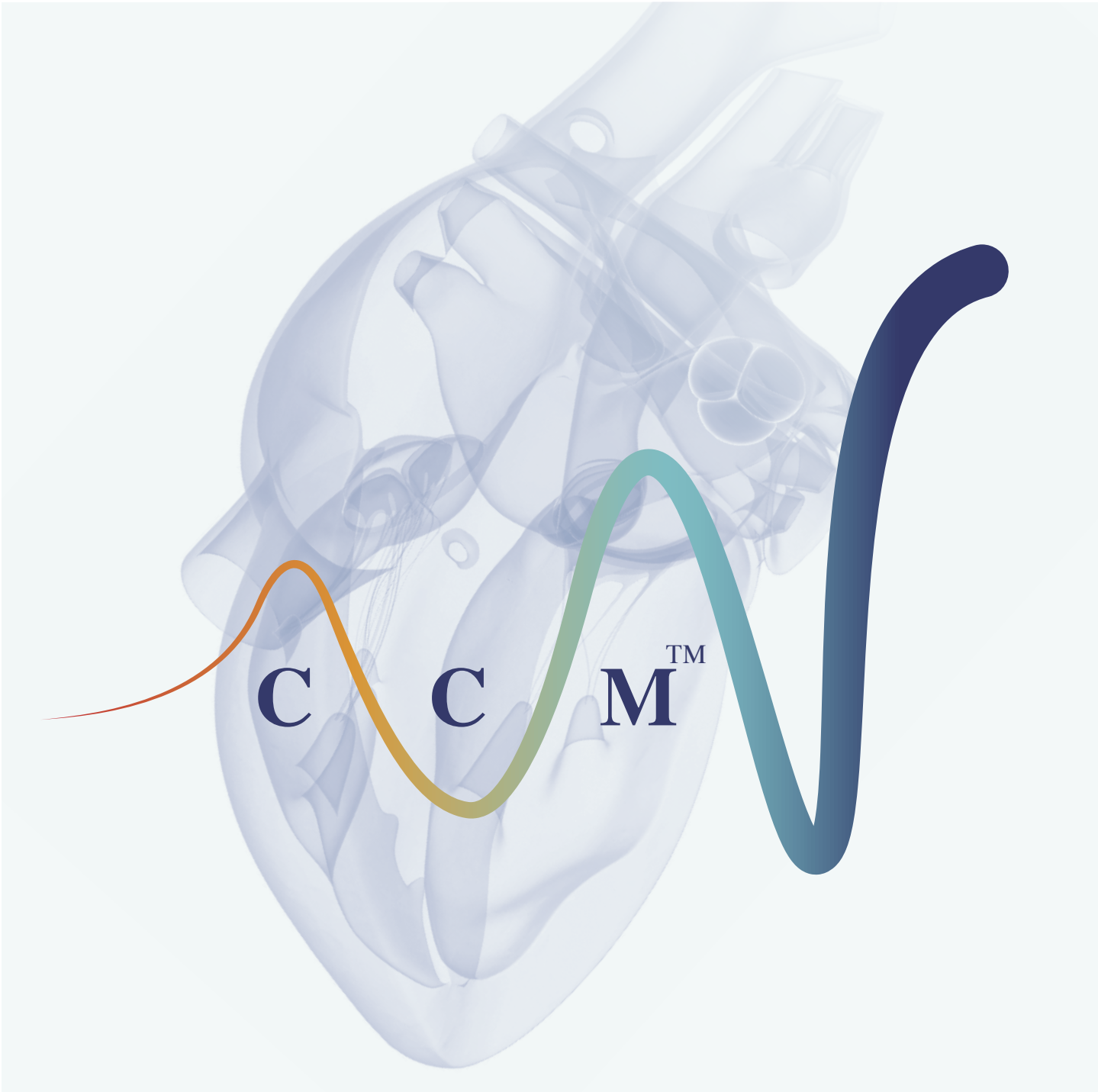
IMPULSE DYNAMICS

CARDIAC CONTRACTILITY MODULATION



AN INNOVATIVE HEART FAILURE THERAPY SOLUTION

Chronic Heart Failure

3.6 million people suffer Chronic Heart Failure (CHF) in Europe[1]. The long-term prognosis associated with CHF is poor. Mortality rates in heart failure are high even for patients compliant with the best available medical treatment.

One in nine patients with heart failure dies within one year of diagnosis while approximately half of all patients diagnosed with CHF die within five years.[25] CHF results in one of the worst 5-year adjusted mortality rates.[26]

Even when heart failure symptoms are stabilized by current treatments, the cardiac stress and the neurohormonal imbalance underlying heart failure continue to grow, resulting in disease progression.[27]

Despite appropriate medical treatment, many heart failure patients suffer frequent hospitalization, weakness and other symptoms including anxiety and depression, and also experience difficulties performing daily activities.[28]

There are some solutions for specific patient groups such as CRT for patients with prolonged QRS or LVADs when the patients reach very advanced heart failure state, but the majority does not have a solution that can alleviate their symptoms and improve their outcomes.

More than two thirds of heart failure patients have a normal QRS duration and are therefore ineligible for CRT.[29] For these patients who are not yet in end stage heart failure, Cardiac Contractility Modulation is an implantable device treatment option which has been validated through several randomized clinical trials.[7, 23]

These trials show benefits in functional and clinical status as well as reduction in hospitalization rates and improved QoL (quality of life). The magnitude of theses benefits are comparable to those experienced by patients with CRT devices.

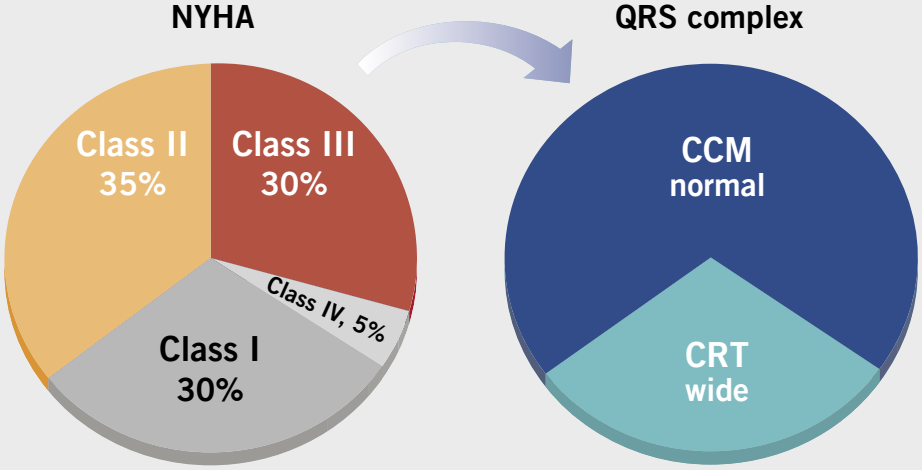


Fig. 1: Subgroups of patients with heart failure.

Cardiac Contractility Modulation

Cardiac Contractility Modulation is a unique and innovative therapy comprising electrical stimulation of the cardiac muscle during the absolute refractory period, as shown in the schematic picture. CCM™ does not affect cardiac rhythm itself or the action potential distribution, and is thus fundamentally different from other implantable systems, such as pacemakers or cardiac resynchronization therapy (CRT).[10, 30]

Cardiac Contractility Modulation therapy is delivered by the Optimizer® Smart, an implantable pulse generator, that delivers the non-excitatory impulses to the right ventricular septum. CCM™ triggers physiological processes in cardiac muscle cells which impact the cellular function on a molecular level and thereby improve cardiac performance without an increase in oxygen consumption and leads to beneficial reverse remodeling.[9, 12, 13]

These benefits are comparable in ischemic as well as non-ischemic HF-patients. The only subgroup showing larger benefits are those with an EF above 35%.

Cardiac Contractility Modulation increases ability to exercise, improves quality of life and reduces hospitalizations.[24]

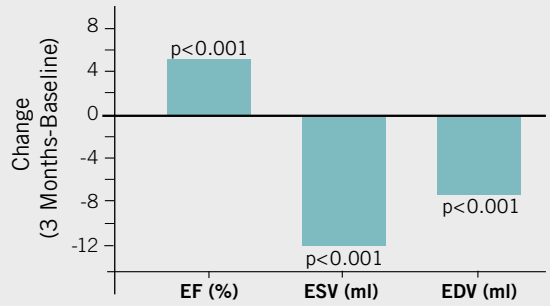


Fig. 4: Improved regional cardiac function induces global improvement and reverse remodeling in patients.[10]

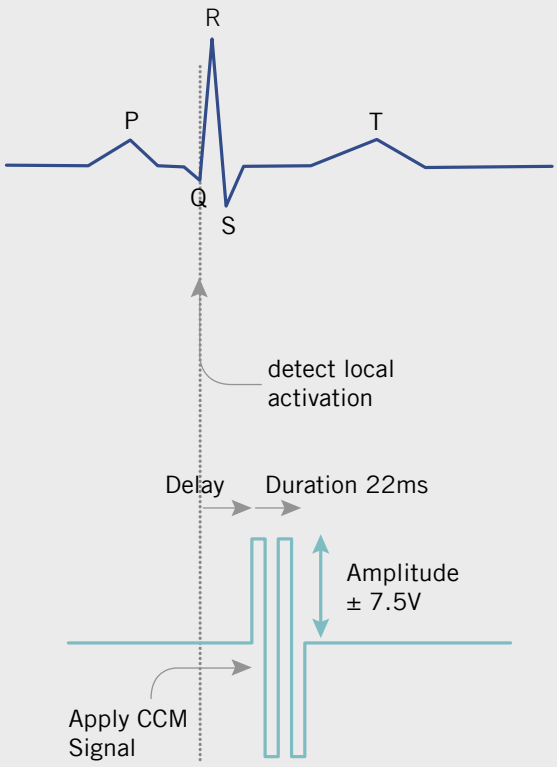


Fig. 2: CCM™ improves cardiac function and leads to reverse remodeling in patients.[10]

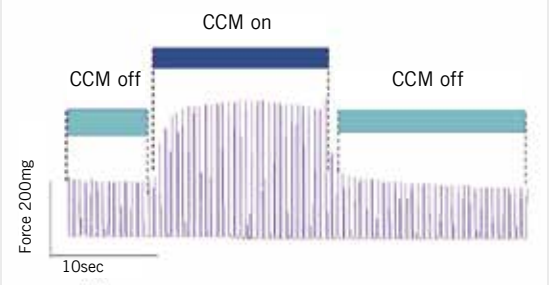


Fig. 3: Representative isometric force tracing from a rabbit papillary muscle showing the rapid onset of inotropic effect due to cardiac contractility modulation signal. The decay of inotropic effect is similarly rapid.[31]

Mechanism of Action

Cardiac Contractility Modulation is a unique therapy that enhances cardiac contractility, improving cardiac muscle cell biochemical calcium handling processes, and restoring a more normal myocardial gene expression, contributing to improved clinical status in heart failure.[13,20]

3-Phase Cardiac Performance Improvement

CHF is associated with remodeling of cardiac gene expression levels, which revert from an adult profile to a fetal gene expression program. Intracellular calcium handling is affected, for example, by reduced phosphorylation of phospholamban and expression of SERCA2a. This decreases contractile capacity and efficiency of the heart.

CCM™ has shown to increase cardiac contractility and cardiac performance by reversing these processes.[9, 20, 21]

Importantly the gain in contractility, achieved via CCM™ therapy is not associated with an increase in cardiac oxygen consumption.[21, 22]

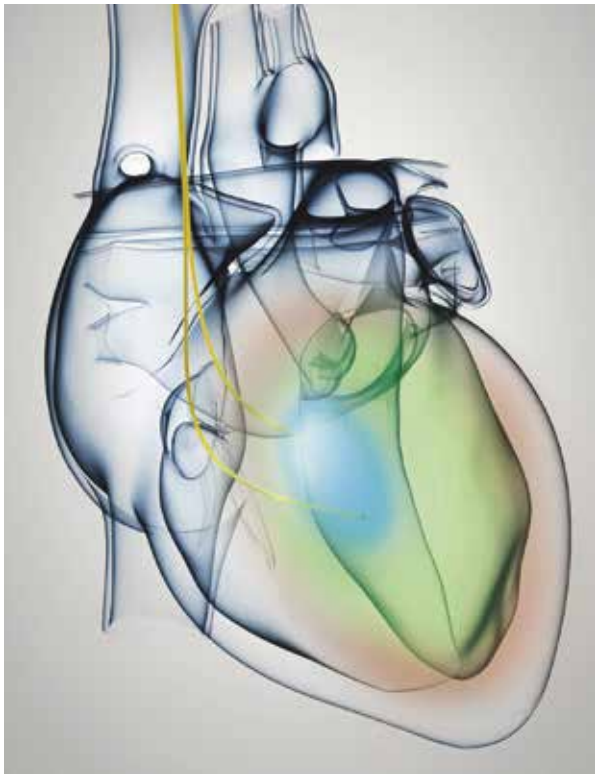


Fig. 5:
Phase 1: Within seconds: *Normalized activity of key proteins related to intra-cellular calcium regulation*
The electrical signals reach an area of the myocardium which is a few centimeters wide. In this area, the activity of key proteins for calcium regulation is normalized within seconds. An improved contractility of the myocardium can already be seen shortly after signal activation.[10]

Phase 2: Within hours: *Reversal of fetal gene program*
Within hours, the pathological fetal gene program is interrupted and reverts towards normal adult gene program. As a result, proteins are now synthesized to a more normal, adult level of expression. Expression of genes related to electrotonic coupling between myocardial cells is also improved. This may potentially increase conductivity, which may be responsible for augmentation beyond the initial stimulus area.

Phase 3: Within months: *Reverse Remodeling*
In the further course of treatment, mechanical and neurohormonal stress in the myocardium is progressively reduced. Studies using cardiac biopsy and echocardiography show a global improvement within three months.[12, 13] The pathological fetal gene program is arrested and reversed globally. Structural and functional reverse remodeling occurs.[12]

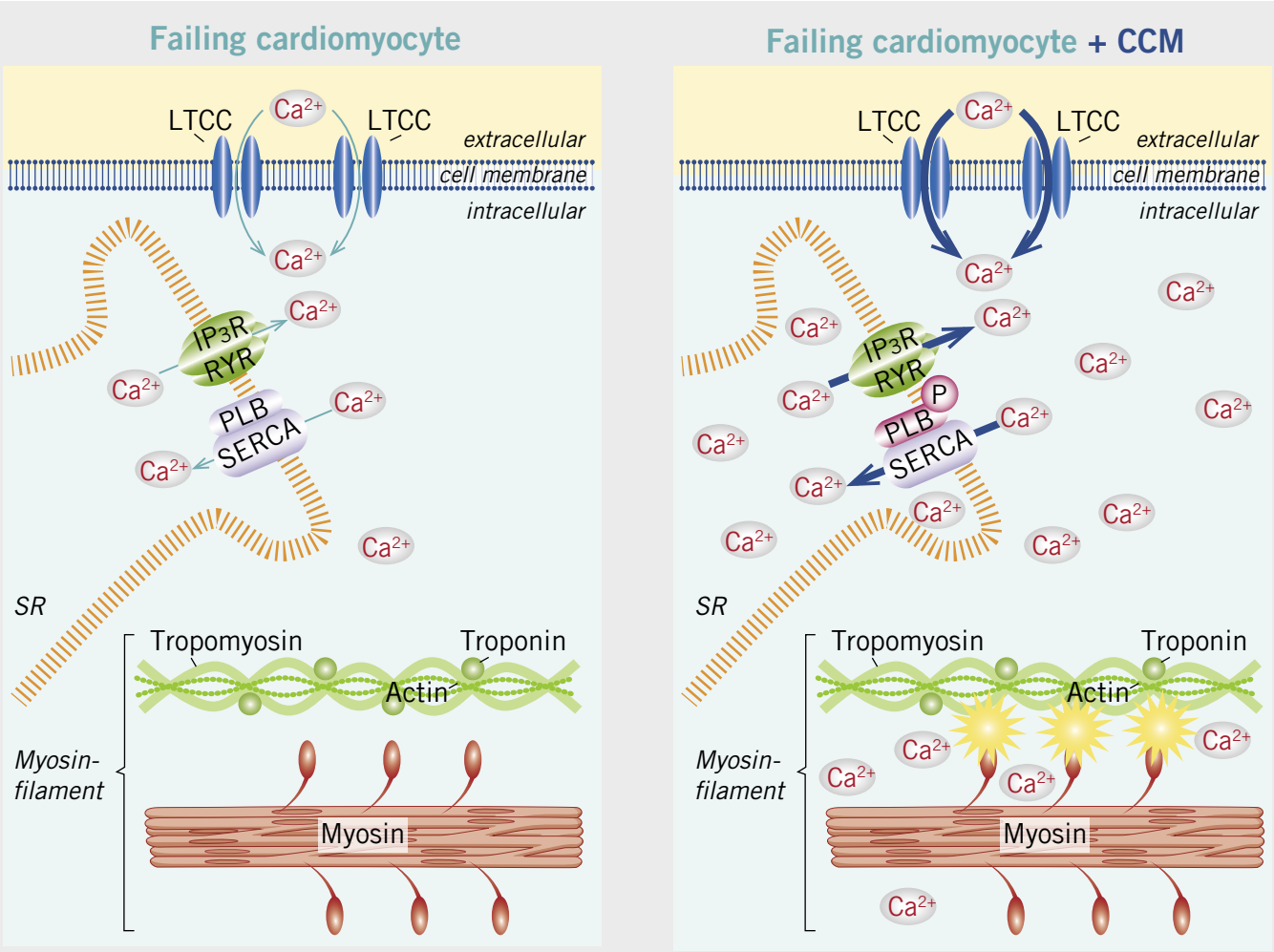


Fig. 6: The non-excitatory electrical signal to the myocardium, during the absolute refractory period of the action potential results in acute changes in calcium handling. It enhances the efficiency of cytoplasmic-sarcoplasmic reticulum calcium transfer and elicits a rapid positive inotropic effect without increasing myocardial oxygen consumption, by strengthening the contractility of the myosin filament.

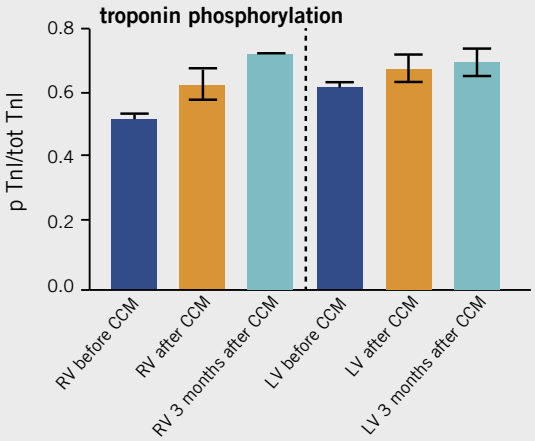


Fig. 7: Troponin phosphorylation is increased under CCM™ in the right as well as the left ventricle.[34]

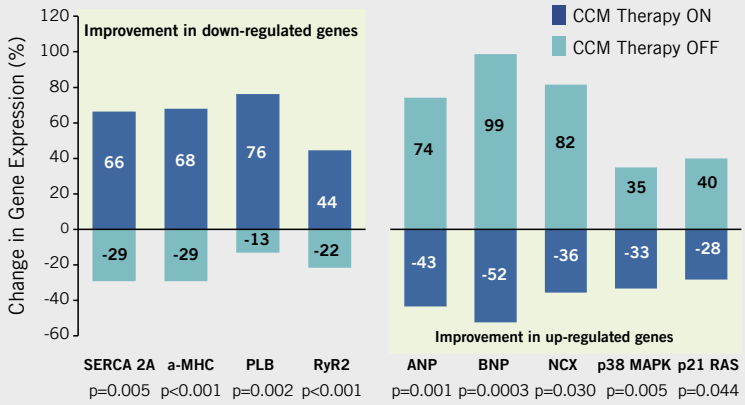


Fig. 8: Findings in human myocardial samples confirm findings in tissue from animal models.[13]

Abbreviations: CCM, cardiac contractility modulation; LTCC, L-type voltage-dependent Ca^{2+} channel; PLB, cardiac phospholamban; RyR, ryanodine receptor; SERCA 2A, sarcoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum

Evidence from Controlled Clinical Trials

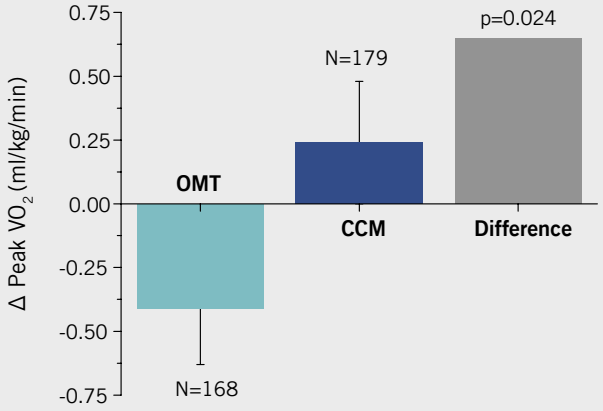
As of end of 2017, over 1300 patients have participated in clinical trials examining cardiac contractility modulation and its effects. Typical patients in most studies were in NYHA class II-IV despite guideline directed medical therapy, EF 20–45%, and a normal QRS duration.

All studies looked at measure for functional and clinical status, like peak VO_2, MLWHFQ, 6 MHW and NYHA classification. Additionally the studies looked at hospitalization rates and potential survival benefits.

FIX-HF-5

This multi-center, randomized US trial included subjects with NYHA Class III or IV, reduced EF and QRS duration <130ms.

Data from 428 patients showed a significant increase in maximum oxygen uptake (Δ Peak VO_2) (Fig. 9) during cardiopulmonary stress testing and an improvement in quality of life and symptoms (MLWHFQ (Fig. 10), NYHA).[19]



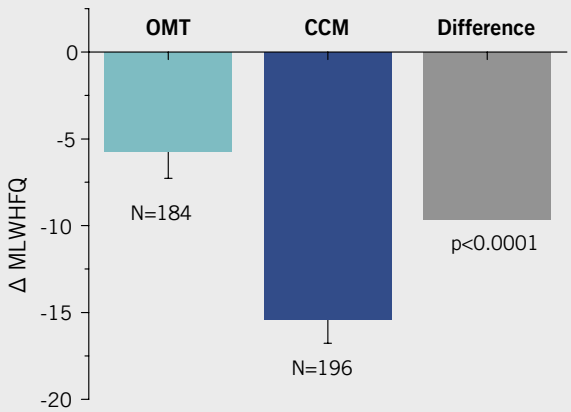


Fig. 9 and 10: Data from the FIX-HF-5 trial. Change in maximum oxygen uptake (Δ Peak VO_2) and quality of life (MLWHFQ) respectively.

FIX-HF-5C

This multi-center, randomized study was conducted to prospectively test the efficacy and safety of Cardiac Contractility Modulation in patients with EF ranging from 25–45%, and to confirm a subgroup analysis of the prior FIX-HF-5 study showing that Cardiac Contractility Modulation significantly improved exercise tolerance and quality of life (QoL) in patients with ejection fraction (EF) between 25 and 45%.

The data from that study suggest that Cardiac Contractility Modulation is safe and significantly improves exercise tolerance (peak VO_2), 6 minute Hall Walk, quality of life (MLWHFQ score), and functional status (NYHA class) in patients with moderate to severe heart failure.[24]

The functional improvements shown in the FIX-HF-5C study for ischemic as well as non-ischemic patients show comparable results to CRT for patients with wide QRS complex.

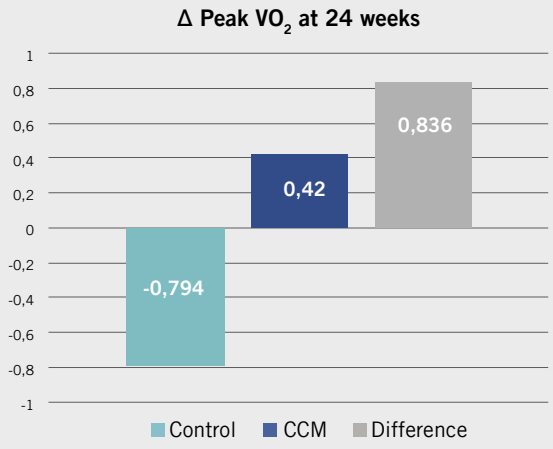


Fig. 11: Primary endpoint from the FIX-HF-5C trial, peak VO_2 changes from baseline. [24]

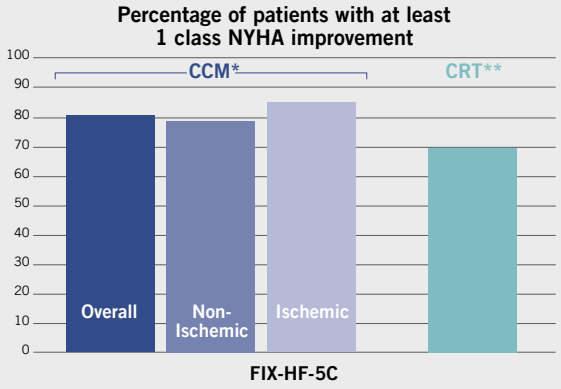


Fig. 12: Improvement in functional status.

** Latest U.S. study and all CCM™ values p=0.001 with control*

*** Weighted average by number of patients in the CRT trials, Higgins JACC 2018, Higgins JACC 2003, Abraham NEJM 2002, Abraham Circulation 2004, Young JAMA 2003, Caseau NEJM 2001, Leclerq EHJ 2002*

Long-Term Results

The FIX-HF-5C study showed a significant reduction in cardiovascular and heart failure hospitalization and mortality as composite endpoint at six months (Fig. 8). Additionally clinical and functional status improved throughout the six months observation period. A registry population of 140 patients (CCM-Reg)[23] matching the FIX-HF-5C show real world experience. The results confirm the short term results on functional and clinical effects: improved NYHA class, MLWHFQ and LVEF. The CCM-Reg population shows a sustained effect over 2 years. The results from the registry also confirm a significant reduction in hospitalization for heart failure when compared to 12 months prior to treatment.

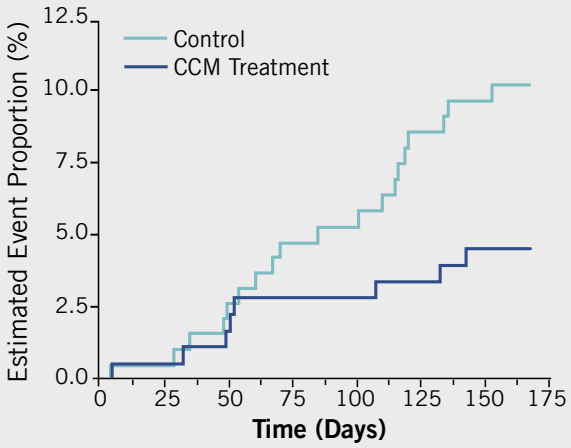


Fig. 13: FIX-HF-5C composite endpoint CV death and hospitalization. [24]

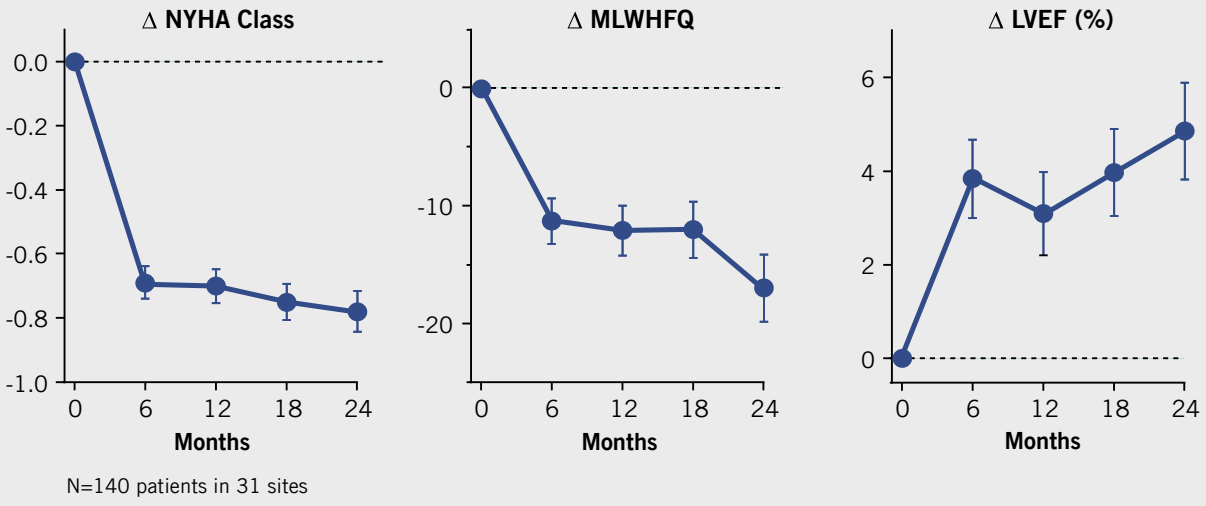


Fig. 14: CCM-REG: Supports durability of effect.

Long-term Results: Retrospective single center analyses

A previous registry[32] including 143 patients and following these over 24 months showed the sustained effects on LVEF, NYHA class and MLWHF (Fig. 15). Again confirming the improvements in clinical and functional status over time. Multiple investigator-initiated retrospective reports demonstrate long-term benefit of Cardiac Contractility Modulation therapy.

A report on 81 CHF patients (NYHA II–IV, reduced EF) showed significant improvement under therapy during a mean follow-up period of 34 months (ranging 6–123 months)[6].

The cohort had significant long-term improvement in left ventricular size and function, quality of life, NYHA class, peak VO_2 and decreased levels of NT-proBNP. Nearly 75% of the patients had an improvement of at least one NYHA class even after long-term follow-up.

Compared with the per patient mortality risk score (calculated by the MAGGIC model), the long-term results indicated that the survival with cardiac contractility treatment was better than expected (p=0.022).[6]

Another report[4] of 68 CHF patients (NYHA II–III, narrow QRS complex) treated by Cardiac Contractility Modulation during a mean follow-up period of 4.5 years (up to 10 years) showed that compared with the per patient mortality risk score (calculated by the SHFM), the survival with cardiac contractility treatment was better than expected (p=0.007).

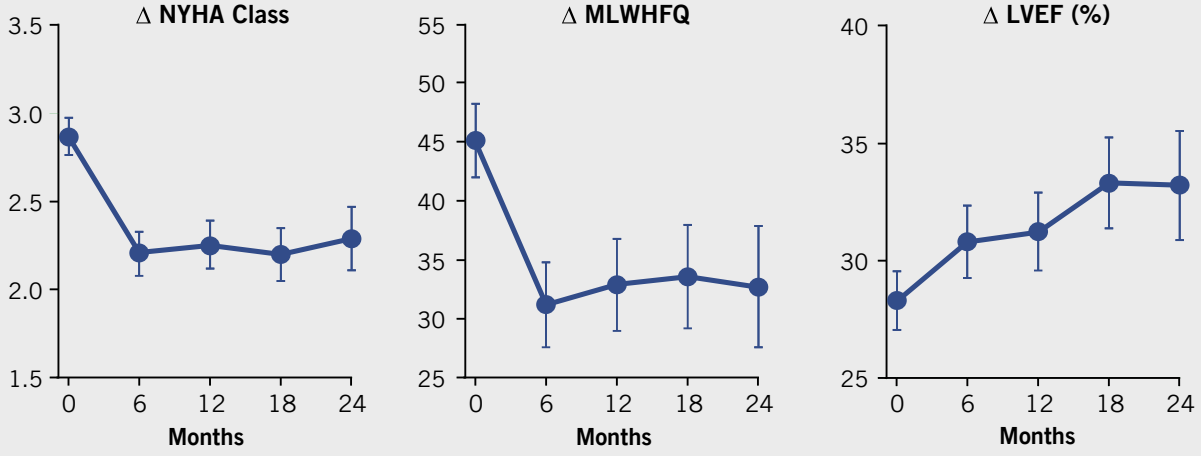


Fig. 15: CCM-HF: Supports durability of effect. [32]

Clinical Benefits of Cardiac Contractility Modulation: A Comparison

A comparison of published results from principal trials examining CCM™ and those of CRT shows a similar improvement in Quality of life, clinical and functional status. Table 1 shows an overview of the results comparing CRT, CCM™ with EF between 25–45% as well as subgroup analyses from patients with EF between 35 and 45%.

The effect of CCM™ in patients with narrow QRS complex is comparable to that obtained by CRT in patients with wide QRS complex. Also both therapies show no increase in oxygen consumption (Fig. 16).

The improvement for Cardiac Contractility Modulation is greater when EF is higher at baseline. Patients treated with Cardiac Contractility Modulation with EF above 35 show a greater improvement. This effect is shown in the FIX-HF-5C study as well as in the registry (CCM-Reg).

All study results confirm that cardiac contractility modulation meet the HF treatment objectives as defined by the ESC guidelines: improve clinical status, functional capacity and quality of life prevent hospital admission. The guidelines even state that improving functional capacity and preventing hospitalization are important benefits to be considered if a mortality excess is ruled out.

Table 1: Comparison of effects CRT versus CCM™ <35% and >35%–45%.

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

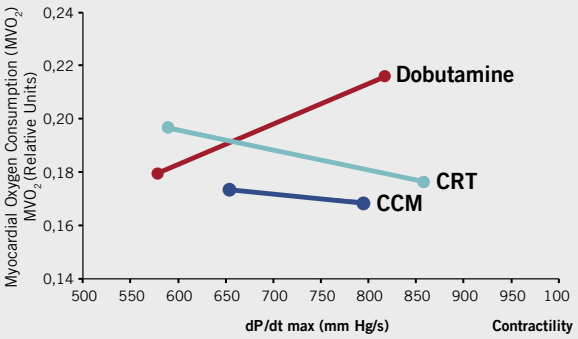


Fig. 16: CCM™ improves LV function without an increase in myocardial oxygen consumption (adapted from Nelson, 2000 Clinical results: Butter, 2007).

Indication

Cardiac Contractility Modulation is indicated for patients with CHF symptoms despite guideline directed medical treatment, with moderately to severely reduced EF (25–45%) resulting from left ventricular dysfunction, and a narrow QRS complex.

The Optimizer® Smart, an IPG applying Cardiac Contractility Modulation therapy, is commercially available since 2016[3] in countries that accept the CE mark. Physicians are advised to refer to the physician manual for exact indications and contraindications for the use of the Optimizer® Smart.

The ESC guidelines published in 2016[3] mention that CCM™ may be considered in selected patients with HF. Furthermore Borggrefe et al. recently suggested to consider CCM™ as a treatment option for CRT non-responders.[33]

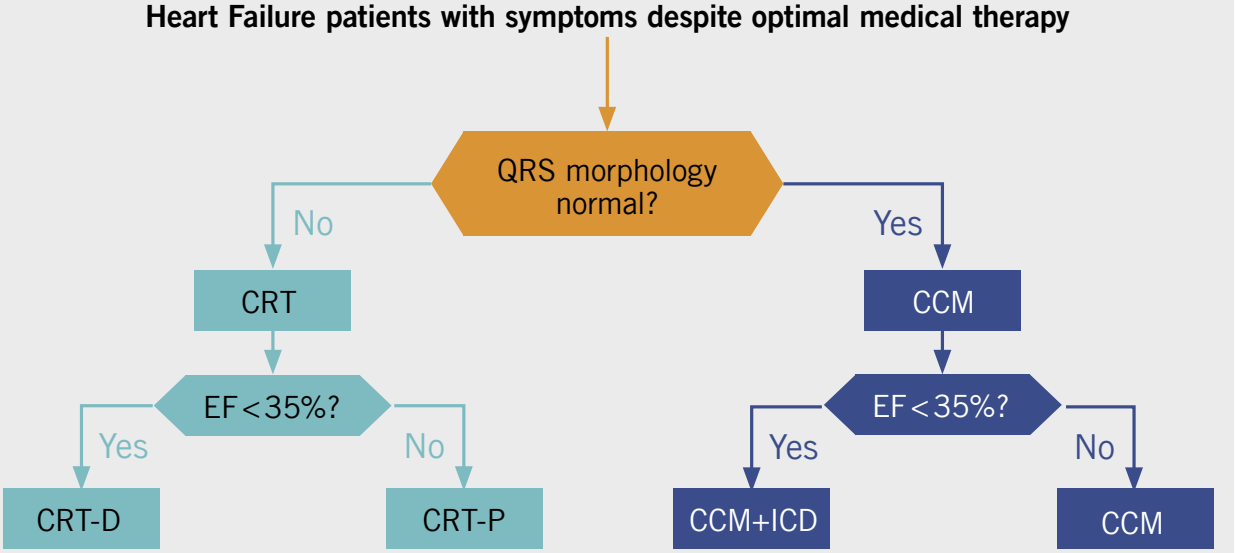


Fig. 17: Potential therapy flow chart for this group of patients.

Common CCM™ patient profile

- *NYHA III/IV*
- *Normal QRS duration*
- *EF 25–45%*
- *Peak VO_2 ≥9ml/kg/min*

Common contraindications

- *Mechanical tricuspid*
- *No venous access*

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