HEMODYNAMIC MONITORING DEVICES IN HEART FAILURE

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I will discuss off label use and/or investigational use in my presentation.

I have financial relationships to disclose:
Employee of: university of florida
Consultant for: st jude's medical, novartis, biocontrol, pfizer, nih, respicardia, sensible medical, celadon, Covance, Lilly.
Stockholder in: none
Research support from: ccs-otsuka
Honoraria from: none
Speaker bureau: none
ENDPOINT COMMITTEES—ARE THEY NEEDED?

• Provide consistency
• Guided by protocol
• Report to the steering committee
• Provide data to the DSMB which determines the course of the study
• Blinded so not biased regarding outcome
ADJUDICATE

• To hear-determine-and settle (a case) by judicial procedure
ENDPOINT METHODOLOGY

• Development of charter

• Definitions-compatible with protocol

• Process-face-to-face; fax; phone; fed-ex; virtual; combination

• Need-source documentation
ENDPOINT COMMITTEE COMPOSITION

- Homogeneous group of heart failure specialists
- Heterogeneous regarding academic/practice
- “Chemistry” integral to the process
- Commitment to the task
Compass HF

- Class III and IV
- Lead with sensor at tip implanted like a pacemaker
- All patients implanted
- All patients transmitted data
Chronicle Implantable Hemodynamic Monitor (IHM)

- Pressures
  - Right Ventricular (RV) Systolic and Diastolic Pressures
  - Estimated Pulmonary Artery Diastolic Pressure (ePAD)
- Heart Rate, Temperature, Activity
Primary Effectiveness Objective (Results)

<table>
<thead>
<tr>
<th></th>
<th>CHRONICLE (n=134)</th>
<th>CONTROL (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Pts with Events</td>
<td>44</td>
<td>60</td>
</tr>
<tr>
<td>Total HF-Related Events</td>
<td>84</td>
<td>113</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>72</td>
<td>99</td>
</tr>
<tr>
<td>Emergency Dept Visits</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Urgent Clinic Visits</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Event Rate / 6 months</td>
<td>0.67</td>
<td>0.85</td>
</tr>
<tr>
<td>% Reduction in Event Rate</td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>

p=0.33

Cumulative Events
ISSUES

- Measured RV outflow pressures
- PA pressures estimated
- Primary outcome not met
- Treating physicians did not change meds
- Adjudication definitions did not specifically address low output state
CHAMPION Hypothesis

The hypothesis of the CHAMPION trial is that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations.

The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical decision making.
The Ambulatory Hemodynamic Pressure Measurement System

Catheter-based delivery system

MEMS-based pressure sensor

Readout electronics

Measurement database

[Image of catheter-based delivery system]

[Image of MEMS-based pressure sensor]

[Graph showing measurement database]
Cumulative HF Hospitalizations Over Entire Randomized Follow-Up Period

Cumulative Number of HF Hospitalizations

<table>
<thead>
<tr>
<th>Days from Implant</th>
<th>Treatment At Risk</th>
<th>Control At Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>270</td>
<td>280</td>
</tr>
<tr>
<td>90</td>
<td>262</td>
<td>267</td>
</tr>
<tr>
<td>180</td>
<td>244</td>
<td>252</td>
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<tr>
<td>270</td>
<td>209</td>
<td>215</td>
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<tr>
<td>360</td>
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<td>450</td>
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<tr>
<td>540</td>
<td>107</td>
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<td>630</td>
<td>81</td>
<td>67</td>
</tr>
<tr>
<td>720</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>810</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>900</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

p < 0.001, based on Negative Binomial Regression
ISSUES

• Small company-first big trial
  Members of adjudication committee selected by interview process
  Initial difficulty finding committee leader (sponsor)
  All patients implanted and had RHC

Novel concept
Issue with endpoint by sponsor
No approval first panel – sponsor calls
LAPTOP

Complex implant

Device is delivered on catheter via atrial septal puncture

- Patient activated
- Pressures available via internet

Treatment plan developed for each patient
HeartPOD™ HF Monitoring and Therapy System

Top, Implantable sensor lead and coil antenna.

Bottom left, Chest radiograph of LAP system implanted from the left axillary vein. CA, coil antenna; SM, sensor module. The there was an existing dual-chamber ICD.

Bottom right, Patient Advisor Module (PAM™) used by patients to communicate with the implanted sensor lead.

Caution: Investigational Device, Limited by Federal Law to Investigational Use

Comparison of HeartPOD ISL to Amplatz Septal Closure Device
ISSUES

• Very complex procedure to implant
• Blinding difficult-1/2 implanted and 1/2 control-only received PAM
• Committee changed sponsor personnel early
• Adjudication process unusual
  • Each member adjudicated all events
  • all events during hospitalization adjudicated
ISSUES 2

• Positives
• Committee chemistry excellent
• Meetings all F to F
• Data for adjudication generally good

• Negatives
• Trial stopped by DSMB—very low likelihood of achieving primary endpoint in the face of up-front risk to patients (4 aortic perforations at end)