Cardiovascular Medicine 2016- Three Disruptive Technologies

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Tufts University School of Medicine
Three Disruptive Technologies

• Transcatheter Aortic Valve Replacement
• Left Atrial Appendage Occlusion
• Continuous Pulmonary Artery Pressure Monitoring
Prevalence of Aortic Stenosis Increases with Age

Symptomatic Aortic Stenosis - A Dismal Prognosis

Largely ignored!

But is this correct?
Asymptomatic patients with severe aortic stenosis:
Good short-term - Poor long-term outcome
Many Patients Do Not Undergo AVR For Reasons Including Real or Perceived Risks Associated with Surgery\(^1\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouma 1999</td>
<td>54</td>
</tr>
<tr>
<td>Pellikka 2005</td>
<td>43</td>
</tr>
<tr>
<td>Charlson 2006</td>
<td>60</td>
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<tr>
<td>Varadarajan 2006</td>
<td>61</td>
</tr>
<tr>
<td>Jan 2009</td>
<td>74</td>
</tr>
<tr>
<td>Bach 2009</td>
<td>52</td>
</tr>
<tr>
<td>Freed 2010</td>
<td>69</td>
</tr>
</tbody>
</table>

AT LEAST 40% OF PATIENTS WITH SEVERE AORTIC STENOSIS DO NOT UNDERGO SURGICAL AORTIC VALVE REPLACEMENT\(^5-11\)
Who is truly “inoperable”?

- STS PROM (surgical mortality) score >10%?
- Major multi-organ system compromise?
- Severe frailty?
What is the fate of patients with severe aortic stenosis who don’t undergo aortic valve replacement?

- Progressive loss in quality of life
- Loss of employment and independence
- Repeat hospitalizations
- Premature death
Transcatheter Aortic Valve Replacement (TAVR)

Replacement of the aortic valve through catheters *without* sternotomy or cardiopulmonary bypass allowing AVR to be offered to elderly, frail patients in a less invasive manner
Balloon-expandable THV
Edwards Sapien XT
(Cobalt chromium stent frame, bovine pericardium)

Self-expandable THV
Medtronic CoreValve
(Nitinol stent frame, porcine pericardium)

- Ascending Aorta
- Aortic sinuses with coronary ostia
- Aortic valve annulus
- Left Ventricle
TAVR: 2 Different Approaches

Transapical

Transfemoral
How do we address this problem of an increasing prevalence of a very lethal disorder?

- New Evidence-Based Guidelines
- New Treatments, i.e., TAVR
- New Multidisciplinary “Valve Teams”
- Patient identification
2014 ACC/AHA Valve Guidelines
What’s New?

• Valve Disease Stages
  No longer only “asymptomatic” or “symptomatic”

• Heart Valve Team
  Breaking down silos of cardiologists and surgeons

• Integrative Approach to Procedural Risk Assessment
  Timing & Choice of SAVR vs. TAVR
### 2014 ACC/AHA Valvular Heart Disease (VHD) Guidelines

#### Aortic Stenosis Disease Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve anatomy and hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>At risk for AS</td>
<td>Bicuspid valve, aortic sclerosis</td>
</tr>
</tbody>
</table>
| **B** | Progressive AS | Mild AS $V_{max} \leq 2.0 – 2.9$ m/s, Mean $\Delta P < 20$ mm Hg  
Mod AS $V_{max} \leq 3.0 – 3.9$ m/s, Mean $\Delta P 20-39$ mm Hg  
(Typically $AVA > 1.0 \text{ cm}^2$) |
| **C** | Asymptomatic severe AS | Severe AS $V_{max} \geq 4.0$ m/s, Mean $\Delta P \geq 40$ mm Hg  
(Typically $AVA \leq 1.0 \text{ cm}^2$)  
Very severe AS $V_{max} \geq 5.0$ m/s, Mean $\Delta P \geq 60$ mm Hg |
| **D** | Symptomatic severe AS | D1: High gradient severe AS  
D2: Low gradient severe AS (low EF)  
D3: Paradoxical low-gradient severe AS (normal EF) |

- C1: Normal LV systolic
- C2: LV ejection fraction < 50%
2014 ACC/AHA Valve Guidelines

Diagnosis and Followup of Aortic Stenosis

AS signs or symptoms
Tricuspid aortic valve

Transcatheter Echo
• Cause & severity of AS
• LV size and function
• Prognosis & Timing of AVR

V_{\text{max}} \geq 4 \text{ m/s}

V_{\text{max}} < 4 \text{ m/s}

AVA \leq 1.0 \text{ cm}^2

EF < 50%

ETT
• BP
• Symptoms?

No ETT

Dobutamine stress echo

AVA_i \leq 0.6 \text{ cm}^2/\text{m}^2 and SVI < 35 \text{ mL/m}^2

Repeat echo
• Changing signs or symptoms
• Every 3-5 yrs for V_{\text{max}} 2-2.9 m/s
• Every 1-2 yrs for V_{\text{max}} 3-3.9 m/s
• Every 6-12 mo for V_{\text{max}} \geq 4 \text{ m/s}
PARTNER IB Trial

Inoperable Patients with Symptomatic Aortic Stenosis Randomized to Medical Therapy or TAVR
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR (N = 179)</th>
<th>Standard Rx (N = 179)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>83.1 ± 8.6</td>
<td>83.2 ± 8.3</td>
<td>0.95</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>45.8</td>
<td>46.9</td>
<td>0.92</td>
</tr>
<tr>
<td>STS Score</td>
<td>11.2 ± 5.8</td>
<td>12.1 ± 6.1</td>
<td>0.14</td>
</tr>
<tr>
<td>NYHA I or II (%)</td>
<td>7.8</td>
<td>6.1</td>
<td>0.68</td>
</tr>
<tr>
<td>NYHA III or IV (%)</td>
<td>92.2</td>
<td>93.9</td>
<td>0.68</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>67.6</td>
<td>74.3</td>
<td>0.20</td>
</tr>
<tr>
<td>COPD Any (%)</td>
<td>41.3</td>
<td>52.5</td>
<td>0.04</td>
</tr>
<tr>
<td>COPD O₂ dependent (%)</td>
<td>21.2</td>
<td>25.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Creatinine &gt; 2 mg/dL (%)</td>
<td>5.6</td>
<td>9.6</td>
<td>0.23</td>
</tr>
<tr>
<td>Frailty (%)</td>
<td>18.1</td>
<td>28.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Porcelain aorta (%)</td>
<td>19.0</td>
<td>11.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Chest wall radiation (%)</td>
<td>8.9</td>
<td>8.4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Kapadia et al. TCT 2014
All-Cause Mortality (ITT)

Crossover Patients Censored at Crossover

**Standard Rx (n = 179)**
- 30.7%
- 50.8%
- 68.0%
- 80.9%
- 87.5%
- 93.6%

**TAVR (n = 179)**
- 43.0%
- 53.9%
- 64.1%
- 71.8%

HR [95% CI] = 0.50 [0.39, 0.65]
p (log rank) < 0.0001

NNT=4.5pts

*In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.*

Kapadia et al. TCT 2014
Repeat Hospitalization (ITT)

Kapadia et al. TCT 2014

HR [95% CI] = 0.40 [0.29, 0.55]

p (log rank) < 0.0001
## Subgroup Analysis

### All-Cause Mortality

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio</th>
<th>[95% CI]</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N=358)</td>
<td>0.50</td>
<td>[0.39-0.65]</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 85 (N=186)</td>
<td>0.46</td>
<td>[0.33-0.66]</td>
<td>0.40</td>
</tr>
<tr>
<td>Age ≥ 85 (N=172)</td>
<td>0.56</td>
<td>[0.39-0.79]</td>
<td>0.40</td>
</tr>
<tr>
<td>Male (N=166)</td>
<td>0.46</td>
<td>[0.32-0.66]</td>
<td>0.34</td>
</tr>
<tr>
<td>Female (N=192)</td>
<td>0.55</td>
<td>[0.40-0.78]</td>
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</tr>
<tr>
<td>BMI ≤ 25 (N=170)</td>
<td>0.58</td>
<td>[0.41-0.84]</td>
<td>0.71</td>
</tr>
<tr>
<td>BMI &gt; 25 (N=188)</td>
<td>0.44</td>
<td>[0.31-0.63]</td>
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</tr>
<tr>
<td>STS ≤ 11 (N=170)</td>
<td>0.52</td>
<td>[0.36-0.76]</td>
<td>0.65</td>
</tr>
<tr>
<td>STS &gt; 11 (N=187)</td>
<td>0.53</td>
<td>[0.37-0.74]</td>
<td></td>
</tr>
<tr>
<td>EF ≤ 55 (N=173)</td>
<td>0.47</td>
<td>[0.33-0.67]</td>
<td>0.09</td>
</tr>
<tr>
<td>EF &gt; 55 (N=171)</td>
<td>0.61</td>
<td>[0.42-0.88]</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (N=136)</td>
<td>0.56</td>
<td>[0.37-0.85]</td>
<td>0.87</td>
</tr>
<tr>
<td>Yes (N=103)</td>
<td>0.51</td>
<td>[0.32-0.82]</td>
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</tr>
<tr>
<td>Mod / Sev MR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No (N=261)</td>
<td>0.58</td>
<td>[0.43-0.77]</td>
<td>0.03</td>
</tr>
<tr>
<td>Yes (N=77)</td>
<td>0.30</td>
<td>[0.17-0.53]</td>
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</tr>
<tr>
<td>Oxygen Dependent COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (N=270)</td>
<td>0.46</td>
<td>[0.35-0.62]</td>
<td>0.14</td>
</tr>
<tr>
<td>Yes (N=88)</td>
<td>0.68</td>
<td>[0.42-1.10]</td>
<td></td>
</tr>
<tr>
<td>Prior CABG or PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (N=182)</td>
<td>0.55</td>
<td>[0.39-0.78]</td>
<td>0.27</td>
</tr>
<tr>
<td>Yes (N=176)</td>
<td>0.46</td>
<td>[0.32-0.66]</td>
<td></td>
</tr>
</tbody>
</table>

Kapadia et al. TCT 2014
NYHA Class Over Time (ITT)

Survivors

<table>
<thead>
<tr>
<th>Time</th>
<th>TAVR</th>
<th>Standard Rx</th>
<th>Baseline</th>
<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=179</td>
<td>N=179</td>
<td>100%</td>
<td>92.2%</td>
<td>93.9%</td>
<td>93.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23.7%</td>
<td>30.0%</td>
<td>14.3%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = NS</td>
<td>p &lt; 0.0001</td>
<td>p = NS</td>
<td>p = NS</td>
</tr>
</tbody>
</table>

Kapadia et al. TCT 2014
Cohort B Inoperable
Higher Incidence of Major Vascular Complications

MAJOR VASCULAR COMPLICATIONS AT 30 DAYS, 1 YEAR, AND 2 YEARS

- 30 Days: Edwards SAPIEN THV (n=179) 16.8%, Standard Therapy (n=179) 1.1%
  \( p < 0.0001 \)
- 1 Year: Edwards SAPIEN THV (n=179) 17.4%, Standard Therapy (n=179) 2.8%
  \( p < 0.0001 \)
- 2 Years: Edwards SAPIEN THV (n=179) 17.4%, Standard Therapy (n=179) 2.8%
  \( p < 0.0001 \)
Main Conclusions of PARTNER IB Trial

• At 5 years follow-up benefits of TAVR compared with medical therapy alone were sustained as measured by:
  – All-Cause Mortality
  – Cardiovascular Mortality
  – Repeat Hospitalization
  – Functional Status

– Valve durability was demonstrated with no increase in transvalvular gradient or attrition of valve area.

Kapadia et al. TCT 2014
PARTNER I: Cohort A

Randomized Clinical Trial comparing TAVR to Surgical AVR in High-Risk Patients
PARTNER I Cohort A

Superior Outcomes for Women Undergoing TAVR vs. SAVR
**Cohort A**

**Paravalvular Aortic Regurgitation**

**AT Population**

<table>
<thead>
<tr>
<th>Time</th>
<th>TAVR 30 Days</th>
<th>AVR 30 Days</th>
<th>TAVR 1 Year</th>
<th>AVR 1 Year</th>
<th>TAVR 2 Years</th>
<th>AVR 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, %</td>
<td></td>
<td>Patients, %</td>
<td></td>
<td>Patients, %</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>10.8%</td>
<td>6.3%</td>
<td>6.3%</td>
<td>6.3%</td>
<td>6.3%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Moderate</td>
<td>40.9%</td>
<td>74.2%</td>
<td>25.6%</td>
<td>78.3%</td>
<td>28.4%</td>
<td>81.3%</td>
</tr>
<tr>
<td>Mild</td>
<td>22.7%</td>
<td>32.7%</td>
<td>36.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>24.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>None</td>
<td>17.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Cohort A Conclusions

At 2 years, in patients with symptomatic severe aortic stenosis who were high-risk candidates for surgical AVR:

- Edwards SAPIEN THV remained equivalent to surgical AVR with similar rates of all-cause and cardiovascular mortality for all pts. Women had reduced mortality with TAVR vs. SAVR
- Symptom improvement was similar in both groups and maintained through two years
- Hemodynamic performance of the Edwards SAPIEN THV was maintained with similar valve gradients and effective orifice areas compared with surgical AVR
Where are we today?
Today, TAVR is an essential part of any comprehensive advanced cardiovascular program with expanding indications.

- **2012**: Inoperable
- **2013**: High-risk
- **2014**: Valve in Valve
- **2015**: Intermediate Risk
- **2016**: Alternative access
Following Patient Referral, the TAVR Team Performs Further Evaluation

1. Confirm the patient is diagnosed with severe symptomatic native aortic stenosis
2. Confirm the patient has been evaluated by two cardiac surgeons
3. Evaluate the coronary arteries with cardiac catheterization
4. Evaluate the aortic valvular complex and peripheral vasculature using CT
5. Evaluate the aortic valvular complex using TEE
6. Determine access route for transcatheter aortic valve replacement

The most important part of the evaluation process is multidisciplinary consultation with:

→ Cardiac surgeons
→ Interventional cardiologists
→ Non-invasive cardiologists
→ Radiologists
→ Anesthesiologists
→ Geriatricians
→ Nurse practitioners
→ OR nursing
→ Cath lab nursing
→ Cath lab techs
→ Perfusionists
→ Data coordinator
→ Administrators
Multiple Modalities for Assessing Frailty

- Columbia Frailty Index
  - Gait speed
  - Grip strength
  - Exhaustion implied in symptomatic AS
  - Serum albumin
  - Katz ADLs - (Independence in dressing, bathing, toileting, transferring, feeding, continence)

CSHA Frailty Scale

**Very fit** — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

**Well** — without active disease, but less fit than people in category 1

**Well, with treated comorbid disease** — disease symptoms are well controlled compared with those in category 4

**Apparently vulnerable** — although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms

**Mildly frail** — with limited dependence on others for instrumental activities of daily living

**Moderately frail** — help is needed with both instrumental and non-instrumental activities of daily living

**Severely frail** — completely dependent on others for the activities of daily living, or terminally ill
TAVR vs SAVR for Intermediate or Low-Risk Patients?
Edwards SAPIEN 3 transcatheter heart valve

Enhanced frame design
- New frame geometry
- High radial strength for circularity and optimal hemodynamics

Bovine pericardial tissue
- Optimized leaflet shape
- Tissue treatment

Low frame height

New outer skirt
Intermediate-Risk Operable*

ASSESSMENT by Heart Valve Team

SAPIEN 3

2 Single Arm Non-Randomized Historical-Controlled Studies

PARNER II A Trial
SAVR

PARNER IA Trial
SAPIEN

High-Risk Operable / Inoperable (HR)

ASSESSMENT: Optimal Valve Delivery Access

Transfemoral (TF)

TF TAVR
SAPIEN 3

Transapical / Transaortic (TA/TAo)

TAA TAVR
SAPIEN 3

Transfemoral (TF)

TF TAVR
SAPIEN 3

Transapical / Transaortic (TA/TAo)

TAA TAVR
SAPIEN 3

Symptomatic Severe Aortic Stenosis

n = 1076 Patients

n = 583 Patients
PARTNER II:

RCT Comparing SAPIEN XT TAVR to SAVR in Intermediate Risk Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>SAVR</th>
<th>TAVR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maj Vasc</td>
<td>5.0</td>
<td>7.9</td>
<td>0.008</td>
</tr>
<tr>
<td>A Fib</td>
<td>26.4</td>
<td>9.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Maj Bleeding</td>
<td>43.4</td>
<td>10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>AKI</td>
<td>3.1</td>
<td>1.3</td>
<td>0.006</td>
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</table>
All-Cause Mortality in Inoperable and High-Risk Patients at 30 Days
(As Treated Patients)

PARTNER I Trial and PARTNER II Trial
Impact of Next Generation Valves

<table>
<thead>
<tr>
<th>Valve</th>
<th>PARTNER I B (TF)</th>
<th>PARTNER I A (All)</th>
<th>PARTNER I A (TF)</th>
<th>PARTNER II B (TF)</th>
<th>PARTNER II B (TF)</th>
<th>PARTNER II HR (TF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.3%</td>
<td>5.2%</td>
<td>3.7%</td>
<td>4.5%</td>
<td>3.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>175</td>
<td>344</td>
<td>240</td>
<td>271</td>
<td>282</td>
<td>491</td>
</tr>
</tbody>
</table>
All Strokes at 30 Days

PARTNER I Trial and PARTNER II Trial

Neurologist Evaluations (Pre- and Post)

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>PARTNER I B (TF)</th>
<th>PARTNER I A (Overall)</th>
<th>PARTNER II B (TF)</th>
<th>PARTNER II B (TF)</th>
<th>PARTNER II HR (TF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>179</td>
<td>344</td>
<td>271</td>
<td>282</td>
<td>491</td>
</tr>
<tr>
<td></td>
<td>SAPIEN Valve</td>
<td>SAPIEN XT Valve</td>
<td>SAPIEN 3 Valve</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2014 ACC/AHA Guidelines for Valvular Heart Disease - Aortic Stenosis

**Surgical Risk**

- **Low**
  - STS PROM <4%
    - No Frailty
      - No organ system compromise
        - No procedure impediments
          - SAVR

- **Intermediate**
  - STS PROM 4-8%
    - Mild (1)
      - One organ system compromise
        - Possible procedure impediments
          - SAVR
  
  - STS PROM >8-15%
    - Mod (2)
      - Two organ system compromise
        - Poss procedure impediments
          - SAVR or TAVR

- **High**
  - STS PROM >15%
    - Severe
      - 3 organ system compromise
        - Severe procedure impediments
          - TAVR

- **Prohibitive**
  - Special Considerations
    - ?BAV
THV degeneration was defined as at least moderate regurgitation AND/OR mean gradient ≥ 20mmHg, which did not appear within 30 days of the procedure and is not related to endocarditis.

KM estimate of THV degeneration included censoring of patients at their date of last known THV functioning well without evidence for degeneration per study definition.
Vancouver
266 pts from before 2011 (> 5 years FU)

Freedom from Severe Failure

Freedom from Reintervention

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>266</td>
</tr>
<tr>
<td>2</td>
<td>122</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
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</table>

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>266</td>
</tr>
<tr>
<td>2</td>
<td>164</td>
</tr>
<tr>
<td>4</td>
<td>101</td>
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<tr>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>
TAVR - UNLOAD Trial Design

Moderate AS + HF
(600 patients, 1:1 randomized)

Primary Endpoint
Hierarchical occurrence of:
- All-cause death
- Disabling stroke
- Hospitalizations for HF, aortic valve disease
- Change in KCCQ

Follow-up:
- 1 month
- 6 months
- 1 year

Clinical endpoints
Symptoms
Echo
QoL

TAVR UNLOAD Trial
International Multicenter Randomized

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

R

TAVR + OHFT

OHFT Alone

Reduced AFTERLOAD
Improved LV systolic and diastolic function

© TVT 2016
Transcatheter Valve Therapies (TVT)
A Multidisciplinary Heart Team Approach

Cardiovascular Research Foundation
Columbia University Medical Center
Atrial Appendage Occlusion in Patients with Atrial Fibrillation
**Atrial Fibrillation & Stroke Risk**

AF is the most common cardiac arrhythmia

AF increases risk of stroke

Blood clots form in the left atrial appendage

Many patients are unprotected

> 33M people with AF Worldwide\(^1\)

5x greater risk of stroke with AF\(^2\)

>90% of stroke-causing clots that come from the left atrium in non-valvular AF are formed in the LAA\(^3\)

~45% of patients eligible for anticoagulation are untreated (tolerance/adherence)\(^4\)

---

**Treatment Goals in Non-Valvular AF**

- **AF Diagnosis**
  - Manage Rhythm
    - Ablation
    - Pacing
    - Drugs for Rhythm & Rate Control
  - Manage AF Related Stroke Risk
    - Warfarin (Coumadin®)
    - New Drugs: Dabigatran, Apixaban, Rivaroxaban, Edoxaban
    - Intervention: Ligation, Clips, LAA Closure Devices

And/Or
2014 AHA/ACC/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with AF

• Assess stroke risk with CHA$_2$DS$_2$-VASc score
  - Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
  - Score ≥2: Annual stroke risk 2%-15%, oral anticoagulants are recommended

• Higher CHADS$_2$ score predicts worse outcomes (stroke, major bleeding & vascular mortality)$^1$

• Balance benefit vs. bleeding risk

---

SH-230506-AD June15

January, CT. et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014; doi: 10.1016/j.jacc.2014.03.022

1 RE-LY trial: JW Cardiol Sep 1 2009
Warfarin is an effective means of stroke reduction in patients with AF but can present challenges

- Many patients spend a significant amount of time outside of the therapeutic range.

- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans

44% of bleeding events occur in patients above therapeutic range\(^1\)

48% of thromboembolic events occur in patients below therapeutic range\(^1\)

2 Budnitz, MD, MPH. et al. Annals of Internal Medicine. 2007;147(11); 229
Stroke Treatment Option: warfarin (Coumadin®)

Warfarin Use by CHADS$_2$ Score

- Medicare claims data, 2006-2007$^1$
  - Warfarin use less than 60% in high-risk patients

Warfarin use declines with increased stroke risk

AF Patients Using Warfarin

CHADS$_2$ Score

1 2 3 4 5 6

0% 20% 40% 60% 80% 100%

p < 0.001
(n=27,164)

**Stroke Treatment Option: Novel Oral Anticoagulants (NOACs)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (rate/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban(^1)</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban(^2)</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran(^3) (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban(^4) (60 mg / 30 mg)</td>
<td>33% / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin(^1)(^-)(^4)</td>
<td>17 – 28%</td>
<td>3.1 – 3.6%</td>
</tr>
</tbody>
</table>

There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs.

This chart is not based on a head-to-head trial and is not intended to suggest head-to-head comparisons of the separate trials or the therapies under study.

WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
  - EP/IC or EP&IC, TEE, General Anesthesia, Surgical Back-up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein (Does not require open heart surgery)
- General anesthesia (typical)
- 1 hour procedure (typical)
- 1-2 day hospital stay (typical)
**WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Overview**

**Nitinol Frame**
- Radially expands to maintain position in LAA
- Available sizes: 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter engage LAA tissue for stability and retention
- Features an intra-LAA design to avoid contact with Left Atrial wall

**160 Micron Membrane**
- Polyethylene terephthalate (PET) cap
- Designed to block emboli from exiting the LAA

*Designed specifically for the left atrial appendage*
# WATCHMAN Clinical Studies

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>CAP Registry</th>
<th>PREVAIL</th>
<th>CAP2 Registry</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrolled</strong></td>
<td>800</td>
<td>566</td>
<td>461</td>
<td>579</td>
<td>2406</td>
</tr>
<tr>
<td><strong>Randomized</strong></td>
<td>707</td>
<td>---</td>
<td>407</td>
<td>---</td>
<td>1114</td>
</tr>
<tr>
<td><strong>WATCHMAN: warfarin (2:1)</strong></td>
<td>463 : 244</td>
<td>566</td>
<td>269 : 138</td>
<td>579</td>
<td>1877 : 382</td>
</tr>
<tr>
<td><strong>Mean Follow-up (years)</strong></td>
<td>4.0</td>
<td>3.7</td>
<td>2.2</td>
<td>0.58</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Patient-years</strong></td>
<td>2717</td>
<td>2022</td>
<td>860</td>
<td>332</td>
<td>5931</td>
</tr>
</tbody>
</table>

SH-230506-AD June15
WATCHMAN™ Device Clinical Program

Pilot
- Early feasibility with >6 years of follow-up

PROTECT-AF
- WATCHMAN primary efficacy, CV death, and all-cause mortality superior to warfarin at 4 years¹

CAP Registry
- Significantly improved safety results²

ASAP
- Expected rate of stroke reduced by 77% in patients contraindicated to warfarin³

PREVAIL
- Improved implant success; procedure safety confirmed with new and experienced operators⁴

CAP2
- Enrolled up to 1500 patients at ~ 60 sites

## WATCHMAN™ PROTECT AF Study Overview Long-Term, Final 5-Year Results

<table>
<thead>
<tr>
<th>Study Design &amp; Objective</th>
<th>Prospective, randomized (2:1), non-inferiority trial of LAA closure vs. warfarin in non-valvular AF patients for prevention of stroke</th>
</tr>
</thead>
</table>
| **Primary Endpoint**     | **Efficacy**: Composite end point of stroke, cardiovascular death or systemic embolization  
                          **Safety**: Major bleeding, device embolization or pericardial effusion |
| **Statistical Plan**     | All analyses by intention-to-treat  
                          Bayesian (stratified for CHADS$_2$ score) : Primary Efficacy and Safety endpoints  
                          Cox Proportional: All Secondary Analyses |
| **Patient Population**   | n = 707  
                          Mean CHADS$_2$ = 2.2, CHA$_2$DS$_2$-VASc = 3.5 |
| **Key Inclusion Criteria** | Paroxysmal / Persistent / Permanent AF  
                          CHADS $\geq$ 1 (93% had a CHA$_2$DS$_2$-VASc Score $\geq$2)  
                          Eligible for long-term warfarin therapy |
| **Mean Follow-Up**       | 2,717 patient-years, 48 months |
| **Number of Sites**      | 59 in the United States and Europe  
                          Enrollment Feb 2005 – June 2008 |
## PROTECT AF: Final, 5-Year Primary Efficacy

Events Consistent with 4-Year Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Event Rate (per 100 Pt-Yrs)</th>
<th>Rate Ratio (95% Crl)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td>2.2</td>
<td>0.61 (0.42, 1.07)</td>
<td>&gt;99.9%</td>
<td>95.4%</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>1.5</td>
<td>0.68 (0.42, 1.37)</td>
<td>99.9%</td>
<td>83%</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.2</td>
<td>N/A</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Death (CV/unexplained)</td>
<td>1.0</td>
<td>0.44 (0.26, 0.90)</td>
<td>&gt;99.9%</td>
<td>98.9%</td>
</tr>
</tbody>
</table>


SH-230506-AD June15
Implant Success & Warfarin Cessation

**PROTECT AF**
- Implant success: 91%

**CAP**
- Implant success: 94%

**PREVAIL**
- Implant success: 95%

*Implant success defined as deployment and release of the device into the left atrial appendage.*

**Warfarin Cessation**

<table>
<thead>
<tr>
<th>Study</th>
<th>45-day</th>
<th>12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>87%</td>
<td>&gt;93%</td>
</tr>
<tr>
<td>CAP</td>
<td>96%</td>
<td>&gt;96%</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>92%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

**PREVAIL Implant Success**

No difference between new and experienced operators
- Experienced Operators
  - n=26
  - 96%
- New Operators
  - n=24
  - 93%

*p = 0.28*

Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>0.79 (0.22)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.95 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.22 (0.004)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.56 (0.21)</td>
<td></td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.48 (0.006)</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>0.73 (0.07)</td>
<td></td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.00 (0.98)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.51 (0.002)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Holmes DR, et al. Holmes, DR et al. JACC 2015; In Press. Combined data set of all PROTECT AF and PREVAIL WATCHMAN patients versus chronic warfarin patients SH-230506-AD June15
WATCHMAN™ Device Patient Selection

1. Increased Risk for Stroke & Recommended for Anticoagulation (CHA₂DS₂-VASc ≥ 2)
   - Yes
   - No

2. Suitable for warfarin
   - Yes
   - No

3. Patient Has Appropriate Rationale To Seek a Non-Pharmacologic Alternative to warfarin
   - Yes
   - No

Patient May Be a Candidate for the WATCHMAN™ LAAC Device

* Please refer to product DFU for more specific details on patient selection
Cessation of warfarin is at physician discretion provided that any peri-device flow demonstrated by TEE is ≤5mm. Before 6 months, when seal is adequate, patients can cease warfarin and should begin clopidogrel 75 mg daily and increase aspirin dosage to 300-325 mg daily. This regimen should continue until a total of 6 months have elapsed after implantation.
Disruptive Technology III:

Outpatient Pulmonary Artery Pressure-Guided Therapy and Repeat Hospitalization for Heart Failure
Heart Failure – A Growing Global Concern

Prevalence and Incidence

- Overall 2.1% prevalence: 5.1M heart failure patients in 2010
- 825,000 people ≥ 45 years of age are newly diagnosed each year with HF
- 15M heart failure patients in the ESC 51-member countries
  - Overall 2-3% prevalence

Mortality

- For AHA/ACC stage C/D patients diagnosed with HF:
  - 30% will die in the first year
  - 60% will die within 5 years

HF prevalence in the US is projected to increase 46% from 2012 to 2030, resulting in > 8M people ≥ 18 years of age with HF.

2. The European Society of Cardiology, ESC HF Guideline, 2008
Worsening Heart Failure Leading to HF Hospitalizations Contributes to Disease Progression

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

Graph adapted from: Gheorghiade MD, et al. Am J. Cardiol. 2005
HF Hospitalizations are a Strong Predictor of Mortality\textsuperscript{1,2}

Data from the EFFECT study, n = 9,138 patients\textsuperscript{1}

Among 1 year survivors after index EFFECT-HF discharge, the number of heart failure hospitalizations in the preceding year stratified the risk of death in crude analysis.\textsuperscript{1}

Data from Setoguchi et al., n = 14,374 patients\textsuperscript{2}

KP cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.\textsuperscript{2}

Studies show each admission decreases a patient’s chance of survival.

Economic Burden of HF Will Continue to Rise Through 2030*

- The AHA estimates that the total medical costs for HF are projected to increase to $70B by 2030 → a 2-fold increase from 2013.¹
- 50% of the costs are attributed to hospitalization.²

*Study projections assume HF prevalence remains constant and continuation of current hospitalization practices

Medicare’s Hospital Readmissions Reduction program penalizes hospitals that have above average all-cause readmissions within 30 days following HF discharge. Percent withholding of all inpatient Medicare payments will increase to up to 3% by 2015 and beyond.

Percent withholding of all inpatient Medicare payments will increase to up to 3% by 2015 and beyond.

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>2013</th>
<th>2014</th>
<th>2015+</th>
</tr>
</thead>
<tbody>
<tr>
<td>% payment withholding</td>
<td>up to 1%</td>
<td>up to 2%</td>
<td>up to 3%</td>
</tr>
</tbody>
</table>

3. CMS Hospitals Readmissions Reductions Program of the Patient Protection and Affordable Care Act (PPACA), 2010.
Increases in Pressure Start the Cycle of Worsening Heart Failure

Adapted from Jaski BE, “Basics of Heart Failure A Problem Solving Approach”
Physiologic Markers of Acute Decompensation

Randomized study of 1653 patients

Primary endpoint: Readmission for any reason or death from any cause within 180 days after enrollment

Control group = Standard-of-care (no telemonitoring)

Treatment group = telemonitoring of symptoms and weight

Results: No difference in number of deaths, readmissions or days in hospital

Clinical Examination has Limited Reliability in Assessing Filling Pressures

Data from clinical evaluations has poor sensitivity and predictive value in determining hemodynamic profile

Capomolla, 2005. N = 366

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate of</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP Edema</td>
<td>RAP</td>
<td>48</td>
<td>78</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>94</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Pulse Press</td>
<td>Cardiac Index</td>
<td>27</td>
<td>69</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>S3 Dyspnea</td>
<td>PCWP</td>
<td>36</td>
<td>81</td>
<td>69</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>73</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>90</td>
<td>60</td>
<td>48</td>
</tr>
</tbody>
</table>

Table adapted from Capomolla S, et al. Eur J Heart Failure, 2005.
Pulmonary Artery Pressure Sensor → Patient Electronics System → CardioMEMS™ HF System Website
The pulmonary artery pressure sensor is implanted via a right heart catheterization procedure via femoral vein approach.

CardioMEMS™ HF System

Target location for pulmonary artery pressure sensor
Patients with moderate NYHA class III HF for at least 3 months, irrespective of LVEF and a HF hospitalization within the past 12 months were included in the study.

**CHAMPION Clinical Trial: The Effect of Pulmonary Artery Pressure-Guided Therapy on HF Hospitalizations vs. Standard of Care**

- **550 Pts with CardioMEMS™ HF System Implants**
  - All Pts Take Daily readings

  - **Treatment**
    - 270 Pts
    - Management Based on PA Pressure + Traditional Info

  - **Control**
    - 280 Pts
    - Management Based on Traditional Info

  - **Primary Endpoint:** Rate of HF Hospitalization
    - 26 (9.6%) Exited < 6 Months
    - 15 (5.6%) Death
    - 11 (4.0%) Other

  - **Secondary Endpoints:**
    - Change in PA Pressure at 6 months
    - No. of patients admitted to hospital for HF
    - Days alive outside of hospital
    - QOL

- **26 (9.6%) Exited < 6 Months**
- **20 (7.1%) Death**
- **6 (2.2%) Other**

Patients managed with PA pressure data had **significantly fewer HF hospitalizations** as compared to the control group.

### CHAMPION CLINICAL Trial: Both Primary Safety Endpoints and All Secondary Endpoints Were Met at 6 months

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Treatment (n = 270)</th>
<th>Control (n = 280)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Safety Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device-related or system-related complications</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8 (1%)*</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pressure-sensor failures</td>
<td>0</td>
<td>0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in PA mean pressure (mean AUC [mm Hg 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)

## CHAMPION Clinical Trial: Device/System

<table>
<thead>
<tr>
<th></th>
<th>Consented Not randomized</th>
<th>Treatment</th>
<th>Control</th>
<th>All patients</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Up to 6-Month Follow-up Visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>25</td>
<td>270</td>
<td>280</td>
<td>575</td>
<td></td>
</tr>
<tr>
<td><strong>Device/System Related Complication&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (8.0%)</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
<td>8 (1.4%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>No</td>
<td>23 (92.0%)</td>
<td>267 (98.9%)</td>
<td>277 (98.9%)</td>
<td>567 (98.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Freedom from Device/System Related Complication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exact 95.2% Confidence Interval&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>(97.3%, 99.4%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>a.</sup> A device/system-related complication is an adverse event that is, or is possibly, related to the system (wireless pressure sensor or external electronics) and at least one of the following: is treated with invasive means (other than intramuscular medication or a right heart catheterization with a Swan-Ganz measurement that is used for diagnostic purposes), results in the death of the patient, results in the explant of the device.

<sup>b.</sup> P-value from exact test of binomial proportions compared to 0.80 for All Patients

<sup>c.</sup> Exact (Clopper-Pearson) confidence limits
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trial</th>
<th>Mean Duration of Randomized Follow-Up</th>
<th>Annualized Reduction in HF Hospitalization Rates</th>
<th>NNT per year to Prevent 1 HF Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>COPERNICUS</td>
<td>10 months</td>
<td>33%</td>
<td>7</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>RALES</td>
<td>24 months</td>
<td>36%</td>
<td>7</td>
</tr>
<tr>
<td>CRT</td>
<td>CARE-HF</td>
<td>29 months</td>
<td>52%</td>
<td>7</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>MERIT-HF</td>
<td>12 months</td>
<td>29%</td>
<td>15</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>SOLVD</td>
<td>41 months</td>
<td>30%</td>
<td>15</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>EMPHASIS-HF</td>
<td>21 months</td>
<td>38%</td>
<td>16</td>
</tr>
<tr>
<td>Digoxin</td>
<td>DIG</td>
<td>37 months</td>
<td>24%</td>
<td>17</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Val-HeFT</td>
<td>23 months</td>
<td>23%</td>
<td>18</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>CHARM</td>
<td>40 months</td>
<td>27%</td>
<td>19</td>
</tr>
<tr>
<td>PA pressure monitoring</td>
<td>CHAMPION</td>
<td>17 months</td>
<td>33%</td>
<td>4</td>
</tr>
</tbody>
</table>
Economic Analysis shows that PA pressure Monitoring is Cost Effective

Cost reduction is attributable to:\(^1\):

Reduction in hospitalization

Reduction in mortality

Improvement in quality of life

\$30,167 ICER

BELOW THE US ACCEPTED ICER THRESHOLD OF $50,000 PER QALY\(^2\)

Well under the World Health Organization threshold of approximately $160,000 for the US\(^3\)

1. Adamson et al HRS 2015
2. Weinstein MC Med Care 2008
3. Neumann et al NEJM 2014
Summary: CHAMPION Clinical Trial

- Pulmonary Artery Pressure
- Medication Changes based on Pulmonary Artery Pressure (p < 0.0001)
- Pulmonary Artery Pressure Reduction (p = 0.008)
- Reduction in Heart Failure Hospitalizations (p < 0.0001)
- Quality of Life Improvement (p = 0.024)

Managing pressures to target goal ranges:
- PA Pressure systolic 15–35 mmHg
- PA Pressure diastolic 8–20 mmHg
- PA Pressure mean 10–25 mmHg

CHAMPION Clinical Trial: PA Pressure-Guided Therapy Improves Outcomes in CRT Patients

HF Hospitalization Reduction (6 mo follow-up)

- With CRT: 24%
- Without CRT: 23%

Relative Risk Reduction

p = 0.0264 vs. control

Weiner et al. Heart Rhythm, 2011
CHAMPION Clinical Trial: PA Pressure-Guided Therapy Improves Outcomes in Patients with Preserved Ejection Fraction

- Preserved Ejection Fraction Heart Failure (HFpEF) or diastolic HF patients represent ~50% of all HF patients
- Pulmonary artery pressure-guided therapy significantly reduced HF hospitalizations in HFpEF patients in the treatment group by 46% at 6 months (p<0.0001) and by 50% at 18 months (p<0.0001)
- The effect in HFpEF patients is even more dramatic than HFrEF or systolic patients with an estimated NNT = 2

# CHAMPION Clinical Trial: PA Pressure-Guided Therapy Benefits Patients with Common HF Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>N size (control)</th>
<th>N size (treatment)</th>
<th>HF Hospitalization rate reduction at 15 months in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of myocardial infarction(^1)</td>
<td>137</td>
<td>134</td>
<td>46% (p &lt; 0.001) vs. control</td>
</tr>
<tr>
<td>COPD(^2,3)</td>
<td>96</td>
<td>91</td>
<td>41% (p = 0.0009) vs. control</td>
</tr>
<tr>
<td>Pulmonary hypertension(^4)</td>
<td>163</td>
<td>151</td>
<td>36% (p = 0.0002) vs. control</td>
</tr>
<tr>
<td>AF(^5)</td>
<td>135</td>
<td>120</td>
<td>41% (p &lt; 0.0001) vs. control</td>
</tr>
<tr>
<td>Chronic Kidney Disease(^6)</td>
<td>150</td>
<td>147</td>
<td>42% (p = 0.0001) vs. control</td>
</tr>
</tbody>
</table>

6. Abraham et al., HFSA 2014
Champion Clinical Trial: Substantial reduction in 30-day readmissions in Medicare-eligible patients

- Retrospective analysis of patients 65 years or older (n = 245)
- Compared 30-day readmissions and HF hospitalizations between patients managed with PA pressure vs. Standard of Care
- Results showed statistically significant reductions in readmissions and HF hospitalizations in treatment group

In Medicare-eligible patients 65 years or older PA pressure monitoring with the CardioMEMS™ HF System significantly reduced 30-day readmissions

Champion Clinical Trial: Substantial reduction in Hospitalizations and Mortality in patients on GDMT

Reduction in Mortality

57%

57% Reduction
[HR 0.43, 95% CI 0.24–0.76, p=0.0026]

Abraham, et al. ACC 2015
Champion Clinical Trial: Substantial reduction in Hospitalizations and Mortality in patients with a CRT or ICD on GDMT

Reduction in Mortality

53%

Abraham, et al. HRS  2015
Champion Clinical Trial: Substantial reduction in Hospitalizations and Mortality in patients with a CRT* on GDMT

Reduction in Mortality

64%

* CRT only with GDMT and PAP

*Abraham, et al. HRS 2015
Summary: Managing Pressures to Maintain Health and Manage Acute Events

Enables proactive and personalized HF management \(^1\)\(^-\)\(^3\)

May be used in risk stratification, but not actionable \(^4\)\(^-\)\(^7\)

Unreliable, late, and indirect markers \(^8\)\(^,\)\(^9\)


References:
9. Anker SD, et al. AHA 2010
Titration and Switching Loop Diuretic and Addition of Thiazide Diuretic