Καρδιακή ανεπάρκεια βαλβιδικής αιτιολογίας. Συντηρητική αντιμετώπιση το 2019;

Νίκος Μεζίλης, MD, FESC

Κλινική «Άγιος Λουκάς»
Degenerative MR

Functional MR
Refining the prognostic impact of functional mitral regurgitation in chronic heart failure

Georg Goliash, Philipp E. Bartko, Noemi Pavo, Stephanie Neuhold, Raphael Wurm, Julia Mascherbauer, Irene M. Lang, Guido Strunk, and Martin Hülsmann

European Heart Journal (2017)
The vicious cycle of secondary MR

Global or regional LV dysfunction

LV dilatation

Mitral leaflet tethering and MR

LV volume overload and LV dilatation

Mitral leaflet tethering and MR

The vicious cycle of secondary MR
The vicious cycle of secondary MR

1. Global or regional LV dysfunction
2. LV dilatation
3. Mitral leaflet tethering and MR
4. LV volume overload and LV dilatation
5. Mitral leaflet tethering and MR
Therapy

- Medical Treatment
  - Surgery?
    - Intervention
Long-term carvedilol therapy in patients with chronic heart failure was able to prevent or partially reverse progressive left ventricular dilatation. The effects on left ventricular remodeling were associated with a concomitant recovery of diastolic reserve and a decrease of mitral regurgitation.

S Capomolla et al Am Heart J 2000
Pharmacological Reduction of Functional, Ischemic Mitral REgurgitation (PRIME)

**Study Design**

- **Study Type:** Interventional (Clinical Trial)
- **Actual Enrollment:** 118 participants
- **Allocation:** Randomized
- **Intervention Model:** Parallel Assignment
- **Masking:** Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
- **Primary Purpose:** Treatment
- **Official Title:** Multicenter, Randomized, Double-blind, Active-controlled Study to Assess the Efficacy of LCZ696 Compared to Valsartan on Reduction of Mitral Regurgitation in Patients With Left Ventricular Dysfunction and Secondary Functional Mitral Regurgitation of Stage B and C

**Timeline**

- **Actual Study Start Date:** March 2016
- **Actual Primary Completion Date:** January 2, 2018
- **Actual Study Completion Date:** January 2, 2018

ClinicalTrials.gov Identifier: NCT02687932

Recruitment Status: Completed
First Posted: February 22, 2016
Last Update Posted: January 9, 2018
Impact of Mitral Valve Annuloplasty on Mortality Risk in Patients With Mitral Regurgitation and Left Ventricular Systolic Dysfunction

Audrey H. Wu, MD, MPH,* Keith D. Aaronson, MD, MS,* Steven F. Bolling, MD, FACC,† Francis D. Pagani, MD, PhD, FACC,‡ Kathy Welch, MS, MPH,‡ Todd M. Koelling, MD, FACC*

*Ann Arbor, Michigan

Figure 1. Event-free survival for non-mitral-valve annuloplasty (MVA) group (solid line) and MVA group (dotted line).

Figure 2. Event-free survival for patients without coronary artery disease in non-mitral-valve annuloplasty (MVA) group (solid line) and MVA group (dotted line).
Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation


Figure 1. Time-to-Event Curves for Death.

Shown are the proportions of patients who died in the mitral-valve (MV) repair group and the mitral-valve replacement group at 2 years. The most frequent underlying causes of death were multisystem organ failure (in 20.8% of patients), heart failure (in 17.0%), and sepsis (in 13.2%). The tick marks indicate censored data.
Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation (I)

In a trial comparing CABG alone with CABG plus mitral-valve repair in patients with moderate ischemic mitral regurgitation

RE Michler et al NEJM 2016
2017 AHA/ACC Valve Guidelines

[Surgical] mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for heart failure.

No recommendation for transcatheter MV repair

Class IIb = weak recommendation; benefit ≥ risk; may be reasonable; effectiveness is uncertain

Nishimura RA et al. J Am Coll Cardiol 2017;70:252–89
Percutaneous mitral valve repair provides a less invasive alternative to surgery but is not approved for clinical use for this indication in the United States.
Edge-to Edge repair with the MitraClip (Abbott Vascular)
Double-orifice technique first performed in 1991

The “vision” of the percutaneous approach in 1998
“Final” Clip Prototype Design - Early 2002
Catheter-Based Approach to Mitral Regurgitation

JOSÉ ANTONIO CONDADO, M.D. and MANUEL VÉLEZ-GIMÓN, M.D.

From the Cardiology Unit, Hospital “Miguel Pérez Carreño,” Caracas, Venezuela

Mitral Regurgitation (MR) is a common medical problem. MR is also a prognostic factor; patients with severe symptomatic MR have a poor prognosis with an annual mortality rate of 5% without surgical intervention. An anatomic understanding of the normal and regurgitant mitral valve is essential in order to evaluate appropriately the severity and impact of MR. We briefly discuss mitral complex anatomy, MR evaluation, and treatment options (surgical and catheter-based alternatives) according to the type of lesion found. In particular, our group has shown temporal percutaneous annuloplasty and definitive percutaneous edge-to-edge mitral valve repair to be a feasible technique. Recently a study evaluating endovascular mitral valve edge-to-edge repair was successfully initiated by our group. Acute and chronic ischemic mitral regurgitation and special situations, such as paravalvular leaks, hypertrophic obstructive cardiomyopathy, and mixed lesions are also discussed. Future directions may include the percutaneous transcatheter implantation of a bioprosthetic valve in mitral position. (J Interven Cardiol 2003;16:523–534)
CONCLUSIONS

Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with **superior safety and similar improvements in clinical outcomes**.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percutaneous Repair</th>
<th>Surgery</th>
<th>Difference between Percutaneous Repair and Surgery (%)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events/total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100/181 (55)</td>
<td>65/89 (73)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63/114 (55)</td>
<td>43/59 (73)</td>
<td>-</td>
<td>0.97</td>
</tr>
<tr>
<td>Female</td>
<td>37/67 (55)</td>
<td>22/30 (73)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 yr</td>
<td>52/86 (60)</td>
<td>23/38 (61)</td>
<td>-</td>
<td>0.009</td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>48/95 (51)</td>
<td>42/51 (82)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td>26/48 (54)</td>
<td>12/24 (50)</td>
<td>-</td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative</td>
<td>74/133 (56)</td>
<td>53/65 (82)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60%</td>
<td>35/68 (51)</td>
<td>15/28 (54)</td>
<td>-</td>
<td>0.06</td>
</tr>
<tr>
<td>≥60%</td>
<td>64/111 (58)</td>
<td>50/61 (82)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Randomized Clinical Trials in FMR: The Long Wait

Capodanno Eurointervention 2017
Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

452 Patients

307 Randomized

145 not eligible

3 consent Issues

Mitraclip

Control

152 Patients

Intention To Treat

152 Patients

Follow-up > 99%

43 Exclusions

15 Exclusions

109 Patients

Per-protocol Analysis

137 Patients
Inclusion Criteria

- **Symptomatic** despite Optimal Treatment (NYHA ≥II).
- At least one hospitalization for HF within 12 months preceding randomization.
- Severe Secondary MR → ERO > 20 mm² or R.vol > 30 mL/beat.
- 15% < EF < 40%.
- Not eligible for surgery “Heart Team”.
- Centralized echocardiographic Corelab.
MITRA-FR

#ESCCongress

Trial design: Patients with severe secondary mitral regurgitation were randomized to percutaneous mitral valve repair (n = 152) vs. medical therapy (n = 152).

RESULTS

- Death or hospitalization for heart failure (HF): 54.6% of the percutaneous mitral valve repair group vs. 51.3% of the medical therapy group (p = 0.53)
- Death: 24.3% of the percutaneous mitral valve repair group vs. 22.4% of the medical therapy group (p = NS)
- Hospitalization for HF: 48.7% of the percutaneous mitral valve repair group vs. 47.4% of the medical therapy group (p = NS)

CONCLUSIONS

- Among patients with severe secondary mitral regurgitation, percutaneous mitral regurgitation repair (MitraClip) was not beneficial
- MitraClip was not associated with a reduction in the composite (or individual components) of death or hospitalization for HF

~420 patients enrolled at up to 75 US sites

Significant FMR (≥3+ by core lab)
High risk for mitral valve surgery
Specific valve anatomic criteria

Randomize 1:1

MitraClip
N=210

Control group
Standard of care
N=210

Clinical and TTE follow-up:
1, 6, 12, 18, 24, 36, 48, 60 months

Protocol conditionally approved by FDA July 26, 2012
All-cause Mortality

HR [95% CI] = 0.62 [0.46-0.82]
NNT (24 mo) = 5.9 [95% CI 3.9, 11.7]
P<0.001

No. at Risk:
MitraClip + GDMT 302 286 269 253 236 191 178 161 124
GDMT alone 312 294 271 245 219 176 145 121 88
Primary Effectiveness Endpoint
All Hospitalizations for HF within 24 months

Cumulative HF Hospitalizations (n)
- Green: MitraClip + GDMT
- Blue: GDMT alone

- 283 in 151 pts
- 160 in 92 pts

HR (95% CI) = 0.53 [0.40-0.70]
P < 0.001

No. at Risk:
- MitraClip: 302, 286, 269, 253, 236, 191, 178, 181, 124
- GDMT: 312, 294, 271, 245, 219, 176, 145, 121, 88

Median (25%, 75%) FU = 19.1 [11.9, 24.0] mos
Death or HF Hospitalization

HR [95% CI] = 0.57 [0.45-0.71]

P<0.001

NNT (24 mo) = 4.5 [95% CI 3.3, 7.2]

1-year
33.9% vs. 46.5%
HR [95% CI] = 0.63 [0.49, 0.82]

P<0.001

No. at Risk:
MitraClip + GDMT  302  264  238  215  194  154  145  126  97
GDMT alone 312  244  205  174  153  117  90  75  55
Proportionate and Disproportionate Functional Mitral Regurgitation

A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials

Paul A. Grayburn, MD, Anna Sannino, MD, Milton Packer, MD
RESHAPE-HF2 trial – the 3rd population

Device group (MitraClip, within 14 days)
plus optimal standard of care

30 days M6 M12 M24

End of study:
At least 2 years follow-up for all patients

Screening

1:1
n=420

Control group
plus optimal standard of care

Statistics:
• Prospective, randomized, parallel-controlled, multi-center
• 1. EP: Recurrent events of CV death & HHF

Organization:
• Legal sponsor: University Medicine Göttingen / Germany (IIT grant from AV)
• Academic leadership / co-ordination: P Ponikowski & SD Anker
RESHAPE-HF2 – Recruitment Overall

We need ca. 10-12 patients per month to end recruitment in 2018

Recruited: 379 by July 2018

Status RESHAPE-HF2 on 15 January, 2018
Dear RESHAPE-HF2 study teams,

Hopefully all of you returned refreshed from the summer holiday break and you are eager for RESHAPE HF2.

We would like to give you an update on the current status and activities in RESHAPE HF2.

1. Recruitment Overview:

<table>
<thead>
<tr>
<th>Site-ID</th>
<th>Activated sites</th>
<th>Country</th>
<th>Randomized patients as of 30-Aug-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS01</td>
<td>Göttingen</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>RS02</td>
<td>Heidelberg</td>
<td>D</td>
<td>2</td>
</tr>
<tr>
<td>RS03</td>
<td>Mainz</td>
<td>D</td>
<td>2</td>
</tr>
<tr>
<td>RS04</td>
<td>Athens</td>
<td>GR</td>
<td>88</td>
</tr>
<tr>
<td>RS05</td>
<td>Thessaloniki</td>
<td>GR</td>
<td>105</td>
</tr>
<tr>
<td>RS06</td>
<td>Wroclaw</td>
<td>PL</td>
<td>37</td>
</tr>
<tr>
<td>RS07</td>
<td>Zabrze</td>
<td>PL</td>
<td>46</td>
</tr>
<tr>
<td>RS12</td>
<td>Krakow</td>
<td>PL</td>
<td>10</td>
</tr>
<tr>
<td>RS08</td>
<td>Katowice</td>
<td>PL</td>
<td>60</td>
</tr>
<tr>
<td>RS09</td>
<td>Brescia</td>
<td>IT</td>
<td>7</td>
</tr>
<tr>
<td>RS11</td>
<td>Lisbon St. Maria</td>
<td>PT</td>
<td>8</td>
</tr>
<tr>
<td>RS17</td>
<td>Lisbon St. Marta</td>
<td>PT</td>
<td>0</td>
</tr>
<tr>
<td>RS13</td>
<td>Vila Nova de Gaia</td>
<td>PT</td>
<td>1</td>
</tr>
<tr>
<td>RS14</td>
<td>Kopenhagen</td>
<td>DK</td>
<td>3</td>
</tr>
<tr>
<td>RS15</td>
<td>Odense</td>
<td>DK</td>
<td>3</td>
</tr>
<tr>
<td>RS10</td>
<td>Leon</td>
<td>ES</td>
<td>6</td>
</tr>
<tr>
<td>RS19</td>
<td>Edinburgh</td>
<td>UK</td>
<td>0</td>
</tr>
<tr>
<td>RS20</td>
<td>Manchester</td>
<td>UK</td>
<td>0</td>
</tr>
<tr>
<td>RS22</td>
<td>Royal Brompton and Harefield</td>
<td>UK</td>
<td>1</td>
</tr>
<tr>
<td>RS24</td>
<td>Glasgow</td>
<td>UK</td>
<td>just activated</td>
</tr>
<tr>
<td>RS23</td>
<td>Stoke-on-Trent</td>
<td>UK</td>
<td>just activated</td>
</tr>
<tr>
<td>RS21</td>
<td>Prague IKEM</td>
<td>CZ</td>
<td>0</td>
</tr>
</tbody>
</table>

Total: 383
ISCHEMIC CARDIOMYOPATHY FMR
EXTREME FMR - NO COAPTATION
60 new devices are currently under evaluation
Implications of COAPT for new devices to treat secondary MR in Heart Failure

1. Will they be as safe as the MitraClip?
2. Will they be as effective as the MitraClip?
3. Will they be as durable as the MitraClip?
4. Will they be able to treat the same or different pts? E.g. MAC, wide/multiple jets, extreme tethering, small annulus
5. Will they be able to treat MitraClip failures or recurrences
The Carillon device
Καρδιακή ανεπάρκεια βαλβιδικής αιτιολογίας. Συντηρητική αντιμετώπιση το 2019;
The Timing of Drugs, Device and Interventions in Heart Failure

- A CE-I/ARNI
- BB
- MRA
- ICD/CRT
- Onset of CHF
- Sudden Death
- Decompensations
- Mitral Interventions
- Advanced HF
- MCS
- VAD
- TX
- Pump Failure

Ruschitzka HFA 2018
mod. after Allen Circulation/2012