Developments In TAVR

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Healthcare for what’s next.
NO DISCLOSURES

Healthcare for what’s next.
Transcatheter aortic valve replacement (TAVR) first performed in 2002 by Cribier. First prototype designed by Cribier and his start-up Percutaneous Valve Technologies.

Evolution of TAVR technology for the last 15 years has been unprecedented.

Randomized trials have demonstrated that TAVR versus SAVR:
- Lower Stroke
- Lower Mortality
- Lower rates of Atrial Fibrillation
- Quicker recovery, no scars
- Better hemodynamics
Aortic Valve Replacement

THE GENIE OUT OF THE BOTTLE
Risk Trends in Transcatheter Aortic Valve Therapy


Healthcare for what’s next.
Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients


Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients

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Endpoints

Primary Endpoint

- Non-hierarchical composite of all-cause mortality, all strokes, or CV re-hospitalization at 1 year
  - Primary analysis was non-inferiority, followed by superiority
  - Analysis cohort was the ‘as-treated’ (AT) population, defined as all randomized patients in whom the procedure was initiated.
  - Multiple sensitivity analyses performed

Study Endpoints

Primary Safety and Effectiveness Endpoint
All-cause mortality or disabling stroke at 2 years

Hierarchical Powered Secondary Endpoints

Noninferiority
- Mean gradient at 1 year
- EOA at 1 year
- Change in NYHA class from baseline to 1 year
- Change in KCCQ score from baseline to 1 year

Superiority
- Mean gradient at 1 year
- EOA at 1 year
- Change in KCCQ score from baseline to 30 days

Other Secondary Endpoints
- 30-day safety composite of
  - All-cause mortality
  - Disabling stroke
  - Life-threatening bleeding
  - Major vascular complications
  - Stage 2 or 3 acute kidney injury
- New pacemaker implantation at 30 days
- Heart failure rehospitalizations at 1 year
- Aortic-valve reintervention at 1 year
- Moderate/severe AR at 1 year
- All stroke at 1 year
- Life-threatening bleeding at 1 year

Healthcare for what’s next.
Primary Endpoint

**Primary Endpoint**

- **Surgery**
- **TAVR**

Upper 95% CI of risk diff = -2.5%

$P_{\text{non-inferiority}} < 0.001$

HR [95% CI] = 0.54 [0.37, 0.79]

$P_{\text{superiority}} = 0.001$

**K-M All-Cause Mortality or Disabling Stroke at 1 Year**

Log-rank $P = 0.065$

**Clinical Implications**

Death, Disabling Stroke and Heart Failure Hospitalizations to 1 Year

<table>
<thead>
<tr>
<th>Composite Rates</th>
<th>TAVR</th>
<th>SAVR</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6%</td>
<td>10.2%</td>
<td>4.6%</td>
<td></td>
</tr>
</tbody>
</table>

$P = 0.002$

- **3.1%** HF Hospitalization
- **2.3%** Death
- **3.1%** Disabling Stroke

**Estimated KM rates %**

- **TAVR**
  - 6.4%
  - 2.3%
- **SAVR**
  - 10.2%
  - 0.7%

Healthcare for what’s next.
All-Cause Mortality

HR [95% CI] = 0.41 [0.14, 1.17]  
P = 0.09

K-M Rates of All-Cause Mortality at 1 Year

Log-rank P = 0.412

Healthcare for what’s next.
Stroke

All Stroke

K-M Rates of All-Cause Mortality at 1 Year
Rehospitalization

Rehospitalization (%)

Number at risk:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at risk</th>
<th>Months from Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>454</td>
<td>0 496 416 399 389 385 382</td>
</tr>
<tr>
<td>TAVR</td>
<td>496</td>
<td>0 477 469 465 459 453</td>
</tr>
</tbody>
</table>

HR [95% CI] = 0.65 [0.42, 1.00]
P = 0.046

K-M Heart Failure Hospitalization at 1 Year

Heart Failure Hospitalization (%)

No. at risk:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>725</td>
<td>0 636 420</td>
</tr>
<tr>
<td>SAVR</td>
<td>712</td>
<td>1 649 358</td>
</tr>
</tbody>
</table>

Log-rank P = 0.006

1 Year

6.4

3.1

Healthcare for what’s next.
TAVR in low surgical risk using the Sapien 3 Valve:

- Significantly reduces the rate of death, stroke, or re-hospitalization at 1 year by 46%
- Secondary endpoints (adjusted) showed that TAVR reduced new-onset atrial fibrillation, index hospitalization days, and measure of poor treatment outcome (death or low KCCQ score at 30 days)
- Other secondary endpoint analysis showed reduced bleeding after TAVR and no difference in the need for new permanent pacemaker placement, major vascular complications, coronary obstruction, and moderate to severe perivalvular leak
- Some secondary endpoints favored surgery, including reduced LBBB, reduced mild PVR, and lower aortic gradients
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Concept of mitral commissurotomy proposed</td>
</tr>
<tr>
<td></td>
<td>Brunton</td>
</tr>
<tr>
<td>1920</td>
<td>1st successful Surgical Mitral Commissurotomy</td>
</tr>
<tr>
<td>1950-60</td>
<td>Transatrial and Transventricular Closed MV commissurotomy</td>
</tr>
<tr>
<td>1982</td>
<td>Inoue</td>
</tr>
<tr>
<td></td>
<td>Percutaneous Transvenous MV Commissurotomy (PTMC)</td>
</tr>
<tr>
<td>1994</td>
<td>PMBV Clinically approved in US</td>
</tr>
<tr>
<td>2014</td>
<td>FDA approval for Mitral Clip in High Risk Degenerative MR</td>
</tr>
<tr>
<td>2019</td>
<td>FDA approval for Mitral Clip in Functional MR</td>
</tr>
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</table>
6 Anatomical Parts of the Mitral Valve

- Leaflets
- Annulus
- Chordae
- Papillary Muscles
- Left Ventricle
- Left Atrium
<table>
<thead>
<tr>
<th>Intervention Mechanism</th>
<th>Abandoned</th>
<th>In Development and/or Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral Repair</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaflet Repair</td>
<td>Mobius Edwards</td>
<td>MitraClip (Degenerative &amp; Functional)</td>
</tr>
<tr>
<td>Indirect Annuloplasty</td>
<td>Monarch Edwards</td>
<td>PASCAL</td>
</tr>
<tr>
<td></td>
<td>PMTA Viacor</td>
<td>MitraFlex</td>
</tr>
<tr>
<td>Direct Annuloplasty</td>
<td>ReCor (US)</td>
<td>Arto-MVRx</td>
</tr>
<tr>
<td>Chordal Repair</td>
<td></td>
<td>Cardioband</td>
</tr>
<tr>
<td>Enhanced Coaptation</td>
<td>Myocor Coapsys</td>
<td>Millipede</td>
</tr>
<tr>
<td>LV Remodeling</td>
<td>Acorn</td>
<td>MitraSpan TASRA</td>
</tr>
<tr>
<td></td>
<td>Myocor</td>
<td>Micardia Encor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitral Bridge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QuantumCor (RF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harpoon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valtech Vchordal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MISTRAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitralis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MitraSpacer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle Peak</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MitrAssisst</td>
</tr>
<tr>
<td><strong>Mitral Replacement</strong></td>
<td></td>
<td>Sapien 3</td>
</tr>
<tr>
<td>Replacement</td>
<td></td>
<td>Cephea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tiara</td>
</tr>
</tbody>
</table>
EVEREST II TRIAL: 5 year Clinical Outcomes Clip vs. Surgery
COAPT
A Randomized Trial of Transcatheter Mitral Valve Leaflet Approximation in Patients with Heart Failure and Secondary Mitral Regurgitation
Primary Safety Endpoint
Freedom from Device-related Complications within 12 months

96.6%*
94.8% [95% LCL]
88% OPC

P<0.001

MitraClip procedure attempted  N=293

<table>
<thead>
<tr>
<th>Device-related complications</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Single leaflet device attachment</td>
<td>2</td>
</tr>
<tr>
<td>- Device embolization</td>
<td>1</td>
</tr>
<tr>
<td>- Endocarditis requiring surgery</td>
<td>0</td>
</tr>
<tr>
<td>- Mitral stenosis requiring surgery</td>
<td>0</td>
</tr>
<tr>
<td>- Left ventricular assist device implant</td>
<td>3</td>
</tr>
<tr>
<td>- Heart transplant</td>
<td>2</td>
</tr>
<tr>
<td>- Any device-related complication requiring non-elective CV surgery</td>
<td>1</td>
</tr>
</tbody>
</table>

*KM estimate; **Calculated from Z test with Greenwood’s method of estimated variance against a pre-specified objective performance goal of 88%
Primary Effectiveness Endpoint
All Hospitalizations for HF within 24 months

- **MitraClip + GDMT**: 283 in 151 pts
- **GDMT alone**: 160 in 92 pts

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

Cumulative HF Hospitalizations (n)

<table>
<thead>
<tr>
<th>Time After Randomization (Months)</th>
<th>MitraClip</th>
<th>GDMT</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>269</td>
<td>271</td>
</tr>
<tr>
<td>6</td>
<td>253</td>
<td>245</td>
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<tr>
<td>9</td>
<td>236</td>
<td>219</td>
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<td>12</td>
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<td>15</td>
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<tr>
<td>18</td>
<td>161</td>
<td>121</td>
</tr>
<tr>
<td>21</td>
<td>124</td>
<td>88</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk:
- MitraClip: 302
- GDMT: 312

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

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
Chordal repair

Harpoon

Incision
Indirect Annuloplasty
Direct Annuloplasty
Mitral Valve Replacement

Braile Biomedica  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  Caisson  Others: MitraHeal, Mitrassist, Mitraltech, Mehr Medical, Mitracath, Mitralix MAESTRO, Nakostech, St. George ATLAS, Transcatheter Technologies Tresilo
Sapien M-3