Relationship Between Residual Mitral Regurgitation and Clinical and Functional Outcomes in the COAPT Trial

Saibal Kar, Michael J. Mack, JoAnn Lindenfeld, William T. Abraham, Neil J. Weissman and Gregg W. Stone, on behalf of the COAPT Investigators

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Saibal Kar, MD

*Disclosure Statement of Affiliations/Financial Relationship*

- **Grant/Research Support**
  Abbott Vascular, Boston Scientific, Gore Medical, Edwards Lifesciences

- **Consulting Fees/Honoraria**
  Abbott Vascular, Boston Scientific, Gore Medical

- **Other Financial Benefit**
  Valcare
• In the COAPT trial treatment of selected patients with heart failure and severe secondary MR with the MitraClip improved 2-year survival, reduced HF hospitalizations (HFH), and improved quality of life compared with maximally-tolerated guideline-directed medical therapy (GDMT) alone

• In addition, the MitraClip was substantially more effective than GDMT alone in reducing MR

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in ~614 patients with heart failure and moderate-to-severe (3+) or severe (4+) SMR (US ASE criteria) who remained symptomatic despite maximally-tolerated GDMT and CRT if appropriate

Randomize 1:1*

MitraClip + GDMT
N=302

GDMT alone
N=312

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

**COAPT Primary Outcomes**

### All Hospitalizations for HF

- **MitraClip + GDMT**: 283 in 151 pts
- **GDMT alone**: 160 in 92 pts

**Cumulative HF Hospitalizations (n)**

HR (95% CI) = 0.53 [0.40-0.70]

P=0.000006; NNT: 3.1 [1.9-7.9]

### All-Cause Mortality

- **MitraClip + GDMT**: 46.1%
- **GDMT alone**: 29.1%

**All-cause Mortality (%)**

HR [95% CI] = 0.62 [0.46-0.82]

P=0.0007; NNT: 5.9 [3.9-11.7]

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MR Reduction in COAPT

• Although the MitraClip was more successful in reducing MR than GDMT alone, the mechanistic relationship between MR reduction and the observed clinical and functional outcomes in the COAPT trial is uncertain:
  • Whether achieving 2+ MR has as favorable a prognostic impact as ≤1+ MR is unknown; and
  • Whether MR reduction with GDMT alone has the same durability and prognostic impact as MR reduction by the MitraClip is unknown

The objective of the present study was to evaluate the durability and impact of the degree of residual MR at 30 days on long-term clinical and functional outcomes in patients enrolled in the COAPT trial, including both the treatment (MitraClip + GDMT) and the control (GDMT alone) groups.
Time to First HFH or All-Cause Mortality

Pooled (MitraClip and Control) Population Stratified by 30-day Residual MR

Follow-up Duration (Months)

<table>
<thead>
<tr>
<th>MR 0/1+ (N=223; 41.8%)</th>
<th>MR 2+ (N=122; 22.8%)</th>
<th>MR 3+/4+ (189; 35.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># At Risk</td>
<td>223</td>
<td>192</td>
</tr>
<tr>
<td>1</td>
<td>122</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>189</td>
<td>120</td>
</tr>
</tbody>
</table>

HR [95% CI] = 0.76 [0.54, 1.07], P=0.12 for 0/1+ vs 2+
HR [95% CI] = 0.38 [0.29, 0.50], P<0.001 for 0/1+ vs 3+/4+
HR [95% CI] = 0.50 [0.36, 0.68], P<0.001 for 2+ vs 3+/4+

P<0.001 Overall
Time to First HFH or All-Cause Mortality

Randomization Groups Stratified by 30-day Residual MR

### MitraClip + GDMT

- MR 0/1+ (N=202; 72.9%)
- MR 2+ (N=55; 19.9%)
- MR 3+/4+ (N=20; 7.2%)

### GDMT Only

- MR 0/1+ (N=21; 8.2%)
- MR 2+ (N=67; 26.1%)
- MR 3+/4+ (N=169; 65.8%)

#### Follow-up Duration (Months)

1. **HFH or All-cause Mortality Rate (%)**

   - **P<0.001 Overall**
   - HR [95% CI] = 0.84 [0.38, 1.84] for 0/1+ vs 2+
   - HR [95% CI] = 0.44 [0.21, 0.90] for 0/1+ vs 3+/4+
   - HR [95% CI] = 0.50 [0.34, 0.76] for 2+ vs 3+/4+

   **P_int=0.93**

#### # At Risk

<table>
<thead>
<tr>
<th># At Risk</th>
<th>1</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR 0/1+</td>
<td>202</td>
<td>176</td>
<td>139</td>
<td>106</td>
<td>66</td>
</tr>
<tr>
<td>MR 2+</td>
<td>55</td>
<td>45</td>
<td>37</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>MR 3+/4+</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>
Cumulative HFH Rate and Time to All-Cause Mortality

**Pooled (MitraClip and Control) Population Stratified by 30-day Residual MR**

### Cumulative Heart Failure Hospitalization Rate

- **MR 0/1+ (N=223; 41.8%)**
- **MR 2+ (N=122; 22.8%)**
- **MR 3+/4+ (N=189; 35.4%)**

#### Follow-up Duration (Months)

- **0%**
- **20%**
- **40%**
- **60%**
- **80%**
- **100%**

#### Cumulative HFH Event Rate (%/Patient-Year)

**P<0.001 Overall**

- HR [95% CI] = 0.94 [0.60, 1.46] for 0/1+ vs 2+
- HR [95% CI] = 0.40 [0.28, 0.56] for 0/1+ vs 3+/4+
- HR [95% CI] = 0.42 [0.28, 0.62] for 2+ vs 3+/4+

### All-Cause Mortality

- **MR 0/1+ (N=223; 41.8%)**
- **MR 2+ (N=122; 22.8%)**
- **MR 3+/4+ (N=189; 35.4%)**

#### Follow-up Duration (Months)

- **0%**
- **20%**
- **40%**
- **60%**
- **80%**
- **100%**

#### All-cause Mortality Rate (%)

**P<0.001 Overall**

- HR [95% CI] = 0.74 [0.48, 1.15] for 0/1+ vs 2+
- HR [95% CI] = 0.46 [0.32, 0.66] for 0/1+ vs 3+/4+
- HR [95% CI] = 0.62 [0.42, 0.93] for 2+ vs 3+/4+

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</tr>
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<td>122</td>
<td>189</td>
</tr>
<tr>
<td>2 months</td>
<td>211</td>
<td>109</td>
<td>164</td>
</tr>
<tr>
<td>3 months</td>
<td>177</td>
<td>96</td>
<td>133</td>
</tr>
<tr>
<td>4 months</td>
<td>138</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>5 months</td>
<td>92</td>
<td>48</td>
<td>54</td>
</tr>
</tbody>
</table>

82.4%  34.1%  32.0%

48.4%  32.1%  23.7%

2019 euroPCR
Cumulative HFH Event Rate

Randomization Groups Stratified by 30-day Residual MR

**MitraClip + GDMT**

- MR 0/1+ (N=202; 72.9%)
- MR 2+ (N=55; 19.9%)
- MR 3+/4+ (N=20; 7.2%)

**GDMT Only**

- MR 0/1+ (N=21; 8.2%)
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**Follow-up Duration (Months)**

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<td>48</td>
<td>19</td>
</tr>
<tr>
<td>MR 3+/4+</td>
<td>161</td>
<td>45</td>
<td>15</td>
</tr>
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</table>

**P = 0.72**

- **HR [95% CI]** = 0.83 [0.47, 1.47] for 0/1+ vs 2+
- **HR [95% CI]** = 0.47 [0.23, 0.97] for 0/1+ vs 3+/4+
- **HR [95% CI]** = 0.40 [0.22, 0.73] for 2+ vs 3+/4+

**Follow-up Duration (Months)**

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<td>169</td>
</tr>
<tr>
<td>MR 2+</td>
<td>20</td>
<td>61</td>
<td>145</td>
</tr>
<tr>
<td>MR 3+/4+</td>
<td>16</td>
<td>51</td>
<td>118</td>
</tr>
</tbody>
</table>

**P = 0.01 Overall**

- **HR [95% CI]** = 1.30 [0.54, 3.16] for 0/1+ vs 2+
- **HR [95% CI]** = 0.49 [0.23, 1.07] for 0/1+ vs 3+/4+
- **HR [95% CI]** = 0.38 [0.22, 0.64] for 2+ vs 3+/4+

**P < 0.001 Overall**

- **HR [95% CI]** = 0.47 [0.23, 0.97] for 2+ vs 3+/4+

**P = 0.72**
Time to All-Cause Mortality

Randomization Groups Stratified by 30-day Residual MR

MitraClip + GDMT

- MR 0/1+ (N=202; 72.9%)
- MR 2+ (N=55; 19.9%)
- MR 3+/4+ (N=20; 7.2%)

P=0.468 Overall
HR [95% CI] = 0.87 [0.48, 1.58] for 0/1+ vs 2+
HR [95% CI] = 0.61 [0.28, 1.36] for 0/1+ vs 3+/4+
HR [95% CI] = 0.71 [0.28, 1.75] for 2+ vs 3+/4+

GDMT Only

- MR 0/1+ (N=21; 8.2%)
- MR 2+ (N=67; 26.1%)
- MR 3+/4+ (N=169; 65.8%)

P=0.037 Overall
HR [95% CI] = 0.44 [0.13, 1.49] for 0/1+ vs 2+
HR [95% CI] = 0.29 [0.09, 0.93] for 0/1+ vs 3+/4+
HR [95% CI] = 0.68 [0.46, 1.12] for 2+ vs 3+/4+

Follow-up Duration (Months)

- # At Risk
  - MR 0/1+: 202 → 191 → 161 → 124 → 82
  - MR 2+: 55 → 48 → 45 → 36 → 27
  - MR 3+/4+: 20 → 19 → 15 → 11 → 7

- # At Risk
  - MR 0/1+: 21 → 20 → 16 → 14 → 10
  - MR 2+: 67 → 61 → 51 → 31 → 21
  - MR 3+/4+: 169 → 145 → 118 → 79 → 47
KCCQ Improvement @ 12-Month Stratified by 30-Day MR
Mean ± SE (ANCOVA Model)

Pooled Population
P = 0.92 for 0/1+ vs 2+
P = 0.15 for 0/1+ vs 3+/4+
P = 0.10 for 2+ vs 3+/4+

MitraClip + GDMT
P = 0.41 for 0/1+ vs 2+
P = 0.37 for 0/1+ vs 3+/4+
P = 0.21 for 2+ vs 3+/4+

GDMT Only
P = 0.71 for 0/1+ vs 2+
P = 0.24 for 0/1+ vs 3+/4+
P = 0.21 for 2+ vs 3+/4+

P_{int} = 0.71

KCCQ Scores

<table>
<thead>
<tr>
<th></th>
<th>12-Month Improvement</th>
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</tr>
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<tbody>
<tr>
<td>N 30-Day MR 0/1+</td>
<td>223</td>
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<td>55</td>
<td>67</td>
</tr>
<tr>
<td>N 30-Day MR 3+/4+</td>
<td>186</td>
<td>20</td>
<td>166</td>
</tr>
</tbody>
</table>

30-Day MR 0/1+  
30-Day MR 2+  
30-Day MR 3+/4+
MR Severity
Subgroup: 30 day residual MR ≤1+

MitraClip + GDMT

<table>
<thead>
<tr>
<th>Time</th>
<th>MitraClip + GDMT</th>
<th>P-value</th>
<th>GDMT Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day</td>
<td>100.0%</td>
<td></td>
<td>18.8%</td>
</tr>
<tr>
<td>12-Months</td>
<td>98.7%</td>
<td>P=0.006</td>
<td>81.3%</td>
</tr>
<tr>
<td>24-Months</td>
<td>100.0%</td>
<td>P&lt;0.001</td>
<td>30.8%</td>
</tr>
</tbody>
</table>

N=199, 154, 82, 21, 16, 13

MR Severity Subgroup: 30 day residual MR ≤1+

Percentage of Patients (%)

- MR≤2+
- MR>2+
MitraClip + GDMT

Subgroup: 30 day residual MR ≥2+

P<0.001
P=0.046

MR Severity

Percentage of Patients (%)

30-Day
(N=54)

12-Months
(N=41)

24-Months
(N=25)

30-Day
(N=67)

12-Months
(N=50)

24-Months
(N=18)

MR≤2+

MR>2+

30-Day

12-Months

24-Months

30-Day

12-Months

24-Months

(N=54)

(N=41)

(N=25)

(N=67)

(N=50)

(N=18)
In the COAPT trial, lower residual MR (≤2+) at 30 days in both the MitraClip and GDMT groups was strongly associated with reduced HFH, all-cause mortality and improved quality of life compared with residual MR of 3+/4+.

- This finding suggests that the greater reduction of MR with the MitraClip compared with GDMT alone underlies the observed clinical benefits from the MitraClip.

- There was no significant difference between achieving 0/1+ and 2+ residual MR on improvements in HFH, all-cause mortality and quality of life at 2 years.

- While some pts with GDMT had improved MR at 30 days, many of these pts later had recurrent severe MR. The improvement in MR achieved at 30 days with the MitraClip was significantly more durable.