Cardiac Contractility Modulation

Francisco Bello Morgado
Hospital de Santa Cruz - Lisboa
Cardiac Contractility Modulation

A new form of electrical therapy, called cardiac contractility modulation (CCM) overview

• Rationale
• Mechanism of Action
• Clinical Results
Cardiac Contractility Modulation

• Cardiac resynchronization therapy (CRT) has become the standard of care for patients with symptomatic heart failure and delayed myocardial activation, indexed by a prolonged QRS duration.

• CRT improves
  • ventricular contractile strength
  • quality of life and exercise tolerance
  • reduces mortality and hospitalizations.

• it is estimated that less than half of heart failure patients have dyssynchrony and as many as 30% of implanted patients are considered non-responders
Guidelines for cardiac pacing and cardiac resynchronization therapy

The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in Collaboration with the European Heart Rhythm Association

Authors/Task Force Members: Panos E. Vardas* (Chairperson) (Greece); Angelo Auricchio (Switzerland); Jean-Jacques Blanc (France); Jean-Claude Daubert (France); Helmut Drexler (Germany); Hugo Ector (Belgium); Maurizio Gasparini (Italy); Cecilia Linde (Sweden); Francisco Bello Morgado (Portugal); Ali Oto (Turkey); Richard Sutton (UK); Maria Trusz-Gluza (Poland)
# CRT – Recomendações

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration $\geq 150$ msec and LBBB QRS morphology and with LVEF $\leq 35%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration $\geq 150$ msec and non-LBBB QRS morphology and with LVEF $\leq 35%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of $130–149$ msec and LBBB QRS morphology and with LVEF $\leq 35%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of $130–149$ msec and non-LBBB QRS morphology and with LVEF $\leq 35%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>CRT rather than RV pacing is recommended for patients with HFpEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT should be considered for patients with LVEF $\leq 35%$ in NYHA Class III–IV despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration $\geq 130$ msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Patients with HFpEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

CRT is contra-indicated in patients with a QRS duration $< 130$ msec.
CCM: Position in the Treatment Paradigm

More than 17m patients globally with NYHA II/III

- 30% eligible for CRT
- 70% eligible for CCM
Cardiac Contractility Modulation (CCM) Signals

- Biphasic
- Relatively high voltage (±7.5V) Duration ~20ms
- Applied during absolute refractory period
- Nonexcitatory
Cardiac Contractility Modulation Therapy Delivery

CCM Signal applied during absolute refractory period to the RV septum via standard pacing leads

- Delivered by an IPG
- Rechargeable Battery
- 1 Atrial Lead (sensing)
- 2 RV Septal Leads (sensing + CCM delivery)
- Signals effect the biology of failing myocardium (genes, proteins, and phosphorylation) that improve function

Rechargeable Implanted Pulse Generator

Biological effects seen remotely over time

Biological effects seen rapidly in region of signal applications
CCM therapy is UNIQUE 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. Restoring Normal Calcium Handling

Upregulation of SERCA
Greater phosphorylation of phospholamban
Increase of SR uptake of calcium resulting in greater release of calcium during the next depolarization
Greater contractility

3. CCM Reduces Cardiac Fibrosis

4. Rebalancing Cardiac Autonomic Tone

CCM: Restoring vagal cardiac tone

A. CCM increases septal contraction
B. Mechanoreceptors activate vagal afferents,
C. NTS is stimulated to inhibit RVLM (rostral ventrolateral medulla) and activate DMNV (dorsal motor nucleus of vagus)
D. Sympathetic outflow is inhibited centrally and peripherally
E. Autonomic balance is restored
Studies in animals and humans show that CCM does not increase myocardial oxygen consumption. Burkhoff et al., Heart Failure Reviews, 2001.

**Dogs - Chronic CHF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>2 Hours of CCM</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>79 ± 3</td>
<td>75 ± 3</td>
<td>.26</td>
</tr>
<tr>
<td>Peak LVp (mm Hg)</td>
<td>101 ± 5</td>
<td>107 ± 8</td>
<td>.23</td>
</tr>
<tr>
<td>LV EDP (mm Hg)</td>
<td>14 ± 1</td>
<td>9 ± 1</td>
<td>.005</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>18 ± 1</td>
<td>21 ± 1</td>
<td>.004</td>
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<tr>
<td>LV EDV (mL)</td>
<td>71 ± 8</td>
<td>68 ± 7</td>
<td>.001</td>
</tr>
<tr>
<td>LV EFV (mL)</td>
<td>53 ± 7</td>
<td>47 ± 6</td>
<td>.001</td>
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<tr>
<td>LV EF (%)</td>
<td>26 ± 1</td>
<td>31 ± 2</td>
<td>.001</td>
</tr>
<tr>
<td>LV CBF (mL/min)</td>
<td>35 ± 4</td>
<td>27 ± 3</td>
<td>.017</td>
</tr>
<tr>
<td>LV Power (watts)</td>
<td>0.32 ± 0.02</td>
<td>0.37 ± 0.03</td>
<td>.049</td>
</tr>
<tr>
<td>MVO₂ (µmol/min)</td>
<td>257 ± 41</td>
<td>180 ± 34</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations are same as in Table 1. CCM, cardiac contractility modulation; P value = probability value of baseline versus CCM.

**Humans - Chronic CHF (PET scan)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CCM deactivated</th>
<th>CCM activated</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>112.6±15.78</td>
<td>113.10±20.28</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>65.7±10.47</td>
<td>70.81±12.82</td>
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<tr>
<td>Rate-pressure product</td>
<td>7.382±1.439</td>
<td>7.967±7.128</td>
<td>.047</td>
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<tr>
<td>MBF (mL/min L g⁻¹)</td>
<td>0.81±0.18</td>
<td>0.80±0.15</td>
<td>.818</td>
</tr>
<tr>
<td>kₘono</td>
<td>0.053±0.01</td>
<td>0.055±0.01</td>
<td>.239</td>
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<tr>
<td>MVO₂ (mL/min/100 g)</td>
<td>6.81±1.69</td>
<td>7.15±1.62</td>
<td>.241</td>
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<tr>
<td>WMI (mmHg ml/m²)</td>
<td>4.94±1.14</td>
<td>5.21±1.36</td>
<td>.344</td>
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<tr>
<td>LVEF (%)</td>
<td>28.37±5.53</td>
<td>28.43±6.48</td>
<td>.928</td>
</tr>
</tbody>
</table>


CCM increases contractility but not oxygen consumption.
6. Cardiac Remodeling
Revision of Fetal Gene Towards Adult Gene Profile

Expression of multiple HF related genes improves with CCM

Findings in human myocardial samples from a double-blind randomized controlled study

Butter et al. JACC, May 2008
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)
Cardiac contractility modulation

Sistema

OPTIMIZER® IVs
Case Report

• 46-year-old male patient
• June/2018 referred to our hospital for heart failure
• He had history of smoking habits and controlled diabetes mellitus type 2
• March/2018 Anterior Myocardial Infarct
• Coronary angiography showed an occluded proximal anterior descending artery that was completely revascularized with implantation of a drug eluting stent (late revascularization)
• Despite being on optimized medical therapy (OMT), which included recommended doses of carvedilol, sacubitril/valsartan, spironolactone and furosemide, he remained symptomatic (New York Heart Association [NYHA] III).
Case Report

• ECG : sinus rhythm ;69 beats/minute, with a narrow QRS (113ms) and presence of Q and negative T waves on anteroseptal leads

• Cardiac Magnetic Resonance evidenced a myocardial scar on anterior and mid segment of anteroseptal walls. LVEF 33%

• Transthoracic Echocardiogram, 3 months after the event, showed a dilated left ventricle with 3D ejection fraction of 38-42%, hipokinesia of cardiac apex, anterior wall and mid-segment of anterior interventricular septum. Right ventricular systolic function was preserved and there were no significant valvular lesions

• Blood test evidenced an elevated NT-proBNP (531pg/mL).
Case Report

- As he remained symptomatic despite OMT and since he would not fulfill criteria to CRT due to narrow QRS on ECG, CCM system was proposed and implanted in July/18
- two pacemaker leads (Saint Jude Medicals, Trendil STS) were actively attached in the right ventricular basal septum, about 2cm apart from each other, via the right cephalic vein and a pulse generator Optimizer® Smart was implanted in the right pectoral region.
- The CCM device was programmed for 9 hours of pacing daily with a stimulus energy of 7.5V and 35ms.
Case Report

• At 1.5-month follow-up
  • patient did not report neither discomfort nor unpleasant sensation related to CCM device.
  • Functional NYHA class went from III to I.
  • significant improvement in QoL, assessed by Minnesota Living with Heart Failure Questionnaire which score decreased from 85 to 21 points
  • NT-proBNP slightly diminished comparing to baseline (531pg/mL to 470pg/mL).
Case Report

- At 3 month follow-up
- Echocardiogram:
  - LVEF 3D: 45% LVEDV 173mL LVESV 96mL
    - Previous 188/114
  - Global Longitudinal Strain: - 11%
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Comments</th>
<th>Randomized</th>
<th>Device</th>
<th>Countries</th>
<th>Total patients</th>
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<tbody>
<tr>
<td>FIX-HF-1</td>
<td>Acute study</td>
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<td>Opt I</td>
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<td>FIX-HF-4</td>
<td>Crossover double-blind, 6 months</td>
<td>Yes</td>
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<td>Italy, Austria, Germany, France, The Netherlands and Czech</td>
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<tr>
<td>FIX-HF-5 Phase I</td>
<td>CCM vs OMT, 6 months</td>
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<td>Opt II</td>
<td>USA</td>
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<td>FIX-HF-5 Phase II</td>
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<td>FIX-CHF-13</td>
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<td>CCM HF</td>
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<td>FIX-CHF-18</td>
<td>Comparison 1 vs 2 leads</td>
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<tr>
<td>CCM-REG</td>
<td>CCM Registry</td>
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<td>Opt IVs, Smart</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>1,511</strong></td>
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## Optimizer®: Randomized Clinical Trial History

<table>
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<tr>
<th>Study Name</th>
<th>Comments</th>
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<td>Italy, Austria, Germany, France, Netherlands</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>and Czech</td>
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<tr>
<td>FIX-HF-5 Phase I</td>
<td>CCM vs OMT, 6 months</td>
<td>Yes</td>
<td>Opt II</td>
<td>USA</td>
<td>49</td>
</tr>
<tr>
<td>FIX-HF-5 Phase II</td>
<td>CCM vs. OMT</td>
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<td>Opt III</td>
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<td>Fix-HF-5c</td>
<td>CCM vs. OMT confirmatory</td>
<td>Yes</td>
<td>Opt IVs</td>
<td>USA, Germany, Czech</td>
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<tr>
<td>Total</td>
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</tbody>
</table>
**FIX-CHF-4 (EU)**
Double Blinded Randomized Controlled Study

- Informed Consent
- Baseline Testing
- Device Implantation
- 2 week Run-In

**Randomization**

- **Group 1 (80)**
  - 3 months Device On 7h/Day
  - 3 months Device Off

- **Group 2 (84)**
  - 3 months Device Off
  - 3 months Device On 7h/Day

160 patients from 15 European centers
All patients received an Optimizer implant.

NYHA II-III
Narrow QRS
Primary Endpoints

- Changes in peak oxygen consumption (VO2,peak)
- Minnesota Living with Heart Failure Questionnaire (MLWHFQ)

N=164

Secondary Endpoint

Changes in 6MW
Conclusions: Meta-analysis of individual patient data from randomized trials suggests that CCM has significant if somewhat modest benefits in improving measures of functional capacity and quality of life.
Cardiac contractility modulation CCM

CCM may be considered in selected patients with HF. The effect of CCM on HF morbidity and mortality remains to be established.

ICC classe II ou III NYHA FEVE<35% estima-se que ≈ 80% sejam candidatos a CCM
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 Phil Wiegn, MD,k Jeffrey L. Hastings, MD,l Andrew J. Kaplan, MD,m Frank Edelmann, MD,n Lars Luthje, MD,o Rami Kahwash, MD,p Gery F. Tomassoni, MD,q David D. Gutterman, MD,r Angela Stagg, BS,s Daniel Burkhoff, MD,t Gerd Hasenfuß, MDu
• **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**

Abraham et al, JACC Heart Failure 2018
### Patient Baseline Demographics*

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

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

Abraham et al, JACC Heart Failure 2018
**FIX-HF-5C Primary Efficacy Endpoint Met**

CCM Significantly Improves Exercise Capacity

Primary Efficacy Endpoint: Improvement in peak VO2

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
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%
Cardiovascular Death + HF Hospitalizations

Abraham et al, JACC Heart Failure 2018
Pre-specified subgroup analysis: EF 35%-45%

Clinical effects larger in patients with EF 35-45%
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%
“Real World Registry”: CCM-REG

Long-Term Experience

• 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-REG25-45 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-REG35-45 cohort

G. Hasenfluss, EHF, Vienna 2018
Significant & Sustained Improvements in MLWHFQ, NYHA and LV EF in the Entire CCM-REG\textsubscript{25-45} Cohort

Changes from baseline before CCM

G. Hasenfuss, EHF, Vienna 2018
**CV and HF Hospitalizations Reduced by ~75%**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>EVENT</th>
<th>Pre-Enrollment</th>
<th>Post-Enrollment</th>
<th>Event-Rate</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Pt-Yrs</td>
<td>Events</td>
<td>Pt-Yrs</td>
<td>Events</td>
</tr>
<tr>
<td><strong>CCM-REG&lt;sub&gt;25-45&lt;/sub&gt;</strong></td>
<td>HF</td>
<td>140.0</td>
<td>134</td>
<td>73</td>
<td>0.96</td>
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<td>HF+CV</td>
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<td>70</td>
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*<sup>p<0.0001</sup>
Seattle Heart Failure Model

Mortality prediction by MAGGIC Parametric model

Heart Failure Risk Calculator

Patient Reference
- Age
- Gender
- Diabetes
- COPD

Heart failure diagnosed within the last 18 months
- Current smoker
- NYHA Class
- Receives beta blockers
- Receives ACEi/ARB

BMI
- Systolic blood pressure
- Creatinine
- Ejection fraction

Integer score: 25
Risk of dying within 1 year: 10%
Risk of dying within 3 years: 36%

The patient is in the 7-8th decile of risk in a heart failure population.

Porock et al: A risk score based on 39,372 patients from 30 studies. European heart journal. 2013

http://www.heartfailurerisk.org
Overall Survival

G. Hasenfuss, EHF, Vienna 2018,

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

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<th>p vs Observed</th>
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<td>82.8%</td>
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<tr>
<td>SHFM</td>
<td>76.7%</td>
<td>0.164</td>
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<td>MAGGIC</td>
<td>63.3%</td>
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<td>74.7%</td>
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<td>67.7%</td>
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Conclusões

A Modulação da Contractilidade Cardíaca demonstrou benefício:
• Capacidade Funcional (avaliada por “peak VO2”)
• Qualidade de Vida e Classe Functional NYHA
• Reversão da Remodelagem VE

Efeito benéfico demonstrado na mortalidade ou hospitalizações que não resulta de estudos randomizados

Doente ideal: NYHA II/III FEVE 25-45%

 Constitui uma alternativa ao CRT em doentes sem QRS alargados