Emerging Options for Transcatheter Mitral Valve Treatment

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Surgery is rare if EF < 40%

Most FMR patients fall in this range

Mirabel - Eur H Journal 2007
Percutaneous Transcatheter Mitral Valve Repair

• Less invasive approaches
• Significant proportion of patients
• Elderly persons or those with significant comorbidities or severe left ventricular (LV) dysfunction, are high risk for surgery
Various technologies for TMVR

• A classification of percutaneous (TMVR) technologies on the basis of functional anatomy
• Groups the devices into those targeting the leaflets (percutaneous leaflet plication, percutaneous leaflet coaptation, percutaneous leaflet ablation)
• The annulus (indirect: coronary sinus approach or an asymmetrical approach)
• Direct: true percutaneous or a hybrid approach, the chordae (percutaneous chordal implantation), or the LV (percutaneous LV remodeling)
• Percutaneous MVR (Mitral Valve Replacement)
TMVR/ Replacement

• Mitral valve leaflet repair
  • MitraClip
  • Neochord

• Mitral valve annular repair
  • Coronary sinus approach: Monarc, Viacor, Carillon
  • Direct: Accucinch, Mitralign
  • Other: Recor, BACE

• Mitral valve replacement
  • Valve in valve
  • Valve in ring
Transcatheter Mitral Valve Repair Outcomes
Challenges of transcatheter MV interventions

- Variability of mitral valve disease
  - Multiple devices
  - Multiple techniques

- Anatomical complexity
  - Most techniques are different from a "stent-based" approach

- Image guidance is more sophisticated
  - Echocardiography is the leading image guidance method
Edge to Edge & MitraClip Concepts

- Facilitates proper leaflet coaptation
  - Degenerative - Anchor flail and prolapsed leaflets
  - Functional - Coapt tethered leaflets to reduce time and force required to close valve
  - Reduces LV volume overload by reducing MR

- Creates tissue bridge
  - May limit dilatation of annulus
    - Septal-lateral (A-P) dimension
  - Supports durability of repair

- Restrains LV wall
  - Limits LV dilatation

Porcine model, 6M
Percutaneous mitral repair with the MitraClip:

- Effective in reducing MR with a low MAE rate
- Significant reverse LV remodeling at 1-year
- Clinical improvement with 58% of patients NYHA Class I at 1-year
- 79% freedom from death, surgery for valve dysfunction and MR > 2+ at 1-year
- Surgical options preserved in majority of patients
- MitraClip facilitates leaflet coaptation reducing MR in functional patients
## CE marked therapies

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbott</th>
<th>NeoChord</th>
<th>CardiacDim</th>
<th>ValTech</th>
<th>Mitralign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>MitraClip</td>
<td>DS1000</td>
<td>Carillon</td>
<td>CardioBand TA and TF</td>
<td>Bident and Tricuspid</td>
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<tr>
<td>Description</td>
<td>Alfieri technique</td>
<td>Neochordal implant from the TA approach</td>
<td>Coronary sinus cinching</td>
<td>Surgical ring implanted percutaneously</td>
<td>Plication device</td>
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<tr>
<td>Strengths</td>
<td>• Minimal invasiveness</td>
<td>• Strong surgical background</td>
<td>simplicity</td>
<td>• Strong surgical background</td>
<td>• simplicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Atrial delivery</td>
<td></td>
</tr>
<tr>
<td>Weaknesses</td>
<td>• Lack of annuloplasty</td>
<td>• TA approach</td>
<td>• Limited efficacy</td>
<td>• Complexity imaging</td>
<td>• Efficacy limited in mitral position</td>
</tr>
<tr>
<td>Status</td>
<td>&gt;35000</td>
<td>&gt;300 pts</td>
<td>500 pts</td>
<td>100 pts</td>
<td>100 pts</td>
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</table>
Abbott Sponsored Clinical Trial Overview

**Enrollment Complete**
- **EVEREST Program - US**
  - EVEREST I – Feasibility Study
  - EVEREST II Randomized Controlled Trial
  - EVEREST II High Risk Registry
  - REALISM Continued Access Study
    - High Risk Arm
    - Non-High Risk Arm
- **EUROPE**
  - ACCESS-EU Phase I
  - ACCESS-EU Phase II

**Enrolling**
- **Randomized HF with FMR - US**
  - COAPT Trial
- **Post-Approval Studies**
  - PAS 1
  - PAS 2
- **Japan**
  - MitraClip Japan Study
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Status</th>
<th>N</th>
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<tbody>
<tr>
<td>EVEREST I (Feasibility)</td>
<td>Feasibility patients</td>
<td>Closed</td>
<td>55</td>
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<tr>
<td>EVEREST II (Pivotal)</td>
<td>Pre-randomized patients</td>
<td>Closed</td>
<td>60</td>
</tr>
<tr>
<td>EVEREST II (Pivotal)</td>
<td>Non-randomized patients (High Risk Study)</td>
<td>Closed</td>
<td>78</td>
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<tr>
<td>EVEREST II (Pivotal)</td>
<td>Randomized patients (2:1 Clip to Surgery)</td>
<td>Closed</td>
<td>279</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>214 Clip</td>
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<td></td>
<td></td>
<td></td>
<td>95 Surgery</td>
</tr>
<tr>
<td>REALISM (Continued Access)</td>
<td>Non-randomized patients</td>
<td>Enrollment Complete.</td>
<td>899</td>
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<tr>
<td></td>
<td></td>
<td>Follow-up ongoing</td>
<td></td>
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<tr>
<td>Compassionate/Emergency Use</td>
<td>Non-randomized patients</td>
<td>Enrollment Complete.</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up ongoing</td>
<td></td>
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<tr>
<td>ACCESS Europe Phase I</td>
<td>Non-randomized patients</td>
<td>Closed</td>
<td>567</td>
</tr>
<tr>
<td>ACCESS Europe Phase II</td>
<td>Non-randomized patients</td>
<td>Closed</td>
<td>296</td>
</tr>
<tr>
<td>Post-Approval Study 1 (PAS1)</td>
<td>Commercial patients</td>
<td>Enrolling</td>
<td>1583(^3)</td>
</tr>
<tr>
<td>Post-Approval Study 2 (PAS2)</td>
<td>Commercial patients</td>
<td>Enrollment to start Q‘16</td>
<td>n/a</td>
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<td>COAPT Trial</td>
<td>Randomized patients (1:1 Clip to Medical Therapy)</td>
<td>Enrolling</td>
<td>47 Roll-Ins(^*)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>317 Randomized(^*)</td>
</tr>
<tr>
<td>MitraClip Japan</td>
<td>Non-randomized patients</td>
<td>Enrolling</td>
<td>10</td>
</tr>
<tr>
<td>Commercial Use</td>
<td>Commercial patients</td>
<td>Ongoing</td>
<td>Over 25000(^*)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>Over 28000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+95 surgery</td>
</tr>
</tbody>
</table>

Data as of: \(^*\)March 2015, \(^*\)December 10, 2015
Source: Abbott Vascular
WORLDWIDE COMMERCIAL IMPLANT EXPERIENCE

>35,000 Patients

Implant Rate: 96%

Etiology

- FMR 65%
- DMR 22%
- Mixed 13%

Data as of Sept 2015. Source: Abbott Vascular
Clinical experience with direct and indirect annuloplasty is increasing.

- **Carillon**: About 500 pts
- **CardioBand**: About 100 pts
- **Mitralign**: About 80 pts
- **Arto**: About 20 pts
- **Valcare**: FIM TA
- **Millipede**: FIM Surgical
Coronary sinus approach for mitral annuloplasty

- The coronary sinus provides the simplest and least invasive approach for percutaneous annuloplasty.
- Its main limitations are the indirect relationship of the coronary sinus to the mitral annulus and the potential for coronary artery compression.
- These anatomical hurdles limit the number of patients suitable for this approach.
- Device fracture has been problematic, and so development of 2 out of 3 of the devices was discontinued after early experience in humans.
- Early clinical results with this approach have demonstrated reductions of MR, and clinical benefit and further investigation of the Carillon device is ongoing.
CARILLON Mitral Contour System

- **Anchor Architecture in CS**
  - Preserves treatment options (e.g., LV lead)
  - Designed to maintain position within the CS

- **Adjustable**
  - Addresses variable anatomy
  - Optimize MR reduction

- **Straightforward Access in CS**
  - Designed for rapid deployment (DA: 7-14 mm)
  - No trans-septal puncture (PA: 12-20 mm)

- **Recapture Feature**
  - Assess and avoid coronary compression
  - Enables repositioning
TITAN Trial

Reduction in Mitral Regurgitation

Reverse Remodeling

Between groups comparison of paired absolute differences from baseline
Direct Annuloplasty by Cardioband

Trans-femoral venous access (transeptal) – best for safety

• Supraannular fixation like in surgery
• Significant Reduction of Annular dimensions – device enables reduction of up to size 28 surgical ring
• Preserves the native anatomy – keeps future options open
### Study Demographics (N=50)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) or Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 39 Female 11</td>
</tr>
<tr>
<td>Euroscore II (%)</td>
<td>7.5</td>
</tr>
<tr>
<td>Baseline NYHA Class of III or IV (%)</td>
<td>84</td>
</tr>
<tr>
<td>Ischemic</td>
<td>31</td>
</tr>
<tr>
<td>Non Ischemic</td>
<td>19</td>
</tr>
<tr>
<td>LVEDD (mm) Avg±SD</td>
<td>61 ± 6</td>
</tr>
<tr>
<td>EF (%) Avg±SD</td>
<td>33 ± 11</td>
</tr>
<tr>
<td>Prev CABG</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Moderate to Severe Renal Failure</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>Severe Pulmonary Hypertension</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Afib</td>
<td>39 (78%)</td>
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</tbody>
</table>
**Patients Experiencing 30 Day Events**

<table>
<thead>
<tr>
<th>Event</th>
<th># (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke**</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Need for elective Mitral</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Operation**</td>
<td></td>
</tr>
<tr>
<td>Ischemic attack</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Major Bleeding Complications</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cardiac Tamponade</td>
<td>1 (2%)</td>
</tr>
</tbody>
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** Part of the Death case
One additional death case per ITT - compassionate

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*Dr. Paul Grayburn - Baylor University*
Annular Reconstruction by Significant Reduction in Septi

30% average reduction in A-P

<table>
<thead>
<tr>
<th>Septo Lateral Dimension [mm]</th>
<th>Baseline</th>
<th>Discharge</th>
</tr>
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<tr>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td></td>
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<tr>
<td>37</td>
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<td>32</td>
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<td>27</td>
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<tr>
<td>22</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A-P Dimension [mm]</th>
<th>Baseline</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>37±4 (29-46)</td>
<td></td>
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<tr>
<td>26±4 (18-35)</td>
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</table>

P<0.01
Septo Lateral (A-P) Dimension (mm) over time
Functional Improvement at 12 Months

6MWT
P < 0.01

<table>
<thead>
<tr>
<th>Meters Walked</th>
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<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>12 Months</td>
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</tbody>
</table>

MLHFQ
P < 0.01

<table>
<thead>
<tr>
<th>MLHFQ Score</th>
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<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>12 Months</td>
</tr>
</tbody>
</table>

NYHA Class
P < 0.01

<table>
<thead>
<tr>
<th>% of population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>12 months</td>
</tr>
</tbody>
</table>

N = 20, 24, 28
Cardioband is a Surgical Annuloplasty Through A Catheter

Transcatheter surgical annuloplasty is feasible.

Significant and consistent reduction in SL dimension and MR

Options remain open for future interventions

Opens the perspective for “surgical Standard” transcatheter repair
Percutaneous Complete Ring Delivery for Adjustable Atrioventricular Valve Annuloplasty: The Cardiac Implants Approach
Adjustable Fabric Covered Ring Implant
Ring Delivery Scaffold

Pre-Shaped Ring Delivery Scaffold

CT Planning
Ring Implant: Complete Control over Cinching

Post ring implantation

"cinching"
RDS Acute Study: Mitral (Porcine) Deployment of Mitral Ring in Porcine Model
Post Deployment of Ring
RDS Acute Study: Mitral (Porcine)
Percutaneous RDS Acute Study: Mitral Final Result
Percutaneous MiCardia (VALCARE)
Apparatus, systems, and methods are provided for repairing heart valves through percutaneous transcatheter delivery and fixation of annuloplasty rings to heart valves via a trans-apical approach to accessing the heart. A guiding sheath may be introduced into a ventricle of the heart through an access site at an apex of the heart. A distal end of the guiding sheath can be positioned retrograde through the target valve. An annuloplasty ring arranged in a compressed delivery geometry is advanced through the guiding sheath and into a distal portion of the guiding sheath positioned within the atrium of the heart. The distal end of the guiding sheath is retracted, thereby exposing the annuloplasty ring. The annuloplasty ring may be expanded from the delivery geometry to an operable geometry. Anchors on the annuloplasty ring may be deployed to press into and engage tissue of the annulus of the target valve.
Concept

• VALCARE™ system is designed to emulate current semi ridged complete D-shaped annuloplastyrings like MiCardia and others used as for surgical repair.

• Unlike surgical annuloplastyrings the VALCARE system is designed for percutaneous, Trans-catheter delivery.
VALCARE System is composed of

• Proprietary Ring
• Special delivery device
• Stabilizing tool
• Anchoring system
The Procedure: Transapical Approach to LA

- Chronic porcine studies have shown
- Stable Implant
  - No Rocking
  - No Dehiscence
- Good Hemodynamics
- Good encapsulation and integration into the annulus
- Perfectly maintained structural integrity of Implant
Next Step

• First in Man
• – Transapical approach for MV repair
• – To date 2 patients have been treated in Prague
• • Detailed presentation of outcomes planned for TCT 2016!!
Valve in Valve (Trans-septal and Transapical)

Patient-Presentation:

- 81-year old female patient with two prior cardiac surgeries
  - 1984: open commissurotomy of the mitral valve (mitral valve stenosis)
  - 2004: Mitral valve replacement with a 27mm Epic™ stented biological prosthesis (mitral valve endocarditis)
- Pulmonary hypertension; renal failure; severely reduced lung capacity

Patient-Presentation:

Logistic EuroScore 48%
STS score 19%
Procedure:
- Transfemoral antegrade implantation of a 26mm Edwards Sapien XT-valve
- General anesthesia
- Puncture of the femoral vein
- Transseptal puncture
- Placement of a super stiff wire into the left ventricle
- Dilatation of the septum with a 10mm and 14mm balloon
Procedure:
-Slow inflation under rapid pacing
Result:
Reduction of mitral regurgitation from severe to none
• 84 year old man
• in 1997
  – Coronary grafts (Right mammary on LAD, Left mammary on marginal, Radial on PDA)
  – Post operative myocardial infarction with ischemic mitral insufficiency
  – Mitral valve replacement : bioprosthesis (Medtronic INTACT 29mm)
Wire through the bioprosthesis
Bioprosthesis introduction
26 mm Sapien-Edwards aortic valve implantation in the bioprosthetic valve by transapical route
No Mitral Regurgitation
Percutaneous MVR

- The EndovalveHerrmann prosthesis (Endovalve Inc., Princeton, New Jersey) is implanted from the LA side via a right mini-thoracotomy on a beating heart.
- The Lutter prosthesis, a nitinol stent-valve, has been implanted transapically in porcine models.
- The CardiAQ (CardiAQ Valve Technologies, Inc., Winchester, Massachusetts) prosthesis is in pre-clinical development and is delivered transseptally.
The **CardiAQ** (CardiAQ Valve Technologies, Inc., Winchester, Massachusetts) prosthesis; this device is delivered transseptally.
Endovalve-Herrmann Prosthesis
Percutaneous Leaflet repair + Percutaneous Annuloplasty = Fully Percutaneous Mitral Repair
Transcatheter MVR: the challenges

- Large anatomy
- Anchoring
  - Cannot use radial force
  - Landing zone is dynamic and fragile
- Asymmetric anatomy
- Interaction with the aortic valve and LVOT
- PVL more problematic
Conclusion

• The percutaneous edge-to-edge repair technology Mitral Clip has been shown to be noninferior to open repair in a randomized clinical trial.

• Several other technologies employing the concepts of direct and indirect annuloplasty and LV remodeling have achieved first-in-man results.

• Most likely a combination of these technologies will be required for satisfactory TMVR.

• In the future, the novel technology of percutaneous MVR might become a possible alternative in a selected group of patients with a low probability of successful repair.

• However, TMVR is not possible for many patients, and MVR will be required.