What Can We Treat and What Should We Treat

Percutaneous Mitral Valve Repair:

Innovative Procedures, Devices & State of the Art Care for Arrhythmias, Heart Failure & Structural Heart Disease

October 8-10, 2015
Hilton Hawaiian Village, Honolulu, HI

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Interventional Cardiology
The Queen’s Medical Center
Associate Professor of Medicine
University of Hawaii

Can treat (FDA approved):
• Moderate to severe, degenerative mitral regurgitation in patients who are deemed too high risk for surgery (STS score >6/8%)

Should treat (Not FDA approved):
• Isolated moderate to severe, functional mitral regurgitation irrespectively of the operability of the patient
Mitral Regurgitation
Needs Assessment

> 9.3% for ≥75 year olds (p<.0001)

Mitral Regurgitation 2009 U.S. Prevalence

1. Total MR Patients\(^1\),\(^2\) 4,100,000
2. Eligible for Treatment\(^3\),\(^4\) (MR Grade ≥3+) 1,670,000
3. Annual Incidence\(^3\) (MR Grade ≥3+) 30,000
4. Annual MV Surgery\(^5\) Only 2% Treated Surgically

Mitral Regurgitation

Anatomy

- Annulus
- Leaflets
- Cordae
- Papillary Muscles
- Adjacent Myocardium

Primary: Anatomic abnormality the mitral valve
- Leaflets
- Subvalvular apparatus
- Chordae and papillary muscles

Secondary: LV dilation; often secondary to ischemic heart disease
- Leads to mitral annular dilation
- Incomplete coaptation of the mitral valve

Mitral Regurgitation

Classification

Primary = Degenerative MR
Secondary = Functional MR
Mitral Regurgitation
Classification

Primary
“The Valve”
Usually myxomatous

Secondary
“The Ventricle”
Ischemic or not

Asymptomatic Degenerative MR
Natural History

Survival %
0 2 4 6 8 10
Years after diagnosis

MR ≥3
or
EF <50%
Risk Factors
Age ≥50 yrs
Atrial fibrillation
LA enlargement
Flail
Mild MR

Asymptomatic Degenerative MR

Severity and Survival

Worse Survival

- ERO <20mm² (91 ±3%)
- ERO 20-39mm² (66 ±6%)
- ERO ≥40mm² (58 ±9%)

Survival (%)

P<0.01

0 1 2 3 4 5

Years

More CV Events

- ERO <20mm² (15 ±4%)
- ERO 20-39mm² (40 ±7%)
- ERO ≥40mm² (62 ±8%)

Rate of Cardiac Events %

P<0.01

0 1 2 3 4 5

Years

EF and Surgical Outcome

- EF ≥60%: 72 ±4%
- EF 50-60%: 53 ±9%
- EF <50%: 32 ±12%

Survival %

P=0.0001

0 1 2 3 4 5 6 7 8 9 10

Years

EF <60% is Abnormal in MR

Enriquez-Sarano M et al., NEJM 2005;352:875-83

Enriquez-Sarano M et al., Circulation 1994;90:830-837
Symptoms and Surgery

- NYHA I-II
- NYHA III-IV

Survival % over Years

- 90 ±2
- 73 ±3
- 76 ±5
- 48 ±4

P<0.0001

Patients without Class I Indications

- Early surgery
- Medical management

Log-rank P<.001

Tribouilloy CM et al., Circulation 1999;99:400-5

Suri R et al., JAMA 2013;310:609-16
Functional MR - No Mortality Benefit with Surgery

Event-free Survival

Time (Days)

0 500 1000 1500 2000


Functional MR - High Risk of Recurrence

Freedom From Mitral Regurgitation

Years

0 1 2 3 4 5 6 7 8 9 10 12 14 16 18 20

DMR >3+
DMR >2+
IMR > 2+

Glower. JACC 2012;60:1315-22
Current General Principals of Therapy

**Degenerative MR**
- No medical option for valve
- Surgery for symptoms or LV dysfunction
- Asymptomatic if repairable and low risk
- Surgery is Class I Indication

**Functional MR**
- Medical therapy first
- Consider CRT
- Surgery only in highly selected patients with HF
- Surgery is Class II b Indication

Nishimura et al. JACC 2014;63:e57

Unoperated MR in Europe

396 patients with symptomatic severe MR
53% degenerative

No surgery in 49%

Predictors were age, morbidity, non-ischemic etiology, MR severity

Percutaneous Mitral Valve Repair
MitraClip® System

EVEREST II Trial
279 Patients enrolled at 37 sites
Significant MR (3+-4+)
Specific Anatomical Criteria
Randomized 2:1

Device Group
MitraClip System
N=184

Control Group
Surgical Repair/Replacement
N=95

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

**EVEREST II Trial**

**Inclusion**
- Candidate for MV Surgery
- Moderate to severe (3+) or severe (4+) MR
  - Symptomatic
    - >25% EF & LVESD ≤55mm
  - Asymptomatic with one or more of the following
    - LVEF 25-60%
    - LVESD ≥40mm
    - New onset atrial fibrillation
    - Pulmonary hypertension

**Exclusion**
- AMI within 12 weeks
- Need for other cardiac surgery
- Renal insufficiency
  - Creatinine >2.5mg/dl
- Endocarditis
- Rheumatic heart disease
- MV anatomical exclusions
  - Mitral valve area <4.0cm²
  - Leaflet flail width (≥15mm) and gap (≥10mm)
  - Leaflet tethering/coaptation depth (>11mm) and length (<2mm)

All Etiologies included!


**EVEREST II Trial – Primary Endpoints (ITT)**

**Safety**
- Major Adverse Events 30 days
  - Device Group, n=180
    - 15.0%
  - Control Group, n=94
    - 47.9%
  - p_{SUP} <0.0001

**Effectiveness**
- Clinical Success Rate 12 months
  - Device Group, n=175
    - 55%
  - Control Group, n=89
    - 73%
  - p_{NI} =0.007

**Met superiority hypothesis**
- Pre-specified margin =2%
- Observed difference = 32.9%
- 97.5% LCB = 20.7%

**Met non-inferiority hypothesis**
- Pre-specified margin = 25%
- Observed difference = 7.3%
- 95% UCB = 17.8%

LCB = lower confidence bound
UCB = upper confidence bound

**EVEREST II Trial – Conclusions**

**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. (Funded by Abbott Vascular; EVEREST II ClinicalTrials.gov number, NCT00209274.)

FDA approval of MitraClip for all patients with mitral regurgitation (degenerative and functional)?


**Prohibitive Surgical Risk DMR Cohort (n=127)**

- **Age:** 82 ±9 years
- **Prior MI:** 24%
- **Prior stroke:** 10%
- **Diabetes:** 30%
- **COPD:** 32%
- **Renal disease:** 28%

**Mean STS Risk**

13.2%

Lim et al. JACC 2014;64:182-192.
Primary Safety Endpoint

- Observed Mortality: 18.2%
- Predicted Mortality: 4.8%
- p < 0.0001

Prohibitive Surgical Risk
DMR Cohort (n=127)

- Clinically Important Reduction of Mitral Regurgitation
- Clinically Important Improvement in NYHA Functional Class
- Clinically Important Reverse LV Remodeling
- Clinically Important Reduction in the Rate of Hospitalization for Heart Failure

ACC 2013, presented by Scott Lim, MD
Summary

• MitraClip® therapy safely reduces DMR in patients at prohibitive risk for MV surgery
• In this group of prohibitive risk DMR patients, MitraClip therapy provides meaningful clinical improvements
  • Reduction of LV volumes
  • Improvements in NYHA Functional Class
  • Improvements in Quality of Life
  • Reduction in Hospitalizations for Heart Failure

FDA Approval

MitraClip Delivery System Approved by FDA on October 24, 2013.
Indication for Use:

“The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve diseased, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

Definition of Prohibitive Risk: STS score of surgical MV repair >6% or mitral valve replacement >8%
Options for Degenerative MR

- STS score > 6/8%
- Less Invasive
- Medical Therapy
- MitraClip®
- MV Surgery
- Increased MR Reduction

Functional Mitral Regurgitation

- Limited treatment options (medications, CRT)
- Surgery with no mortality benefit
- High recurrence rate after surgical MV repair
- Class IIb indication in recent guidelines to consider surgery
Worldwide MitraClip Experience

- Treating Centers: 491
- Patients: 20,018
- Implant Rate: 96%
- Etiology
  - Functional MR 65%
  - Degenerative MR 22%
  - Mixed 13%

Realism: 70% FMR
Access-EU: 69% FMR
TRAMI: 71% FMR

Data as of 03/31/2015. Source: Abbott Vascular.

Realism: 70% FMR
Access-EU: 69% FMR
TRAMI: 71% FMR

Functional Mitral Regurgitation

<table>
<thead>
<tr>
<th>First Author/Study (Ref. #)</th>
<th>N</th>
<th>Patient Characteristics</th>
<th>LV Reduction/NYHA FC</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franzen et al. 2010 (21)</td>
<td>51</td>
<td>FMR 69% (35 of 51) LVEF 36 ± 17% NYHA FC = III 98% Logistic EuroSCORE 15 ± 11</td>
<td>67% FC = III post-procedure NYHA FC improvement = I FC 90% 98% with ≥2L MR at 30 days</td>
<td>No mortality at 30 days</td>
</tr>
<tr>
<td>Franzen et al. 2011 (51)</td>
<td>50</td>
<td>All with FMR ≥3+ and LVEF ≥25% NYHA FC = III 100% Logistic EuroSCORE 34 ± 29</td>
<td>92% with MR ≥2+ at 30 days 82% with MR ≥3+ at 6 months</td>
<td>6% at 30 days 19% at 6 months</td>
</tr>
<tr>
<td>Auricchio et al. 2011 (52)</td>
<td>51</td>
<td>All patients CRT nonresponders with FMR ≥3+ LVEF ≥27 ± 8.7% NYHA FC = III 98% Logistic EuroSCORE 29.7 ± 19.4% STS score 13.9 ± 14.6</td>
<td>NYHA FC at discharge, 73% (p &lt; 0.001) More than 85% with MR ≥2+ at 1 yr Significant reduction of LVEDV at 4.7 months</td>
<td>2.1% peri-procedural 4.2% at 30 days 18% at median follow-up of 14 months</td>
</tr>
<tr>
<td>Van den Branden et al. 2012 (53)</td>
<td>52</td>
<td>FMR, 90% (47 of 51) all ≥3+ NYHA FC = III, 98% Logistic EuroSCORE 37.1 ± 17% STS score 10.1 ± 7.6</td>
<td>84% NYHA FC = III at 6 months 79% with MR ≥2+ at 6 months LVEDV ≤ 35 mL/m² trend in reduction</td>
<td>3.6% (2 patients) peri-procedural 11.5% at 6 months</td>
</tr>
<tr>
<td>Taramasso et al. 2013 (54)</td>
<td>109</td>
<td>FMR 100% Logistic EuroSCORE 22 ± 16.5% 82% NYHA FC = III Mean EF 27 ± 10%</td>
<td>86% NYHA FC = III at 1 yr 70% MR ≥2+ at 2.5 yrs LVEDV increased to 34 ± 10% at 1 yr (p = 0.0001) Significant reduction in LVEDV at 1 yr</td>
<td>1.8% at 30 days 25% at 3 yrs</td>
</tr>
</tbody>
</table>

Beigel et al. JACC 2014;64:2688-2700
Transcatheter Valve Treatment Sentinel Pilot Registry (TCVT)

Percutaneous Mitral Valve Edge-to-Edge Repair

In-Hospital Results and 1-Year Follow-Up of 628 Patients of the 2011–2012 Pilot European Sentinel Registry

Georg Nickenig, MD, PhD,* Rodrigo Estevez-Louzado, MD, PhD; Olaf Fransen, MD; Corrado Tamburino, MD, PhD; Marc Vanderheyden, MD; Thomas F. Lüscher, MD, PhD; Neil Moat, MS; Susanna Price, MD, PhD; Gianni Dall’Ara, MD; Reidar Winter, MD, PhD; Roberto Corti, MD; Carmelo Grassi, MD; Thomas M. Snow, MD; Raban Jeger, MD; Stefan Blankenberg, MD; Magnus Settergren, MD, PhD; Klaus Tiroch, MD; Jan Balzer, MD; Anna Sonia Petronio, MD; Keino Joachim Bittrrer, MD; Federico Bettini, MD; Hent Sievert, MD; Maria Giovanna Fiorino, MD; Marc Claeys, MD, PhD; Gian Paolo Usala, MD; Helen Rut Bunschoten, MD; Salvatore Scandali, MD; Farag Alamgir, MD; Freidoon Keshavarsi, MD; Antonio Colombo, MD; Francesco Maisano, MD, PhD; Herning Ebelt, MD; Patricia Aruta, MD; Edith Lahos, MD; Björn Pacht, MD; Robert Schueler, MD; Michele Pigni, MD; Carlo Di Mario, MD, PhD; on behalf of the Transcatheter Valve Treatment Sentinel Registry Investigators of the EUROrorvival Research Programme of the European Society of Cardiology

- TCVT: Transcatheter Valve Treatment Sentinel Pilot Registry
- Part of European Society of Cardiology
- Prospective, independent registry of consecutive patients
- 628 Patients at 25 centers in 8 countries

Nickenig G. Et al. J Am Coll Cardiol 2014;64:875-84

TCVT – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 628)</th>
<th>Mixed/Other (n = 17)</th>
<th>Functional MR (n = 452)</th>
<th>Degenerative MR (n = 143)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>74.2 ± 9.7</td>
<td>78.0 ± 8.4</td>
<td>72.8 ± 9.8</td>
<td>78.3 ± 8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>63.1</td>
<td>41.2</td>
<td>67.7</td>
<td>52.5</td>
<td>&lt;0.001</td>
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<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.6</td>
<td>0.0</td>
<td>1.1</td>
<td>3.5</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>II</td>
<td>12.9</td>
<td>23.5</td>
<td>10.4</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>68.7</td>
<td>52.9</td>
<td>70.3</td>
<td>63.6</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>16.8</td>
<td>23.5</td>
<td>18.2</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Afib/flutter</td>
<td>31.7</td>
<td>18.8</td>
<td>27.2</td>
<td>50.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>32.8</td>
<td>12.5</td>
<td>42.0</td>
<td>2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline SCR, µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>132.0 ± 80.5</td>
<td>115.7 ± 37.2</td>
<td>137.7 ± 88.0</td>
<td>112.6 ± 45.8</td>
<td>0.002</td>
</tr>
<tr>
<td>CKD</td>
<td>30.5</td>
<td>17.7</td>
<td>32.8</td>
<td>24.1</td>
<td>0.051</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>9.2</td>
<td>0.0</td>
<td>9.3</td>
<td>10.5</td>
<td>0.634</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>20.4 ± 16.7</td>
<td>15.5 ± 11.2</td>
<td>21.9 ± 17.6</td>
<td>16.3 ± 13.7</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Nickenig G. Et al. J Am Coll Cardiol 2014;64:875-84
TCVT – Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 628)</th>
<th>Functional MR (n = 452)</th>
<th>Degenerative MR (n = 143)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.9</td>
<td>2.0</td>
<td>4.9</td>
<td>0.075</td>
</tr>
<tr>
<td>Tamponade</td>
<td>1.1</td>
<td>0.7</td>
<td>1.8</td>
<td>0.298</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.2</td>
<td>0.0</td>
<td>0.7</td>
<td>0.241</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>1.1</td>
<td>0.9</td>
<td>2.1</td>
<td>0.368</td>
</tr>
<tr>
<td>Transfusion</td>
<td>10.1</td>
<td>9.7</td>
<td>12.4</td>
<td>0.406</td>
</tr>
<tr>
<td>Vascular complication requiring intervention</td>
<td>0.7</td>
<td>1.0</td>
<td>0.0</td>
<td>0.581</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>11.7</td>
<td>12.6</td>
<td>10.2</td>
<td>0.599</td>
</tr>
<tr>
<td>Acute procedural success</td>
<td>95.4</td>
<td>95.8</td>
<td>93.7</td>
<td>0.304</td>
</tr>
<tr>
<td>Clip embolization</td>
<td>0.7</td>
<td>0.5</td>
<td>0.9</td>
<td>0.521</td>
</tr>
<tr>
<td>Inability to reduce MR</td>
<td>3.5</td>
<td>3.0</td>
<td>4.4</td>
<td>0.387</td>
</tr>
<tr>
<td>Implant ≥2 clips</td>
<td>37.5</td>
<td>36.5</td>
<td>44.3</td>
<td>0.098</td>
</tr>
<tr>
<td>Procedure duration, min</td>
<td>138.3 ± 67.9</td>
<td>137.2 ± 68.2</td>
<td>132.1 ± 65.6</td>
<td>0.463</td>
</tr>
</tbody>
</table>

TCVT – NYHA Class

![NYHA Class Graphs](image)
TCVT – Degree of MR

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Discharge</th>
<th>1-Year FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (368)</td>
<td>86.1</td>
<td>72.8</td>
<td>58.6</td>
</tr>
<tr>
<td>Functional (264)</td>
<td>84.7</td>
<td>71.9</td>
<td>59.1</td>
</tr>
<tr>
<td>Degenerative (58)</td>
<td>90.2</td>
<td>72.2</td>
<td>57.4</td>
</tr>
</tbody>
</table>

TCVT – Echo Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Discharge</th>
<th>1-Year FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV Overall</td>
<td>159.4</td>
<td>157.1</td>
<td>154.8</td>
</tr>
<tr>
<td>LVEDV Functional</td>
<td>171.1</td>
<td>172.5</td>
<td>171.3</td>
</tr>
<tr>
<td>LVEDV Degenerative</td>
<td>113.4</td>
<td>118.3</td>
<td>118.9</td>
</tr>
<tr>
<td>LVESV Overall</td>
<td>103.0</td>
<td>107.2</td>
<td>105.4</td>
</tr>
<tr>
<td>LVESV Functional</td>
<td>110.2</td>
<td>114.5</td>
<td>113.4</td>
</tr>
<tr>
<td>LVESV Degenerative</td>
<td>111.9</td>
<td>110.8</td>
<td>110.3</td>
</tr>
<tr>
<td>LA Overall</td>
<td>103.9</td>
<td>108.3</td>
<td>109.4</td>
</tr>
<tr>
<td>LA Functional</td>
<td>114.5</td>
<td>118.3</td>
<td>118.9</td>
</tr>
<tr>
<td>LA Degenerative</td>
<td>54.5</td>
<td>56.8</td>
<td>54.5</td>
</tr>
</tbody>
</table>
Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

Purpose

- COAPT is a landmark trial to further study the MitraClip device in symptomatic FMR patients with heart failure
- COAPT is the first randomized controlled clinical trial to compare non-surgical (medical) standard of care treatment to a percutaneous intervention to reduce MR
To evaluate the safety and effectiveness of the MitraClip System for treatment of functional mitral regurgitation (FMR ≥3+) in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site’s local heart team as not appropriate for mitral valve surgery.

STS score is no inclusion or exclusion criterion!

**Objective**

**Trial Design**

**Goals: 430 patients at up to 79 US sites**

Significant FMR (≥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
Can treat (FDA approved):
- Moderate to severe, degenerative mitral regurgitation in patients who are deemed too high risk for surgery (STS score >6/8%)

Should treat (Not FDA approved):
- Isolated moderate to severe, functional mitral regurgitation irrespectively of the operability of the patient