Outcomes and Indications of Transcatheter Mitral Valve Therapies

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Disclosures

- Proctoring activities for Abbott Vascular, Edwards Lifesciences

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- ABBOTT Vascular, Europe, Edwards Lifesciences, Medtronic

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Radiologists: F Laspas, C Mourmouris
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Challenges of the Mitral Valve

- Asymmetric shape
- Saddle shape, not flat
- Dynamic changes during systole
- High pressure closure valve
- Multiple chords / subV apparatus
- Proximity to LV outflow tract
- Easier to form thrombus
- Annulus much larger than aortic
- Annulus changes with disease process
- Role not only hemodynamic, but also structural
- Mitral regurgitation, not a single disease
Degenerative Mitral Regurgitation
Functional Mitral Regurgitation
Mechanisms of Mitral Regurgitation

Pathophysiologic Triad
- Disease causing MR
- Lesions
- Valve dysfunction

- Mitral regurgitation with normal leaflet motion
  - e.g. perforated leaflet, annular calcification or annular dilatation (I)

- Excessive valve motion
  - e.g. flail leaflet from rupture chordae or myxomatous degeneration (II)

- Restricted valve motion (III)
  - In Diastole e.g. rheumatic (IIIa)
  - In Systole e.g. ischemic (IIIb)
## Transcatheter MV Repair: Device Landscape 2017

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

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

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

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

*In patients • CE mark • FDA approved
Classification of Technologies for MV Repair and Replacement

Classification according to:
  Site of action
  Device mechanism

- **Leaflets**
  - (leaflet plication / edge to edge repair) e.g. MitraClip, PASCAL
- **Annuloplasty**
  - Indirect / coronary sinus approach (e.g. Carillon device)
  - Direct (percutaneous and hybrid approaches, e.g CardioBand, Mitralign)
- Percutaneous **chords** (for degenerative MR, e.g. Neochords, Harpoon)
- LV remodeling

- Mitral Valve **Replacement**
Repair vs. Replacement

<table>
<thead>
<tr>
<th>TVMI</th>
<th>TMVRep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>More natural haemodynamics</td>
</tr>
<tr>
<td>Simplicity</td>
<td>No need for long-term anti-coagulation</td>
</tr>
<tr>
<td>Versatility</td>
<td>Favourable safety profile</td>
</tr>
<tr>
<td>Predictable results</td>
<td></td>
</tr>
<tr>
<td>Challenges</td>
<td></td>
</tr>
<tr>
<td>Dynamic mitral structure</td>
<td>Need for advanced imaging</td>
</tr>
<tr>
<td>Asymmetric anatomy</td>
<td>Variability of disease/need for multiple devices</td>
</tr>
<tr>
<td>Deliverability (profile, rigidity)</td>
<td>Possible need for combined therapies</td>
</tr>
<tr>
<td>Fixation (not relying on radial force)</td>
<td>Steeper learning curve</td>
</tr>
<tr>
<td>Need for chronic oral anti-coagulation (?)</td>
<td>Residual/recurrent regurgitation</td>
</tr>
<tr>
<td>Risk of LVOT, CS, and LCX obstruction</td>
<td></td>
</tr>
<tr>
<td>Risk of <em>para</em>-valvular leak</td>
<td></td>
</tr>
</tbody>
</table>
Transcatheter Repair
Benefits / Problems

• Safer than replacement
• Less invasive, mostly transfemoral / transvenous
• Patient preference
• Prohibitive surgical risk patients treatable
• Robust effectiveness data for functional MR patients (COAPT trial)

• Less predictable acute results
• Difficult to combine repair techniques at present
• Long term durability may be inferior to replacement
• May limit future options for repair or replacement
Transcatheter Replacement
Benefits / Problems

• More predictable immediate result
• Intermediate durability better, less need for repeat procedures
• One shot deployment, “easier” to perform
• Devices similar to surgical leaflet technologies

• More invasive, mainly transapical
• Procedural risk higher, many patients screening failure
• Thrombosis is an issue and requires longer term anticoagulation
• Long term durability likely similar to surgical → Valve in valve?
The Prototype of Mitral Valve Repair: The MitraClip Device

• Implant made of cobalt chromium
• Polyester-covered to promote healing
• MRI Safe to 3 Tesla
• Real-time positioning during procedure
• Surgically removable when required
MitraClip NT: Next generation device

- Active nitinol grippers with 120° opening
- Redesigned delivery system and handle (single operator device)
  - Enhanced steerability
  - Less sleeve shortening
- Less need of M Knob rotation resulting in less tension
- Facilitated delivery system removal in case clip not implanted
Third-Generation MitraClip Systems

- Original MC size
- Improved delivery system

- Longer clip arms (+3mm)
- Longer grippers (2 additional rows of frictional elements)
- Improved delivery system
<table>
<thead>
<tr>
<th>Product Change</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery Catheter Improvements</td>
<td>Improved Clip Positioning &amp; Shaft Straightness</td>
</tr>
<tr>
<td>Lock Line Improvements</td>
<td>Improved Usability with Clip Unlocked</td>
</tr>
<tr>
<td>Longer Clip Arms (XTR)</td>
<td>Improved Ease of Leaflet Grasping</td>
</tr>
<tr>
<td>New CDS Packaging and Branding</td>
<td>Clear product differentiation on packaging and CDS</td>
</tr>
</tbody>
</table>

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MITRALCLIP NTR / MITRALCLIP XTR
DELIVERY CATHETER IMPROVEMENTS

Delivery Catheter Improvements: Multi-lumen extrusion with reinforced braid and Pebax jacket.
– Provides more predictable Clip positioning in Left Atrium and Left Ventricle.
– Potential for less rotation of Clip Arms and straighter advancement into Left Ventricle
– Optimized bending stiffness to enable “Always Unlocked Clip”
– Modified Handle Coupler length to increase Delivery Catheter Shaft extension out of sleeve by ~1.5cm

Precise and Predictable Clip Positioning
**Lock Line improvements**: Line design is a Braided polyester core and ultra-high molecular weight polyethylene sheath.

- Increased lock line strength to allow “Always Unlocked Clip”.
- Improved Usability with Clip Unlocked during Clip positioning, advancement and Grasping.
MITRACLIP NTR / MITRACLIP XTR
CLIP ARMS OVERVIEW

NTR

XTR

Clip Length

15 mm

18 mm

Coaptation Length

9 mm

12 mm

Clip Arms at 120 degrees

17 mm

22 mm

Improved Ease of Leaflet Grasping

MitraClip XTR Clip: 3mm longer Clip Arms & Grippers

– Increased leaflet coaptation length

– Grippers with 6 rows of frictional elements with spacing identical to MitraClip NT

– Longer Clip and Gripper covers to support longer Clip Arms

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MitraClip Timeline

October 2011

- **2003**: First Implant
- **2004**: EVEREST I (Feasibility Study) (55 Patients Enrolled)
- **2005**: High Risk Study (78 Patients Enrolled)
- **2006**: ACCESS Europe (Commercial Registry) (567 Commercial Patients Enrolled)
- **2007**: EVEREST II (Randomized Controlled Trial) (279 Patients Enrolled)
- **2008**: CE Mark
- **2009**: REALISM (Continued Access) (899 Patients Enrolled)
- **2011**: COAPT (Currently Enrolling)
- **2013**: Available in U.S.
- **2016**: MitraClip® NT Launch
EVEREST II: 5-year results

MR Grade

NYHA Class
MitraClip in Greece

N=202 cases

Data up to April 30th 2018
MitraClip in Greece

Data up to April 30th 2018
Advantages of the MitraClip

• Transvenous procedure
  – Low risk of vascular complications
  – Low stroke risk

• Repositionable – Removable

• Echocardiographic guided procedure
  – Low risk of arrhythmias
  – Low risk of cardiac perforation
MitraClip in a patient with Functional MR

- 77 year-old male with severe ischemic MR, NYHA IV dyspnea, considered inoperable
MitraClip in a patient with Degenerative MR

- 81 year-old male with severe degenerative MR, NYHA III dyspnea, prior CABG, considered inoperable
MitraClip Acute Hemodynamic Effects
Organic / Primary Mitral Regurgitation
Degenerative / Primary Mitral Regurgitation: Guidelines for MitraClip

Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with **chronic severe primary MR** (stage D) who have favorable anatomy for the repair procedure and a reasonable **life expectancy** but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal GDMT for HF (Level of Evidence: B)
EVEREST II: 5-year results

MR Grade

NYHA Class
MitraClip in an Octogenarian with DMR

- 83 year-old female
- NYHA-III dyspnea, despite optimal HF therapy
- EF 65%
- MR 4+ due to P2 prolapse (fibroelastic deficiency, ruptured chord)
- Pulmonary HTN (sPAP 80 mmHg)
- Chronic Atrial Fibrillation
- STS risk 3.3% Intermediate risk patient
Safety of MV Surgery in Octogenarians

24 studies- 5,572 Patients
Operative mortality 15.0%; stroke 3.9%; dialysis 2.7%

Univariable predictors of operative mortality
- Early date of study (p=0.01)
- Increased age (p=0.006)
- MV replacement vs repair (p=0.008)
- Procedure other than isolated MV surgery (p=0.01)
- CABG + MV surgery (p=0.03)
- Aortic cross-clamping time (p<0.001)
- Cardiopulmonary bypass time (p<0.001)

Multivariable predictors of operative mortality
- Aortic cross-clamping time (p=0.005)

Survival at 1, 3, and 5 years = 76.1%, 67.7%, and 56.5%
Isolated Mitral Valve Surgery Patient Risk

STS Database

N=77,836

Chatterjee S. Ann Thorac Surg 2013: 96;1587-95
MitraClip Systematic Review

MitraClip vs Surgery 30 Day Outcomes
High Risk Patients

- **Death**: MitraClip 3.3, Surgery 15.2
- **Stroke**: MitraClip 1.1, Surgery 4.5
- **Bleeding**: MitraClip 4.2, Surgery 59
- **Prolonged Vent**: MitraClip 1.7, Surgery 36.3
- **ICU Days**: MitraClip 3, Surgery 15
- **Hospital Days**: MitraClip 7, Surgery 26

21 studies

*Phillip et al, Cathet Cardiovasc Intervent 84:581, 2014*
X-Plane with Color Flow Doppler
Double Orifice Mitral Valve post Mitra Clip Deployment
MitraClip in a patient with degenerative MR treated with 1 MitraClip:
5 years later

Clinically doing well, ambulatory, no heart failure readmissions, mainly geriatric issues
STS/ACC TVT Registry
Transcatheter Mitral Valve Repair

- Collaboration of STS, ACC, CMS, medical industry
- Patient-level data housed at DCRI
- Participation satisfies NCD
MitraClip in Degenerative Mitral Regurgitation: The US Experience - Outcomes

Leaflet Clip – Procedure Details

<table>
<thead>
<tr>
<th>Count of Leaflet Clips (used during the procedure)</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Leaflet Clip</td>
<td>51.8%</td>
<td>54.3%</td>
</tr>
<tr>
<td>2 Leaflet Clips</td>
<td>39.8%</td>
<td>38.4%</td>
</tr>
<tr>
<td>&gt;=3 Leaflet Clips</td>
<td>7.0%</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

Leaflet Clip Procedures

<table>
<thead>
<tr>
<th></th>
<th>At discharge</th>
<th>2014 (n=1,023)</th>
<th>2015 (n=3,362)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral Regurgitation (&lt;=2+)</td>
<td>92.0%</td>
<td>92.0%</td>
<td></td>
</tr>
<tr>
<td>MV Mean Gradient &lt;=8 mmHg</td>
<td>92.3%</td>
<td>93.8%</td>
<td></td>
</tr>
<tr>
<td>Single Leaflet Device Attachment</td>
<td>1.2%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>MV Re-intervention</td>
<td>0.4%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>ASD requiring closure</td>
<td>1.6%</td>
<td>1.6%</td>
<td></td>
</tr>
</tbody>
</table>

Source: STS/ACC TVT Registry Data Mart 3,362 pt records from 2014-15, as of 4-24-16
MitraClip in Degenerative Mitral Regurgitation: The US Experience - Outcomes

Leaflet Clip Procedures

<table>
<thead>
<tr>
<th></th>
<th>2014 (n=1,023)</th>
<th>2015 (n=3,362)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of Stay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total LOS (mean/median)</td>
<td>5.3/3 days</td>
<td>5.1/2 days</td>
</tr>
<tr>
<td>Post procedure LOS (mean/median)</td>
<td>3.7/2 days</td>
<td>3.5/2 days</td>
</tr>
<tr>
<td><strong>Discharge Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>84.2%</td>
<td>87.0%</td>
</tr>
<tr>
<td>Extended care facility</td>
<td>10.4%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

Source: STS/ACC TVT Registry Data Mart 3,362 pt records from 2014-15, as of 4-24-16

Mortality

Source: STS/ACC TVT Registry Database 3,657 pt records from 2014-15, as of 10-12-16.
30 day endpoint among records with 30 day follow-up status not missing.
Outcomes With Transcatheter Mitral Valve Repair in the United States

An STS/ACC TVT Registry Report

Paul Sorajja, MD,a Sreekanth Vermulapalli, MD,b Ted Feldman, MD,c Michael Mack, MD,d David R. Holmes, Jr, MD,e Amanda Stebbins, MS,b Saibal Kar, MD,f Vinod Thourani, MD,f Gorav Ailawadi, MDf

- N=2,952 patients, DMR in 86%
  - 11/2013-9/2015
- Median age 82 years
- STS-PROM (MVR) 9.2%

J Am Coll Cardiol 2017;70:2315–27
Echocardiographic Data

- Degenerative MR 85.9%
- LVEF ≥50% in 64.6%
- LVESD ≥40mm in 32%
- Mitral annular Ca⁺² in 36.7%
- Mean MV gradient ≥5mmHg in 9.2%
- MV area <4.0cm² in 20.5%
- Moderate TR 34.9% / Severe TR 16%
Clinical Outcomes during Index Admission
STS/ACC TVT Registry

• In-hospital mortality 2.7%
• Procedural success 91.8%
• Single Leaflet Device Attachment 1.5%
• Length-of-stay 2 days
• Discharge home 85.9%

J Am Coll Cardiol 2017;70:2315–27
Clinical Outcomes at 1-year post MV-repair

- Either 37.9%
- Death 25.9%
- HF re-hospitalization 20.2%
- Repeat MitraClip 6.2%
- MV surgery 2.1%

No. at risk
Death/HF hosp. 1867 1095 723 464 263
Death 1867 1293 889 570 336
HF hosp. 1867 1095 723 464 263

J Am Coll Cardiol 2017;70:2315–27
Clinical Outcomes According to MR type

A

Cumulative incidence of Mortality

Follow-Up (Months)

0 2 4 6 8 10 12

50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%

No. at risk

FMR 297 196 123 73 40
DMR 1485 1024 726 472 287

p = 0.02

B

Cumulative incidence of Heart Failure

Re-Hospitalization

Follow-Up (Months)

0 2 4 6 8 10 12

50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%

No. at risk

FMR 297 166 93 55 23
DMR 1485 884 609 397 228

p = 0.008

J Am Coll Cardiol 2017;70:2315–27
Post-procedural Mitral Regurgitation and Clinical Events

A

![Cumulative Incidence of Mortality](#)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Follow-Up (Months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ III</td>
<td>0</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>47</td>
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<tr>
<td></td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>= II</td>
<td>0</td>
<td>591</td>
</tr>
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<td></td>
<td>2</td>
<td>408</td>
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<tr>
<td></td>
<td>4</td>
<td>278</td>
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<tr>
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<td>6</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>104</td>
</tr>
<tr>
<td>≤ I</td>
<td>0</td>
<td>1146</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td>373</td>
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<tr>
<td></td>
<td>8</td>
<td>213</td>
</tr>
</tbody>
</table>

B

![Cumulative Incidence of Death or HF Re-Hospitalization](#)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Follow-Up (Months)</th>
<th>No. at risk</th>
</tr>
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<tbody>
<tr>
<td>≥ III</td>
<td>0</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>55</td>
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<td>4</td>
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<td>24</td>
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<td></td>
<td>8</td>
<td>16</td>
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<tr>
<td>= II</td>
<td>0</td>
<td>591</td>
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<td>336</td>
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<td>4</td>
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<tr>
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<td>696</td>
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<td></td>
<td>4</td>
<td>451</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>292</td>
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<tr>
<td></td>
<td>8</td>
<td>159</td>
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</table>
Severity of Tricuspid Regurgitation and Clinical Events

![Graph showing cumulative incidence of mortality over follow-up months for different severity levels of tricuspid regurgitation (TR)].

- **Severe TR**: Cumulative incidence increases significantly over follow-up months.
- **Moderate TR**: Cumulative incidence shows moderate increase over follow-up months.
- **Mild or no TR**: Cumulative incidence shows the least increase over follow-up months.

**Statistical Significance**: $p < 0.0001$

**Table of No. at Risk**:

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<thead>
<tr>
<th>Severity</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
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<tbody>
<tr>
<td>Severe</td>
<td>298</td>
<td>198</td>
<td>141</td>
<td>83</td>
<td>47</td>
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<td></td>
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<tr>
<td>Moderate</td>
<td>666</td>
<td>451</td>
<td>307</td>
<td>203</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/none</td>
<td>883</td>
<td>631</td>
<td>431</td>
<td>277</td>
<td>153</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*J Am Coll Cardiol 2017;70:2315–27*
Multivariate Predictors of 1-year Outcomes

- Age
- End-stage kidney disease on dialysis
- Lung disease (moderate or severe)
- Tricuspid regurgitation (severe)
- Ejection fraction
- Functional mitral regurgitation
- Residual 3+/4+ mitral regurgitation
## MitraClip Registries

### U.S. vs. Other Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Age (yrs)</th>
<th>DMR*</th>
<th>MR ≤2</th>
<th>In-hospital death</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS/ACC TVT (US)</td>
<td>80</td>
<td>79.7%</td>
<td>92%</td>
<td>2.4%</td>
</tr>
<tr>
<td>SENTINEL (EU)</td>
<td>74</td>
<td>28%</td>
<td>95%</td>
<td>2.9%</td>
</tr>
<tr>
<td>ACCESS (EU)</td>
<td>74</td>
<td>23%</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>TRAMI (DE)</td>
<td>74</td>
<td>29%</td>
<td>95%</td>
<td>2.9%</td>
</tr>
<tr>
<td>MitraSwiss (CH)</td>
<td>75</td>
<td>38%</td>
<td>85%</td>
<td>4.0%</td>
</tr>
<tr>
<td>France (FR)</td>
<td>77</td>
<td>23%</td>
<td>88%</td>
<td>3.3%</td>
</tr>
<tr>
<td>GRASP (IT)</td>
<td>73</td>
<td>24%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Netherlands (NL)</td>
<td>72</td>
<td>18%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>MARS (Asia)</td>
<td></td>
<td>46%</td>
<td>94%</td>
<td>4.2%</td>
</tr>
<tr>
<td>EVEREST I</td>
<td>71</td>
<td>79%</td>
<td>74%</td>
<td>0.9%</td>
</tr>
<tr>
<td>EVEREST II RCT</td>
<td>67</td>
<td>51%</td>
<td>77%</td>
<td>1.1%</td>
</tr>
<tr>
<td>EVEREST II HRS</td>
<td>76</td>
<td>30%</td>
<td>85%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

*The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR = 3+) due to primary abnormality of the mitral apparatus [regenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.*

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ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC
Indications for mitral valve intervention in chronic secondary mitral regurgitation (continued)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF &gt;30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>In patients with severe secondary mitral regurgitation and LVEF &lt;30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider percutaneous edge-to-edge procedure or valve surgery after careful evaluation for ventricular assist device or heart transplant according to individual patient characteristics.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Heart Failure Patient with Significant Ischemic MR

- 56 year old male
- NYHA III-IV dyspnea
- 11/2016 AMI, primary PCI in LCx
- Staged LAD PCI with multiple stents
- Gradually developing SOB symptoms together with MR (initially mild)
- ECHO MR 4/4, ERO 50mm², RV 66ml, LVEF 30-35%, PAP 60mmHg
- Paroxysmal AF, TIAs (most recent 3m ago)
- HEART TEAM decision: MitraClip
TEE X-plane
MitraClip: alignment
2 Clip bridge
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
Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50% and LVESD ≤70 mm

2. Moderate-to-severe (3+) or severe (4+) secondary MR confirmed by an independent echo core laboratory prior to enrollment (US ASE criteria)

3. NYHA functional class II-IVa (ambulatory) despite a stable maximally-tolerated GDMT regimen and CRT (if appropriate) per societal guidelines

4. Pt has had at least one HF hospitalization within 12 months and/or a BNP ≥300 pg/ml* or a NT-proBNP ≥1500 pg/ml*

5. Not appropriate for mitral valve surgery by local heart team assessment

6. IC believes secondary MR can be successfully treated by the MitraClip

Adjusted by a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m² in BMI >20 kg/m²
### Primary Endpoints

**Primary effectiveness endpoint:** All HF hospitalizations through 24 months*

Powered for superiority of the Device group compared with the Control group

**Primary safety endpoint:** Freedom at 12 mos from device-related complications:

- Single leaflet device attachment
- Device embolization
- Endocarditis requiring surgery
- Echo core laboratory-confirmed mitral stenosis requiring surgery
- Left ventricular assist device implant
- Heart transplant
- Any device-related complication requiring non-elective cardiovascular surgery

Powered for superiority of the Device group vs. a pre-specified OPG**

---

*Analyzed when the last subject completes 12 months of follow-up; **Objective performance goal
## Baseline Characteristics (i)

<table>
<thead>
<tr>
<th></th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.7 ± 11.8</td>
<td>72.8 ± 10.5</td>
<td>27.0 ± 5.8</td>
<td>27.1 ± 5.9</td>
</tr>
<tr>
<td>Male</td>
<td>66.6%</td>
<td>61.5%</td>
<td>50.9 ± 28.5</td>
<td>47.8 ± 25.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35.1%</td>
<td>39.4%</td>
<td>- ≤60 ml/min</td>
<td>71.6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80.5%</td>
<td>80.4%</td>
<td>75.2%</td>
<td>62.7%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>55.0%</td>
<td>52.2%</td>
<td>BNP (pg/mL)</td>
<td>1015 ± 1086</td>
</tr>
<tr>
<td>Prior MI</td>
<td>51.7%</td>
<td>51.3%</td>
<td>1017 ± 1219</td>
<td>5174 ± 6567</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>43.0%</td>
<td>49.0%</td>
<td>NT-proBNP (pg/mL)</td>
<td>5944 ± 8438</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>40.1%</td>
<td>40.4%</td>
<td>STS replacement sc</td>
<td>7.8 ± 5.5</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>18.5%</td>
<td>15.7%</td>
<td>≥8</td>
<td>41.7%</td>
</tr>
<tr>
<td>PVD</td>
<td>17.2%</td>
<td>18.3%</td>
<td>Surgical risk (central eligibility committee)</td>
<td>68.6%</td>
</tr>
<tr>
<td>COPD</td>
<td>23.5%</td>
<td>23.1%</td>
<td>- High*</td>
<td>31.4%</td>
</tr>
<tr>
<td>H/o atrial fibr</td>
<td>57.3%</td>
<td>53.2%</td>
<td>- Not-high</td>
<td>30.1%</td>
</tr>
</tbody>
</table>

* STS repl score ≥8% or one or more factors present predicting extremely high surgical risk
<table>
<thead>
<tr>
<th>HF parameters</th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
<th>Echo core lab</th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology of HF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ischemic</td>
<td>60.9%</td>
<td>60.6%</td>
<td>MR severity</td>
<td>- Mod-to-sev (3+)</td>
<td>49.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Severe (4+)</td>
<td>51.0%</td>
</tr>
<tr>
<td>- Non-ischemic</td>
<td>39.1%</td>
<td>39.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td>EROA, cm²</td>
<td>0.41 ± 0.15</td>
<td>0.40 ± 0.15</td>
</tr>
<tr>
<td>- I</td>
<td>0.3%</td>
<td>0%</td>
<td>LVESD, cm</td>
<td>5.3 ± 0.9</td>
<td>5.3 ± 0.9</td>
</tr>
<tr>
<td>- II</td>
<td>42.7%</td>
<td>35.4%</td>
<td>LVEDD, cm</td>
<td>6.2 ± 0.7</td>
<td>6.2 ± 0.8</td>
</tr>
<tr>
<td>- III</td>
<td>51.0%</td>
<td>54.0%</td>
<td>LVESV, mL</td>
<td>135.5 ± 56.1</td>
<td>134.3 ± 60.3</td>
</tr>
<tr>
<td>- IV</td>
<td>6.0%</td>
<td>10.6%</td>
<td>LVEDV, mL</td>
<td>194.4 ± 69.2</td>
<td>191.0 ± 72.9</td>
</tr>
<tr>
<td><strong>HF hosp w/i 1 year</strong></td>
<td>58.3%</td>
<td>56.1%</td>
<td>LVEF, %</td>
<td>31.3 ± 9.1</td>
<td>31.3 ± 9.6</td>
</tr>
<tr>
<td><strong>Prior CRT</strong></td>
<td>38.1%</td>
<td>34.9%</td>
<td>- ≤40%</td>
<td>82.2%</td>
<td>82.0%</td>
</tr>
<tr>
<td><strong>Prior defibrillator</strong></td>
<td>30.1%</td>
<td>32.4%</td>
<td>RVSP, mmHg</td>
<td>44.0 ± 13.4</td>
<td>44.6 ± 14.0</td>
</tr>
</tbody>
</table>
## MitraClip Procedure (n=302)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MitraClip procedure attempted</td>
<td>293/302 (97.0%)</td>
</tr>
<tr>
<td>Clip implanted (MitraClip procedure attempted)</td>
<td>287/293 (98.0%)</td>
</tr>
<tr>
<td>Clip implanted (all patients)</td>
<td>287/302 (95.0%)</td>
</tr>
<tr>
<td>Mean # of clips implanted</td>
<td>$1.7 \pm 0.7$ (n=293)</td>
</tr>
<tr>
<td>- 0 clips implanted</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>- 1 clip implanted</td>
<td>106 (36.2%)</td>
</tr>
<tr>
<td>- 2 clips implanted</td>
<td>157 (53.6%)</td>
</tr>
<tr>
<td>- 3 clips implanted</td>
<td>23 (7.9%)</td>
</tr>
<tr>
<td>- 4 clips implanted</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Procedure duration (mins)</td>
<td>$162.9 \pm 118.1$</td>
</tr>
<tr>
<td>- Device procedure time (mins)</td>
<td>$118.9 \pm 63.5$</td>
</tr>
<tr>
<td>- Device time (mins)</td>
<td>$82.7 \pm 80.8$</td>
</tr>
<tr>
<td>- Fluoroscopy time (mins)</td>
<td>$33.9 \pm 23.2$</td>
</tr>
</tbody>
</table>

### TTE at discharge (n=260)

<table>
<thead>
<tr>
<th>MR grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1+</td>
<td>1.5%</td>
</tr>
<tr>
<td>2+</td>
<td>12.7%</td>
</tr>
<tr>
<td>3+</td>
<td>82.3%</td>
</tr>
<tr>
<td>4+</td>
<td>3.3%</td>
</tr>
</tbody>
</table>
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
Primary Safety Endpoint
Freedom from Device-related Complications within 12 months

- 96.6%*
- 94.8% [95% LCL]
- 88% OPC
- P<0.001

<table>
<thead>
<tr>
<th>MitraClip procedure attempted</th>
<th>N=293</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related complications</td>
<td>9 (3.4%)</td>
</tr>
<tr>
<td>- Single leaflet device attachment</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>- Device embolization</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>- Endocarditis requiring surgery</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>- Mitral stenosis requiring surgery</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>- Left ventricular assist device implant</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>- Heart transplant</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>- Any device-related complication requiring non-elective CV surgery</td>
<td>1 (0.3%)</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%
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
Death or HF Hospitalization

HR [95% CI] = 0.57 [0.45-0.71]
P < 0.001

NNT (24 mo) = 4.5 [95% CI 3.3, 7.2]

<table>
<thead>
<tr>
<th>Time After Randomization (Months)</th>
<th>MitraClip + GDMT</th>
<th>GDMT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>302</td>
<td>312</td>
</tr>
<tr>
<td>3</td>
<td>264</td>
<td>244</td>
</tr>
<tr>
<td>6</td>
<td>238</td>
<td>205</td>
</tr>
<tr>
<td>9</td>
<td>215</td>
<td>174</td>
</tr>
<tr>
<td>12</td>
<td>194</td>
<td>153</td>
</tr>
<tr>
<td>15</td>
<td>154</td>
<td>117</td>
</tr>
<tr>
<td>18</td>
<td>145</td>
<td>90</td>
</tr>
<tr>
<td>21</td>
<td>126</td>
<td>75</td>
</tr>
<tr>
<td>24</td>
<td>97</td>
<td>55</td>
</tr>
</tbody>
</table>
# MR Severity (Core Lab)

<table>
<thead>
<tr>
<th>MR grade</th>
<th>≤1+</th>
<th>2+</th>
<th>3+</th>
<th>4+</th>
<th>P_trend</th>
<th>≤2+</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>----</td>
<td>----</td>
<td>---------</td>
<td>-----</td>
<td>---------</td>
</tr>
<tr>
<td>MitraClip (n=302)</td>
<td>-</td>
<td>-</td>
<td>49.0%</td>
<td>51.0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GDMT (n=311)</td>
<td>-</td>
<td>-</td>
<td>55.3%</td>
<td>44.7%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td>7.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MitraClip (n=273)</td>
<td>72.9%</td>
<td>19.8%</td>
<td>5.9%</td>
<td>1.5%</td>
<td>&lt;0.001</td>
<td>92.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDMT (n=257)</td>
<td>8.2%</td>
<td>26.1%</td>
<td>37.4%</td>
<td>28.4%</td>
<td>&lt;0.001</td>
<td>34.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td>6.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MitraClip (n=240)</td>
<td>66.7%</td>
<td>27.1%</td>
<td>4.6%</td>
<td>1.7%</td>
<td>&lt;0.001</td>
<td>93.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDMT (n=218)</td>
<td>9.2%</td>
<td>28.9%</td>
<td>42.2%</td>
<td>19.7%</td>
<td>&lt;0.001</td>
<td>38.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td>5.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MitraClip (n=210)</td>
<td>69.1%</td>
<td>25.7%</td>
<td>4.3%</td>
<td>1.0%</td>
<td>&lt;0.001</td>
<td>94.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDMT (n=175)</td>
<td>11.4%</td>
<td>35.4%</td>
<td>34.3%</td>
<td>18.9%</td>
<td>&lt;0.001</td>
<td>46.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
<td>0.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MitraClip (n=114)</td>
<td>77.2%</td>
<td>21.9%</td>
<td>0%</td>
<td>0.9%</td>
<td>&lt;0.001</td>
<td>99.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDMT (n=76)</td>
<td>15.8%</td>
<td>27.6%</td>
<td>40.8%</td>
<td>15.8%</td>
<td>&lt;0.001</td>
<td>43.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions

- In pts with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite maximally-tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, quality-of-life and functional capacity during 24-month follow-up.

- As such, the MitraClip is the first therapy shown to improve the prognosis of patients with HF by reducing secondary MR due to LV dysfunction.
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

**COAPT**

- MitraClip + GDMT
  
- GDMT alone

**HR [95% CI]** = 0.63 [0.49–0.82]

**P** < 0.001

---

**No. at Risk:**

**Control Group**

- 152
- 123
- 109
- 94
- 86
- 80
- 73
- 73
- 67

**Device Group**

- 151
- 114
- 95
- 91
- 81
- 81
- 73
- 67

---

**Control Group**

- 312
- 244
- 226
- 205
- 194
- 174
- 174
- 153

**Device Group**

- 302
- 264
- 238
- 215
- 194

---

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><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</td>
</tr>
<tr>
<td><strong>EROA (mean ± SD)</strong></td>
<td>$31 \pm 10$ mm$^2$</td>
<td>$41 \pm 15$ mm$^2$</td>
</tr>
<tr>
<td><strong>LVEDV (mean ± SD)</strong></td>
<td>$135 \pm 35$ mL/m$^2$</td>
<td>$101 \pm 34$ mL/m$^2$</td>
</tr>
<tr>
<td><strong>GDMT 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 / $\geq$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 $\geq$3+ MR</strong></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*
<table>
<thead>
<tr>
<th></th>
<th>COAPT (n=614)</th>
<th>MITRA-FR (n=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EROA, mm² (mean ± SD)</td>
<td>41 ± 15</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>- &lt;30 mm²</td>
<td>14% (80/591)</td>
<td>52% (157/301)</td>
</tr>
<tr>
<td>- 30 – 40 mm²</td>
<td>46% (270/591)</td>
<td>32% (95/301)</td>
</tr>
<tr>
<td>- &gt;40 mm²</td>
<td>41% (241/591)</td>
<td>16% (49/301)</td>
</tr>
<tr>
<td>LVEF, % (mean ± SD)</td>
<td>31 ± 9</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>LVEDV, mL/m² (mean ± SD)</td>
<td>101 ± 34</td>
<td>135 ± 35</td>
</tr>
</tbody>
</table>
Impact of EROA and LVEDV: EROA >40 mm²

All-cause mortality or HF hospitalization through 12 months

LVEDVI >96 ml/m² (N=130; 23.7%)

- MitraClip + GDMT (n=67)
- GDMT alone (n=63)

HR [95% CI] = 0.60 [0.35, 1.01]  
P=0.05

- All-cause mortality or HF hospitalization (%)
- Time after randomization (months)

LVEDVI ≤96 ml/m² (N=92; 16.8%)

- MitraClip + GDMT (n=45)
- GDMT alone (n=47)

HR [95% CI] = 0.61 [0.33, 1.12]  
P=0.11

- All-cause mortality or HF hospitalization (%)
- Time after randomization (months)

N at Risk:
- MitraClip + GDMT: 67, 62, 56, 48, 42
- GDMT: 63, 49, 41, 31, 26

N at Risk:
- MitraClip + GDMT: 45, 40, 34, 32, 27
- GDMT: 47, 37, 30, 25, 21
Impact of EROA and LVEDV: EROA >30-40 mm²
All-cause mortality or HF hospitalization through 12 months

LVEDVI >96 ml/m² (N=88; 16.1%)
- MitraClip + GDMT (n=48)
- GDMT alone (n=40)
HR [95% CI] = 0.49 [0.25, 0.97]
P=0.04

LVEDVI ≤96 ml/m² (N=131; 23.9%)
- MitraClip + GDMT (n=64)
- GDMT alone (n=67)
HR [95% CI] = 0.37 [0.20, 0.67]
P<0.001
Impact of EROA and LVEDV: EROA ≤30 mm²
All-cause mortality or HF hospitalization through 12 months

LVEDVI >96 ml/m² (N=56; 10.2%)
- MitraClip + GDMT (n=22)
- GDMT alone (n=34)

HR [95% CI] = 0.90 [0.33, 2.43]  
P=0.83

33.1%  
27.8%

LVEDVI ≤96 ml/m² (N=51; 9.3%)
- MitraClip + GDMT (n=23)
- GDMT alone (n=28)

HR [95% CI] = 0.45 [0.16, 1.29]  
P=0.13

44.4%  
21.7%
Conclusion ➔

Safety + Efficacy on MR + Prognosis -

Coapt?
MR > 30mm²
20% < EF < 50%

Reshape?
MR > 20mm²
15% < EF < 40%

Coapt?
MR > 30mm²
20% < EF < 50%

Reshape?
MR > 20mm²
15% < EF < 40%
<table>
<thead>
<tr>
<th></th>
<th>COAPT</th>
<th>RESHAPE-HF-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N patients, sites</strong></td>
<td>610 pts @ 100 NA and EU sites</td>
<td>380 pts @ 50 EU sites</td>
</tr>
<tr>
<td><strong>Control arm</strong></td>
<td>GDMT ± CRT</td>
<td>GDMT ± CRT</td>
</tr>
<tr>
<td><strong>FMR grade</strong></td>
<td>≥3+ (EROA ≥30 mm² and/or Rvol &gt;45 mL by ECL)</td>
<td>≥3+ (EROA ≥30 mm² and/or Rvol &gt;45 mL by ECL)</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td>II, III, or ambulatory IV</td>
<td>III or ambulatory IV</td>
</tr>
<tr>
<td><strong>Other inclusion criteria</strong></td>
<td>HF hosp within 12 months or BNP ≥300 pg/ml or nT-proBNP ≥1500 pg/ml within 12 months; MV surgery is not local standard of care</td>
<td>HF hosp within 12 months or BNP ≥350 pg/ml or nT-proBNP ≥1400 pg/ml within 90 days; not eligible for MV surgery</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td>≥20% - ≤50%</td>
<td>≥15% - ≤40%</td>
</tr>
<tr>
<td><strong>LV volumes</strong></td>
<td>LVESD ≤70 mm</td>
<td>LVEDD ≥55 mm</td>
</tr>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td>Recurrent HF hospitalization at 24 months</td>
<td>Death or recurrent HF hospitalization at 12 months</td>
</tr>
<tr>
<td><strong>Primary safety endpoint</strong></td>
<td>SLDA, device embolizations, endocarditis/MS/device-related complications requiring non-elective CV surgery, LVAD, OHT at 12 mo</td>
<td>All-cause mortality, stroke, MI, new renal replacement therapy, non-elective CV surgery for device related complications</td>
</tr>
<tr>
<td><strong>Total follow-up</strong></td>
<td>5 years</td>
<td>1 year</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td>GW Stone, M Mack</td>
<td>P Ponikowski, S Anker</td>
</tr>
</tbody>
</table>
MitraClip: Initial Inclusion Criteria (EVEREST studies)

• **Valve geometry features:**
  – Coaptation length ≥2 mm, coaptation depth <11 mm,
  – Flail gap <10 mm, flail width <15 mm

• **Ventricle function/ geometry:**
  – Ejection fraction [EF] >25%,
  – LV end-systolic diameter ≤55mm
MitraClip Anatomic Evaluation: Basic Requirements

• Ability to approximate leaflets

• Adequate *mitral valve orifice area* (to avoid iatrogenic mitral stenosis)

• Adequate transesophageal *imaging* to guide the procedure

• ➔ Expanding indications to non-EVEREST anatomies
Percutaneous interventional mitral regurgitation treatment using the Mitra-Clip system

P. Boekstegers · J. Hausleiter · S. Baldus · R. S. von Bardeleben · H. Beucher · C. Butter · O. Franzen · R. Hoffmann · H. Ince · K. H. Kuck · V. Rudolph · U. Schäfer · W. Schillinger · N. Wunderlich

Table 2 Morphology for a Mitraclip therapy

<table>
<thead>
<tr>
<th>Optimal valve morphology</th>
<th>Conditionally suitable valve morphology</th>
<th>Unsuitable valve morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central pathology in Segment 2</td>
<td>Pathology in Segment 1 oder 3</td>
<td>Perforated mitral valve leaflet or cleft</td>
</tr>
<tr>
<td>No leaflet calcification</td>
<td>Mild calcification outside of the grip-zone of the clip system; ring calcification, post annuloplasty</td>
<td>Severe calcification in the grip-zone</td>
</tr>
<tr>
<td>Mitral valve opening area &gt;4 cm²</td>
<td>Mitral valve opening area &gt;3 cm² with good residual mobility</td>
<td>Haemodynamically significant mitral stenosis (valve opening area &lt;3 cm²; MPG ≥ 5 mmHg)</td>
</tr>
<tr>
<td>Mobile length of the posterior leaflet ≥10 mm</td>
<td>Mobile length of the posterior leaflet 7–&lt;10 mm</td>
<td>Mobile length of the posterior leaflet &lt;7 mm</td>
</tr>
<tr>
<td>Coaption depth &lt;11 mm</td>
<td>Coaption depth ≥11 mm</td>
<td>Rheumatic leaflet thickening and restriction in systole and diastole(Carpentier IIIA)</td>
</tr>
<tr>
<td>Normal leaflet strength and mobility</td>
<td>Leaflet restriction in systole (Carpentier IIIB)</td>
<td>Barlow’s syndrome with multisegment flail leaflets</td>
</tr>
<tr>
<td>Flail-width &lt;15 mm</td>
<td>Flail-width &gt;15 mm only with a large ring width and the option for multiple clips</td>
<td></td>
</tr>
<tr>
<td>Flail-Gap &lt;10 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Optimal Anatomy for MitraClip

Optimal valve morphology

- Central pathology in Segment 2
- No leaflet calcification
- Mitral valve opening area >4 cm²
- Mobile length of the posterior leaflet ≥10 mm
- Coaption depth <11 mm
- Normal leaflet strength and mobility
- Flail-width <15 mm Flail-Gap <10 mm

HYGEIA Hospital Heart Team
Conditionally Suitable Anatomy for MitraClip

Conditionally suitable valve morphology

Pathology in Segment 1 oder 3

Mild calcification outside of the grip-zone of the clip system; ring calcification, post annuloplasty
Mitrval valve opening area > 3 cm² with good residual mobility
Mobile length of the posterior leaflet 7–<10 mm

Coaption depth ≥11 mm
Leaflet restriction in systole (Carpentier IIIB)

Flail-width >15 mm only with a large ring width and the option for multiple clips

Clin Res Cardiol (2014) 103:85–96
Conditionally Suitable Anatomy for MitraClip

Conditionally suitable valve morphology

Pathology in Segment 1 oder 3

Mild calcification outside of the grip-zone of the clip system; ring calcification, post annuloplasty
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Clin Res Cardiol (2014) 103:85–96
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Mitra valve opening area >3 cm² with good residual mobility

Mobile length of the posterior leaflet 7–<10 mm

Coaption depth ≥11 mm

Leaflet restriction in systole (Carpentier IIIB)

Flail-width >15 mm only with a large ring width and the option for multiple clips

Clin Res Cardiol (2014) 103:85–96
Conditionally Suitable Anatomy for MitraClip

Conditionally suitable valve morphology

Pathology in Segment 1 oder 3

Mild calcification outside of the grip-zone of the clip system; ring calcification, post annuloplasty
Mitral valve opening area $\geq 3$ cm$^2$ with good residual mobility
Mobile length of the posterior leaflet 7–$<10$ mm

Coaption depth $\geq 11$ mm
Leaflet restriction in systole (Carpentier IIIB)

Flail-width $>15$ mm only with a large ring width and the option for multiple clips

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Clin Res Cardiol (2014) 103:85–96
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Coaption depth ≥11 mm

Leaflet restriction in systole (Carpentier IIIB)

Flail-width >15 mm only with a large ring width and the option for multiple clips
Unsuitable Valve Morphology for MitraClip

Perforated mitral valve leaflet or cleft

Severe calcification in the grip-zone

Haemodynamically significant mitral stenosis (valve opening area <3 cm$^2$, MPG ≥ 5 mmHg)
Mobile length of the posterior leaflet <7 mm

Rheumatic leaflet thickening and restriction in systole and diastole (Carpentier IIIA)
Barlow’s syndrome with multisegment flail leaflets
MitraClip in 2018

- Larger flail gaps and widths
- Commissural jets
- Multiple jets
- Diminutive posterior leaflet
- Post surgical repair
- Acute MI mechanical complications
- Bridge to transplant
MitraClip as a Bridge to Heart Transplant

LETTER TO THE EDITORS

Percutaneous mitral valve repair using the MitraClip in acute cardiogenic shock

C. S. Zuern · J. Schreieck · H. J. Weig · M. Gawaz · A. E. May

Clin Res Cardiol (2011) 100:719–721

Mitraclip Procedure as a Bridge Therapy in a Patient With Heart Failure Listed for Heart Transplantation

Andrea Garatti, MD, Serenella Castelvecchio, MD, Francesco Bandera, MD, Massimo Medda, MD, Lorenzo Menicanti, MD

Cardiac Surgery and Heart Failure Units, IRCCS Policlinico San Donato, Milan, Italy

MitraClip in a Patient with Advanced Heart Failure

Baseline

Final

55 year old male with dilated cardiomyopathy, NYHA IV, on maximal medical Rx, BIV-AICD, paroxysmal atrial fibrillation, BNP 2210,
Post MitraClip, clinical stabilization x12months, eventual cardiac transplantation
Acute Heart Failure Complicating Myocardial Infarction

- 85 year-old female
- Subacute dyspnea on exertion
- Delayed presentation anterior myocardial infarction
- Coronary angiography: PCI stent to large ramus intermedius
- LVEF ~40%
- Initial improvement and response to medical Rx
- Clinical deterioration
- Acute pulmonary edema despite high doses of iv Lasix
MitraClip in Decompensated Heart Failure with Severe Functional MR and EF of 14%
Baseline Hemodynamics

IABP Off

IABP On
Hemodynamics post MV repair

After 1\textsuperscript{st} MitraClip

Final after 2 MitraClips
Edwards PASCAL Repair System: Designed to reduce mitral regurgitation

- Spacer is clasped between both Mitral Valve leaflets
- Independent leaflet clasping
- Simple “Commander-like” delivery system
- Transfemoral/ transeptal approach
Edwards PASCAL Transcatheter Mitral Valve Repair System

**Implant**

- Spacer intended to fill the regurgitant jet area
- Paddles designed to avoid stress concentration on native leaflets
- Clasps allow for independent leaflet capture and the ability to fine-tune leaflet position
Edwards PASCAL Transcatheter Mitral Valve Repair System

Delivery System

- 22 French Guide Sheath
- Independent catheters allow for simplified maneuvering in 3 planes
- Stabilizers lock handles in place for procedural ease
Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study


- N=23 patients
- Functional MR 12 (57%), Degenerative MR 6 (26%), Mixed 5 (22%)

Findings Between Sept 1, 2016, and March 31, 2017, 23 patients (median age 75 years [IQR 61–82]) had treatment for moderate-to-severe (grade 3+) or severe (grade 4+) mitral regurgitation using the Edwards PASCAL TMVr system. At baseline, the median EuroScore II score was 7·1% (IQR 3·6–12·8) and the median Society of Thoracic Surgeons predicted risk of mortality for mitral valve repair was 4·8% (2·1–9·0) and 6·8% (2·9–10·1) for mitral valve replacement. 22 (96%) of 23 patients were New York Heart Association (NYHA) class III or IV at baseline. The implantation of at least one device was successful in all patients, resulting in procedural residual mitral regurgitation of grade 2+ or less in 22 (96%) patients. Six (26%) of 23 patients had two implants. Periprocedural complications occurred in two (9%) of 23 patients (one minor bleeding event and one transient ischaemic attack). Despite the anatomical complexity of mitral regurgitation in the patients in this compassionate use cohort, technical success was achieved in 22 (96%) of 23 patients, and device success at 30 days was achieved in 18 (78%) patients. Three patients (13%) died during the 30 day follow-up. 19 (95%) of 20 patients alive 30 days after implantation were NYHA class I or II.

Interpretation This study establishes feasibility of the Edwards PASCAL TMVr system with a high rate of technical success and reduction of mitral regurgitation severity. Further research is needed on procedural and long-term clinical outcomes.
Edwards PASCAL Transcatheter Valve Repair System
Compassionate use experience

- Multicenter, observational, first-in-human experience
- 8 hospitals in 5 countries
- 29 high-risk or inoperable patients
- Symptomatic, severe mitral regurgitation
- Anatomical complexity making successful TMVr with MitraClip less likely or off-label[1]

Edwards PASCAL Mitral FIH
Baseline demographics (N=29)

<table>
<thead>
<tr>
<th><strong>Age (Years)</strong></th>
<th>73 ± 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>19 (66%)</td>
</tr>
<tr>
<td><strong>STS score for repair</strong></td>
<td>7.2 ± 6.5</td>
</tr>
<tr>
<td><strong>EuroScore II</strong></td>
<td>9.4 ± 8.0</td>
</tr>
<tr>
<td><strong>NYHA Class III or IV</strong></td>
<td>27 (93%)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>20 (69%)</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>16 (55%)</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>10 (34%)</td>
</tr>
<tr>
<td><strong>ICD/CRT</strong></td>
<td>7 (24%)</td>
</tr>
<tr>
<td><strong>Previous cardiac surgery</strong></td>
<td>9 (31%)</td>
</tr>
<tr>
<td><strong>Chronic renal failure (GFR&lt;60ml/min)</strong></td>
<td>19 (66%)</td>
</tr>
<tr>
<td><strong>Chronic lung disease</strong></td>
<td>9 (31%)</td>
</tr>
<tr>
<td><strong>Hospitalized for CHF within the past year</strong></td>
<td>20 (69%)</td>
</tr>
</tbody>
</table>

Edwards PASCAL Mitral FIH
Baseline echocardiography (N=29)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>DMR</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>MR Grade 3-4+</td>
<td>29 (100%)</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %±SD</td>
<td>43 ± 14</td>
</tr>
<tr>
<td>LVEDD, mm±SD</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>LVESD, mm±SD</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Vena contracta width, mm±SD</td>
<td>7.0 ± 1.2</td>
</tr>
<tr>
<td>EROA, cm²±SD</td>
<td>0.37 ± 0.17</td>
</tr>
<tr>
<td>Regurgitant volume, ml±SD</td>
<td>62 ± 33</td>
</tr>
<tr>
<td>Mean transmitral gradient, mmHg ±SD</td>
<td>2 ± 1</td>
</tr>
</tbody>
</table>

Edwards PASCAL Mitral FIH
Favorable procedural hemodynamics

3D mitral valve area was reduced from 5.4 cm$^2$ to 2.9 cm$^2$
Edwards PASCAL Mitral FIH
Safety profile at 30 days

<table>
<thead>
<tr>
<th>Event</th>
<th>n=29 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device success(^1)</td>
<td>23 (79%)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Re-hospitalizations for heart failure</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Reintervention for MV dysfunction</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure requiring dialysis</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Thrombus formation on device</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\)According to the MVARC criteria

Edwards PASCAL Mitral FIH

Safety profile at 6 months

<table>
<thead>
<tr>
<th>Event</th>
<th>n=22a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Re-hospitalizations for heart failure</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Re-intervention for MV dysfunction</td>
<td>2 (9%)</td>
</tr>
<tr>
<td><strong>1 patient successful implantation of 2nd PASCAL device</strong></td>
<td></td>
</tr>
<tr>
<td><strong>1 patient surgical MVR</strong></td>
<td></td>
</tr>
<tr>
<td>LVAD implantation</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure requiring dialysis</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Thrombus formation on device</td>
<td>0</td>
</tr>
</tbody>
</table>

aAt 6 months 22/29 reached follow up and the remainder are pending.

Edwards PASCAL Mitral FIH

Early durability at 6 months: 95% of patients with MR ≤ 2+ without significant gradient increase

95% patients with MR ≤ 2+ [1]

Sustained low mean gradient [1]

Clinically significant and stable improvements at 6 months

Praz F, Spargias K, Lancet 2017;390:773-780
Evidence of reverse LV remodeling at 6 months

20% increase in LVEF

7% reduction in LVEDD [1]

p-values calculated using paired t-test

Edwards PASCAL Transcatheter Mitral Valve Repair System

• The Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study (CLASP)
• Prospective, multi-center, multi-national, single arm study
• Purpose: Assess the safety, performance and clinical outcomes of the Edwards PASCAL TMVr System
• Global Principal Investigators: Ted Feldman, Gideon Cohen, Ulrich Shafer

Patients with Clinically Significant Mitral Regurgitation

MR ≥ 3+ as assessed by echocardiography; NYHA Class II-IVa (ambulatory)

Heart Team Assessment

Patient deemed appropriate for the Edwards PASCAL Transcatheter Mitral Valve System by Heart Team and the Central Screening Committee

N=120 (including 60 roll in patients)

The Edwards PASCAL Transcatheter Mitral Valve Repair System

Primary Endpoint: Composite of major adverse events (MAE) defined as cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications at 30 days.

Currently recruiting patients (NCT03170349)
PASCAL in a patient with flail P2

Flail P2 Scallop $\rightarrow$ Severe Eccentric MR
PASCAL Delivery to the Mitral Valve
Final result with one PASCAL at the A2-P2 flail
PASCAL in a patient with functional MR

Baseline severe Functional MR
First PASCAL in A2-P2: Initial Result
Second PASCAL medial A2-P2: Final Result
Final result after 2 PASCALs
Classification of Technologies for MV Repair and Replacement

Classification according to:
Site of action
Device mechanism

• Leaflets
  – (leaflet plication / edge to edge repair) MitraClip

• Annuloplasty
  – Indirect / coronary sinus approach
  – Direct (percutaneous and hybrid approaches)

• Percutaneous chords (for degenerative MR)
• LV remodeling

• Mitral Valve Replacement
## A Sampling of Mitral Annuloplasty Devices

* CE mark

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Dimensions Carillon *</th>
<th>MVRx ARTO</th>
<th>Mitralign TAMR *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Coronary sinus mediated posterior annulus cinching</td>
<td>A-P shortening via coronary sinus - LA band</td>
<td>Retrograde aortic pledget-mediated annular plication</td>
</tr>
<tr>
<td><strong>N pts treated</strong></td>
<td>~600 (113 in studies)</td>
<td>45</td>
<td>71 (51 with 2nd gen)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Edwards Cardioband *</th>
<th>Ancora Heart Accucinch</th>
<th>Millipede IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>LA semi-rigid posterior partial annuloplasty band with anchor cinching</td>
<td>LV postero-basal annuloventriculoplasty via anchor cinching</td>
<td>Complete circumferential semi-rigid direct annuloplasty ring</td>
</tr>
<tr>
<td><strong>N pts treated</strong></td>
<td>~100</td>
<td>39 (6 versions)</td>
<td>11</td>
</tr>
</tbody>
</table>
Transcatheter Direct Annuloplasty: Cardioband
Cardioband: MR reduction

90% patients with MR≤2+ At 24 Months By Core Lab*
Cardioband: Functional Improvement at 12 months
Classification of Technologies for MV Repair and Replacement

Classification according to:
  Site of action
  Device mechanism

• Leaflets
  – (leaflet plication / edge to edge repair) MitraClip
• Annuloplasty
  – Indirect / coronary sinus approach
  – Direct (percutaneous and hybrid approaches)
• Percutaneous chords (for degenerative MR)
• LV remodeling

• Mitral Valve Replacement
# A Sampling of Artificial Chords and Leaflets

* CE mark

<table>
<thead>
<tr>
<th>Features</th>
<th>NeoChord DS 1000*</th>
<th>HARPOON Medical</th>
<th>Babic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N pts treated</td>
<td>&gt;600 (surgical)</td>
<td>13 + ongoing studies</td>
<td>11 (as of 10/15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Features</th>
<th>Middle Peak Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>N pts treated</td>
<td>6 (3 temporary, 3 permanent)</td>
</tr>
</tbody>
</table>
Neochord Implantation
Classification of Technologies for MV Repair and Replacement

Classification according to:
  Site of action
  Device mechanism

- Leaflets
  - (leaflet plication / edge to edge repair) MitraClip
- Annuloplasty
  - Indirect / coronary sinus approach
  - Direct (percutaneous and hybrid approaches)
- Percutaneous chords (for degenerative MR)
- LV remodeling

- Mitral Valve Replacement

*J Am Coll Cardiol Intv* 2011;4:1–13)
Expanded Use of TAVI Valves in the Mitral Space

- Valve in Valve (for degenerated mitral bioprosthesis)
- Valve in Ring (for relapse of significant MR following surgical annuloplasty)
- Valve in Calcified Mitral Annulus
Patients undergoing procedures in 160 sites in Europe, North-America, Australia, New Zealand, South Africa, South America and the Middle-East (n = 3,751)

Aortic Valve in Valve (n = 2,505)

Transcatheter Mitral implants in failed valves post surgery (n = 816)

Mitral Valve in Valve (n = 660)

Mitral Valve in Ring (n = 156)

Tricuspid Valve in Valve / Valve in Ring (n = 430)
Transcatheter Mitral Valve in Valve: Treatment of Degenerated Surgical Bioprostheses

- 78 year old female, NYHA III dyspnea
  - Progressively worse with heart failure hospitalizations

11 years prior (at age 67) multiple valve surgery
- Mitral valve replacement
  - Edwards Perimount 27mm
- Aortic valve replacement
  - Magna 19mm
- Tricuspid valve annuloplasty
  - Edwards 34mm ring
Transseptal SAPIEN 3 MViV is currently the most common approach
Transseptal SAPIEN3 MViV is currently the most common approach.
Transseptal approach is increasingly utilized for mitral viv/vir

Transseptal Instead of Transapical Valve Implantation
Making Mitral Great Again?*

TABLE 1 Characteristics That May Favor Either Transapical or Transseptal Approach in Transcatheter Mitral Valve Implantation*

<table>
<thead>
<tr>
<th>Features</th>
<th>Favors Transapical†</th>
<th>Favors Transseptal‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operator characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive experience with transapical</td>
<td>Extensive experience with transseptal mitral interventions</td>
<td></td>
</tr>
<tr>
<td>procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient and anatomical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined mitral and aortic valve implantation</td>
<td>Combined mitral and pulmonary/tricuspid valve implantation</td>
<td></td>
</tr>
<tr>
<td>Need for very precise positioning§</td>
<td>Aiming for a shorter hospital stay</td>
<td></td>
</tr>
<tr>
<td>Crossing the surgical valve with a transcatheter heart valve is predicted to be challenging¶</td>
<td>Chest wall deformity or when aiming for avoiding thoracotomy¶</td>
<td></td>
</tr>
<tr>
<td>Future transseptal procedure is planned#</td>
<td>Clinical need to avoid general anesthesia**</td>
<td></td>
</tr>
<tr>
<td>Peripheral venous system abnormality†</td>
<td>Apical scar or recent myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Atrial septal anatomy is challenging##</td>
<td>Left ventricular systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Thrombus in left atrial cavity or appendage###</td>
<td>Chronic renal failure¶¶</td>
<td></td>
</tr>
<tr>
<td>Mitral valve characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor fluoroscopic markers##</td>
<td>Severely calcified and bulky subvalvular apparatus</td>
<td></td>
</tr>
<tr>
<td>Small surgical valve***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical valve with paravalvular leakage of uncertain significance†††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcatheter valve characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device enables retrograde implantation only</td>
<td>Device enables antegrade implantation only</td>
<td></td>
</tr>
<tr>
<td>Currently available retrievable devices###</td>
<td>Using a longer transcatheter heart valve§§§</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Using a smaller and better trackable delivery system§§§</td>
<td></td>
</tr>
</tbody>
</table>

Transapical Approach: Benefits and Risks

• Familiar surgical approach (e.g. for transapical TAVR, PVL closures)
• Proximity to the mitral valve
• Precise control of position and delivery of prosthesis
• Large devices / sheaths can be accommodated
• Combined procedures (mitral and aortic can be performed)

• Surgery with attendant risks and complications (e.g. bleeding from apex, postoperative pain, reduction in FEV-1)
• Subvalvular apparatus may be difficult to navigate
• Apical puncture not benign for patients with low EF
• Hostile chest, obesity may complicate
Transeptal Approach: Benefits and Difficulties

• Familiar access, less x-ray exposure
• Femoral venous access $\rightarrow$ low rate of vascular complications
• No incisions, less pain, faster recovery
• Patient preference

• Complex curve from IVC to mitral valve $\rightarrow$ requires two 90 degree bends
• Delivery of large sheaths / devices more difficult
• Coaxiallity more challenging
• Iatrogenic ASD
Access during Mitral VinV / VinR procedures

- Jugular Vein
- Direct left atrium
- Total trans-septal
- Femoral vein
- Transapical
Coaxiality differences

transapical

transseptal
LVEF dynamics according to access

* In patients with LVEF<50% in baseline

Dvir D.
Examples of TMVR with human implantations

Tiara: Minimally invasive treatment for a common form of mitral valve disease

CardioValve (Valtech Cardio)
Tendyne Transcatheter Mitral Valve

**Tendyne Device**

- D-Shaped Self-Expanding Nitinol Outer Frame
  - Designed to Conform to Native MV Anatomy
- Circular Self-Expanding Nitinol Inner Frame
  - Large Effective Orifice Area (>3.0cm²)
  - Larger EOA than any Surgical Valve
- Porcine Pericardial Tri-Leaflet Valve
- Large Valve Size Matrix to Treat Varying Anatomies
  - Outer Frame Sizes: 30-43mm AP x 34-50mm CC
- Valve Tether to Apex
  - Provides Valve Stability - Designed to Reduce PVL
- Apical Pad Assists in Access Closure
Tendyne Device 3D EnFace View

Image courtesy of N. Moat, A. Duncan, Royal Brompton Hospital
First 100 Patients Treated with the Tendyne Transcatheter Mitral Prosthesis

Results from the Global Feasibility / CE Mark Study

Paul Sorajja, MD, Neil Moat, MBBS, Vinay Badhwar, MD, Darren Walters, MBBS, Gaetano Paone, MD, Brian Bethea, MD, Gry Dahle, MD, Mubashir Mumtaz, MD, Paul Grayburn MD, Samir Kapadia, MD, Vasilis Babaliaros, MD, Mayra Guerrero, MD, Lowell Satler, MD, Vinod Thourani, MD, Francesco Bedogni, MD, David Rizik, MD, Paolo Denti, MD, Nicolas Dumonteil, MD, Thomas Modine, MD, Arjay Sinhal, MBBS, Michael Chuang, MD, Jeffrey Popma, MD, Philipp Blanke, MD, Jonathon Leipsic, MD, and David Muller, MBBS
# Tendyne Experience (n=100)

## Tendyne Global Feasibility / CE Mark Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Population (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>75.4 ± 8.1</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>69% (69/100)</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>34% (34/100)</td>
</tr>
<tr>
<td>Class III</td>
<td>62% (62/100)</td>
</tr>
<tr>
<td>Class IV</td>
<td>4% (4/100)</td>
</tr>
<tr>
<td>STS-PROM</td>
<td>7.9 ± 5.7 %</td>
</tr>
<tr>
<td>≥8%</td>
<td>38% (38/100)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>55% (55/100)</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>9% (9/100)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38% (38/100)</td>
</tr>
<tr>
<td>Outside US</td>
<td>40% (40/100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echo Core Lab Assessments</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Etiology</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>10% (10/100)</td>
</tr>
<tr>
<td>Secondary/mixed</td>
<td>90% (90/100)</td>
</tr>
<tr>
<td>MR Grade</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>1% (1/100)</td>
</tr>
<tr>
<td>3+</td>
<td>7% (7/100)</td>
</tr>
<tr>
<td>4+</td>
<td>92% (90/100)</td>
</tr>
<tr>
<td>LVEF</td>
<td>46.4 ± 9.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical Risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>STS-PROM</td>
<td>7.9 ± 5.7 %</td>
</tr>
<tr>
<td>≥8%</td>
<td>38 (38%)</td>
</tr>
</tbody>
</table>
### Tendyne Global Feasibility / CE Mark Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Outcome</th>
<th>N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve implanted</td>
<td>97</td>
<td>(97%)</td>
</tr>
<tr>
<td>Technical success</td>
<td>96</td>
<td>(96%)</td>
</tr>
<tr>
<td>Implant aborted</td>
<td>3</td>
<td>(3%)</td>
</tr>
<tr>
<td>• Retrieved (SAM, LVOT obstruction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Retrieved (non-orthogonal access)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abandoned (pulmonary edema)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural mortality</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Procedural strokes</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Emergency surgeries</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>ECMO required</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Major apical bleeding</td>
<td>1</td>
<td>(1%)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>6</td>
<td>(6%)</td>
</tr>
</tbody>
</table>

**O/E 30-day mortality:** 0.76
1 Year Clinical Outcomes

Tendyne Global Feasibility / CE Mark Study

Patient Survival
100 Treated Patients

Clinical Events
Patients with 1-yr follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mortality</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>CV death</td>
<td>18 (21%)</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Re-intervention for tether tensioning</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Embolization or late migration</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Thrombus*</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

1-Year Survival = 72%

*All prior to mandatory coumadin
Improvement in Mitral Regurgitation

Tendyne Global Feasibility / CE Mark Study

Baseline

98.0% with no MR at 1-year

p<0.0001 vs. baseline

N=100, N=86, N=82, N=67, N=64, N=51
Symptom Improvement (NYHA)

Tendyne Global Feasibility / CE Mark Study

- **Symptom Improvement (NYHA)**
  - **Baseline**: 61.9%
  - **1 mo**: 60.9%
  - **3 mo**: 62.7%
  - **6 mo**: 60.0%
  - **12 mo**: 51.9%

- **NYHA I/II at 1-year**: 86.5%

- **p<0.0001 vs. baseline**
Tendyne Global Feasibility Summary

- High implant success rate (97%)
- Significant MR reduction
  - 98.7% none/trace at 30 days (p<0.0001)
- Significant 30-day improvement in symptoms
  - 75% NYHA Class I/II at 30 days; +7.5 point mean improvement in KCCQ
- Low 30-day mortality and SAE rates in high-risk population
  - No operative deaths, no CV surgery
  - 6% mortality at 30-day (STS-PROM = 7.9%)
  - 1.3% stroke
SUMMIT Trial Design

Subject has symptomatic, severe mitral regurgitation

**Surgical Arm**
- Eligible for Surgery?*
  - Yes: Secondary/Mixed MR?
    - Yes: 2:1 Randomization N=537
      - Treatment Group: Tendyne
      - Control Group: Surgical MVR/TV**
    - No: Exclude Subject (Primary MR)
  - No: Exclude Subject

**Non-Surgical Arm**
- Valve anatomy suitable for transcatheter repair?
  - Yes: Tendyne N=313
  - No: Up to 160 Roll-In Subjects (Max 2 per site without prior implant experience)

*Assessed by site heart team and approved by trial Subject Eligibility Committee
**Surgical MVR/TV includes standard of care repair or total chordal-sparing replacement
Tendyne in Severe MAC

Sorajja P et al. JACC Intv 2017
Tendyne in MAC

- **Objective**
  - To evaluate the use of Tendyne TMVR in the treatment of mitral regurgitation in patients with severe mitral annular calcification (MAC)

- **Type/Design**
  - Prospective, single-arm, multi-center
  - Up to 10 sites, up to 30 subjects

- **Principal Investigators**
  - Paul Sorajja, MD
  - Vinod Thourani, MD

- **Endpoints**
  - Primary Safety – Freedom from device or procedure-related SAEs at 30 days
  - Other – Technical, Patient, Device (MVARC-defined)
• Conformable Outer Stent engages the annulus and leaflets providing fixation & sealing while isolating the inner stent from the dynamic anatomy
• Circular Inner Stent houses a 27 mm tricuspid bovine pericardium valve
• Conformable Brim aids imaging during delivery & subsequent platform for healing
• Variable stiffness along the height of the Outer Stent helps wedge the implant – similar to a champagne-cork
• Outer stent engaging with, and conforming dynamically to, the annulus
• Circular inner stent isolated from the fixation and sealing
MEDTRONIC INTREPID™ TMVI
HYDRAULIC DEPLOYMENT OF SELF-EXPANDING STENT

1. Advance into LA
2. Expand brim & align with annulus target
3. Retract to target & deploy

Working length ~32.9cm
OD≤11.7mm / 35Fr

CAUTION: INVESTIGATIONAL DEVICE. LIMITED BY FEDERAL LAW (USA) TO INVESTIGATIONAL USE. These tests may not be indicative of clinical performance. These statements have not been evaluated by the FDA and are not intended to represent claims of human clinical performance or serve as a substitute for medical judgment.
Early Experience with New Transcatheter Mitral Valve Replacement

Vinayak Bapat, Vivek Rajagopal, Christopher Meduri, R. Saeid Farivar, Antony Walton, Stephen J. Duffy, Robert Gooley, Aubrey Almeida, Michael J. Reardon, Neal S. Kleiman, Konstantinos Spargias, Stratis Pattakos, Martin K. Ng, Michael Wilson, David H. Adams, Martin Leon, Michael J. Mack, Sharla Chenoweth, Paul Sorajja and for the Intrepid Global Pilot Study Investigators*
N=50 consecutive patients, age 73±9 years, male 58%
• Functional MR in 84%
• NYHA III/IV 86%
• High operative risk STS mortality 6.4±5.5%

RESULTS
• Successful implantation in 48/50 patients
• 30-day mortality 14%
• At a median follow up of 173 days:
  • NYHA I/II 79%, improved quality of life metrics
Transcatheter Mitral Valve Implantation in Patient with severe Functional MR

- 78 year old female, NYHA III
- Severe functional mitral regurgitation
  - ERO 47mm², $R_{vol}$ 55ml
- LVEDD 62mm, LVESD 51mm, EF33%
- Moderate TR, sPAP 50mmHg
- Fractured pelvis (5/2016), chronic atrial fibrillation, LBBB, BMI 22kg/m²
- Coronaries, no stenoses
Baseline Severe Mitral Regurgitation: Live 3D-with Color Doppler
SURGICAL PLANNING

ANNULUS SIZING

- 46 mm implant
- 17% perimeter oversizing
- 24% diameter oversizing
- 13% CC compression
- Patent LVOT
SURGICAL PLANNING
NEO-LVOT & LV ASSESSMENT

- Min neo-LVOT area: 1.6cm²
Valve Release under Rapid Ventricular Pacing
Final X-Plane with Color Doppler
Interaction Mitral – LVOT
Final 3D Color
Follow up at 3 months: Improved symptoms
Early Experience With New Transcatheter Mitral Valve Replacement

Vinayak Bapat, MBBS, MS, MCh,a,b Vivek Rajagopal, MD,a,c Christopher Meduri, MD, MPH,a R. Saeed Farivar, MD,a,b Anthony Walton, MD,a Stephen J. Duffy, MBBS, PhD,a Robert Gooley, MBBS, PhD,a Aubrey Almeida, MD,a Michael J. Reardon, MD,a Neal S. Kleiman, MD,a Konstantinos Spargias, MD,a Stratis Pappas, MD,a,b Martin K. Ng, MBBS, PhD,a Michael Wilson, MD,a David H. Adams, MD,a Martin Leon, MD,a Michael J. Mack, MD,a Sharla Chenoweth, MS,a Paul Sorajja, MD,a,b for the Intrepid Global Pilot Study Investigators*

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

FIGURES Survival During Follow-Up

Follow-up time for the 50 patients is illustrated with patient cohort on the y-axis and time before index event on the x-axis. 95% confidence intervals are shown.
30 DAY ECHO

Pre-Procedure

Latest f/u
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

- 1:1 Randomization
  - Treatment Arm TMVR
  - Control Arm MV surgery

- Single-arm Cohort
  - TMVR

Ineligible for surgical procedure
Intrepid TMVR
Next Generation Systems
1. Recoverable Design

Intrepid Current Design

Intrepid Recoverable Design

Ventricular section allows recoverability

Closed-cell inner structure facilitates recoverability
Intrepid TMVR
Next Generation Systems
2. Trans-septal Design

- Trans-septal, trans-femoral system in development (enabled by implant design not requiring rotational alignment or need to capture leaflets)
- One implant platform regardless of delivery approach: TS or TA
Cardiovalve TMVR: 1, 2, 3…

3 Implantation Steps
- Leaflets grasping
- Atrial flange delivery
- Full release

1 Valve

2 Frames
Atrial + Ventricular
Cardiovalve TMVR: 1, 2, 3…

- Transfemoral Access: Femoral vein, transseptal approach, 28 Fr
- Multi-steerable catheter for coaxial implantation
- No AV loop required - Single step TF implantation
- Echo main guidance, Fluoro assistance
- 3-steps procedure

1. Leaflet grasping
2. Atrial flange delivery
3. Full release
Cardiovalve TMVR: 1, 2, 3…

Cardiovalve follows a proven surgical design adapted for transcatheter use:

- **Low ventricular profile**, no atrial protruding
- Robust frame and **classic leaflet design for durability**
- **3 sizes to fit all anatomies**
- Proprietary **anchoring and sealing element**

Surgical gold-standard

Edwards Perimount Magna

Transcatheter Solution

Cardiovalve
AHEAD EU Study

*European Feasibility Study of High Surgical Risk Patients with Severe Mitral Regurgitation treated with the Cardiovalve Transfemoral Mitral Valve System (AHEAD Study)*

**AHEAD EU Sites**
Up to 10 sites: **Italy, Switzerland (Approved)** – Germany, France (Approval in process)

**Study Design**
Prospective, multi-center, single arm pilot clinical study

**Enrollment**
A total of 30 subjects will be enrolled in this pilot study

**Target patients**
Symptomatic subjects (NYHA Class ≥ II-IV) with severe mitral regurgitation requiring mitral valve replacement who are at high risk for open chest surgery according to the Heart Team decision

**Study Enrollment Duration**
1 year
## Cardiovalve TMVR: Promising First 5 Cases

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PVL</td>
<td>No</td>
<td>Trace</td>
<td>Trace</td>
<td>No</td>
<td>Trace</td>
</tr>
<tr>
<td>LVOT obstruction</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gradients</td>
<td>5 mmHg</td>
<td>6 mmHg</td>
<td>2 mmHg</td>
<td>6 mmHg</td>
<td>3 mmHg</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Normal</td>
<td>Normal</td>
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In Summary

• Transcatheter MV repair safe and effective in well selected patients
  • Edge to edge (e.g. MitraClip, PASCAL); Annuloplasty devices (e.g. Cardioband); Chord implantation (e.g. Neochords) are main modalities

• Patient selection for E2E repair in Functional MR will need to be clarified
  • Robust clinical data from the COAPT and the MITRA-FR trials suggest true benefit of MITRACLIP in selected patients with severe FMR
  • RESHAPE-HF2 will further refine selection criteria

• Transcatheter MV replacement very effective in eliminating MR, promising early results, but with very strict patient selection

• Heart Teams are critical for implementation of newer techniques and deciding between competing options of REPAIR vs. REPLACEMENT