MHIF FEATURED STUDY:
REPAIR-MR

DESCRIPTION:
Purpose: to compare the clinical outcome of MitraClip™ device versus open surgical repair in patients with severe primary MR who are at moderate surgical risk.

Primary endpoint: survival, free of stroke and any cardiovascular hospitalization at 2 years; MR ≤ mild at 30 days; QOL improvement of at least 5 points at 2 years compared to baseline; hospital length of stay; rate of mitral valve replacement at index procedure

CRITERIA LIST/ QUALIFICATIONS:

Inclusion: severe primary MR (Grade III or greater mitral regurgitation mixed etiology is acceptable if principal mechanism is a degenerative mitral valve); symptomatic NYHA class II, III, or asymptomatic with EF ≤ 60%, PAS >50 mm HG, or LVESD >40 mm; 75 years or if < 75 years subject with STS predicted risk of mortality repair score >2%, or presence of comorbidities

Exclusion: ischemic or non-ischemic secondary MR; EF <30%; severe TR; severe annular calcification; valve anatomy which would preclude reducing MR to mild or less

CONDITION: Severe primary MR who are at moderate surgical risk
PI: Paul Sorajja, MD
RESEARCH CONTACT: Jane Fox
SPONSOR: Abbott

Jane.fox@allina.com | 612-863-6289

Coming soon!
EPIC message: Research MHIF Patient Referral
**MHIF FEATURED STUDY: HighLife**

**DESCRIPTION:**

**Purpose:** to evaluate the safety and efficacy of the HighLife trans-septal access 28mm Transcatheter Mitral valve and its delivery system (*transfemoral venous access and interatrial puncture*) in patients with moderate-severe or severe mitral regurgitation who are at a high risk for surgical treatment.

**Primary Feasibility endpoint:** technical success

**Safety:** all cause mortality at 30 days

**Performance:** total MR reduction to 1+ or less as assessed by core lab

**CRITERIA LIST/ QUALIFICATIONS:**

**Inclusion:** moderate-severe or severe mitral regurgitation; NHYA class II, III; or ambulatory class IV

**Exclusion:** mitral stenosis; Flail Leaflet or prolapse; severe calcification; prior mitral intervention; mitral annulus <30 mm & >45 mm; Aortic prosthesis; LVEF<30%; PAS >70mmHg; TR requiring intervention

**CONDITION:**
Symptomatic mitral regurgitation

**PI:**
Paul Sorajja, MD

**RESEARCH CONTACT:**
Jane Fox

Jane.fox@allina.com | 612-863-6289

**SPONSOR:**
HighLife Medical, Inc.

**OPEN AND ENROLLING:**
EPIC message: Research MHIF Patient Referral
Functional MR

MHIF-2020

Maurice E. Sarano, MD, FACC

Functional MR (secondary)
FMR in the community

65% of all MR cases

- Structurally normal mitral valve
- Mitral Regurgitation $\geq$ moderate

LV Remodeling  Atrial Enlargement

38%  27%
Functional MR-Atrial enlargement

- Observed
- Expected
- P<0.0001
- RR=1.67 (1.32, 2.12)
Clinical characteristics according to MR etiology

<table>
<thead>
<tr>
<th></th>
<th>FMR ventricular remodeling</th>
<th>FMR isolated atrial dilatation</th>
<th>OMR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases (%)</td>
<td>278 (38)</td>
<td>194 (27)</td>
<td>233 (32)</td>
<td>.0001</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>73±14</td>
<td>80±10</td>
<td>68±21</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>59</td>
<td>32</td>
<td>51</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Dyspnea, %</td>
<td>74</td>
<td>66</td>
<td>49</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter,%</td>
<td>28</td>
<td>54</td>
<td>13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>History of Heart failure,%</td>
<td>49</td>
<td>32</td>
<td>12</td>
<td>&lt;.0001</td>
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<tr>
<td>History of MI,%</td>
<td>17</td>
<td>9</td>
<td>3</td>
<td>&lt;.0001</td>
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<tr>
<td>Diabetes,%</td>
<td>29</td>
<td>24</td>
<td>9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Charlson index, median</td>
<td>3.5[2-5]</td>
<td>3[2-5]</td>
<td>2[0-3]</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

ESC Congress
Munich 2018
Evidence of Atrial Functional Mitral Regurgitation Due to Atrial Fibrillation
Reversal With Arrhythmia Control

Zachary M. Gertz, MD,* Amresh Raina, MD,* Laszlo Saghy, MD,† Erica S. Zado, PA-C,*
David J. Trivedi, MD, MSc

Distribution of etiologies of isolated moderate-severe MR in the community by age

OMR
FMR due to atrial dilataion
FMR due to LV remodeling
## Echocardiographic differences by MR etiology

<table>
<thead>
<tr>
<th></th>
<th>FMR ventricular remodeling</th>
<th>FMR isolated atrial dilatation</th>
<th>OMR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA volume, ml</td>
<td>102±33</td>
<td>94±30</td>
<td>91±35</td>
<td>0.005</td>
</tr>
<tr>
<td>MV RVol, ml</td>
<td>38±13</td>
<td>37±11</td>
<td>51±24</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MV ERO, cm²</td>
<td>0.24±0.10</td>
<td>0.20±0.08</td>
<td>0.31±0.19</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33±14</td>
<td>57±11</td>
<td>61±10</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LV EDD, mm</td>
<td>59±8</td>
<td>48±5</td>
<td>51±8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LV ESD, mm</td>
<td>49±10</td>
<td>32±6</td>
<td>32±7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>135±34</td>
<td>106±30</td>
<td>108±29</td>
<td>&lt;.0001</td>
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<tr>
<td>PASP, mmHg</td>
<td>52±14</td>
<td>48±14</td>
<td>44±18</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

## Outcomes of MR by etiology

![Outcomes of MR by etiology diagram](image)

- p=0.0001
- FMR LV remodeling
- FMR atrial dilatation
- OMR
FMR-Atrial Dilatation

- An entity almost completely ignored despite representing ~1/3 of all MR
- Affecting mostly elderly women often with AF
- Peculiar hemodynamics: Low Rvol, normal LV, PHTN
- Very frequent HF preceding excess mortality
- Almost never mitral surgery
- Role of the MR ??
Functional MR-LV Remodeling

Survival (%)

Years

Observed
Expected
P<0.0001
RR=3.50 (2.93, 4.19)

Type IIIb FMR
Conundrum #1
How does FMR happen?

Functional MR
Ventricular disease

Normal MV leaflets
Normal chordae
LV
LA
Ao
PM
Tethered MV leaflets
Tethered Chordae
Local left ventricular remodeling
LV
PM
Ao
LA
MR
Try to close The orifice!

What do we learn from 3D quantitation in FMR
Normal vs. Functional MR
Conundrum #2
Is FMR significant?
How to grade FMR?
Ischemic MR-Quantitation

ERO = 0.34 cm²  RVol = 46 mL

r = 0.75 cm  MR Vel = 420 cm/sec

Ischemic MR Post MI

Cardiovascular survival

Days

P = 0.002

Ischemic Mitral Regurgitation
Long-Term Outcome and Prognostic Implications With Quantitative
Doppler Assessment

Francesco Grigioni, MD; Maurice Enriquez-Sarano, MD; Kenton J. Zehr, MD;
Kent R. Bailey, PhD; A. Jamil Tajik, MD

Background—Myocardial infarction (MI) can directly cause ischemic mitral regurgitation (IMR), which has been touted as an indicator of poor prognosis in acute and early phases after MI. However, in the chronic post-MI phase, prognostic implications of IMR presence and degree are poorly defined.

Methods and Results—We analyzed 303 patients with previous (>16 days) Q-wave MI by ECG who underwent transmural echocardiography. 194 with IMR quantitatively assessed in routine practice and 109 without IMR matched for baseline age (71±11 versus 70±9 years, P=0.20), sex, and ejection fraction (EF, 33±14% versus 34±11%, P=0.14). In IMR patients, regurgitant volume (RVol) and effective regurgitant orifice (ERO) area were 36±24 mL/beat and 21±12 mm², respectively. After 5 years, total mortality and cardiac mortality for patients with IMR (63±5% and 50±6%, respectively) were higher than for those without IMR (39±6% and 30±5%, respectively) (both P<0.001). In multivariate analysis, independently of all baseline characteristics, particularly age and EF, the adjusted relative risks of total and cardiac mortality associated with the presence of IMR (1.88, P=0.003 and 1.63, P=0.014, respectively) and quantified degree of IMR defined by RVol ≥30 mL (2.05, P=0.002 and 2.01, P=0.009) and by ERO ≥20 mm² (2.23, P=0.003 and 2.38, P=0.004) were high.

Conclusions—In the chronic phase after MI, IMR presence is associated with excess mortality independently of baseline characteristics and degree of ventricular dysfunction. The mortality risk is related directly to the degree of IMR as defined by ERO and RVol. Therefore, IMR detection and quantification provide major information for risk stratification and clinical decision making in the chronic post-MI phase. (Circulation. 2001;103:1759–1764.)
Asymptomatic patients post-MI CHF during follow-up

P<0.0001

ERO, mm²

- ≥20
- 1-19
- 0

Incidence of CHF (%)


Discordant outcomes
Is it dependent on whether I did the echo?
Whether FMR is a surrogate?
Limits of quantification: PISA

- Non circular orifice

Chandra S, Am J Physiol Heart Circ Physiol 2011 Sep;301(3);


FMR in Europe

Lancellotti et al; Circulation 2003;108:1713
FMR in Europe
Impact on Outcome
Functional Class Survival
Rossi et al, Heart 2011;97:1675

Recent FMR Studies?

2018
Quantitative Definition of Severe Functional Mitral Regurgitation

2019
A Unifying Concept for the Quantitative Assessment of Secondary Mitral Regurgitation
The risk-curve flattens early for low EROA. The 95% CI is close to 1, i.e., barely significant.
Previous Cohorts display Discordant results regarding FMR outcome

Interactions between FMR and other determinants of outcome?
What did Paul forget?

RF = RVol/Total LV SV
RF = RVol/(RVol+FSV)
RF = ERO*RTVI

RTVI = LA compliant: 150 cm
LVAD 50 mL, RF 47%
LA non-compliant: RTVI 100
RVol 30 mL, RF 38%
Congratulations
All patients in COAPT
were already dead
with no forward SV !!!

Previous Cohorts display
Discordant results
regarding FMR outcome

COAPT Echo measure of
LV volumes was severely
underestimated

Forget “disproportionate” FMR
However, legitimate questions
remain for FMR interactions
Overall Non-ischemic

Coronary Artery Bypass Surgery With or Without Mitral Valve Annuloplasty in Moderate Functional Ischemic Mitral Regurgitation

Final Results of the Randomized Ischemic Mitral Evaluation (RIME) Trial

K.M. John Chan, FRCS CTh; Prakash P. Punjabi, FRCS CTh; Marcus Flather, MD, FRCP; Riccardo Wage, DCR (R); Karen Symmonds, DCR (R); Isabelle Roussin, MD; Shelley Rahman-Haley, MD, FRCP; Dudley J. Pennell, MD, FRCP; Philip J. Kilner, MD, PhD; Gilles D. Dreyfus, MD; John R. Pepper, MChir, FRCS; for the RIME Investigators

Patients with CAD referred to CABG with moderate MR with EF >30%, NYHA I-III
Randomized 1/1 to CABG alone or CABG + Mitral repair
Coronary Artery Bypass Surgery With or Without Mitral Valve Annuloplasty in Moderate Functional Ischemic Mitral Regurgitation

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<table>
<thead>
<tr>
<th>Variable</th>
<th>CABG (n=32)</th>
<th>CABG + MVR (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.4±7.9</td>
<td>70.9±18.5</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>10 (26)</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.4±5.0</td>
<td>25.3±6.4</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>5 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Prior coronary artery</td>
<td>22 (69)</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Diabetic on treatment</td>
<td>16 (50)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1 (3)</td>
<td>2 (8)</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>
</tbody>
</table>

Results

Table 3. Study End Points at 1 Year

<table>
<thead>
<tr>
<th>End Points</th>
<th>CABG (n=32)</th>
<th>CABG + MVR (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO2, ml/kg/min</td>
<td>15.1±3.3</td>
<td>15.9±2.5</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ESV, ml/m²†</td>
<td>71.8±16.1</td>
<td>67.4±20.4</td>
</tr>
<tr>
<td>LV EF volume, ml/beat†</td>
<td>31.9±14.8</td>
<td>27.7±14.6</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>681.4±197.3</td>
<td>286.7±132.0</td>
</tr>
</tbody>
</table>
Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation

**Table: MR and surgery**

<table>
<thead>
<tr>
<th></th>
<th>FMR ventricular remodeling (n=278)</th>
<th>FMR isolated atrial dilatation (n=194)</th>
<th>OMR (n=233)</th>
<th>Total (n=705)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV repair/ replacement, (%)</td>
<td>10(4%)</td>
<td>6(3%)</td>
<td>86(37%)</td>
<td>102(14%)</td>
</tr>
<tr>
<td>Any cardiac surgery, n(%)</td>
<td>25(9%)</td>
<td>12(6%)</td>
<td>86(37%)</td>
<td>123(17%)</td>
</tr>
</tbody>
</table>

**MV repair/ replacement by MR severity**

<table>
<thead>
<tr>
<th></th>
<th>Moderate MR, n(%) in subset</th>
<th>Severe MR, n(%) in subset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4(2%) (n=192)</td>
<td>6(7%) (n=86)</td>
</tr>
<tr>
<td></td>
<td>5(3%) (n=175)</td>
<td>1(5%) (n=19)</td>
</tr>
<tr>
<td></td>
<td>22(18%) (n=124)</td>
<td>64(59%) (n=109)</td>
</tr>
<tr>
<td></td>
<td>31(6%) (n=491)</td>
<td>71(33%) (n=214)</td>
</tr>
</tbody>
</table>

Severe Undertreatment of FMR
Previous Cohorts display Discordant results regarding FMR outcome

What about Interventional data?
Mitral Regurgitation
What can the MitraClip achieve

LA pressure

LA pressure
Previous RCTs display discordant results regarding FMR outcome.

What about Guidelines?

2003 Guidelines
American Society of Echocardiography: Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-dimensional and Doppler Echocardiography

2007 Guidelines
Guidelines on the management of valvular heart disease
The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology

An unprecedented guideline instability and discordance.

2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease
MR severity

ASE GUIDELINES AND STANDARDS

Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation

A Report from the American Society of Echocardiography
Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance

William A. Zoghbi, MD, FASE (Chair), David Adams, RCS, RDMS, FASE, Robert O. Bonow, MD,
Maurice Enriquez-Sarano, MD, Elise Foster, MD, FASE, Paul A. Grayburn, MD, FASE,
Rebecca T. Hahn, MD, FASE, Yunchi Han, MD, MMSc,* Judy Hung, MD, FASE, Roberto M. Lang, MD, FASE,
Stephen H. Little, MD, FASE, Dipan J. Shah, MD, MMSc,* Stanton Sherron, MD, FASE,
Paulinith Thavendranathan, MD, MSc, FASE,* James D. Thomas, MD, FASE,* and
Neil J. Weissman, MD, FASE, Houston and Dallas; Young; Durham, North Carolina; Chicago, Illinois; Rochester,
Minneapolis; San Francisco, California; New York, New York, Philadelphia, Pennsylvania; Baton, Massachusetts;
Toronto, Ontario, Canada; and Washington, DC

ASE Regurgitation committee meeting
**MR Grading algorithm**

**Chronic Mitral Regurgitation by Doppler Echocardiography**

- **Does MR meet specific criteria for mild or severe MR?**
  - **Yes, mild**
    - Indeterminate MR
      - Poor TEE quality or low confidence in measured Doppler parameters
      - Discordant quantitative and qualitative parameters and/or clinical data
  - **Yes, severe**
    - Intermediate Values: MR Probability Moderate
      - Perform quantitative methods whenever possible
    - Specific criteria for severe MR
      - Thalassemia
      - EOA ≤ 0.6 cm²
      - EOA ≤ 0.5 cm² at velocity < 40 cm/s
      - EOA ≤ 0.4 cm² at velocity < 30 cm/s

**2-3 criteria**

- Definitively mild
- Definitively severe

**Mild MR**

**Moderate MR**

**Severe MR**

**Functional MR**

- **CAUSE**
  - LV dysfunction
  - EOA ≤ 0.6 cm²
  - EOA ≤ 0.5 cm² at velocity < 40 cm/s
  - EOA ≤ 0.3 cm² at velocity < 30 cm/s

- **EFFECT**
  - Volume overload

- **Indeterminate MR**
  - Consider further testing: TEE or CMR for quantitation
Resolving the FMR Conundrum

We need new data
Very large cohorts
Comprehensively characterized
With long-term outcome
With comparison FMR-DMR

Heart Failure with reduced Ejection Fraction (HFrEF) stage B and C
2003-2011 N= 17146

Age < 50 y
N=1889

Diagnosis of cancer
N=3812

No mitral ERO
N=5064

HFrEF patients with FMR quantification
N=6381

No FMR, ERO=0
N=3823

ERO 0.01-0.09
N=195
ERO 0.10-0.19
N=1067
ERO 0.20-0.29
N=793
ERO ≥ 0.30
N=503
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=3823)</th>
<th>NO FMR (68%, 2599)</th>
<th>NO FMR-EROA &gt;/= 0 (37%, 1421)</th>
<th>NO FMR-EROA &lt; 0 (37%, 1408)</th>
<th>NO FMR-EROA &gt;/= 0 (37%, 1421)</th>
<th>NO FMR-EROA &lt; 0 (37%, 1408)</th>
<th>p-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
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<td></td>
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<tr>
<td>Age (years)</td>
<td>76±11</td>
<td>76±11</td>
<td>76±11</td>
<td>76±11</td>
<td>76±11</td>
<td>76±11</td>
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</tr>
<tr>
<td>Female (%)</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.1±6.8</td>
<td>29.1±6.8</td>
<td>29.1±6.8</td>
<td>29.1±6.8</td>
<td>29.1±6.8</td>
<td>29.1±6.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Atrial Fibrillation (%)</td>
<td>14±26</td>
<td>14±26</td>
<td>14±26</td>
<td>14±26</td>
<td>14±26</td>
<td>14±26</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>70±18</td>
<td>70±18</td>
<td>70±18</td>
<td>70±18</td>
<td>70±18</td>
<td>70±18</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132±23</td>
<td>132±23</td>
<td>132±23</td>
<td>132±23</td>
<td>132±23</td>
<td>132±23</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>71±14</td>
<td>71±14</td>
<td>71±14</td>
<td>71±14</td>
<td>71±14</td>
<td>71±14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1724 (28%)</td>
<td>1724 (28%)</td>
<td>1724 (28%)</td>
<td>1724 (28%)</td>
<td>1724 (28%)</td>
<td>1724 (28%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>4316 (68%)</td>
<td>4316 (68%)</td>
<td>4316 (68%)</td>
<td>4316 (68%)</td>
<td>4316 (68%)</td>
<td>4316 (68%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Charlson-Comorbidity-index</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
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<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td>Dyspnea (N, %)</td>
<td>3363 (55%)</td>
<td>3363 (55%)</td>
<td>3363 (55%)</td>
<td>3363 (55%)</td>
<td>3363 (55%)</td>
<td>3363 (55%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angina (N, %)</td>
<td>1722 (27%)</td>
<td>1722 (27%)</td>
<td>1722 (27%)</td>
<td>1722 (27%)</td>
<td>1722 (27%)</td>
<td>1722 (27%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Palpitations (N, %)</td>
<td>787 (12%)</td>
<td>787 (12%)</td>
<td>787 (12%)</td>
<td>787 (12%)</td>
<td>787 (12%)</td>
<td>787 (12%)</td>
<td>0.2</td>
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<tr>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>LV EDD (mm)</td>
<td>36±15</td>
<td>36±15</td>
<td>36±15</td>
<td>36±15</td>
<td>36±15</td>
<td>36±15</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV EDV (ml)</td>
<td>46±10</td>
<td>46±10</td>
<td>46±10</td>
<td>46±10</td>
<td>46±10</td>
<td>46±10</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ESV-index (mm2/m2)</td>
<td>28±6</td>
<td>28±6</td>
<td>28±6</td>
<td>28±6</td>
<td>28±6</td>
<td>28±6</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>36±10</td>
<td>36±10</td>
<td>36±10</td>
<td>36±10</td>
<td>36±10</td>
<td>36±10</td>
<td>0.0001</td>
</tr>
<tr>
<td>WMS-index</td>
<td>2.1±0.5</td>
<td>2.1±0.5</td>
<td>2.1±0.5</td>
<td>2.1±0.5</td>
<td>2.1±0.5</td>
<td>2.1±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV SV index (ml/m2)</td>
<td>38±10</td>
<td>38±10</td>
<td>38±10</td>
<td>38±10</td>
<td>38±10</td>
<td>38±10</td>
<td>0.0001</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.8±0.6</td>
<td>0.8±0.6</td>
<td>0.8±0.6</td>
<td>0.8±0.6</td>
<td>0.8±0.6</td>
<td>0.8±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2±0.6</td>
<td>1.2±0.6</td>
<td>1.2±0.6</td>
<td>1.2±0.6</td>
<td>1.2±0.6</td>
<td>1.2±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DTI (m/s)</td>
<td>1.9±0.5</td>
<td>1.9±0.5</td>
<td>1.9±0.5</td>
<td>1.9±0.5</td>
<td>1.9±0.5</td>
<td>1.9±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/e'</td>
<td>17±5.4</td>
<td>17±5.4</td>
<td>17±5.4</td>
<td>17±5.4</td>
<td>17±5.4</td>
<td>17±5.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EROA (cm²)</td>
<td>0.09±0.3</td>
<td>0.09±0.3</td>
<td>0.09±0.3</td>
<td>0.09±0.3</td>
<td>0.09±0.3</td>
<td>0.09±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVSV (ml)</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>2.4±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MR severity by integrative grading %</td>
<td>11±5</td>
<td>11±5</td>
<td>11±5</td>
<td>11±5</td>
<td>11±5</td>
<td>11±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S-PAP (mmHg)</td>
<td>39±15</td>
<td>39±15</td>
<td>39±15</td>
<td>39±15</td>
<td>39±15</td>
<td>39±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Medical Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aze-Antibiotics - ADH (%)</td>
<td>360±(78%)</td>
<td>360±(78%)</td>
<td>360±(78%)</td>
<td>360±(78%)</td>
<td>360±(78%)</td>
<td>360±(78%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Beta Blockers (%)</td>
<td>5028 (83%)</td>
<td>5028 (83%)</td>
<td>5028 (83%)</td>
<td>5028 (83%)</td>
<td>5028 (83%)</td>
<td>5028 (83%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diltiazem (%)</td>
<td>434±68</td>
<td>434±68</td>
<td>434±68</td>
<td>434±68</td>
<td>434±68</td>
<td>434±68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amlodipine (%)</td>
<td>314±78</td>
<td>314±78</td>
<td>314±78</td>
<td>314±78</td>
<td>314±78</td>
<td>314±78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>1024 (17%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cardiac Revascularization Therapy (%)</td>
<td>13±(2.7)</td>
<td>13±(2.7)</td>
<td>13±(2.7)</td>
<td>13±(2.7)</td>
<td>13±(2.7)</td>
<td>13±(2.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Distribution of MR severity

- Functional MR: 49% (450 patients), 31% (276 patients), 12% (105 patients), 8% (68 patients)
- Degenerative MR: 27% (211 patients), 21% (166 patients), 14% (109 patients), 38% (294 patients)

Mortality risk within cohort by ERO values

- Average mortality of the cohort
- Excess mortality

Effective regurgitant orifice area (cm²)
Long-term mortality risk under medical management

<table>
<thead>
<tr>
<th>Model</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPOSED GRADING</td>
<td>ERO groups vs No FMR</td>
<td>ERO continuous increase vs No FMR</td>
</tr>
<tr>
<td></td>
<td>ACC/AHA GRADING</td>
<td>ESC GRADING</td>
</tr>
<tr>
<td>HR (95% CI); p value</td>
<td>HR (95% CI); p value</td>
<td>HR (95% CI); p value</td>
</tr>
<tr>
<td>HR (95% CI); p value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01-0.09 cm²</td>
<td>1.28 [1.05-1.55]; p=0.01</td>
<td>0.01-0.19 cm²</td>
</tr>
<tr>
<td>0.10-0.19 cm²</td>
<td>1.41 [1.28-1.55]; &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>0.20-0.29 cm²</td>
<td>1.69 [1.32-1.99]; &lt;0.0001</td>
<td>0.20-0.39 cm²</td>
</tr>
<tr>
<td>&gt;= 0.30 cm²</td>
<td>2.20 [1.91-2.51]; &lt;0.0001</td>
<td>0.40 cm²</td>
</tr>
</tbody>
</table>

Follow up (years)

| Survival (%) | 0 | 1 |
| No FMR | 36 of 45 |
| EROA 0.01-0.09 cm² | 36 of 45 |
| EROA 0.10-0.19 cm² | 36 of 45 |
| EROA 0.20-0.29 cm² | 36 of 45 |
| EROA 0.30 cm² | 36 of 45 |

No FMR
EROA 0.01-0.09 cm²
EROA 0.10-0.19 cm²
EROA 0.20-0.29 cm²
EROA 0.30 cm²

Follow up (years)

Values are presented as mean ± standard deviation.
Spline curve of Mortality
Observed vs. expected

- No added risk
  - Mild MR
- Moderate risk
  - Moderate MR
- Moderate-severe risk
  - Moderate-severe MR
- Very high risk
  - Severe MR
**Interactions**

**ERoa**
- Age > 65 years
- Age < 65 years
- Male
- Female
- Diabetic
- Non-diabetic
- Hypertensive
- Non-hypertensive
- EF < 30%
- EF > 30%
- LV echo < 44 mm
- LV echo > 44 mm
- DTE = 144 cm
- DTE = 144 cm
- Atrial fibrillation
- No atrial fibrillation
- Coronary artery disease
- No coronary artery disease
- Myocardial infarction
- No myocardial infarction
- Coronary revascularization
- No coronary revascularization
- Charlon index
- Charlon index 2
- Diabetes
- No diabetes
- Diastole
- No diastole

**RVol**
- Risk of mortality under medical management for 0.1 cm² of EROA increase.
- Risk of mortality under medical management for 10 ml of RVol increase.

---

**Interactions**

**Left Ventricular Ejection Fraction**

- LV EF I quartile
  - ≤ 27.5%
- LV EF II quartile
  - 27.5-57.5%
- LV EF III quartile
  - 57.5-87.5%
- LV EF IV quartile
  - > 87.5%

**LV indexed End-Diastolic diameter**

- LV-EDD I quartile
  - ≤ 24.5 mm
- LV-EDD II quartile
  - > 24.5 mm
- LV-EDD III quartile
  - > 24.5 mm
- LV-EDD IV quartile
  - > 24.5 mm

**B**

**Mortality-risk LV Interaction Analysis**

**P for interaction**: 0.07

**P for interaction**: 0.3
FMR Outcome

- Despite criticisms of the methods FMR severity measured by EROA measured in routine practice is a strong and independent determinant of survival in HFrEF
- There is no evidence of modulation of risk, in particular by LV size or function
- The risk of mortality appears for low EROA (0.1 cm²) and increases exponentially with higher EROA thereafter compared to expected mortality

FMR Grading

Despite what the guidelines say, FMR type IIIb has a scale of severity and of risk:
- Completely different from DMR and skewed towards lower EROA imposing high risk
- Best associated with outcome with an expanded grading scale

It is time to harmonize FMR grading between ACC/AHA and ESC around an expanded grading scale
Conundrum #3
How to treat FMR-ν?
### Similar populations?

<table>
<thead>
<tr>
<th>Condition</th>
<th>MITRA-FR</th>
<th>COAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
<td>Symptomatic FMR due to LVD</td>
<td>Symptomatic FMR due to LVD</td>
</tr>
<tr>
<td>Intervention/center</td>
<td>Standard MitraClip</td>
<td>Standard MitraClip</td>
</tr>
<tr>
<td>Age</td>
<td>~4 yrs</td>
<td>~4 yrs</td>
</tr>
<tr>
<td>Male sex</td>
<td>71 yrs</td>
<td>72 yrs</td>
</tr>
<tr>
<td>Ischemic</td>
<td>60%</td>
<td>61%</td>
</tr>
<tr>
<td>EF</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>GFR</td>
<td>50 mL/min</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>STS/Euroscore</td>
<td>6.5%</td>
<td>8%</td>
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</table>
### What is different?

<table>
<thead>
<tr>
<th>Case selection: EDVI</th>
<th>MITRA-FR</th>
<th>COAPT</th>
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<tbody>
<tr>
<td>LV ED diameter</td>
<td>69 mm</td>
<td>62 mm</td>
</tr>
<tr>
<td>ERO</td>
<td>0.31 cm²</td>
<td>0.41 cm²</td>
</tr>
<tr>
<td>NT-ProBNP</td>
<td>3300 pg/mL</td>
<td>5500 pg/mL</td>
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</table>

<table>
<thead>
<tr>
<th>Intervention:</th>
<th>MITRA-FR</th>
<th>COAPT</th>
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<tbody>
<tr>
<td>Achieved Implant</td>
<td>90.7%</td>
<td>95%</td>
</tr>
<tr>
<td>2 Clips</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Complications ≤1+</td>
<td>14.6%</td>
<td>8.5%</td>
</tr>
<tr>
<td>MR discharge ≤2</td>
<td>75.6%</td>
<td>82.3%</td>
</tr>
<tr>
<td>~80%</td>
<td>~95%</td>
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</table>

<table>
<thead>
<tr>
<th>Process</th>
<th>MITRA-FR</th>
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<tbody>
<tr>
<td>Serious Med Rx Local</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive Med Rx pre-randomization by panel</td>
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</table>

**Residual MR**

**Mitral Regurgitation**

What determines the success of repair?
Mitral-Valve Repair versus Replacement

A Death

Hazard ratio, 0.79 (95% CI, 0.42–1.47)
P = 0.45

Two-Year Outcomes of Surgical Treatment

Figure 2. Cumulative Failure of Mitral-Valve Repair or Replacement.
Failure of the intervention was defined as death, moderate or severe mitral regurgitation (MR) as seen on transthoracic echocardiography, or mitral-valve reintervention.
COAPT Trial—Impact of residual MR

FMR-LV dysfunction

- Represents ~1/3 of all MR
- An independent determinant of survival and HF
- Specific scale of grading
- Profoundly Undertreated
- We have now a potentially successful method of MR treatment, but the result has to be “perfect”
Thank You