Safety and Performance of a Novel Beating-Heart Mitral Valve Repair System: 1-Year Outcomes

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James S. Gammie, MD on behalf of the HARPOON EFS and CE trial investigators:

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>• Consulting Fees/Honoraria</td>
<td>• Edwards Lifesciences</td>
</tr>
<tr>
<td>• Founder</td>
<td>• Harpoon Medical</td>
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</tbody>
</table>
The Majority of Severe Degenerative Mitral Regurgitation Patients are Untreated


4,100,000
Total MR patients

1,670,000
Eligible for treatment (MR 3/4+)

30,000
Annual MV surgery rate: ~2%

Reasons eligible patients do not receive mitral surgery include:

- Asymptomatic
- Symptomatic but not diagnosed
- Not referred
- Patients refuse surgery
Mitral repair is associated with better outcomes than replacement for patients with degenerative leaflet prolapse, repair rates have been stable between 2011 and 2016 and approximated 80%.
Individual Surgeon Volume Influences MV Repair Rate and Outcomes

5,475 DMR patients underwent MV operations in NY state

MV repair rate in degenerative MV disease 67%

Higher total annual surgeon volume associated with
• Increased repair rates
• Steady decrease in reoperation risk
• Improved 1-year survival

Surgeons perform median of 10 mitral valve procedures / year

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Although Mitral Repair is the Gold Standard for Severe DMR, Challenges Remain

Cleveland Clinic Experience

- 2,575 patients with isolated posterior leaflet repair
- Recurrent MR at 2 weeks:
  - Moderate: 6%
  - Severe or moderate-severe: 5%
- 89% of patients with ≤ mild MR at 2 weeks

Surgical Arm of EVEREST II

- 80 patients with surgical repair
- Replacement 14%
- One year:
  - Death: 6%
  - Reoperation 2%
  - Recurrent moderate or severe MR: 17%
- 76% of patients with ≤mild MR at 1 year

Feldman. NEJM 2011
HARPOON Beating-Heart Mitral Valve Repair System

Beating-heart, image-guided chordal mitral valve repair

Goals:

- Replicate ePTFE non-resectional MV repair
- Transventricular, beating-heart
- Address the needs of DMR surgical candidates early in the treatment continuum

Image Courtesy A. M. Gillinov, MD
HARPOON Beating-Heart Mitral Valve Repair System

Delivery System and Introducer

- Simple, minimally-invasive, beating-heart, off pump repair
- Echo-guided chordal placement
- Real-time confirmation MR reduction

- Pre-loaded ePTFE suture
- Low-profile 9F shaft
- Hemostatic valve
- Self-tying, double-helix knot on ePTFE suture
Two Prospective, Multicenter, Single-Arm Trials

- Patients with severe mitral regurgitation due to isolated posterior leaflet prolapse were treated with HARPOON system*
- Follow-up ongoing to 3 years
- Serious Adverse Events adjudicated by a Clinical Events Committee
- Echocardiographic analyses: Independent Core Laboratory (Massachusetts General Hospital – Judy Hung, M.D.)
- Aggregated experience from EFS and CE studies are reported here

*For EFS, patients with moderate-to-severe MR were included

Early Feasibility Study (EFS)
N=13
2 Sites in Poland
Patients enrolled Feb 2015-Feb 2016

TRACER CE Mark Trial
N=52
6 Sites in Europe
Patients enrolled Mar 2016-Nov 2017
### Inclusion and Exclusion Criteria

#### Key Inclusion Criteria
- ≥18 years of age
- Severe degenerative mitral regurgitation*
- Isolated posterior leaflet prolapse
- Good predicted surface of coaptation

#### Key Exclusion Criteria
- Anterior or bileaflet prolapse
- Functional mitral regurgitation
- Infective endocarditis
- Severely calcified mitral leaflets
- Severe left ventricular dysfunction
- Renal insufficiency
- STS risk score* >6% or EuroSCORE >8%

*For EFS, patients with moderate-to-severe MR were included

* For mitral valve repair
Participating Sites

**EFS**

John Paul II University Hospital, Krakow, Poland  
(n=10)

Institute of Cardiology, Warsaw, Poland  
(n=3)

**TRACER CE Trial**

John Paul II University Hospital, Krakow, Poland  
(n=11)

Institute of Cardiology, Warsaw, Poland  
(n=15)

The Royal Brompton Hospital, London, UK  
(n=8)

Southampton General Hospital, Southampton, UK  
(n=8)

Ospedale San Raffaele, Milan, Italy  
(n=4)

University of Padova Hospital, Padova, Italy  
(n=6)
Patient Enrollment and Follow-Up

Enrolled (Intent to Treat)
N=65

Implanted (As Treated)
N=62 (95.4%)

1-Year Follow-Up
N=52

Converted to open surgery n=2
Procedure aborted n=1
Death n=2
Study exit due to secondary intervention n=8

Mean study follow up is 1.4 ± 0.6 years
One year clinical follow up was 100%
One year Echo core lab follow up for the 52 patients at 1 year was 100%
## Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>% or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 12</td>
</tr>
<tr>
<td>Male</td>
<td>76%</td>
</tr>
<tr>
<td>STS</td>
<td>0.6 ± 0.6%</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>1.2 ± 1.1%</td>
</tr>
<tr>
<td>NYHA Functional Class I / II / III / IV</td>
<td>41 / 41 / 19 / 0%</td>
</tr>
<tr>
<td>LVEF</td>
<td>69 ± 6%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>19%</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>53.2 ± 5.2</td>
</tr>
</tbody>
</table>
# Intraoperative Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Procedure Time (minutes)</td>
<td>126 ± 36 (72-222)</td>
</tr>
<tr>
<td>Introducer Time (minutes)</td>
<td>42 ± 18 (18-126)</td>
</tr>
<tr>
<td>Intraoperative Blood Loss* (mL)</td>
<td>272 ± 182 (50-949)</td>
</tr>
<tr>
<td>Chords Implanted</td>
<td>4.0 ± 1.1 (0-7)</td>
</tr>
</tbody>
</table>

* Data collected for TRACER CE Mark study only, N=51
<table>
<thead>
<tr>
<th>Outcome</th>
<th>% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0% (0/62)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0% (0/62)</td>
</tr>
<tr>
<td>Reintubation**</td>
<td>0% (0/49)</td>
</tr>
<tr>
<td>Blood transfusion***</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>Atrial Fibrillation****</td>
<td>18% (9/50)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>0% (0/62)</td>
</tr>
</tbody>
</table>

* Perioperative is defined as from new onset complications from procedure to discharge
** Data collected for TRACER CE Mark study only
*** Blood transfusion only collected in EFS.
**** Atrial Fibrillation only summarized for those without baseline Atrial Fibrillation

EFS+CE AT cohort
# Safety Outcomes at 1 Year

<table>
<thead>
<tr>
<th>Event</th>
<th>Cumulative Events</th>
<th>Probability Event Free (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2</td>
<td>0.967 (0.922-1.000)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1.000 (1.000,1.000)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td>0.984 (0.952,1.000)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>0</td>
<td>1.000 (1.000,1.000)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>8</td>
<td>0.866 (0.780, 0.953)</td>
</tr>
</tbody>
</table>

*EFS+CE AT cohort*
Severity of Mitral Regurgitation (including reoperations)*

- **Baseline** (N=57): 7% Severe, 93% None/Trace
- **Discharge** (N=58): 2% Severe, 74% None/Trace
- **30 Day** (N=61): 2% Severe, 61% None/Trace
- **6 Month** (N=60): 8% Severe, 50% None/Trace
- **1 Year** (N=60): 2% Severe, 45% None/Trace

*Three patients had moderate MR at baseline per TTE but pre-procedure TEE showed severe MR.*
Severity of Mitral Regurgitation*

* Three patients had moderate MR at baseline per TTE but pre-procedure TEE showed severe MR
98% of Patients in NYHA Functional Class I/II at 1 Year

- Baseline: 19% NYHA Class I, 41% NYHA Class II, 41% NYHA Class III
- 30 Day: 21% NYHA Class I, 79% NYHA Class II
- 6 Month: 5% NYHA Class I, 95% NYHA Class II
- 1 Year: 2% NYHA Class I, 92% NYHA Class II

N=59, N=58, N=57, N=52
# Cardiac Remodeling Improvements Sustained at 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 Day</th>
<th>1 Year</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEDD (mm)</strong></td>
<td>53 ± 5</td>
<td>49 ± 5</td>
<td>47 ± 6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>69 ± 6</td>
<td>61 ± 5</td>
<td>63 ± 6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>LVEDV (mL)</strong></td>
<td>153 ± 41</td>
<td>120 ± 28</td>
<td>120 ± 28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MV Annular Diameter (mm)</strong></td>
<td>35 ± 5</td>
<td>32 ± 5</td>
<td>31 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MV Gradient (mmHg)</strong></td>
<td>NA</td>
<td>1.3 ± 0.5</td>
<td>1.4 ± 0.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

*P-values were based on testing of baseline versus 1 year EFS+CE AT cohort*
Reoperations Within One Year (n = 8/62)

<table>
<thead>
<tr>
<th>Findings</th>
<th>N</th>
<th>Days to Reop</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td>27</td>
<td>Proper pre-operative screening</td>
</tr>
<tr>
<td>Indentation at LV insertion site due to excessive reverse remodeling and tension on the chords</td>
<td>1</td>
<td>279</td>
<td>Procedural technique</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sufficient tissue-to-gap ratio</td>
</tr>
<tr>
<td>ePTFE chord damage due to sharp clamp</td>
<td>1</td>
<td>253</td>
<td>Procedural technique</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Minimum of 3 chords</td>
</tr>
<tr>
<td>ePTFE knot untied at ventricle</td>
<td>1</td>
<td>72</td>
<td>Procedural technique</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Proper imaging, target analysis</td>
</tr>
<tr>
<td>Damage to the native chord</td>
<td>1</td>
<td>231</td>
<td>Procedural technique</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Updated surgeon training</td>
</tr>
<tr>
<td>ePTFE chordal rupture</td>
<td>2</td>
<td>230, 352</td>
<td></td>
</tr>
<tr>
<td>Insufficient chord placement resulting in rupture</td>
<td>1</td>
<td>226</td>
<td></td>
</tr>
</tbody>
</table>

* P-values were based on testing of baseline versus 1 year
Early Learnings Led to Key Improvements

**Patient Screening**

- Tissue-to-gap length of 1.5 → 2.0
- Exclude excessive leaflet or annular calcium
- 3D echo images required for screening

**Procedural Steps**

- Avoid annular reduction more than 5mm
- Implant minimum of 3 chord pairs
- Verify relaxation of the chords during diastole
Conclusions

- These results demonstrate a good safety profile of the HARPOON beating-heart mitral valve repair system.

- Favorable cardiac remodeling and MR reduction was observed at 1 year; early learnings will inform and likely improve future results.

- Proper patient selection, procedural technique, and training are crucial for success.

- Ongoing follow-up and additional investigation will assess the longer term safety and performance of this novel technology.
Thank you

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