Next Generation Mitral Devices for Repair and Replacement

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I, Eberhard Grube have the following financial interest/arrangement that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

**Speaker Bureau/ SAB:** Medtronic, Boston Scientific, HighLife, Jena Valve

**Equity Interest:** Cardiovalve, Claret, Shockwave, Valve medical, CardioMech, Millipede, Imperative Care, Pie-Cardia, Ancora, Laminar

**Co-Founder:** ReNiva Medical
Structure of my presentation

- Some brief remarks about surgical and transcatheter MV therapies
- Update on treatment options for TMV-repair
- New Innovative Solutions for TMV therapy
- Update on MV replacement devices
- Some Final Remarks
With this claim we started the TAVR journey...!

All things being equal, less-invasive therapies will always reign supreme. Have we achieved this goal in MV disease yet?
TMV repair and replacement - design goals

<table>
<thead>
<tr>
<th></th>
<th>Safety</th>
<th>Efficacy</th>
<th>Ease of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Reduction/ Elimination</td>
<td></td>
<td>⭐</td>
<td></td>
</tr>
<tr>
<td>No PVL</td>
<td></td>
<td>⭐</td>
<td></td>
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<tr>
<td>Trans-septal/ transfemoral Access</td>
<td>⭐</td>
<td></td>
<td>⭐</td>
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<tr>
<td>Minimal Anatomical Exclusions</td>
<td></td>
<td>⭐</td>
<td>⭐</td>
</tr>
<tr>
<td>Predictable Deployment</td>
<td>⭐</td>
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</table>
Surgery is still the gold standard for MV-replacement and MV-repair.

Transcathether approaches have not achieved that level of safety and efficacy yet.

We might have to find new, innovative solutions outside the surgical ”toolbox“ to achieve the same results as surgery.
Mitral Regurgitation
Current (Surgical) Treatment Options – Bullit Points

- **Surgical treatment of MR utilizes a “toolbox” approach** due to the complexity of the mitral valve.
- Annuloplasty, leaflet resection, and implantation of artificial chords are performed most often.
- **Mitral valve replacement is performed at a rate of 34%** according to an STS database report on 87,214 patients who underwent isolated primary MV operations.
- **Management of secondary MR with conventional surgery is less common** due to the lack of evidence showing improved outcomes, so medical therapy is the first-line treatment.

Mitral Regurgitation
Unmet Treatment Need

• There is an unmet treatment need in the MR population.
• High surgical risk patients are often denied surgery due to comorbidities.
• A U.S. community cohort study of patients with moderate/severe MR found mitral valve surgery was performed in only 14% of patients with either primary or secondary MR.
• These results suggest the unmet need in this patient population may be higher than expected.

### Table 2
Mitral valve surgery and any cardiac surgery, by aetiology and severity of mitral regurgitation

<table>
<thead>
<tr>
<th></th>
<th>FMR-v (n = 278)</th>
<th>FMR-a (n = 194)</th>
<th>OMR (n = 233)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV repair/ replacement, n (%)</td>
<td>10 (4%)</td>
<td>6 (3%)</td>
<td>86 (37%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiac surgery, n (%)</td>
<td>25 (9%)</td>
<td>12 (6%)</td>
<td>86 (37%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV repair/replacement by MR severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate MR, n operated (%), n in subset</td>
<td>4 (2%) (n = 192)</td>
<td>5 (3%) (n = 175)</td>
<td>22 (18%) (n = 124)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe MR, n operated (%), n in subset</td>
<td>6 (7%) (n = 86)</td>
<td>1 (5%) (n = 19)</td>
<td>64 (59%) (n = 109)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Any cardiac surgery includes mitral/aortic/tricuspid valve repair or replacement, coronary artery bypass grafting, left ventricular assist device implantation, Maze procedure, heart transplant. **FMR-v:** Functional/Secondary MR linked to LV remodeling; **FMR-a:** Functional/Secondary MR linked to isolated atrial dilatation; **OMR:** Organic/Primary MR.
Transcatheter MV Repair: Device Landscape 2020

Numerous transcatheter mitral valve repair devices are under development.

**MV replacement**
- Edwards CardiAQ*
- Edwards Fortis*
- Edwards M3*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
  - HighLife*
  - MValve*
  - Cephea
- NCSI NaviGate*
- St. Jude
- Transcatheter Technologies Tresillo
- Venus
- Verso
- Transmural Systems
  - Microport
  - Valcare Corona

**MV replacement (cont)**
- MitralHeal
- Innova Saturn
  - Lutter valve
- Transcatheter Technologies Tresillo
  - Venus
  - Verso

Other approaches
- Cardiosolutions Mitra-Spacer*
  - Valtech Vchordal
  - Mitralix

**Posterior leaflet repair/replacement**
- Polares
- St. Jude leaflet plication*
- Sutra
- Half Moon Medical
- Angel Valve Butterfly

**Coronary sinus annuloplasty**
- Cardiac Dimensions Carillon**
  - Cerclage annuloplasty*
  - MVRx ARTO*

**Direct annuloplasty and basal ventriculoplasty**
- Edwards Cardioband**
  - Ancora Accucinch*
  - Millipede IRIS*
- Valcare Amend*
- Mardil BACE*
- Mitraspan*
- Valfix*
- Micardia enCor
- Cardiac Implants RDS
- QuantumCor (RF)

... which could also indicate that none of them really work well

*In patients  *CE mark  *FDA approved
# TMV repair devices

The repair devices target the MV leaflets, annulus, and chordae.

<table>
<thead>
<tr>
<th>Anatomic Target</th>
<th>Device</th>
<th>Description</th>
<th>Main Indications</th>
<th>Status</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>
</tr>
<tr>
<td></td>
<td>Pascal</td>
<td>Edge-to-Edge</td>
<td>Primary and Secondary MR</td>
<td>CE Mark</td>
</tr>
<tr>
<td>Mitral Annulus</td>
<td>Carillon</td>
<td>Coronary Sinus cinching</td>
<td>Secondary MR</td>
<td>CE Mark</td>
</tr>
<tr>
<td></td>
<td>Cardioband</td>
<td>Direct annuloplasty</td>
<td>Secondary MR</td>
<td>CE Mark</td>
</tr>
<tr>
<td></td>
<td>Millipede</td>
<td>Direct annuloplasty</td>
<td>Secondary MR</td>
<td></td>
</tr>
<tr>
<td>Chordaal Apparatus</td>
<td>NeoChord</td>
<td>Artificial chordal implantation</td>
<td>Posterior leaflet flail/prolapse</td>
<td>CE Mark</td>
</tr>
<tr>
<td></td>
<td>Harpoon</td>
<td>Artificial chordal implantation</td>
<td>Posterior leaflet flail/prolapse</td>
<td>CE Mark</td>
</tr>
</tbody>
</table>
Transcatheter edge-to-edge repair is based on the surgical Alfieri suture approach
Utilizes transfemoral/Transseptal delivery
MitraClip has the largest experience of any transcatheter mitral repair or replacement device with >100,000 cases worldwide
PASCAL received CE Mark in 2019 and will compete with MitraClip in the future
The global EXPAND study evaluated real-world outcomes of 1,041 patients treated with MitraClip NTR and XTR system. At 1-year results showed:

- 97.5% of patients achieved MR \( \leq 1 \) at 365 days
- MR \( \leq 1 \) was achieved more often with NTR and XTR compared to earlier device iterations
- Significant MR reduction was associated with improvements in QoL

Presented by Dr. Kar at TCT Connect 2020
The CLASP Study evaluated safety and efficacy in 109 patients with severe primary and secondary MR. Results showed:

- The procedure was safe with a composite MAE rate of 14.5%
- 82% of patients had MR ≤ 1 at 1-year
- Sustained improvements in QoL

Presented by Dr. Smith at TCT Connect 2020
The CLASP IID/IIF Trial will evaluate the safety and effectiveness of the PASCAL system compared to the MitraClip system.

The next-generation (PASCAL ACE) device will be narrower with the ability to fine-tune to optimize MR reduction.
Carillon received CE Mark in 2009 and has the largest experience of repair devices targeting the mitral annulus.

The device is a coronary cinching system positioned in the coronary sinus/great cardiac vein.

Transjugular access.

Results of the randomized, sham-controlled REDUCE-FMR trial showed:

- Excellent safety
- Reduced MR severity
- Resulted in favorable remodeling

Of note: 71.4% of patients were in Class 1 or 2 and 28.8% in 3 or 4`

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Carillon Mitral Contour System Efficacy – ECHO

(Remodeling of the LV and decrease of MR)

Before

After 1 month
Cardioband is a percutaneous direct annuloplasty system

Utilizes transseptal access

Current data comes from 61 patients included in the single arm, multicenter, prospective CE Mark Study. Results showed:

- Favorable safety profile
- Reduced MR sustained out to 2 years
- Poor technical success (78.3%) due to anchor disengagement

1 Presented by Dr. Whisenant at TCT 2019

2 Presented by Dr. Nickening at TCT 2020
TMVr
Mitral Annulus | Millipede

- Millipede is a percutaneous direct annuloplasty system
- Transseptal access
- Evidence on the Millipede system is limited. The largest series included 11 patients
- Millipede was acquired by Boston Scientific in 2019
- A feasibility study was initiated in 2019 and is currently enrolling with a redesigned device

Adapted from Rogers, presented at TCT 2018
Mitral Interventions – Transapical Chordal Repair Devices

EW – Harpoon 8F

Neochord
Mitral Interventions – *Transseptal Chordal Repair Devices*

**Pipeline**
- #1 Anchor
- #2 Pledget
- #3 Adjust / Lock

Anchor → Pledget → Adjust & Lock
GORE-Tex Chords & Pledgets
FIM cases already performed in Paraguay
EFS planned

**CardioMech**
- Leaflet → Anchor → Adjust & Lock
- Unique anchor
- EFS planned

**CoreMedic**
- Leaflet → Anchor
- Fixed length chords ranging from 10 to 30mm
- Surgical cases done in Lithuania

**NeoChord**
- Leaflet capture → Anchor → Tensioning
- Girth hitch knot & chords identical to TA system with long-term human data
- Edge-to-edge possible
- EFS planned
• Neochord chordal implant system utilizes a leaflet grasping tip and needle
• Transapical access
• Relatively large experience with >1100 patients treated
• Studies have provided patient selection recommendations based on mitral valve morphology

1Colli et. al., *Eur J Cardio-Thoracic Surg* 2018; 0:1-7,
2Adapted from Tang, presented at TVT 2019
The prospective, multicenter ReChord Trial aims to enroll up to 585 patients of which 60 will be non-randomized roll-in patients, 450 randomized to NeoChord repair vs. surgical repair, and 75 non-randomized, high-risk patients.
Harpoon chordal implant system utilizes a needle with an ePTFE suture used to fix the MV leaflet to the apex

- Transapical access
- Minimally-invasive, beating-heart, off pump repair
- Echo-guide chordal placement
- Real-time confirmation MR reduction

Adapted from Gammie, presented at AATS Mitral Conclave 2019
The HARPOON clinical experience evaluated safety and performance across two prospective multicenter studies.

At 1-year results showed:

- Primary end point was met in 91% patients.
- Mortality at 1 year was 3%
- Reoperation required in 13% of patients.
- MR ≤ 1 achieved in 75% of patients

1Gammie et al. Eur J Cardiothorac Surg. 2020; ezaa256..
Combination Therapies with Annuloplasty

Carillon + MitraClip

Cardioband + MitraClip

Millipede + MitraClip

Cardioband + NeoChord

Image courtesy of R.S. von Bardeleben

Image courtesy of Latib - Agricola

Image courtesy of Rogers et al. JCIN 2018;11:323-324

Image courtesy of von Bardeleben & Colli
Posterior leaflet enhancement and replacement is a rather new focus area for TMVr and these devices are early in their experience.

- **Polares**
  - Implant made from nitinol and ePTFE
  - Compassionate use cases in Germany & Switzerland

- **Sutra**
  - Trileaflet valve design with annular anchoring
  - Pre-clinical

- **Half-Moon**
  - Posterior leaflet baffle with atrial anchor
  - Pre-clinical
  - EFS planned

- **Avvie**
  - Comprised of nitinol stent (atrial wing + swing arm) and polymer mesh
  - Swing arm serves as artificial papillary muscle
  - Only DMR??
  - Pre-clinical
  - EFS planned
Early Pre-clinical Results 4D CT from one animal

Neo-Leaflet coapting well with AML
Polares PLAR System

The implant, its delivery and anchoring system

Posterior view

Anterior view

Primary anchor

Secondary anchors
First in Human case, November 22, 2019,
U. Schaefer MD, Hamburg

Implant Deployment and Acute Result
Polares Pre and Post Result

Pre Implant

Post Implant
Half Moon Medical Repair

COAPTATION REPAIR DEVICE DESIGN

- Intended to restore valve coaptation
- Augments the surface of the posterior leaflet to fill the regurgitant orifice
- Maintains physiologic function of the anterior leaflet
- Delivered via transfemoral access; fully repositionable and recoverable
- Intended to preserve options for re-intervention

Designed to eliminate regurgitation by restoring physiologic coaptation in a diseased mitral valve
Half Moon Medical Repair

COAPTATION REPAIR DEVICE DESIGN

Designed to eliminate regurgitation by restoring physiologic coaptation in a diseased mitral valve
TCMV replacement devices in Humans

- Twelve Medtronic
- Neovasc Tiara
- Tendyne Abbott
- Valtech CardioValve
- Cephea
- HighLife
- Evoque Edwards
- Edwards M3 Sapien
Transcatheter Mitral Valve Implantation

Timeline of the TMVR Devices (Tendyne CE certified)

2012
- Neovasc Tiara (February)
- CardiAQ (June)

2014
- Edwards Fortis (March)
- Intrepid (November)
- Caisson (June)

2015
- Tendyne (October)
- Navigate (November)

2016
- HighLife (January)

2017
- Cardiovalve

2018
- Edwards M3

2019
- Cephea

4C AltaValve
# Transcatheter Mitral Valves (in Humans)

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Reported Human Experience</th>
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<tbody>
<tr>
<td>Tendyne</td>
<td>&gt;300+</td>
</tr>
<tr>
<td>Intrepid</td>
<td>&gt;230+</td>
</tr>
<tr>
<td>Tiara</td>
<td>71+</td>
</tr>
<tr>
<td>Edwards M3</td>
<td>45+</td>
</tr>
<tr>
<td>Evoque</td>
<td>23+</td>
</tr>
<tr>
<td>HighLife</td>
<td>15+</td>
</tr>
<tr>
<td>CardioValve</td>
<td>7+</td>
</tr>
<tr>
<td>Cephea</td>
<td>7+</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>&gt;700+</strong></td>
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</tbody>
</table>
TMVR Device Parade
The largest TMVR experience is with the retrievable and repostionable Tendyne device.

The transapical device anchors with a tether and apical pad.

**Tendyne received CE Mark in 2020**

2-year follow-up of TMVR in 100 patients showed:

- **Mortality rate:** 39%
- **MR ≤ 1 in 100%**
- Reduced HFH rate post procedure compared with pre
- KCCQ score improved 19.1 points from baseline
- **Improvement in NYHA functional class:** 81.7% in class I/II

Adapted from Ailawadi, presented at TCT 2018
TMVR
Tendyne | SUMMIT revised pivotal trial design

Symptomatic MR Grade III/IV, or severe mitral annular calcification (MAC)**

Heart Team deems transcatheter treatment more appropriate than surgery and anatomy amenable to Tendyne TMVI?

Randomization (1:1) (N=382)

Heart Team deems valve anatomy amenable to transcatheter repair, meets MitraClip indications?

Subject has severe MAC?

Tendyne (Treatment)

MitraClip (Control)

Tendyne (MAC Cohort) N=103

Tendyne (Non-randomized Cohort) N=313

*2017 ASE Guidelines
**With MR ≥ Grade III, severe mitral stenosis (MS), or moderate MR with moderate or greater MS
TMVR
Tendyne | Next Generation

VALVE AND SHEATH INTEGRATED

COMPLETE RETRIEVAL POSSIBLE

1Presented by Dr. Rogers at TCT 2019
The recoverable Intrepid device has a self-expanding outer stent that anchors using a cork effect.

Reported outcomes were generated with the transapical device but the transfemoral Early Feasibility Study was recently FDA approved.

Results of the Pilot Study were reported in 2017 and the most recent evidence comes from 51 APOLLO roll-in patients.

- A 2% 30-day mortality rate was reported.

Presented by Dr. Leon at TCT 2019
**APOLLO Trial**

**Current Valve & Study Design**

**Intrepid Transcatheter Valve**

*Dual Stent Design*
Addresses anatomic and physiologic challenges of mitral valve replacement
+ Anchors without capturing leaflets

**APOLLO Trial Design**

Evaluate safety and efficacy of Medtronic Intrepid™ TMVR System in patients with severe symptomatic mitral regurgitation (1st or 2nd MR)

1:1 Randomization
N=450, 550, 650 (stratified 1st and 2nd MR)

- Treatment Arm: TMVR
- Control Arm: MV surgery

Assessment by Multidisciplinary Heart Team

Roll-in subjects
Max N=300

Eligible for surgery

Ineligible for surgery

Single-arm Cohort
N=250, 350, 550 (1st and 2nd MR)

TMVR Analysis Cohort
TMVR MAC Registry
• The self-expanding Tiara device anchors using ventricular posterior and anterior tabs to fix the valve onto the fibrous trigone and posterior annulus
• Utilizes transapical access
• Current evidence comes from 79 patients included in the **TIARA-I and –II Trials** and showed:
  • 12.7% mortality at 30 days
  • Mild or less MR in 100% of patients at 1 year

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1Presented by Dr. Conradi at TCT 2020
• System ≤ 30Fr
• Smaller ventricular footprint with less structural material
• Retrievable up to the last point of full device following anchor release*
0% patients had MR ≥ 2+ @ 1 year with current transapical TMVR Technologies
• The SAPIEN M3 system is a dual-stage system
  • Docking station is delivered first and encircles the native MV leaflets followed by delivery of the SAPIEN 3 TAVI valve – transseptal access

• Early feasibility and compassionate use outcomes in 45 patients showed:
  • Mortality at 30 days was 2.2%
  • Mild or less MR in 92.7% of patients

A US/Canada Pivotal study planned.

Mitral Regurgitation

<table>
<thead>
<tr>
<th></th>
<th>Baseline N=45</th>
<th>30 Day N=41</th>
</tr>
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<tbody>
<tr>
<td>Moderate/Severe (3+/4+)</td>
<td>6.7%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Mild-Moderate (2+)</td>
<td>93.3%</td>
<td>92.7%</td>
</tr>
<tr>
<td>None/Trace/Mild (0-1+)</td>
<td>93.3%</td>
<td>92.7%</td>
</tr>
</tbody>
</table>

1Presented by Dr. Webb at TCT 2019  
2Presented by Dr. Bapat at TCT 2020
TMVR HighLife Overview

- **Valve**
  - Bovine pericardium

- **Stent (Ring)**
  - Nitinol self-expanding
    - 31 mm

- **Fixation / Sealing**
  - Mimics valve-in-ring procedure by placement of ring prosthesis around native leaflets, followed by valve delivery within the ring.
  - Transseptal or transapical
Highlife Case Example
The Saturn TMVR is a single device characterized by:

An Annular Structure mechanically connected to a Central Valve.
TMVR
SATURN adaptive technology

A solution to address the challenges and wide variability of native annulus sizes.

- Size reduction of the Mitral Annulus
- Stabilization of the Mitral Annulus
Compliant to LA anatomy

Bovine tissue valve
27mm diameter

Stent (Nitinol)
Multiple sizes to fit left atrium (LA)

Atraumatic end

Large cells
Fits 24 Fr catheter

Skirt fabric
Enhances tissue ingrowth

Annular ring
No active MV engagement

Courtesy P. Genereux
First TA Approach Alta-Valve: Quebec September 5th 2018 – 1 yr f/u: NO MR

Courtesy of Dr Josep Rodes-Cabau
First-in Human *Trans-Septal 4C Alta Valve* – No significant MR

Morristown Medical Center (Morristown, NJ, USA)
Philippe Généreux, Robert Kipperman, Kosta Koulogiannis, Jim Slater, Leo Marcoff, Sept 23 2019
Transseptal Delivery

For TMVR to become a viable therapy, the safety profile must reach that seen with TMVr.

TMVR devices are being designed for transseptal delivery and most devices currently using transapical access are actively moving toward transseptal delivery systems.

Minimal Anatomic Exclusions:

Studies are reporting better safety outcomes, but exclusion rates are high. Better understanding of how to image for LVOT obstruction, smaller device profiles, well defined patient selection criteria will reduce exclusion rates.

Improved Imaging

Pre-procedural multimodality imaging is essential for TMVR planning. Echocardiography is the primary imaging modality for the diagnosis and quantification of MR, but CT is the preferred modality for preprocedural TMVR evaluation.
Take Home Message

• Edge-to-Edge techniques are currently standard of care
  • Large numbers of patients treated; well-studied; RCTs to support indication in DMR and FMR
  • Excellent safety & acceptable efficacy
  • Limitations: residual MR, future options, results not predictable, not all anatomies suitable

• Other repair options that will be important for toolbox include:
  • Annuloplasty
  • Transeptal chords
  • Posterior leaflet enhancements

• TMVR
  • Has been slower than expected but continues to grow & innovate
  • Transeptal valve programs showing promising feasibility
  • Patient selection remains a challenge
Thank you for your kind attention!