Reducing Heart Failure Hospitalizations

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Disclosures

- Thoratec – consultant, grant funding
- St. Jude – consultant, grant funding
- CareDx – medical advisory board
- Abiomed – travel reimbursement
HF Maladaptation (Simplified)

\[ \text{CO} = \text{SV} \times \text{HR} \]

- **Remodeling (\(\beta\) stimulation)**
- **\(\uparrow\) Sympathetic Tone**
- **\(\downarrow\) SV → \(\downarrow\) CO → \(\uparrow\) Afterload**
- **\(\uparrow\) Afterload**
- **Remodeling (\(\text{AT}_2\) pathways)**
- **\(\uparrow\) RAAS**
- **\(\downarrow\) Renal Perfusion**
- **\(\uparrow\) \(\text{O}_2\) Demand**
- **\(\uparrow\) Symptoms**
- **\(\uparrow\) Apoptosis**
- **\(\uparrow\) \(\text{Na}^+ + \text{H}_2\text{O}\) Retention**
Treating HF (Simplified)

- β-Blockers
- ↑Sympathetic Tone
- ↓SV → ↓CO
- ↑Afterload
- Nitrates*
- Hydralazine*
- ACEi/ARBs
- Aldo-antagonism
- ARNI
- ↑RAAS
- Diuretics
- ↑O₂ Demand
- ↑Renal Perfusion
- Na⁺ + H₂O Retention
- Digoxin(?)
- Ivabradine
Ivabradine
SHIFT Study: Primary objective

To evaluate whether the $I_f$ inhibitor ivabradine improves cardiovascular outcomes in patients with

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction $\leq 35\%$
3. Heart rate $\geq 70$ bpm in sinus rhythm
4. Best recommended therapy
   *Maximally tolerated dose of beta-blocker

Study Design

Study Endpoints

**Primary composite endpoint**
- Cardiovascular death
- Hospitalization for worsening heart failure

**Other endpoints**
- All-cause / CV / HF death
- All-cause / CV / HF hospitalization
- Composite of CV death, hospitalization for HF or non-fatal MI
- NYHA class / Patient & Physician Global Assessment

In total population and in patients with at least 50% target dose of beta-blockers
Primary composite endpoint
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR = 0.82 (0.75–0.90)
\( P < 0.0001 \)

Hospitalization for HF

Cumulative frequency (%)

HR = 0.74 (0.66–0.83)  
\( P < 0.0001 \)

Death from heart failure

Cumulative frequency (%)

HR = 0.74 (0.58–0.94)

P = 0.014

Ivabradine

- In patients on at least 50% target dose of β-blocker, only hospitalizations were reduced

- In a separate trial, no improvement was seen with ivabradine used for stable CAD without HF
  - Patients with limiting angina may do worse

Ivabradine

- Approved (April 4, 2015) by FDA
  - Approved for reduction in HF hospitalizations only
- Corlanor (Amgen)
- Symptomatic HFrEF (LVEF < 35%) on GDMT
- HR > 70 (max tolerated beta blocker)
- Adverse effects
  - Bradycardia
  - Caution with CYP3A4 inhibitors
  - Caution with drugs prolonging QTc
  - Don’t use with 1st gen Ca Channel blockers
  - Luminous phenomena 14%
Angiotensin-Nephrilysin Inhibitors (ARNIs)

- Newest kid on the block
- Originally named LCZ696
- Combination of valsartan + AHU377 (sacubitril)
- AT2 receptor blockade + nephrilysin inhibition
- Blocks angiotensin II at receptor / increase natriuretic peptides
- Lower BP, promote sodium excretion,

PARADIGM: LCZ696

- December 2009 to March 2014
- > 8000 patients HFrEF
- Received LCZ696 vs enalapril
- Primary: CV death or HF hospitalization
- Secondary: overall mortality

McMurray J, NEJM 2014; 371:993-1004
PARADIGM: LCZ696

Results showed improvement in primary and secondary endpoints.

McMurray J, *NEJM* 2014; 371:993-1004
PARADIGM Conclusions

- Angiotensin receptor – neprilysin inhibition:
  - Reduces CV death and hospitalization for HF
  - Reduces overall mortality
  - Reduces symptoms and improves physical function

McMurray J, *NEJM* 2014; 371:993-1004
LCZ696 – A Game Changer?

Excitement because trial was stopped early

- Met pre-specified end-points
- “Boundary for overwhelming benefit with LCZ696 had been crossed”
LCZ696 – Concerns

- Hypotension due to more vasodilation
- 10,500+ patients screened
- 1100 discontinued during ACEi run-in phase
- Almost 1000 discontinued during ARNI run-in phase
- Angioedema not an issue in this trial
  - But was with previous neprilysin inhibitors
- Cough and hyperkalemia no different than enalapril group.
  - Hyperkalemia more of an issue with previous ANRIs

McMurray J, *NEJM* 2014; 371:993-1004
ARNIs

- FDA approved sacubitril/valsartan on July 7, 2015
  - Approved to reduce HF hospitalizations and CV death
- Brand name: Entresto
- If patients are on ACEi’s, must stop at least 36 hours prior to starting ARNI
- Neprilysin breaks down BNP
  - ARNIs may elevated BNP levels
  - Unclear if BNP threshold will be useful
  - Consider NT-proBNP or ST-2

Entreso PI, www.novartis.com
Emani S, et al, Future Cardio 2015
Remote monitoring

- The next major development in HF management?
- Help prevent hospitalizations?
- Prevent negative effects of playing “catch-up?”

(Thanks to Dr. William Abraham for slides)
What Do We Need to Monitor to Accomplish This Goal?

- Fluid in the lungs / pressures in the heart
- How do we currently assess these in patients with chronic heart failure?
  - Symptoms
  - Daily weights
  - Physical examination
  - Device-based diagnostics
  - Biomarkers

- How well do these assessments perform?
  - Not very well

Surrogates for fluid retention and increased filling pressures
The Development of Acute Decompensation

Physiologic markers of the development of acute decompensation:

- Pressure Changes
- Autonomic Adaptation
- Impedance Changes
- Weight Changes, HF Symptoms

Time

Stable → Decompensation → Hospitalization
# Unreliability of Weight Change in Identifying Heart Failure Decompensation

Weight change has **low sensitivity** for identifying decompensation

<table>
<thead>
<tr>
<th>Weight Change</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 kg weight gain over 48-72 hrs(^1)</td>
<td>9%</td>
<td>97%</td>
</tr>
<tr>
<td>2% weight gain over 48-72 hrs(^1)</td>
<td>17%</td>
<td>94%</td>
</tr>
<tr>
<td>3 lbs in 1 day or 5 lbs in 3 days(^2)</td>
<td>22.5%</td>
<td>-</td>
</tr>
</tbody>
</table>

Lewin, 2005. N=77\(^1\)

Abraham, 2011. N=156\(^2\)

TELE-HF Trial: Telemonitoring of Weight Changes and Heart Failure Symptoms

- NIH-sponsored randomized controlled trial of 1653 patients
- Primary endpoint: readmission for any reason or death from any cause within 180 days after enrollment
- Control group: usual care (no telemonitoring)
- Treatment group: telemonitoring of symptoms and weight by telephone-based interactive voice-response system
- Result: no difference in number of deaths, readmissions, or days in hospital

TELE-HF Trial: Telemonitoring of Weight Changes and Heart Failure Symptoms

Is There Value in Monitoring Pressure Changes?

HF decompensation leads to increase in intracardiac and pulmonary artery pressures.

Stable → Pressure Changes → Neurohormonal Adaptation → Impedance Changes → Weight Changes, HF Symptoms → Hospitalization

Decompensation
The Pulmonary Artery Pressure Measurement System*

Catheter-based delivery system
MEMS-based pressure sensor

Home electronics
PA Measurement database

*CardioMEMS Inc., Atlanta, Georgia, USA
Patient Management Database

Trend Data
- Easy-to-read
- Physician alerts
- Home transmission
- Secure, encrypted web-based access

Discrete Data

<table>
<thead>
<tr>
<th>Reading</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic:</td>
<td>24</td>
</tr>
<tr>
<td>Mean:</td>
<td>19</td>
</tr>
<tr>
<td>Diastolic:</td>
<td>16</td>
</tr>
<tr>
<td>Heart Rate:</td>
<td>81</td>
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</tbody>
</table>
Champion: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients

- Trial Designed by Steering Committee with active FDA input
- Prospective, multi-center, randomized, controlled single-blind clinical trial
- All subjects followed in their randomized single-blind study assignment until the last patient reached 6 months of follow-up
- 64 US Centers

550 Pts w/ CM Implants
All Pts Take Daily Readings

- Treatment 270 Pts
  Management Based on Hemodynamics + Traditional Info

- Control 280 Pts
  Management Based on Traditional Info

Primary Endpoint: HF Hospitalizations at 6 Months

Additional Analysis: HF Hospitalizations at All Days (~15 M mean F/U)

Multiple Secondary Endpoints

Hypothesis of the CHAMPION Trial

In addition to basing treatment on signs and symptoms

Medications should be adjusted based on pulmonary artery pressures unless contraindicated by clinical status of patient

Heart failure hospitalizations

# Protocol Guidelines: PA Pressure Management

## Treatment Recommendations for Elevated PA Pressures

- **Add or increase diuretic**
  - increase/add loop diuretic
  - change loop diuretic
  - add thiazide diuretic
  - IV loop diuretic

- **Add or increase vasodilator**
  - add or increase nitrate

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Cumulative HF Hospitalizations Reduced At 6 Months and Full Duration of Randomized Study

- ≤ 6 Months: 28% RRR, p = 0.0002
- > 6 Months: 45% RRR, p < 0.0001

Study Duration: 37% RRR, p < 0.0001
## Primary Efficacy Endpoint Met

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=270)</th>
<th>Control (n=280)</th>
<th>Relative Risk Reduction</th>
<th>p-value(^{[1]})</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy Endpoint:</td>
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<tr>
<td>HF Related Hospitalizations</td>
<td>84 (0.32)</td>
<td>120 (0.44)</td>
<td>28%</td>
<td>0.0002</td>
<td>8</td>
</tr>
<tr>
<td>(Rate for 6 months)</td>
<td></td>
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<tr>
<td>Supplementary Analysis:</td>
<td></td>
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<tr>
<td>HF Related Hospitalizations</td>
<td>158 (0.46)</td>
<td>254 (0.73)</td>
<td>37%</td>
<td>&lt;0.0001</td>
<td>4</td>
</tr>
<tr>
<td>(Full Duration - Annualized Rate)</td>
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\(^{[1]}\) p-value from negative binomial regression
NNT = Number Needed to Treat

Summary

- Implantable hemodynamic monitors provide direct and actionable measurements of intra-cardiac and pulmonary artery pressures.

- Management guided by such monitors reduces the risk of heart failure hospitalizations.

- This approach promises to revolutionize the management of heart failure patients.
  - Crisis management ➔ Stability management.
CardioMEMS: Current Status

- Approved for use in NYHA III HF patients

- Intended to:
  - Reduced HF hospitalizations
  - Improved QoL
  - No indication to improved survival
Challenges with Hemodynamic Monitoring

- **Implantation**
  - Minimal challenges
  - Need anticoagulation for 30 days

- **Reimbursement**
  - Implant is covered (generally)
  - New CPT codes
  - Data monitoring not really reimbursed
Hemodynamic Monitoring: Stress on System

- Beneficial when monitoring routinely & frequently
  - Not once every 30 days

- Requires patient compliance with transmission

- Requires medical staff to read/interpret/act upon data

- Need to have medical options to act upon data
Ohio State CardioMEMS Work-Flow

- Remote hemodynamic program is evolving
- Currently ~40 patients being followed
- More automation of system-smart data analysis needed
Thank you