Transcatheter Mitral Valve Repair: Current Status and Future Perspectives

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## Disclosure Eberhard Grube, MD

<table>
<thead>
<tr>
<th>Physician Name</th>
<th>Company/Relationship</th>
</tr>
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</table>
| Speaker Bureau/Advisory Board: | Medtronic: C, SB, AB, OF  
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Jena Valve: C,SB, AB  
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Mitral Technology: C, SB, AB |
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Cardiovalve: E, SB,  
Claret: E, AB  
Shockwave: E, AB  
Valve Medical: E, AB  
Millipede E, AB, SB  
Pie-Cardia: E, AB, SB  
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"Aaaaahhh – Mitral!"

"The next TAVI!"
Well that is (unfortunately) not the Case

Aortic Valve

Mitral Valve
The Mitral Valve is very Special

• High Variability und Instability of the Anatomy

• Complex Apparatus /Annulus, Leaflets, Chordae, Papillary Muscles, LV etc...

• Access:
  • Trans-apical
  • Trans-atrial
  • Trans septal

• Two Pathologies:
  • Primary and Secondary Mitral Insufficiency
Mitral Valve
Two Types of Mitral Disease

Degenerative MR: Prolapse/Flail

Functional MR: Ventricular Problem
Degenerative MR *is not* Functional MR
TMVR – CE certified Therapy Options

2008

2015

2016

2017

Waiting for CE approval:
Mitral Repair Devices in Use

- MitraClip: >60,000
- Carillon: >1,000
- Cardioband: ≈75
- Mitralign: Not in use
- Pascal: Not in use
• Surgical treatment of MR yields acceptable results, especially for primary MR

• However, patients with severe mitral regurgitation are denied surgery. Reasons include:
  ✓ Impaired LVEF
  ✓ Older Age
  ✓ Comorbidities / surgical risk status

➢ Transcatheter treatment strategies are needed for this large group of patients

Mitral Valve Repair
A number of devices targeting the MV leaflets, chordal apparatus, and mitral annulus are under development. This presentation will focus on some. Overall, TMV repair (TMVr) devices show good safety outcomes, but improvements in ease of use and efficacy are required.

<table>
<thead>
<tr>
<th>Anatomic Target</th>
<th>Device</th>
<th>Description</th>
<th>Main Indications</th>
<th>Status</th>
<th>Reported # of Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral Leaflets</td>
<td>MitraClip</td>
<td>Edge-to-Edge</td>
<td>Primary and Secondary MR</td>
<td>FDA Approved CE Mark</td>
<td>&gt;80,000</td>
</tr>
<tr>
<td></td>
<td>Pascal</td>
<td>Edge-to-Edge</td>
<td>Primary and Secondary MR</td>
<td>CE Mark</td>
<td>&gt;62</td>
</tr>
<tr>
<td>Mitral Annulus</td>
<td>Carillon</td>
<td>Coronary Sinus cinching</td>
<td>Secondary MR</td>
<td>CE Mark</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>Cardioband</td>
<td>Direct annuloplasty</td>
<td>Secondary MR</td>
<td>CE Mark</td>
<td>&gt;100</td>
</tr>
<tr>
<td></td>
<td>Millipede</td>
<td>Direct annuloplasty</td>
<td>Secondary MR</td>
<td>-</td>
<td>&gt;65</td>
</tr>
<tr>
<td>Chordal Apparatus</td>
<td>NeoChord</td>
<td>Artificial chordal implantation</td>
<td>Posterior leaflet flail/prolapse</td>
<td>CE Mark</td>
<td>&gt;1100</td>
</tr>
<tr>
<td></td>
<td>Harpoon</td>
<td>Artificial chordal implantation</td>
<td>Posterior leaflet flail/prolapse</td>
<td>-</td>
<td>&gt;65</td>
</tr>
</tbody>
</table>
Mitral Interventions

Annulus MV Repair Systems

- **Direct Annuloplasty**
  - Mitralign
  - Valcare AMEND
  - Cardiac Implants
  - Edwards Cardioband
  - BSC IRIS Millipede Ring

- **Ventricular Repair**
  - Ancora

- **Indirect Annuloplasty**
  - Carillon (coronary sinus approach)
  - Mitral Cerclage
  - MVRx
[Surgical] 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 heart failure.

No recommendation for transcatheter MV repair

Class IIb = weak recommendation; benefit ≥ risk; may be reasonable; effectiveness is uncertain

Nishimura RA et al. J Am Coll Cardiol 2017;70:252–89
Imitate Prof Alfieri

Atrial element

Ventricular element
Next generation MitraClip devices aim to improve ease-of-use. The EXPAND observational study is currently enrolling and an interim analysis of the first 500 patients showed significant MR reduction and improvements in QoL. In addition, it provided considerations for NTR and XTR device selection.

Overall MR Reduction

| Leaflet Repair | MitraClip | Next Generation | Overall MR Reduction |

NYHA Classification

KCCQ Assessment

30 Day Improvement of 20.6

* Pairwise Compared to Baseline

Adapted from Hausleiter, presented at EuroPCR 2019
MV World after COAPT
Words of Caution

STS/ACC TVT Registry (n= 2.952 pts)

MitraClip TVT Registry
As of Sept, 2015; linked records to CMS claims data

- 40% with post-procedural MR ≥ 2
- SLDA, 1.5%
- In-hospital mortality = 2.7%
- 85.9% discharged home
- Median LOS, 2 days
  (1, 5 days)
- Acute procedure success = 91.8%
The „Mitral World“ after COAPT

• Increased optimism with MV therapies
• Trial recruitment for other devices will become more difficult
• If the Clip becomes standard of care it might become the comparator for other mitral innovations
• HF specialists are now more actively involved
• Safety of the Clip procedure will be difficult to match
• The results of the COAPT trial are difficult to replicate in all patients. More devices are needed.
• Surgery remains an option for DMR in younger patients and more complex anatomies....
Leaflet Repair
PASCAL

• Edge-to-edge repair
  • Based on Alfieri edge-to-edge suture approach

• System consists of
  • 22 Fr steerable guide sheath
  • Steerable catheter
  • Pascal device
    • Spring-loaded paddles
    • 10 mm central spacer

• Transseptal approach

1Adapted from Feldman, presented at CRT 2019
30-Day outcomes of the CLASP Early Feasibility Study showed significant improvements in MR severity, NYHA Functional class, and quality of life.

Leaflet Repair
PASCAL

\(^1\text{Lim et al., J Am Coll Cardiol 2019; 22(14): 1369-1378}\)
The PASCAL device received CE Mark in February 2019.

The CLASP IID/IIF Pivotal Trial is currently underway and will evaluate the safety and effectiveness of PASCAL compared to MitraClip in patients with primary and secondary MR.
Annular Repair
Carillon

Delivery System

Distal Anchor
(in great cardiac vein)

Implant lengths:
60 - 80 mm

Proximal Anchor
(in coronary sinus)

Anchor sizes:
Individually selected
for each patient

Coronary sinus cinching

System consists of

- 9 Fr delivery catheter
- Fixed-length, double-anchor, self-expanding nitinol device
- Positioned with the coronary sinus/great cardiac vein
- Once in place device cinched and tethered

Transjugular/Coronary sinus access

Adapted from Kapadia, presented at CRT 2019
Annular Repair
Carillon

Results of the randomized, sham-controlled REDUCE-FMR trial that assessed the safety and efficacy of transcatheter mitral annuloplasty with the Carillon device were presented in September, 2018.

<table>
<thead>
<tr>
<th></th>
<th>Implanted (n=73)</th>
<th>Control (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Yr.</td>
<td>70±9</td>
<td>69±9</td>
</tr>
<tr>
<td>Male</td>
<td>78%</td>
<td>73%</td>
</tr>
<tr>
<td>Etiology, Ischemic</td>
<td>68%</td>
<td>64%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>52.1%</td>
<td>51.5%</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>47.9%</td>
<td>44.5%</td>
</tr>
<tr>
<td>III</td>
<td>49.3%</td>
<td>51.5%</td>
</tr>
<tr>
<td>IV</td>
<td>5.5%</td>
<td>0</td>
</tr>
<tr>
<td>A Fib</td>
<td>58.6%</td>
<td>60.6%</td>
</tr>
<tr>
<td>HFH in Prior Year</td>
<td>46%</td>
<td>42%</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32.8 ± 8.6</td>
<td>37.1 ± 8.7</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.5 ± 0.9</td>
<td>6.4 ± 0.9</td>
</tr>
<tr>
<td>EROA (cm²)</td>
<td>0.25 ± 0.15</td>
<td>0.24 ± 0.14</td>
</tr>
<tr>
<td>RV (ml)</td>
<td>38.6 ± 23.5</td>
<td>38.1 ± 24.0</td>
</tr>
<tr>
<td>MR Grade (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>34.2%</td>
<td>32.3%</td>
</tr>
<tr>
<td>2+</td>
<td>37.0%</td>
<td>25.8%</td>
</tr>
<tr>
<td>3+</td>
<td>23.3%</td>
<td>35.5%</td>
</tr>
<tr>
<td>4+</td>
<td>5.5%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

1Adapted from Sievert, presented at TCT 2018
Annular Repair
Carillon

After 12 months, investigators showed
• No difference in the cumulative major adverse event rates between the study and sham procedure arms (16.1% vs 18.2%).
• Those who received the Carillon device saw a 22% reduction in regurgitant volume compared with an 8% increase in those who had sham procedures ($P = 0.03$, ITT population).
• Trends for positive remodeling were observed in the as-treated analysis.

Change in Regurgitant Volume (RV) at 1-year (ITT)

After 12 months, investigators showed:

- No difference in the cumulative major adverse event rates between the study and sham procedure arms (16.1% vs 18.2%).
- Those who received the Carillon device saw a 22% reduction in regurgitant volume compared with an 8% increase in those who had sham procedures ($P = 0.03$, ITT population).
- Trends for positive remodeling were observed in the as-treated analysis.

Adapted from Sievert, presented at TCT 2018
The Carillon Pivotal Study design in the US was recently revised in light of the U.S. MitraClip approval.

Key Changes:
- Randomization scheme changed from 2:1 to 1:1
- New clinically relevant hierarchical endpoint
  - Accommodates alternative therapies with 24 month follow up
  - Trial becomes a viable option for physicians who embrace COAPT, as well as those who remain skeptical based on Mitra-FR
- Primary Endpoint analysis timeframe extended to 2 years
  - Acknowledging relative benefits seen in COAPT between year one and year two
- Blinded Central Review Committee
  - Provides consistent patient selection and adjudication of alternative therapy primary endpoint events

1. Adapted from Kapadia, presented at TVT 2019
Annular Repair
Cardioband

- Percutaneous annuloplasty
- System consists of
  - 24 Fr steerable guide catheter and implant catheter
  - Variable length tubular Dacron band with helicoidal anchors that fix implant into annulus
- Transseptal

1Adapted from Maisano, presented at CRT 2019
Annular Repair
Cardioband

The CE Mark Trial showed a favorable safety profile with reduced MR that was sustained out to 2 years. Technical success in this early experience was only 78.3% due to anchor disengagement. Recent device iterations aim to improve this complication.

### Adjudicated Events

<table>
<thead>
<tr>
<th>Event</th>
<th>30 Days n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Multi-organ failure and sepsis following elective mitral surgery</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Major bleeding complications</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

1Adapted from Maisano, presented at TCT 2016

### Mitral Regurgitation

[Bar chart showing mitral regurgitation rates at various time points: baseline (61), discharge (58), 30 days (54), 6 months (43), 1 year (39), and 2 years (26).]
The MiBAND Trial is a Prospective, multicenter, single arm European Post-Market Study

The purpose is to assess the safety and efficacy of the Cardioband Mitral System

- Symptomatic Patients with Mitral Regurgitation
  - MR ≥ 2+ as assessed by echocardiography
  - NYHA Class II-III-IV ambulatory despite GDMT, including CRT, if indicated
  - Patient deemed appropriate for the device

N=200 Cardioband Mitral System

Follow-up: 30 days, 1 year, 2 years, 3 years

Primary Outcome:
Change in severity of mitral regurgitation from baseline to discharge

Currently recruiting patients (NCT03600688)

Whisenant, presented at TVT 2019
Annular Repair
Millipede

- Percutaneous annuloplasty
- System consists of
  - 23 Fr delivery catheter
  - Complete, semi-rigid, nitinol ring
  - Pre-attached anchors
  - Repositionable and retrievable until ring released
  - Implemented ICE catheter
- Transseptal

Adapted from Bolling, presented at CRT 2019
Millipede Transcatheter Annuloplasty Ring System with Integrated ICE Imaging
Boston Scientific Millipede IRIS™
Transcatheter Mitral Repair System

2D and 3D Echo Positioning
Chordal Repair Devices
Neochord

• Chordal implant
• System consists of
  • Delivery instrument with leaflet grasping tip and needle
    • Leaflet grasp confirmed by fiber optics in the tip
  • Needle pre-loaded with PTFE suture used to fix MV leaflet to LV apex
• Transapical access

Adapted from Sievert, presented at CRT 2015
The experience with NeoChord is relatively large with >1100 patients treated. Early European experience in 213 patients helped to identify those patients who are most likely to benefit from chordal repair with the NeoChord system.

Type A = isolated P2; Type B = posterior multi-segment; Type C = anterior/bileaflet/paracommissural

1Colli et al., Eur J Cardio-Thoracic Surg 2018, 0:1-7
Chordal Repair Devices

Harpoon

- Chordal implant
- System consists of
  - 9 Fr delivery system
  - Needle with ePTFE suture used to fix MV leaflet to LV apex
- Transapical access

Adapted from Gammie, presented at TVT 2019
Successful implantation of cords with MR reduction to mild or less occurred in 95% of patients at discharge. The procedure was safe with no deaths or strokes. At 1-year MR was mild or less in 79% of patients, and favorable cardiac remodeling was observed.
Future Study Summary: 65 Subjects in Two Studies in EU

**Harpoon System**
Clinical Experience  
N = 65

- Early Feasibility Study  
  Enrollment Complete  
  N = 13 (2 Sites)
- CE Mark Study  
  Enrollment Complete  
  N = 52 (6 Sites)

• Follow up is ongoing  
• Current status: 48 subjects completed 1 yr, and 19 completed 2 yr follow-ups  
• Enrollment in Harpoon clinical studies is currently on pause

“In April 2018, a very small number of patients from the Harpoon studies were diagnosed with recurrent severe mitral regurgitation and subsequently underwent reoperation.”

“Edwards decided to temporarily pause study enrollment until the potential root causes of these reoperations can be better understood.”

- Dr. Bartus, TCT 2018

Adapted from Bartus, presented at TCT 2018
Summary

• Transcatheter options are needed to treat the large group of patients with secondary MR who are currently denied surgery.

• Recent results with the MitraClip device show select patients with secondary MR can benefit from TMVr therapy.

• Current devices target the MV leaflets, chordal apparatus, and mitral annulus.

• Experience with TMVr devices is limited, with the exception of MitraClip.

• Overall, TMVr devices show good safety outcomes, but improvements in ease of use and efficacy are required.