Cardiac Contractility Modulation
Innovative Therapy for the Treatment of Chronic Heart Failure
Chronic Heart Failure

3.6 million people are diagnosed with chronic heart failure (CHF) in Europe. 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. With the exception of lung cancer, CHF is associated with the worst 5-year adjusted mortality.

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. With the exception of lung cancer, CHF is associated with the worst 5-year adjusted mortality.

When heart failure symptoms are stabilized by current treatments, it may seem that patients are doing well, but the cardiac stress and the neuro-hormonal imbalance underlying heart failure are still silently occurring, resulting in disease progression.

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.

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) ≤ 35% and prolonged QRS duration are indicated for Cardiac Resynchronization Therapy (CRT).

However, more than two thirds of heart failure patients have a normal QRS duration. 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.

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Fig. 1: Subgroups of patients with chronic heart failure.
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).10,11

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.12

CCM treatment increases patients exercise capacity and quality of life (QoL).13

Preliminary 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.14

The CCM therapy is delivered by the Optimizer™ IV_S implantable pulse generator.

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

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**Indication**

Generally, the Optimizer™ IV is indicated for adult patients with chronic heart failure resulting from left ventricular dysfunction despite appropriate medical treatment.

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

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 IV. For example the Optimizer IV is contraindicated for patients with permanent or long-standing persistent atrial fibrillation or flutter.

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**Heart Failure patients with symptoms despite optimal medical therapy**

- CRT indication?
  - Yes
    - CRT-P/CRT-D
  - No
    - EF<35% ?
      - No
        - CCM
      - Yes
        - CCM+ICD

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**Common patient profile**

- NYHA II / III
- Normal QRS
- EF >20%
- Peak VO$_2$ $\geq$ 10 ml/kg/min
- Ventricular ectopies or bigeminies $<$10000/day

**Common Contraindications**

- Long-standing persistent or permanent atrial fibrillation or flutter.
- Mechanical tricuspid valve
- No venous access
- Programmed to 100% VVI pacing

*Fig. 3: Potential therapy flow chart for this group of patients.*
The Optimizer IVₕ System

The Optimizer IVₕ system comprises the following components:

- an implantable CCM delivery device
- a charging unit (MINI CHARGER™)
- an OMNI™ II programmer
- a portable Bluetooth printer

The Optimizer IVₕ 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 IVₕ.
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.15, 16

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.17, 18

3-Phase Cardiac Performance Improvement

Chronic heart failure 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.19, 20

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.

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.

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 effect 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 medication, 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 VO₂) in cardiopulmonary stress test and an improvement in quality of life (MLWHFQ, NYHA). (Fig 4, 5) ²¹

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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.22

Patients with EF ≥ 25 % and NYHA III showed much greater improvement in all endpoints. This improvement appeared to be even higher in subjects with EF ≥ 35 %.23

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.24, 25, 26 (for CCM); 27, 28, 29 (for CRT)
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.

### Notable Publications

- **Abraham W. T. et al.** "Subgroup analysis of a randomized control trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure". *Journal of Cardiac Failure*. September 2011
- **Butter C.** "Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients with heart failure". *Journal of the American College of Cardiology*. May 2008
- **Borggrefe M.M. et al.** "Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure". *European Heart Journal*. January 2008

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**Fig. 7: Giallauria, Vigorito, Piepoli, Coats, IJC, 2014**
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 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. 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)\textsuperscript{30}.

![Survival curve](image)

**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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Long-term follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>3.0 (0.5)</td>
<td>2.3 (0.9)</td>
<td>0.001</td>
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<tr>
<td>MLHF, score</td>
<td>49.9 (17.7)</td>
<td>32.2 (18.2)</td>
<td>0.001</td>
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<tr>
<td>LVEF, %</td>
<td>23.1 (7.9)</td>
<td>29.4 (8.6)</td>
<td>0.001</td>
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<tr>
<td>LVEDD, mm</td>
<td>66.5 (7.7)</td>
<td>64.6 (8.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>57.9 (7.8)</td>
<td>54.8 (9.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak VO$_2$, ml/kg/min</td>
<td>13.9 (3.3)</td>
<td>14.6 (3.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>NT-proBNP, mg/dl</td>
<td>4395 (3818)</td>
<td>2762 (3490)</td>
<td>0.001</td>
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<tr>
<td>QRS duration, ms</td>
<td>112.0</td>
<td>112.8</td>
<td>ns</td>
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</tbody>
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**Table 1.** Efficacy parameters at baseline and at long-term follow-up (mean and SD).

Abbreviations:

NYHA: New York Heart Association  
MLHF: Minnesota living with heart failure questionnaire  
LVEF: left ventricular ejection fraction  
LVEDD: left ventricular end-diastolic diameter  
LVESD: left ventricular end-systolic diameter  
VO$_2$ peak: peak oxygen uptake  
NT-proBNP: N-terminal pro brain natriuretic peptide.