Endovascular Device Therapy
For Mitral Valve Disease

J. Stephen Jenkins, MD
Ochsner Medical Center
New Orleans
Conflicts of Interest

I proctor for:
• St. Jude/AGA Medical
• Endologics/Trivascular

I speak for:
• Abbott Vascular
• AngioDynamics
Scope of the problem and etiology

- MR represents 25% of patients with VHD
- Prevalence: 7% of the population over 75
- Two types: Degenerative and Functional MR
- The pathophysiology of MR is complex and heterogenous
  - Mitral Annulus
  - Leaflets
  - Papillary muscles
  - chordae tendineae
  - Left Ventricle
  - Left Atrium
Pathophysiology of MR

Increasing Mitral Regurgitation

Dilation of Left Ventricle

1 year mortality up to 57%¹

Increase Load/Stress

Dysfunction of Left Ventricle

Muscle Damage/Loss

Structural Heart Disease

Increases with Age

> 9.3% for ≥75 year olds (p<.0001)

Classification of MR – 2 Types

Incompetent mitral valve closure
Systolic retrograde blood flow from the LV into the LA

Primary:
Anatomic abnormality of the mitral valve
- Leaflets
- Subvalvular apparatus
- Chordae and papillary muscles

Secondary:
LV dilation; often secondary to ischemic heart disease
- Leads to mitral annular dilation
- Incomplete coaptation of the mitral valve
Classification of MR

Primary

“The Valve”

Usually myxomatous

Secondary

“The Ventricle”

Ischemic or not

Sorajja, Paul, MD; Abbott Northwestern Hospital
INDICATIONS FOR MITRAL VALVE OPERATION

**CLASS I**

1. MV surgery is recommended for the symptomatic patient with acute severe MR.* (Level of Evidence: B)
2. MV surgery is beneficial for patients with chronic severe MR* and NYHA functional class II, III, or IV symptoms in the absence of severe

3. MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest or greater than 60 mm Hg with exercise). (Level of Evidence: C)

4. MV repair is recommended over MV replacement in the majority of patients with severe chronic MR* who require surgery, and patients should be referred to surgical centers experienced in MV repair. (Level of Evidence: C)

**CLASS IIa**

1. MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR* with preserved LV function (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) in whom the likelihood of successful repair without residual MR is greater than 90%. (Level of Evidence: B)
2. MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and new onset of atrial fibrillation. (Level of Evidence: C)

**CLASS III**

1. MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) in whom significant doubt about the feasibility of repair exists. (Level of Evidence: C)
2. Isolated MV surgery is not indicated for patients with mild or moderate MR. (Level of Evidence: C)
Repair Techniques

• Surgical repair techniques are aimed at correcting abnormalities of these structures of the mitral apparatus
  
  • Annuloplasty rings
  • Leaflet repair
  • Chordal shortening
  • LV reshaping

• Percutaneous techniques have mirrored the surgical techniques
Targets of Transcatheter MV Repair

- Leaflets
- Annulus
- Chordae tendinae
- LV
Mitral Clip

Edge-to-edge repair based on the Alfieri Technique
Treatment in the USA dependent on Protocol IC/EC
Percutaneous Repair or Surgery for Mitral Regurgitation

Ted Feldman, M.D., Elyse Foster, M.D., Donald G. Glower, M.D., Saibal Kar, M.D., Michael J. Rinaldi, M.D., Peter S. Fain, M.D., Richard W. Smalling, M.D., Ph.D., Robert Siegel, M.D., Geoffrey A. Rose, M.D., Eric Engoron, M.D., Catalin Loghin, M.D., Alfredo Trento, M.D., Eric R. Skipper, M.D., Tommy Fudge, M.D., George V. Letsou, M.D., Joseph M. Massaro, Ph.D., and Laura Mauri, M.D., for the EVEREST II Investigators*

CONCLUSIONS

Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. (Funded by Abbott Vascular; EVEREST II ClinicalTrials.gov number, NCT00209274.)
Key Inclusion/Exclusion Criteria
EVEREST II RCT

Inclusion
• Candidate for MV Surgery
• Moderate to severe (3+) or severe (4+) MR
  • Symptomatic
    • >25% EF & LVESD ≤55mm
  • Asymptomatic with one or more of the following
    • LVEF 25-60%
    • LVESD ≥40mm
    • Pulmonary hypertension
    • Atrial fibrillation

Exclusion
• AMI within 12 weeks
• Need for other cardiac surgery
• Renal insufficiency
• Creatinine >2.5mg/dl
• Endocarditis
• Rheumatic heart disease
• MV anatomical exclusions
• Mitral valve area <4.0cm²
• Leaflet flail width (≥15mm) and gap (≥10mm)
• Leaflet tethering/coaptation depth (>11mm) and length (<2mm)

<table>
<thead>
<tr>
<th>Event</th>
<th>Percutaneous Repair</th>
<th>Surgery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy end point</strong></td>
<td>no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freedom from death, from surgery for mitral-valve dysfunction,</td>
<td>100 (55)</td>
<td>65 (73)</td>
<td>0.007</td>
</tr>
<tr>
<td>and from grade 3+ or 4+ mitral regurgitation†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>11 (6)</td>
<td>5 (6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Surgery for mitral-valve dysfunction‡</td>
<td>37 (20)</td>
<td>2 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3+ or 4+ mitral regurgitation</td>
<td>38 (21)</td>
<td>18 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Major adverse event at 30 days‡</strong></td>
<td>no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major adverse event</td>
<td>27 (15)</td>
<td>45 (48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any major adverse event excluding transfusion</td>
<td>9 (5)</td>
<td>9 (10)</td>
<td>0.23</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Reoperation for failed surgical repair or replacement</td>
<td>0</td>
<td>1 (1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Urgent or emergency cardiovascular surgery for adverse event</td>
<td>4 (2)</td>
<td>4 (4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Major stroke</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Deep wound infection</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Mechanical ventilation for &gt;48 hr</td>
<td>0</td>
<td>4 (4)</td>
<td>0.02</td>
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<tr>
<td>Gastrointestinal complication requiring surgery</td>
<td>2 (1)</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>New onset of permanent atrial fibrillation</td>
<td>2 (1)</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Transfusion of ≥2 units of blood</td>
<td>24 (13)</td>
<td>42 (45)</td>
<td>&lt;0.001</td>
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</table>
Kaplan-Meier Freedom From Mortality
EVEREST II RCT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
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</thead>
<tbody>
<tr>
<td>MitraClip</td>
<td>178</td>
<td>165</td>
<td>158</td>
<td>154</td>
<td>143</td>
<td>133</td>
<td>119</td>
<td>58</td>
</tr>
<tr>
<td>Surgery</td>
<td>80</td>
<td>76</td>
<td>70</td>
<td>70</td>
<td>65</td>
<td>57</td>
<td>52</td>
<td>24</td>
</tr>
</tbody>
</table>

93.7%  
92.3%  
1 year  

81.2%  
79.0%  
5 years
EVEREST II RCT – 5 Year Results

Summary

- The EVEREST II RCT is the longest prospective follow-up of two therapies for treating MR
- Clinical benefits provided by MitraClip and MV surgery are durable through 5 years
  - Reduction in MR Severity
  - Improvement in LV Volumes and Dimensions
  - Improvements in NYHA Functional Class
- Low rate of adverse events from 1 year to 5 years in both groups
- Beyond 6 months, the rate of MV surgery is low in the MitraClip group
Everest II Conclusions

• The majority of patients had degenerative MR and were low risk for surgery.

• MitralClip is safer than surgery
  • Unless you exclude the requirement for transfusion as a major adverse event.

• Surgery is more effective than MitralClip.

• Long term freedom from severe MR is good in both groups.

• US FDA approval for non-surgical degenerative MR.

• For select patients with significant MR, the MitraClip procedure is a therapeutic option with measurable clinical benefits and no late safety concerns.
**EVEREST II**
(Randomized Controlled Trial)

- 73%
- 27%
- 10%
- 90%

- 178 patients
- Implant rate – 89%

**REALISM**
(Continued Access Registry)

- 53%
- 47%

- 54%
- 46%

- 34%
- 66%

- 571 patients
- Implant rate – 94%

**Commercial**
(Europe, Canada, Asia, Australia)

- 34%
- 66%
- 25%
- 75%

- 2,472 patients
- Implant rate – 95%

*DMR*¹ = DMR¹
*FMR*¹ = FMR¹

*Standard Risk*² = Standard Risk²
*High Risk*² = High Risk²
## EVEREST II
### Sungroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percutaneous Repair</th>
<th>Surgery</th>
<th>Difference between Percutaneous Repair and Surgery (%)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>100/181 (55)</td>
<td>65/89 (73)</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63/114 (55)</td>
<td>43/59 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37/67 (55)</td>
<td>22/30 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>≥70 yr</td>
<td>52/86 (60)</td>
<td>23/38 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>48/95 (51)</td>
<td>42/51 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td>26/48 (54)</td>
<td>12/24 (50)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative</td>
<td>74/133 (56)</td>
<td>53/65 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60%</td>
<td>35/68 (51)</td>
<td>15/28 (54)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>≥60%</td>
<td>64/111 (58)</td>
<td>50/61 (82)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk

~420 patients enrolled at up to 75 US sites

- Significant FMR ≥3+ core lab
- High risk for mitral valve surgery
- Specific valve anatomic criteria

Randomize 1:1

MitraClip
- Control group
  - Standard of care

Safety: Composite death, stroke, worsening renal function, LVAD implant, heart transplant at 12 months

Effectiveness: Recurrent heart failure hospitalizations

Protocol conditionally approved by FDA July 26, 2012
Summary

• MR represents roughly 1/4 of patients with valvular heart disease, millions in the USA.

• MV Repair is recommended over replacement.
  • Class Ia, Level of Evidence C.

• Transcatheter mitral valve repair and replacement is much more complicated than TAVR.

• Everest II RCT - FDA approval for degenerative MR. High-risk CoApt trial currently enrolling.

• Ongoing research will determine which patient populations are most suitable for which therapies in the pipeline of transcatheter technology.
Thank You!