HeartWare HVAD for the Treatment of Patients with Advanced Heart Failure Ineligible for Cardiac Transplantation: Results of the ENDURANCE Destination Therapy Trial

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Relevant Financial Relationship Disclosure Statement

Investigational use of the HeartWare® Ventricular Assist Device will be discussed.

FD Pagani: HeartWare research contract managed by the University of Michigan.
**Study Timelines**

**ADVANCE (BTT+CAP)**
- CAP initiated
- BTT enrollment complete
- Favorable FDA panel recommendation
- FDA Approval, November 2012

**ENDURANCE (DT)**
- DT enrollment begins
- DT enrollment complete
- Improved Pump Sintering/Coring Tool
- Primary Endpoint complete
- Enrollment begins (protocol BP management)
- ENDURANCE Supplemental
ENDURANCE Trial Design

A prospective and randomized trial to compare the safety and effectiveness of the HeartWare® HVAD System to a FDA-approved LVAD in patients with end-stage heart failure who do not qualify for heart transplantation.

Primary endpoint:

- Survival at two years free from disabling stroke (Modified Rankin Score ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery

Secondary endpoints:

- Adverse events per INTERMACS definition (version 2.3)
- KCCQ and EuroQol EQ-5D Health Status
- NYHA functional class and 6-minute walk distance
### ENDURANCE Study Devices

**Treatment Device:**
- Continuous flow centrifugal HVAD® Pump
- Pericardial placement
- FDA approved for BTT in 2012

**Control Device:**
- Continuous flow axial pump
- Sub-diaphragmatic placement
- FDA approved for BTT in 2008, DT in 2010
ENDURANCE Trial Design

Patients randomized from 04 August 2010 through 08 May 2012

Advanced HF Patients not eligible for HTX (n=559)

Randomized 2:1 (n=446)

Screening Failures (n=113)

Top 3 reasons for Screen Failure:
• Body habitus
• Unwillingness to comply with study requirements
• LVEF

Intent-to-treat (primary endpoint)

control (n=148)

Control (n=149)

As treated* (safety population)

HVAD (n=296)

HVAD (n=294) 99.3%

2-year follow up

*Crossovers: HVAD to control (N=4); control to HVAD (N=3)
## Patient Characteristics and Demographics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>HVAD (n=297)</th>
<th>Control (n=148)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.9</td>
<td>66.2</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76.4%</td>
<td>82.4%</td>
<td>0.18</td>
</tr>
<tr>
<td>Female</td>
<td>23.6%</td>
<td>17.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>173.8</td>
<td>175.5</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Body Surface Area (m²)</strong></td>
<td>2.0</td>
<td>2.0</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>INTERMACS Profile</strong></td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>1</td>
<td>3.4%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29.0%</td>
<td>31.1%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40.4%</td>
<td>40.5%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19.9%</td>
<td>18.2%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.0%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.3%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.0%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic Etiology of Heart Failure</strong></td>
<td>57.9%</td>
<td>60.1%</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>68.0%</td>
<td>62.2%</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Stroke/TIA</strong></td>
<td>19.2%</td>
<td>16.2%</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Arrhythmia</strong></td>
<td>78.1%</td>
<td>83.1%</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Severe Tricuspid Insufficiency</strong></td>
<td>11.8%</td>
<td>5.4%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Inotropes (pre-implant)</strong></td>
<td>71.3%</td>
<td>71.1%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td><strong>Hypertension requiring medication</strong></td>
<td>65.3%</td>
<td>70.9%</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Zone of Non-Inferiority
Pre-specified Margin = 15%

Difference in Success Outcomes

Non-inferior
P < 0.001

Non-inferior
P = 0.005

Inferior
P = 0.095

Inferior
P = 0.25

Upper 1-sided 95% Confidence Intervals
P values provided for example only

Non-inferiority Margins

-10%  -5%   0%    5%    10%   15%   20%
Primary Endpoint - Achieved

Survival at two years free from disabling stroke (MRS ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery.

Non-Inferiority

P value = 0.0060
Primary Endpoint Non-inferiority Margins

Zone of Non-Inferiority
Pre-specified Margin = 15%

Difference in Success Outcomes

-10% -5% 0% 5% 10% 15% 20%

ITT (As randomized) n=297
P-value 0.0060

As treated n=296
P-value 0.0060

Sintered (As treated) n=200
P-value 0.0025

Sintered HVAD Pump = currently available pump
Primary Endpoint - Sintered HVAD vs. Control

Survival at two years free from disabling stroke (MRS ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery.

Non-Inferiority
P value = 0.0025

Event Free Rate

<table>
<thead>
<tr>
<th>Days</th>
<th>HVAD (n=200)</th>
<th>Control (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>200</td>
<td>149</td>
</tr>
<tr>
<td>365</td>
<td>145</td>
<td>106</td>
</tr>
<tr>
<td>730</td>
<td>109</td>
<td>80</td>
</tr>
<tr>
<td>1095</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

Sintered HVAD Pump = currently available pump
### Binary Summary of Primary Efficacy Endpoint

#### Stroke Free Survival at 2 years

<table>
<thead>
<tr>
<th></th>
<th>HeartWare (n=297)</th>
<th>Control (n=148)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success</strong></td>
<td>164 (55.2%)</td>
<td>85 (57.4%)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>133 (44.8%)</td>
<td>63 (42.6%)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

#### Reasons for Failure

<table>
<thead>
<tr>
<th>Reason</th>
<th>HeartWare (n)</th>
<th>Control (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient dies</td>
<td>103 (34.7%)</td>
<td>39 (26.4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Device malfunction, failure requiring exchange, urgent transplant, explant</td>
<td>26 (8.8%)</td>
<td>24 (16.2%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Subject has disabling stroke (MRS ≥4 at 24 weeks)</td>
<td>3 (1.0%)</td>
<td>0 (0.0%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Imputed failure*</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

* Patient experienced a stroke prior to their 2 year endpoint, and died beyond the 2 year endpoint, but before the 24 week MRS assessment.

Note: ENDURANCE defined each component hierarchically – e.g., if a patient has a disabling stroke and dies, they are counted as a death.
Kaplan-Meier Survival

**Overall HVAD Compared to Control**

Log rank P value = 0.170

- HVAD (n=296) 67.6%
- Control (n=149) 60.2%

Days 0 365 730

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>212</th>
<th>158</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVAD</td>
<td>296</td>
<td>212</td>
<td>158</td>
</tr>
<tr>
<td>Control</td>
<td>149</td>
<td>108</td>
<td>86</td>
</tr>
</tbody>
</table>
**Kaplan-Meier Survival**

**Sintered HVAD Compared to Control**

![Graph showing Kaplan-Meier Survival](Image)

- **Event Free Rate**
  - HVAD (n=200) vs Control (n=149)

- **Log rank P value = 0.284**
  - HVAD: 67.6%
  - Control: 61.4%

- Sintered HVAD Pump = currently available pump
NYHA Classification and 6 Minute Walk

Sustained improvements in patients’ NYHA Classification*

Sustained and significant increase in total distance walked in both cohorts.*

*P=NS for all HVAD vs. Control comparisons
EQ-5D VAS and Overall KCCQ

Statistically significant improvements compared to baseline in EuroQol-5D Visual Analog Scores in both cohorts*

Sustained and significant improvements in Kansas City Cardiomyopathy Questionnaire overall summary scores in both cohorts*

*P=NS for all HVAD vs. Control comparisons
# Overall CEC Adjudicated Adverse Events

**INTERMACS defined events through 2 years**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>HVAD (n=296)</th>
<th>Control (n=149)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of events</td>
<td>EPPY (410.02PY)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Bleed</td>
<td>176 (59.5%)</td>
<td>400</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>103 (34.8%)</td>
<td>225</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Cardiac Arrhythmia</strong></td>
<td>111 (37.5%)</td>
<td>175</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driveline Infection</td>
<td>201 (67.9%)</td>
<td>452</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>56 (18.9%)</td>
<td>72</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>85 (28.7%)</td>
<td>110</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>50 (16.9%)</td>
<td>65</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemorrhagic CVA</td>
<td>42 (14.2%)</td>
<td>45</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>24 (8.1%)</td>
<td>27</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Renal Dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43 (14.5%)</td>
<td>54</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Right Heart Failure</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>110 (37.2%)</td>
<td>129</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Pump Exchange</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 (7.8%)</td>
<td>27</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*There was no statistical difference in the rate of RHF in the sintered cohort vs. Control.
Sintering reduced the overall rate of any suspected pump thrombus, and both overall thrombus rates and exchanges for thrombus were less frequent in patients with the currently available HVAD pump compared to control.
HVAD Thrombus Risk Factor Multivariable Analysis

- MAP (>90 mmHg) [Odds Ratio: 6.6, P-value: <0.0001]
- ASA (≤81 mg) [Odds Ratio: 3.3, P-value: 0.002]
- Non-therapeutic INR [Odds Ratio: 2.7, P-value: 0.006]
- Non-Sintered Pump [Odds Ratio: 2.1, P-value: 0.033]

Statistically significantly more HVAD patients (7.3%, 0.07 EPPY) had a sub-therapeutic INR <2.0 compared to control patients (2.2%, 0.02 EPPY), P=0.04.
Statistically significantly more HVAD patients (7.3%, 0.07 EPPY) had a subtherapeutic INR ≤2.0 compared to control patients (2.2%, 0.02 EPPY), P=0.04.
HCVA Risk Factor Multivariable Analysis (HVAD)

- MAP (> 90 mmHg): Odds Ratio 9.5, P-value <0.0001
- ASA (≤ 81 mg): Odds Ratio 4.5, P-value <0.0001
- INR (> 3): Odds Ratio 5.0, P-value 0.001
Influence of Blood Pressure on Stroke (HVAD)

- BP management is associated with improved neurological outcomes.
- Blood pressure management was not mandated in ENDURANCE.

**ICVA**
- 34/208 (17%)
- 11/88 (13%)
- 34% fewer

**HCVA**
- 34/208 (17%)
- 8/88 (10%)
- 44% fewer
Limitations

• Randomization was not stratified by site

• Changes to the study device and implant tools introduced mid-study may have impacted adverse events and/or outcomes

• Blood pressure management was not mandated in the protocol and varied among sites during follow-up

• Treatment arm had a higher rate of sub-therapeutic anticoagulation during follow-up
Summary

• Primary Endpoint achieved

• Patients had significant and sustained improvements in functional and quality of life measures

• Device malfunctions leading to exchange or urgent transplant were more frequent in the control group, whereas strokes occurred more frequently in the HVAD group

• Device and design improvements, including sintering of the inflow cannula, resulted in a reduction in pump thrombosis

• Elevated MAP was the strongest predictor of stroke by multivariable analysis. HVAD patients with well-managed blood pressure had fewer strokes
Conclusion

- There was no difference between HVAD and control in survival at two years free from disabling stroke (Modified Rankin Score $\geq 4$ at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery.
Future Directions

• Blood pressure management appears to reduce neurologic events and is being studied in the ongoing ENDURANCE Supplemental Trial
Acknowledgements

• ENDURANCE Investigators
• Clinical site coordinators
• Patients and families