MitraClip in the Management of Heart Failure

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Consultancy fees and speaker’s honoraria from:
ABBOTT VASCULAR
The Conundrum of Functional Mitral Regurgitation

- **Definition and Epidemiology**  
  *Dimension of the problem*

- **Pathophysiology**

- **Clinical Consequences**  
  *Natural history*

- **Management Options**  
  *How and when to intervene? Role of MitraClip*
Secondary MR = ‘functional MR’ – valve leaflets and chordae are structurally normal and MR results from geometrical distortion of the subvalvular apparatus, secondary to LV enlargement and remodelling due to idiopathic cardiomyopathy or CAD

Functional MR - **ventricular disease**, characterized by restricted mitral valve leaflet motion in the setting of segmental wall motion abnormalities or dilated cardiomyopathies or normal leaflet motion in the setting of annular dilatation and LV dysfunction

ESC Guidelines 2012

Punnoose L et al. J Card Fail 2014
Functional Mitral Regurgitation - epidemiology

- HF patients who underwent cardiac catheterization; N=2057; MR: mild – 39%, moderate-severe – 17%
  
  Trichon BH et al. Am J Cardiol 2003;91:538-43

- Patients with incident MI; echo within 30 days; N=773; MR: mild – 38%, moderate-severe – 12%


- HF outpatients; N=469; MR: grade 1-2 – 51%, grade 3-4 – 45%


- CRT recipients; N=794; MR: mild-moderate – 36-73%, advanced – 17-54%

The Conundrum of Functional Mitral Regurgitation

- Epidemiology
  - Dimension of the problem

- Pathophysiology

- Clinical Consequences
  - Natural history

- Management Options
  - How and when to intervene?
Functional Mitral Regurgitation – pathophysiology

Myocardial damage

LV remodeling
- LV dilation
- ↑ LV sphericity
- local remodeling of MV apparatus

FMR begets LV remodeling
LV remodeling begets FMR

FMR contributes to LV dysfunction

Is this concept proven?

LV dysfunction
HF symptoms

• Volume overload
• ↑LV wall stress
• ↑ workload
The Conundrum of Functional Mitral Regurgitation

- Epidemiology  
  *Dimension of the problem*

- Pathophysiology

- Clinical Consequences  
  *Natural history*

- Management Options  
  *How and when to intervene?*
Functional Mitral Regurgitation – clinical consequences

FMR in ischemic & non-ischemic cardiomyopathies is associated with more severe symptoms and predicts (independently) poor outcome.

**Ischaeimic MR, post-MI pts**

- ERO 0
- ERO 1-19
- ERO ≥20

**Ambulatory HF pts**

- No MR and Grade I 37%
- Grade II 19%
- Grade III 30%
- Grade IV 14%

*Grigioni F et al. Circulation 2001;103:1759-1764*

*Bursi F et al. Eur J Heart Fail 2010;12:382-388*
The Conundrum of Functional Mitral Regurgitation

- Epidemiology
  * Dimension of the problem
- Pathophysiology
- Clinical Consequences
  * Natural history
- Management Options
  * How and when to intervene?
Primary vs functional MR: key question for the current management

- **Primary MR** – derangement of one or more components of MV itself
  MR → LV volume overload → remodeling with subsequent clinical consequences
  "correction of primary MR in a timely fashion reverses these consequences"

- **Functional MR** – damaged LV causes MR
  "primarily a ventricular problem it is less obvious that correcting the MR by itself will be curative or even beneficial"

*Carabello BA, JACC 2008;52:319-26*
The Conundrum of Functional Mitral Regurgitation

- Epidemiology
  - Dimension of the problem
- Pathophysiology
- Clinical Consequences
  - Natural history
- Management Options
  - How and when to intervene?
  - Optimal medical therapy
  - CRT
  - Surgery
    - MV surgery
    - Surgical treatment of LV
  - Percutaneous techniques
Percutaneous Mitral Valve Repair
MitraClip® System
Worldwide Clinical Experience

- Over 12,000 patients have been treated with the MitraClip Therapy worldwide.¹
  - 75% are considered high risk* for mitral valve surgery
  - 67% have functional mitral regurgitation (MR)
  - 96% Implant Rate
- The use of the MitraClip is supported by a rigorous clinical trial program.¹
  - 50% are considered high risk* for mitral valve surgery
  - 60% have functional MR

¹ Data as of 30/01/2014. Source: Abbott Vascular.
* Determination of high surgical risk based on: logistic EuroSCORE ≥ 20%, or STS calculated mortality ≥ 12%, or pre-specified high surgical risk co-morbidities specified in EVEREST II High Risk Study protocol.
Growing Number of Clinical Publications

361 total publications on MitraClip therapy (2003-2013)

The NEW ENGLAND JOURNAL of MEDICINE

Percutaneous Repair or Surgery for Mitral Regurgitation

Acute and 12-Month Results With Catheter-Based Mitral Valve Leaflet Repair
The EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study

Guidelines on the management of valvular heart disease (version 2012)
The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry
MitraClip as therapeutic option for MR first (and strong) evidence

**EVEREST II:** 279 patients with moderately severe or severe (grade 3+ or 4+) MR randomized in a 2:1 ratio to percutaneous repair or conventional surgery

LVEF – 60%, functional MR – 27%

<table>
<thead>
<tr>
<th>Event</th>
<th>12 months</th>
<th>Percutaneous Repair</th>
<th>Surgery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Primary efficacy end point</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation</td>
<td>100 (55)</td>
<td>65 (73)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>11 (6)</td>
<td>5 (6)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Surgery for mitral-valve dysfunction</td>
<td>37 (20)</td>
<td>2 (2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Grade 3+ or 4+ mitral regurgitation</td>
<td>38 (21)</td>
<td>18 (20)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

**MR**

- Functional: 26/48 (54) versus 12/24 (50)
- Degenerative: 74/133 (56) versus 53/65 (82)

**LVEF**

- <60%: 35/68 (51) versus 15/28 (54)
- ≥60%: 64/111 (58) versus 50/61 (82)

MitraClip as therapeutic option for MR first (and strong) evidence

EVEREST II: 4-year results

Sustained clinical benefits comparable to those after surgery
Improvement in MR durable through 4 years

Mauri et al., JACC (in press)
**MitraClip as therapeutic option for MR**

**Real World Experience**

**ACCESS-EU:** 567 pts with significant MR who underwent MitraClip therapy at 14 European sites; 69% functional MR, 85% NYHA III-IV, 53% LVEF <40%

Implant rate – 99.6%; mortality: 30-day – 3.4%, 1-year – 81.8%

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**Severity of MR at baseline and during follow-up**

**Changes in 6MWT in patients with MitraClip**

*Maisano F et al., JACC 2013;62:1052–61*
MitraClip as therapeutic option for MR
Real World Experience

Data from Israel: 20 pts with significant MR who underwent MitraClip therapy
90% functional/mixed MR, 90% NYHA III-IV, 68% LVEF <40%
In 18 reduction of MR to ≤ 2; during follow-up 2 pts died

Severity of MR at baseline and during follow-up

Changes in NYHA class in patients with MitraClip

Koifman E et al., IMAJ 2014;16:91-95
MitraClip as therapeutic option for functional MR – current experience

- 50 CHF pts with severe FMR
- NYHA III-IV, EF – 19%
- optimally managed (74% with ICD/CRT)
- logistic EuroSCORE of 34%

Table 2: Changes from baseline to 6 months in echocardiographic variables of successfully treated patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline</th>
<th>6 months</th>
<th>Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve orifice area (cm² ± SD)</td>
<td>12</td>
<td>4.9 ± 1.6</td>
<td>32 ± 0.9</td>
<td>-1.7 ± 1.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean transmirtal gradient (mmHg ± SD)</td>
<td>19</td>
<td>1.7 ± 1.4</td>
<td>30 ± 2.6</td>
<td>13 ± 2.3</td>
<td>0.018</td>
</tr>
<tr>
<td>LV ejection fraction (%) ± SD)</td>
<td>28</td>
<td>20 ± 4</td>
<td>25 ± 9</td>
<td>6 ± 9</td>
<td>0.023</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm ± SD)</td>
<td>30</td>
<td>71 ± 8</td>
<td>69 ± 8</td>
<td>-2 ± 6</td>
<td>0.051</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm ± SD)</td>
<td>30</td>
<td>62 ± 9</td>
<td>61 ± 8</td>
<td>-1 ± 6</td>
<td>0.083</td>
</tr>
<tr>
<td>LA diameter (mm ± SD)</td>
<td>20</td>
<td>51 ± 7</td>
<td>45 ± 9</td>
<td>-6 ± 9</td>
<td>0.023</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL ± SD)</td>
<td>27</td>
<td>253 ± 73</td>
<td>237 ± 66</td>
<td>-15 ± 35</td>
<td>0.010</td>
</tr>
<tr>
<td>LV end-systolic volume (mL ± SD)</td>
<td>26</td>
<td>196 ± 65</td>
<td>172 ± 55</td>
<td>-24 ± 39</td>
<td>0.003</td>
</tr>
</tbody>
</table>
MitraClip as therapeutic option for functional MR – current experience
MitraClip as therapeutic option for functional MR – current experience

MitraClip in Nonresponders to CRT: PERMIT-CARE Survey

NYHA class

Echocardiographic parameters

Auricchio A et al. JACC 2011;58:2183-9
RCT demonstrated overall concept and clinical safety but in surgical population only.

Specific patient populations addressed (high risk, HF, CRT non-responders, ...) with positive outcomes but observational non-randomized only

MitraClip as therapeutic option for functional MR – current experience

EVEREST II RCT

ACCESS EU, REALISM, EVEREST II HR cohort Registries

Franzen, Schillinger, Pleger, Treede, Auricchio Large cohorts*

But observational non randomized only
The role of isolated mitral valve surgery in patients with severe functional mitral regurgitation and severe LV systolic dysfunction who cannot be revascularized or have non-ischaemic cardiomyopathy is questionable, and in most patients conventional medical and device therapy are preferred. In selected cases, repair may be considered in order to avoid or postpone transplantation.

In patients with an indication for valve repair but judged inoperable or at unacceptably high surgical risk, percutaneous edge-to-edge repair may be considered in order to improve symptoms.
A Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation
RESHAPE-HF: objectives

1. To further study the safety and effectiveness of the MitraClip System for the treatment of clinically significant functional mitral regurgitation in NYHA Functional Class III or Class IV chronic heart failure (CHF) patients.

2. The trial is designed to provide the evidence necessary to determine appropriate recommendations for use of the MitraClip System in the ESC Guidelines on the treatment options for CHF patients with functional mitral regurgitation.

3. Additionally, the trial will evaluate cost-effectiveness of the MitraClip System and gather data to support reimbursement of the device for use in CHF patients.
RESHAPE-HF clinical trial

Device group (MitraClip) plus optimal standard of care

Control group plus optimal standard of care

1:1
n=800

Screening

End of study: At least 1 year follow-up for all patients

Statistics:
- Prospective, randomized, parallel-controlled, multi-center
- 800 CHF patients
- NYHA III-IV

Primary endpoint: Composite of all-cause mortality and recurrent heart failure hospitalizations during 12 months
# Future of MR Management

<table>
<thead>
<tr>
<th></th>
<th>RESHAPE MitraClip vs. medical therapy</th>
<th>COAPT MitraClip vs. medical therapy</th>
</tr>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>800</td>
<td>420</td>
</tr>
<tr>
<td>FMR grade</td>
<td>≥ 3+</td>
<td>≥ 3+</td>
</tr>
<tr>
<td>NYHA</td>
<td>III, IV</td>
<td>II, III, IV</td>
</tr>
<tr>
<td>LVEF</td>
<td>≥ 15% - ≤ 40%</td>
<td>≥20% - ≤60%</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Death or HF Rehospitalization at 1 year</td>
<td>HF Rehospitalization at 1 year</td>
</tr>
<tr>
<td>Primary safety endpoint</td>
<td></td>
<td>Death, stroke LVAD, cardiac transplant</td>
</tr>
<tr>
<td>Follow up</td>
<td>2 years</td>
<td>5 years</td>
</tr>
</tbody>
</table>
Future of MR Management?

Sunrise or sunset?