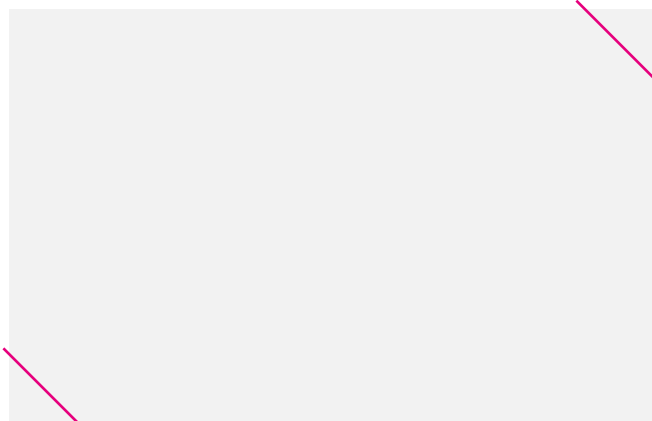


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Cardiac Contractility Modulation

Innovative HF Therapy Solution delivered by the Optimizer® Smart



Chronic Heart Failure

3.6 million people are diagnosed with 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 treatments.²

1 in 4 heart failure patients die within one year of diagnosis while approximately half of all patients diagnosed with CHF die within five years.³ CHF results in one of the worst 5-year adjusted mortality rates.⁴

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.⁵

Despite appropriate medical treatment, many heart failure patients suffer frequent hospitalization, weakness, comorbidities and other symptoms including anxiety and depression, and also experience difficulties performing daily activities.⁶

Some of the patients reach end stage heart failure and are therefore candidates for a left ventricular assist device or heart transplant. Some of the CHF patients having left ventricular ejection fraction (EF) $\leq 35\%$ and prolonged QRS duration are indicated for Cardiac Resynchronization Therapy (CRT).^{7,8} However, more than two thirds of heart failure patients have a normal QRS duration.⁹ For these patients who are not yet in end stage heart failure, Cardiac Contractility Modulation (CCM™) is an implantable device treatment option which has been validated through several randomized clinical trials.¹⁰

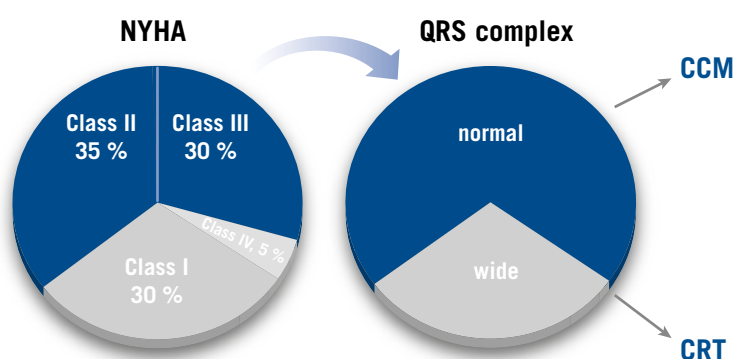


Fig. 1: Subgroups of patients with chronic heart failure.

¹ Facts and Figures: Heart Failure. European Society of Cardiology website. http://www.escardio.org/static_file/Escardio/Press-media/Facts-Figures-HF09.pdf. Accessed 22 June 2015.

² Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008.

³ Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397-1402.

⁴ Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail*. 2001; 3:315-322.

⁵ Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008.

⁶ Cowie MR, Anker SD, Cleland JGF. Improving Care for Patients With Acute Heart Failure: Before, During and After Hospitalization. *Oxford PharmaGenesis*; 2014. http://www.oxfordhealthpolicyforum.org/A_HF_report. Accessed June 22, 2015.

⁷ J.J.V. McMurray, et al. (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *European Heart Journal* 2012; 33, 1787-1847.

⁸ P. Ponikowski, et al. 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart J* 2016; 37, 2129-2200

⁹ L.H. Lund, et al. (2012) Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *European Heart J* 2013; 34: 529-539.

¹⁰ K.-H. Kuck, et al. (2014) New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association. *Europace* 2014; 16: 109-128.

Cardiac Contractility Modulation

CCM is a unique and innovative therapy concept comprising electrical stimulation of the cardiac muscle during the absolute refractory period. CCM does not affect cardiac rhythm and is thus fundamentally different from other implantable systems such as the cardiac resynchronization therapy (CRT).^{11, 12}

CCM triggers physiological processes in cardiac muscle cells which enhance the cellular function on a molecular level and thereby improve cardiac performance and leads to reverse remodeling.^{13, 14, 15}

CCM treatment increases patients exercise capacity and quality of life (QoL).¹⁶

Observational long-term survival data show that CCM is associated with lower long-term mortality in heart failure patients when compared with expected rates among similar patients not treated with CCM.^{17, 18}

The CCM therapy is delivered by the Optimizer[®] Smart implantable pulse generator.

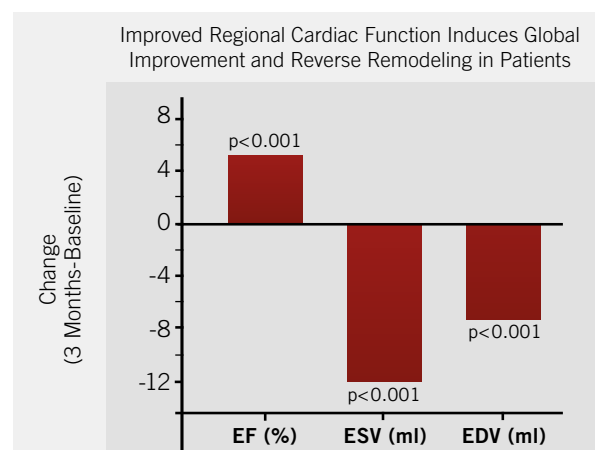
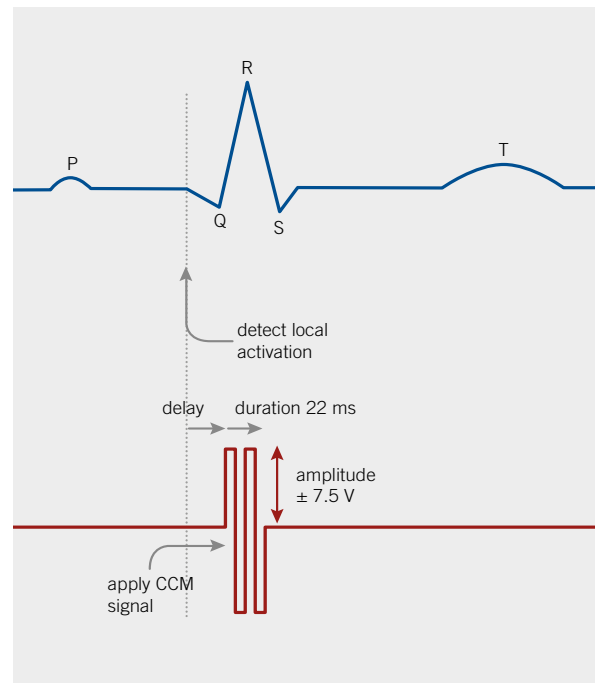


Fig. 2: CCM improves cardiac function and leads to reverse remodeling in patients.¹²

¹¹ W.T. Abraham, S.A. Smith (2013) Devices in the management of advanced, chronic heart failure. *Nat Rev Cardiol.* 2013; 10: 98–110.
¹² M. Borggrefe, D. Burkhoff (2012) Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. *Eur J Heart Fail* 2012; 14: 703–712.
¹³ C.M. Yu, et al. (2009) Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. *JACC Cardiovasc Imaging* 2009; 2: 1341–1349.
¹⁴ C. Butter, et al. (2008) Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *J Am Coll Cardiol.* 2008;51(18):1784-9.
¹⁵ AR. Lyon, et al. (2013) Cardiac contractility modulation therapy in advanced systolic heart failure. *Nat Rev Cardiol.* 2013;10(10):584-98.
¹⁶ F. Giallauria, et al. (2014) Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. *Int J Cardiol* 175 (2): 352–357.
¹⁷ J. Kuschyk, et al. (2015) Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients. *Int J Cardiol* 2015 (183C): 76–81.
¹⁸ A. Kloppe, et al. (2016) Long-term survival with Cardiac Contractility Modulation in patients with NYHA II or III symptoms and normal QRS duration. *Int J Cardiol.*2016; 21968.

Indication

Generally, the Optimizer® Smart is indicated for adult patients with CHF resulting from left ventricular dysfunction despite appropriate medical treatment.

CCM™ is approved in countries that accept the CE mark and is not commercially available in the USA.

Physicians are advised to refer to the physician manual for exact indications and contraindications for the use of the Optimizer® Smart.

Therapy in combination with CRT or ICD systems is also possible.

The recent published 2016 ESC Guidelines mention that CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (<120 ms) and state that CCM may be considered in selected patients with HF.¹⁹

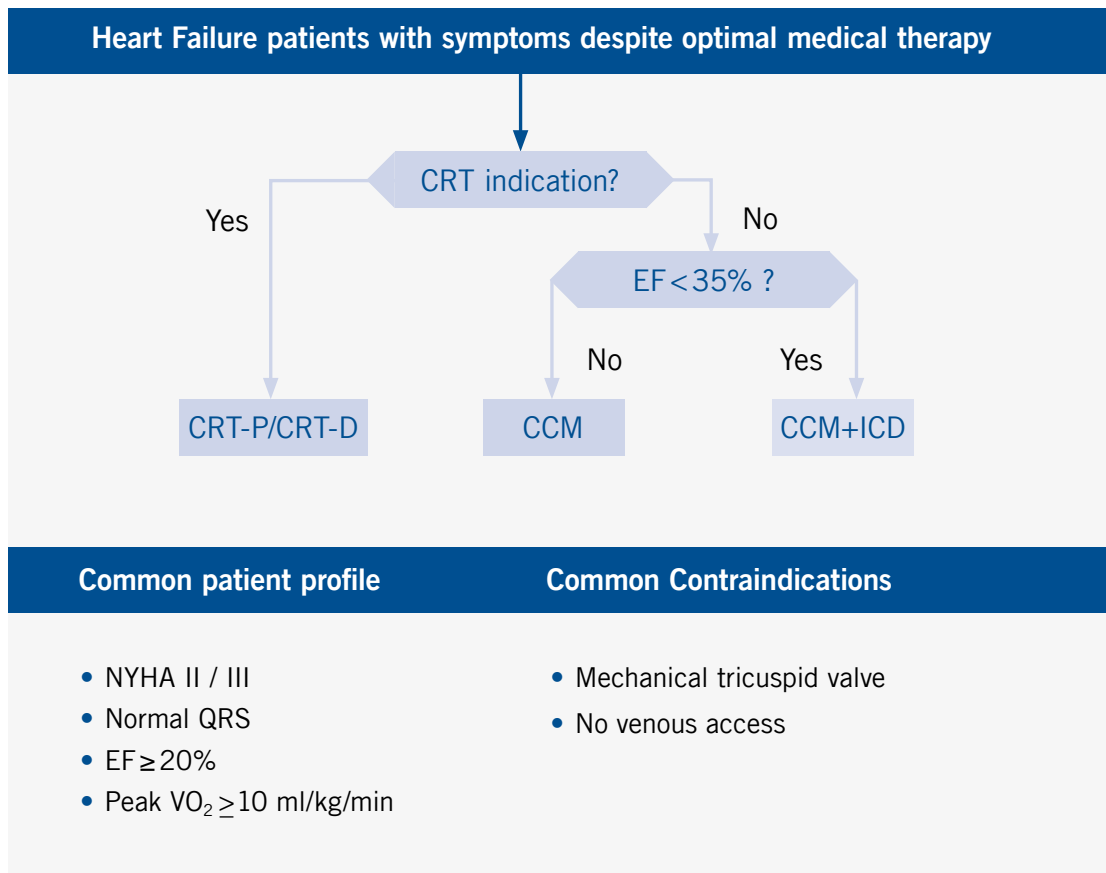


Fig. 3: Potential therapy flow chart for this group of patients.

The Optimizer[®] Smart System

The Optimizer[®] Smart system comprises the following components:

- an implantable CCM delivery device
- a charging unit (MINI CHARGER™)
- an OMNI II Programmer with Optimizer[®] Smart Programmer Application Software
- a portable Bluetooth printer

The Optimizer[®] Smart is designed for quick and straightforward implantation. The OMNI II Programmer and the MINI CHARGER units are portable, intuitive and safe to use. Further details can be found in the product brochure and physician manual of the Optimizer[®] Smart.



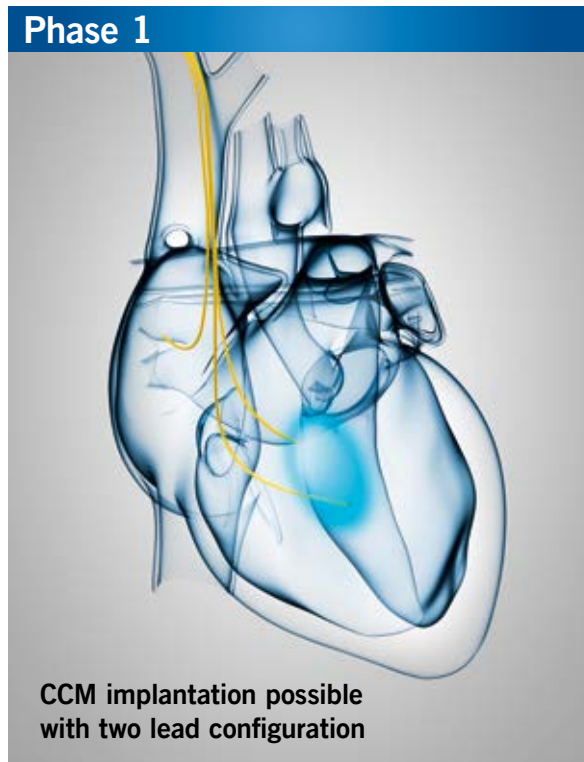
CCM Mechanism of Action

CCM™ is an established method for enhancing cardiac contractility, improving cardiac muscle cell biochemical calcium handling processes, and may evoke a favorable change in the cardiac autonomic profile to improve cardiac function in heart failure.^{20, 21}

CCM signals are delivered to the right side of the intraventricular septum, during the absolute refractory period of the ventricular contraction and do not trigger a new action potential. Importantly, the gain in contractility with CCM is not associated with an increase in cardiac oxygen consumption.^{22, 23}

3-Phase Cardiac Performance Improvement

CHF is associated with remodeling of cardiac gene expression levels which revert from an adult profile of expression to a more fetal gene program. Intra-cellular 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 was shown to increase cardiac contractility and cardiac performance by reversing these processes.^{24, 25, 26}



Within seconds:

Normalized activity of key proteins related to intra-cellular calcium regulation

CCM signals directly reach an area of the myocardium of a few centimeters wide. In this area, the activity of key proteins of calcium regulation is normalized within seconds.

An improved contractility of the myocardium can already be seen shortly after CCM signals activation.

²⁰ RC Gupta, et al. (2009) Ca(2+)-binding proteins in dogs with heart failure: effects of cardiac contractility modulation electrical signals. Clin Transl Sci. 2009; 2(3):211-5.

²¹ C Butter, et al. (2008) Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. J Am Coll Cardiol. 2008; 51(18):1784-9.

²² C Butter, et al. (2007) Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. J Card Fail. 2007; 13(2):137-42.

²³ G Goliash, et al. (2012) The effect of device-based cardiac contractility modulation therapy on myocardial efficiency and oxidative metabolism in patients with heart failure. Eur J Nucl Med Mol Imaging. 2012; 39(3):408-15.

²⁴ RC Gupta, et al. (2009) Ca(2+)-binding proteins in dogs with heart failure: effects of cardiac contractility modulation electrical signals. Clin Transl Sci. 2009; 2(3):211-5.

²⁵ C Butter, et al. (2007) Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. J Card Fail. 2007; 13(2):137-42.

²⁶ AR. Lyon, et al. (2013) Cardiac contractility modulation therapy in advanced systolic heart failure. Nat Rev Cardiol. 2013;10(10):584-98.

Phase 2

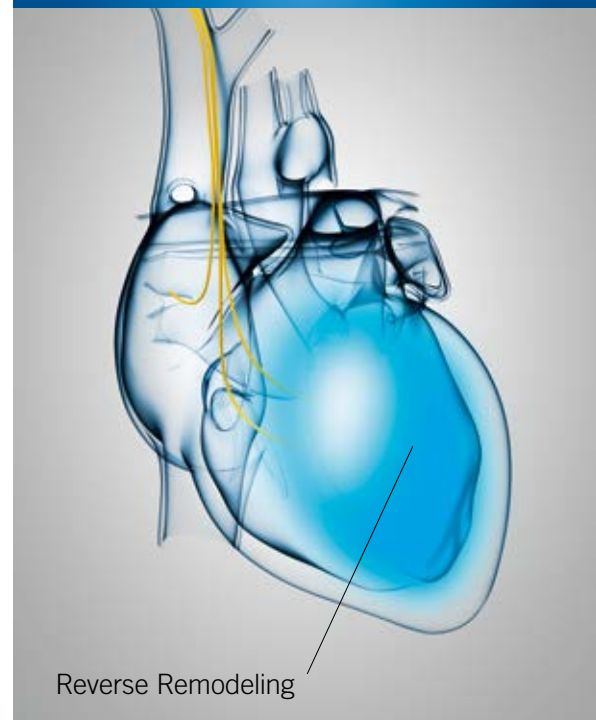


Within hours: Reversal of fetal gene program

Within hours, the pathological fetal gene program is interrupted and reverts towards normal adult gene program. Accordingly, proteins are gradually synthesized towards a normal adult pattern of expression levels.

Expression of genes related to electrotonic coupling between cells of the myocardium is also improved, which means that conductivity is potentially increased, which may result in potentially further augmentation of the impacted area.

Phase 3



Within months: Reverse Remodeling

In the further course of the treatment, mechanical and neurohormonal stress in the myocardium is progressively reduced. Studies using cardiac biopsy and echocardiography show a global improvement within three months.

The pathological fetal gene program is arrested and reversed globally. Structural and functional reverse remodeling occurs.

Evidence from Controlled Clinical Trials

As of mid-2015, over 900 patients have participated in CCM™ clinical trials. Typical patients in most of the studies had NYHA II-IV symptoms despite use of guideline-directed medical therapy, EF 20-40 %, and normal QRS.

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) during cardiopulmonary stress testing and an improvement in quality of life (MLWHFQ, NYHA). (Fig 4, 5) ²⁷

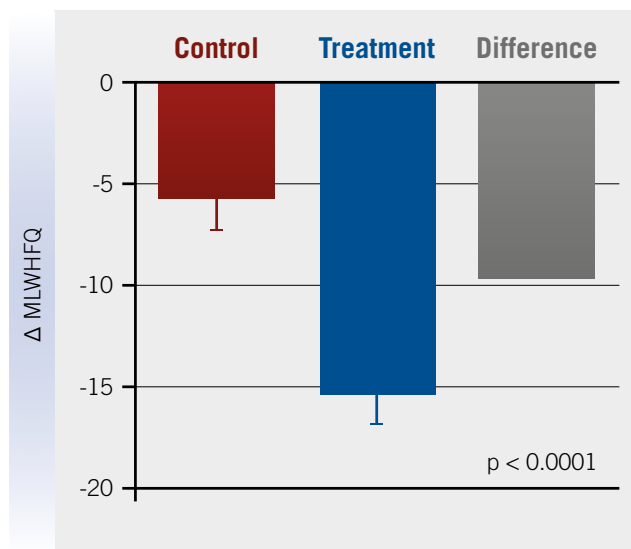
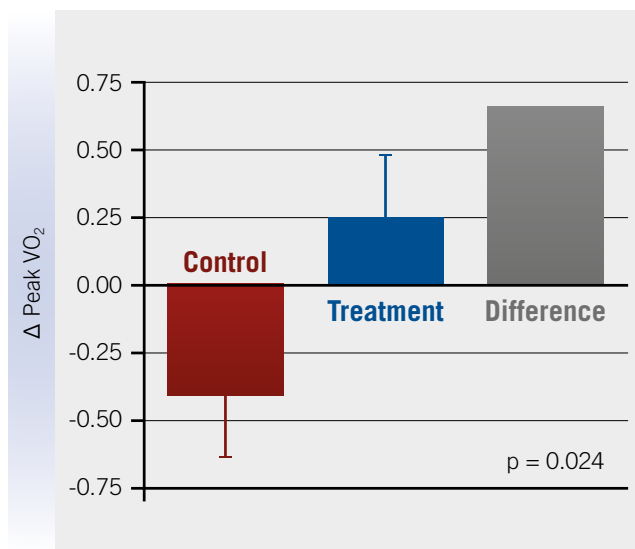


Fig. 4 and 5: Data from the FIX-HF-5 Trial. Change in maximum oxygen uptake (Δ Peak VO_2) and quality of life (MLWHFQ) respectively.

²⁷ A. Kadish, et al. (2011) A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011; 161(2):329-337.e1-2.

Clinical Benefit by CCM – a Comparison

A comparison of published results of the main trials of CCM and those of CRT and ICD shows a significant improvement in both Quality of Life and function with CCM treatment.

The effect of CCM in narrow QRS patients is comparable with that obtained by CRT in wide QRS patients.²⁸

Patients with EF \geq 25 % and NYHA III showed much greater improvement in all endpoints. This improvement appeared to be even higher in subjects with EF \geq 35 %.²⁹

These results prompted an ongoing confirmatory trial that includes 230 patients with EF between 25% and 45%.

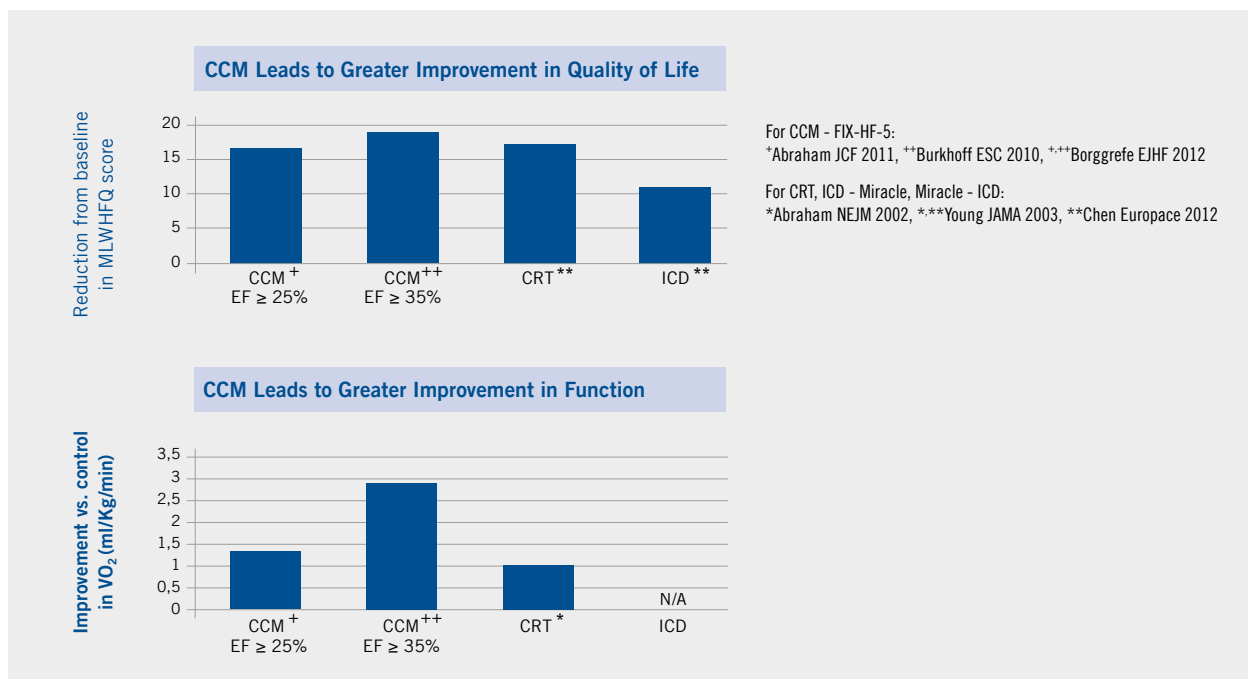


Fig. 6: CCM leads to greater improvement in function and quality of life.^{30, 31, 32 (for CCM); 33, 34, 35 (for CRT)}

²⁸ M. Borggreffe, D. Burkhoff (2012) Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. Eur J Heart Fail 2012; 14: 703–712.

²⁹ W.T. Abraham, et al. (2011) Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. J Card Fail. 2011; 17(9):710-7.

³⁰ W.T. Abraham, et al. (2011) Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. J Card Fail. 2011; 17(9):710-7.

³¹ D. Burkhoff, et al. (2010) Cardiac contractility modulation by electrical signals applied during the absolute refractory period as a treatment for chronic heart failure. Heart Failure Device Management. Edited by AM Feldman. 2010;44-58.

³² M. Borggreffe, D. Burkhoff (2012) Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. Eur J Heart Fail 2012; 14: 703–712.

³³ W.T. Abraham, et al. (2002) Cardiac Resynchronization in Chronic Heart Failure. N Engl J Med 2002; 346:1845-1853.

³⁴ J.B. Young, et al. (2003) Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003; 289(20): 2685-94.

³⁵ S. Chen, et al. (2012) Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: a meta-analysis. Europace. 2012 Nov;14(11):1602-7.

Published meta-analysis of all randomized studies

A meta-analysis of individual patient data of 641 cases from 3 randomized studies showed that CCM™ has significant benefit in functional capacity and Quality of Life.

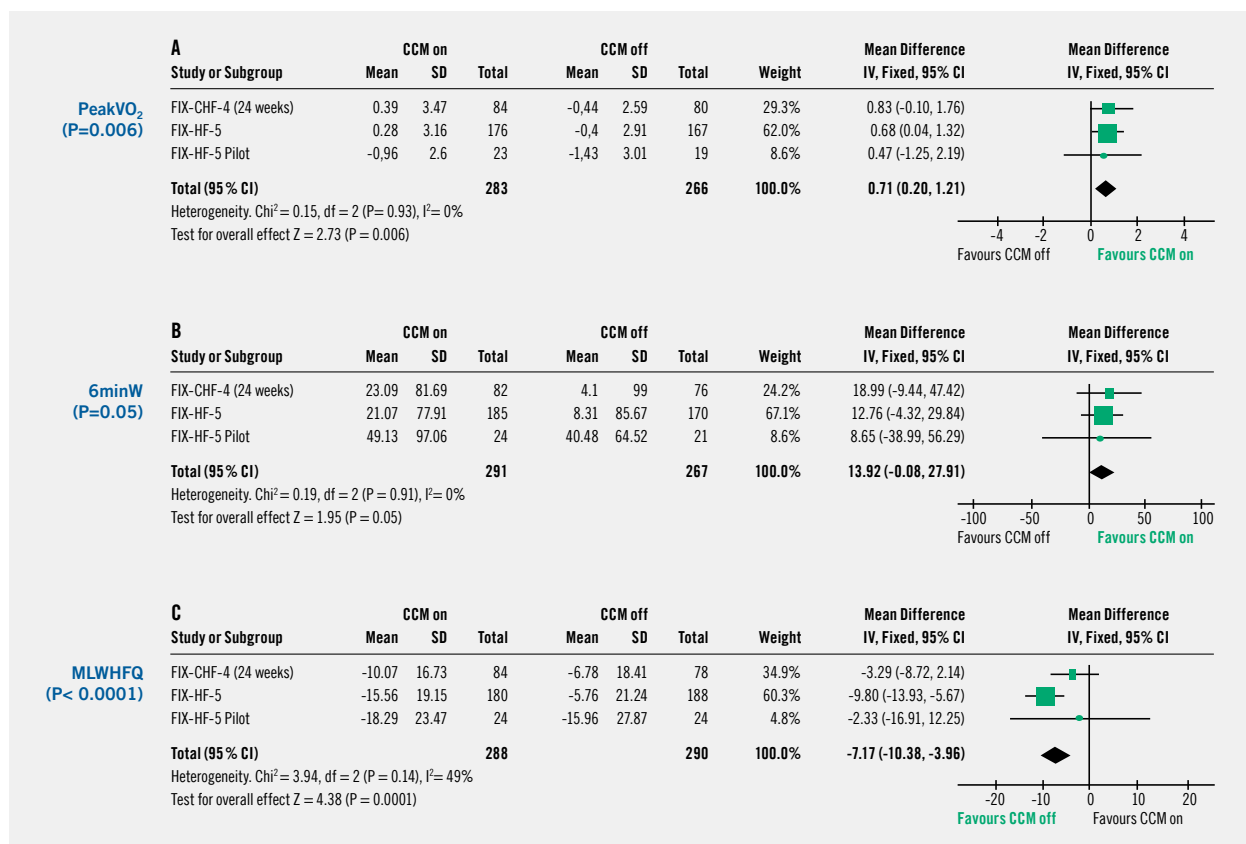


Fig. 7: Giallauria et al. (IJC 2014) Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials.

Long-term survival in patients with CCM: retrospective single center analysis

Multiple investigators initiated retrospective reports related to the long-term benefit of CCM therapy. A report on 81 CHF patients (NYHA II-IV, reduced EF) showed significant improvement by CCM during a mean follow-up period of 34 months (ranging 6-123 months). The cohort had significant long-term improvement in left ventricular size and function, quality of life, NYHA class, peak VO₂ 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. Importantly, compared with the per patient mortality risk score (calculated by the MAGGIC model), the long-term results indicated that long-term survival with CCM was better than expected (p=0.022).³⁶

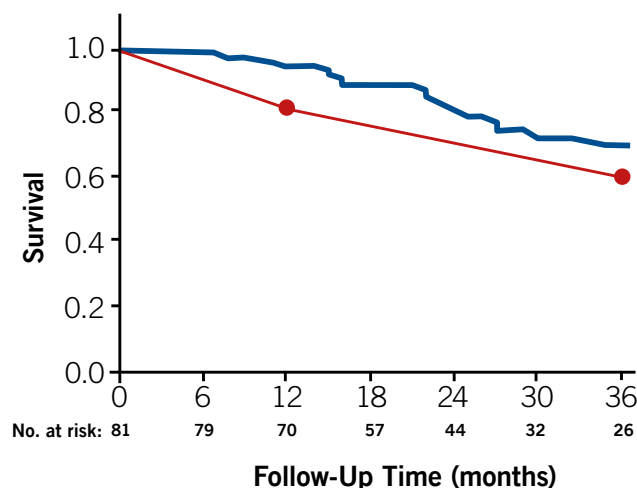


Fig. 8: Observed Kaplan-Meier survival curve (blue) compared to point estimates of survival at 1 and 3 years provided per patient by the MAGGIC score.

³⁶ J. Kuschyk, et al. (2015) Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients. Int J Cardiol 2015 (183C): 76–81.

Another report of 68 CHF patients (NYHA II-III, narrow QRS) treated by CCM 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 CCM was better than expected ($p=0,007$).³⁷

Parameter	Baseline	Long-term follow-up	P
NYHA	3.0 (0.5)	2.3 (0.9)	0.001
MLWHFQ	49.9 (17.7)	32.2 (18.2)	0.001
LVEF, %	23.1 (7.9)	29.4 (8.6)	0.001
LVEDD, mm	66.5 (7.7)	64.6 (8.9)	0.003
LVESD, mm	57.9 (7.8)	54.8 (9.2)	0.001
Peak VO ₂ , ml/kg/min	13.9 (3.3)	14.6 (3.5)	0.1
NT-proBNP, mg/dl	4395 (3818)	2762 (3490)	0.001
QRS duration, ms	112.0	112.8	ns

Table 1. Efficacy parameters at baseline and at long-term follow-up (mean and SD).³⁸

Abbreviations:

NYHA:	New York Heart Association	LVEDD:	left ventricular end-diastolic diameter
MLWHFQ:	Minnesota living with heart failure questionnaire	LVESD:	left ventricular end-systolic diameter
LVEF:	left ventricular ejection fraction	Peak VO ₂ :	peak oxygen uptake
		NT-proBNP:	N-terminal pro brain natriuretic peptide.

Notable Publications

- **Abi-Samra F, Gutterman D. Cardiac contractility modulation: a novel approach for the treatment of heart failure. *Heart Failure Review*, 2016**
- **Ponikowski P, A. Voors, S. Anker, et al. 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*, 2016**
- **Kloppe A, Lawo T, Mijic D, et al. Long-term survival with Cardiac Contractility Modulation in patients with NYHA II or III symptoms and normal QRS duration. *International Journal of Cardiology*, 2016**
- **Liu Ming, Fang Fang, Luo Xiu Xia, et al. Improvement of long-term survival by cardiac contractility modulation in heart failure patients: A case-control study. *International Journal of Cardiology*, 2016**
- **Kuschyk J, Roeger S, Schneider R, et al. Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients. *International Journal of Cardiology*, 2015**
- **Giallauria F, Vigorito C, Piepoli MF, Stewart Coats AJ. Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. *International Journal of Cardiology*, 2014**
- **Kuck KH, Bordachar P, Borggrefe M, et al. New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association. *Europace*, 2014**
- **Lyon AR, Samara MA, Feldman DS. Cardiac contractility modulation therapy in advanced systolic heart failure. *Nature Reviews Cardiology*, 2013**
- **Borggrefe M, Burkhoff D. Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. *European Journal of Heart Failure*, 2012**
- **Abraham WT, Nademanee K, Volosin K, et al. Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Journal of Cardiac Failure*, 2011**
- **Yu CM, Chan JY, Zhang Q, et al. Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. *JACC Cardiovascular Imaging*, 2009**
- **Butter C, Rastogi S, Minden HH, Meyhöfer J, Burkhoff D, Sabbah HN. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *Journal of the American College of Cardiology*, 2008**
- **Borggrefe MM, Lawo T, Butter C, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. *European Heart Journal*, 2008**

³⁷ A. Kloppe, et al. (2016) Long-term survival with Cardiac Contractility Modulation in patients with NYHA II or III symptoms and normal QRS duration. *Int J Cardiol*.2016; 21968.

³⁸ J. Kuschyk, et al. (2015) Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients. *Int J Cardiol* 2015 (183C): 76-81.