MHIF FEATURED STUDY:
REDUCE LAP-HF RCT II

DESCRIPTION:
A study to evaluate the Corvia Medical, Inc. IASD® System II to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure

CRITERIA LIST/QUALIFICATIONS:

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt; 40 years – GDMT for 4 weeks</td>
<td>• Inability to perform 6-minute walk test (distance &lt; 50 m), or 6-minute walk test &gt; 600 m</td>
</tr>
<tr>
<td>• HF requiring current treatment w/ diuretics for ≥ 30 days AND NYHA class II if a prior history of &gt; NYHA class II, to ambulatory NYHA class IV</td>
<td>• Resting RAP &gt; 14 mmHg</td>
</tr>
<tr>
<td>• IV diuretics or need for intensification of oral diuresis for HF 12 months prior; OR an NT-pro BNP value &gt; 150 pg./ml in normal sinus rhythm, &gt; 450 pg./ml in AFIB, or a BNP value &gt; 50 in NSR or, &gt; 150 in AFIB within past 6 months</td>
<td>• MI and/or percutaneous cardiac intervention within past 3 months; CABG in past 3 months, or current indication for coronary revascularization; AVR (surgical AVR or TAVR) within past 12 months</td>
</tr>
<tr>
<td>• EF ≥ 40% within the past 6 months, without EF &lt;30% in the past 5 years</td>
<td>• Significant PH with PVR &gt; 3.5 Woods units at rest or at peak exercise</td>
</tr>
<tr>
<td>• End-expiratory PCWP during supine ergometer exercise ≥ 25mm Hg, and RAP by ≥ 5 mm Hg.</td>
<td></td>
</tr>
</tbody>
</table>
**Do you have a patient with DYSPNEA?**

**MHIF FEATURED STUDY:**
**ALTFLO**

**CONNECTION:**
Symptomatic clinically significant heart failure and elevated atrial pressures

**PI:**
Paul Sorajja, MD

**RESEARCH CONTACT:**
Karen Meyer, RN
Karen.meyer2@allina.com | 612-863-5855

**SPONSOR:**
Edwards LifeScience

**DESCRIPTION:**
Multi-center, prospective, early feasibility study to evaluate initial clinical safety, device functionality and effectiveness of the Edwards Transcatheter Atrial Shunt System.

**CRITERIA LIST/QUALIFICATIONS:**

**Inclusion**
1. Chronic symptomatic Heart Failure (HF)
2. Stable Guideline Directed Medical Therapy (GDMT) for heart failure management
3. Elevated LA (or PCWP) pressure of >15 mmHg at rest or >25 mmHg during supine ergometer exercise stress test.

**Exclusion**
1. Severe HF
   - ACC/AHA/ESC Stage D, non ambulatory NYHA IV
   - Cardiac index <2.0L/min/m2
   - Inotropic infusion
   - Listed for cardiac transplant
   - LVEF <20%
2. Presence of significant valve disease (>3+MR, >2+TR, >2+ AR or > moderate AS)

**OPEN AND ENROLLING:**
Please Refer Patients!
Minneapolis Heart Institute Foundation® Cardiovascular Grand Rounds

Title: Cardiac Contractility Modulation
Speaker(s): Michael Samara, MD
Cardiologist
Minneapolis Heart Institute® at Abbott Northwestern Hospital

Date: December 16, 2019
Time: 7:00 – 8:00 AM
Location: Minneapolis Heart Institute Building, Suite 100, Learning Center

OBJECTIVES
At the completion of this activity, the participants should be able to:
1. Understand the role of deranged intracellular calcium handling and autonomic function on the pathophysiology of heart failure.
2. Identify the beneficial acute and long-term physiologic effects that CCM elicits.
3. Interpret the clinical data supporting the use of CCM in patients with systolic heart failure.

DISCLOSURE POLICY & STATEMENTS
Allina Health, Learning & Development intends to provide balance, independence, objectivity and scientific rigor in all of its sponsored educational activities. All speakers and planning committee members participating in sponsored activities and their spouse/partner are required to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of this conference.

The ACCME defines a commercial interest as “any entity” producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests - unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest.

Moderator(s)/Speaker(s)
Dr. Michael Samara has disclosed that he DOES NOT have any real or apparent conflicts with any commercial interest as it relates to presenting the content in this activity/course.

Planning Committee
Dr. Alex Campbell, Jake Cohen, Jane Fox, Dr. Kevin Harris, Dr. Kasia Hryniewicz, Rebecca Lindberg, Amy McMeans, Dr. Michael Miedema, Dr. JoEllyn Moore, Pamela Morley, Dr. Scott Sharkey, Maia Hendel and Jolene Bell Makowesky have disclosed that they DO NOT have any real or apparent conflicts with any commercial interest as it relates to the planning of this activity/course. Dr. Mario Gössl has disclosed the following relationships -Grant/Research Support: Edwards Life Sciences; Consultant: Abbott Vascular, Caisson; Speaker’s Bureau: Edwards Lifesciences. Dr. David Hurrell has disclosed the following relationship -Chair, Clinical Events Committee: Boston Scientific. Dr. João Cavalcante has disclosed the following relationships -Grant/Research Support: Boston Scientific, Medtronic, Abbott Vascular, Circle Cardiovascular Imaging, Siemens Healthineers; Consultant: Boston Scientific, Medtronic; Speaker’s Bureau: Medtronic, Siemens Healthineers; Honoraria: Medtronic, Siemens Healthineers.
NON-ENDORSEMENT OF COMMERCIAL PRODUCTS AND/OR SERVICES

We would like to thank the following company for exhibiting at our activity.

**Akcea Therapeutics**

**Janssen Pharmaceutical Companies of Johnson & Johnson**

Accreditation of this educational activity by Allina Health does not imply endorsement by Allina Learning & Development of any commercial products displayed in conjunction with an activity.

A reminder for Allina employees and staff, the Allina Policy on Ethical Relationship with Industry prohibits taking back to your place of work, any items received at this activity with branded and or product information from our exhibitors.
Cardiac Contractility Modulation

Michael A. Samara, MD FACC
Advanced Heart Failure, Cardiac Transplant & Mechanical Circulatory Support

MHIF CV Grand Rounds – December 16, 2019

No financial disclosures
At present only one device manufacturer
Heart Failure Stages:
Recommended Therapies

WE UNDERUTILIZE
HF PHARMACOTHERAPY

THERE IS A LARGE DIVIDE
BETWEEN GDMT AND
ADVANCED THERAPIES

Cardiac Contractility Modulation
Where Does It All Fit In?

“We cannot do everything for every patient.” Clyde Yancy
We Have Homogenized the Management of HF Patients
A Case for Deep Phenotyping

Echocardiographic Features of Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction

<table>
<thead>
<tr>
<th>HFpEF-RVD</th>
<th>HFpEF-LVH</th>
<th>HFpEF-LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(RV dysfunction)</td>
<td>(Severe LVH)</td>
<td>(impaired LA function)</td>
</tr>
</tbody>
</table>

Nature Rev. Cardiol. 2013; 10, 584–598

Cardiac Contractility Modulation: Non-excitatory Stimulation + Absolute Refractory Period

CCM is the application of non-excitatory electrical signals (NES) to the myocardium during the absolute refractory period of the action potential to augment contraction.
Post-extrasystolic potentiation
1. Depolarization opens voltage-dependent L-type Ca²⁺ (LTCC) gates

2. “Ca²⁺ induced Ca²⁺ release” (CICR):
   Small influx of Ca²⁺ results in large release of Ca²⁺ (10x) from the sarcoplasmic reticulum via the type 2 ryanodine receptor (RyR2)

3. Ca²⁺ binds troponin C resulting in conformational change that elicits myocyte shortening

4. Active Relaxation: Ca²⁺ must be dissociated from troponin and removed from the cytosol by SR- Ca²⁺ ATPase 2a (SERCA2a) + the Na⁺- Ca²⁺ exchanger (NCX)

---

**Excitation-Contraction Coupling**

**Normal Ca²⁺ Homeostasis**

---

**Excitation-Contraction Coupling**

**Extrasystolic and Post-extrasystolic Beats**

---

**Intracellular Ca²⁺ Flux:**

- Low
- High

**Normal Beat**

- Ca²⁺

**Post-extrasystolic beat**

- Ca²⁺
Mechanical Restitution & Post-extrasystolic Potentiation

Mechanical Restitution:
As ESI gets longer generated force of the extrasystolic beat approaches normal

Post-extrasystolic Potentiation:
As ESI gets longer generated force of the post-extrasystolic beat approaches normal
Inotropic Effects of Electric Currents

I. POSITIVE AND NEGATIVE EFFECTS OF CONSTANT ELECTRIC CURRENTS OR CURRENT PULSES APPLIED DURING CARDIAC ACTION POTENTIALS

II. HYPOTHESES: CALCIUM MOVEMENTS, EXCITATION-CONTRACTION COUPLING AND INOTROPIC EFFECTS

By Earl H. Wood, Richard L. Hoppner, and Silvio Weidmann
Sustained depolarization contracture yields the same potentiation that is seen in the post-extrasystolic beats.

Sustained subthreshold direct current

50 ms pulses 125 ms after paced stimuli

190% increase in systolic tension

35% increase in systolic tension

1. L-type Ca\(^{2+}\) (LTCC) gates are down regulated
2. Decreased “Ca\(^{2+}\) induced Ca\(^{2+}\) release” (CICR)
3. Decreased cytosolic Ca\(^{2+}\) resulting in decreased contractile force
4. Downregulation of SR- Ca\(^{2+}\) ATPase 2a (SERCA2a) + unphosphorylated PLB inhibition
5. Upregulation of the Na\(^{+}\)-Ca\(^{2+}\) exchanger (NCX)

↓ Peak Cytosolic Ca\(^{2+}\) & ↓Ca\(^{2+}\) Flux
Cardiac Contractility Modulation:
Increase in Force Generation, dP/dT, LV pressure

Force generation increases instantaneously. Inhibited with pretreatment with ryanodine confirming central role of sarcoplenal calcium handling.

Further confirmation of central role of Ca\textsuperscript{2+}. Both LV force and Ca\textsuperscript{2+} transient amplitude measured by aequorin fluorescence are increased with each CCM signal.

Cardiac Contractility Modulation:
Systolic Force Impacted by Duration, Amplitude, and Polarity of CCM Pulse

Increase in duration or amplitude of CCM pulse increases systolic force.

Negative (cathode) current hyperpolarization has negative inotropic effect.

Systolic force is additive to inotrope but is not abated by β-blocker therapy.

Nature Rev. Cardiol. 2013; 10, 584–598
Cardiac Contractility Modulation:
Acutely Results in Increased Contractility


Cardiac Resynchronization Therapy:

Cardiac Contractility Modulation: Acutely Results in Local Increase in Contractility

- LV pressure
- LV volume
- ESPVR

Cardiac Inotropes: Calcitropes Enhance dP/dT but at a Cost

**CARDIAC CALCITROPES**
- Dobutamine: Catecholamines; ß-adrenergic receptor → cAMP → ↑Ca²⁺
- Dopamine: Catecholamines; ß-adrenergic receptor → cAMP → ↑Ca²⁺
- Epinephrine: Catecholamines; ß-adrenergic receptor → cAMP → ↑Ca²⁺
- Milrinone: Phosphodiesterase-3 inhibitor: cAMP → ↑Ca²⁺
- Levosimendan: Phosphodiesterase-3 inhibitor + Calcium sensitizer: ↓troponin and tropomyosin inhibition; cAMP → ↑Ca²⁺
- Cardiac Glycosides: Na⁺-K⁺ ATPase inhibitor: ↓NCX Ca²⁺ extrusion → ↑Ca²⁺
- Istaroxime: Na⁺-K⁺ ATPase inhibitor & SERCA2a Activator: ↓NCX Ca²⁺ extrusion → ↑Ca²⁺, ↑SERCA2a → ↑Ca²⁺ in SR

**CARDIAC MYOTROPES**
- Omecamtiv mecarbil: Direct myosin activator: ↑Myosin participation in systole

**CARDIAC MITOTROPES**
- Perhexiline: Carnitine palmitoyl transferase inhibitor: ↓mitochondrial fatty acids → ↑glucose metabolism
- Trimetazidine: Thiolase I inhibitor: ↓fatty acid oxidation → ↑glucose metabolism
- Elamipretide: Cardiolipin stabilizer

Energetics (mitotropes)
- Calcium Fluxes (calcitropes)

Sarcomere
- Actin
- Troponin
- Myosin
- Troponin T
- Twitching
Inotropic Therapy:
Calcitropes are Associated with Increased Morbidity and Mortality

Increased mortality
- Milrinone 1,2
- Enoximone 3
- Imazodan 4
- Vesnarinone 5
- Dobutamine 6,7
- Xamoterol 8
- Ibopamine 9

Increased risk of hospitalization1

Increased arrhythmia
- Milrinone 10,11
- Dobutamine 12
- Dopamine 13,14

Increased myocardial MVO215

Neurohormonal activation16

---

Cardiac Contractility Modulation:
↑ Contractility without ↑ in Myocardial MVO2

Mean 10-20% improvement in dP/dt with CCM with no change in MVO2

Unlike Calcitropes, CCM and CRT increase contractility without increasing MVO2

---
**Cardiac Contractility Modulation:**

**↑ Contractility without ↑ in Myocardial MVO₂**

**¹¹C-Acetate positron emission tomography (PET) is a sensitive noninvasive method for monitoring MVO₂ and for estimating myocardial efficiency in patients with HF.**

![Diagram of metabolic pathways and MVO₂ calculation](image)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Dobutamine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>kmono (min⁻¹)</td>
<td>0.054 ± 0.04</td>
<td>0.85 ± 0.01</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MVO₂ (ml/min/100g)</td>
<td>6.94 ± 2.44</td>
<td>12.46 ± 4.97</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Cardiac Contractility Modulation:**

**Increased Troponin Phosphorylation**

Sensitivity of myofilaments for Ca²⁺ is primarily regulated by phosphorylation state of TnI and MLC2.

Increase in phosphorylation of TnI and MBPC in both the left and right ventricle occurs within 30 minutes of CCM signal delivery and increases after 3 months of therapy.

![Graph of troponin and MVO₂ changes](image)
Cardiac Contractility Modulation: Acutely Biochemical Effects Restricted to Treated Site

Nature Rev. Cardiol. 2013; 10, 584–598

Cardiac Contractility Modulation: Molecular Remodeling

Buter, C. et al. J Am Coll Cardiol 2008;51:1784–9

Fetal vs Adult gene expression program in patients +/- CCM

Expected trend towards "normalization"
Cardiac Contractility Modulation: 
In Time Biochemical Effects Migrate to Untreated Sites

Cardiac Contractility Modulation: 
Global Effects Occur via Gap Junctions
Cardiac Contractility Modulation: Global Effects Occur via Source—Sink Relationship

Local CCM pulse creates molecular and metabolic sink

Nature Rev. Cardiol. 2013; 10, 584–598

Proapoptotic Factors

Intercellular gradients lead to diffusion across gap junctions

CCM Attenuates Myocardial Fibrosis: Via Inhibition of TGF-β1/Smad3 Signaling Pathway

Masoson's trichrome staining (collagen)

**Autonomic Nervous System: Interplay with Renal Angiotensin Aldosterone System**

**RAAS Activation**
- ATII-mediated ↑ central SNS output
- ATII-mediated ↑ carotid body chemoreceptor sensitivity
- Abnormal sodium and water homeostasis
- Pathologic LV remodeling

**PNS Withdrawal**
- NO dysregulation
- Inflammatory cytokines
- Resting HR
- Arrhythmia susceptibility
- Loss of inhibition of SNS reflexes

**Progressive Heart Failure**

**SNS Activation**
- Subcellular myocardial dysfunction (abnormal calcium handling, apoptosis)
- Interstitial fibrosis
- Synergistic activation of excitatory SNS reflexes
- Arrhythmia susceptibility
- Peripheral vascular resistance

**Measures of Autonomic Balance Independently Predict Survival in HFrEF**

- 985 NYHA FC II-III patients in the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure)
- At all LVEFs a 123I-MIBG heart-to-mediastinum ratio of < 1.6 was associated with a higher risk of death or potentially lethal arrhythmic event and of the composite of cardiovascular death, arrhythmic event, and HF progression.

_J Am Coll Cardiol Img_ 2012;5:1139 – 46
Autonomic Neuromodulation in HF: Evolving Device Therapies

Challenges with Neuromodulation Studies:
- Lack of reliable physiologic biomarkers
- Challenges proper dose (current/voltage, duty cycle, location, duration)
- Relative benefits of afferent vs. efferent stimulation


Vagal Nerve Stimulation: Key Trials

<table>
<thead>
<tr>
<th></th>
<th>INOVATE-HF</th>
<th>ANTHEM-HF</th>
<th>NECTAR-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>650</td>
<td>60</td>
<td>96 (87 with paired data)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>II-IV</td>
<td>II-IV</td>
<td>II-IV</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>&lt;40%</td>
<td>&lt;40%</td>
<td>&lt;35%</td>
</tr>
<tr>
<td>LVEDD</td>
<td>50-80 mm</td>
<td>50-80 mm</td>
<td>≥55 mm</td>
</tr>
<tr>
<td>QRS width</td>
<td>&lt;120 ms</td>
<td>&lt;120 ms</td>
<td>≤150 ms</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized 3:1 (implant vs. no implant)</td>
<td>Open label, randomized right vs. left VNS</td>
<td>Randomized 2:1 (VNS on vs. off)</td>
</tr>
<tr>
<td>Control</td>
<td>Optimal medical treatment</td>
<td>Right vs. left</td>
<td>Stimulation off</td>
</tr>
<tr>
<td>Device used</td>
<td>CardioFit System, BioControl Medical, Israel</td>
<td>Demipulse model 103, Cyberonics, United States</td>
<td>Precision, Boston Scientific, United States</td>
</tr>
<tr>
<td>Side stimulated</td>
<td>Right</td>
<td>Right and left</td>
<td>Right</td>
</tr>
<tr>
<td>Stimulation protocol</td>
<td>Target output: 3.3-5.5 mA, titrated on/off times to maximum of 10 s on/30 s off</td>
<td>Target output 1.5-3.0 mA (average achieved 2.0 mA), frequency 10 Hz, pulse width 130 μs, 14 s on/66 s off</td>
<td>Target output: maximal 4 mA (average achieved 1.4 mA), frequency 20 Hz, pulse width 300 μs, 10 s on/50 s off</td>
</tr>
<tr>
<td>Intracardiac lead</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Study duration</td>
<td>18 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Primary efficacy endpoints</td>
<td>Death or HF hospitalization (up to 5.5 years)</td>
<td>Change in LVEF and LVEF at 6 months</td>
<td>Change in LVESD from baseline at 6 months</td>
</tr>
<tr>
<td>Primary efficacy endpoint met</td>
<td>No</td>
<td>Yes, LVEF improvement of 4.5% (95% CI: 2.4-6.6)</td>
<td>No</td>
</tr>
</tbody>
</table>

Autonomic Neuromodulation in HF: Evolving Device Therapies

A. CCM increases force of septal contraction
B. Mechanoreceptors activate vagal afferents via C-fibers
C. NTS is stimulated and activates vagal efferents via the DMNV and Nucleus ambiguus (nAmb)
D. NTS inhibits the RVLM and sympathetic outflow is inhibited centrally and peripherally

Cardiac Contractility Modulation: Engaging the Bezold-Jarisch Reflex

NTS = nucleus tractus solitarius
DMNV = dorsal motor nucleus of vagus
nAmb = nucleus ambiguous
RVLM = rostral ventrolateral medulla
In 18 vagal nerve fibers with cardiac receptive fields, CCM produced an intensity dependent increase (p<0.05) in firing frequency of 10 fibers (4.2 ± 1.2 Hz at 7.5V vs. 1.4 ± 0.66 Hz at baseline).

Cardiac Contractility Modulation: Activates Vagal Afferents

Vagal Afferents are Similarly Activated with Non-excitatory Gastric Stimulation during Antral Contraction
Summary of Preclinical Findings

- ↑ systolic force and dP/dT without ↑ myocardial MVO₂
- ↑ Intracellular Ca²⁺ metabolism and diastolic Ca²⁺ levels
- ↑ phosphorylation of myofilaments (TnI, MLC, MBPC)
- Molecular remodeling from fetal to adult gene profile
- Effects are propagated throughout the myocardium over time
- ↓ myocardial fibrosis through TGFβ and Smad signaling
- Rebalances autonomic tone by engaging a Bezold-Jarisch like reflex

Clinical Data

Investigators undertake clinical studies emulating early CRT trials
Cardiac Contractility Modulation:
Non-excitatory Stimulation During the Absolute Refractory Period

- Biphasic
- Duration ~ 20 ms
- Amplitude ± 7.5 V
- Nonexcitatory
- Applied during absolute refractory period

![Diagram showing normal QRS and CCM QRS with annotations](image)
**Cardiac Contractility Modulation: Transcutaneous Energy Transfer**

Transcutaneous energy transfer requires weekly charging with each charge taking 40-60 minutes.

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### Cardiac Contractility Modulation: Clinical Studies to Date

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Comments</th>
<th>Randomized</th>
<th>Device</th>
<th>Countries</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIX-HF-1</td>
<td>Ongoing study</td>
<td>Yes</td>
<td>Opt I</td>
<td>Italy</td>
<td>1</td>
</tr>
<tr>
<td>FIX-HF-2</td>
<td>First chronic study</td>
<td>Yes</td>
<td>Opt I</td>
<td>Italy</td>
<td>6</td>
</tr>
<tr>
<td>FIX-HF-3</td>
<td>Pilot study, OMT</td>
<td>Opt II</td>
<td>Italy, Germany, Austria</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>FIX-CHF-4</td>
<td>Crossover double-blind, 6 months</td>
<td>Yes</td>
<td>Opt II</td>
<td>Italy, Austria, Germany, France, The Netherlands and Czech</td>
<td>164</td>
</tr>
<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>
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<tr>
<td>FIX-HF-5 Phase II</td>
<td>CCM vs. OMT</td>
<td>Yes</td>
<td>Opt III</td>
<td>USA</td>
<td>428</td>
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<tr>
<td>FIX-HF-9</td>
<td>CCM vs. OMT</td>
<td>Yes</td>
<td>Opt III</td>
<td>Hong Kong</td>
<td>42</td>
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<tr>
<td>FIX-CHF-12</td>
<td>CRT non-responder study</td>
<td></td>
<td>Opt III</td>
<td>Germany</td>
<td>19</td>
</tr>
<tr>
<td>FIX-CHF-13</td>
<td>CCM dosage (5 vs. 12 hours)</td>
<td></td>
<td>Opt III</td>
<td>Germany</td>
<td>20</td>
</tr>
<tr>
<td>CCM HF</td>
<td>CCM Registry</td>
<td></td>
<td>Opt III</td>
<td>Germany</td>
<td>143</td>
</tr>
<tr>
<td>FIX-CHF-18</td>
<td>Comparison 1 vs 2 leads</td>
<td></td>
<td>Opt IV</td>
<td>Germany</td>
<td>48</td>
</tr>
<tr>
<td>Fix-5c</td>
<td>CCM vs. OMT confirmatory</td>
<td>Yes</td>
<td>Opt IV</td>
<td>USA, Germany, Czech</td>
<td>160</td>
</tr>
<tr>
<td>CCM-REG</td>
<td>CCM Registry</td>
<td></td>
<td>Opt IV</td>
<td>Germany, Russia, France, Italy</td>
<td>370</td>
</tr>
<tr>
<td>FIX-HF-5C2</td>
<td>2-Lead CCM Device</td>
<td></td>
<td>Opt Smart (2-lead)</td>
<td>US, Germany</td>
<td>60</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,571</td>
</tr>
</tbody>
</table>
Clinical Data:

**FIX-HF-4**

Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure

- 164 patients with LVEF < 35% and NYHA Class II (24%) or III (76%)
- Group 1: 3 months CCM → 3 months sham treatment
- Group 2: 3 months sham treatment → 3 months CCM
- Co-primary endpoints: peak VO₂ and MLWHFQ

Cardiac Contractility Modulation:

**FIX-HF-4**

Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure

- Significant placebo effect observed in CCM off→on group
Cardiac Contractility Modulation: Echocardiographic Evidence of Remodelling

<table>
<thead>
<tr>
<th>Systolic function</th>
<th>Baseline</th>
<th>3 Months</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.0 ± 6.5</td>
<td>33.1 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>115 ± 35</td>
<td>103 ± 37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>159 ± 40</td>
<td>150 ± 40</td>
<td>0.002</td>
</tr>
<tr>
<td>LV end-systolic sphericity index</td>
<td>1.77 ± 0.24</td>
<td>1.88 ± 0.30</td>
<td>0.008</td>
</tr>
<tr>
<td>LV end-diastolic sphericity index</td>
<td>1.66 ± 0.20</td>
<td>1.72 ± 0.21</td>
<td>0.015</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>2.9 ± 1.1</td>
<td>3.3 ± 1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral regurgitation (% LA area)</td>
<td>22 ± 14</td>
<td>17 ± 15</td>
<td>0.032</td>
</tr>
<tr>
<td>LV + dp/dt (mm Hg/s)</td>
<td>736 ± 112</td>
<td>882 ± 128</td>
<td>0.010</td>
</tr>
<tr>
<td>MPI</td>
<td>0.72 ± 0.26</td>
<td>0.62 ± 0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean Sm-6 (cm/s)</td>
<td>2.5 ± 0.6</td>
<td>3.0 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Sm-12 (cm/s)</td>
<td>2.2 ± 0.6</td>
<td>2.5 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cardiac Contractility Modulation: Improved Regional Systolic Function (S')

Tissue Doppler Parameters after CCM

<table>
<thead>
<tr>
<th>Systolic function</th>
<th>Baseline</th>
<th>3 Months</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm, basal septal (cm/s)</td>
<td>2.8 ± 0.9</td>
<td>3.1 ± 0.9</td>
<td>0.064</td>
</tr>
<tr>
<td>Sm, basal lateral (cm/s)</td>
<td>2.4 ± 1.0</td>
<td>2.9 ± 1.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Sm, basal anterior (cm/s)</td>
<td>2.3 ± 0.9</td>
<td>2.8 ± 1.3</td>
<td>0.024</td>
</tr>
<tr>
<td>Sm, basal inferior (cm/s)</td>
<td>2.9 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sm, basal anteroseptal (cm/s)</td>
<td>2.2 ± 0.9</td>
<td>2.8 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sm, basal posterior (cm/s)</td>
<td>2.5 ± 0.9</td>
<td>3.0 ± 1.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Diastolic function

| Em, basal septal (cm/s)          | 3.4 ± 1.9 | 3.1 ± 1.6 | 0.219   |
| Em, basal lateral (cm/s)         | 3.5 ± 2.1 | 3.6 ± 2.3 | 0.815   |
| Em, basal anterior (cm/s)        | 3.3 ± 2.0 | 3.5 ± 1.7 | 0.559   |
| Em, basal inferior (cm/s)        | 3.4 ± 1.5 | 3.5 ± 1.5 | 0.570   |
| Em, basal anteroseptal (cm/s)    | 2.5 ± 1.4 | 2.8 ± 1.5 | 0.191   |
| Em, basal posterior (cm/s)       | 3.7 ± 2.3 | 3.2 ± 1.7 | 0.059   |
| Am, basal septal (cm/s)          | 3.6 ± 1.9 | 3.9 ± 2.1 | 0.152   |
| Am, basal lateral (cm/s)         | 2.4 ± 1.6 | 2.7 ± 1.6 | 0.105   |
| Am, basal anterior (cm/s)        | 2.7 ± 1.7 | 3.3 ± 1.6 | 0.015   |
| Am, basal inferior (cm/s)        | 3.9 ± 2.0 | 4.3 ± 2.0 | 0.140   |
| Am, basal anteroseptal (cm/s)    | 2.9 ± 1.5 | 3.2 ± 1.7 | 0.050   |
| Am, basal posterior (cm/s)       | 3.0 ± 1.6 | 3.2 ± 1.7 | 0.369   |
Cardiac Contractility Modulation: FIX-HF-5

- 428 patients with NYHA III or ambulatory IV symptoms, narrow QRS and EF ≤35% randomized to optimal medical therapy (OMT) plus CCM (n = 215) versus OMT alone (n = 213).
- Efficacy was assessed by ventilatory anaerobic threshold (VAT; primary endpoint), pVO₂, and MLWFQ at 6 months.

---

FIX-HF 5:
Ventilatory Anaerobic Threshold (VAT)

Most activities of daily living do not require maximal effort!
AT is an index of submaximal exercise capacity.

Glucose

\[ \text{2 ATP} \rightarrow \text{2 NADH} \]

Anaerobic Metabolism
Pyruvate
Aerobic Metabolism
Lactic Acid
Deprotonation
\[ [H^+] + [HCO_3^-] \rightleftharpoons [H_2O] + [CO_2] \]

\[ \text{Citric Acid Cycle + ETC} \]

34 ATP

Unlike peak VO₂, THE VAT is not effort dependent.
MHIF CV Grand Rounds – December 16, 2019

**FIX-HF 5: Ventilatory Anaerobic Threshold (VAT)**

![Graph showing VAT analysis with V-slope method](image)

- **Lactic Acid Deprotonation**
  \[ [H^+] + [HCO_3^-] \rightleftharpoons [H_2O] + [CO_2] \]

- **Exercise Time**
  - VCO₂ (L/min)
  - VO₂ (L/min)
  - V-slope Method

**End-tidal method**
- Ventilatory Threshold
- P_{ETCO₂}
- P_{EVO₂}
- Exercise Time
- Ventilatory equivalents method

**Cardiac Contractility Modulation: FIX-HF-5**

![Graph showing Cardiac Contractility Modulation results](image)

- **Δ Peak VO₂**
  - OMT
  - CCM
  - Difference
  \[ p=0.001 \]

- **Δ Anoxic Threshold (mg/dL)**
  - OMT
  - CCM
  - Difference
  \[ N = 154; N = 159 \]

- **Six Minute Walk (m)**
  - OMT
  - CCM
  - Difference
  \[ p=0.044 \]

- **NYHA**
  - % Patients with >2 Point Reduction
  - OMT
  - CCM
  - Difference
  \[ p=0.0023 \]

---


Am J Journal 2011;16 (2):329-337

J Cardiac Fail 2011;17:710e717

An H Journal 2011/08/2(329-337)

J Cardiac Fail 2011,17(10):710-717
Cardiac Contractility Modulation:
FIX-HF-5: Subgroup Analysis (LVEF > 25%; NYHA FC III)

Am Heart J 2011;162(2):219-227
J Card Fail 2011;17:710e717

Cardiac Contractility Modulation:
FIX-HF-5: Subgroup Analysis (LVEF > 25%; NYHA FC III)

J Card Fail 2011;17:710e717
Cardiac Contractility Modulation:
FIX-HF-5C (Prospectively Test Findings in FIX-HF 5 Subgroup Analysis)

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

- 160 patients with NYHA FC III-IV + LVEF 25-45%
- OMT (n = 86) or CCM (n = 74) for 24 weeks
- pVO2 (primary endpoint), MLWHFQ, NYHA FC, 6MW
- Bayesian repeated measures linear modeling was used for the primary endpoint analysis with 30% borrowing from the FIX-HF-5 subgroup

Cardiac Contractility Modulation:
FIX-HF-5C (Baseline Characteristics)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>CCM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86+112 (198)*</td>
<td>n=74+117 (191)*</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>CHF Etiology (Ischemic)</td>
<td>64.7%</td>
<td>68.1%</td>
<td>0.52</td>
</tr>
<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>
</tr>
<tr>
<td>MLWHFQ</td>
<td>57±23</td>
<td>59±23</td>
<td>0.36</td>
</tr>
<tr>
<td>6MW (meters)</td>
<td>324±91</td>
<td>322±86</td>
<td>0.08</td>
</tr>
<tr>
<td>CPX (core lab)</td>
<td>Peak VO2 (ml/kg/min)</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>15.0±3.0</td>
<td>15.0±2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercise Time (minutes)</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>11.2±3.3</td>
<td>11.3±3.1</td>
<td></td>
</tr>
</tbody>
</table>

*Primary analysis cohort from FIX-HF-5C + FIX-HF-5 25±34 Subgroup
Cardiac Contractility Modulation: FIX-HF-5C (Prospectively Test Findings in FIX-HF 5 Subgroup Analysis)

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Abraham et al. JACC: Heart Failure May 2018, 882

FIX-HF-5C: Primary Efficacy Endpoints Met
CCM Significantly Improves QoL and Functional Capacity

Abraham et al. JACC: Heart Failure May 2018, 882
Cardiac Contractility Modulation: Improvement in Peak VO$_2$ Comparable to CRT

Clinical Data: A Summary of Efficacy Comparisons to CRT

<table>
<thead>
<tr>
<th>Variable</th>
<th>CCM</th>
<th>CCM 35% +</th>
<th>CRT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>pVO$_2$</td>
<td>0.84</td>
<td>1.76</td>
<td>0.91</td>
</tr>
<tr>
<td>MLWHF</td>
<td>-11.4</td>
<td>-14.9</td>
<td>-9.5</td>
</tr>
<tr>
<td>NYHA 1 class improvement</td>
<td>81%</td>
<td>82%</td>
<td>70%</td>
</tr>
<tr>
<td>6MW</td>
<td>24.6</td>
<td>57.1</td>
<td>20.0</td>
</tr>
</tbody>
</table>

**FIX-HF-5 + FIX-HF-5C:**

**Cardiovascular Death and HF Hospitalization**

- **Control**
- **CCM Treatment**

*Primarily driven by HF hospitalizations*

*p = 0.036 comparing K-M estimates*

---

**Cardiac Contractility Modulation:**

↓ in VE/VCO₂ and Exercise Oscillatory Ventilation

- **Exercise Oscillatory Ventilation**
- **VE/VCO₂**

*Schote, D et al. European Society of Cardiology 2019*
Ventilatory Efficiency (VE/VCO2)

NORMAL

VE/VCO₂ = 15

4 lpm

60 lpm

[CO₂]

HEART FAILURE

VE/VCO₂ = 40

80 lpm

2 lpm

[CO₂]

• Reflects V/Q mismatch related to:
  - ↑ anatomic dead space ventilation
  - ↑ physiologic dead space ventilation due to under-perfused lung
  - ↓ capillary-alveolar gas gradient
  - CO₂ shunting to systemic circulation

CPET Parameters and Risk Prediction:
EOV is a Potent Predictor of Adverse Outcomes

Persistence of EOV ≥ 60% of exercise at ≥ 15% of the average resting value

EOV + VE/VCO₂ slope ≥ 36

→ Hazard ratio 11.4 for all-cause mortality (95% CI, 4.9-26.5; P < .001)

**CPET Parameters and Risk Prediction:**

**EOV is a Potent Predictor of Adverse Outcomes**

The presence of EOV is the strongest CPET predictor of mortality

Mostly driven by reduction in SCD

---

**CPET Parameters and Risk Prediction:**

**Ventilatory Instability and Inefficiency**

**EOV**

- Ventilatory Instability
- Ventilatory Inefficiency

**VE/VCO<sub>2**

- Stimulation of Juxtaglomerular receptors + vagal afferents
- RV-pulmonary vasc dysfunction
- Pulm. Congestion
- ↑ LV filling pressures

* physiologic target of CCM

---


Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction

Stefan D. Anker¹,², Martin Borgefre³,⁴,⁵, Hans Neuser⁶, Marc-Alexander Ohlow⁷, Susanne Röger³,⁴,⁵, Andreas Goette⁸,⁹, Bjoern A. Remppis¹⁰, Karl-Heinz Kuck¹¹, Kevin B. Najarian¹², David D. Gutterman¹³, Benny Rousso¹⁴, Daniel Burkhoff¹⁵, and Gerd Hasenfuss²

Real world European registry focusing on patients meeting FIX-HF-5 enrollment criteria
Assessed MLWHFQ and Survival (indexed to SHFM predicted survival)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pre-Enrollment</th>
<th>Post-Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVENT</td>
<td>Pt-Yrs</td>
</tr>
<tr>
<td>CCM-REG25-45</td>
<td>HF</td>
<td>140.0</td>
</tr>
<tr>
<td></td>
<td>CV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HF+CV</td>
<td></td>
</tr>
<tr>
<td>CCM-REG35-45</td>
<td>HF</td>
<td>57.0</td>
</tr>
<tr>
<td></td>
<td>CV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HF+CV</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.0001
European CCM Registry:
Survival vs. Seattle Heart Failure Model

CCM-REG_{25-45}
Significant and Sustained Improvement in NYHA FC, QoL, and LVEF

\[ N = 143 \text{ patients, NYHA II–IV in 28 centers} \]
Summary of Clinical Study Findings

- After initial blinded cross-over study, trialists have abandoned idea of sham-controlled trials
- Results susceptible to placebo and Hawthorne effects
- QOL metrics difficult to rely on in this context
- That said, clear signal of ↑ exercise capacity both by pVO₂ and VAT comparable to that seen in CRT trials
  - ↑ LVEF
  - Improved ventilatory efficiency and instability
  - Possible reduction in HF and CV hospitalizations

Cardiac Contractility Modulation

- In 2018 FDA granted Expedited Access Pathway because the device potentially provided a treatment for an underserved population (symptomatic HFrEF patients despite GDMT, not eligible for CRT, and not sufficiently symptomatic to justify VAD support)
- 3/22/19 FDA Approved for
  - HFrEF with LVEF 25-45%
  - NYHA FC III or amb IV
  - Not a candidate for CRT
Cardiac Contractility Modulation: Ongoing and Upcoming Trials

- **Post-Approval Study (2-lead device)**
  - 3-year follow-up
  - 620 subjects
  - MLWHFQ, Mortality vs SHFM, Safety

- **CCM-HFpEF (in development)**
  - # subjects TBD
  - Randomized, blinded, CCM ON versus OFF, 1-year endpoint
  - CV Mortality and HF Hospitalizations

- **Integra CCM-D**
  - Breakthrough Designation Request

Cardiac Contractility Modulation

Summary

- **Concerns:**
  - We don’t yet have the kind of data that led to the sustained enthusiasm for CRT.
  - Likely no sham controlled double blinded trial for HFrEF.
  - Likely no adequately powered survival trial will be performed in HFrEF.
  - It may be that improving functional capacity is enough... but data needs to be beyond reproach.
  - "We can’t do everything for every patient." Clyde Yancy
  - Jeopardizing upper extremity vascular access (particularly in patients who might ultimately require advanced HF therapies)

- **An ideal candidate might be:**
  - Persistent NYHA FC III despite GDMT
  - Low anticipation of long-term need/candidacy for advanced HF therapies
  - LVEF > 35% and select patients with LVEF 25-35% who are not advanced therapy candidates
Deep Phenotyping:
Personalized HF Care

- Severe HFpEF (reduced LA function)
  + Exercise RHC
- HFpEF-LVH (Severe LVH)
  + CHAD-STOP
  + Assess for infiltrative CMP
- HFpEF-LA (impaired LA function)
  + Interatrial shunt
- HFpEF-RVD (RV dysfunction)
  + GDMT
- HFmrEF
  + Persistent activity intolerance
  + MIBG Scan
  + EOV and ↑ VE/VCO₂
  + GDMT
  + MitraClip
- Mod-Sev HFpEF
  + CHF
  + Disproportionate FMR
- GDMT
- CCM??

- Diuresis
- Macitentan?
- Phrenic Nerve Stimulator
- GDMT
- MitraClip
- GDMT
- Interatrial shunt
- GDMT
- Interatrial shunt
- CHAD-STOP
- Assess for infiltrative CMP

- GDMT
- Early ICD
- Prepare for advanced therapies

- Severe HFpEF (reduced LA function)
  + Exercise RHC

- HFpEF-LVH (Severe LVH)
  + CHAD-STOP
  + Assess for infiltrative CMP

- HFpEF-LA (impaired LA function)
  + Interatrial shunt

- HFpEF-RVD (RV dysfunction)
  + GDMT

- HFmrEF
  + Persistent activity intolerance
  + MIBG Scan
  + EOV and ↑ VE/VCO₂
  + GDMT
  + MitraClip

- Mod-Sev HFpEF
  + CHF
  + Disproportionate FMR

- GDMT
- CCM??

Thank you!

michael.samara@allina.com