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

CONDITION:
Heart Failure

PI:
Michael Samara, MD

RESEARCH CONTACT:
Jane Fox
jane.fox@allina.com | 612-863-6289

SPONSOR:
Corvia Medical Inc.

OPEN AND ENROLLING:
EPIC message to Pools “Research MHIF Patient Referral”

EXCLUSION:
- Inability to perform 6-minute walk test (distance < 50 m), OR 6-minute walk test > 600m
- Resting RAP > 14 mmHg
- 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
- Significant PH with PVR > 3.5 Woods units at rest or at peak exercise

CRITERIA LIST/QUALIFICATIONS:

Inclusion:
- Age > 40 years – GDMT for 4 weeks
- HF requiring current treatment w/ diuretics for ≥ 30 days AND NYHA class II if a prior history of > NYHA class II, to ambulatory NYHA class IV
- IV diuretics or need for intensification of oral diuresis for HF 12 months prior; OR an NT-pro BNP value > 150 pg./ml in normal sinus rhythm, > 450 pg./ml in AFIB, or a BNP value > 50 in NSR or, > 150 in AFIB within past 6 months
- EF ≥ 40% within the past 6 months, without EF < 30% in the past 5 years
- End-expiratory PCWP during supine ergometer exercise ≥ 25mm Hg, and > RAP by ≥ 5 mm Hg.
Do you have a patient with DYSPNEA?

MHIF FEATURED STUDY: ALTFLO

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

PI: Paul Sorajja, MD
RESEARCH CONTACT: Karen Meyer, RN
Karen.meyer2@allina.com | 612-863-5855
SPONSOR: Edwards LifeScience

CONDITION:
Symptomatic clinically significant heart failure and elevated atrial pressures

OPEN AND ENROLLING:
Please Refer Patients!

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.

**ACCREDITATION**  
*Physician -* Allina Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.  

*Nurse -* This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.0 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

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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. Mario Gössl, Dr. Kevin Harris, Dr. Kasia Hryniewicz, Rebecca Lindberg, Amy McMeans, Dr. Michael Miedema, Dr. JoEllyn Moore, Pamela Morley, Dr. Scott Sharkey, 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. David Hurrell has disclosed the following relationship – Boston Scientific: Chair, Clinical Events Committee.

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

Akcea Therapeutics  
Janssen Pharmaceutical Companies of Johnson & Johnson

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If audited by a licensing board or submitting for license renewal or certification renewal, boards will ask you not the entity providing the education for specific information on each activity you are using for credit. You will need to demonstrate that you attended the activity with a copy of your certificate/evidence of attendance, a brochure/flier and/or the conference handout.

Each attendee at an activity is responsible for determining whether an activity meets their requirements for acceptable continuing education and should only claim those credits that he/she actually spent in the activity.

Maintaining these details are the responsibility of the individual.

**PLEASE SAVE A COPY OF THIS FLIER AS YOUR CERTIFICATE OF ATTENDANCE.**

Signature: ___________________________________________________________  

My signature verifies that I have attended the above stated number of hours of the CME activity.

Allina Health - Learning & Development - 2925 Chicago Ave - MR 10701 - Minneapolis MN 55407
Cardiac Contractility Modulation

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

No financial disclosures
At present only one device manufacturer

Nature Reviews Cardiology
Cardiac contractility modulation therapy in advanced systolic heart failure

Heart Failure Stages:
Recommended Therapies

1. Diuretics
2. Beta blockers
3. ACEi/ARB/ARNi
4. Digoxin
5. Oral Vasodilators
6. Cardiac Rehab
7. Revascularization
8. ICD/CRTP/CRTD
9. Valve surgery or percutaneous therapy
10. Mechanical Circulatory Support
11. Transplantation

CARDIAC CONTRACTILITY MODULATION
Where Does It All Fit In?

NEPRILYSIN INHIBITORS
SGLT2i
IVABRADINE

WE UNDERUTILIZE HF PHARMACOTHERAPY
THERE IS A LARGE DIVIDE BETWEEN GDMT AND ADVANCED THERAPIES

“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

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

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.
Postextrasystolic potentiation
1. Depolarization opens voltage-dependent L-type Ca\(^{2+}\) (LTCC) gates

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

3. Ca\(^{2+}\) binds troponin C resulting in conformational change that elicits myocardial shortening

4. Active Relaxation: Ca\(^{2+}\) must be dissociated from troponin and removed from the cytosol by SR-Ca\(^{2+}\) ATPase 2a (SERCA2a) + the Na\(^{+}\)-Ca\(^{2+}\) exchanger (NCX)
Excitation-Contraction Coupling
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

Normalized contractile force (%) vs. Extrasystolic Interval

Excitation-Contraction Coupling
Mechanical Restitution & Post-extrasystolic Potentiation

Normalized contractile force (%) vs. SS, SS, ESI, PESI

- SS 500 ms
- SS 500 ms
- ESI 200 ms
- PESI 800 ms
Excitation-Contraction Coupling
Mechanical Restitution & Post-extrasystolic Potentiation

Normalized contractile force (%)

SS 500 ms  SS 500 ms  ESI 300 ms  PESI 800 ms
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

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)

\[ \downarrow \text{Peak Cytosolic Ca}^{2+} \quad \& \quad \downarrow \text{Ca}^{2+} \text{Flux} \]
Cardiac Contractility Modulation: Increase in Force Generation, dP/dT, LV pressure

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

Further confirmation of central role of Ca\(^{2+}\) Both LV force and Ca\(^{2+}\) 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 ß-blocker therapy.

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

![Graph A](image1.png)

![Graph B](image2.png)


Cardiac Resynchronization Therapy:

![Graph C](image3.png)

Cardiac Contractility Modulation: Acutely Results in Local Increase in Contractility

LV pressure

Preload recruitable stroke work

LV volume

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

<table>
<thead>
<tr>
<th>CARDIAC CALCITROPES</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>Catecholamines; ß-adrenergic receptor → cAMP → ↑Ca²⁺</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Catecholamines; ß-adrenergic receptor → cAMP → ↑Ca²⁺</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Catecholamines; ß-adrenergic receptor → cAMP → ↑Ca²⁺</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Phosphodiesterase-3 inhibitor: cAMP → ↑Ca²⁺</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>Phosphodiesterase-3 inhibitor + Calcium sensitizer: ↓troponin and tropomyosin inhibition; cAMP → ↑Ca²⁺</td>
</tr>
<tr>
<td>Cardiac Glycosides</td>
<td>Na⁺-K⁺ ATPase inhibitor: ↓NCX Ca²⁺ extrusion → ↑Ca²⁺</td>
</tr>
<tr>
<td>Istaroxime</td>
<td>Na⁺-K⁺ ATPase inhibitor &amp; SERCA2a Activator: ↓NCX Ca²⁺ extrusion → ↑Ca²⁺, ↑SERCA2a → ↑Ca²⁺ in SR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIAC MYOTROPES</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omecamtiv mecarbil</td>
<td>Direct myosin activator</td>
</tr>
<tr>
<td></td>
<td>↑Myosin participation in systole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIAC MITOTROPES</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Perhexiline</td>
<td>Carnitine palmitoyl transferase inhibitor: ↓mitochondrial fatty acids → ↑glucose metabolism</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>Thiolase I inhibitor: ↓fatty acid oxidation → ↑glucose metabolism</td>
</tr>
<tr>
<td>Elamipretide</td>
<td>Cardiolipin stabilizer</td>
</tr>
</tbody>
</table>

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

Cardiac Contractility Modulation: Acutely Results in Local Increase in Contractility

Energetics (mitotropes)

<table>
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<tr>
<th>Enzyme</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>↑glycolysis</td>
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Calcium Fluxes (calcitropes)

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>ATPase</td>
<td>↑ATPase activity</td>
</tr>
<tr>
<td>SERCA2a</td>
<td>↑serca2a activity</td>
</tr>
<tr>
<td>Cardiolipin</td>
<td>↑Cardiolipin synthesis</td>
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Cardiac Inotropes:
Calcitropes Enhance dP/dT but at a Cost

Cardiac Contractility Modulation: Acutely Results in Local Increase in Contractility

Energetics (mitotropes)

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</tr>
<tr>
<td>Cardiolipin</td>
<td>↑Cardiolipin synthesis</td>
</tr>
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</table>
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 hospitalization**
- Milrinone 10,11
- Dobutamine 12
- Dopamine 13,14

**Increased arrhythmia**
- Milrinone 10,11
- Dobutamine 12
- Dobutamine 13

**Increased myocardial MVO2**

**Neurohormonal activation**

![Graph showing survival and mortality rates between milrinone and dobutamine](image)

---

**Cardiac Contractility Modulation:**

↑ Contractility without ↑ in Myocardial MVO2

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

![Diagram showing cardiac contractility modulation](image)

 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.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Dobutamine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>kmono</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>

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.
Cardiac Contractility Modulation: Acutely Biochemical Effects Restricted to Treated Site

On-phase
Off-phase
Expected trend towards "normalization"

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

Prosurvival Factors

Proapoptotic Factors

Intercellular gradients lead to diffusion across gap junctions

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

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

Masson's trichrome staining (collagen)

Autonomic Nervous System: Interplay with Renal Angiotensin Aldosterone System

RAAS Activation
- AT1-mediated ↑ central SNS output
- AT1-mediated ↑ carotid body chemoreceptor sensitivity
- Abnormal sodium and water homeostasis
- Pathologic LV remodeling

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

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

Progressive Heart Failure

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>≥40%</td>
<td>≥40%</td>
<td>≤35%</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>50–80</td>
<td>50–80</td>
<td>≥55</td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>&lt;120</td>
<td>&lt;130</td>
<td>≤150</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized 3:2 (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 LVEDV and LVEF at 6 months</td>
<td>Change in LVEF 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. Mechanoceptors 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 ambiguus
RVLM = rostral ventrolateral medulla
Cardiac Contractility Modulation: Activates Vagal Afferents

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).

CCM applied to the base of the LV elicits a prominent vagal afferent response that is:
- Sustained
- Reversible
- Voltage dependent
- Not observed when stimuli is applied outside the heart

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

Normal QRS

\[ P \quad Q \quad S \quad T \]

CCM QRS

\[ P \quad Q \quad S \quad T \]

± 7.5 V

~30 ms

Cardiac Contractility Modulation:
Optimizer®
Smart
Mini
+ ICD

Mini Charger

LS Lead

RV Lead

RF Projection

ICD Lead
Transcutaneous energy transfer
Requires weekly charging with each charge taking 40-60 minutes.

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>Acute 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 II</td>
<td>Italy, Germany, Austria</td>
<td>6</td>
</tr>
<tr>
<td>FIX HF-3</td>
<td>CCM study / Opt I</td>
<td></td>
<td></td>
<td>Italy, Germany, Austria</td>
<td>22</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>
</tr>
<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>
</tr>
<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. 1/2 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 IVs</td>
<td>Germany</td>
<td>48</td>
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<tr>
<td>Fix Sc</td>
<td>CCM vs. OMT confirmatory</td>
<td>Yes</td>
<td>Opt IVs</td>
<td>USA, Germany, Czech</td>
<td>160</td>
</tr>
<tr>
<td>CCM RGB</td>
<td>CCM Registry</td>
<td></td>
<td>Opt IVs, Smart</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>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>1,571</td>
</tr>
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</table>
Clinical Data:

**FIX-HF-4**

Randomized, double blind study of non-excitative, 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

Clinical Data:

**FIX-HF-4**

Cardiac Contractility Modulation:

**FIX-HF-4**

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

Cardiac Contractility Modulation:

**FIX-HF-4**

MUSTIC-CRT

**FIX-HF-4**

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 S'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 S'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></th>
<th>Baseline</th>
<th>3 Months</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Em, basal septal (cm/s)</td>
<td>3.4 ± 1.9</td>
<td>3.1 ± 1.6</td>
<td>0.219</td>
</tr>
<tr>
<td>Em, basal lateral (cm/s)</td>
<td>3.5 ± 2.1</td>
<td>3.6 ± 2.3</td>
<td>0.815</td>
</tr>
<tr>
<td>Em, basal anterior (cm/s)</td>
<td>3.3 ± 2.0</td>
<td>3.5 ± 1.7</td>
<td>0.559</td>
</tr>
<tr>
<td>Em, basal inferior (cm/s)</td>
<td>3.4 ± 1.5</td>
<td>3.5 ± 1.5</td>
<td>0.570</td>
</tr>
<tr>
<td>Em, basal anteroseptal (cm/s)</td>
<td>2.5 ± 1.4</td>
<td>2.8 ± 1.5</td>
<td>0.191</td>
</tr>
<tr>
<td>Em, basal posterior (cm/s)</td>
<td>3.7 ± 2.4</td>
<td>3.2 ± 1.7</td>
<td>0.059</td>
</tr>
<tr>
<td>Am, basal septal (cm/s)</td>
<td>3.6 ± 1.9</td>
<td>3.9 ± 2.1</td>
<td>0.152</td>
</tr>
<tr>
<td>Am, basal lateral (cm/s)</td>
<td>2.4 ± 1.6</td>
<td>2.7 ± 1.6</td>
<td>0.105</td>
</tr>
<tr>
<td>Am, basal anterior (cm/s)</td>
<td>2.7 ± 1.7</td>
<td>3.3 ± 1.6</td>
<td>0.015</td>
</tr>
<tr>
<td>Am, basal inferior (cm/s)</td>
<td>3.9 ± 2.0</td>
<td>4.3 ± 2.0</td>
<td>0.140</td>
</tr>
<tr>
<td>Am, basal anteroseptal (cm/s)</td>
<td>2.9 ± 1.5</td>
<td>3.2 ± 1.7</td>
<td>0.050</td>
</tr>
<tr>
<td>Am, basal posterior (cm/s)</td>
<td>3.0 ± 1.6</td>
<td>3.2 ± 1.7</td>
<td>0.369</td>
</tr>
</tbody>
</table>
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-4 demonstrated prominent placebo effect in 6MW and MLWHFQ**

**Oversight committee did not feel long-term trial with sham device requiring weekly charging was tenable**

**Given the lack of double-blinding, VO₂ at the anaerobic threshold was selected as primary functional capacity endpoint**

---

**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 ➔ 2 ATP  
2 NADH ➔ Pyruvate ➔ Aerobic Metabolism ➔ Citric Acid Cycle + ETC 
Lactic Acid ➔ Deprotonation ➔ [H⁺] + [HCO₃⁻] ⇌ [H₂O] + [CO₂] ➔ 34 ATP

Unlike peak VO₂, THE VAT is not effort dependent.
### Ventilatory Anaerobic Threshold (VAT)

**End-tidal method**

- Ventilatory Threshold
- $F_{O_2}$
- $F_{CO_2}$

**Expiratory equivalents method**

- Ventilatory Threshold
- $VE/VO_2$
- $VE/VCO_2$

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

**Delta Peak VO2**

- OMT vs CCM vs Difference

- $\Delta$ Peak VO2 (L/min)

**Delta MWHFQ**

- OMT vs CCM vs Difference

- $\Delta$ MWHFQ

**NYHA**

- % Patients with $\geq 1$ Point Reduction

- OMT vs CCM vs Difference

- NYHA

---


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

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

(After Image References)

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

(After Image References)
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>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>6MHW (meters)</td>
<td>324±91</td>
<td>322±86</td>
<td>0.08</td>
</tr>
<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>
</tr>
<tr>
<td>Exercise Time (minutes)</td>
<td>11.2±3.3</td>
<td>11.3±3.1</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Primary analysis cohort from FIX-HF-5C + FIX-HF-5 25±3 Subgroup
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

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 VO₂ Comparable to CRT

- **CCM: Normal QRS duration**
- **CRT: Prolonged QRS duration**

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>pVO₂</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**

Estimated Event Proportion (%)

Primarily driven by HF hospitalizations

\[ p = 0.036 \] comparing K-M estimates

\[ \begin{align*}
0.0 & \quad 2.5 & \quad 5.0 & \quad 7.5 & \quad 10.0 & \quad 12.5 \\
0 & \quad 25 & \quad 50 & \quad 75 & \quad 100 & \quad 125 & \quad 150 & \quad 175 \\
\end{align*} \]

**Cardiac Contractility Modulation:**

\[ \downarrow \text{in VE/VCO}_2 \text{ and Exercise Oscillatory Ventilation} \]

**Exercise Oscillatory Ventilation**

\[ \text{Pre} \quad \text{Post} \quad P<0.05 \]

**VE/VCO}_2**

\[ \text{Pre} \quad \text{Post} \quad P<0.05 \]

\[ \text{Pre} \quad \text{Post} \quad P<0.05 \]

**Fix-HF-5 + Fix-HF-5C:**

Cardiovascular Death and HF Hospitalization

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

Estimated Event Proportion (%)

Primarily driven by HF hospitalizations

\[ p = 0.036 \] comparing K-M estimates

\[ \begin{align*}
0.0 & \quad 2.5 & \quad 5.0 & \quad 7.5 & \quad 10.0 & \quad 12.5 \\
0 & \quad 25 & \quad 50 & \quad 75 & \quad 100 & \quad 125 & \quad 150 & \quad 175 \\
\end{align*} \]
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

Central Chemoreceptors Brainstem/Medulla

Peripheral Chemoreceptors Carotid Bodies/Aorta

Circulatory Delay ↑Chemosensitivity

EOV

Ventilatory Instability + Periodic Breathing

↑ Ventilatory Drive

↑ rate and depth of breathing

↓ PaCO₂

Hypopnea/Apnea

↑ PaCO₂, ↓ PaO₂

↑ Heart Failure Severity

Reduced Cardiac Output

VE/VCO₂

Stimulation of Juxtaglomerular receptors + vagal afferents

RV-pulmonary vasc dysfunction

Pulm. Congestion

↑ LV filling pressures

EOV VE/VCO₂

* 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 Borggrefe³,⁴,⁵, Hans Neuser⁶, Marc-Alexander Ohlow⁷, Susanne Röger³,⁴,⁵, Andreas Goette⁸,⁹, Bjørn A. Remppis¹⁰, Karl-Heinz Kuck¹¹, Kevin B. Najarian¹², David D. Guterman¹³, 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)


### CCM-REG₂₅-₄₅
CV and HF Hospitalizations Reduced by ~75%

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pre-Enrollment</th>
<th>Post-Enrollment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVENT</td>
<td>Pt-Yrs</td>
<td>Events</td>
<td>Event-Rate</td>
</tr>
<tr>
<td>CCM-REG₂₅-₄₅</td>
<td>HF</td>
<td>140.0</td>
<td>134</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>CV</td>
<td></td>
<td>34</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>HF+CV</td>
<td></td>
<td>168</td>
<td>1.20</td>
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<td>Events</td>
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<td>Event-Rate</td>
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<td>97</td>
<td>0.35*</td>
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<tr>
<td>CCM-REG₃₅-₄₅</td>
<td>HF</td>
<td>57.0</td>
<td>47</td>
<td>0.82</td>
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<tr>
<td></td>
<td>CV</td>
<td></td>
<td>23</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>HF+CV</td>
<td></td>
<td>70</td>
<td>1.23</td>
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<td>113.5</td>
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<td>Events</td>
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<td>18</td>
<td>0.16*</td>
</tr>
<tr>
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<td>Event-Rate</td>
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<td>9</td>
<td>0.08*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>0.24*</td>
</tr>
</tbody>
</table>

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

**A**
- Probability of Survival vs. Time Since Optimizer Implant (days)
- CCM-REG\(_{25-45}\)
- CCM-REG\(_{35-45}\)

**B**
- Probability of Survival vs. Time Since Optimizer Implant (days)
- CCM-REG\(_{25-45}\)

**C**
- Probability of Survival vs. Time Since Optimizer Implant (days)
- LVEF 35-45%

**CCM-REG\(_{25-45}\)**
Significant and Sustained Improvement in NYHA FC, QoL, and LVEF

- **△ NYHA Class**
  - Months: 0, 6, 12, 18, 24
  - Values: 2.0, 2.5, 3.0, 3.5

- **△ MLWHFQ**
  - Months: 0, 6, 12, 18, 24
  - Values: 30, 35, 40, 45, 50

- **△ LVEF (%)**
  - Months: 0, 6, 12, 18, 24
  - Values: 30, 35, 40, 45, 50

N=143 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

- GDMT
- Early ICD
- Prepare for advanced therapies
- Severe HFpEF (enlarged heart)
- HFpEF-LA (impaired LA function) + Exercise RHC
- HFpEF-LVH (Sever LVH)
- CHAD-STOP
- Assess for infiltrative CMP
- Mod-Sev HFpEF (RV dysfunction) + MIBG Scan + EOV and↑VE/VCO2
- Persistent activity intolerance?
- GDMT
- MitraClip
- GDMT
- CCM??
- GDMT
- Interatrial shunt
- HFmrEF
- Severe HFrEF
- LAMIN A/C mutation
- Mod-Sev HFrEF disproportionate FMR
- Persistent activity intolerance?
- Diuresis
- Macitentan?
- Phrenic Nerve Stimulator
- HFpEF-RVD (RV dysfunction) + Severe central sleep apnea
- GDMT
- Early ICD
- Prepare for advanced therapies
- Interatrial shunt
- CHAD-STOP
- Assess for infiltrative CMP
- HFmrEF
- Persistent activity intolerance?
- Diuresis
- Macitentan?
- Phrenic Nerve Stimulator

Thank you!

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