Welcome & Opening Remarks

Robert T. Smith, MD, FACP
Introduction of Conference Theme & Speaker

Brian Schwartz, MD, FACP, FACC, FSCAI
Kettering Heart and Vascular Medical Director
Keynote Speaker

Javed Butler, MD, PhD
Heart Failure 2018: Where Are We and Where Are We Going!
Evolution to HFpEF
Q&A With Dr. Butler

Robert T. Smith, MD, FACP
Break, Vendor Fair, and Refreshments
Understanding HFrEF/Advanced HF

Deepthi Mosali, MD, FACC
Mechanisms of HFrEF
Myocardial Remodeling in HFPEF, HFREF, and Advanced HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes. In advanced HFREF, both mechanisms get superimposed. Abbreviations as in Figures 1 and 2.
Figure 1. Activation of neuroendocrine systems in heart failure.

Decreased cardiac output in patients with heart failure with reduced EF results in the unloading of high-pressure baroreceptors (black circles) in the left ventricle, carotid sinus, and aortic arch. This unloading leads to generation of afferent signals to the central nervous system (CNS) that, in turn, lead to activation of efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles. This unloading also leads to afferent signals to the CNS that stimulate cardioregulatory centers in the brain that stimulate the release of arginine vasopressin from the posterior pituitary.
Effects of persistent SNS activation

- ↓ β-AR responsiveness
- Myocyte hypertrophy
- Myocyte necrosis and apoptosis, fibrosis
- ↓ Norepinephrine stores
- ↓ Sympathetic innervation

- ↑ Tubular reabsorption of Na+
- Activation of RAS
- ↑ Renal vascular resistance
- ↓ Response to natriuretic factors
- ↑ Renin release

- Neurogenic vasoconstriction
- Vascular hypertrophy

HEART & VASCULAR CARE
RAAS System activation

- Sympathetic efferent activity
- Diuretic therapy
- Distal tubular sodium load
- Renal perfusion pressure
- Prostaglandins
- ANP, BNP
- Vasopressin

Renin release

Angiotensinogen (liver)

Angiotensin I

Angiotensin-converting enzyme

Angiotensin II

Sodium retention (direct tubular effect)

- Thirst
- Vasoconstriction
- Aldosterone secretion

HEART & VASCULAR CARE
Natriuretic Peptides
Beta-Adrenergic signaling
Excitation-Contraction coupling
<table>
<thead>
<tr>
<th></th>
<th>ALPHA&lt;sub&gt;1&lt;/sub&gt; MEDIATED</th>
<th>BETA MEDIATED</th>
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<tbody>
<tr>
<td>Electrophysiologic effects</td>
<td>±</td>
<td>++ Conduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pacemaker</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Heart</strong> rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- AP duration</td>
</tr>
<tr>
<td>Myocardial mechanics</td>
<td>±</td>
<td>++ Contractility, lusitropy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac output</td>
</tr>
<tr>
<td>Myocardial metabolism</td>
<td>± Glycolysis</td>
<td>++ O&lt;sub&gt;2&lt;/sub&gt; uptake ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATP</td>
</tr>
<tr>
<td>Signal systems</td>
<td>GPCR, can activate PKC and</td>
<td>GPCR, activates cAMP and</td>
</tr>
<tr>
<td></td>
<td>MAPK</td>
<td>PKA</td>
</tr>
<tr>
<td>Coronary arterioles</td>
<td>++ Constriction</td>
<td>+ Direct dilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+++ Indirect dilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(metabolic)</td>
</tr>
<tr>
<td>Peripheral arterioles</td>
<td>+++ Constriction</td>
<td>+ Dilation</td>
</tr>
<tr>
<td></td>
<td>SVR ↑</td>
<td>SVR ↓</td>
</tr>
<tr>
<td></td>
<td>SBP ↑</td>
<td>SBP ↓</td>
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</table>

AP = action potential; SBP = systolic blood pressure; SVR = systemic vascular resistance.
Changes in the biology of the failing heart

<table>
<thead>
<tr>
<th>PROTEIN</th>
<th>CHANGE IN HUMAN</th>
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<tr>
<td><strong>Plasma Membrane</strong></td>
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<tr>
<td>L-type calcium channels</td>
<td>Decreased&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium/calcium exchanger</td>
<td>Increased&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium pump</td>
<td>Reexpression of fetal isoforms</td>
</tr>
<tr>
<td>Beta&lt;sub&gt;2&lt;/sub&gt;-adrenergic receptor</td>
<td>Decreased&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beta&lt;sub&gt;1&lt;/sub&gt;-adrenergic receptor</td>
<td>Increased*</td>
</tr>
<tr>
<td>Alpha&lt;sub&gt;1&lt;/sub&gt;-adrenergic receptor</td>
<td>Increased*</td>
</tr>
<tr>
<td><strong>Contractile Proteins</strong></td>
<td></td>
</tr>
<tr>
<td>Myosin heavy chain (MYHC)</td>
<td>Reversion to fetal isoform (MYHC6:MYHC7)</td>
</tr>
<tr>
<td>Myosin light chain (MYLC)</td>
<td>Reversion to fetal isoform</td>
</tr>
<tr>
<td>Actin</td>
<td>Normal*</td>
</tr>
<tr>
<td>Titin</td>
<td>Isoform switch (αN2BA:N2B), hypophosphorylated</td>
</tr>
<tr>
<td>Troponin I</td>
<td>Normal*, hypo- and hyperphosphorylated&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Troponin T</td>
<td>Isoform switch, hyperphosphorylated&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Troponin C</td>
<td>Normal*</td>
</tr>
<tr>
<td>Tropomyosin</td>
<td>Normal*</td>
</tr>
<tr>
<td><strong>Sarcoplasmic Reticulum</strong></td>
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<tr>
<td>SERCA2A</td>
<td>Decreased&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phospholamban</td>
<td>Hypophosphorylated</td>
</tr>
<tr>
<td>Ryanodine receptor</td>
<td>Hyperphosphorylated&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calsequestrin</td>
<td>Normal*</td>
</tr>
<tr>
<td>Calreticulin</td>
<td>Normal*</td>
</tr>
<tr>
<td>Mechanical Disadvantages Created by Left Ventricular Remodeling</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
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<tr>
<td>Increased wall stress (afterload)</td>
<td></td>
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<tr>
<td>Afterload mismatch</td>
<td></td>
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<tr>
<td>Episodic subendocardial hypoperfusion</td>
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<tr>
<td>Increased oxygen utilization</td>
<td></td>
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<tr>
<td>Functional mitral regurgitation</td>
<td></td>
</tr>
<tr>
<td>Worsening hemodynamic overloading</td>
<td></td>
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<tr>
<td>A stretch-induced activation of maladaptive signal transduction pathways</td>
<td></td>
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<tr>
<td>Stretch-induced activation of maladaptive gene programs</td>
<td></td>
</tr>
<tr>
<td>TABLE e22-2 Mechanical Disadvantages Created by Left Ventricular Remodeling</td>
<td></td>
</tr>
</tbody>
</table>

- Increased wall stress (afterload)
- Afterload mismatch
- Episodic subendocardial hypoperfusion
- Increased oxygen utilization
- Functional mitral regurgitation
- Worsening hemodynamic overloading
- A stretch-induced activation of maladaptive signal transduction pathways
- Stretch-induced activation of maladaptive gene programs

![Diagram A: Normal LV: Prolate ellipse](image1)

![Diagram B: Dilated LV: Spherical](image2)
Box 1

Myocardial changes in LV remodelling

- Alterations in myocyte biology
  - Hypertrophy
  - Myosin heavy chain (fetal) gene expression
  - Myocytolysis
  - Changes in cytoskeletal proteins
  - β-Adrenergic desensitization
  - Excitation–contraction coupling

- Myocardial changes
  - Myocyte loss
    - Necrosis
    - Apoptosis
    - Autophagy
  - Alterations in the extracellular matrix
    - Matrix degradation
    - Myocardial fibrosis

- Alterations in LV chamber geometry
  - Increased size
  - Increased sphericity
  - Wall thinning
  - Mitral valve incompetence
  - LV, left ventricular.
Key points

Heart failure with reduced ejection fraction (HFrEF) is initiated when an ‘index event’ causes the pumping capacity of the heart to be impaired.

Reduced pumping capacity of the heart results in compensatory activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, which together are referred to as ‘neurohormonal activation’.

Neurohormonal activation results in a series of coordinated responses that collectively work to restore cardiovascular homeostasis in the short-term.

Sustained neurohormonal activation drives the progression of HFrEF through the deleterious effects exerted on the circulation and the myocardium.

Antagonism of neurohormonal systems forms the basis of modern therapy for HFrEF.
Is that it?

- Lot of patients with so called “stable” chronic ds are indeed not stable with most patients exhibiting elevated cardiac biomarkers such as troponin reflective of continued cardiomyocyte necrosis or loss. This is reflective of a underlying dynamic process contributing to ds progression
Mechanisms that drive LV Dysfunction: 

**Intrinsic**

1. **Cardiac Apoptosis** – cardiomyocyte loss is the hallmark of HFrEF. Limited capacity for self renewal so gradual loss of functional units through cell death leads to disease progression.

2. **Mitochondrial abnormalities**: abnormalities of ATP synthesis and excess production of ROS.

3. **Impaired intracellular calcium cycling** (calcium signalling plays an important role in modulating systolic and diastolic function and in regulating excitation-contraction coupling. Abnormalities of intracellular calcium handling such as reduced SERCA activity, impaired phosphorylation of phospholamban and ryanodine channel leading to calcium leaks. This can cause calcium overload, arrhythmias, cardiomyocyte dysfunction and death.

4. **Wall stress** (Laplace’s law, increased MVO2)

5. **Fibrosis and cardiomyocyte hypertrophy** (reactive interstitial fibrosis, reduced capillary density, increased oxygen diffusion all causing hypoxia and increasing LV stiffness and contributing to LV dysfunction.)
Physiology

• Hemodynamics and PV loops
Hemodynamic Derangements in HFrEF: A Progression

- Normal
- Stage B HF (ASLVD) NYHA II-III
- Stage C HF NYHA IV

- SV: Stroke Volume
- SBP: Systolic Blood Pressure
- LVEDP: Left Ventricular End-Diastolic Pressure
- EDV: End-Diastolic Volume

LV Pressure vs. LV Volume
The Failing Heart is More Afterload-Sensitive than the Normal LV

Vasoconstriction
Vasodilation

LV Pressure
LV Volume
Normal
Systolic HF
“Flat” Starling Curve: ↓ LV preload-sensitivity in HFrEF

LV Stroke Work

Normal

Systolic HF

Diuretic

PCWP or LVDP

HEART & VASCULAR CARE
"Flat" Starling Curve: ↓ LV preload-sensitivity in HFrEF

- Normal
- Advanced HFrEF

LV Stroke Work vs. PCWP or LVDP

Diuretic

Heart & Vascular Care
Enhanced Diastolic Ventricular Interaction in Advanced HFrEF
PCWP 32 mmHg

RAP 30 mmHg

LV transmural FP = PCW – RA = 2 mmHg

Diuretic

PCWP 27 mmHg

RAP 18 mmHg

LV transmural FP = PCW – RA = 9 mmHg
Therapeutics

• Targeting the Neuroharmononal pathways
• Treating at the “periphery”
• Despite blockade of the “maladaptive” processes there is still progression of disease
β1-adrenergic signaling

Progressive Desensitization:

Yin

Yang

Ideal anti-adrenergic Rx

Myopathic pathways, PKA independent

Fetal gene Program induction

Apoptosis

Cardiac function, PKA dependent

Systolic function

Diastolic function

Other (↓ P-PLN, altered metabolism ↑ P-RyR2, etc)

Arrhythmias

↑ Heart rate

HEART & VASCULAR CARE
Mechanism of ARNI
Figure 1: Mechanism of action for sacubitril/valsartan. Reprinted from Langenickel TH, Dole WP. Angiotensin receptor–nephrilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. Drug Discov Today Ther Strateg 2013; 9:e131–e139. ANG, angiotensin; AT₁, angiotensin-II type 1; cGMP, cyclic guanosine monophosphate; GTP, guanosine-5'-triphosphate; NP, natriuretic peptide (e.g., atrial natriuretic peptide, BNP); NPR-A, NP receptor-A; RAAS, renin–angiotensin–aldosterone system. *In vitro evidence.
Ivabradine: Postulated Mechanisms of Benefit for HR Reduction
- Decreased myocyte ischemia
- Increased energy for myocyte maintenance and repair
- Decreased LVEDP, cardiac volumes and remodelling
- Increased LV relaxation
- Increased endothelial cell proliferation and eNOS
- Increased collateral function

Heart rate control

Sinus node cell

Acetylcholine
Muscarinic receptor

Norepinephrine
Beta receptor

cAMP
PKA

\( I_{ca,T} \)
\( I_{ca,L} \)
\( I_K \)

f-channel

f-current is cAMP and "use"-dependent
**FIGURE 1** Biomarkers indications for Use

Colors correspond to COR in Table 1.

*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin.

ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.
Figure 5. Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.
Progression to Stage D or Advanced HF
Advanced HF is the presence of progressive and/or persistent severe symptoms of heart failure despite optimized medical, surgical and device therapy.

Fig. 1. Classification schemes for heart failure severity. Overlapping classification systems provide complementary descriptive and prognostic information for patients with advanced heart disease. NYHA classifies dynamic functional limitation, the American Heart Association/American College of Cardiology-Stage of Heart Failure highlight antecedent risk factors and disease progression, while the INTERMACS patient profiles integrate symptom burden and ongoing measures use to treat evolving shock.
HFrEF now becomes a systemic ds

- Passive liver congestion, ascites
- Bone marrow dysfunction and anemia
- Endothelial dysfunction
- Sleep disordered breathing
- Renal dysfunction
- Skeletal muscle abnormalities
- Persistent venous congestion causes inflammation with elevated biomarkers and systemic inflammation
A
Cardiovascular Disease

B
Altered Cardiac Structure/Function

C
Symptoms of HF

D
Advanced HF

Death

Overt HF
OMT

Compensation

NHFD
SCD
NHFD

Subset CRT

Stage D

Tiny Subset

Transplant LVAD

Mode of Death

Time

NHFD
SCD
HF

Poor
High

Functional Status
Hospitalization Risk
Resource Utilization

Good
Low

HEART & VASCULAR CARE
A depiction of the clinical course of heart failure with associated types and intensities of available therapies.


Transition to Advanced Heart Failure:
- Oral therapies failing
- A time for many major decisions
- Consider MCS and/or transplantation, if eligible
- Consider inversion of care plan to one dominated by a palliative approach, which may involve formal hospice
ACC/AHA/HFSA focused updated guidelines for HF.
Impact of recurrent heart failure hospitalization on mortality. Median survival (50% mortality) with 95% confidence limits in patients with heart failure after each heart failure hospitalization. (From Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007;154(2):262.)
Kaplan-Meier cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.
Who Has Advanced Heart Failure? Definition and Epidemiology

![Diagram showing causes of death in HF patients in the community and causes of all hospitalizations after HF diagnosis in the community.](image-url)

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**Cause of Death in HF Patients in the Community**

- Non-CV
- CAD
- HF + CVA

**Cause of All Hospitalizations after HF Diagnosis in the Community**

- Non-CV
- Other CV
- HF
• END OF PRESENTATION
### Genetic
- **HCM**
- **ARVC/D**
- **LVNC**
  - Glycogen storage
  - Conduction defects
  - Mitochondrial myopathies
  - **PRKAG2**
  - **Danon**

### Mixed
- **DCM**
- **Restrictive**
  - (non-hypertrophied and non-dilated)

### Acquired
- **Inflammatory** (myocarditis)
- **Stress-provoked** (takotsubo)
- **Peripartum**
- **Tachycardia-induced**
- Infants of insulin-dependent diabetic mothers
<table>
<thead>
<tr>
<th>Gene</th>
<th>Percentage of Familial DCM; Mode of Inheritance</th>
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<tbody>
<tr>
<td>Titin (TIN)</td>
<td>20–25% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Lamin A/C (LMNA)</td>
<td>~5% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Myosin heavy chain 7 (MYH7)</td>
<td>~4% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Troponin T (TNNT2)</td>
<td>~2% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Myosin-binding protein C (MYBPC3)</td>
<td>~2% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Myopalladin (MYPN)</td>
<td>~2% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Sodium channel α unit (SCN5A)</td>
<td>~2% of familial DCM; autosomal dominant mode</td>
</tr>
<tr>
<td>Phospholamban (PLN)</td>
<td>~1% of familial DCM; autosomal dominant mode</td>
</tr>
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**Neuromuscular disorders**

- Duchenne muscular dystrophy (DMD): X-linked mode; creatine kinase elevation
- Becker muscular dystrophy (BMD): X-linked mode; creatine kinase elevation
<table>
<thead>
<tr>
<th>Infection (myocarditis)</th>
<th></th>
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<tbody>
<tr>
<td>Viral (including parvovirus B19, HPV6, HIV)</td>
<td>..</td>
</tr>
<tr>
<td>Bacterial (including Lyme disease)</td>
<td>Atrioventricular block in Lyme disease</td>
</tr>
<tr>
<td>Fungal</td>
<td>..</td>
</tr>
<tr>
<td>Parasitic</td>
<td>..</td>
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<tr>
<td>Rickettsial</td>
<td>..</td>
</tr>
<tr>
<td>Protozoal</td>
<td>..</td>
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<tr>
<td>Autoimmune diseases</td>
<td></td>
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<tr>
<td>Organ specific</td>
<td></td>
</tr>
<tr>
<td>Giant cell myocarditis</td>
<td>Multinucleated giant cells; frequent AV block and ventricular arrhythmias</td>
</tr>
<tr>
<td>Non-organ specific</td>
<td></td>
</tr>
<tr>
<td>Non-infectious myocarditis</td>
<td>..</td>
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<tr>
<td>Peripartum</td>
<td></td>
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<td>---</td>
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</tr>
<tr>
<td></td>
<td>Risk factors include multiparity, African descent, familial DCM, autoimmunity</td>
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</table>

### Toxicity and overload

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<thead>
<tr>
<th>Substance</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ethanol</td>
<td>Risk proportionate to extent and duration of alcohol intake</td>
</tr>
<tr>
<td>Cocaine, amphetamines, ecstasy</td>
<td>Chronic users</td>
</tr>
<tr>
<td>Other toxins</td>
<td>Arsenic, cobalt, anabolic or androgenic steroids</td>
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<tr>
<td>Iron overload</td>
<td>Transfusions, haemachromatosis</td>
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### Nutritional deficiency

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Selenium deficiency</td>
<td>Rare, high frequency in some parts of China (Keshan disease)</td>
</tr>
<tr>
<td>Thiamine deficiency (Beriberi)</td>
<td>High output heart failure, contributing factors include malnutrition and alcohol abuse</td>
</tr>
<tr>
<td>Zinc and copper deficiency</td>
<td>Possible contributors to DCM</td>
</tr>
</tbody>
</table>

### Inborn errors of metabolism

<table>
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<tr>
<th>Process</th>
<th>Description</th>
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<tbody>
<tr>
<td>Fatty acid oxidation</td>
<td>Many inborn errors of metabolism cause a mixed phenotype with varying degrees of hypertrophy and reduced systolic function</td>
</tr>
<tr>
<td>Category</td>
<td>Examples</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Antineoplastic drugs</td>
<td>Anthracyclines, antimetabolites, alkylating agents, paclitaxel, hypomethylating agents, tyrosine kinase inhibitors, immunomodulating agents</td>
</tr>
<tr>
<td>Psychiatric drugs</td>
<td>Clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, tricyclic antidepressants, phenothiazines</td>
</tr>
<tr>
<td>Others</td>
<td>Chloroquine, all-trans retinoic acid, antiretroviral agents</td>
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**Endocrinology**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
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<tbody>
<tr>
<td>Hypothyroidism</td>
<td>..</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>..</td>
</tr>
<tr>
<td>Cushing's and Addison disease</td>
<td>..</td>
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<tr>
<td>Pheochromocytoma</td>
<td>..</td>
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<tr>
<td>Takotsubo cardiomyopathy</td>
<td>Stress-related</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>..</td>
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<tr>
<td>Diabetes mellitus</td>
<td>..</td>
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Figure 1. Two-Minute Assessment of Hemodynamic Profile

Diagram indicating 2 x 2 table of hemodynamic profiles for patients presenting with heart failure. Most patients can be classified in a 2-minute bedside assessment according to the signs and symptoms shown although in practice some patients may be on the border between the warm-and-wet and cold-and-wet profiles. This classification helps guide initial therapy and prognosis for patients presenting with advanced heart failure. Although most patients presenting with hypoperfusion also have elevated filling pressures (cold and wet profile), many patients present with elevated filling pressures without major reduction in perfusion (warm and wet profile). Patients presenting with symptoms of heart failure at rest or minimal exertion without clinical evidence of elevated filling pressures or hypoperfusion (warm and dry profile) should be carefully evaluated to determine whether their symptoms result from heart failure. Reprinted with permission from Dr Stevenson.
Virtual Heart Failure Clinic

“Smart” HF management

Sateesh Kesari MD FACC
Disclosures

• I have no current or past relationships with commercial entities

• Speaking fees for current program:
  • I have received no speaker’s fee for this learning activity

• Acknowledgements: Slides courtesy of
  • Abbott/ST Jude
  • Medtronic
  • Boston Scientific
Scope of the presentation

• Financial and clinical burden of heart failure
• Tele monitoring
• Device monitoring
• Hemodynamic monitoring
Scope of the presentation

• Financial and clinical burden of heart failure

• Tele monitoring

• Device monitoring

• Hemodynamic monitoring
Heart Failure is a Growing Economic Burden

UNITED STATES

HOSPITALIZATIONS AND READMISSESIONS

| > 1,100,000 hospitalizations for HF \(^1\) | > 3,000,000 hospitalizations include HF as a contributor. \(^2\) |
| ~5 days average length of hospital stay \(^3\) | ~25% all-cause readmission within 30 days; ~50% within 6 months. \(^4,5\) |

Despite advances in medical therapies to treat heart failure, the hospitalization rate has not changed significantly from 2000. As a result, heart failure continues to be a MAJOR DRIVER OF OVERALL HEALTH CARE COSTS.

*Study projections assumes HF prevalence remains constant and continuation of current hospitalization practices
Heart Failure is a Growing Global Clinical Burden

- UNITED STATES

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th>INCIDENCE</th>
<th>MORBIDITY AND MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2% Prevalence&lt;sup&gt;1&lt;/sup&gt;</td>
<td>915,000 people ≥ 45 years of age are newly diagnosed each year with HF.&lt;sup&gt;1&lt;/sup&gt;</td>
<td>For AHA/ACC stage C/D patients diagnosed with HF:</td>
</tr>
<tr>
<td>5.7m HF patients&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>50% Readmitted within 6 months.&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Projected to increase to &gt;8M people ≥ 18 years of age with HF by 2030&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>50% Will die within 5 years.&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**HIGH INCIDENCE, HIGH PREVALENCE, AND POOR PROGNOSIS**
despite advances in the treatment of heart failure over the past few decades.

Long-term Mortality Risk Increases with Multiple Hospitalizations

Mortality

Survival

Goal of Heart Failure Management:
SLOW DISEASE PROGRESSION BY PREVENTING DECOMPENSATION

• EACH EVENT ACCELERATES DOWNWARD SPIRAL OF MYOCARDIAL FUNCTION

With each subsequent HF-related admission, the patient leaves the hospital with a further decrease in cardiac function.

THE GOAL:
Maintain fluid volume to avoid acute decompensation and hospitalization

HF HOSPITALIZATION is a valid endpoint for measuring decompensation

Scope of the presentation

• Financial and clinical burden of heart failure

• Tele monitoring

• Device monitoring

• Hemodynamic monitoring
Monitored days of a HF patient.
Parameters

- Daily Impedence
- Heart rate variability
- Patient Activity
- Biventricular pacing < 90%

- Ventricular pacing (ICD)
- Night time HR
- Atrial fibrillation/AT/AFL
- Ventricular tachycardia/ICD shocks
## Remote monitoring HF trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>N</th>
<th>PARAMETER MONITORED</th>
<th>IMPACT ON HF HOSPITALIZATION</th>
<th>JOURNAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TELE-HF¹</td>
<td>1,653</td>
<td>Signs/symptoms, daily weights</td>
<td>None</td>
<td>The New England Journal of Medicine, 2010</td>
</tr>
<tr>
<td>TIM-HF²</td>
<td>710</td>
<td>Signs/symptoms, daily weights</td>
<td>None</td>
<td>Circulation, 2011</td>
</tr>
<tr>
<td>TEN-HMS³</td>
<td>426</td>
<td>Signs/symptoms, daily weights, BP, nurse telephone support</td>
<td>None</td>
<td>Journal of the American College of Cardiology, 2005</td>
</tr>
<tr>
<td>BEAT-HF⁴</td>
<td>1,437</td>
<td>Signs/symptoms, daily weights, nurse communications</td>
<td>None</td>
<td>American Heart Association, 2016</td>
</tr>
<tr>
<td>INH⁵</td>
<td>715</td>
<td>Signs/symptoms, telemonitoring, nurse coordinated DM</td>
<td>None</td>
<td>Circulation Heart Failure, 2012</td>
</tr>
<tr>
<td>DOT-HF⁶</td>
<td>335</td>
<td>Intrathoracic impedance with patient alert</td>
<td>Increased</td>
<td>Circulation, 2011</td>
</tr>
<tr>
<td>Optilink⁷</td>
<td>1,002</td>
<td>Intrathoracic impedance</td>
<td>None</td>
<td>European Journal of Heart Failure, 2011</td>
</tr>
<tr>
<td>REM-HF⁸</td>
<td>1,650</td>
<td>Remote monitoring via ICD, CRT-D or CRT-P</td>
<td>None</td>
<td>European Society of Cardiology, 2017</td>
</tr>
<tr>
<td>MORE CARE⁹</td>
<td>865</td>
<td>Remote monitoring of advanced diagnostics via CRT-D</td>
<td>None</td>
<td>European Journal of Heart Failure, 2016</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8,793</strong></td>
<td></td>
<td></td>
<td>MULTIPLE TRIALS, &gt; 8,500 PATIENTS: No reduction in HF hospitalization</td>
</tr>
</tbody>
</table>

Impedence

OptiVol®: Concept
- Heart Failure Exacerbation
- Fluid Retention
- Decrease in Impedance (Ω)

Tissue Resistivity
- Fluid: 70 Ω·cm
- Blood: 160 Ω·cm
- Myocardium: 450 Ω·cm
- Lung: 2,200 Ω·cm
- Bone: 4,800 Ω·cm
- Fat: 2,500 Ω·cm
- Air: ∞

Impedance Prior to CHF Admission
- Days Before Hospitalization vs. Impedance Reduction

Overview of Detection Algorithm
- Fluid Index (Bars) vs. Days
- Impedance (Ω) vs. Days
Impedence

Overview of Detection Algorithm

Fluid Index (Ω days)

Impedance (Ω)

Days

Impedence cases

Example # 1

- Drop in Impedence
- Preceded by AT/AF
- High Ventricular rates
- Loss of CRT pacing

Example # 2

- Drop in impedance
- Followed by VT storm
Device monitoring with multiple parameters

• Heart Logic
  • Multisense trial
  • Manage HF trial

• Beacon HF system
  • Partners HF trial
Multisense trial for HeartLogic

(A) Development Set. (B) Test Set. Each point corresponds to an alert threshold. The shaded regions represent the 95% confidence interval (CI) of the mean. The red lines indicate the pre-specified performance goals.
HeartLogic index trend in pts with and without HFE
Dec 31, 2013

HF Hospitalization

Admitted for exacerbated CHF and treated with IV Lasix 40 mg for three days.
Partners HF study showed monthly review of HF diagnostic data could have identified patients at higher risk of HF hospitalizations within the subsequent month. OptiVol/HFMR identified patients were 5.5 times as likely to be hospitalized within 30 days.

**PARTNERS-HF: COMBINED DIAGNOSTICS**

**+ Diagnostic**

TWO diagnostic criteria met:

- Fluid Index ≥ 100
- Fluid Index ≥ 60
- Avg. Activity < 1 hr over 1 week
- Avg. night HR > 85 bpm for 7 consecutive days
- HRV < 60 ms for 7 consecutive days
- % V pacing < 90% for 5 of 7 days
- One or more shocks
- AF > 6 hrs on at least one day in pts without persistent AF
- AF > 24 hrs & VR-AF > 90 bpm

N = 694 patients
Monthly Evaluations = 5693
HF Events = 78

---

**Triage**

Combining Device Diagnostics & External Biometrics

**Broad Clinical Inputs**
- Device Diagnostics
- Biometrics
- Symptoms
- IP/ER Event Status

**Robust Risk Analysis**
- OptiVol + Parameters
- Symptom Acuity
- Care Plan Adherence

**Expert CHFN* Assessment**
- Clinical Intervention
- Ongoing Education
- CHFN Analysis

**Actionable Reporting**
- Multiple High Risk Markers Identified, Follow up 24 hours
- High Risk Markers Identified, Follow up 72 hours
- Limited High Risk Markers Identified, Follow Up 1 week
- Low Risk, Routine Clinical Follow Up

---

*Certified Heart Failure Nurse, certified by the American Association of Heart Failure Nurses*
Patients with a high risk score were **10 times** more likely to have a heart failure event in the next 30 days than those with a low risk score. 

---

Scope of the presentation

• Burden of heart failure with financial and clinical impact

• Tele monitoring

• Device monitoring

• Hemodynamic monitoring
Current Parameters for Managing HF are Reactive and Inexact

Monitoring for Increased Filling Pressures is Proactive and Actionable, and Predictive of Acute Decompensation

Monitoring Pulmonary Artery Pressures, Proactive and Actionable

Hemodynamically Stable

-30

Presymptomatic Congestion

-20

Decompensation

-10

Time Preceding Hospitalization (Days)

Clinical Congestion

HOSPITALIZATION

Filling Pressure INCREASE

Hemodynamic Congestion

Autonomic Adaptation

Transthoracic Impedance CHANGE

GAIN IN TIME

Weight Change

Symptoms

Symptoms

Congestion

Hemodynamic Congestion

HOSPITALIZATION

Presymptomatic Congestion

-20

Hemodynamically Stable

-30

Decompensation

0

Monitoring Pulmonary Artery Pressures, Proactive and Actionable

GAIN IN TIME

Hemodynamic Congestion

Filling Pressure INCREASE

Autonomic Adaptation

Transthoracic Impedance CHANGE

HOSPITALIZATION

Clinical Congestion

Weight Change

Symptoms

Physical exam

Tele monitoring

Hemodynamically Stable

Presymptomatic Congestion

Decompensation

Time Preceding Hospitalization (Days)

Monitoring Pulmonary Artery Pressures, Proactive and Actionable


Hemodynamically Stable: -30
Presymptomatic Congestion: -20
Hemodynamic Congestion: -10
Decompensation: 0

Device monitoring
Physical exam
Tele monitoring

GAIN IN TIME

Clinical Congestion
HOSPITALIZATION

Weight Change
Symptoms
Autonomic Adaptation
Transthoracic Impedance CHANGE
Filling Pressure INCREASE

Hemodynamic Stable

Item approved for global use. 92
Monitoring Pulmonary Artery Pressures, Proactive and Actionable


GAIN IN TIME

Hemodynamic Congestion

- Filling Pressure INCREASE
- Autonomic Adaptation

Transthoracic Impedance CHANGE

Hemodynamic monitoring

- Hemodynamically Stable
- Presymptomatic Congestion

Physical exam
- Tele monitoring

Device monitoring

- Device monitoring

Weight Change
- Symptoms

HOSPITALIZATION

Time Preceding Hospitalization (Days)

- 30
- 20
- 10
0

Clinical Congestion

- Physical exam

- Symptom Congestion

- Hemodynamic Congestion

- Hemodynamically Stable

Presymptomatic Congestion

- Autonomic Adaptation

- Transthoracic Impedance CHANGE
Intracardiac hemodynamics


Chronicle device
CardioMEMS™ HF System for the Management of HF

- Delivers insight into the early onset of worsening HF to more proactively manage HF patients and improve outcomes

Microelectrical Mechanical System (MEMS)

No lead or battery, no need for replacement

\[ f = \frac{1}{2\pi \sqrt{L \cdot C(P)}} \]

- \( f_{\text{P=0}} \)
- \( f_{\text{P=max}} \)

Nanometer deflections

Pressure Waveform

Sensor Cross section
The CardioMEMS™ HF System Implant Procedure

- PA PRESSURE SENSOR IS INSERTED DURING A RIGHT HEART CATHETERIZATION PROCEDURE VIA FEMORAL VEIN APPROACH.
Summary of CHAMPION Randomized Clinical Trial:

550 PREVIOUSLY HOSPITALIZED NYHA CLASS III PATIENTS

MANAGING PRESSURES TO TARGET GOAL RANGES:

• PA pressure systolic 15–35 mmHg
• PA pressure diastolic 8–20 mmHg
• PA pressure mean 10–25 mmHg

Using diuretics and vasodilators, in addition to guideline-directed medical therapies

Primary Efficacy Endpoint Met with Significantly Reduced Heart Failure Hospitalization

• **PART 1: RANDOMIZED ACCESS**

![Cumulative Hazard Rate Graph](image)

### 33% RELATIVE RISK REDUCTION IN HF HOSPITALIZATIONS:
**TREATMENT GROUP VS. CONTROL GROUP**

<table>
<thead>
<tr>
<th>Days From Implant</th>
<th>CONTROL</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>280</td>
<td>270</td>
</tr>
<tr>
<td>90</td>
<td>267</td>
<td>262</td>
</tr>
<tr>
<td>180</td>
<td>254</td>
<td>246</td>
</tr>
<tr>
<td>270</td>
<td>241</td>
<td>235</td>
</tr>
<tr>
<td>360</td>
<td>210</td>
<td>197</td>
</tr>
<tr>
<td>450</td>
<td>175</td>
<td>164</td>
</tr>
<tr>
<td>540</td>
<td>131</td>
<td>125</td>
</tr>
<tr>
<td>630</td>
<td>101</td>
<td>105</td>
</tr>
<tr>
<td>720</td>
<td>62</td>
<td>75</td>
</tr>
<tr>
<td>810</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>900</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>990</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>1080</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- **No. at Risk**
  - CONTROL: 280, 267, 254, 241, 210, 175, 131, 101, 62, 27, 12, 5, 0
  - TREATMENT: 270, 262, 246, 235, 197, 164, 125, 105, 75, 38, 8, 3, 0

- **p < 0.0001**

Both Primary Safety Endpoints Met

- 1167 patient-years of follow-up
- 8 device/system-related complications (DSRC)
- 0.007 DSRC per patient-year
- All DSRC occurred within 30 days of implant
- No sensor failures
All Secondary Endpoints Met

### PART 1: RANDOMIZED ACCESS

<table>
<thead>
<tr>
<th>SECONDARY ENDPOINTS</th>
<th>TREATMENT (N = 270)</th>
<th>CONTROL (N = 280)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in PA mean pressure (mean AUC [mmHg x days])</td>
<td>-156</td>
<td>33</td>
<td>0.008</td>
</tr>
<tr>
<td>Number and proportion of patients hospitalized for HF (%)</td>
<td>55 (20%)</td>
<td>80 (29%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Days alive and out of hospital for HF (mean ± SD)</td>
<td>174.4 ± 31.1</td>
<td>172.1 ± 37.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Quality of life (Minnesota Living with Heart Failure Questionnaire, mean ± SD)</td>
<td>45 ± 26</td>
<td>51 ± 25</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Total of 8 DSRCs including 2 events in Consented not implanted patients (n = 25)

Real-world Use of the CardioMEMS™ HF System:

ASSOCIATED HF HOSPITALIZATION COSTS

Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database
Monitoring Pulmonary Artery Pressures, Proactive and Actionable


Hemodynamically Stable

-30

Presymptomatic Congestion

-20

Hemodynamic Congestion

-10

Filling Pressure INCREASE

Autonomic Adaptation

Transthoracic Impedance CHANGE

Physical exam

Tele monitoring

GAIN IN TIME

Clinical Congestion

HOSPITALIZATION

Time Preceding Hospitalization (Days)

-30

-20

-10

0

Symptoms

Weight Change

Prehospitalization

Decompensation

Weight Change

Symptoms
Monitoring Pulmonary Artery Pressures, Proactive and Actionable

Hemodynamically Stable

Presymptomatic Congestion

Decompensation

Time Preceding Hospitalization (Days)

-30

-20

-10

0

Filling Pressure INCREASE

Autonomic Adaptation

Transthoracic Impedance CHANGE

Clinical Congestion

Weight Change

Symptoms

HOSPITALIZATION

GAIN IN TIME

Hemodynamic Congestion

Device monitoring

Physical exam

Tele monitoring

Monitoring Pulmonary Artery Pressures, Proactive and Actionable


GAIN IN TIME

Hemodynamic Congestion

Filling Pressure INCREASE

Autonomic Adaptation

Transthoracic Impedance CHANGE

Hemodynamic monitoring

Device monitoring

Physical exam

Tele monitoring

HOSPITALIZATION

Clinical Congestion

Weight Change

Symptoms

Time Preceding Hospitalization (Days)

-30  -20  -10  0

Hemodynamically Stable

Presymptomatic Congestion

Decompensation

Information Overload

MA/Nurse

APP/Physician
Workflow

Patient transmits daily

MA/Nurse reviews twice weekly initially and then prn for alerts

HF NP Reviews and adjusts treatment plan

HF Physician

EP Nurse reviews and adjusts treatment

EP Physician
Virtual HF clinic-Key elements

- Identify key team members
- Patient selection
- Policies and procedures for monitoring
- Establish workflows/Orders
- Staffing
  - Buy in from other providers
  - Network support for resources and staffing
- Alerts
  - Keep medication changes on website
- Education
  - Providers
  - Patients
  - Staff
The CHAMPION Trial
Subgroup Analyses

PROSPECTIVE ANALYSES:
• Effects of PAP pressure monitoring on:
  - HFpEF subgroup
  - HFrEF subgroup, HFrEF subgroup already on GDMT

RETROSPECTIVE SUBGROUP ANALYSES:
• Therapy guided by PAP alone vs. signs and symptoms
• Medicare-eligible populations
• PAP-guided medical management
• HF patients with common comorbidities
Prospective Subgroup Analysis:

HFpEF PATIENTS MANAGED WITH THE CardioMEMS™ HF SYSTEM SHOW SIGNIFICANT REDUCTION IN HF Hospitalization

- 50% reduction in HF Hospitalization

**Graph:**
- Cumulative Heart Failure Hospitalizations vs. Days After Implant
- Control Group, HFpEF vs. Treatment Group, HFpEF

**Statistics:**
- Avg. 18 months follow-up
- 50% RRR, p < 0.0001

**References:**
Prospective Subgroup Analysis:
HFrEF PATIENTS SHOWS SIGNIFICANT REDUCTION IN HF Hospitalization AND STRONG TREND TOWARDS IMPROVED SURVIVAL*

Retrospective Subgroup Analysis:
HFrEF PATIENTS SHOW SYNERGY BETWEEN OPTIMAL GDMT AND HEMODYNAMIC CARE

Partial GDMT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF Hospitalization/Patient-yr</td>
<td>0.75</td>
</tr>
<tr>
<td>Deaths/Patient-yr</td>
<td>0.18</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>0.05</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.01</td>
</tr>
</tbody>
</table>

p = 0.0002

“Optimal” GDMT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF Hospitalization/Patient-yr</td>
<td>0.75</td>
</tr>
<tr>
<td>Deaths/Patient-yr</td>
<td>0.18</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>0.02</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.00</td>
</tr>
</tbody>
</table>

p = 0.0002

*The CardioMEMS™ HF System is not labeled for a reduction in mortality
Managing medical therapy based on PA pressures, along with follow-up lab and patient assessment led to **SIGNIFICANTLY BETTER OUTCOMES THAN MANAGING BASED ON CLINICAL SIGNS AND SYMPTOMS**

Subgroup Analysis:

MEDICARE-ELIGIBLE POPULATION SHOWS SIGNIFICANT REDUCTION IN 30-DAY READMISSIONS

STATISTICALLY SIGNIFICANT REDUCTIONS in 30-day readmission and HF Hospitalization in Medicare-eligible patients 65 years or older (n = 245), when PA pressures are monitored using the CardioMEMS™ HF System.

Subgroup Analysis:

HFrEF PATIENTS WITH CRT-D FOLLOWING GDMT

PA Pressure Guided HF Management Reduces All-Cause Mortality in CRT-D Population Therapy

64% reduction (p = 0.028)

Medication changes based on PA pressure information were **MORE EFFECTIVE IN REDUCING HF HOSPITALIZATIONS** than using signs and symptoms alone.
Medication Increases and Decreases in Response to PAP

![Bar chart showing medication dose increases/decreases from baseline to 6 months.](image)

- **ALL MEDICATION CHANGES**
- **DIURETIC (LOOP AND THIAZIDE)**
- **VASODILATOR (NITRATE AND HYDRALAZINE)**
- **ACE/ARB**
- **BETA BLOCKER**
- **ALDOSTERONE ANTAGONIST**

- **PA Pressure Guided HF Management (Treatment Group)**
- **Standard of Care HF Management Only (Control Group)**

*p < 0.05 PA Pressure Guided HF Management vs. Standard of Care HF Management

No Change represents where a medication was changed (i.e., dose frequency, route, etc.) which resulted in no net dose equivalent change

# The CHAMPION Trial Subgroup Analyses:

## REDUCTION OF HF HOSPITALIZATION IN PATIENT GROUPS WITH COMMON COMORBIDITIES

<table>
<thead>
<tr>
<th>Sub-Group or Comorbidity</th>
<th>n (control)</th>
<th>n (treatment)</th>
<th>Follow-up Period (months)</th>
<th>Reduction of HF Hospitalization Rate in Treatment Group vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare population¹</td>
<td>125</td>
<td>120</td>
<td>18</td>
<td>49%, p &lt; 0.0001</td>
</tr>
<tr>
<td>HFrEF²</td>
<td>56</td>
<td>59</td>
<td>18</td>
<td>50%, p &lt; 0.0001</td>
</tr>
<tr>
<td>HFrEF following GDMT³</td>
<td>174</td>
<td>163</td>
<td>17</td>
<td>43%, p &lt; 0.0001</td>
</tr>
<tr>
<td>CRT-D or ICD following GDMT⁴</td>
<td>146</td>
<td>129</td>
<td>18</td>
<td>43%, p &lt; 0.0001</td>
</tr>
<tr>
<td>History of myocardial infarction⁵</td>
<td>137</td>
<td>134</td>
<td>15</td>
<td>46%, p &lt; 0.001</td>
</tr>
<tr>
<td>COPD⁶,⁷</td>
<td>96</td>
<td>91</td>
<td>15</td>
<td>41%, p = 0.0009</td>
</tr>
<tr>
<td>Pulmonary hypertension⁶</td>
<td>163</td>
<td>151</td>
<td>15</td>
<td>36%, p = 0.0002</td>
</tr>
<tr>
<td>AF⁹</td>
<td>135</td>
<td>120</td>
<td>15</td>
<td>41%, p &lt; 0.0001</td>
</tr>
<tr>
<td>Chronic kidney disease¹⁰</td>
<td>150</td>
<td>147</td>
<td>15</td>
<td>42%, p = 0.0001</td>
</tr>
</tbody>
</table>

Patients with common HF comorbidities and patients in important subgroups **HAVE CONSISTENT REDUCTION IN HF HOSPITALIZATIONS** with PA pressure-guided therapy.

In the post-approval study, there were 56 HF Hospitalizations (0.20 events/pt-6m) in 43 pts.
Medication Changes Significantly Reduced in First 90 Days vs. Second 90 Days in the PAS

Medication Changes – First 90 days vs. second 90 days

65% of the overall HF medication changes were made in the first 90 days, with trends of stabilization and significantly fewer medication changes during the second 90 days.

The CardioMEMS™ HF System PAS Short-term Results

REDUCED HF Hospitalization AND MEAN PAP

AUC (mmHg day)

<table>
<thead>
<tr>
<th></th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMPION Control</td>
<td>3.1 ± 6.7 (270 pts)</td>
<td>-5.5 ± 24.7 (251 pts)</td>
<td>42.0 ± 65.0 (228 pts)</td>
</tr>
<tr>
<td>CHAMPION Treatment</td>
<td>-7.0 ± 7.7 (266 pts)</td>
<td>-59.3 ± 27.6 (257 pts)</td>
<td>-150.1 ± 71.0 (236 pts)</td>
</tr>
<tr>
<td>PAS</td>
<td>-27.7 ± 7.0 (291 pts)</td>
<td>-112.6 ± 26.0 (275 pts)</td>
<td>-281.0 ± 63.5 (262 pts)</td>
</tr>
</tbody>
</table>

**SIGNIFICANTLY GREATER REductions in MEAN PAP** for the PAS cohort relative to the CHAMPION control group after 6 months, and **QUALITATIVELY GREATER REDUCTIONS** compared to the CHAMPION treatment group.

Pressures are Reduced Equally Well in HFrEF and HFpEF, as well as Male and Female
Greatest reduction in mean PAP observed for the CardioMEMS™ HF System patients with higher baseline PAP.

Patients in the treatment group with baseline PAP at goal, remained at goal over time.
Real-world Use of the CardioMEMS™ HF System: 

REDUCED HF HOSPITALIZATIONS

Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database

Cumulative HF Hospitalization During Period Before and After CardioMEMS™ HF System Implant

45% reduction at 6 months (p < 0.001)

Cumulative HF Hospitalizations

Pre-implant

Post-implant

Time (months)

PRE-IMPLANT

0

-1

-2

-3

-4

-5

-6

POST-IMPLANT

0

+1

+2

+3

+4

+5

+6

Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database
Real-world Use of the CardioMEMS™ HF System: ASSOCIATED HF HOSPITALIZATION COSTS

Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database

SIGNIFICANT IMPROVEMENT IN FC AND QoL IN PATIENTS IMPLANTED WITH THE CardioMEMS™ HF SYSTEM

**KCCQ: 3-fold greater improvement in scores**

![KCCQ Graph](chart1.png)

**6-minute walk: Avg. increase of 96 meters at 90 days versus no increase in the SoC group**

![6-minute Walk Graph](chart2.png)

CONCLUDING SUMMARY

• The CardioMEMS™ HF System is safe, reliable and clinically proven in clinical trials and real-world settings.

• It provides a proactive, personalized approach to prevent acute decompensation in both HFrEF and HFpEF patients.
Panel Discussion: Clinical Care Management Studies

Acute Heart Failure, Cardiorenal Syndrome, Evolution to HFpEF
Closing Remarks

Jayne Testa, CMPE
Kettering Heart & Vascular Executive Director