The best in heart valve disease

Organic mitral regurgitation

Ewa Szymczyk
Department of Cardiology
Medical University of Lodz, Poland

I have nothing to declare
Organic mitral regurgitation

- leaflet abnormality is the primary cause of MR
  - degenerative disease -> most common in Europe
    - Barlow disease
    - fibroelastic degeneration
    - Marfan disease
    - Ehler’s-Danlos disease
    - annular calcification
  - rheumatic disease
  - endocarditis

- development of surgical MV repair introduced in 1970’ by Alain Carpentier has dramatically changed the prognosis and the management of severe MR
Mitral regurgitation – current therapeutic options

• **Medical management**
  – Effective in symptom management
  – Ineffective in patients with underlying pathophysiology and progression of disease

• **Surgical Repair or Replacement (standard of care)**
  – Effective (invasive) with associated morbidity
  – Only ~20% of patients with significant MR undergo MV surgery (high surgical risk, co-pathologies)

• **Need for an effective less invasive option!**
Percutaneous Mitral Valve Repair

MitraClip® System

Source: Abbott Vascular
MitraClip – global experience

Until 04.2011

• 3,135 pts treated with Mitraclip
  – 80 hospitals in EU
  – 40 clinical trial sites in US

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST I</td>
<td>55</td>
</tr>
<tr>
<td>EVEREST II Roll-in</td>
<td>60</td>
</tr>
<tr>
<td>EVEREST II HRR</td>
<td>78</td>
</tr>
<tr>
<td>EVEREST II randomized</td>
<td>184</td>
</tr>
<tr>
<td>REALISM (continued access)</td>
<td>571</td>
</tr>
<tr>
<td>Commercial use (EU)</td>
<td>2187</td>
</tr>
</tbody>
</table>

Source: Abbott Vascular
MitraClip

- 4-mm-wide Co–Cr device
- two arms opened/closed with the use of the delivery-system handle
- mitral leaflets grasped, and the device is closed to approximate the leaflets

- procedure under general anesthesia
- fluoroscopic and TEE guidance
- atrial transseptal puncture

Feldman T et al. NEJM 2011;364:1395-406
Case selection

• Important anatomical prerequisites for MitraClip
  – sufficient leaflet tissue for mechanical coaptation
  – resting mitral valve effective orifice area over 4 cm²
    (small reduction in valve area on the transformation to a double orifice)

• In cases of degenerative MR with flail segments
  – the flail gap should be <10 mm
  – the flail width <15 mm
  – coaptation length should be ≥2mm

• Exclusion - rheumatic MR and calcified leaflets!!!

Commercial EU Implant Experience

Etiology

- Functional MR: 66%
- Degenerative MR: 28%
- Mixed: 6%

Source: Abbott Vascular
Percutaneous Repair or Surgery for Mitral Regurgitation

Ted Feldman, M.D., Elyse Foster, M.D., Donald D. Glower, M.D., Saibal Kar, M.D., Michael J. Rinaldi, M.D., Peter S. Fail, M.D., Richard W. Smalling, M.D., Ph.D., Robert Siegel, M.D., Geoffrey A. Rose, M.D., Eric Engeron, M.D., Catalin Loghin, M.D., Alfredo Trento, M.D., Eric R. Skipper, M.D., Tommy Fudge, M.D., George V. Letsou, M.D., Joseph M. Massaro, Ph.D., and Laura Mauri, M.D., for the EVEREST II Investigators*
EVEREST II Randomized Clinical Trial

Study Design

279 Patients enrolled at 37 sites

Significant MR (3+-4+)
Specific Anatomical Criteria

Randomized 2:1

MitraClip System
n=184

Surgical Repair or Replacement
n=95

Echocardiography Core Lab and Clinical Follow-Up:
Baseline, 30 days, 6 months, 1 year, 18 months, and
annually through 5 years

Feldman T et al. NEJM 2011;364:1395-406
## EVEREST II – MR etiology characteristic

<table>
<thead>
<tr>
<th>Cause of MR</th>
<th>Percutaneous repair (N=184)</th>
<th>Surgery (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>49 (27%)</td>
<td>26 (27%)</td>
</tr>
<tr>
<td>Degenerative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- with anterior of bileaflet fail or prolapse</td>
<td>58 (32%)</td>
<td>25 (26%)</td>
</tr>
<tr>
<td>- with posterior flail or prolapse</td>
<td>72 (39%)</td>
<td>42 (44%)</td>
</tr>
<tr>
<td>- with no flail and no prolapse</td>
<td>5 (3%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Feldman T et al. NEJM 2011;364:1395-406
EVEREST II - primary endpoints (safety & effectiveness)

Safety
Major Adverse Events
30 days

- Device Group, n=136: 9.6%
  - Control Group, n=79: 57.0%
  - \( p_{SUP} < 0.0001 \)

Effectiveness
Clinical Success Rate*
12 months

- Device Group, n=134: 72.4%
  - Control Group, n=74: 87.8%
  - \( p_{NI} = 0.0012 \)

* freedom from death, MV surgery, \( \geq 3+MR \)

Feldman T et al. NEJM 2011;364:1395-406
EVEREST II – secondary efficacy end points at 12 months

- improvement in comparison to baseline in both groups according to:
  - NYHA functional class
  - left ventricular size
  - quality-of-life measures

---

Feldman T et al. NEJM 2011;364:1395-406
EVEREST II RTC Mitraclip Arm
MR reduction by etiology

DMR Cohort

Baseline
n=135

12 Months
n=87

FMR Cohort

Baseline
n=49

12 Months
n=32

Ted Feldman, TCT 2010
EVEREST II RTC Mitraclip Arm
LV function by etiology

DMR Cohort
n=88, matched data

FMR Cohort
n=30, matched data

LVEDV
LVESV

Baseline
12 Months

p<0.0001
p=0.002
P=0.0002
p=0.04

Ted Feldman, TCT 2010
EVEREST II RTC Mitraclip Arm NYHA class by etiology

DMR Cohort
n=93, matched data

FMR Cohort
n=31, matched data

p<0.0001

97.8% NYHA Class I/II

96.7% NYHA Class I/II

Ted Feldman, TCT 2010
EVEREST II - conclusions

• Percutaneous repair was associated with **superior safety** and **similar improvements in clinical outcomes** compared to conventional surgery, despite being **less effective** at reducing MR.

• The first prospective randomized trial comparing a percutaneous mitral repair technique to conventional surgery.

• MitraClip percutaneous repair is a **safe** and **effective** technique that will be particularly applicable to high surgical risk patients or younger patients seeking a less invasive approach.

Feldman T et al. NEJM 2011;364:1395-406
Comparison of 2D TEE (n=80) vs. 3D/2D TEE (n=57) for MitraClip Repair

- Combined imaging:
  - resulted in greater confidence of interpretation of MV anatomy and MR jet origin (p<0.001),
  - facilitated correct clip positioning
  - resulted in shorter procedural time (241± 58 vs 201 ±68 min, p=0.035)

- Procedural success and final MR grade were similar

Biner et al. J Am Soc Echocardiogr 2011;24:611-7
RT-3D-TEE for assessment of MV anatomy in pts with prolapse-related regurgitation

- 222 pts undergoing repair for prolapse-related MR

- aim of the study: evaluation the additional diagnostic value of RT-3D-TEE for surgical findings in comparison to other echo modalities

Correlation between echocardiographic imaging and surgical site of prolapse

Correlation between echocardiographic imaging and surgical site of prolapse

3 middle scallops of posterior leaflet split by complete clefts

RT3D-TEE provided more accurate mapping of MV prolapse than 2D imaging and RT3D-TTE, adding quantitative recognition of dominant and secondary lesions and MV anatomy details.

monolobe P2 separated by 2 clefts from lateral and medial scallops of posterior leaflet

LA size is a potent predictor of mortality in MR due to flail leaflets

Overall survival by LA diameter under conservative treatment

- 788 pts in sinus rhythm with organic MR due to flail leaflets
- LA diameter was independently associated with survival after diagnosis (HR 1.08 per 1mm increment)

Left atrial size > 55mm as a potent predictor of mortality in mitral regurgitation due to flail leaflets

- LA≥55mm - lower 8-year overall survival (P<0.001)
- LA≥55mm independently predicted overall (HR=3.67) and cardiac mortality (HR=3.74) under medical treatment
- Mitral surgery was associated with greater survival benefit in pts with LA≥55 mm (vs LA≤55 mm) (P=0.008)

Prognostic value of BNP in asymptomatic organic MR – study material & methods

• Optimal timing of surgery is crucial in MR to avoid excess mortality and morbidity! Role of BNP?

• 87 pts with asymptomatic severe organic MR
• LVEF > 60%
• LVESD < 26 mm/m2
• SPAP < 50mmHg
• Serial BNP assessment

• **Primary endpoint** - development of symptoms or LV dysfunction
• **Secondary endpoint** – FA, pulmonary hypertension

BNP as predictor of primary endpoint within 6-months following measurement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 87)</th>
<th>Primary endpoint not reached (n = 67)</th>
<th>Primary endpoint reached (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.0 ± 15.1</td>
<td>50.1 ± 14.2</td>
<td>65.8 ± 11.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>33.5 (16.8–82.0)</td>
<td>25.1 (14.3–44.5)</td>
<td>94.0 (57.4–153.0)</td>
<td>—</td>
</tr>
<tr>
<td>log BNP (pg/mL)</td>
<td>3.5 ± 1.0</td>
<td>3.2 ± 1.0</td>
<td>4.5 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>116.6 (56.0–223.7)</td>
<td>91.5 (39.0–175.5)</td>
<td>225.3 (174.3–525.2)</td>
<td>—</td>
</tr>
<tr>
<td>log NT-proBNP (pg/mL)</td>
<td>4.7 ± 1.1</td>
<td>4.4 ± 1.0</td>
<td>5.6 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>36.1 ± 10.3</td>
<td>35.0 ± 9.4</td>
<td>39.0 ± 12.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESi (mm/m²)</td>
<td>18.1 ± 2.7</td>
<td>17.6 ± 2.6</td>
<td>19.2 ± 2.6</td>
<td>0.0504</td>
</tr>
<tr>
<td>FS (%)</td>
<td>41.8 ± 4.8</td>
<td>42.1 ± 4.8</td>
<td>40.9 ± 5.0</td>
<td>0.3369</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>64.4 ± 5.5</td>
<td>64.3 ± 3.1</td>
<td>64.7 ± 8.5</td>
<td>0.8796</td>
</tr>
</tbody>
</table>

**Univariate analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value</th>
<th>Estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0040</td>
<td>0.1296</td>
<td>0.0627</td>
</tr>
<tr>
<td>Log BNP</td>
<td>0.0003</td>
<td>1.9401</td>
<td>0.0309</td>
</tr>
<tr>
<td>Log NT-proBNP</td>
<td>0.0017</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.4245</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FS (%)</td>
<td>0.9636</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVESi (mm/m²)</td>
<td>0.2690</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVEDi (mm/m²)</td>
<td>0.4512</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>0.0011</td>
<td>0.1088</td>
<td>0.0433</td>
</tr>
</tbody>
</table>

Primary endpoint development of symptoms or LV dysfunction

BNP as predictor of primary endpoint within 6-months following measurement

- BNP independently predicts outcome in pts with asymptomatic MR and normal LV function (controversial indication for surgery)

- Low plasma BNP levels, with high NPV - helpful by identifying individuals at low risk

- Serial measurements of BNP or NT-proBNP may help to improve the timing of intervention in MR.

Asymptomatic MR pts with normal LV function, low BNP levels, and SPAP<40 mmHg can be safely followed.

Pocket-sized echo for evaluation of mitral and tricuspid regurgitation

- Electronic miniaturization – portable transthoracic echocardiography imaging devices (pocket-sized echo)
- Capability of color Doppler imaging

Kono et al. J Am Coll Cardiol Img 2011
Pocket-sized echo for evaluation of mitral and tricuspid regurgitation

- Measurements feasible in 100% pts
- Excellent correlations in MR jet area, left atrial area, %MR between pocket and standard echo (r=0.89-0.96, p<0.001)
- Very high sensitivity/specificity for detecting moderate and significant MR (both 96%)
  - Same as for standard echo

- Limitations:
  - Small display
  - Limited control features

- Conclusion – pocket-sized TTE with color Doppler feature is feasible and accurate in the assessment of severity and etiology of MR and should enhance the widespread its use in clinical practice

Kono et al. J Am Coll Cardiol Img 2011
Diagnostic Utility and Clinical Usefulness of the Pocket Echocardiographic Device

Błażej Michalski, M.D., Jarosław D. Kasprzak, M.D., Ph.D., F.E.S.C., F.A.C.C., Ewa Szymczyk, M.D., and Piotr Lipiec, M.D., Ph.D., F.E.S.C.

Department of Cardiology, Medical University of Lodz, Poland

<table>
<thead>
<tr>
<th>Echocardiographic Parameter</th>
<th>Agreement (Kappa Value)</th>
<th></th>
<th>Agreement (Kappa Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Examined by ICU</td>
<td>Outpatients</td>
<td>Patients Examined by ICU</td>
</tr>
<tr>
<td>Wall motion abnormalities</td>
<td>88% (0.571)</td>
<td>90% (0.863)</td>
<td>94% (0.788)</td>
</tr>
<tr>
<td>LV function (ejection fraction)</td>
<td>90% (0.863)</td>
<td>93% (0.886)</td>
<td>94% (0.907)</td>
</tr>
<tr>
<td>Aortic valve morphological pathology (including fibrosis, calcification, decreased surface)</td>
<td>95% (0.760)</td>
<td>96% (0.918)</td>
<td>94% (0.855)</td>
</tr>
<tr>
<td>Mitral valve morphological pathology (including fibrosis, calcification, decreased surface)</td>
<td>98% (0.9)</td>
<td>95% (0.849)</td>
<td>98% (0.878)</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>90% (0.795)</td>
<td>98% (0.955)</td>
<td>96% (0.922)</td>
</tr>
<tr>
<td>Mitral valve regurgitation</td>
<td>88% (0.767)</td>
<td>95% (0.894)</td>
<td>94% (0.896)</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>88% (0.789)</td>
<td>90% (0.866)</td>
<td>94% (0.900)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>98% (0.912)</td>
<td>98% (0.880)</td>
<td>100% (1)</td>
</tr>
<tr>
<td>Aortic stenosis (defined as turbulent flow)</td>
<td>84% (0.654)</td>
<td>90% (0.778)</td>
<td>94% (0.831)</td>
</tr>
<tr>
<td>Mitral stenosis (defined as turbulent flow)</td>
<td>90% (0.567)</td>
<td>96% (0.831)</td>
<td>98% (0.847)</td>
</tr>
<tr>
<td>Respiratory collapse of the IVC</td>
<td>93% (0.677)</td>
<td>98% (0.733)</td>
<td>96% (0.875)</td>
</tr>
</tbody>
</table>

ICU = Intensive care unit; IVC = Inferior vena cava; LV = left ventricle.
2011 year

Percutaneous MV Repair

Edge-to-edge
- Evalve MitraClip*

Chordal shortening and other
- Cardiosolutions Mitra-Spacer*
- NeoChord
- Valtech VChordal

Coronary sinus annuloplasty
- Edwards Monarch*
- Viacor PTMA*
- Cardiac Dimensions Carillon*
- Cerclage annuloplasty

MV replacement
- EndoValve
- CardiAQ
- Valtech Cardiovalve
- ValveXchange

Direct annuloplasty
- Mitralign Bident*
- GDS Accucinch*
- ReCor (US)*
- Quantum Cor (RF)
- Valtech Cardioband
- Micardia enCor

*In patients

Stone G, TCT 2011
Organic mitral regurgitation - summary

• percutaneous less-invasive therapeutic option for pts with organic MR – MitraClip as a safe and effective technique (high surgical risk pts)

• RT3D-TEE provides
  – more accurate mapping of MV anatomy details
  – adds quantitative recognition of dominant and secondary lesions in MVP
  – enhance the confidence of interpretation concerning catheter-clip system location (shorter MV repair time)
Organic mitral regurgitation - summary

- Left atrial size > 55mm as a potent predictor of mortality in MR due to flail leaflets, mitral surgery was associated with greater survival benefit in this group.

- Asymptomatic MR pts with normal LV function, low BNP levels, and SPAP<40 mmHg can be safely followed.

- Pocket-sized TTE with color Doppler is feasible and accurate in the assessment of severity and etiology of MR (possible widespread its use in clinical practice).
# Definition of Severe Mitral Valve Regurgitation - An Integrative Approach

<table>
<thead>
<tr>
<th>Criteria Mitral Regurgitation</th>
<th>Specific signs of severe regurgitation</th>
<th>Supportive signs</th>
<th>Quantitative parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Vena contracta width ≥ 0.7 cm <em>with</em> large central MR jet (area &gt; 40% of LA) or <em>with</em> a wall impinging jet of any size, swirling in LA</td>
<td>• Dense, triangular CW Doppler MR jet</td>
<td>Reg. Vol (ml/beat) ≥ 60</td>
</tr>
<tr>
<td></td>
<td>• Large flow convergence</td>
<td>• E-wave dominant mitral inflow (E &gt; 1.2m/s)</td>
<td>RF (%) ≥ 50</td>
</tr>
<tr>
<td></td>
<td>• Systolic reversal in pulmonary veins</td>
<td>• Enlarged LV and LA size (particularly when normal LV function is present)</td>
<td>ERO (cm²) ≥ 0.40</td>
</tr>
<tr>
<td></td>
<td>• Prominent flail mitral valve or ruptured papillary muscle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Indications for Surgery in Severe Chronic Organic Mitral Regurgitation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic patients with LV EF &gt;30% and ESD &lt; 55 mm*</td>
<td>IB</td>
</tr>
<tr>
<td>Asymptomatic patients with LV dysfunction (ESD &gt; 45 mm* and/or LV EF ≤ 60%)</td>
<td>IC</td>
</tr>
<tr>
<td>Asymptomatic patients with preserved LV function and AF or pulmonary hypertension (sPAP &gt;50 mmHg at rest)</td>
<td>IIaC</td>
</tr>
<tr>
<td>Patients with severe LV dysfunction (LV EF &lt; 30% and/or ESD &gt; 55 mm*) refractory to medical therapy with high likelihood of durable repair and low comorbidity</td>
<td>IIaC</td>
</tr>
<tr>
<td>Asymptomatic patients with preserved LV function, high likelihood of durable repair, and low risk for surgery</td>
<td>IIbB</td>
</tr>
<tr>
<td>Patients with severe LV dysfunction (LV EF &lt; 30% and/or ESD &gt; 55 mm*) refractory to medical therapy with low likelihood of repair and low comorbidity</td>
<td>IIbC</td>
</tr>
</tbody>
</table>

* Lower values can be considered for patients of small stature.

Management of Asymptomatic Severe Chronic Organic Mitral Regurgitation

Severe asymptomatic organic MR

LVEF > 60% and LVESD < 45 mm

Yes
No

Atrial fibrillation or sPAP > 50 mmHg at rest

No
Yes

Follow-up*

Surgery (repair whenever possible)

* valve repair can be considered when there is a high likelihood of durable valve repair at a low risk

Management of Symptomatic Severe Chronic Organic Mitral Regurgitation

Severe symptomatic organic MR

LVEF > 30%

Yes

No

Refractory to medical therapy

Yes

Valve repair is likely and low comorbidity

Yes

Medical therapy* Transplantation

No

Medical therapy

* valve replacement can be considered in selected patients
