Percutaneous Mitral Valve Repair: Results of the EVEREST II Trial

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The Cardiovascular Research Foundation
Catheter-based mitral valve repair
MitraClip System
Post Procedure
Atrial view
**evalve clip MV repair: clinical experience**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST I (Feasibility)*</td>
<td>Non-randomized</td>
<td>55</td>
</tr>
<tr>
<td>EVEREST II*</td>
<td>Pre-randomization</td>
<td>60</td>
</tr>
<tr>
<td>EVEREST II</td>
<td>High Risk Registry</td>
<td>78</td>
</tr>
<tr>
<td>EVEREST II (Pivotal)</td>
<td>Randomized patients</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>(2:1 MitraClip to Surgery)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>184 MitraClip</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95 Surgery</td>
</tr>
<tr>
<td>REALISM (Continued Access)</td>
<td>High Risk &amp; Non High Risk</td>
<td>266</td>
</tr>
<tr>
<td>European Experience</td>
<td></td>
<td>472</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,115 MitraClip</strong></td>
<td></td>
</tr>
</tbody>
</table>

EVEREST II: randomized clinical trial

Study design

279 Patients enrolled at 37 sites

Significant MR (3+-4+)
Specific Anatomical Criteria

Randomized 2:1

Device Group
MitraClip System
N=184

Control Group
Surgical Repair or Replacement
N=95

Echocardiography Core Lab and Clinical Follow-Up:
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years
## EVEREST II: randomized clinical trial

### Key inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Candidate for MV Surgery</td>
<td>• AMI within 12 weeks</td>
</tr>
<tr>
<td>• Moderate to severe (3+) or severe (4+) MR</td>
<td>• Need for other cardiac surgery</td>
</tr>
<tr>
<td>- Symptomatic</td>
<td>• Renal insufficiency</td>
</tr>
<tr>
<td>o &gt;25% EF &amp; LVESD ≤55mm</td>
<td>- Creatinine &gt;2.5mg/dl</td>
</tr>
<tr>
<td>- Asymptomatic with one or more of the following</td>
<td>• Endocarditis</td>
</tr>
<tr>
<td>o LVEF 25-60%</td>
<td>• Rheumatic heart disease</td>
</tr>
<tr>
<td>o LVESD ≥40mm</td>
<td>• MV anatomical exclusions</td>
</tr>
<tr>
<td>o New onset atrial fibrillation</td>
<td>- Mitral valve area &lt;4.0cm²</td>
</tr>
<tr>
<td>o Pulmonary hypertension</td>
<td>- Leaflet flail width (≥15mm) and gap (≥10mm)</td>
</tr>
<tr>
<td>ACC/AHA Guidelines</td>
<td>- Leaflet tethering/coaptation depth (&gt;11mm) and length (&lt;2mm)</td>
</tr>
</tbody>
</table>

JACC 52:e1-e142, 2008
### Baseline demographics and co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Device (%)</th>
<th>Control (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=184</td>
<td>n=95</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>67.3 years</td>
<td>65.7 years</td>
<td>0.32</td>
</tr>
<tr>
<td>Male</td>
<td>62.5</td>
<td>66.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>90.8</td>
<td>77.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>47.0</td>
<td>46.3</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21.9</td>
<td>21.3</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Angina</td>
<td>31.9</td>
<td>22.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>33.7</td>
<td>39.3</td>
<td>0.42</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>7.6</td>
<td>5.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>6.5</td>
<td>11.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>17.9</td>
<td>14.7</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>61.0</td>
<td>62.8</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72.3</td>
<td>78.9</td>
<td>0.25</td>
</tr>
<tr>
<td>Moderate to severe renal disease</td>
<td>3.3</td>
<td>2.1</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.6</td>
<td>10.5</td>
<td>0.50</td>
</tr>
<tr>
<td>Previous cardiovascular surgery</td>
<td>22.3</td>
<td>18.9</td>
<td>0.54</td>
</tr>
<tr>
<td>MR Severity: 3+ to 4+</td>
<td>95.7</td>
<td>92.6</td>
<td>0.48</td>
</tr>
<tr>
<td>MR Etiology: Degenerative / Functional</td>
<td>73 / 27</td>
<td>73 / 27</td>
<td>0.81</td>
</tr>
</tbody>
</table>
**EVEREST II: randomized clinical trial demographic comparison**

<table>
<thead>
<tr>
<th></th>
<th>EVEREST II RCT n=279</th>
<th>2008 STS Database</th>
<th>Isolated 1st Elective Operation for MR* High Volume Hospitals (&gt;140/Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs (mean)</td>
<td>68</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>≥65 yrs</td>
<td>58%</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>≥75 yrs</td>
<td>32%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>50%</td>
<td>26%</td>
<td>45%</td>
</tr>
<tr>
<td>CHF</td>
<td>86%</td>
<td>41%</td>
<td>58%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75%</td>
<td>60%</td>
<td>67%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>9%</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>COPD / Chronic Lung Disease</td>
<td>15%</td>
<td>17%</td>
<td>29%</td>
</tr>
<tr>
<td>EF (mean)</td>
<td>60%</td>
<td>53%</td>
<td>55%</td>
</tr>
</tbody>
</table>
EVEREST II: randomized clinical trial
Primary endpoints

Safety
- Major Adverse Event Rate at 30 days
- Per protocol cohort
- Superiority hypothesis

Effectiveness
- Clinical Success Rate
  - Freedom from the combined outcome of
    - Death
    - MV surgery or re-operation for MV dysfunction
    - MR >2+ at 12 months
- Per protocol cohort
- Non-inferiority hypothesis

Pre-Specified MAEs
- Death
- Major Stroke
- Re-operation of Mitral Valve
- Urgent / Emergent CV Surgery
- Myocardial Infarction
- Renal Failure
- Deep Wound Infection
- Ventilation >48 hrs
- New Onset Permanent Atrial Fib
- Septicemia
- GI Complication Requiring Surgery
- All Transfusions ≥2 units
EVEREST II: randomized clinical trial
Additional analysis

Intention to Treat
- Safety
  - Major Adverse Event Rate at 30 days
- Effectiveness
  - Freedom from the combined outcome of death, MV surgery >90 days or re-operation for valve dysfunction >90 days post Index procedure, and MR >2+ at 12 months

Clinical Benefit (per protocol cohort)
- MR Severity
- Left Ventricular Function
- NYHA Functional Class
- Quality of Life (SF-36 Survey)
EVEREST II: Patient flow

Per protocol cohort: Analysis of device performance

Randomized Cohort
n=279

Device Group
n=184

Treated
n=178

Acute Procedural Success
Not Achieved
n=41

Acute Procedural Success
Achieved
n=137

30 days
n=136
99% Clinical Follow-up

12 months
n=134
98.5% Clinical Follow-up
98% Echo Follow-up

Control Group
n=95

Treated
n=80
(86% MV repair)

Randomized, not treated
Device, n=6
Control, n=15

30 days
n=79
99% Clinical Follow-up

12 months
n=74
94% Clinical Follow-up
92% Echo Follow-up

Acute procedural success (APS)=MR ≤ 2 at discharge

Investigational device limited by Federal (U.S.) law to investigational use only. PML02827 Rev. A 03/2010
EVEREST II: Patient flow
Post MitraClip procedure

Acute Procedural Success Not Achieved
n=41

- No Additional Intervention n=11
- 2nd MitraClip Procedure n=2
- MV Surgery Post MitraClip Procedure n=28

Acute Procedural Success Achieved
n=137

- MV Surgery Post MitraClip Procedure n=9
- 2nd MitraClip Procedure n=3

n=37
81% Follow-up
96% MR ≤2+
at 12 months
Everest II: Primary endpoints
Per protocol cohort

Safety
Major Adverse Events
30 days

Device Group, n=136: 9.6%
Control Group, n=79: 57.0%

Effectiveness
Clinical Success Rate*
12 months

Device Group, n=134: 72.4%
Control Group, n=74: 87.8%

Met superiority hypothesis
• Pre-specified margin = 6%
• Observed difference = 47.4%
• 97.5% LCB = 34.4%

Met non-inferiority hypothesis
• Pre-specified margin = 31%
• Observed difference = 15.4%
• 95% UCB = 25.4%

*Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR≥2+ at 12 months

LCB=lower confidence bound
UCB=upper confidence bound
### EVEREST II: Primary safety endpoint

Per protocol cohort

<table>
<thead>
<tr>
<th>30 Day MAE, non-hierarchical</th>
<th># Patients experiencing event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Group (n=136)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Re-operation of Mitral Valve</td>
<td>0</td>
</tr>
<tr>
<td>Urgent / Emergent CV Surgery</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>0</td>
</tr>
<tr>
<td>Deep Wound Infection</td>
<td>0</td>
</tr>
<tr>
<td>Ventilation &gt;48 hrs</td>
<td>0</td>
</tr>
<tr>
<td>New Onset Permanent Atrial Fib</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
</tr>
<tr>
<td>GI Complication Requiring Surgery</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>All Transfusions ≥2 units*</td>
<td>12 (8.8%)</td>
</tr>
</tbody>
</table>

**TOTAL % of Patients with MAE**

<table>
<thead>
<tr>
<th>Device Group</th>
<th>9.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>57.0%</td>
</tr>
</tbody>
</table>

\[ p<0.0001^* \]

(95% CI 34.4%, 60.4%)

*p<0.0001 if include Major Bleeding only
EVEREST II: Safety and effectiveness
Intention to treat cohort

Safety
Major Adverse Events
30 days

- Device Group, n=180
  - 15.0%
  - \( p_{\text{SUP}} < 0.0001 \)

- Control Group, n=94
  - 47.9%

**Met superiority hypothesis**
- Pre-specified margin = 2%
- Observed difference = 32.9%
- 97.5% LCB = 20.7%

Effectiveness
Clinical Success Rate*
12 months

- Device Group, n=175
  - 66.9%
  - \( p_{\text{NI}} = 0.0005 \)

- Control Group, n=89
  - 74.2%

**Met non-inferiority hypothesis**
- Pre-specified margin = 25%
- Observed difference = 7.3%
- 95% UCB = 17.8%

*Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR\( \geq 2^+ \) at 12 months
EVEREST II: MR reduction per protocol cohort

**Device Group**
- Baseline: 3+/4+ 18.5%, ≤2+ 81.5%
- 12 Months: 3+/4+ 18.5%, ≤2+ 81.5%

**Control Group**
- Baseline: 3+/4+ 97.0%, ≤2+ 3.0%
- 12 Months: 3+/4+ 97.0%, ≤2+ 3.0%
EVEREST II: LV volume
Per protocol cohort (pre-specified hypothesis)

Device Group
n=118, matched data

Control Group
n=65, matched data

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LVESV</td>
<td>p=0.0005</td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LVESV</td>
<td>p=0.0255</td>
<td></td>
</tr>
</tbody>
</table>

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EVEREST II: LV dimension

Per protocol analysis (pre-specified hypothesis)

Device Group
n=118, matched data

Control Group
n=65, matched data

- LVID diastole: p=0.0564
- LVID systole: p<0.0001

Baseline vs 12 Months:

- LVID diastole, Device Group: p<0.0001
- LVID systole, Device Group: p=0.0564
- LVID diastole, Control Group: p<0.0001
- LVID systole, Control Group: p=0.4785
EVEREST II: NYHA functional class
per protocol cohort

- **Device Group:**
  - Baseline: 44% Class I, 22% Class II, 20% Class III, 4% Class IV
  - 12 months: 97.6% Class I/II
  - p<0.0001

- **Control Group:**
  - Baseline: 44% Class I, 22% Class II, 20% Class III, 4% Class IV
  - 12 months: 87.9% Class I/II
  - p<0.0001

Data: n=124, Matched data (Device Group), n=66, Matched data (Control Group)
EVEREST II: Quality of life, SF-36 survey
Per protocol cohort

### 30 Day Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>PCS Score (n=120, matched pairs)</th>
<th>MCS Score (n=64, matched pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Group</td>
<td><img src="chart" alt="Device Group PCS score" /></td>
<td><img src="chart" alt="Device Group MCS score" /></td>
</tr>
<tr>
<td>Control Group</td>
<td><img src="chart" alt="Control Group PCS score" /></td>
<td><img src="chart" alt="Control Group MCS score" /></td>
</tr>
</tbody>
</table>

- Device Group: p<0.0001, p=0.0043
- Control Group: p=0.2910

### 12 Month Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>PCS Score (n=110, matched pairs)</th>
<th>MCS Score (n=60, matched pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Group</td>
<td><img src="chart" alt="Device Group PCS score" /></td>
<td><img src="chart" alt="Device Group MCS score" /></td>
</tr>
<tr>
<td>Control Group</td>
<td><img src="chart" alt="Control Group PCS score" /></td>
<td><img src="chart" alt="Control Group MCS score" /></td>
</tr>
</tbody>
</table>

- Device Group: p<0.0001, p<0.0001, p=0.0017
- Control Group: p=0.0057
EVEREST II: summary

- Safety & effectiveness endpoints met
  - Safety: MAE rate at 30 days
    - MitraClip device patients: 9.6%
    - MV surgery patients: 57%
  - Effectiveness: Clinical Success Rate at 12 months
    - MitraClip device patients: 72%
    - MV Surgery patients: 88%

- Clinical benefit demonstrated for MitraClip System and MV surgery patients through 12 months
  - Improved LV function
  - Improved NYHA Functional Class
  - Improved Quality of Life

- Surgery remains an option after the MitraClip procedure