New Devices for Mitral Valve Repair

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Conflicts of Interest

• Research Grants: Abbott Vascular
• Consultant: Abbott Vascular, Guided Delivery Systems
• Scientific Advisory Board/Equity: QuantumCor
• Leaflet repair
  – MitraClip® (Abbott Vascular)

• Coronary sinus annuloplasty
  – Edwards Monarc
  – Cardiac Dimensions Carillon
  – Viacor Shape Changing Rods

• Direct annuloplasty
  – Mitralign Suture-Based Plication
  – Guided Delivery Anchor-Cinch Plication
  – Quantum Cor

• Chamber + annular remodeling
  – Myocor iCoapsys
  – Ample PS3

• Chordal replacement

• Combined approaches

• Mitral valve replacement
Catheter-Based Mitral Valve Repair

MitraClip® System (Abbott Vascular)
57 yr old Lady from Beverly Hills with Bileaflet Prolapse
57 yr old lady with bileaflet prolapse 3 years following MitraClip Procedure

Baseline

At three years
## Clinical Experience

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST I (Feasibility)*</td>
<td>Non-randomized</td>
<td>55</td>
</tr>
<tr>
<td>EVEREST II*</td>
<td>Pre-randomization</td>
<td>60</td>
</tr>
<tr>
<td>EVEREST II</td>
<td>High Risk Registry</td>
<td>78</td>
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<tr>
<td>EVEREST II (Pivotal)</td>
<td>Randomized patients</td>
<td></td>
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<tr>
<td></td>
<td>(2:1 MitraClip to Surgery)</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td></td>
<td>184 MitraClip</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95 Surgery</td>
</tr>
<tr>
<td>REALISM (Continued Access)</td>
<td>High Risk &amp; Non High Risk</td>
<td>310</td>
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<tr>
<td>European Experience</td>
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<td>629</td>
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<tr>
<td>Total</td>
<td></td>
<td>1,316 MitraClip</td>
</tr>
</tbody>
</table>


Evidence of Safety

High Risk Registry: Actual vs. Predicted 30 day Mortality*

* Based on STS Risk Calculator, or Surgeon Estimate (required specific co-morbidities, 12% risk used if score not provided by surgeon)
Evidence of Safety
EVEREST II Randomized Arm

Safety, Per Protocol Cohort
Major Adverse Events
30 days

- Device Group, n=136: 9.6%
- Control Group, n=79: 57.0%

Met superiority hypothesis
- Pre-specified margin = 6%
- Observed difference = 47.4%
- 97.5% LCB = 34.4%

Safety, Intention to Treat Cohort
Major Adverse Events
30 days

- Device Group, n=180: 15%
- Control Group, n=94: 47.9%

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

LCB = lower confidence bound
Evidence of Efficacy
EVEREST II High Risk registry

MitraClip therapy results in sustained MR reduction

**FMR, n=34**
- Baseline: 97%
- 30 day: 18%
- 12 month: 21%

**DMR, n=20**
- Baseline: 100%
- 30 day: 20%
- 12 month: 25%

Grade 1+ = Mild MR
Grade 2+ = Moderate MR
Grade 3+ = Moderate - Severe MR
Grade 4+ = Severe MR

12 month Matched data
**Evidence of Efficacy**

**EVEREST II: Clinical efficacy at 12 months**

**Effectiveness, Per Protocol Cohort**

- **Clinical Success Rate**
  - Device Group, n=134: 72.4%
  - Control Group, n=79: 87.8%

**Effectiveness. Intention to Treat Cohort**

- **Clinical Success Rate**
  - Device Group, n=175: 66.9%
  - Control Group, n=89: 74.2%

### Met effectiveness hypothesis

- Pre-specified margin = 31%
- Observed difference = **15.4%**
- 95% one-sided UCB = 25.4%

* Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR >2+ at 12 months

### Met effectiveness hypothesis

- Pre-specified margin = 25%
- Observed difference = **7.3%**
- 95% one-sided UCB = 17.8%

^ Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction >90 days post Index procedure, MR >2+ at 12 months

UCB = upper confidence bound
Evidence of Efficacy

HRR: LV Volume

MitraClip therapy results in reverse LV remodeling

**FMR**, n=34

**DMR**, n=20

12 month Matched data
Summary using the MitraClip

• MitraClip is repositionable/removable

• Safe and Effective
  – Both high and low risk patients
  – Selected cases of functional and degenerative MR

• Sustained clinical benefit
  – Adequate MR reduction
  – Decreased hospitalizations
  – Reverse LV remodeling

• Surgical options preserved
Percutaneous Mitral Approaches

- Leaflet repair
  - MitraClip® (Abbott Vascular)

- Coronary sinus annuloplasty
  - Edwards Monarc
  - Cardiac Dimensions Carillon
  - Viacor Shape Changing Rods

- Direct annuloplasty
  - Mitralign Suture-Based Plication
  - Guided Delivery Anchor-Cinch Plication
  - Quantum Cor

- Chamber + annular remodeling
  - Myocor iCoapsys
  - Ample PS3

- Chordal replacement

- Combined approaches

- Mitral valve replacement
Percutaneous Mitral Valve Therapies: Coronary Sinoplasty

- Close Proximity of the Coronary sinus to the Mitral annulus
- Relatively easy access via the jugular or femoral vein
Indirect Annuloplasty: Issues and Problems - Relation of LCX and CS

Maselli et al: Circ 2006;114:377-380
LCx crossed under 64%
Diag / ramus 16%

Courtesy Samir Kapadia, MD, Cleveland Clinic
Coronary Sinus Annuloplasty
Edwards MONARC System

12F guiding catheter
9F delivery system

Location of Implant (Internal)
Sliding Knob
Handle

Bridge
Proximal Anchor
Distal Anchor

Elongated bridge at implant
Foreshortened state at ~4-6 weeks
Percutaneous Coronary Sinoplasty
VIACOR PTMA™ Device
CARILLON™ Procedural Steps

1) Release / Deploy Distal Anchor

2) Apply System Tension / Deploy Proximal Anchor / Assess Result
   - Echo for MR Reduction
   - Angio for Artery Integrity

3) Remove Safety Lock / Release Implant

- Straight-forward Coronary Sinus approach
- Results Immediately observable
- Tension / Plication is controlled by operator
- Recapture Feature allows for “Management of Coronary Arteries”
- Does not preclude other HF therapies such as Bi-V pacing or surgery
Clinical Experience with Coronary Sinoplasty devices

- Primary experience in Europe
- Variable success rate (32 to 80%)
- Only useful in functional MR
- Modest reduction of MR
- Improvement of quality of life
- Small chance of late circumflex artery thrombosis: Acute MI
Percutaneous Mitral Approaches

- **Leaflet repair**
  - EV valve Mitraclip
  - Mobius (Edwards Lifesciences)

- **Coronary sinus annuloplasty**
  - Edwards Monarc
  - Cardiac Dimensions Carillon
  - Viacor Shape Changing Rods

- **Direct annuloplasty**
  - Mitralign Suture-Based Plication
  - Guided Delivery Anchor-Cinch Plication
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- **Chamber + annular remodeling**
  - Myocor iCoapsys
  - Ample PS3

- **Chordal replacement**

- **Combined approaches**

- **Mitral valve replacement**
Five-year experience with a suture annuloplasty for mitral valve repair

93.4% freedom from re-operation

n=130

Fig. 1. The modified mitral plication suture. A double semicircular suture is placed in the mitral annulus around the posterior leaflet. The suture is reinforced with pledgets at each commissure and at the centre point of the posterior leaflet. When tying the suture, the mitral annulus can be tightened to appropriate size.

Nagy ZL et al  Scand Cardiovasc J 2000
Transventricular Approach
Guided Delivery System™ Percutaneous Accucinch™ System

Anterior Commissure

Anterior Leaflet

Cinching Cable

Posterior Commissure

P1

P2

P3

9 - 12 Anchors
Transventricular Approach
GDS™ Percutaneous Accucinch™ System

Ovine Safety Model: Left Ventricle & Mitral Valve

ACUTE (implant placed behind chordae)

3 MONTHS (Leaflet resected)
Combination of Mitral Valve Annuloplasty and Edge to Edge Repair

Joachim Schofer

Patient follow up 1 week after the procedure: NYHA I, MR 1+, PAP 35 mmHg
Percutaneous Mitral Approaches

- **Leaflet repair**
  - EVaIve Mitraclip
  - Mobius (Edwards Lifesciences)

- **Coronary sinus annuloplasty**
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- **Chamber + annular remodeling**
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  - Ample PS3

- **Chordal replacement**

- **Combined approaches**

- **Mitral valve replacement**
Conclusions

- Percutaneous Mitral Valve Repair seems to be safe and effective in selected patients of functional degenerative MR.

- Surgical Options are preserved.

- MitraClip and the Carillon devices are the only approved devices available in Europe.

- Most other technologies are in early phase of development.

MitraClip Device is an investigational device available in US in a Continuous Access Registry.
Dr Trento (PGY 32)
1 month post Clip procedure

Courtesy Twitter
Surgical Principle of edge to edge repair (double orifice valve)

Relatively Simple

Effective in both degenerative and functional MR
Percutaneous mitral repair with the MitraClip® System based on the Alfieri Technique

Repositionable

Real time assessment of reduction of MR

Received CE Mark Approval
The MitraClip Procedure
MitraClip Concepts

• Creation of Double orifice
  – Helps of coaptation of leaflets

• Creates tissue bridge
  – Limits dilatation of annulus
    • Septal-lateral (A-P) dimension
  – Supports durability of repair

• Restrains LV wall
  – Limits LV dilatation
Relaxed atmosphere: No rapid pacing,
No arrhythmias,
Imaging is essential (3D TEE is preferable)
Case 1.

- Degenerative Mitral Valve diseases: Barlows bi-leaflet prolapse
Hemodynamic Assessment

Preprocedure
CO  2.2 L/min

Following two clips
CO  4.5 L/min
Human Studies
EVEREST Initial Cohort
Surgery Following Clip Procedure
N = 107

67% underwent Repair

88% (28) were performed as planned

SURGERY FREE
75/107
Median Follow-up 386 Days

SURGERY
32/104

8%
HRR: NYHA Functional Class

MitraClip therapy results in sustained symptomatic improvement

**FMR, n=34**

**DMR, n=20**

12 month Matched data
# Worldwide MitraClip Experience

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Population</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST I (100% enrolled)</td>
<td>Registry patients</td>
<td>55</td>
</tr>
<tr>
<td>EVEREST II (100% enrolled)</td>
<td>Roll-in</td>
<td>60</td>
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<tr>
<td></td>
<td>Randomized Clip</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>Randomized Surgery</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>High Risk Registry</td>
<td>78</td>
</tr>
<tr>
<td>EVEREST II: REALISM</td>
<td>Registry Patients (non HRR and HRR)</td>
<td>266</td>
</tr>
<tr>
<td>Continued Access Registry</td>
<td></td>
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<tr>
<td>European Experience</td>
<td></td>
<td>472</td>
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<tr>
<td>TOTAL MitraClip Therapy Patients</td>
<td></td>
<td>1,115</td>
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</table>

* Data as of September 15, 2009
EVEREST II Randomized Clinical Trial

Study Design

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 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
EVEREST II Randomized Clinical Trial
Primary Endpoints

Safety
- Major Adverse Event Rate at 30 days
- Per protocol cohort
- Superiority hypothesis

Effectiveness
- Clinical Success Rate
  - Freedom from the combined outcome of
    - Death
    - MV surgery or re-operation for MV dysfunction
    - MR >2+ at 12 months
- Per protocol cohort
- Non-inferiority hypothesis

Pre-Specified MAEs
- Death
- Major Stroke
- Re-operation of Mitral Valve
- Urgent / Emergent CV Surgery
- Myocardial Infarction
- Renal Failure
- Deep Wound Infection
- Ventilation >48 hrs
- New Onset Permanent Atrial Fib
- Septicemia
- GI Complication Requiring Surgery
- All Transfusions ≥2 units

Investigational device limited by Federal (U.S.) law to investigational use only. PML02827 Rev. A 03/2010
EVEREST II RCT: Primary Endpoints
Per Protocol Cohort

Safety
Major Adverse Events
30 days

- Device Group, n=136: 9.6%
- Control Group, n=79: 57.0%
  - Pre-specified margin = 6%
  - Observed difference = 47.4%
  - 97.5% LCB = 34.4%
  - $p_{SUP} < 0.0001$

Effectiveness
Clinical Success Rate*
12 months

- Device Group, n=134: 72.4%
- Control Group, n=74: 87.8%
  - Pre-specified margin = 31%
  - Observed difference = 15.4%
  - 95% UCB = 25.4%
  - $p_{NI} = 0.0012$

Met superiority hypothesis

Met non-inferiority hypothesis

* Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR >2+ at 12 months

LCB = lower confidence bound
UCB = upper confidence bound

Investigational device limited by Federal (U.S.) law to investigational use only. PML02827 Rev. A 03/2010
### EVEREST II RCT: Primary Safety Endpoint

**Per Protocol Cohort**

<table>
<thead>
<tr>
<th>30 Day MAE, non-hierarchical</th>
<th># Patients experiencing event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Group (n=136)</td>
</tr>
<tr>
<td></td>
<td>Control Group (n=79)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Re-operation of Mitral Valve</td>
<td>0</td>
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<tr>
<td>Urgent / Emergent CV Surgery</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
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<tr>
<td>Renal Failure</td>
<td>0</td>
</tr>
<tr>
<td>Deep Wound Infection</td>
<td>0</td>
</tr>
<tr>
<td>Ventilation &gt;48 hrs</td>
<td>0</td>
</tr>
<tr>
<td>New Onset Permanent Atrial Fib</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
</tr>
<tr>
<td>GI Complication Requiring Surgery</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>All Transfusions ≥2 units*</td>
<td>12 (8.8%)</td>
</tr>
</tbody>
</table>

**TOTAL % of Patients with MAE**

- **Device Group**: 9.6%
- **Control Group**: 57.0%

\[ p<0.0001^* \]

\[ (95\% \text{ CI} \ 34.4\%, \ 60.4\%) \]

*\( p<0.0001 \) if include Major Bleeding only
EVEREST II RCT: MR Reduction
Per Protocol Cohort

Device Group
- Baseline: n=137
- 12 Months: n=119

- 3+/4+ ≤2+
  - 81.5%

Control Group
- Baseline: n=80
- 12 Months: n=67

- 3+/4+ ≤2+
  - 97.0%
EVEREST II RCT: Left Ventricular Volume
Per Protocol Cohort

Device Group
n=118, matched data

Control Group
n=65, matched data

LVEDV = left ventricular end diastolic volume
LVESV = left ventricular end systolic volume

Pre-specified hypothesis for statistical analysis

Investigational device limited by Federal (U.S.) law to investigational use only. PML02827 Rev. A 03/2010
EVEREST II RCT: Summary

- Safety & effectiveness endpoints met
  - Safety: MAE rate at 30 days
    - MitraClip device patients: 9.6%
    - MV surgery patients: 57%
  - Effectiveness: Clinical Success Rate at 12 months
    - MitraClip device patients: 72%
    - MV Surgery patients: 88%

- Clinical benefit demonstrated for MitraClip System and MV surgery patients through 12 months
  - Improved LV function
  - Improved NYHA Functional Class
  - Improved Quality of Life

- Surgery remains an option after the MitraClip procedure
EVEREST II RCT: Conclusion

The MitraClip procedure is an important therapeutic option for selected patients with significant mitral regurgitation given the demonstrated safety, effectiveness and clinical benefit.
Clinical Experience with the MitraClip Device

- >1100 pts have been treated with MitraClip
- Safe and effective in selected pts with degenerative and functional MR
- Sustained improvement up till 2 years
- Surgical options preserved

First Percutaneous Mitral Valve technology to receive CE Mark approval in 2008
MITRALIGN Bident Design
Permanent Implants

- Two plications in two locations: P1-P2 and P2-P3
- Minimum permanent implants
  - 4 surgical pledgets
  - 2 locks to lock the sutures after plication
Direct Annuloplasty
Radiofrequency shrinkage of the annulus
Straightforward Annuloplasty
Radiofrequency shrinkage of the annulus (Quantum Cor)
Chamber and Annular Remodelling

• Percutaneous Septal Sinus Shortening (PS³) System (Ample Medical)

• i-Coapsys (Myocor)
Chamber and Annular Remodelling

PS³ System Components
• Preclinical Studies shown sustained reduction of septo lateral diameter
• Two pts surgical Functional MR pts treated acutely in cath lab.
• Phase I Café Trial Underway
Conclusions

• There is a definite need for less invasive percutaneous approaches for Mitral regurgitation

• The MitraClip and Carillon devices have received CE mark approval, and have shown to be safe and effective in selected patients with MR

• Most other devices are in the early clinical phase

• Improvements of technology will improve clinical success rates
• Patients who are at high risk for surgery or younger patients seeking a less invasive procedure will be candidates for percutaneous mitral repair
• To Cure sometimes
• To Relieve Often
• To Comfort Always
Percutaneous treatment of structural defects

Rather a collaboration between surgeons and cardiologists

It's not out with the old and in with the new
Criteria of severity of Aortic Valve Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Mod</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&lt;25</td>
<td>25-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Peak Jet Velocity (m per second)</td>
<td>&lt;3</td>
<td>3-4</td>
<td>&gt;4</td>
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<tr>
<td>Valve Area (cm²)</td>
<td>&gt;1.5</td>
<td>1-1.5</td>
<td>&lt;1</td>
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<tr>
<td>Valve Area Index (cm² per m²)</td>
<td></td>
<td></td>
<td>&lt;0.6</td>
</tr>
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</table>

Zoghbi WA et J of the Am Society of Echocardiography 2003
Edwards SAPIEN Transcatheter Heart Valve Evolution

Andersen hand-made Percutaneous Aortic Valve
First pig implant, May ’89

Cribier-Edwards™ THV
23mm
FIM, April 2002

Edwards SAPIEN™ THV
23mm, 26mm
August, 2007