Ventricular Restraint Therapies: Beyond Acorn and HeartNet

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Disclosure

• Consultant to Acorn
• PI of Acorn MV Pivotal Trial
Ventricular Restraint Devices

Clinical Trial
CorCap (Acorn)
HeartNet (Paracor)

Pre-Clinical
Agisyl-LVR (Symphony)
Theory of Operation
Restraining Device

Injury

Ventricular remodeling

Systemic neurohormonal activation

Reduced cardiac function

Ventricular dilation

CSD Implant

Reduces wall stress, myocardial stretch

Reverse remodeling

Improved efficiency

Improved cardiac function

Increased ventricular wall stress, stretch

Modified gene expression
Impact on Heart Failure Progression

CorCap™ CSD Therapy

- Provides Diastolic Support
- Reduces Wall Stress/Myocardial Stretch
- Halts Progressive Dilation
- Promotes Reverse Remodeling
- Improves Cardiac Function

Diastolic Wall Stress = \frac{\text{Radius} \times \text{Transmural Pressure}}{\text{Wall Thickness}}

\text{(Myocyte Stretch)}

\text{Transmural Pressure} = \text{LVEDP} - \text{CorCap™ CSD Counter Pressure}

10\text{mmHg} = 15\text{mmHg} - 5\text{mmHg}
The CorCap is designed to:

- Provide end-diastolic ventricular support to reduce wall stress and myocardial stretch
- Reduce the stimulus for ventricular remodeling and promote reverse remodeling
- Improve cardiac structure and patient functional status

CorCap Reverses the Progression of Heart Failure
Sep 2000 -- CorCap CE Marking
Jun 2004 -- US 300-pt randomized trial completed which meets pre-specified primary and secondary endpoints

2005-2006 – Two FDA advisory panels:
- Mitral stratum showed safety but needed more efficacy data
- CorCap-only stratum showed efficacy but needed more safety data
- Recommended more confirmatory clinical data (not new trial)

Per panel recommendations, Acorn and FDA negotiated confirmatory trials for MVR and CorCap-only (Gen II-minimal invasive)
--separate trials of both started in US
Acorn Randomized Trial Design

300 Patients

Mitral Surgery Stratum
- 193 Patients
  - Control: MVR Alone, 102 Patients
  - Treatment: MVR plus CSD, 91 Patients

No Mitral Surgery Stratum
- 107 Patients
  - Control: Med Rx Alone, 50 Patients
  - Treatment: Med Rx plus CSD, 57 Patients

(Randomized)

Inclusion Criteria:
- NYHA class II – IV HF of ischemic or non-ischemic etiology
- LVEF < 35% and LVEDD > 60 mm
- Stable optimal medical therapy
Primary Endpoint: Clinical Composite

Assessment of patient functional status after a minimum of 12 months of follow-up

<table>
<thead>
<tr>
<th>Patient Classification</th>
<th>Any One Of</th>
<th>Survival</th>
<th>MCP(^{(1)})</th>
<th>Worsened NYHA</th>
<th>Same NYHA</th>
<th>Improved NYHA</th>
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</thead>
<tbody>
<tr>
<td>Worsened</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Improved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

(1) Adjudicated Major Cardiac Procedures indicative of HF Progression: Transplant, LVAD, CABG, BiV Pacing, and MV surgery (repeat)
# Primary Composite Endpoint Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>38%</td>
<td>27%</td>
<td>1.73 (1.07, 2.79)</td>
<td>0.024</td>
</tr>
<tr>
<td>Same</td>
<td>25%</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>37%</td>
<td>45%</td>
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</tbody>
</table>

As of common closing date (4 July 2004)
Median Follow-up = 23 months
Comparative Changes in LVEDV

- SOLVD(1) Enalapril
- ANZ(2) Carvedilol
- Miracle(3) CRT
- Miracle(4) ICD
- CorCap No MVR (12 Mos.)
- CorCap MVR (12 Mos.)

2. Doughty et al, JACC 1997; 29:1060  
3. Medtronic SSE P010015  
4. Young et al JAMA 2003;289:2689
Patient subgroups based on LVEDDi
Best responses in \( \geq 30 \text{ mm/m}^2 \) and \( \leq 40 \text{ mm/m}^2 \) subgroup
Implications for Patient Selection
Focused Cohort Analysis

In patients with LVEDDi ≥ 30 mm/m² and ≤ 40 mm/m²:
- Stronger primary endpoint (OR=2.45; p=0.011)
- 34% reduction in mortality (p=0.17)
- Significant reduction in MCP (p=0.013)
- Significant reduction in Death/HF related hospitalizations (p=0.04)
- In No MVR stratum, primary endpoint OR=8.33; p=0.006
- Consistent benefit in secondary endpoints
  MLHF (p=0.045), SF-36 (p=0.0001), LVEDD (p=0.008), LVESD (p=0.12), LV Mass (p=0.18)

Avoid patients LVEDDi ≥ 40 mm/m²
Major Cardiac Procedures
Focused Cohort n=159

Logrank = 6.1839
p = 0.013
Death/CHF Hospitalization
Focused Cohort n=159

Logrank = 4.1516
p = 0.042
No MVR (CSD only) Stratum

5 year Follow Up Data

Patients Enrolled:  6/00 – 6/03
5 Year follow up Complete:  6/08
# Reportable Adverse Events (> 5% Incidence)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=152)</th>
<th>CSD (n=148)</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td># Patients</td>
<td>%</td>
<td># Patients</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>58</td>
<td>38.2</td>
<td>48</td>
</tr>
<tr>
<td>Bleeding</td>
<td>14</td>
<td>9.2</td>
<td>9</td>
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<tr>
<td>Hemodynamic Compromise</td>
<td>73</td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>Infection/Pneumonia</td>
<td>35</td>
<td>23.0</td>
<td>46</td>
</tr>
<tr>
<td>Neurological Deficit/Stroke</td>
<td>11</td>
<td>7.2</td>
<td>16</td>
</tr>
<tr>
<td>Pulmonary Compromise</td>
<td>22</td>
<td>14.5</td>
<td>29</td>
</tr>
<tr>
<td>Renal Compromise</td>
<td>8</td>
<td>5.3</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>58</td>
<td>38.2</td>
<td>59</td>
</tr>
<tr>
<td>Any of the Above AE</td>
<td>118</td>
<td>77.6</td>
<td>120</td>
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</tbody>
</table>

No device related AEs; No AEs related to Cardiac Constriction up to 5 yrs follow up
No MVR Stratum: 5 year follow up LVEDV

Key Findings: Control group worsens over time (as expected) but CorCap has durable/persistent effect to reduce LV size now over 5 years of follow up.

<table>
<thead>
<tr>
<th>Trt</th>
<th>39</th>
<th>40</th>
<th>33</th>
<th>19</th>
<th>27</th>
<th>17</th>
<th>11</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Ctl</td>
<td>34</td>
<td>33</td>
<td>28</td>
<td>19</td>
<td>14</td>
<td>19</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>
5 year follow up – No MVR Stratum – Sphericity index

Key finding: Effect of Cor Cap persists over 5 years but is not significant

Est. Treatment Diff. = 0.036
p-value = 0.285
Key Finding: Treatment group tends to have fewer deaths and MCPs
MVR Stratum: 5 year follow up LVEDV

Key finding: CorCap still adds benefit to MV surgery – durable effect without attenuation

![Graph showing LVEDV over follow-up months for treatment and control groups.](chart)

- Treatment group: Trt
  - 72, 64, 64, 45, 49, 29, 24, 15
- Control group: Ctl
  - 72, 63, 60, 36, 44, 23, 27, 12

Est. Treatment Diff. = -16.5
p-value = 0.050
CorCap/MVR Confirmatory Trial Overview

- CorCap implant concomitant to mitral valve repair or replacement utilizing focused cohort criteria
  - \( \text{LVEDDi} > 30 \text{ mm/m}^2 \) and \( < 40 \text{ mm/m}^2 \)

- 50 patients at up to 15 sites (treatment only)

- Patients “enrolled” at the time of CorCap implant

- Primary endpoints based on 6-month follow-up

- Patients followed annually out to 5 years

- Interim look allowed with potential expansion without statistical penalty (can go up to 75 patients)
CorCap/MVR Confirmatory Trial
Endpoints

• Primary Efficacy Endpoints (must meet 3 of 4):
  ▪ Minnesota Living with Heart Failure (MLHF)
    ▪ Patients must show ~ 20 point improvement
  ▪ Death and heart failure related hospitalization
    ▪ approximate maximum of 13 patients
  ▪ Six minute walk test
    ▪ ~ 38 m improvement
  ▪ Cardiopulmonary exercise test (PVO$_2$)
    ▪ ~ 1 ml/kg/min improvement in PVO$_2$

• Primary Safety Endpoint: Peri-operative mortality
  ▪ No more than 3 peri-operative deaths
CorCap Gen2 CSD - Modifications

- High compliance fabric to eliminate hand tailoring (self fitting)
  - Changes to Manufacturing process

- Incorporation of a silicone band into the hem of the device to facilitate fit and stabilization of the device on the heart
  - Sutures no longer required to keep the device in place around the AV groove
  - A pattern of tungsten printed on the band so that it is visible under fluoroscopy

- Open Apex for placement via thoracotomy
Gen2 CorCap Differences

Gen1 CorCap (sternotomy)
- Attachment Sutures in AV Groove
- Low Compliance Fabric
- Tailored Anterior Seam

Gen2 CorCap (min invasive)
- Elastic Band (self attaching with radiopaque markers)
- Open Apex (tailored to length)
- High Compliance Fabric - self fitting
Gen2 System – What is it?

4 Components to Gen2 System:
1. Gen2 CorCap
2. Delivery Tool
3. Pericardial Edge Management Strips (PEMS)
4. Epicardial Management Strips (EMS)
Gen2 – The Procedure

- Access apex of heart through pericardium
Gen2 – The Procedure

- (Loaded Delivery Tool)
Gen2 – The Procedure

- Perform fine adjustments (2 inch) to individual fingers
Close opening in CSD, trim excess material, and verify CorCap location
20 pts received Gen II min invasively in US successfully as sole intervention

New pivotal trial of Gen II Acorn CorCap planned
HeartNet Implant

- Super-elastic compliant nitinol structure
- Defibrillation & pacing compatible
- MRI compatible

- Delivered with special delivery system through mini-thoracotomy
- Self-anchoring, self-tensioning
- Pre-sized based on echo measurements
## Safety and Feasibility Trial: Echo Paired Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6-mo F/U</th>
<th>12-mo F/U</th>
<th>18-mo F/U</th>
<th>24-mo F/U</th>
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<tbody>
<tr>
<td></td>
<td>Mean Δ</td>
<td>n</td>
<td>p-val</td>
<td>Mean Δ</td>
</tr>
<tr>
<td>LVEDD [cm]</td>
<td>-0.3</td>
<td>39</td>
<td>0.01</td>
<td>-0.4</td>
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<tr>
<td>LVESD [cm]</td>
<td>-0.1</td>
<td>39</td>
<td>0.3</td>
<td>-0.2</td>
</tr>
<tr>
<td>LVEDV [ml]</td>
<td>-29</td>
<td>43</td>
<td>0.004</td>
<td>-22</td>
</tr>
<tr>
<td>LVESV [ml]</td>
<td>-26</td>
<td>43</td>
<td>0.006</td>
<td>-19</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>1.4</td>
<td>43</td>
<td>0.1</td>
<td>1.2</td>
</tr>
<tr>
<td>LV Mass [gm]</td>
<td>-18</td>
<td>36</td>
<td>0.06</td>
<td>-6</td>
</tr>
<tr>
<td>MR</td>
<td>0</td>
<td>40</td>
<td>0.64</td>
<td>-0.2</td>
</tr>
<tr>
<td>E / E’</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-2.7</td>
</tr>
</tbody>
</table>
PEERLESS-HF (randomized prospective multi centered)

**Purpose**
- To determine the safety and efficacy of the HeartNet™ Ventricular Support System when used in addition to optimal medical and device therapy in patients with heart failure
Pivotal trial stopped early for failure to meet predetermined endpoints.
The primary component of the device is a “self-gelling”, biocompatible, absorbable hydrogel implant that consists of alginate.

Direct implantation (injection) of the alginate biopolymer into the myocardium of the left ventricular wall is intended to reshape and reduce the LV chamber size and prevent the progressive ventricular dilation and remodeling associated with HF.
Summary of Proof of Concept
Algisyl-LVR in a Chronic Heart Failure Model

- Strategically placed therapeutic injections of small amounts of a biopolymer restores left ventricular geometry and can reverse effects of acute and chronic remodeling, preserving function.

- Based on studies in a large animal heart failure model, small quantities of biopolymer injected at specific local points significantly reduce wall stress and suggest a positive therapeutic impact as presented in the pre-meeting materials.
Canine Model of Chronic Heart Failure
Alginate Implants (struts) at 3 months
Canine Model of Chronic Heart Failure
Direct injections of biopolymers prevent the progression in LV end-diastolic

Canine Model of Chronic Heart Failure
Direct injections of biopolymers prevent the deterioration in LV ejection fraction

Algisyl-LVR in a Chronic HF Model
Beneficial Changes in LV Size and Shape

End-Systole LAO Projection (# 07-052)

Pre-Treatment 2 weeks Post-Treatment
Summary of Proof of Concept
Algisyl-LVR in a Chronic Heart Failure Model

Demonstrated:
Meaningful changes in size, shape and function of the LV
Changes are produced rapidly - within 2 weeks
Changes are durable - at least 6 months

Clinical Studies began in Europe 2009
Summary and Future Implications

Medical therapies are excellent but do not prevent progressive adverse remodeling.

**Ventricular Restraint Devices** that actively reshape, resize, and reverse remodel the heart have proven effective in short term and will be the focus of clinical investigation in heart failure.

CorCap has demonstrated sustained ventricular reverse remodeling and safety up to 5 yrs with significant decrease in death and MCPs (focus cohort);

Can be placed minimally invasively (Gen II)—feasibility/safety study completed; new pivotal study pending.

Follow-up FDA sponsored single arm study in MV Repair pts on going.

Long term follow up is required to establish if the natural history of heart failure is altered.