Managing Mitral Regurgitation in HF Patients: *Is it the Chicken or the Egg?*

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

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

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

“The Valve”

Usually myxomatous

“The Ventricle”

Ischemic or not

Srihari S. Naidu, MD, MitraClip Program, Winthrop University Hospital
Chicken (LV) or Egg (MV)?
How we’ve thought of things so far …

Primary MR → LV Dysfx → Mixed MR and Worsening EF/HF

Fix the MR prior to LV dysfunction/AF/pHTN to avoid progression
If EF already reduced, probably still worthwhile to fix until EF < 20-25

LV Dysfx → Sec MR → Worsening EF/HF

Improve heart function to minimize MR and progression
- Revascularization
- Bi-V pacemaker/ICD
- Medications for Remodeling

Continued 3-4+ MR → ?
Both MR and LV Dysfunction Contribute to Progressive Heart failure and Secondary Worsening of Each Other

1 year mortality up to 57% \(^1\)

- Dilation of Left Ventricle
- Increase Load/Stress
- Dysfunction of Left Ventricle
- Muscle Damage/Loss

Prevalence of Valve Disease According to Age


> 9.3% for ≥75 year olds
Heart Failure and significant MR are inseparable

Moderate or severe MR present in ~40%
The Egg: Degenerative (Primary) MR
Asymptomatic Primary MR
Natural History

Risk Factors:
- Age ≥50 yrs
- Atrial fibrillation
- LA enlargement
- Flail
- Mild MR
- MR ≥3
- or
- EF <50%

Asymptomatic Primary MR
Severity and Survival

Worse Survival

 survival (%)

Years

P<0.01

ERO <20mm² (91 ±3%)

ERO 20-39mm² (66 ±6%)

ERO ≥40mm² (58 ±9%)

More CV Events

Rate of Cardiac Events %

Years

P<0.01

ERO ≥40mm² (62 ±8%)

ERO 20-39mm² (40 ±7%)

ERO <20mm² (15 ±4%)

Enriquez-Sarano M et al. NEJM 2005;352:875-83
Flail Mitral Leaflet
Natural History

Survival %

Years After Diagnosis

Mortality
4% per year

34% per year

Class I or II

Class III or IV

$P < 0.001$

EF and Surgical Outcome

EF <60% is Abnormal in MR

Enriquez-Sarano M, et al., Circulation 1994;90:830-837
Symptoms and Surgery
Outcome with Primary MR

Survival %

- NYHA I-II
- NYHA III-IV

Years

90 ±2
73 ±3
76 ±5
48 ±4

P<0.0001

Tribouilly CM et al., Circulation 1999;99:400-5
Early Surgery Is Better
Patients without Class I Indications

Suri R et al., JAMA 2013;310:609-16
Summary for Primary MR

- Prognosis governed by:
  - Number of related risk factors
  - Severity (ERO or MR grade)
  - Ejection Fraction
  - NYHA Class

- Outcome governed by:
  - Surgical repair/replacement once indicated
  - Early consideration
The Chicken: Secondary (Functional) MR
Secondary Mitral Regurgitation
A Ventricular Problem

Regional or Global Dysfunction

• Papillary muscle displacement
• Annular flattening
• Leaflet tethering

Secondary Mitral Regurgitation
A Harbinger of Poor Outcome

Two-fold Increase Risk of Death

Basket JF, et al. Can J Cardiol 2007;23:797-800
Secondary Mitral Regurgitation
Increased Severity = Increased Morbidity

Hospitalization-free survival decreased with increased MR severity

Transplant-free survival decreased with increased MR severity


Surgery for Secondary MR

No Mortality Benefit

Summary for Secondary MR

• Prognosis governed by:
  – Severity of MR
  – Underlying degree of LV dysfunction, NYHA class, and comorbidities

• Outcome not apparently improved by surgical repair or replacement
Untreated severe MR (degenerative OR functional) is associated with increased morbidity and mortality

What are our options?
Consider surgery *when*

Symptoms

*or*

LV dysfunction (EF<60%, ESD≥40 mm)

Repair preferred over replacement

Nishimura R, et al., J Am Coll Cardiol 2014;63:2438-88
Timing of Surgery

ACC/AHA Guidelines – Primary MR

For patients **without** symptoms:

Can be done *if*

- likelihood of repair success >95%
- mortality rate <1%

Nishimura R, et al., J Am Coll Cardiol 2014;63:2438-88
Surgical Intervention
ACC/AHA Guidelines – Secondary MR

Surgery may be considered for severe symptoms despite optimal GDMT (IIb)

Also while undergoing other CV surgery, if severe (IIa) or moderate (IIb)

Nishimura R, et al., J Am Coll Cardiol 2014;63:2438-88
### General Principles: The World Prior to MitraClip

#### Primary

- No medical option for valve
- Surgery for symptoms or LV dysfunction
- Asymptomatic pts if repairable and low risk

#### Secondary

- Revascularization and Medical therapy first
- Consider CRT
- Surgery only in highly selected patients with HF
An Untreated Population
Mitral Regurgitation 2009 U.S. Prevalence

Total MR Patients\(^1,2\)  
\(4,100,000\)

Eligible for Treatment\(^3,4\)  
(MR Grade ≥3+)
\(1,670,000\)

Annual Incidence\(^3\)  
(MR Grade ≥3+)
\(30,000\)

Annual MV Surgery\(^5\)

Untreated Large and Growing Clinical Unmet Need
14% Newly Diagnosed Each Year

Only 2% Treated Surgically

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Would New Options Change the Paradigm and Outcome?

- Medical Therapy
- MitraClip®
- MV Surgery

Less Invasive

Increased MR Reduction
In DMR: Too Late, EF severely reduced, surgery becomes risky

In FMR: Myopathy continues to progress, there is an acute LV insult at surgery on an already diseased heart, and/or complete elimination of MR increases afterload
EVEREST II Randomized

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
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 4 Year Results

<table>
<thead>
<tr>
<th></th>
<th>Percutaneous (n = 161)</th>
<th>Surgical (n = 73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite Efficacy Endpoint</strong></td>
<td>39.8%</td>
<td>53.4%</td>
<td>0.070</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>17.4%</td>
<td>17.8%</td>
<td>0.914</td>
</tr>
<tr>
<td><strong>Surgery or Re-operation for Mitral Valve Dysfunction</strong></td>
<td>24.8%</td>
<td>5.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>MR 3+ or 4+</strong></td>
<td>21.7%</td>
<td>24.7%</td>
<td>0.745</td>
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</tbody>
</table>

Roughly 75% were DMR
A

NYHA Functional Class at Baseline and 12 Months

B

NYHA Functional Class at Baseline and 48 Months
Prohibitive Surgical Risk
DMR Cohort (n=127)

Age: 82 ±9 years
Prior MI: 24%
Prior stroke: 10%
Diabetes: 30%
COPD: 32%
Renal disease: 28%

Mean STS Risk
13.2%

Prohibitive Surgical Risk
DMR Cohort (n=127)

Mitral Regurgitation Grade

- 12 Months
  - 4+ (30%)
  - 3+ (20%)
  - 2+ (40%)
  - 1+ (10%)
  - 0 (0%)

- Baseline
  - 4+ (10%)
  - 3+ (20%)
  - 2+ (60%)
  - 1+ (10%)
  - 0 (0%)

Hospitalizations for Heart Failure

- 1 Year Prior
  - 0.67
- 1 Year Post
  - 0.18

73% Reduction

NYHA Functional Class

- 12 Months
  - I (60%)
  - II (20%)
  - III (20%)
  - IV (0%)

- Baseline
  - I (60%)
  - II (40%)

Left Ventricular Volumes

Left Ventricular End Diastolic Volume

- Baseline (N=69)
  - 125 mL
- 1 Year
  - 109 mL
- Reduction: -16 mL

Left Ventricular End Systolic Volume

- Baseline (N=69)
  - 49 mL
- 1 Year
  - 46 mL
- Reduction: -3 mL

Paired Data

- 30 Days
  - Baseline
  - 0 mL
  - 1 Year
  - 70 mL
- 12 Months
  - Baseline
  - 0 mL
  - 1 Year
  - 49 mL
The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR $\geq 3+$) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.
May be considered for prohibitive risk patients with primary MR and severe symptoms despite GDMT (class IIb)

Why not functional MR??
Interaction of Age and MR Type

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Percutaneous repair</th>
<th>Surgery</th>
<th>Difference (CI)</th>
<th>Difference between percutaneous and surgery (%)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
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</tr>
<tr>
<td>&lt;70</td>
<td>38.1% (32/84)</td>
<td>66.7% (26/39)</td>
<td>-28.6% (-46%, -10.5%)</td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>≥70</td>
<td>41.6% (32/77)</td>
<td>38.2% (13/34)</td>
<td>3.3%</td>
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<tr>
<td>MR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Degenerative</td>
<td>41.9% (49/117)</td>
<td>66.7% (34/51)</td>
<td>-24.8% (-40.5%, -9.1%)</td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>Functional</td>
<td>34.1% (15/44)</td>
<td>22.7% (5/22)</td>
<td>11.4%</td>
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</tbody>
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Note: The chart shows the comparison between percutaneous repair and surgery for different subgroups, including age and MR type. The differences are expressed as percentages, indicating whether surgery or percutaneous repair is better.
Trial Design
Goals: 430 patients at 75 US sites

Significant FMR (≥3+ by core lab)
Symptomatic heart failure subjects who are treated per standard of care
Determined by the site’s local heart team as not appropriate for mitral valve surgery
Specific valve anatomic criteria

Randomize 1:1

MitraClip
N=215

Control group
Standard of care
N=215

Clinical and TTE follow-up:
Baseline, Treatment, 1-week (phone)
1, 6, 12, 18, 24, 36, 48, 60 months
Summary of MitraClip

- MitraClip therapy safely reduces DMR in patients at prohibitive risk for MV surgery

- In this group of prohibitive risk DMR patients, MitraClip therapy provides meaningful clinical improvements
  - Reduction of LV volumes
  - Improvements in NYHA Functional Class
  - Improvements in Quality of Life
  - Reduction in Hospitalizations for Heart Failure

- Results in FMR may be even better but await COAPT
Managing MR in HF

Is it the Chicken or the Egg?

Yes! But it doesn’t matter ….
as significant MR is always contributory to worse prognosis
Thank You