Transcatheter Mitral Valve for fMR: The Era of Too Many Options...

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Disclosure Statement of Financial Interest
Isaac George, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Honoraria/Consulting</td>
<td>Edwards, Medtronic, Gore Associates, Bolton</td>
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<td>Steering Committee</td>
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Mitral Regurgitation (MR) occurs as a result of Leaflet Malcoaptation

Primary Disorder of the Valve
Degenerative MR
- Flail, Prolapse
Rare disease
- endocarditis, rheumatic

Functional MR
Leaflets are normal
MR occurs due to LV enlargement, annular dilatation etc
Secondary MR (fMR)

- Occurs when imbalance of the closing and the tethering forces of the MV, annulus, and LV wall
- Due to papillary muscle displacement from increased LV sphericity or remodeling of LV wall (inferior, posterior), as well as annular dilatation (in SL dimension)
- MR occurs half the time after AMI
Secondary mitral regurgitation: 
...a marker of a sicker LV
- or -
...a contributor to a sicker LV?
Secondary mitral regurgitation: 
...a marker of a sicker LV  
- or -  
...a target for therapy?

Therapies that produce beneficial reverse remodeling also reduce severity of functional MR
Surgery for secondary MR

• Annuloplasty ring undersizing was mainstay of repair (the Bolling effect)
  • Replacement
  • Edge-to-edge

• ?Ring: is it effective for primary disease process
Repair vs Replacement for fMR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation


N ENGL J MED 374;4  NEJM.ORG  JANUARY 28, 2016
Repair vs Replacement for fMR

- 58.8% recurrent moderate or greater MR with repair vs. 3.8% with replacement
Should we replace all fMR valves?

- CTSN trial data suggests an unacceptably high rate of recurrent MR with MV repair
Secondary mitral regurgitation can be repaired. But should it be repaired?

There is no surgical data that shows a mortality benefit for MVR or MVr in secondary MR!\(^2\)

Wu et al. J Am Coll Cardiol 2005;45:381-387

\(^2\)DrSalvo et al. J Am Coll Cardiol 2010;55:272-82
Secondary mitral regurgitation

**class I**

Guideline-directed medical therapy for heart failure, including CRT

**class II**

Mitral valve surgery is reasonable for patients with severe secondary MR (stage C and D) undergoing CABG or AVR
Transcatheter Mitral Valve Replacement (TMVR)
Basic Premise of Transcatheter Valve Therapy Development

- Transcatheter devices mimic established surgical therapies
- Therapies should demonstrate benefit (i.e. lower or equivalent mortality and/or improved quality of life) when compared with “gold-standard” established therapies (presumably surgery)
Transcatheter MV Implantation: Challenges

• **Fixation**
  – More complex structure
  – Asymmetric annulus
  – MAC
  – Coronaries

• **Delivery**
  – Catheter size
  – Approach (TA, TF, atrial)

• **Seal**
  – Paravalvular leak likely less well tolerated than with TAVR (hemolysis)

• **Function**
  – LVOT obstruction risk
  – Need to preserve the subvalvular apparatus

• **Valve**
  – Thrombosis
  – durability
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<th>Transcatheter Mitral Valve Prosthesis Anchoring Mechanisms</th>
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<tr>
<td>Apical Tether</td>
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<tr>
<td>![Diagram of Apical Tether]</td>
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<tr>
<td>Annular Winglets</td>
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<td>![Diagram of Annular Winglets]</td>
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<tr>
<td>Native Leaflet Engagement</td>
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<tr>
<td>![Diagram of Native Leaflet Engagement]</td>
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<tr>
<td>Radial Force</td>
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<tr>
<td>![Diagram of Radial Force]</td>
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<tr>
<td>Mitral Annulus Clamping</td>
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<tr>
<td>![Diagram of Mitral Annulus Clamping]</td>
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<tr>
<td>External Anchor</td>
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<td>![Diagram of External Anchor]</td>
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Understand LVOT Risk
TMVR – Early Pioneers

- **Edwards Fortis TMVR (TA)**
  - ~20 patients treated
  - Trial stopped May 2015 due to concerns about leaflet thrombosis

- **Neovasc Tiara TMVR (TA)**
  - 47 patients treated as of Dec ’17 (9.5% 30 day mortality)
  - US trial paused
  - Tiara II trial ongoing (CE Mark study with goal of 115 patients)

- **Edwards CardiAQ TMVR (TA/TS)**
  - US Feasibility trial initiated 2016
  - US trial paused and initiation of CE mark trial delayed in Feb ‘17 for further design validation and testing
Pitfalls in early feasibility trials

1. Very high screen failure rate - >50-90%
   1. Only 1 valve size
   2. LVOT obstruction
2. Valve thrombosis
3. Early and late death – non valve related
4. Transapical access
5. Hemodynamic instability immediately prior to deployment
# Current Human Experience – Mid 2018

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Reported Human Experience</th>
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<tr>
<td>ABT Tendyne</td>
<td>100+</td>
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<tr>
<td>MDT Intrepid</td>
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<tr>
<td>EW M3 Sapien</td>
<td>10+</td>
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<tr>
<td>EW CardiAQ</td>
<td>23+</td>
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<tr>
<td>Neovasc Tiara</td>
<td>52+</td>
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<tr>
<td>Caisson</td>
<td>17+</td>
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<tr>
<td>HighLife</td>
<td>15+</td>
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<tr>
<td>Cardiovalve</td>
<td>5+</td>
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Medtronic Intrepid TMVR

Differentiated, dual stent design
• Separates fixation & sealing from valve function
• Isolates valve from the dynamic anatomy
• Preserves native mitral apparatus
• US Feasibility Trial Ongoing
Early Experience With New Transcatheter Mitral Valve Replacement

Vinayak Bapat, MBBS, MS, MCh, Vivek Rajagopal, MD, Christ Antony Walton, MD, Stephen J. Duffy, MBBS, PhD, Robert Go, Michael J. Reardon, MD, Neal S. Kleiman, MD, Konstantinos S Martin K. Ng, MBBS, PhD, Michael Wilson, MD, David H. Adar, Sharla Chenoweth, MS, Paul Sonajja, MD, for the Intrepid Glob

CENTRAL ILLUSTRATION Early Clinical Experience of TMVR with the New Valve Prosthesis

Device implant success = 98%
No device malfunction or thrombosis
30-day mortality = 14%
Mild or no residual MR in all patients
Symptom improvement in follow-up = 79%

Follow-up time for the 50 patients is illustrated with patients listed on the y-axis in descending order of treatment. X-axis indicates duration of follow-up. All deaths occurred before 365 days (dotted line). Blue = surviving patients; orange = deceased patients; MR = mitral regurgitation; TMVR = transcatheter mitral valve replacement.

Abbott Tendyne TMVR

- Transapical deployment
- Apical anchor ensures stable deployment
- US feasibility trial ongoing

Images Courtesy of Dr. Neil Moat
Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation

A Global Feasibility Trial

David W.M. Muller, MBBS, MD, a Robert Saeid Farivar, MD, b Paul Jansz, MBBS, FSD, b Richard Bae, MD, b Darren Walters, MBBS, MPH, a Andrew Clarke, MBBS, a Paul A. Grayburn, MD, b Robert C. Stoler, MD, b Gyn D Kjell A. Rein, MD, c Marty Shaw, MBBS, b Gregory M. Scalia, MBBS, b Mayra Guerrero, MD, b Paul Pearson, b Samir Kapadia, MD, b Marc Gillinov, MD, b Augusto Pichard, MD, b Paul Corso, MD, b Jeffrey Popma, MD, b Michael Chuang, MD, b Philipp Blanke, MD, b Jonathon Leipsic, MD, b Paul Sorajja, MD, b on behalf of the Tendyne Global Feasibility Trial Investigators

(A) Change in mitral regurgitation (MR) with transcatheter mitral valve replacement (TMVR). Of the 30 patients treated, 26 had successful transcatheter mitral valve implantation with no MR at 30-day follow-up. One patient had mild central MR. One patient with a successful implant and no MR died on day 13. Two patients with unsuccessful device implantation had residual grade 4 MR. (B) Left ventricular (LV) end-diastolic volume index at baseline and after transcatheter mitral valve implantation (day 30). Individual patient data are shown. (C) LV end-systolic volume index at baseline and after transcatheter mitral valve implantation (day 30). Individual patient data are shown. Vertical lines represent standard deviations of the means.

Caisson TMVR

- Transvenous, Transeptal approach
- 2 step implant (anchor, valve)
- Fully reversible
- D-shaped Nitinol self-expanding frame with porcine pericardial valve

PRELUDE: US Early Feasibility Study

Percutaneous Mitral Valve Replacement Evaluation Utilizing IDE Early Feasibility Study (Initiated June 2016)
Other TMVR Systems

**Navigate TMVR**
- Low profile design
- FIH case (Nov ‘15) via transatrial approach

**Highlife TMVR**
- 2 component system
  - Combined TF and TA delivery
- FIH performed (Jan ‘16)

**MValve System**
- Docking station
- FIH performed with Lotus (Oct ’15)
Other TMVR Systems

**CardiaQ TMVR**
- Trileaflet pericardial
- TA and TS approach
- Leaflet capture

**Epygon TMVR**
- D-shaped monoleaflet
- Asymmetric ventricular profile

**Sutra Hemi-Valve**
- Posterior valve
- Keeps native AML intact
TMVR Devices

- Is there an EF cutoff?
- Will large bulky devices adversely impact LV mechanics?
- LVOT obstruction – It’s not an all or none phenomenon
- Is Transapical approach viable?
- Anticoagulation strategies?
Transcatheter Mitral Valve Repair (TMVR)
Advantages of TMV repair

1. More physiologic hemodynamics
2. Easier for TS approach
3. Less invasive
4. Less risky
5. Allows for future risk re-intervention
Challenges of TMV repair

1. Significantly more complex
2. Unknown benefit in secondary MR
3. MR reduction less predictable
4. Unknown durability
5. Likely leaves residual MR
# The many flavors of Repair

<table>
<thead>
<tr>
<th>Approach</th>
<th>Commercial</th>
<th>In Development</th>
<th>Abandoned</th>
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<tr>
<td>Edge-to-Edge Repair</td>
<td>Abbott Vascular</td>
<td>St. Jude Medical</td>
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<tr>
<td>Direct Annuloplasty</td>
<td>Kardium mtralis Valcare</td>
<td>Guided Delivery Systems</td>
<td>ReCor Medical</td>
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<td>neoCHORD</td>
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<td>CardioKinetix Inc. Mardil</td>
<td>Myocor</td>
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<td>Enhanced coaptation</td>
<td>middle peak cardiosolutions</td>
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<tr>
<td>MV Replacement</td>
<td>Medtronic Valtech Highlife</td>
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*Maisano. Zurich Valve, 2016*
Transcatheter Mitral-Valve Repair in Patients with Heart Failure

The COAPT Trial
Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

Randomize 1:1*

MitraClip + GDMT  
N=305

GDMT alone  
N=305

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site
Primary Effectiveness Endpoint
All Hospitalizations for HF within 24 months

Cumulative HF Hospitalizations (n)

- MitraClip + GDMT
- GDMT alone

No. at Risk:
- MitraClip: 302, 286, 269, 253, 236, 191, 178, 161, 124
- GDMT: 312, 294, 271, 245, 219, 176, 145, 121, 88

Time After Randomization (Months)

HR (95% CI) = 0.53 [0.40-0.70]
P<0.001

Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos

283 in 151 pts
160 in 92 pts
All-cause Mortality

HR [95% CI] = 0.62 [0.46-0.82]

P<0.001

NNT (24 mo) = 5.9 [95% CI 3.9, 11.7]

Time After Randomization (Months)

No. at Risk:
MitraClip + GDMT 302 286 269 253 236 191 178 161 124
GDMT alone 312 294 271 245 219 176 145 121 88
Challenges with MitraClip

- Anatomic limitations of the device
- MR reduction not complete
- FMR is a dynamic disease
- Medical optimization is hard
TMVr: Annuloplasty

• Stand alone treatment for functional MR
  – Reduction annuloplasty
• Improve durability of mitral valve repair in primary MR
  – Annular stabilization
Edwards Cardioband
Transcatheter Mitral Annuloplasty in Chronic Functional Mitral Regurgitation
6-Month Results With the Cardioband Percutaneous Mitral Repair System
Millipede IRIS System
Transfemoral Transseptal Complete Ring

Jason Rogers, TVT 2017
The ARTO System

• Immediate and Direct A-P Diameter Shortening to Treat FMR
• Venous Based Delivery Under X-ray and Fluoroscopic Imaging
• Acutely Reversible or Removable
• 12 Fr Delivery System
• No residual ASD
• Little Impact to Potential Future Therapy
MR Grade Reduction Maintained to 3 years (Phase I)

MAVERIC Trial Results: ASE MR

- Baseline N=11: 4+ (2), 3+ (4), 2+ (1), 1+ (1), 0-TR (1)
- 1 Month N=11: 1+ (1), 0-TR (10)
- 1 Year N=10: 1+ (1), 0-TR (9)
- 2 Years N=8: 1+ (1), 0-TR (7)
- 3 Years N=7: 1+ (1), 0-TR (6)
Carillon Coronary Sinus Annuloplasty

Pivotal CARILLON Trial Planned
Carillon + GDMT vs. GDMT in FMR
The Ancora Heart Concept
(Accucinch)

- Directly targets LV dysfunction and dilatation
  - Treat underlying cause of FMR
- Percutaneous trans-femoral arterial-retrograde technique
  - Not trans-septal or trans-apical
- Preserves the natural mitral structures
- Preserves all future treatment options

Sievert TCT 2017
Edwards Pascal

95% patients with MR ≤ 2+ [1]  

Sustained low mean gradient [1]

- 95% patients with MR ≤ 2+ at Baseline, 30 days, and 6 months.
- Sustained low mean gradient at Baseline, 30 days, and 6 months.

- P-values calculated using paired t-test.
Has this gone too far?
Atrial docking...

• AltaValve 4C

*Supra-annular placement preserves native mitral valve and left ventricle (LV)*
- Minimum risk of LVOT obstruction
- Minimal LV presence or footprint

*Expands treatable patient population*
- MR mechanism agnostic
- Applicable to a broader patient population

*eProvides transseptal and transapical delivery options*
- Ease of use
AValue

- Conformational atrial cage for securing and anchoring
- TA approach
- ? Improve diastolic function
At least 54 companies:
- 26 replacement
- 28 repair

Others: Coramaze, Mitralix MISTRAL, MVRX Arto, Mitral Butterfly Vienna university, Bioventrix, Mardil BACE, MitraClip, SAT Mitral Clip, St. Jude leaflet pllication, Cardiac Implants, Mitrantrip, TAU-PNU CTV, PolyCor MIATM, Transmural cerclage system, Valcara AMEND, Babic chords, CoreMedic, Harpoon Medical
Variety of Repair techniques
Combination of Techniques

= Fully Percutaneous Mitral Repair
Remaining Questions

• Is annuloplasty enough as a standalone therapy?
• How much reduction in MR needs to occur?
• When should patients be treated (ERO 20, 40 or 60)?
• Which therapy should be implemented first?
• Can you leave moderate MR when the EF is low?
### Where does this leave us?

<table>
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<tr>
<th>Primary MR</th>
<th>Secondary MR</th>
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<tr>
<td><strong>Low Risk</strong></td>
<td></td>
</tr>
<tr>
<td>• Open Surgery</td>
<td>• ? Surgery</td>
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<tr>
<td></td>
<td>• Mitraclip?</td>
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<tr>
<td></td>
<td>• TMVR?</td>
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<td><strong>High Risk</strong></td>
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TMVR ≠ TAVR

- Indications for Treatment
- Comparator Population
- Anatomic Challenges

TAVR Devices Approved in the US
Transcatheter Mitral Valve Treatment

• The field is in its infancy and many technical challenges remain

• Treatment paradigms for functional MR remain uncertain

• Trial designs for transcatheter devices unclear
  – MR etiology – Functional vs Degenerative
  – Control arm – Surgical vs Medical Therapy
  – Primary endpoint ?