Functional mitral regurgitation: What do the guidelines say?

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Mitral Valve Anatomy: Surgical View from Above

Carpentier Classification of MR: Leaflet Motion

- Type I: Normal leaflet motion
  - Endocarditis
  - Dilated annulus
  - Atrial fibrillation
  - Restrictive CM

- Type II: Prolapse or flail leaflet
  - MVP
  - Papillary rupture
  - Trauma

- Type IIIa: Leaflet restriction systole & diastole
  - Rheumatic
  - SLE
  - Radiation
  - Drugs

- Type IIIb: Leaflet restriction systole only
  - Ischemic Heart Disease
  - Dilated CM
Degenerative vs Functional MR

~ 10% Primary MR (DMR) (90%)
Myxomatous Degeneration (DMR) (90%)
Type II

~ 90% Secondary MR (FMR)
Other (10%) Rheumatic, post-inflammatory, radiation, drugs, etc
Type IIIa

Mitrval valve is structurally normal for age
Type I or Type IIIb

Secondary MR: a rose by any other name....

- Functional MR (vs. Degenerative)
- Secondary MR (vs. Primary)
- Ischemic MR (vs. Non-Ischemic)

- Mitral regurgitation that occurs in the setting of left ventricular dysfunction with normal (or nearly normal) mitral leaflet and chordal structure
**HF and Secondary MR**

- **Secondary MR (FMR)**
  - Inferobasal MI
    - Normal LVEF
  - Dilated LV
    - Low LVEF
  - Dilated Annulus
    - Normal LVEF
  - Ischemic DCM
  - Nonischemic DCM

**Pathology of FMR is Complex and Heterogeneous**

- Coronary Artery Disease
  - Ischemic vs Nonischemic etiology
- Left Ventricle
  - Global vs regional wall motion abnormalities
  - Dilated or non-dilated
- Mitral Annulus
  - Normal, dilated, calcified
  - Symmetric or asymmetric dilation
- Electrical Activation
  - MR reduction occurs with CRT in some patients
- Dynamic
  - Preload and afterload sensitive
Severe MR Criteria Different for Primary vs Secondary MR

<table>
<thead>
<tr>
<th></th>
<th>Primary (Organic) MR</th>
<th>Secondary (Functional) MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EROA</td>
<td>≥0.4 cm²</td>
<td>≥0.2 cm²*</td>
</tr>
<tr>
<td>Regurgitant volume</td>
<td>≥60 ml</td>
<td>≥30 ml</td>
</tr>
<tr>
<td>Regurgitant fraction</td>
<td>≥50%</td>
<td>≥50%</td>
</tr>
<tr>
<td>Vena contracta</td>
<td>≥0.7 cm</td>
<td>–</td>
</tr>
<tr>
<td>Jet area</td>
<td>Central jet &gt;40% LA</td>
<td>or holosystolic eccentric jet</td>
</tr>
</tbody>
</table>

Relationship between EROA, RVol, & LVEDV

[Graphs showing the relationship between EROA, RVol, & LVEDV]
### Secondary MR: ACC/AHA Guideline Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics†</th>
<th>Associated Cardiac Findings</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of MR</td>
<td>Normal valve leaflets, chords, and annulus in a patient with coronary artery disease or cardiomyopathy</td>
<td>No MR jet or small control jet area &lt;20% LA on Doppler</td>
<td>Small area contractile &lt;0.30 cm</td>
<td>Normal or mildly dilated LV size with fixed (infarction) or inducible ischemia, regional wall motion abnormalities, Primary myocardial disease with LV dilation and systolic dysfunction</td>
</tr>
<tr>
<td>B</td>
<td>Progressive MR</td>
<td>Regional wall motion abnormalities with mild thickening of mitral leaflet</td>
<td>ERO &lt; 0.20 cm (^2)</td>
<td>Regurgitant volume &lt;30 mL, Regurgitant fraction &lt;50%</td>
<td>Regional wall motion abnormalities with reduced LV systolic function, LV dilation and systolic dysfunction due to primary myocardial disease</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe MR</td>
<td>Regional wall motion abnormalities and/or LV dilation with severe thickening of mitral leaflet</td>
<td>ERO ≥ 0.20 cm (^2)</td>
<td>Regurgitant volume ≥30 mL, Regurgitant fraction ≥50%</td>
<td>Regional wall motion abnormalities with reduced LV systolic function, LV dilation and systolic dysfunction due to primary myocardial disease</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe MR</td>
<td>Regional wall motion abnormalities and/or LV dilation with severe thickening of mitral leaflet</td>
<td>ERO ≥ 0.20 cm (^2)</td>
<td>Regurgitant volume ≥30 mL, Regurgitant fraction ≥50%</td>
<td>Regional wall motion abnormalities with reduced LV systolic function, LV dilation and systolic dysfunction due to primary myocardial disease</td>
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Nishimura R et al. ACC/AHA Guidelines 2014

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### Prognosis of MR in Post MI LVSD – SAVE Trial

![Prognosis of MR in Post MI LVSD – SAVE Trial](image)

FMR at Duke: Survival by Severity at 1, 3, 5 and 10 years

FMR Severity and Mortality in CABG Eligible Patients

MR Grade | Hazard Ratio | 95% CI |
---|---|---|
Mild MR: None or Trace MR | 1.54 | 1.14, 2.07 |
Moderate or Severe MR: None or Trace MR | 2.01 | 1.42, 2.85 |

Severe MR in symptomatic patients

5737 pts with ≥3+ MR
• ~20% HF symptoms
• Primary (degenerative) 26%
  – Most undergo surgery
• Secondary (functional) 74%
  – Most receive medical therapy

Therapeutic Approaches – Lots of Questions, Limited Answers

• What should we do about patients with moderate or severe FMR and LVSD going to CABG?
  – MV repair or MV replacement? Neither?

• What should we do about patients with severe FMR and LVSD but no CAD surgical indication?
  – MV repair/replacement? Continue medical therapy? MCSD?

• What should we do with patients with severe FMR and LVSD who are not otherwise CT surgical candidates?
  – MitraClip?
  – Medical therapy only?
CRT Can Reduce FMR

AND REDUCED MR IS ASSOCIATED WITH LOWER MORTALITY

Table 4. Uni- and Multivariate Cox Proportional Hazards Models for Time to All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.01 (0.97-1.05)</td>
<td>0.939</td>
</tr>
<tr>
<td>Men</td>
<td>1.10 (0.57-2.22)</td>
<td>0.794</td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>1.36 (0.35-5.96)</td>
<td>0.154</td>
</tr>
<tr>
<td>NYHA class IV vs III</td>
<td>2.42 (1.23-4.78)</td>
<td>0.011</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.63 (0.83-3.22)</td>
<td>0.156</td>
</tr>
<tr>
<td>GFR duration, ms</td>
<td>1.00 (0.99-1.01)</td>
<td>0.947</td>
</tr>
<tr>
<td>eGFR ml, min-1/1.73 m²-1</td>
<td>0.96 (0.97-0.96)</td>
<td>0.902</td>
</tr>
<tr>
<td>MR Improvement</td>
<td>0.82 (0.49-0.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>LVESV Response</td>
<td>0.25 (0.12-0.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Low EF and Moderate to Severe FMR with CAD

Effect of treatment vs. medical therapy - Adjusted

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR</th>
<th>95% CI</th>
<th>Chi-Square</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>0.78</td>
<td>0.61, 1.00</td>
<td>3.83</td>
<td>0.50</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>0.56</td>
<td>0.42, 0.76</td>
<td>14.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MV surgery</td>
<td>0.64</td>
<td>0.33, 1.27</td>
<td>1.63</td>
<td>0.202</td>
</tr>
<tr>
<td>CABG + MV surgery</td>
<td>0.58</td>
<td>0.44, 0.78</td>
<td>13.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Samad, Z ... Velazquez EJ. European Heart J 2016.
STICH Trial Moderate- Severe MR- Effect of MVR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG : MED</td>
<td>1.20</td>
<td>0.77, 1.87</td>
</tr>
<tr>
<td>CABG+ MVR : MED</td>
<td>0.68</td>
<td>0.41, 1.12</td>
</tr>
<tr>
<td>CABG+ MVR : CABG</td>
<td>0.62</td>
<td>0.35, 1.08</td>
</tr>
</tbody>
</table>


CTSN Severe MR Trial Design

Assessed for Eligibility (n=3458)

Randomized (n = 281)

Excluded (n = 3207)
  - Did not meet inclusion criteria (n=3011)
  - Refused to participate (n=131)
  - Other (n=65)

Allocated to Mitral Valve Repair (n=126)
  - Received MV Repair (n=115)
  - Received MV Replacement (n=11)

Allocated to Mitral Valve Replacement (n=125)
  - Received MV Replacement (n=124)
  - Received MV Repair (n=1)

Follow-Up Allocation
  - Withdrawal before month 12 (n=3)
  - Death before month 12 (n=10)
  - Withdrawal before month 12 (n=1)
  - Death before month 12 (n=22)

Analysis
  - Primary Endpoint Analysis (n=128)
    - Excluded from analysis (n=6)
  - Primary Endpoint Analysis (n=126)
    - Excluded from analysis (n=4)

Median change in LVESVI

Median with 95% CI for change in LVESVI from baseline to 1 yr

Z=1.33, p=0.18 (All pts)

Recurrence MR at 1 year

32.6

p < 0.001
CTSN Moderate MR Trial Design

- Patients Screened for Moderate Ischemic MR (n=6,676)
- Randomized Patients (n=301)
  - CABG Alone (n=151)
  - CABG + Valve Repair Undersized Ring (n=150)
- Outcomes Measured at 6, 12 and 24 months
- Primary Endpoint Analysis (n=301)

Operative Conduct and Length of Stay

<table>
<thead>
<tr>
<th></th>
<th>CABG Alone</th>
<th>CABG + MV Repair</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Grafts</td>
<td>3.3±0.9</td>
<td>3.2±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic XClamp (min)</td>
<td>74.7±36.7</td>
<td>117.2±35.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>106.8±49.7</td>
<td>163.1±54.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU stay</td>
<td>4.0±5.7</td>
<td>4.8±6.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Postoperative LOS</td>
<td>9.4±5.9</td>
<td>11.3±8.2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data presented as mean±std
Change in LVESVI at 1 Year

Median with 95% CI for change in LVESVI (1 Year – baseline)

Z=0.50, p=0.61
(All patients)

MACCE at 12 Months

Hazard Ratio, 0.99 (95% CI, 0.62-1.59)
P=0.97

<table>
<thead>
<tr>
<th>Months</th>
<th>CABG Alone</th>
<th>CABG + MV Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>151</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>132</td>
</tr>
<tr>
<td>6</td>
<td>124</td>
<td>123</td>
</tr>
<tr>
<td>9</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>12</td>
<td>114</td>
<td>116</td>
</tr>
</tbody>
</table>
CTSN II - Mitral Regurgitation

CTSN – II Quality of Life at 1 year

\[ \Delta = 12\%\]  \[\Delta = 14\%\]

\[\Delta = 45\%\]  \[\Delta = 48\%\]

\(\Delta\) = Median improvement from baseline to 12 months

SF-12 (Physical Function)  MLHF
Mitra-Clip Edge-to-Edge Repair
MitraClip Reduces MR

Before MitraClip

After MitraClip

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EVEREST II Randomized Control Trial of MitraClip® vs. Surgical Repair

- 279 pts at 37 sites
- ACC/AHA indications for MV repair
- >Moderate MR by quantitative, core lab assessment

MitraClip Repair (n=184)

Surgery Repair or Replacement (n=95)

One year outcome
Freedom from death, surgery for mitral valve dysfunction, or >moderate mitral regurgitation
EVEREST II RCT – Freedom from Death & MV Surgery

279 randomized – 194 MitraClip (FMR 27%)
Age 67/ Women 37.5%
HF Hx 91%/ CAD 47%
NYHA III/IV 51.1%
LVEF 60%

30d – 1.1%
12m – 6.3%
2y – 12.5%
4y – 15.9%

EVEREST II High Risk Registry:
12 month Survival

351 enrolled – FMR 70%
Age 75.7/ Women 39.6%
HF Hx 98%/ CAD 82.2%
NYHA III/IV 84.9% (IV 23.4%)
LVEF 47.5%
Procedural – 0 (15); 1 (201); 2 (135)

30d – 4.8%
12m – 22.8%
EVEREST II High Risk Registry:
MR Grade & NYHA Functional Class

MitraClip in CRT Non-Responders
N=51, age 70, LVEF 27%, NT-BNP 3702

NYHA

MR

Auricchio, JACC, 2011
Indications for mitral valve intervention in chronic secondary mitral regurgitation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery is indicated in patients with severe secondary mitral regurgitation undergoing CABG and LVEF &gt; 30%</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation, LVEF &lt; 30% but with an option for revascularization and evidence of myocardial viability.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF &gt; 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

When revascularization is not indicated and surgical risk is low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF > 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.

In patients with severe secondary mitral regurgitation and LVEF < 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.
Transcatheter MV Replacement?

A

B

C

Valtech
Conclusions

• FMR is a disease of the left ventricle.
• FMR and HF occur commonly together.
• FMR causes LV remodelling, HF, and death.
• The vast majority of FMR is treated medically.
• Therapy that improves LV function likely improves FMR.
• The optimal approach to FMR beyond medical therapy remains controversial.
• More RCTs are needed.

Thank You