The Future of Transcatheter Mitral Valve Repair and Replacement

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## Disclosure Statement of Financial Interest

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

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>Consultant or equity</td>
<td>Neovasc, Ancora, Valfix, Gore</td>
</tr>
<tr>
<td>Institutional conflict</td>
<td>Columbia University, receives royalties for sale of the MitraClip</td>
</tr>
</tbody>
</table>
Updated US and EU Valve and HF Guidelines

Treatment of Chronic Symptomatic MR

Severe Mitral Regurgitation

Primary (degenerative) MR
  -
  Class I
  Class IIb*

Secondary (functional) MR

Medical Rx and CRT
  Class I

MV surgery (w/o CABG)
  Class IIb

Transcatheter MV repair
  Class IIb**

*In non-operative candidates
**In the US and EU HF guidelines and the EU Valve guidelines but not the US Valve guidelines

2017 ESC/EACTS Valve; 2017 ACC/AHA/HFSA HF; 2017 ACC/AHA Valve
EVEREST II Randomized Clinical Trial

279 patients enrolled at 37 sites
Severe MR (3+ or 4+)
73% DMR, 27% FMR
Specific anatomical criteria
Randomized 2:1

Device Group
MitraClip System
N=184

Control Group
Surgical Repair or Replacement
N=95

Echocardiography Core Lab and Clinical Follow
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

Feldman T et al. NEJM 2011;364:1395-406
EVEREST II: 279 pts with 3+/4+ MR randomized 2:1 to MitraClip vs. Surgical Repair
Primary Endpoints (per protocol cohort)

Safety†
Major Adverse Events
30 days

- Device Group, n=136: 9.6% (P_sup <0.0001)
- Control Group, n=79: 57.0%

Effectiveness‡
Clinical Success Rate
12 months

- Device Group, n=134: 72.4% (p_NI =0.001, P_sup =0.046)
- Control Group, n=74: 87.8%

† Death, major stroke, reoperation of MV, urgent/emergent CV surgery, MI, renal failure, deep wound infection, sepsis, ventilation >48 hrs, new permanent AF, GI complication requiring surgery, transfusion ≥2U

‡ Freedom from death, MV surgery or reoperation for MV dysfunction, or MR >2+ at 12 months

Feldman T et al. NEJM 2011;364:1395-406
**EVEREST II:** Primary EP at 1 and 5 Years - DMR (73%) vs. FMR (27%) -
(Freedom from Death, MV Surgery, or 3+ or 4+ MR): ITT

<table>
<thead>
<tr>
<th>Etiology</th>
<th>MitraClip</th>
<th>Surgery</th>
<th>Difference between MitraClip and Surgery (%)</th>
<th>P value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Functional</td>
<td>26/48 (54.2%)</td>
<td>12/24 (50.0%)</td>
<td>-2.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative</td>
<td>74/133 (55.6%)</td>
<td>53/65 (81.5%)</td>
<td></td>
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<tr>
<td>5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td>17/42 (40.5%)</td>
<td>4/14 (28.6%)</td>
<td>1.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative</td>
<td>51/112 (45.5%)</td>
<td>32/42 (76.2%)</td>
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</table>

Surgery better MitraClip better
The MitraClip is approved for treatment of patients with 3+-4+ primary (degenerative) MR who are at “prohibitive risk” for mitral valve surgery and are likely to benefit from MR reduction.
MitraClip Therapy
STS/ACC TVT Registry

2,952 patients
Median age: 82 years
STS-PROM (MVR): 9.2%
Etiology: DMR 85.9%
Mixed 8.8%, FMR 8.6%
Median LVEF: 55%
MAC: 36.7%
TR: Severe 16.0%, moderate 34.9%
Procedure success: 91.8%
In-hosp death: 2.7%

MitraClip Therapy
Global Use, November 2018

Centers >800
Patients >75,000
Implant rate 97%
Functional MR 64%
Degenerative MR 22%
mixed 14%

Data source: Abbott Vascular
Prognostic Utility of FMR
Prospective study of 576 pts with HFrEF; 47% died during median 5-year FU; severe FMR in 21%, mod FMR in 32%

Severe FMR was an independent predictor of long-term mortality after MV adjustment for clinical variables

HR [95%CI] = 1.61 [1.22, 2.12], $P=0.001$, and after MV adjustment for clinical, echo, biomarker and medication variables

HR [95%CI] = 1.38 [1.03, 1.84], $P=0.03$

The MITRA-FR Trial

304 pts with SMR due to LV dysfunction with LVEF 15-40%, NYHA II-IV, HF hospitalization within the prior 12 months

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

**MITRA-FR: 12-Month Outcomes**

**Primary endpoint:** Freedom from death or HF hospitalizations

### Graph
- **Freedom from Death or HF Hospitalization**
  - **Months:** 0, 2, 4, 6, 8, 10, 12
  - **Lines:** MitraClip + medical therapy, Medical therapy

### Table

<table>
<thead>
<tr>
<th>Event</th>
<th>MitraClip + MT</th>
<th>MT alone</th>
<th>OR [95% CI] or HR [95% CI]*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° EP:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Death or HF hosp</td>
<td>54.6%</td>
<td>51.3%</td>
<td>1.16 [0.73–1.84]</td>
<td>0.53</td>
</tr>
<tr>
<td>Death</td>
<td>24.3%</td>
<td>22.4%</td>
<td>1.11 [0.69–1.77]*</td>
<td>0.65</td>
</tr>
<tr>
<td>CV death</td>
<td>21.7%</td>
<td>20.4%</td>
<td>1.09 [0.67–1.78]*</td>
<td>0.74</td>
</tr>
<tr>
<td>HF hosp</td>
<td>48.7%</td>
<td>47.4%</td>
<td>1.13 [0.81–1.56]*</td>
<td>0.59</td>
</tr>
<tr>
<td>MACE*</td>
<td>56.6%</td>
<td>51.3%</td>
<td>1.22 [0.89–1.66]*</td>
<td>–</td>
</tr>
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</table>

* MACE = Death, MI, CVA, HF hosp

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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 (US ASE criteria) who remained symptomatic despite maximally-tolerated GDMT and CRT if appropriate

Randomize 1:1*

MitraClip + GDMT
N=302

GDMT alone
N=312

Primary endpoint
All HF hospitalizations through 24 months

All HF Hospitalizations
Primary Effectiveness

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]

### Why are the COAPT Results so Different from MITRA-FR? Possible Reasons

<table>
<thead>
<tr>
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<th>MITRA-FR (n=304)</th>
<th>COAPT (n=614)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe MR entry criteria</strong></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 or PSVFR or other</td>
</tr>
<tr>
<td><strong>EROA (mean ± SD)</strong></td>
<td>31 ± 10 mm(^2)</td>
<td>41 ± 15 mm(^2)</td>
</tr>
<tr>
<td><strong>LVEDV (mean ± SD)</strong></td>
<td>135 ± 35 mL/m(^2)</td>
<td>101 ± 34 mL/m(^2)</td>
</tr>
<tr>
<td><strong>GDFT at baseline and FU</strong></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><strong>Acute results: No clip / ≥3+ MR</strong></td>
<td>9% / 9%</td>
<td>5% / 5%</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td>14.6%</td>
<td>8.5%</td>
</tr>
<tr>
<td><strong>12-mo MitraClip &lt;3+ MR</strong></td>
<td>83%</td>
<td>95%</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
March 14th, 2019

FDA approves MitraClip for treatment of select patients with severe secondary MR who remain symptomatic despite GDMT.
## Transcatheter MV Repair: Device Landscape 2019

### Edge-to-edge
- Abbott MitraClip***
- Edwards Pascal*
- MitraFlex

### Direct and indirect annuloplasty
- CDI Carillon**
- Mitralign TAMR**
- Edwards Cardioband**
- Ancora Heart Accucinch*
- Millipede IRIS*
- MVRx Arto*
- Mardil VenTouch*
- Mitraspan TASRA*
- Valcare Amend*
- Micardia enCor*
- MitraLoop Cerclage*
- Cardiac Implants RDS*
- QuantumCor (RF)
- Valfix

### MV replacement
- Edwards CardiAQ*
- Edwards Sapien M3*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
- HighLife*
- Caisson*
- NCSI NaviGate*
- MValve*
- CardioValve*
- Cephea*
- St. Jude
- Micro Interventional
  - ValveXchange
  - MitrAssist
  - Braile Quattuor
  - Direct Flow
  - Sinomed Accufit
  - Valcare Corona
  - Epigen

### MV replacement (cont)
- MitralHeal
- HT Consultant Saturn
- Lutter valve
- Transcatheter Technologies
  - Tresillo
  - Venus
  - Verso
- Transmural Systems
- Saturn (InnovaHeart)
- 4C Altara
- Other approaches
  - NeoChord DS 1000**
  - Harpoon neochords*
  - Babic chords*
  - Pipeline Medical (Gore)
  - Middle Peak Medical*
  - St. Jude leaflet plication*
  - Cardiosolutions Mitra-Spacer*
  - Mitralix*
  - Mitraltech Vchordal
  - Coramaze Mitramaze

*In patients  *CE mark  *FDA approved
Implications of COAPT for New Devices to Treat Secondary MR in Heart Failure

For MV repair technologies

• Will they be as safe as the MitraClip?
• Will they be as effective as the MitraClip?
• Will they be as durable as the MitraClip?
• Will they be able to treat the same or different pts? E.g. MAC, wide/multiple jets, extreme tethering, small annulus
• Will they be able to treat MitraClip failures or recurrences (or will the MitraClip be able to treat their failures or recurrences)?

For MV replacement technologies

• Given the likelihood of greater procedural complications and the need to anticoagulate, they must be shown to be more effective than the MitraClip, or able to treat MitraClip ineligible pts
PASCAL
PAddles,Spacer,Clasps,ALfieri

- Spacer placed between both MV leaflets
- Independent leaflet clasping
- Longer and wider paddles for better leaflet capture
- Minimal dependence on septal puncture height
- Simple “Commander-like” delivery system
- Transfemoral/transseptal approach
CLASP IID
Edwards PASCAL TrAnScatheter Mitral Valve RePair System
Pivotal Clinical Trial

675 pts with 3+ or 4+ degenerative MR at prohibitive risk for mitral valve surgery by local heart team assessment

Primary safety endpoint: Major adverse events at 30 days (powered for noninferiority)

Primary effectiveness endpoint: MR severity at 6 months (powered for noninferiority)

PIs: J. Popma, J. Bavaria, W. Abraham
# Novel MV Repair Devices with Ongoing US Pivotal Randomized Trials

<table>
<thead>
<tr>
<th>Mechanism and study population</th>
<th>Cardiac Dimensions Carillon</th>
<th>Edwards Cardioband</th>
<th>NeoChord DS1000</th>
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<tr>
<td>Coronary sinus mediated posterior annulus cinching for FMR</td>
<td>LA semi-rigid posterior partial annuloplasty band with anchor cinching for FMR</td>
<td>Transapical PTFE neochords for DMR</td>
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## Novel MV Repair Devices with Ongoing US Pivotal Randomized Trials

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<td><strong>Trial acronym</strong></td>
<td>CARILLON NCT03142152</td>
<td>ACTIVE NCT03016975</td>
</tr>
<tr>
<td><strong>N rand</strong></td>
<td>N=400; FMR 2:1 vs. GDMT</td>
<td>N=375; FMR 2:1 vs. GDMT</td>
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| **Primary endpoints** | 1-year efficacy: Requires superiority of both a) hierarchical composite endpoint of death, HF hospitalization, and improvement in 6MWD; b) change in regurgitant vol | 1-year efficacy: Prevalence of MR ≤2+ and superiority in the hierarchical composite endpoint of CV death, HF hospitalization, and improvement in 6MWD and KCCQ (Win ratio) | Safety at 30 days: Major Adverse Events (superiority)  
Efficacy at 1 year: Grade II, III or IV MR, MV replacement or MV reintervention (noninferiority) |
12 Transcatheter MVR Systems in Human Use

Abbott Tendyne
Medtronic Intrepid
Edwards CardiAQ
Neovasc Tiara
HighLife
Edwards Sapien M3
Caisson
NaviGate
Cardiovalve
Abbott Cephea
4C AltaValve
Edwards Fortis
More than 60 transcatheter devices have been developed to address the multi-dimensional disease state of MR

One device (MitraClip) is firmly established and is in widespread use in the US and EU; 4 others have CE mark in EU; most have been used in small numbers of patients or are still in pre-clinical testing; and more than a handful have failed.
The COAPT trial has demonstrated that the MitraClip improves prognosis in selected pts with HF and secondary MR who remain symptomatic despite maximally-tolerated GDMT – a paradigm shift for HF Rx

- Annuloplasty devices, neochords, TMVR and other novel approaches offer great potential to expand treatment options for pts with severe primary and secondary MR - studies are ongoing!

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<th>TMV Repair and Replacement: 2019 Status Update (ii)</th>
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