Mitral Valve Annuloplasty plus CABG versus CABG alone in moderate Functional Ischemic Mitral Regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) Trial

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Background: Functional Ischemic MR

- Occurs in up to 40% of patients following myocardial infarction.
- Result of LV remodeling & dilatation.
- Mitral valve tethered and pulled apart.
- MR usually mild or moderate in severity.
- Heart failure and death increased up to 3x.
- Most have 3-vessel coronary artery disease, benefit from CABG.

Persistent increased risk of heart failure and death (up to 1.5x) with coronary artery revascularization alone.

Efficacy of adding mitral valve repair to CABG uncertain: reduction in MR severity reported in observational, non-randomized studies, but no improvement in functional capacity, heart failure or survival.

Significant recurrence rates of MR reported in studies due to suboptimal surgical techniques (use of flexible annuloplasty bands, inadequate downsizing, incomplete coronary revascularization).
Randomized Ischemic Mitral Evaluation (RIME) Trial

Methods: Study design

• Single blinded randomized controlled trial: 7 centers.

• Randomization into two groups (1:1 ratio):

• **Group 1: CABG only**
  - Complete coronary artery revascularization.
  - Pedicled left internal mammary artery grafted to the LAD.

• **Group 2: CABG + Mitral Valve Repair**
  - Complete rigid or semi-rigid mitral annuloplasty ring used.
  - Carpentier-McCarthy-Adams IMR ETlogix ring recommended.
  - Sized by measurement of anterior mitral valve leaflet.
  - Downsized by 2 sizes if alternative complete ring used.
  - Aim: coaptation length of at least 8 mm between the anterior and posterior mitral valve leaflets with no more than trace MR.
Methods: Eligibility

• Inclusion criteria
  
  ▪ Patients referred for elective CABG.
  
  ▪ Moderate functional ischemic MR as defined by the AHA/ACC/ASE criteria measured at rest or peak exercise by echocardiography:
    
    o Effective Regurgitant Orifice Area (EROA) 0.20–0.39 cm²
    o Regurgitant Volume 30–59 ml/beat
    o Regurgitant Fraction 30–49%
    o Vena Contracta Width 0.3–0.69 cm
Methods: Eligibility

- **Main exclusion criteria**
  - Severe LV dysfunction: EF < 30%.
  - Structural abnormalities of the mitral valve (including papillary muscle rupture).
  - Significant aortic valve disease.
  - Previous or active endocarditis.
  - Significant co-morbidities: severe renal, liver or respiratory impairment.
  - NYHA class IV, unstable angina, acute pulmonary edema, cardiogenic shock.
  - Previous cardiac surgery.
Methods: Hypothesis

• **Primary hypothesis**
  - Adding mitral valve annuloplasty to CABG in patients with moderate functional ischemic MR improves functional capacity.

• **Secondary hypothesis**
  - Adding mitral valve annuloplasty to CABG in patients with moderate functional ischemic MR improves LV reverse remodelling, MR severity, and BNP levels.
Methods: Endpoints

• Primary endpoint (one year):
  ▪ Functional capacity (Peak oxygen consumption)

• Secondary endpoints (one year):
  ▪ LV reverse remodeling (LVESVI)
  ▪ Mitral regurgitation (MR volume)
  ▪ BNP levels.
Methods: Statistics

• Power calculations

  ▪ Using 90% power, $\alpha = 0.05$, and S.D. = 3.5, 82 patients required to detect difference of $\geq 2.5$ ml/kg/min in primary endpoint, peak VO$_2$.

  ▪ Two planned interim analysis performed.

  ▪ Benefit demonstrated for CABG + MVR group, ($P=0.008$ for primary endpoint).

  ▪ Recruitment stopped after results of second interim analysis (73 patients randomised).
Results: Enrollment

Assessed for eligibility (n=172)

Excluded (n=99)
- Not meeting inclusion criteria (n=91)
- Withdrawal from study (n=5)
- Died prior to surgery (n=3)

Randomized (n=73)
Randomized Ischemic Mitral Evaluation (RIME) Trial

Results: Treatment Allocation & Follow-up

Randomized (n=73)

Allocation

Allocated to CABG only (n=39)
- Received allocated intervention (n=38)
- Did not receive allocated intervention (n=1)
  1 death prior to surgery

Allocated to CABG+MVR (n=34)
- Received allocated intervention (n=33)
- Did not receive allocated intervention (n=1)
  1 death prior to surgery

Follow-Up

Unavailable for analysis (n=6)
- 2 deaths (1 post-operative)
- 4 withdrawals from study

Unavailable for analysis (n=6)
- 3 deaths (1 post-operative)
- 3 withdrawals from study

Analysis

Analysed (n=32)

Analysed (n=27)
### Results: Baseline

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>CABG + MVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – mean (range)</td>
<td>70 (51-83)</td>
<td>71 (47-86)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>NYHA class (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>III</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EROA (cm²)</td>
<td>0.18 ± 0.10</td>
<td>0.21 ± 0.09</td>
</tr>
<tr>
<td>Regurgitant volume (ml/beat)</td>
<td>30.3 ± 13.8</td>
<td>35.5 ± 13.3</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>43.3 ± 9.5</td>
<td>45.7 ± 7.4</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>56.5 ± 12.0</td>
<td>56.5 ± 12.6</td>
</tr>
<tr>
<td>LV Ejection fraction (%)</td>
<td>40.3 ± 16.1</td>
<td>40.0 ± 17.3</td>
</tr>
</tbody>
</table>
# Results: Surgery

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>CABG + MVR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of bypass grafts (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td><strong>CPB time (min) – median (Q1-Q3)</strong></td>
<td>84 (70-106)</td>
<td>147 (133-169)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cross clamp time (min) – median (Q1-Q3)</strong></td>
<td>51 (41-55)</td>
<td>95 (90-110)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mitral Annuloplasty ring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CMA IMR ETlogix (%)</td>
<td></td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>• CE Physio (%)</td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>• Mean ring size (mm)</td>
<td></td>
<td></td>
<td>28</td>
</tr>
</tbody>
</table>
## Randomized Ischemic Mitral Evaluation (RIME) Trial

### Results: Post-operative

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>CABG + MVR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensive care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IABP use (%)</td>
<td>29</td>
<td>33</td>
<td>0.57</td>
</tr>
<tr>
<td>Intubation time (hours)</td>
<td>17 (12-20)</td>
<td>28 (17-102)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Blood loss &amp; transfusion – median (Q1-Q3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>755 (479-933)</td>
<td>672 (511-1006)</td>
<td>0.89</td>
</tr>
<tr>
<td>Blood transfused (ml)</td>
<td>153 (0-818)</td>
<td>900 (225-1439)</td>
<td>0.016</td>
</tr>
<tr>
<td>Platelet transfused (ml)</td>
<td>0 (0-0)</td>
<td>0 (0-306)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fresh frozen plasma transfused (ml)</td>
<td>0 (0-0)</td>
<td>0 (0-636)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
## Randomized Ischemic Mitral Evaluation (RIME) Trial

### Results: Post-operative

<table>
<thead>
<tr>
<th>Complications</th>
<th>CABG</th>
<th>CABG + MVR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemofiltration (%)</td>
<td>8</td>
<td>12</td>
<td>0.70</td>
</tr>
<tr>
<td>Re-operation for bleeding or tamponade (%)</td>
<td>5</td>
<td>12</td>
<td>0.41</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0</td>
<td>3</td>
<td>0.47</td>
</tr>
<tr>
<td>30 day mortality (%)</td>
<td>3</td>
<td>3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital stay</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay – median (Q1-Q3)</td>
<td>9 (7-12)</td>
<td>15 (11-16)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical events</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>One year survival (%)</td>
<td>95</td>
<td>91</td>
<td>0.66</td>
</tr>
<tr>
<td>Hospital admission for heart failure (%)</td>
<td>8</td>
<td>3</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Results: Primary endpoint
Functional Capacity at 1 Year

Improvement in functional capacity was greater following CABG + MV repair compared to CABG alone.

Randomized Ischemic Mitral Evaluation (RIME) Trial

Peak VO₂ (% change)
Mean ± 95% CI

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ (% change)</td>
<td>5</td>
<td>22</td>
</tr>
</tbody>
</table>

P<0.001
LV reverse remodelling was greater following CABG + MV repair compared to CABG alone.
Reduction in mitral regurgitation was greater following CABG + MV repair compared to CABG only.
Results: Secondary endpoints
Mitral regurgitation at 1 Year

Mitral regurgitation was less following CABG + MV repair compared to CABG only.

Randomized Ischemic Mitral Evaluation (RIME) Trial

P<0.001
Reduction in BNP was greater following CABG + MV repair compared to CABG only.

### Randomized Ischemic Mitral Evaluation (RIME) Trial

#### Results: Secondary endpoints

**BNP at 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>CABG + MVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (% change)</td>
<td>-58</td>
<td>-75</td>
</tr>
</tbody>
</table>

Mean ± 95% CI

P = 0.003
Results: Symptoms at 1 Year

NYHA class was better following CABG + MV repair compared to CABG only.

Randomized Ischemic Mitral Evaluation (RIME) Trial

NYHA class was better following CABG + MV repair compared to CABG only.
Limitations

- Study stopped early for benefit after review of interim results.

- Single (not double) blinded study.

- Endpoints determined at one year; longer follow-up necessary.

- Study not designed and not powered to evaluate clinical events and survival.
Conclusions

• Compared to CABG alone, addition of MV annuloplasty to CABG in patients with moderate functional ischemic MR improves:
  ▪ Functional capacity and symptoms
  ▪ LV reverse remodelling
  ▪ Mitral regurgitation
  ▪ BNP levels

• The impact of these benefits on longer term clinical outcomes remain to be defined.

• CABG plus MV annuloplasty required longer operation times, increased intubation and hospital stay duration, and blood transfusion.

• Concomitant CABG plus MV annuloplasty should be considered in patients with moderate functional ischemic MR.
Acknowledgement

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