TMVR Technologies and View of the Future

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## Disclosure Eberhard Grube, MD

<table>
<thead>
<tr>
<th>Physician Name</th>
<th>Company/Relationship</th>
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<tr>
<td>Speaker Bureau/Advisory Board:</td>
<td>Medtronic: C, SB, AB, OF</td>
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<td>LivaNova: C, SB, AB</td>
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<td>Highlife: AB, SB</td>
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<td>Boston Scientific: C, SB, AB</td>
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<td>Jena Valve: C, SB, AB</td>
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<td>CardioMech: C, AB</td>
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<td>Equity Interest:</td>
<td>InSeal Medical: E, AB,</td>
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<td>Imparative Medical: E, AB</td>
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<td>Ancora: E, AB, SB</td>
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**Key**
- **G** – Grant and or Research Support
- **E** – Equity Interests
- **S** – Salary, AB – Advisory Board
- **C** – Consulting fees, Honoraria
- **R** – Royalty Income
- **I** – Intellectual Property Rights
- **SB** – Speaker’s Bureau
- **O** – Ownership
- **OF** – Other Financial Benefits
MV Replacement (TMVR)
Transcatheter Mitral Valve Replacement (TMVR) will be a key therapy for MR patients with evidence to prove safety and efficacy.

TMVR valve design will address current limitations and along with other procedural improvements such as imaging and trans-septal/transfemoral access will help make the procedure easier.
## TMVR Design of the Future
### Procedure Goals

<table>
<thead>
<tr>
<th></th>
<th>Safety</th>
<th>Efficacy</th>
<th>Ease of Use</th>
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</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>
</tr>
<tr>
<td>Trans-septal/ transfemoral</td>
<td>✭</td>
<td></td>
<td>✭</td>
</tr>
<tr>
<td>Access</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal Anatomical Exclusions</td>
<td>✭</td>
<td></td>
<td>✭</td>
</tr>
<tr>
<td>Predictable Deployment</td>
<td>✭</td>
<td></td>
<td>✭</td>
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Transcatheter Mitral Valve Implantation

First-in-man (none CE marked)

- Neovasc Tiara (February)
- CardiAQ (June)
- Intrepid (October)
- Caisson (June)
- Edwards Fortis (March)
- Tendyne (November)
- Intrepid (November)
- Navigate (November)
- HighLife (January)
- Cardiovalve
- Edwards M3
- Cephea

- 2012
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
TCMV replacement devices in Humans

**TMVR TRANSAPICAL**
- Abbott Tendyne
- Medtronic Intrepid
- Neovasc Tiara
- Valtech CardioValve
- Edwards M3 Sapien
- Cephea

**TMVR TRANSSEPTAL**
- Caisson
- HighLife
Mitral Regurgitation
Transcatheter Replacement Devices (in Humans)

MV replacement (TMVR) devices in Humans that show excellent MR reduction, but poor safety outcomes compared to transcatheter repair devices.

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Reported Human Experience</th>
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<tr>
<td>Tendyne</td>
<td>280+</td>
</tr>
<tr>
<td>Intrepid</td>
<td>230+</td>
</tr>
<tr>
<td>Sapien M3</td>
<td>45+</td>
</tr>
<tr>
<td>Tiara</td>
<td>71+</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>685+</strong></td>
</tr>
</tbody>
</table>
TMVR Device Parade
TCMV replacement devices in Humans

Abbott Tendyne
Medtronic Intrepid
Neovasc Tiara

TMVR TRANSAPICAL
0% patients had MR ≥ 2+ @ 1 year with current transapical TMVR Technologies
TCMV replacement devices in Humans

- Tendyne Abbott
- Twelve Medtronic
- Neovasc Tiara
- Valtech CardioValve
- Edwards M3 Sapien
- HighLife
- Evoque Edwards
- Cephea
On November 20, 2019, LivaNova announced it is ending its Caisson TMVR program.

“As we evaluated these changes along with those in the structural heart market, we determined it was no longer viable to continue to invest in our TMVR program. As a result, we will close our Caisson TMVR operations.”

The EVOQUE TMVR valve is the newest iteration of CardiAQ.

- Valve
  - Tricuspid bovine pericardium
- Stent
  - Nitinol self-expanding
- Fixation / Sealing
  - Anchors to annulus, leaflets, and chords
- Transseptal delivery – 28 Fr

Early Feasibility study currently enrolling (NCT02718001)

1Adapted from Herrmann, presented at CRT 2019
# EVOQUE

**Compassionate Use and Early Feasibility Studies**

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## 30-Day Clinical Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>CU (N=8)</th>
<th>EFS (N=6)</th>
<th>Total (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>1</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>0</td>
<td>2</td>
<td>2 (14)*</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Heart Failure Hospitalization</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Bleeding complications</strong></td>
<td>0</td>
<td>1</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Renal Failure</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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### MR Severity

- **Severe (4+)**: 100%
- **Moderate-Severe (3+)**: 80%
- **Mild-Moderate (2+)**
- **Mild (1+)**
- **None/Trace (0+)**

<table>
<thead>
<tr>
<th>Baseline N=14</th>
<th>100%</th>
<th>20%</th>
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<tbody>
<tr>
<td>30 Days N=10</td>
<td>80%</td>
<td>20%</td>
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1 Adapted from Webb, presented at London Valves 2019

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**Early feasibility study is currently enrolling**
SAPIEN M3 TMVR System

Overview

- **Valve**
  - SAPIEN 3 tissue and frame
  - Knitted PET skirt

- **Stent (Dock)**
  - Docking station for 29 mm SAPIEN 3 valve

- **Fixation / Sealing (Assembled Valve)**
  - Dock encircles native MV leaflets, followed by valve delivery

- **Transseptal delivery**
  - 20 Fr eSheath compatibility

The US/Canada EFS Study is currently enrolling
SAPIEN M3 TMVR System
Overview
# Technical Success at Procedure Completion

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>CU (N=10) % (n/N)</th>
<th>EFS (N=35) % (n/N)</th>
<th>Total (N=45) % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Success</td>
<td>90 (9/10)</td>
<td>88.6 (31/35)</td>
<td>88.9 (40/45)</td>
</tr>
<tr>
<td>Alive</td>
<td>100 (10/10)</td>
<td>100 (35/35)</td>
<td>100 (45/45)</td>
</tr>
<tr>
<td>Successful access, delivery, and retrieval of delivery systems</td>
<td>90 (9/10)*</td>
<td>91.4 (32/35)**</td>
<td>91.1 (41/45)</td>
</tr>
<tr>
<td>Deployment of devices in intended position</td>
<td>90 (9/10)*</td>
<td>94.3 (33/35) †</td>
<td>93.3 (42/45)</td>
</tr>
<tr>
<td>Freedom from emergency surgery or reintervention related to device or access</td>
<td>100 (10/10)</td>
<td>97.1 (34/35) ‡</td>
<td>97.8 (44/45)</td>
</tr>
</tbody>
</table>

* One patient had an aortic hematoma during encircling and case was aborted  
** One patient had separate transseptal punctures for deployment of the docking system and valve; one patient's left ventricle was too small to allow for encircling of chordae; one patient had an aortic hematoma during encircling and the case was aborted  
† Same as latter two cases above with unsuccessful delivery  
‡ One patient underwent percutaneous PVL closure during the index procedure
MR at 30 days

SAPIEN M3 TMVR System

MR at 30 days

- **Moderate/Severe (3+/4+)**: 6.7% Baseline (N=45) vs. 4.9% 30 Day (N=41)
- **Mild-Moderate (2+)**: 93.3% Baseline (N=45) vs. 92.7% 30 Day (N=41)
**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
Global Feasibility Study

<table>
<thead>
<tr>
<th>Type</th>
<th>Patients</th>
<th>Geography</th>
<th>Status</th>
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<tbody>
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<td>Compassionate use</td>
<td>4</td>
<td>🇩🇪 &amp; 🇨🇭</td>
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<tr>
<td>First-in-man study</td>
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<tr>
<td>Feasibility study</td>
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<tr>
<td>HL-2016-01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-in-man study</td>
<td>4</td>
<td>🇺🇦</td>
<td>Approved &amp; Enrolling</td>
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<tr>
<td>HL-2017-01</td>
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<tr>
<td>Feasibility studies</td>
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<td>Amended &amp; Approved</td>
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<tr>
<td>HL-2017-02</td>
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<td>Amended HL-2016-01 - EFS</td>
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<td>Feasibility studies</td>
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<td>Australia, Poland, US</td>
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<tr>
<td>HL-2018 HL-2019</td>
<td></td>
<td></td>
<td>Germany, UK, Belgium, others</td>
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</table>

Geography:
- Australia
- Poland (3-4)
- Germany (6-7)
- UK (6)
- France
- Belgium
- Sweden
- Spain
- Holland

TMVR HighLife
Global Feasibility
Novel TMVR Technologies
View of the Future
Saturn Technology

The Saturn TMVR is a single device characterized by:

an annular structure mechanically connected to a central valve.
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
Saturn Adaptive Technology

Mitral annulus size is reduced adapting the native anatomy to the prosthesis

Swine model  \( CC_{diam} = 47.5 \text{mm} \)

Baseline

Post-implant

Perfect apposition of the native MV annulus to the prosthesis
Perfect sealing, no PVL
Saturn designed to reduce risk of SAM

• Anterior Leaflet secured by Connecting Arm
  • Reduced risk of SAM
Saturn Trans-Septal TMVR

Simple procedure designed to preserve all the advantages of the TA approach

Guidewires & Annular Segments Positioned

Connect the Valve & Annular Segments

Saturn TMVR Deployed
AltaValve Features

- **Stent cap**
  - Atraumatic end

- **Stent (Nitinol)**
  - Multiple sizes to fit left atrium (LA)
  - Compliant to LA anatomy

- **Bovine tissue valve**
  - 27mm diameter

- **Large cells**
  - Fits 24 Fr catheter

- **Skirt fabric**
  - Enhances tissue ingrowth

- **Annular ring**
  - No active MV engagement

Courtesy P. Genereux
Transseptal and Transapical Delivery Options

Transseptal Delivery

AltaValve’s shape allows the device to be:
- Directable for optimal fit
- Adjustable during placement

Sizing and variable anatomy overcome by:
- Highly compliant implant
- Overexpansion fit

Courtesy P. Genereux
Sept 5th 2018
First TA Approach AltaValve Quebec

1 Year Follow-up; No MR

Courtesy of Dr Josep Rodes-Cabau
First-in Human TransSeptal 4C AltaValve
First-in Human TransSeptal 4C AltaValve
No Significant MR
AltaValve Next Steps

- **EFS US and Japan**
  - 15 to 30 patients
  - TA or TF
  - High-risk patients for surgical MVR as determined by Heart Team
  - Anticipated fast enrolment since AltaValve is suitable for most anatomy
Innovative (Alternative) MV Solutions
SUTRA TMVR Solution

Native Mitral Valve

Anterior leaflet

Posterior leaflet

P1

P2

P3

Optimal Coaptation

Anterior leaflet

SUTRA Tri-leaflet Posterior Leaflet Design

Anterior leaflet

SUTRA
SUTRA TMVR Solution

1. **Crescent shaped stent frame**
   - Small crimped profile
   - No LVOT obstruction
   - Allows normal AML motion

2. **Tri-leaflet valve design**
   - Enhances systolic coaptation with native leaflet
   - Designed to reduce leaflet stress and enhance durability

3. **Annular anchoring**
   - Conforms to native anatomy
   - Prevents PVL
   - Prevents migration
   - Anchors can be deployed without rapid pacing
   - Excellent stability during valve release
   - Annular cinching capability
Good coaptation between the prosthetic leaflets and the native anterior leaflet

Early Pre-clinical Results
4D CT from one animal

P2 coapting with AML well
Early Pre-clinical Results
Fluoroscopy at Day 30

Sutra stent has stable motion
SUTRA TMVR Solution

• Replaces **ONLY** the native posterior leaflet
• Preserves the (normal motion of) native anterior leaflet
• Half frame → requires little space in LV → no LVOT obstruction
• Anchors on the mitral annulus
• Anchors deployed in beating heart
• Small crimp profile for delivery → enables trans-septal delivery
Posterior Leaflet Augmentation & Restoration
Polares PLAR System

- The implant, its delivery and anchoring system
Polares PLAR

Implantation procedure

• In-vivo transseptal implantation - Implant released (ovine 71909)
First Case in Human, November 22, 2019
(Ulrich Schaefer MD, Ralf Bader MD, Felix Kreidel MD)
Hamburg, Germany
Interventional Mitral Valve Therapy

Final Thoughts

Reality (cruel)  Future (promising)

Modified from MB Leon
1. There has been progress with EFS with multiple technologies
2. Several EFS have already transitioned to pivotal trials
3. Progress mad in transseptal TMVR but remains at earlier stage than transapical
4. Despite early experience, some studies have observed mortality lower than predicted by STS score (observed : expected ratio <1)
5. Early experience in MAC seems promising and a MAC arm has been added in pivotal trials (SUMMIT and APOLLO)
6. Risk of LVOTO remains a concern for some technologies
7. New innovative solutions are under way and early results seem promising
8. Despite all challenges the field of TMVR is moving but slower than expected. (NOT TAVR)
Thank you for your kind attention!