Mitraclip: What and When does it promise
Διαδερμική επιδιόρθωση Μιτροειδούς,
pόσο αλλάζει την αντιμετώπιση

Dr Vlasis Ninios
St. Luke’s Hospital
Thessaloniki
2018
Disclosures

• Proctor for Mitraclip Abbott Vascular
Secondary (Functional) Mitral Regurgitation Is More Common than Primary MR

Normal

Left Ventricular Dysfunction
Relative Sizes of Clinical Needs

Primary vs Functional MR

Expected WW Ann. Incidence

Degenerative MR
~650,000

e-Valve

Functional MR
~2,570,000

Cardiac Dimensions
Guided Delivery Systems
Mitralign
Myocor
Viacor
Ample
Edwards
e-Valve
others
Management of patients with severe MR

- FMR Medical Rx: 47.5%
- FMR MV Surgery: 26.8%
- DMR Medical Rx: 3.3%
- DMR MV Surgery: 17.4%
- Other Medical Rx: 1.9%
- Other MV Surgery: 3.1%

(Goel et al. J Am Coll Cardiol 2014;63:185-90.)
Surgery may be high risk

Mitral valve replacement in elderly patients

- Hemodynamic Instability?
  - No
  - Renal Failure?
    - No
    - NYHA Class IV?
      - No
      - Concomitant CABG?
        - Yes
        - Mortality: 25.3
        - Mortality: 11.4
        - Mortality: 7.7
      - Yes
      - Mortality: 15.7
    - Yes
      - Mortality: 31.9
  - Yes
    - Mortality: 997

(Mehta, Ann Thorac Surg 2002)
Edge-to Edge repair with the MitraClip (Abbott Vascular)
## MitraClip Clinical Trial Experience

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Study Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>First case</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>EVEREST I Feasibility (N=55)</td>
<td>Study closed</td>
</tr>
<tr>
<td>2005</td>
<td>CE Mark</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>EVEREST II Roll-In &amp; RCT (N=339)</td>
<td>Study enrolling</td>
</tr>
<tr>
<td>2007</td>
<td>EVEREST II HRR (N=78)</td>
<td>Study closed</td>
</tr>
<tr>
<td>2008</td>
<td>REALISM (N=965)</td>
<td>Study closed</td>
</tr>
<tr>
<td>2009</td>
<td>ACCESS-EUROPE (N=853)</td>
<td>Study closed</td>
</tr>
<tr>
<td>2010</td>
<td>MITRACLIP ANZ (N=78)</td>
<td>Study closed</td>
</tr>
<tr>
<td>2011</td>
<td>COAPT (N=188)</td>
<td>Study closed</td>
</tr>
<tr>
<td>2012</td>
<td>HIRIDE</td>
<td>Study closed</td>
</tr>
<tr>
<td>2013</td>
<td>Reshape2</td>
<td>Study closed</td>
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<tr>
<td>2015</td>
<td>Matterhorn</td>
<td>Study closed</td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* As of 02-Mar-2015
Kaplan-Meier Freedom from MV Surgery in MitraClip group or Re-operation in Surgery group
All Treated Patients (N = 258) – Landmark Analysis

MitraClip (N = 178) vs. Surgery (N = 80)

- 1 year: 98.7% vs. 97.1%
- 2 years: 97.2% vs. 96.3%
- 3 years: 95.6% vs. 95.5%
• Not high risk patients! All surgical candidates!
• Only 27% with FMR
• No data comparing MitraClip vs surgery vs conservative treatment in high surgical risk patients
## Mitral Regurgitation Aetiology

<table>
<thead>
<tr>
<th></th>
<th>MitraSwiss (378 pts)</th>
<th>German Registry (878 pts)</th>
<th>Everest II (72 pts)</th>
<th>ACCESS Eu (567pts)</th>
<th>Pilot European Sentinel Registry (628 pts)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional MR</strong></td>
<td>53%</td>
<td>65%</td>
<td>59%</td>
<td>77%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Degenerative MR</strong></td>
<td>47%</td>
<td>35%</td>
<td>41%</td>
<td>23%</td>
<td>28%</td>
</tr>
</tbody>
</table>

# Eggbrecht et al. Catheter Cardiovasc Interv 2015, Jan 19
↓ Nickening et al. J Am Coll Cardiol. 2014 Sep 2;64(9):875-84
Table 1: Baseline clinical profile.

<table>
<thead>
<tr>
<th></th>
<th>EVEREST II – HR</th>
<th>ACCESS-EU Phase I</th>
<th>Sentinel Registry</th>
<th>TRAMI (LES &gt;20)</th>
<th>Mitra Swiss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.7 ± 9.8</td>
<td>73.7 ± 9.6</td>
<td>74.2 ± 9.7</td>
<td>77.0</td>
<td>72 ± 12</td>
</tr>
<tr>
<td>≥75 y</td>
<td>61.5%</td>
<td>45.1%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male</td>
<td>62.8%</td>
<td>63.8%</td>
<td>63.1%</td>
<td>64.8%</td>
<td>73%</td>
</tr>
<tr>
<td>NYHA ≥III</td>
<td>89.8%</td>
<td>84.9%</td>
<td>85.5%</td>
<td>88.4%</td>
<td>–</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>–</td>
<td>23.0 ± 18.3</td>
<td>20.4 ± 16.7</td>
<td>33.0 (25–47)</td>
<td>21 ± 17</td>
</tr>
<tr>
<td>STS score</td>
<td>14.2 ± 8.2</td>
<td>–</td>
<td>–</td>
<td>14.0 (8–22)</td>
<td>–</td>
</tr>
<tr>
<td>EF ≤40%</td>
<td>–</td>
<td>52.7%</td>
<td>32.8%</td>
<td>37.4%</td>
<td>–</td>
</tr>
<tr>
<td>FMR/DMR</td>
<td>59.0%</td>
<td>77.1%</td>
<td>72%</td>
<td>71.4%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>41.0%</td>
<td>22.9%</td>
<td>28%</td>
<td>28.6%</td>
<td>38%</td>
</tr>
<tr>
<td>MR ≥3+</td>
<td>98.7%</td>
<td>97.7%</td>
<td>96.3%</td>
<td>94.7%</td>
<td>100%</td>
</tr>
</tbody>
</table>

DMR = degenerative mitral regurgitation; EF = ejection fraction; FMR = functional mitral regurgitation; MR = mitral regurgitation; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons
# Safety/Efficacy

<table>
<thead>
<tr>
<th></th>
<th>MitraSwiss (378 pts)</th>
<th>German Registry (878pts)#</th>
<th>Everest II (78pts)¶</th>
<th>ACCESS EU (576pts)+</th>
<th>Pilot European Sentinel Registry (628pts)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Procedural success</strong></td>
<td>92.4%</td>
<td>&gt;95%</td>
<td>96%</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Nr Clips implanted</strong></td>
<td>1.7 (50%: 2 clips)</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>30 Days Mortality</strong></td>
<td>2.1%</td>
<td>2.2%</td>
<td>7.7%</td>
<td>3.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Early Surgery</strong></td>
<td>0.5%</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

# Eggbrecht et al. Catheter Cardiovasc Interv. 2015, Jan 19
* Nickening et al. J Am Coll Cardiol. 2014 Sep 2;64(9):875-84
### Table 3: One-year safety and efficacy outcome.

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>EVEREST II - HR</th>
<th>ACCESS-EU Phase I</th>
<th>Sentinel Registry</th>
<th>TRAMI (LES &gt;20)</th>
<th>Mitra Swiss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>22.8%</td>
<td>17.3%</td>
<td>15.3%</td>
<td>13.4%</td>
<td>19%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.4%</td>
<td>1.1%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AMI</td>
<td>2.3%</td>
<td>1.4%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>5.4%</td>
<td>8.6%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>New onset AF</td>
<td>0.3%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SLDA</td>
<td>2.4%</td>
<td>4.8%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MV stenosis</td>
<td>0.9%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clip embolisation</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
<td>–</td>
<td>0%</td>
</tr>
<tr>
<td>MV surgery</td>
<td>0.9%</td>
<td>6.3%</td>
<td>0.9%</td>
<td>1.4%</td>
<td>5%</td>
</tr>
<tr>
<td>Re-MitraClip</td>
<td>1.1%</td>
<td>3.4%</td>
<td>2.9%</td>
<td>–</td>
<td>1%</td>
</tr>
</tbody>
</table>

### Efficacy Outcome

<table>
<thead>
<tr>
<th>MR ≤2+</th>
<th>EVEREST II - HR</th>
<th>ACCESS-EU Phase I</th>
<th>Sentinel Registry</th>
<th>TRAMI (LES &gt;20)</th>
<th>Mitra Swiss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83.6%</td>
<td>79%</td>
<td>94%</td>
<td>–</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td><em>p &lt;0.0001</em></td>
<td><em>p &lt;0.0001</em></td>
<td><em>p &lt;0.001</em></td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NYHA ≤II</th>
<th>EVEREST II - HR</th>
<th>ACCESS-EU Phase I</th>
<th>Sentinel Registry</th>
<th>TRAMI (LES &gt;20)</th>
<th>Mitra Swiss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>82.9%</td>
<td>71%</td>
<td>74.2%</td>
<td>64.1% n.s.</td>
<td>ca. 65%</td>
</tr>
<tr>
<td></td>
<td><em>p &lt;0.0001</em></td>
<td><em>p &lt;0.0001</em></td>
<td><em>p &lt;0.001</em></td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

6MWT (metre)          | –               | 59.5 *p <0.0001*  | –                 | –               | –           |

| MHLFQ                | –               | 13.5 ± 20.5       | –                 | –               | –           |

| Re-hosp. for HF      | 19.8%           | –                 | 22.8%             | 38.6%           | –           |

6MWT = 6-minute walk test; AF = atria fibrillation; AMI = acute myocardial infarction; HF = heart failure; MHLFQ = Minnesota Living with Heart Failure questionnaire; MR = mitral regurgitation; MV = mitral valve; NYHA = New York Heart Association; SLDA = single leaflet device attachment.
MitraClip - Worldwide Experience 2017

- Treating Centers: 764
- Patients: > 50,000
- Implant Rate: 96%
- Etiology
  - Secondary MR 65%
  - Primary MR 22%
  - Mixed 13%

Etiology:
- FMR 65%
- DMR 21%
- Mixed 13%
Chronic secondary mitral regurgitation

- Class I
  - Medical heart failure therapy
    (diuretics, betablockers, ACE-I/ARBs)
  - Cardiac resynchronization therapy
    (if indicated)
- Class II

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 HF.
ESC guidelines

**functional mitral regurgitation**

<table>
<thead>
<tr>
<th>EF &lt;30%</th>
<th>Surgical risk &gt; low</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.

When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.

In patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.
Ongoing RCTs in secondary MR

- 5 trials randomizing ~1641 patients with heart failure and secondary (functional) MR to MitraClip vs. GDMT or MV Surgery
  - As of July, 2016:
    - COAPT – 450/555 (81%)
    - MITRA-FR – 210/288 (73%)
    - RESHAPE-HF-2 – 86/380 (23%)
    - MATTERHORN – 29/210 (14%)
    - EVOLVE-HF – 0/168 (0%)

(Courtesy of T Feldman)
COAPT Trial Design

430 patients enrolled at up to 75 US sites
Significant PMR (≥3+ by core lab)
Symptomatic heart failure subjects who are treated per standard of care
Determined by the site's local heart team as not appropriate for mitral valve surgery
Specific valve anatomic criteria

Randomize 1:1

MitraClip
N=215

Control Group
Standard of Care
N=215

Clinical and TTE follow-up:
Baseline, Treatment, 1-week (phone)
1, 6, 12, 18, 24, 36, 48, 60 months

The recruitment goal of 420 patients is coming closer and closer!

Thank you for your contribution to this in 2017!

**Recruitment Overview:**

<table>
<thead>
<tr>
<th>Study site</th>
<th>Site activation</th>
<th>Randomized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS05 - Thessaloniki</td>
<td>26JAN2016</td>
<td>84</td>
</tr>
<tr>
<td>RS04 – Athen</td>
<td>16DEC2015</td>
<td>69</td>
</tr>
<tr>
<td>RS07 – Zabrze</td>
<td>03JUN2016</td>
<td>42</td>
</tr>
<tr>
<td>RS08 – Katowice</td>
<td>09JUN2016</td>
<td>42</td>
</tr>
<tr>
<td>RS06 – Wroclaw</td>
<td>28JAN2016</td>
<td>30</td>
</tr>
<tr>
<td>RS11 – Lisbon</td>
<td>26NOV2016</td>
<td>6</td>
</tr>
<tr>
<td>RS12 – Krakow</td>
<td>14SEP2016</td>
<td>9</td>
</tr>
<tr>
<td>RS09 – Brescia</td>
<td>14SEP2016</td>
<td>7</td>
</tr>
<tr>
<td>RS01 – Göttingen</td>
<td>25MAR2015</td>
<td>4</td>
</tr>
<tr>
<td>RS10 – Leuon</td>
<td>16DEC2016</td>
<td>5</td>
</tr>
<tr>
<td>RS14 – Copenhagen</td>
<td>09DEC2016</td>
<td>2</td>
</tr>
<tr>
<td>RS02 – Heidelberg</td>
<td>06JUL2015</td>
<td>1</td>
</tr>
<tr>
<td>RS13 - VN de Galia</td>
<td>12SEP2016</td>
<td>1</td>
</tr>
<tr>
<td>RS03 - Mainz</td>
<td>08JUN2016</td>
<td>1</td>
</tr>
<tr>
<td>RS15 - Odense</td>
<td>19APR2017</td>
<td>1</td>
</tr>
<tr>
<td>RS16 - Barcelona</td>
<td>29APR2017</td>
<td>0</td>
</tr>
<tr>
<td>RS18 - Catania</td>
<td>24SEP2017</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>304</strong></td>
</tr>
</tbody>
</table>
## Recruitment Overview:

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<td>02JUN2016</td>
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<td>28JAN2016</td>
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</tr>
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<td>26NOV2016</td>
<td>6</td>
</tr>
<tr>
<td>RS12 – Krakow</td>
<td>14SEP2016</td>
<td>9</td>
</tr>
</tbody>
</table>
Mitraclip: St. Luke’s experience

- We started 4 years ago (9/2013)
- 95 patients (45 male- 40 female)
- Age: 37-89 years old
- Successful procedure: 94 patients
- Inability to deliver clip: 1 patient (patient no 5)
- In Hospital Mortality: 0%
- 30 day mortality: 1 patient (1.0%)
- Total mortality: 18 patients (18.94%)
MR etiology

85

15%

65.6%

20.8%

13.6%

FMR
DMR
Functional MR
Degenerative MR
Mixed Etiology
EMR sites
MR GRADE

Baseline

30 days

4+

2+

1+
NYHA class

Baseline:
- NYHA IV: 60%
- NYHA III: 30%

30 days:
- NYHA IV: 30%
- NYHA III: 20%
- NYHA II: 20%
- NYHA I: 10%
Severe MR- Tenting A2-P2
GRASPING
2\textsuperscript{ND} CLIP
2\textsuperscript{ND} CLIP
FINAL RESULT
Moderate MR after 2 clips... Patient had tremendous improvement
Final Result

BEFORE

AFTER
88 Y. OLD PATIENT - ISCHEMIC CARDIOMYOPATHY - RECENT PULMONARY OEDEMA
COMBINED PATHOLOGIES
FLAIL P₃- TENTING A₂-P₂
PLAN: IMPLANT 2 CLIPS A₃-P₃ AND A₂-P₂
GRASP A3-P3

1st GRASP

2nd GRASP
GRASP A2-P2
FINAL RESULT

BEFORE

AFTER
A2–A3 PROLAPSE
1ST CLIP A3-P3
2^{ND} CLIP A2-P2
FINAL RESULT
FINAL RESULT

BEFORE

AFTER
Extreme case- severe FMR
CE Mark Device for PMVR

- 2007: CARILLON Mitral Contour System Cardiac Dimensions (February)
- 2008: MitraClip Evolve-Abbott
- 2009: Enhanced CARILLON Mitral Contour System Cardiac Dimensions (September)
- 2010:
- 2011:
- 2012:
- 2013: NeoChord (January)
- 2014: Cardioband Valtech (September)
- 2015: Mitraling (February)
- 2016:
Valtech Cardioband

Direct annuloplasty with supra annular fixation of a band with anchors
Transseptal approach

- 80 pts treated
- FMR
- Safe (Death @30d 4%)
- Effective
  - significant reduction of septo lateral dimension average up to 30%
  - significant MR reduction ≤ 2 in 92% @discharge
- Sustained results @12 mo
  - MR ≤ 2, 91%
  - NYHA I/II, 70%

Surgical-like annuloplasty
Carillion Cardiac Dimension

Indirect annuloplasty with nitinol device anchored into the coronary sinus to reduce annulus dimensions
Transgiugular approach

- 500 pts treated for commercial use
- 66 pts implanted in trial
- FMR
- Safe (Death @30d 0% device related)
- Results @12 mo
  - 1 grade of MR reduction
  - 1 NYHA Class improvement (from III to II)

Easy and Safe but modest improvement
Combining leaflet and ring repair: a surgical standard
Isolated indirect percutaneous annuloplasty
A: Coronary sinus with calibration catheter indicating 1 cm distances
B: Chinch effect of the Carillon annuloplasty system
C: 3D annulus and 3D 2D Color Doppler regurgitation before intervention
D: 3D annulus with anchor impingement and annulus reduction
   3D and 2D Color Doppler analysis of FMR reduction

Percutaneous Annuloplasty combined with percutaneous edge-to-edge leaflet therapy in a single surgical-like procedure
A: MitraClip and Carillon System
B: 3D echocardiography after a combined procedure
C: Low hemodynamic transvalvular gradients after combined Tx
Transcatheter Mitral Valve Implantation: Challenges

- **Delivery**
  - Fold/compress, size (larger than aortics)

- **Fixation**
  - More complex structure
  - No calcium to grab radially
  - Not a round valve, particularly when diseased and less pliable
  - Orientation may be important

- **Seal**
  - Paravalvular leak likely less well tolerated than aortic (hemolysis)

- **Function**
  - LVOT obstruction a concern
  - Need to preserve the subvalvular apparatus
November 2014 FiH (Dr Moat)
12 pts treated, TransApical, 91.6 procedural success, 30-d Mortality 0%
1 intraprocedural LVOT obstr., No PVL

Tendyne Device

- D-Shaped Self-Expanding Nitinol Outer Frame
  - Designed to Conform to Native MV Anatomy
- Circular Self-Expanding Nitinol Inner Frame
  - Large Effective Orifice Area (>3.0cm²)
  - Larger EOA than any Surgical Valve
- Porcine Pericardial Tri-Leaflet Valve
- Large Valve Size Matrix to Treat Varying Anatomies
  - Outer Frame Sizes: 30-43mm AP x 34-50mm CC
- Valve Tether to Apex
  - Provides Valve Stability - Designed to Reduce PVL
- Apical Pad Assists in Access Closure
Differentiated, dual stent design

- Conforms to native anatomy
- Separates fixation & sealing from valve function
- Isolates valve from the dynamic anatomy
- Preserves native mitral apparatus
- Ensures LVOT patency
- Addresses both primary & secondary mitral valve disease
- Accommodates a very wide range of mitral annular dimensions
Conclusions

• There is a big unmet clinical need for interventional treatment of Mitral regurgitation.
• Repair of the MV by using Mitraclip is safe and effective.
• Miraclip system reliably offers symptom and quality of life improvement in patients with FMR (IMR).
• Miraclip reduces hospitalizations.
• The concept of hybrid complementary treatment with other evidence-based Heart Failure strategies (medication, CRT-D) can potentially augment the effectiveness of Miraclip therapy at low risk.
• Weather prognostic (mortality) benefit exists with Miraclip therapy in FMR patients remains to be seen following the results of RCTs.