Transcatheter Management of Valvular Disease Beyond the Aortic Valve (mitral - tricuspid valve)

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Structural Heart Disease

Increases with Age

> 9.3% for ≥75 year olds (p<.0001)
Functional Mitral Regurgitation: The Clinical Problem and Competitive Landscape

Relative Sizes of Clinical Need – Primary vs Functional MR
Expected Global Annual Worldwide Incidence

DMR
~650,000

FMR
~2,750,000
>4x

Competitors
MVRx ARTO™
MitraClip™
Cardioband™
Carillon™
Others
## Current Mitral Regurgitation related Devices

### Leaflet/Chordal Solutions
- MitraClip, PASCAL
- Neochord, Harpoon
- Cardiosolutions, Middle Peak Medical

### Direct Annular Shape Change
- Millipede IRIS
- Edwards/Valtech Cardioband
- ValCare Amend

### Indirect Annuloplasty
- Ancora Accucinch
- Carillon, MVRx ARTO
- Mitral Valve Cerclage

### Mitral Valve Replacement
MitraClip® Therapy
Worldwide Clinical Experience

- Received CE mark in 2008.
- Received FDA approval in 2013 for significant symptomatic degenerative mitral regurgitation (DMR) in patients at prohibitive risk (PR) for MV surgery.
- >60,000 patients treated worldwide.
Primary MR: Who Should Get Clip vs Surgery?

**Surgery**
- Low or Intermediate Risk
- Surgically Repairable Valve
- Experienced MV Surgeon
- MV Surgical Center of Excellence

**MitraClip**
- Prohibitive Risk
- “Clippable” Valve
- Good Mitraclip Operator
- Mitraclip Center of Excellence

Overlap considerations:
- TR, Afib, RV Fxn
- Surgical approach (minimally invasive)
- Patient preference
- Consider referral to valve center
**The MITRA-FR Trial**

304 pts with SMR due to LV dysfunction with LVEF 15-40%, NYHA II-IVa, hospitalization for HF within the previous 12 mos, not eligible for mitral surgery. MR defined by EU “severe” criteria as EROA > 20 mm² or RVol > 30 mL/beat. Both groups with “real-world” HF meds (not maximally-tolerated GDMT).

Randomize 1:1 at 37 French centers.

- **MitraClip + MT**
  - N=152

- **MT alone**
  - N=152

Primary endpoint: Freedom from death or HF hospitalizations through 12 months.


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**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 614 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT. 89 centers in the US and Canada (September 25th, 2012 to June 23rd, 2017) -

Randomize 1:1*

- **MitraClip + GDMT**
  - N=302

- **GDMT alone**
  - N=314

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

Stone GW et al. NEJM. 2018 Sept 23.
COAPT vs. MITRA-FR: 12-Month Death or HF Hosp

MITRA-FR

- MitraClip + MT
- MT alone

OR [95% CI] = 1.16 [0.73–1.84]
P=0.53

54.6% 51.3%

Death or HF Hospitalization (%)

No. at Risk:
Control Group 152 123 109 94 86 80 73 67
Device Group 151 114 95 91 81 73 67

COAPT

- MitraClip + GDMT
- GDMT alone

HR [95% CI] = 0.63 [0.49–0.82]
P<0.001

46.5% 33.9%

Death or HF Hospitalization (%)

No. at Risk:
Control Group 312 244 205 174 153
Device Group 302 264 238 215 194

Months

Obadia JF et al. NEJM. 2018 Aug 27. doi: 10.1056/NEJMoa1805374

Stone GW et al. NEJM. 2018 Sept 23.
Why are the COAPT Results so Different from MITRA-FR? Possible Reasons

<table>
<thead>
<tr>
<th></th>
<th>MITRA-FR (n=304)</th>
<th>COAPT (n=614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe MR entry criteria</td>
<td>Severe FMR by EU guidelines: EROA &gt;20 mm$^2$ or RV &gt;30 mL/beat</td>
<td>Severe FMR by US guidelines: EROA &gt;30 mm$^2$ or RV &gt;45 mL/beat</td>
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<tr>
<td>EROA (mean ± SD)</td>
<td>31 ± 10 mm$^2$</td>
<td>41 ± 15 mm$^2$</td>
</tr>
<tr>
<td>LVEDV (mean ± SD)</td>
<td>135 ± 35 mL/m$^2$</td>
<td>101 ± 34 mL/m$^2$</td>
</tr>
<tr>
<td>GDMT at baseline and FU</td>
<td>Receiving HF meds at baseline – allowed variable adjustment in each group during follow-up per “real-world” practice</td>
<td>CEC confirmed pts were failing maximally-tolerated GDMT at baseline – few major changes during follow-up</td>
</tr>
<tr>
<td>Acute results: No clip / ≥3+ MR</td>
<td>9% / 9%</td>
<td>5% / 5%</td>
</tr>
<tr>
<td>Procedural complications*</td>
<td>14.6%</td>
<td>8.5%</td>
</tr>
<tr>
<td>12-mo MitraClip ≥3+ MR</td>
<td>17%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg
MITRA-FR vs COAPT SUMMARY

- Twofold difference in sample size
- Twofold difference in follow-up time for primary endpoint
- Lower severity of secondary MR in MITRA-FR than COAPT
- CEC confirmed maximal medical treatment in COAPT versus uncertain status in MITRA-FR
- Higher proportion of patients with no Mitraclip-implant in MITRA-FR than COAPT
- Higher peri-procedural complication rate in MITRA-FR than COAPT
- Lower acute and long-term procedural success rate in MITRA-FR than COAPT
PAddles, Spacer, Clasps, ALfieri

- 23 compassionate use cases as of 5/2017
- 52% FMR, 26% DMR, 22% mixed
- Technical success 22 (96%)
- MR at discharge (n=22)
  - 0+: 3 (14%)
  - 1+: 14 (63%)
  - 2+: 5 (23%)
- 95% MR ≤2+ and 95% NYHA I/II at 30 days
Transcatheter mitral valve devices

**TMV Replacement devices**

- Braile Biomedica
- CardiAQ 1st G
- CardiAQ, Edwards
- Cephea
- Direct Flow Medical
- Twelve Medtronic
- M-Valve
- Edwards Fortis
- HighLife
- Navigate
- Neovasc Tiara
- PermaValve MID
- Sinomed
- Tendyne Abbott
- SATURN TMVR
- Valtech CardioValve
- Daidalos sutureless clamp
- Others: Caisson, MitraHeal, MitraAssist, MitraLife, Mehr Medical, Mitracath, Mitralix MAESTRO, Nakostech, St. George ATLAS, Transcatheter Technologies Tresillo

**TMV Repair devices**

- CoraMaze, Mitralix MISTRAL, MVRX Arto, Mitral Butterfly Vienna university, Bioventrix, Mardil BACE, Mitraklamp, SAT Mitral Clip, St. Jude leaflet plication, Cardiac Implants, Mitraspan, TAU-PNU CSTV, PolyCor MIATM, Transmural cerdage system, Valcare AMEND, Babic chords, CoreMedic, Harpoon Medical

At least 54 companies:
Transcatheter MV Implantation: Challenges

- **Fixation**
  - More complex structure
  - Asymmetric annulus
  - MAC

- **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
  - Thrombus formation risk
TMVR Candidates

MR Patient Subsets*

High Surgical Risk for Open MVR

?: MAC (some)

MR Recurrence after Surgical Repair

TMVR

Alternative to Surgical MVR

?: RHD (some)

Unable to Perform Surgical Repair

* Acceptable anatomy for TMVR

M. Leap
TMVR for Degenerated Bioprostheses, Failed Annuloplasty Rings, and Mitral Annular Calcification

- Excellent outcomes of TMVR for patients with degenerated mitral bioprosthetic valves (ViV) despite high surgical risk

- Suboptimal procedural outcomes of ViR and ViMAC: second valve implantation, LVOT obstruction and post-procedural MR

- Higher mid-term mortality with ViR and ViMAC due to adverse events and underlying mitral valve disease

- Higher incidence of valve thrombosis without anticoagulation

- Optimal patient selection and procedure refinement likely to improve the outcomes of TMVR

Sung-Han Yoon et al Eur Heart J 2018 (in press)
Transcatheter Mitral Valve approved for Early Feasibility Study in US

Transapical
- Tendyne (Abbott)
- Intrepid TMVI (Medtronic)
- Tiara (Neovasc)

Transfemoral
- CardiaQ (Edwards)
- Highlife M3 (Edwards)
- Caisson (LivaNova)
~480 patients treated worldwide
7 Early Feasibility Studies in US
3 Pivotal trials started or will start 2018
## Ongoing Pivotal Trials in TMVR Replacement

<table>
<thead>
<tr>
<th>Device</th>
<th>Comparator</th>
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<tbody>
<tr>
<td>Intrepid</td>
<td>Medtronic TMVR</td>
</tr>
<tr>
<td>Tendyne</td>
<td>Abbott TMVR</td>
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**INTREPID DIFFERENTIATED DUAL STENT DESIGN**

- **Conformable Outer Stent** engages the annulus providing fixation & sealing while isolating the inner stent from the dynamic anatomy.

- **Circular Inner Stent** houses a 27 mm tricuspid bovine pericardium valve ($EOA = 2.4cm^2$).

- Flexible Brim aids imaging during delivery.

- One valve size significantly reduces development & manufacturing complexity/cost.

- One implant platform regardless of delivery method, vessel diameter, or patient type.
Early Experience With New Transcatheter Mitral Valve Replacement

Vivek Y. Bavaria, MBBS, MD, FACC; Vivek Rajagopalan, MD; Christopher Meduri, MD, FACC; R. Saeed Farivar, MD; Antony Mokbel, MD; Stephen I. Duffy, MBB, MD, PhD; Robert Gooey, MBBS, PhD; Anthony Amols, MD; Michael J. Bollinger, MD; Neal S. Kleiman, MD; Konstantinos Spargias, MD; Stephen G. Pickard, MD; Martin R. Ng, MBBS, MD; Michael Wilson, MD; David A. Adams, MD; Martin Leon, MD; Michael J. Mack, MD; Sauria Chennuweth, MD; Paul Suna, MD; for the Intrepid Global Pilot Study Investigators

Central Illustration: Early Clinical Experience of TMVR with the New Valve Replacement

Figure 1: Survival During Follow-Up

One-year survival reported as % (95% confidence interval). TMVR = transcatheter mitral valve replacement.

30 DAYS ECHO
APOLLO

Principal Investigators: David Adams and Marty Leon
Study Chair: Michael Mack

Evaluate safety and efficacy of Medtronic Intrepid™ TMVR System in patients with symptomatic mitral regurgitation

Assessment by Multidisciplinary Heart Team

Ineligible for surgical procedure

1:1 Randomization

Single-arm Cohort

Treatment Arm TMVR
Control Arm MV surgery
TMVR
Tendyne TMVR – CE Mark Study

- Fully retrievable, repositionable device
- Predictable deployment, well tolerated hemodynamically
- No procedural deaths, strokes or urgent surgery

Encouraging 30-day clinical and echo results:
- Low mortality (6.0%, O:E 0.76), low adverse event rate
- Excellent control of MR (no/trace MR in 98.7%)
- Significant reduction in LV volumes
- Significant improvements in NYHA class, KCCQ score

- FDA-approved US pivotal trial (SUMMIT) expected to enrol first patient by Q3 2018
STS Database: TR is Surgically “ignored” in 2018

MR - 4,000,000
TR - 1,600,000

60,000

250,000

8,000

MR + TR
Annual New MR
Annual MR Surgeries
Annual TR Surgeries
Moderate to Severe TR affect Survival

![Graph showing survival rates with annotations](image)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>353</th>
<th>308</th>
<th>252</th>
<th>194</th>
<th>70</th>
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<tbody>
<tr>
<td>ERO &lt;40</td>
<td>285</td>
<td>253</td>
<td>210</td>
<td>163</td>
<td>46</td>
<td>23</td>
<td></td>
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<tr>
<td>ERO ≥40</td>
<td>68</td>
<td>55</td>
<td>42</td>
<td>31</td>
<td>24</td>
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Topilsky. JACC 2014
New tricuspid therapies
TRANSCATHETER TECHNOLOGIES

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<th>Mechanism</th>
<th>New Technologies</th>
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<tr>
<td>Annuloplasty (Direct and Indirect)</td>
<td>TriAlign, Cardioband, 4Tech, Millepode</td>
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<td>Leaflet Devices</td>
<td>Fossa, MitraxClp</td>
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<td>Stented Valves in IVC/SVC</td>
<td>Trinity/Sapien, NVT</td>
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<tr>
<td>Valve Replacement</td>
<td>Navigate</td>
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Transcatheter Tricuspid Therapy