Mitral Valve Therapies for Heart Failure Patients

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Disclosures

- Proctor: Edwards Lifesciences, Medtronic Inc.
- Speaker Bureau: Abbott Vascular, Edwards Lifesciences, Medtronic Inc.
- Consultant: Silk Road Medical
All MR Are Not Created Equal

For primary MR, the disease is solely a valvular lesion

For secondary MR, LV pathology is the primary issue

Carabello. JACC 2014;64:193-5
MR Leads to Heart Failure

- Mitral Regurgitation
- Increased Load/Stress
- LV Dilatation
- LV Dysfunction
- Myocardial Injury
- CHF
Hospital Admissions for CHF

Markwick et al. TCT 2012
Impact of MR on Survival

Survival of Heart Failure Patients with MR by Degree of MR
Adjusted for demographics and clinical variables at baseline

A Randomized Controlled Phase IIb Trial of Beta-Blocker Blockade for

Effect of Losartan on Degree of Mitral Regurgitation Quantified

Effect of Enalapril Therapy on Left Ventricular Mass and Volumes in Asymptomatic Chronic, Severe Mitral Effects of angiotensin-converting enzyme inhibition on mitral regurgitation severity, left ventricular size, and Effects of Afterload Reduction on Vena Contracta Width in Mitral Regurgitation
CLASS IIa

1. Medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic primary MR (stage D) and LVEF less than 60% in whom surgery is not contemplated (382–386). (*Level of Evidence: B*)

CLASS III: No Benefit

1. Vasodilator therapy is not indicated for normotensive asymptomatic patients with chronic primary MR (stages B and C1) and normal systolic LV function (386–391). (*Level of Evidence: B*)
Outcomes with Medical Management of MR

- Mortality
- Proportion of Surviving Patients Hospitalized for Heart Failure

% of Patients

<table>
<thead>
<tr>
<th>Years</th>
<th>Mortality</th>
<th>Surviving Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

Troubling Data

For asymptomatic pts with primary severe MR and EF 50-60%, only 57% of Canadian cardiologists referred these patients to surgery.\(^1\)

EuroHeart survey, 49% of symptomatic pts with severe MR did not receive a surgical evaluation.\(^2\)

Univ of Michigan, \(\frac{1}{2}\) of the 112 pts with severe primary MR underwent surgery. Of those who did not have surgery, 75% had \(\geq 1\) indication.\(^3\)

Surgery is Underutilized

What Are Our Options?

"Your medical problems are more complicated than I thought. I am going to refer you to another doctor, who has more medical insurance than I have."
Need for Alternative Therapies

- Evolving technologies are all based upon surgical techniques
  - Edge-to-Edge Repair (Alfieri technique)
  - Annuloplasty
    - Indirect
    - Direct
  - Chordal Replacement
  - Percutaneous Mitral Valve Implant
Edge-to-Edge Repair: Alfieri Technique

- Described in 1992
  - Suture part of anterior and posterior leaflet edges together
  - Usually applied to A2-P2 central segment

- Usually used in conjunction with mitral annuloplasty
The MitraClip System
## EVEREST II RCT: Efficacy Results

<table>
<thead>
<tr>
<th>Event</th>
<th>MitraClip</th>
<th>Surgery</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Efficacy Endpoint</td>
<td>100 (55%)</td>
<td>65 (73%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Death</td>
<td>11 (6%)</td>
<td>5 (6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Surgery for MV dysfunction</td>
<td>37 (20%)</td>
<td>2 (2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Grade 3+ or 4+ MR</td>
<td>38 (21%)</td>
<td>18 (20%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
# EVEREST II RCT: Safety Results

<table>
<thead>
<tr>
<th>Event</th>
<th>MitraClip</th>
<th>Surgery</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Major Adverse Event</td>
<td>27 (15%)</td>
<td>45 (48%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>- Excluding transfusion</td>
<td>9 (5%)</td>
<td>9 (10%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Transfusion ≥ 2U PRBC</td>
<td>24 (13%)</td>
<td>42 (45%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urgent CT surgery</td>
<td>4 (2%)</td>
<td>4 (4%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (&lt; 1%)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Mechanical ventilation ≥ 48 hrs</td>
<td>0 (0%)</td>
<td>4 (4%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
## EVEREST II: Secondary Endpoints

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MitraClip (N=184)</th>
<th>Surgery (N=95)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LVEF</td>
<td>-2.8 ± 7.2 *</td>
<td>-6.8 ± 10.1 *</td>
<td>0.005</td>
</tr>
<tr>
<td>Change in EDV</td>
<td>-25.3 ± 28.3 *</td>
<td>-40.2 ± 35.9 *</td>
<td>0.004</td>
</tr>
<tr>
<td>Change in QOL score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo. (physical)</td>
<td>4.4 ± 9.8 *</td>
<td>4.4 ± 10.4 *</td>
<td>0.98</td>
</tr>
<tr>
<td>12 mo. (mental)</td>
<td>5.7 ± 9.6 *</td>
<td>3.8 ± 10.3 *</td>
<td>0.24</td>
</tr>
<tr>
<td>Severity of MR</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0-1+</td>
<td>66 (43%)</td>
<td>52 (76%)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>59 (39%)</td>
<td>14 (20%)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>21 (14%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>7 (5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

* - p value < 0.01 from baseline
EVEREST II High Risk Registry

[Graph showing freedom from mortality with time points at 30 days, 6 months, and 12 months.]

At Risk (n)
- HRS: 78, 65, 54
- CCG: 36, 27, 22

https://doi.org/10.1016/j.jacc.2013.12.062
Current Status of the MitraClip

- October 24, 2013: FDA approved the MitraClip for the following commercial indication:
  
  “The MitraClip is intended to treat patients with significant symptomatic degenerative mitral regurgitation with MR ≥ 3+ who have too high a risk for surgery”
What about Functional MR?
Caveats:

- Only moderate MR was required for enrollment
- Majority of MC patients had ≥ 2+ MR at 12 months
- Optimal medical therapy was not mandated
- Small sample size
COAPT Trial

• **Design:** Prospective, multicenter, RCT

• **Objective:**
  – examine safety and efficacy of MitraClip device used in addition to standard care for *functional* MR and CHF compared to standard care alone

• **Primary Endpoints**
  – *Efficacy:* recurrent HF hospitalizations at 12 months
  – *Safety:* composite of mortality, stroke, LVAD, heart transplant or worsening kidney function at 12 months
COAPT Trial
All Hospitalizations for HF within 24 months

HR (95% CI] = 0.53 [0.40-0.70] P<0.001

Cumulative HF Hospitalizations (n)

0 3 6 9 12 15 18 21 24
0 50 100 150 200 250 300

MitraClip + GDMT
GDMT alone

160 in 92 pts
283 in 151 pts

Time After Randomization (Months)
No. at Risk:
MitraClip 302 286 269 253 236 191 178 161 124
GDMT 312 294 271 245 219 176 145 121 88

Saint Luke’s
MID AMERICA HEART INSTITUTE
# COAPT Trial
## Powered Secondary Endpoints

- Tested in hierarchical order<sup>1</sup> -

<table>
<thead>
<tr>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MR grade ≤2+ at 12 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. All-cause mortality at 12 months&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4. Change in QOL (KCCQ) from baseline to 12 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5. Change in 6MWD from baseline to 12 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6. All-cause hospitalizations through 24 months</td>
<td>0.03</td>
</tr>
<tr>
<td>7. NYHA class I or II at 12 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8. Change in LVEDV from baseline to 12 months</td>
<td>0.003</td>
</tr>
<tr>
<td>9. All-cause mortality at 24 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days&lt;sup&gt;3&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>1</sup>All powered for superiority unless otherwise noted;  
<sup>2</sup>Powered for noninferiority of the device vs. the control group;  
<sup>3</sup>Powered for noninferiority against an objective performance goal
Change in KCCQ from Baseline to 12 Months

**KCCQ Summary Score**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDMT alone</td>
<td>52.9 ± 23.3</td>
<td>49.6 ± 32.0</td>
</tr>
<tr>
<td>MitraClip + GDMT</td>
<td>54.2 ± 22.7</td>
<td>66.4 ± 28.6</td>
</tr>
<tr>
<td><strong>n=228</strong></td>
<td><strong>n=236</strong></td>
<td><strong>n=228</strong></td>
</tr>
</tbody>
</table>

**Adjusted change**

<table>
<thead>
<tr>
<th></th>
<th>GDMT alone</th>
<th>MitraClip + GDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ΔLSM ± SE</strong></td>
<td>-6 ± 1.9</td>
<td>12.5 ± 1.8</td>
</tr>
</tbody>
</table>

*P<0.001*  

*Ancova*
Current Status of the MitraClip

- **October 24, 2013:** FDA approved the MitraClip for the following commercial indication:
  - "The MitraClip is intended to treat patients with significant symptomatic degenerative mitral regurgitation with MR ≥ 3+ who have too high a risk for surgery"

- **March 14, 2019:** FDA approved Mitraclip for FMR:
  - "The Mitraclip System, when used with maximally tolerated guideline-directed medical therapy, is indicated for the treatment of symptomatic moderate-to-severe secondary (or functional) mitral regurgitation"
Case Presentation

- 89 y/o female, known severe mitral regurgitation
- **Chief Complaint:** increasing fatigue, dyspnea on exertion, weakness
- **Hx:** CKD, Hx Breast Cancer 2003 s/p lumpectomy, right nephrectomy 1970, osteoporosis
- TEE: Diffusely myxomatous mitral valve with bileaflet prolapse. Severe mitral regurgitation. Regurgitant fraction is 50%.
- Dr. Borkon: Patient is at prohibitive risk for mitral valve surgery
Pre-procedure TEE

Lossy compression - not intended for diagnosis
Pre-procedure TEE
Clip Alignment
Clip in LV

Lossy compression - not intended for diagnosis
Failed Grasp

Lossy compression - not intended for diagnosis
Successful Grasp

Lossy compression - not intended for diagnosis
3D Imaging
Advancing 2nd Clip

Lossy compression - not intended for diagnosis
2nd Grasp

Lossy compression - not intended for diagnosis

CLIP 2

JPEG
Mitral Valve Gradient
3D imaging – 2 clips
Final Result

Lossy compression - not intended for diagnosis

FINAL CLIP 2
Home the Next Day!
Annuloplasty: Surgical Theory

• **Principles**
  - All valves with significant chronic MR have some degree of annular dilation
  - Re-establishing physiologic configuration of mitral annulus will improve leaflet coaptation

• **Percutaneous Approaches**
  - *Indirect*: Implant device within coronary sinus with aim of “pushing” posterior annulus anteriorly
  - *Direct*: Device reshapes and cinches mitral annulus directly without involving coronary sinus
Indirect Mitral Annuloplasty
The Carillon XE Device
Direct Mitral Annuloplasty: Mechanical Cinching Approach

• **Principle**
  - Devices implanted onto/near annulus and used to directly cinch the annulus

• **Devices**
  - Mitralign
  - Accucinch
  - Cardioband
  - Millipede
Direct Mitral Annuloplasty: Millipede
Chordal Reconstruction: Transcatheter Technology

Current Devices

- NeoChord
- MitraFlex
- Babic
Transcatheter Mitral Valve Replacement

- Currently in various stages of testing
  - Tendyne
  - Intrepid
  - M3

- Involves variety of approaches
  - Trans-septal
  - Trans-apical
  - Mini-thoractomy

- Challenges
  - Risk of paravalvular leaks
  - Possible LVOT obstruction
TMVR: Tendyne
Tendyne: Early Feasibility

**CENTRAL ILLUSTRATION:** Clinical Outcomes With Transcatheter Mitral Valve Replacement With the Prosthesis

First 100 Patients Treated

- No intra-procedural deaths
- Technical success in 96%
- 30-day death, 6%; 1-year mortality, 26%
- Among survivors at 1 year, 88.5% with mild or no symptoms

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Conclusions

• TMVr with Mitraclip is approved for treatment of patients with degenerative MR whose surgical risk is high

• Mitraclip is approved for patients with symptomatic functional MR on optimal medical therapy

• Challenges of mitral valve anatomy may make developing a one-size-fits-all strategy difficult

• Many new devices are on the horizon
Thank You