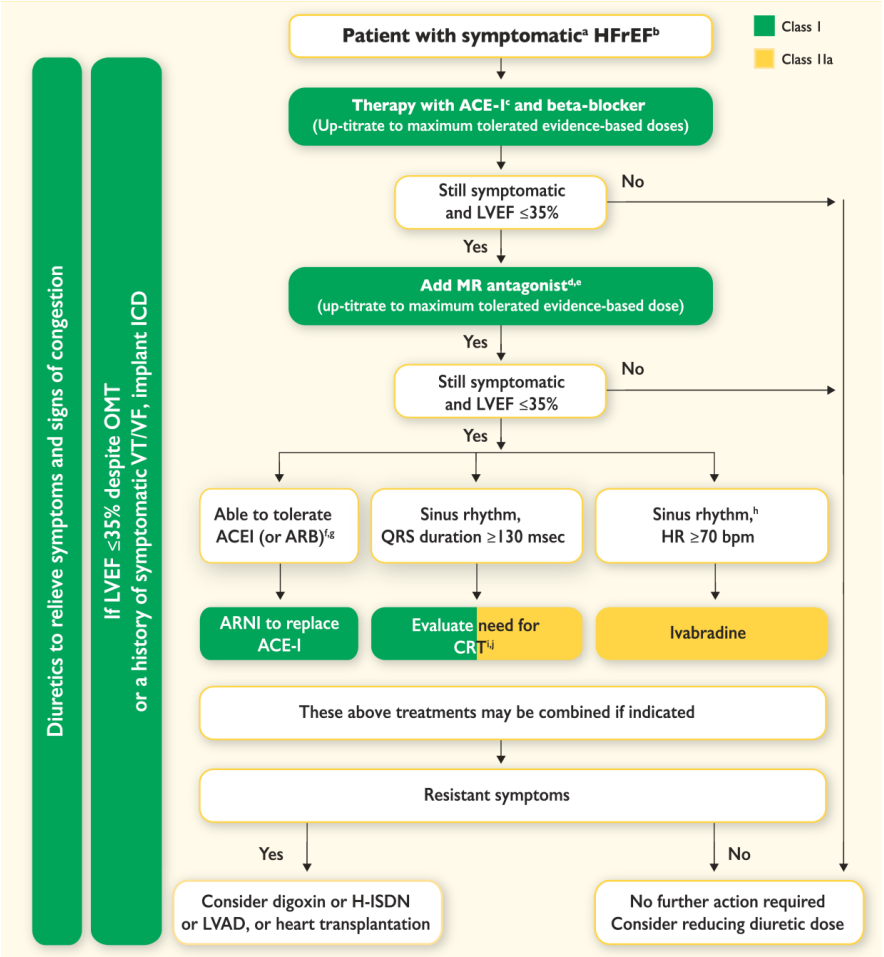
Putting It In Context: CCM Clinical Benefit





For CCM - FIX-HF-5: Abraham JCF 2011, Burkhoff ESC 2010, Borggrefe EJHF 2012
For CRT, ICD - MIRACLE, MIRACLE-ICD: Abraham NEJM 2002, Young JAMA 2003, Chen Europace 2012

CCM Referenced in 2016 ESC HF Guidelines



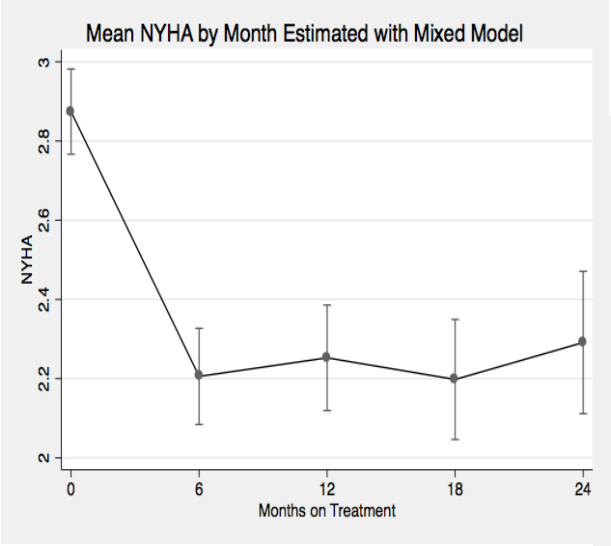
- CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (<120 ms)
- An individual patient data meta-analysis demonstrated an improvement in exercise tolerance (peak VO2) and quality of life (Minnesota Living with Heart Failure questionnaire)
- **CCM may be considered in selected patients with HF**
- The effect of CCM on HF morbidity and mortality remains to be established.

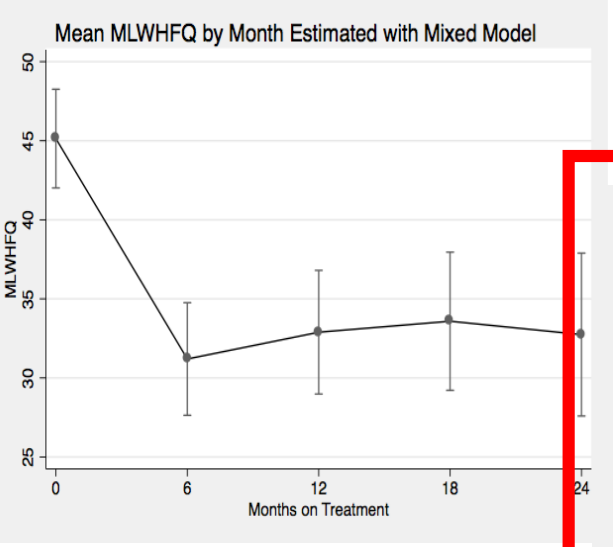
Ponikowski et al, European Heart Journal 2016

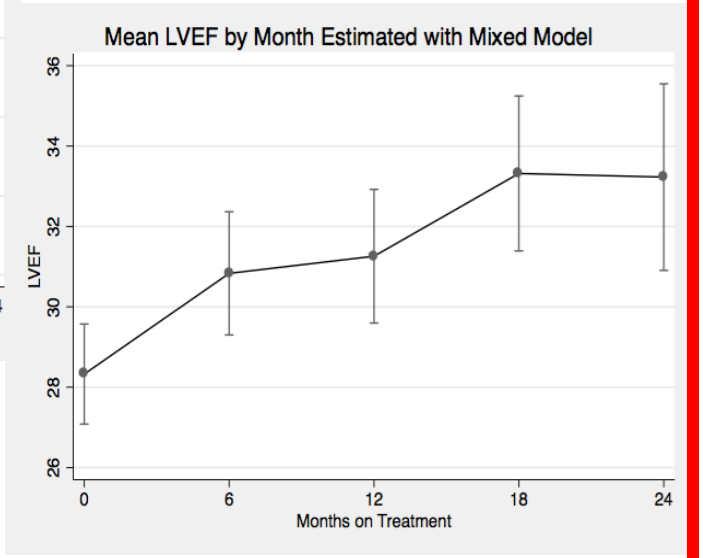
US FDA Status

- FDA granted Impulse Expedited Access Pathway (EAP) status in July 2015
- Trial enrolled in February 2017 with data anticipated in September 2017
  - **Target population:** heart failure patients with EF 25% to 45%
  - **Efficacy Endpoint:** Improvement in exercise tolerance measured by pVO_2
- Data to be combined with 229 patients from earlier study for a total of 389
- FDA submission in Q4 2017; Priority Review already granted
- PMA approval anticipated in 1H2018

CCM EU Clinical Registry – 2yr Follow Up



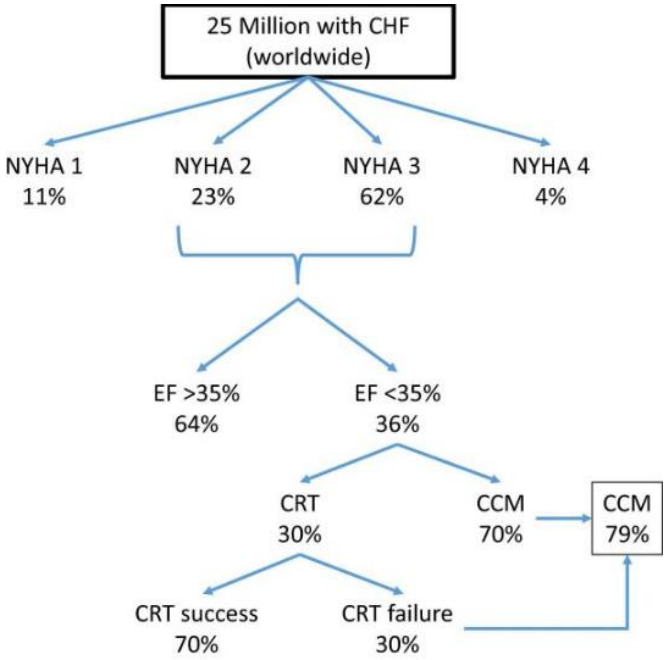


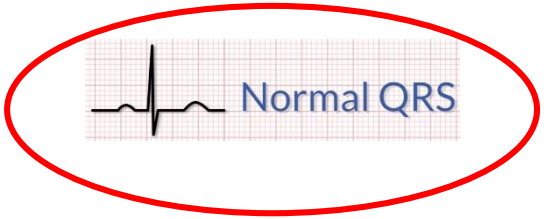


- N=143, NYHA II-IV in 28 centers
- EF up to 45% mean 28.3 ± 6.4 (20% had EF ≥35%)

Remppis et al, in submission

CCM: Position in the Treatment Paradigm



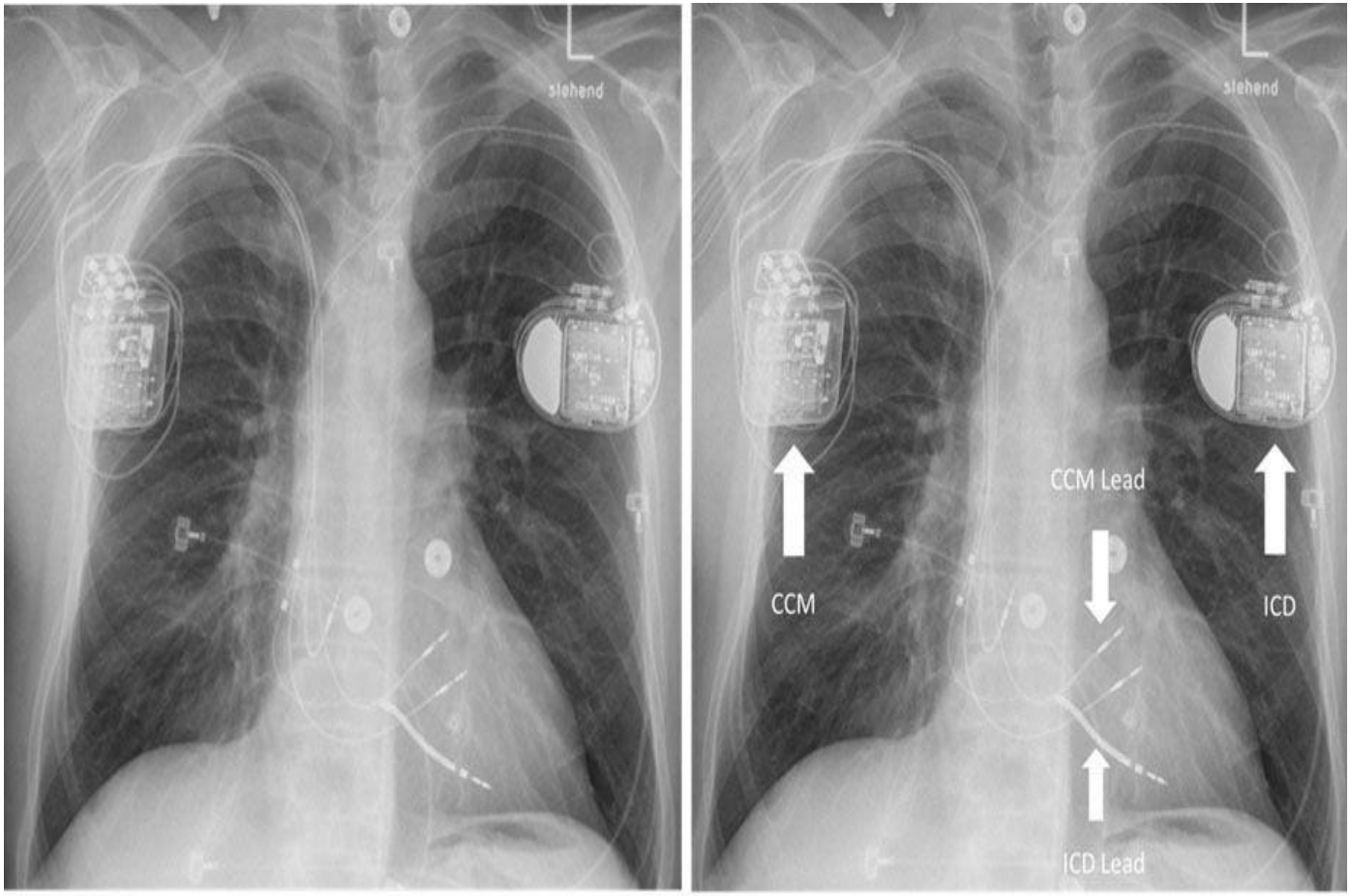


More than 17m patients globally with NYHA II/III

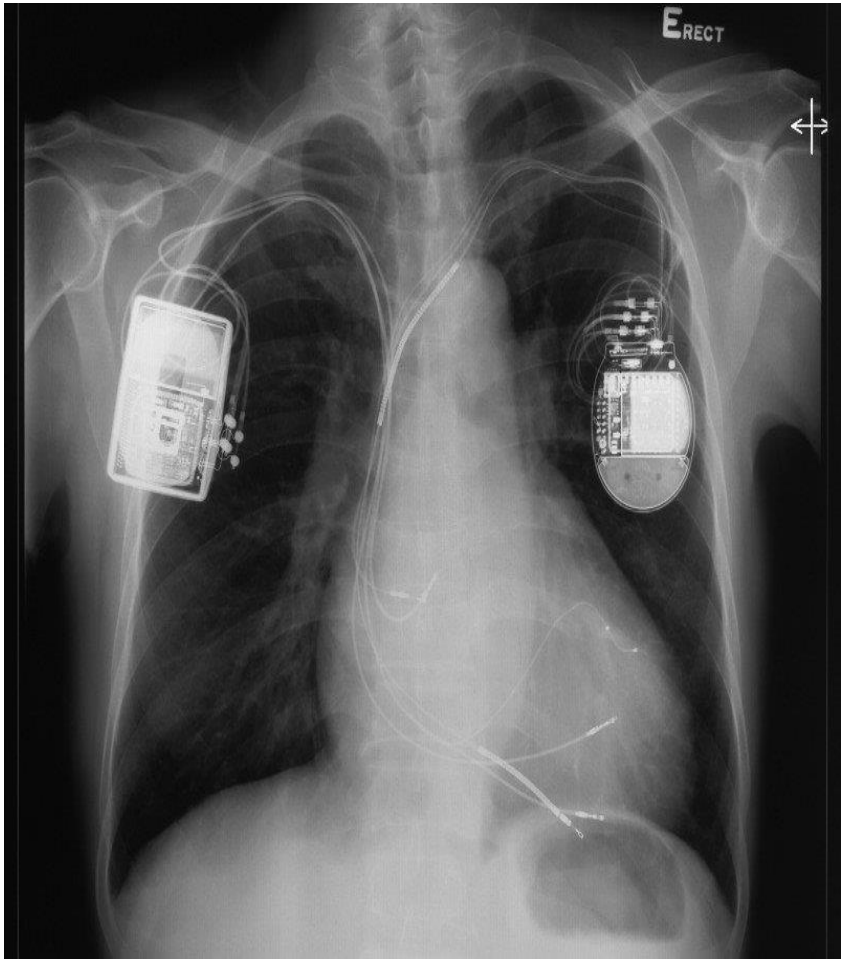
- Only 30% eligible for CRT (~5m patients)
- Remaining candidates for CCM

Esempio di impianto CCM OPTIMIZER SMART alone

Esempio di impianto CCM OPTIMIZER SMART + ICD



Esempio di impianto CCM OPTIMIZER III + CRT-D

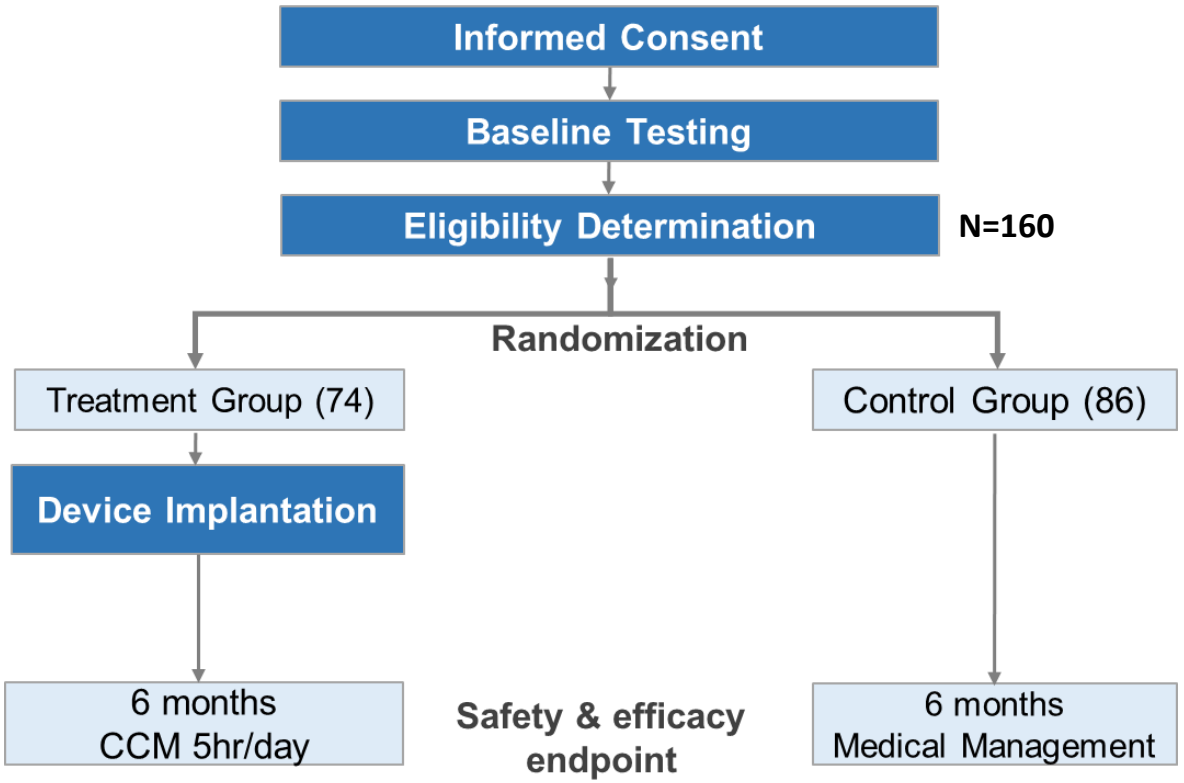


FIX-HF-5C “Confirmatory” Study

- 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 VO2**
- **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%**
- 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

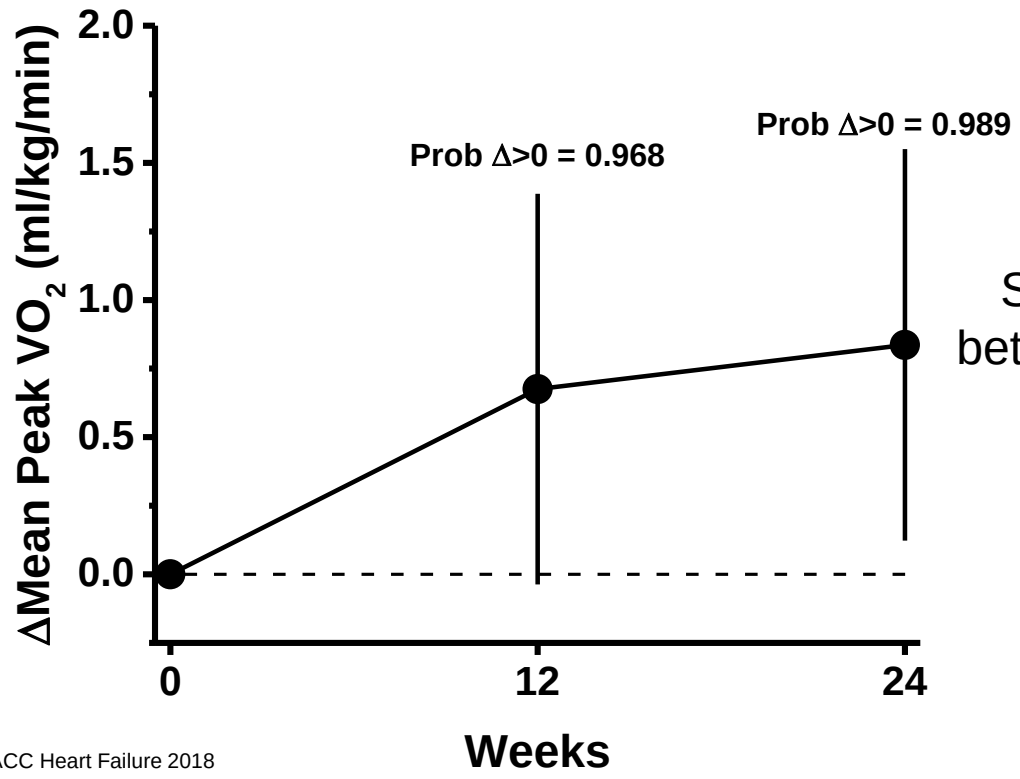
Abraham et al, JACC Heart Failure 2018

FIX-HF-5C “Confirmatory” Study Schematic



Abraham et al, JACC Heart Failure 2018

FIX-HF-5C Primary Efficacy Endpoint Met
CCM Significantly Improves Exercise Capacity

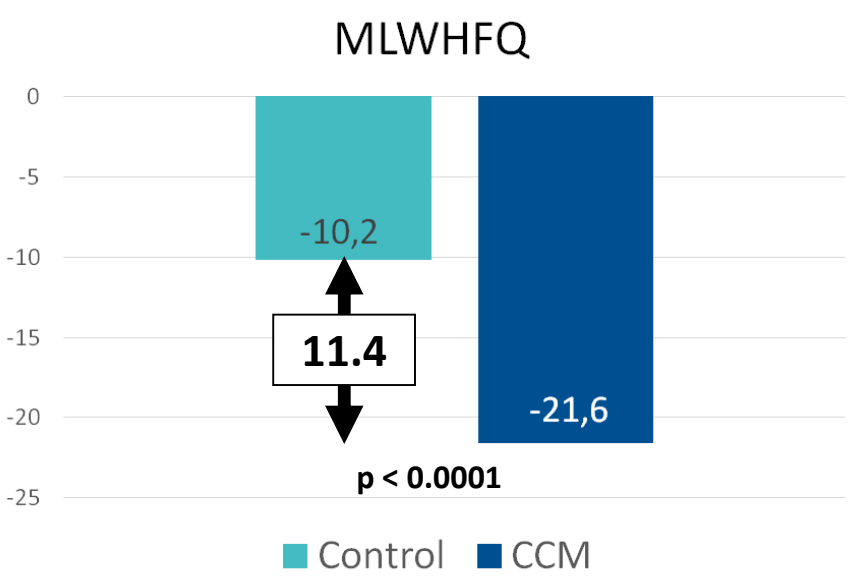


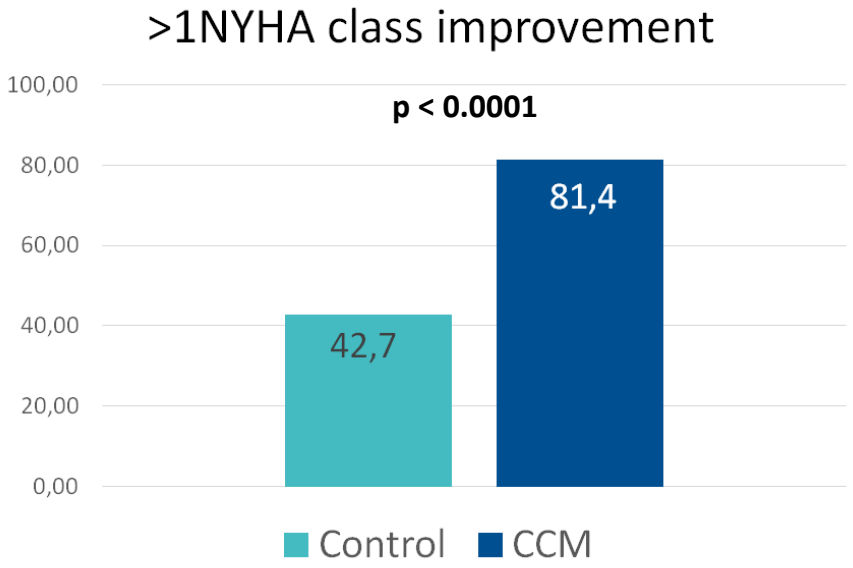
Statistically significant between group difference At 24 weeks: 0.84 mlO2/kg/min

Abraham et al, JACC Heart Failure 2018

FIX-HF-5C: Secondary Efficacy Endpoints Met

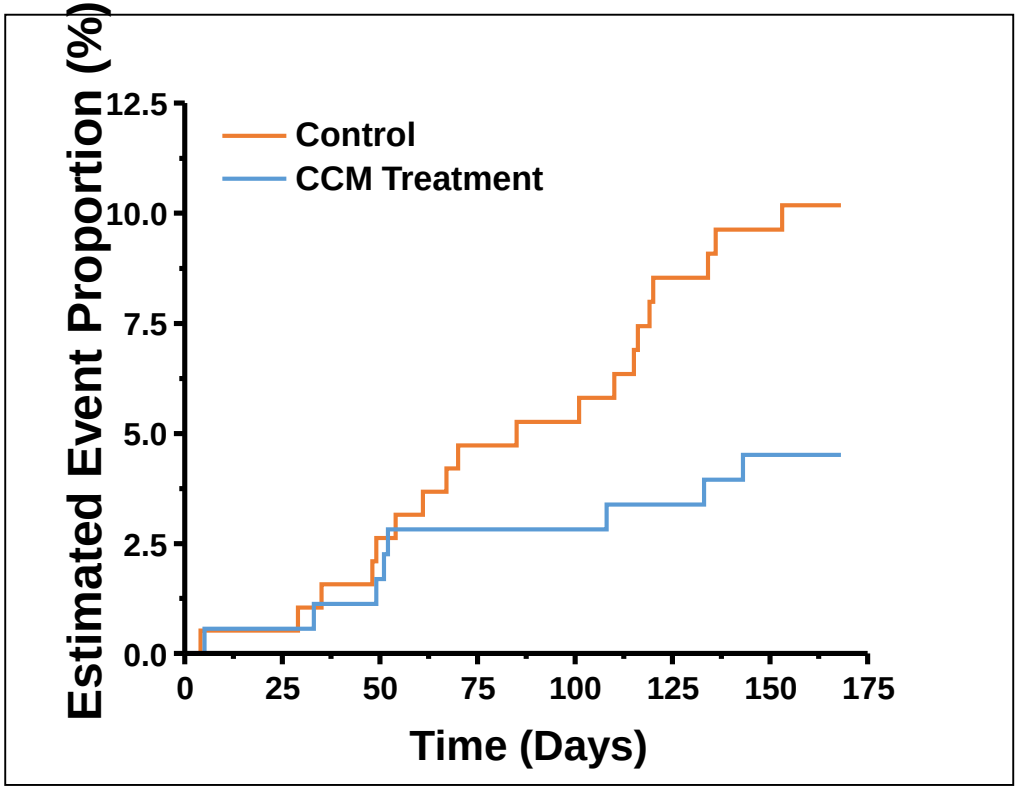
CCM Significantly Improves QoL and Functional Status





Abraham et al, JACC Heart Failure 2018

FIX-HF-5 & FIX-HF-5C:
Cardiovascular Death & HF Hospitalizations



p= 0.036
comparing K-M estimates

Abraham et al, JACC Heart Failure 2018

FIX-HF-5 & FIX-HF-5C:
Hospitalization rates

		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

Abraham et al, JACC Heart Failure 2018

Pre-specified subgroup analysis: EF 35%-45%

Variable	CCM	CCM 35%+
pVO_2	0.84	1.76 (p=0.009)
MLWHFQ	-11.4	-14.9 (p=0.003)
NYHA 1 class improvement from baseline	81%	82% (p=0.012)*
6 Minute Walk	24.6	57.1 (p=0.009)

* p value vs. control)

A Summary of Efficacy Comparisons to CRT

Variable	CCM	CCM 35%+	CRT*
pVO_2	0.84	1.76	0.91
MLWHF	-11.4	-14.9	-9.5
NYHA 1 class improvement	81%	82%	70%
6MW	24.6	57.1	20.0

* Weighted average by number of patients from: Higgins JACC 2003, Abraham NEJM 2002, Abraham Circulation 2004, Young JAMA 2003, Caseau NEJM 2001, Leclercq EHJ 2002

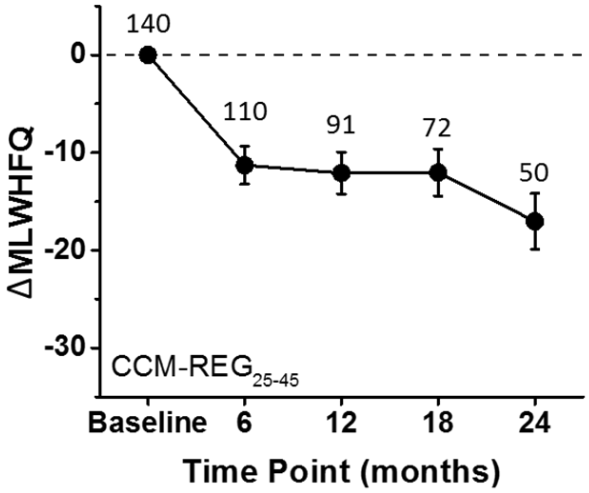
“Real World Registry”: CCM-REG

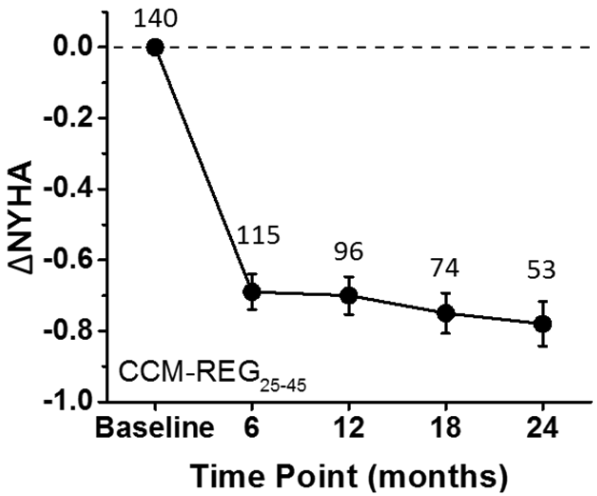
- European prospective registry study @ 31 sites aimed to assess longer-term impact of CCM on hospitalizations and mortality in a real-world experience with the same population as FIX-HF-5C (25≤EF≤45%)
- 140 patients with EF 25% - 45% receiving CCM therapy for clinical indication:
  CCM-REG$_{25\text{-}45}$ cohort
- 2 Year Follow-up: Minnesota Living with Heart Failure Questionnaire (MLWHFQ), LVEF, Cardiovascular and HF hospitalizations (compared to hospitalizations during the year prior to CCM)
- 3 year Follow-up: Mortality (compared to predicted mortality by the Seattle Heart Failure Model, SHFM)
- A separate analysis was performed on patients with 35% ≤ LVEF ≤ 45% :
  CCM-REG$_{35\text{-}45}$ cohort

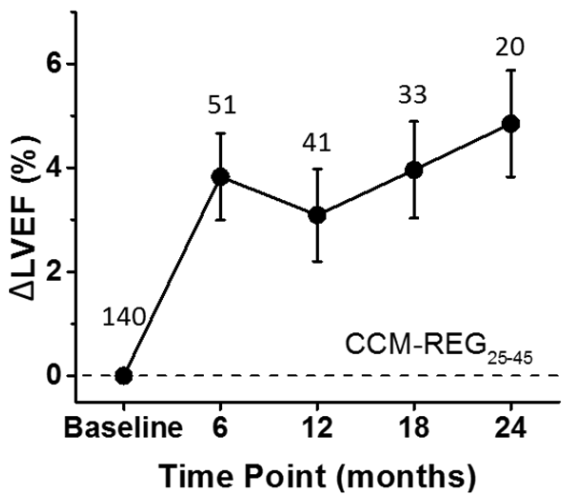
G. Hasenfuss, EHF, Vienna 2018

Significant & Sustained Improvements in MLWHFQ,NYHA and LV EF in the Entire CCM-REG$_{25\text{-}45}$ Cohort

Changes from baseline before CCM

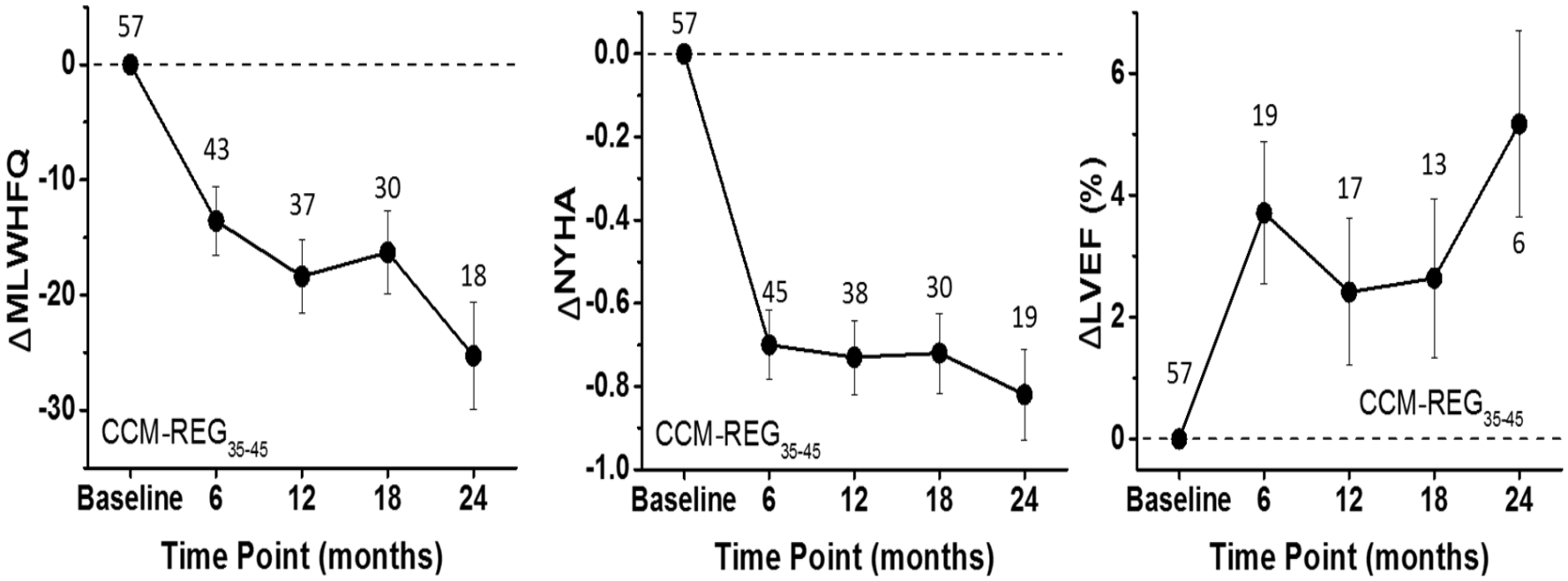






G. Hasenfuss, EHF, Vienna 2018

Similar Significant and Sustained Improvements in the Higher EF Cohort (CCM-REG$_{35-45}$)



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CV and HF Hospitalizations Reduced by ~75%

Cohort	EVENT	Pre-Enrollment			Post-Enrollment		
		Pt-Yrs	Events	Event-Rate	Pt-Yrs	Events	Event-Rate
$CCM\text{-}REG_{25\text{-}45}$	HF	140.0	134	0.96	279.6	73	0.26*
	CV		34	0.24		24	0.09*
	HF+CV		168	1.20		97	0.35*
$CCM\text{-}REG_{35\text{-}45}$	HF	57.0	47	0.82	113.5	18	0.16*
	CV		23	0.40		9	0.08*
	HF+CV		70	1.23		27	0.24*

*p<0.0001

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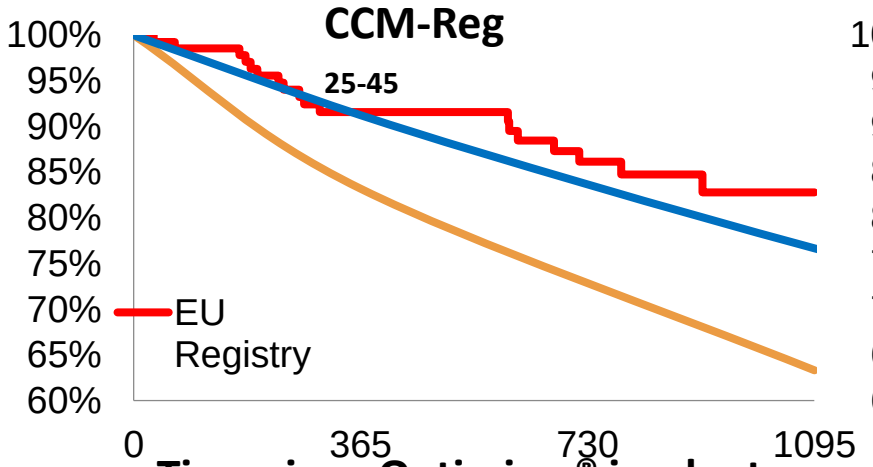
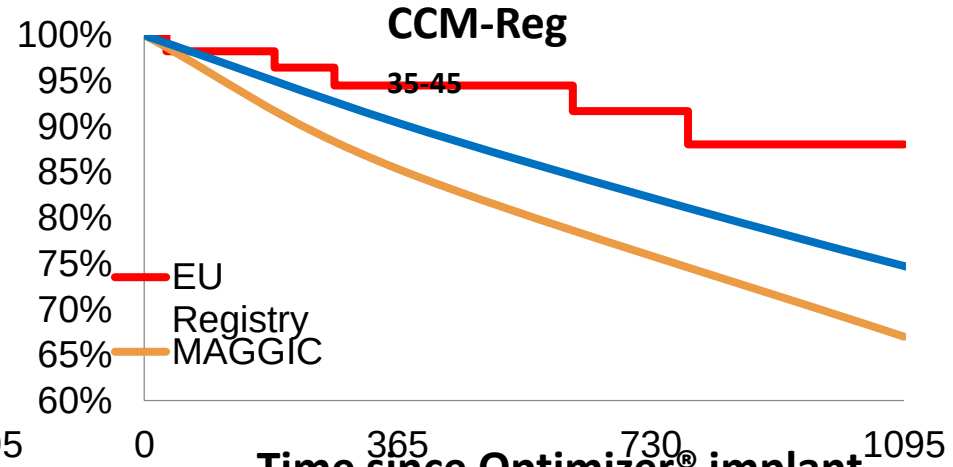
Overall Survival





	3Yr Survival	p vs Observed
Observed	82.8%	
SHFM	76.7%	0.164
MAGGIC	63.3%	0.0001

	3Yr Survival	p vs Observed
Observed	88.0%	
SHFM	74.7%	0.046
MAGGIC	67.7%	0.004

G. Hasenfuss, EHF, Vienna 2018,

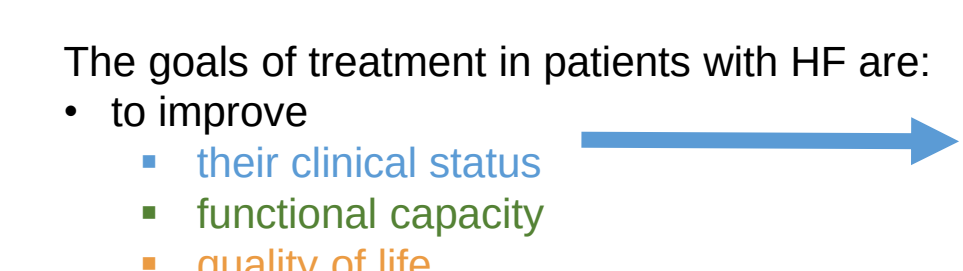
SHFM: Seattle Heart Failure Model, MAGGIC: Meta Analysis Global Group in Chronic HF

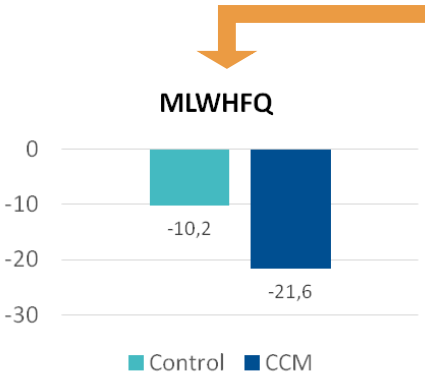
In conclusion: CCM meets the needs for HF patients as defined in the ESC Guidelines

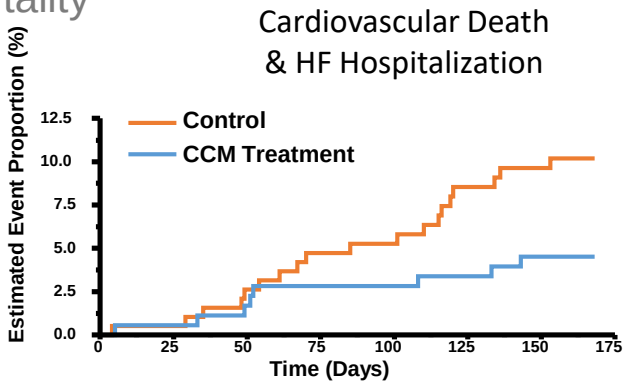
7.1. Objectives in the management of Heart Failure

The goals of treatment in patients with HF are:

- to improve
  - their clinical status
  - functional capacity
  - quality of life
- to prevent hospital admission and
- reduce mortality







Thank You