MITRAL REGURGITATION: SCOPE OF PROBLEM AND LANDSCAPE OF TMVR

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Prevalence of Mitral Regurgitation Increases with Age

MR – Survival and HF hospitalizations

- Patients with MR have:
  - 2-fold shorter survival
  - 2-fold more heart failure hospitalizations

ANATOMY OF THE MITRAL VALVE

<table>
<thead>
<tr>
<th>Table 5 Etiology of primary and secondary MR</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary MR (leaflet abnormality)</strong></td>
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<tr>
<td>MVP myxomatous changes</td>
</tr>
<tr>
<td>Degenerative changes</td>
</tr>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td><strong>Secondary MR (ventricular remodeling)</strong></td>
</tr>
<tr>
<td>Ischemic etiology secondary to coronary artery disease</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
</tr>
<tr>
<td>Annular dilation</td>
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</tbody>
</table>
Figure 2  Schematic of (A) normal, (B) prolapse, and (C) flail leaflet coaptation. (A) In a normal valve, the leaflets and the point of coaptation are below the AP plane of the annulus. (B) In valvular prolapse leaflet, tissue rises above the annular plane, however, the leaflet tips remain directed towards the LV. (C) In flail leaflet, due to chordal rupture the leaflet tip is no longer tethered, and the leaflet tips extend into the LA exposing the ventricular surface of the leaflet to the LA.
PROLAPSED LEAFLET
PRIMARY or “Degenerative” MITRAL REGURGITATION

Normal

Barlow’s Disease

SECONDARY or “FUNCTIONAL” MITRAL REGURGITATION

Normal mitral valve

- Left ventricle
- Papillary muscle
- Chordae
- Mitral annulus
- Left atrium
- Aorta

Secondary mitral regurgitation

- LV distortion
- Papillary muscle displacement
- Tethered chordae
- Reduced closing forces
- Annular dilation
- MR
# Stages of Progression of VHD

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DEFINITION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At Risk</td>
<td>Patients with risk factors for development of VHD</td>
</tr>
<tr>
<td>B</td>
<td>Progressive</td>
<td>Patients with progressive VHD (mild-to-moderate severity and asymptomatic).</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic Severe</td>
<td>Asymptomatic patients who have the criteria for severe VHD:</td>
</tr>
<tr>
<td>• C1</td>
<td></td>
<td>Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated</td>
</tr>
<tr>
<td>• C2</td>
<td></td>
<td>Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic Severe</td>
<td>Patients who have developed symptoms as a result of VHD</td>
</tr>
</tbody>
</table>
SCOPE OF MITRAL REGURGITATION

• We are operating after the onset of left ventricular dysfunction
• We need lower risk, effective and durable interventions
• Still need to determine the patients that will benefit
EVEREST II Randomized Clinical Trial

279 patients enrolled in 37 sites
Severe MR (3+ or 4+)
73% degenerative MR, 27% functional MR
Randomized 2:1

DEVICE GROUP
Percutaneous mitral valve repair (MitraClip)
N=184

CONTROL GROUP
Surgical repair or replacement
N=95

Echo and Clinical Follow up - 5 years
EVEREST II Randomized Clinical Trial

Safety†
Major Adverse Events
30 days

MitraClip
N=136
9.6%

Surgery
N=79
57.0%

P_{sup}<0.0001

† 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

Effectiveness‡
Clinical Success Rate
12 months

MitraClip
N=134
72.4%

Surgery
N=74
87.8%

P_{Ni}=0.001, P_{SUP}=0.046

‡ Freedom from death, MV surgery or reoperation for MV dysfunction, or MR >2+ at 12 months
EVEREST II Randomized Clinical Trial

Primary End Point at 1 and 5 years: Freedom from death, MV surgery, or 3-4+ MR
Degenerative Mitral Regurgitation, Functional Mitral Regurgitation

<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>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td>26/48 (54.2%)</td>
<td>12/24 (50.0%)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative</td>
<td>74/133 (55.6%)</td>
<td>53/65 (81.5%)</td>
<td></td>
<td></td>
</tr>
<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></td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative</td>
<td>51/112 (45.5%)</td>
<td>32/42 (76.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary or Functional MR Due to Left Ventricular Dilation

ISCHEMIC Cardiomyopathy

IDIOPATHIC DILATED Cardiomyopathy
Top Advances in 2019

1. Edge-to-Edge Mitral Valve Repair Trials
   - MitraClip
     - MitraFR
     - COAPT
   - PASCAL
     - CLASP Study

2. Transcatheter Mitral Valve Replacement (TMVR)
   - SAPIEN 3 MViV
MITRA-FR Trial

304 patients with SMR due to LV dysfunction, EF 15-40%, NYHA II-IVa, hospitalization for HF within the previous 12 months, not surgical candidates
Randomized 1:1
37 French centers

MitraClip + Medical Therapy
N=152

Medical Therapy alone
N=152

Primary Endpoint: Freedom from death or HF hospitalization through 12 months

MITRA-FR Trial

**Primary endpoint**

Freedom from Death or HF Hospitalization

<table>
<thead>
<tr>
<th>Months</th>
<th>Control Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>152</td>
<td>151</td>
</tr>
<tr>
<td>2</td>
<td>123</td>
<td>114</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>67</td>
</tr>
</tbody>
</table>
COAPT Trial

610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated goal-directed medical therapy
Randomized 1:1

MitraClip + Medical Therapy  
N=305

Medical Therapy  
N=305

Primary Endpoint: All HF hospitalizations through 24 months
COAPT Trial

Primary Effectiveness Endpoint: All hospitalizations for HF within 24 months

**Graph:**
- Cumulative HF Hospitalizations (n)
- Time After Randomization (Months)
- HR (95% CI) = 0.53 [0.40-0.70]
- P<0.001

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

**Legend:**
- Green line: MitraClip + GDMT
- Blue line: GDMT alone

**Note:**
- Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos
NNT to prevent 1 death

2. SOLVD Investigators. NEJM 1991;325:294-302

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Landscape following COAPT trial

- Optimism with MV therapies
- Heart failure specialists are now more actively involved
MitraClip

- Primary (Degenerative) MR
- Prohibitive surgical risk
- 10/24/2013

- Secondary (Functional) MR
- All surgical risk
- 3/14/2019
TREATMENT OPTIONS:
MITRAL REPAIR VS REPLACEMENT

Leaflet Repair  Annuloplasty  Chordal Replacement

Surgical  Surgical

Cardioband  NeoChord

MitraClip  Mitralign

MitraClip  Mitralign

Carillon  Tendyne  Tiara  MVaIve

Valve Replacement

Harpoton  Caisson

Courtesy of E Grube
ALFIERI STICH

Figure 6 Transcatheter edge-to-edge mitral valve repair. The MitraClip device (Abbott Vascular Structural Heart) (A) is a 4 mm wide cobalt/chromium implant with two clip arms covered with polyester fabric to promote tissue ingrowth. The distal gripping elements secure the leaflet fixation (arrow, B). Real-time three-dimensional transoesophageal echocardiography demonstrates the final double-orifice mitral valve viewed from the left atrial side (arrow, C). Adapted with permission from Silvestry et al.\textsuperscript{58} and Swaans et al.\textsuperscript{59} AoV, aortic valve; LA, left atrium.


Fig. 12.3
The MitraClip device implanted. A double-orifice valve is obtained during ventricular diastole at the 3-D trans-esophageal echocardiogram.
PERCUTANEOUS THERAPY FOR MR

• Standard therapy for select patients
• Excellent safety
• Comparable efficacy
• Durability up to 4 years
The 4th Generation MitraClip
MitraClip G4

- WIDER CLIP ARMS
- 4 CLIP SIZES
  - BETTER COAPTATION
- CONTROLLED GRASPING
- CONTINUOUS LEFT ATRIAL PRESSURE MONITORING
- MORE PRECISE AND PREDICTABLE STEERING
REPAIR-MR

• RANDOMIZED CLINICAL TRIAL
• INTERMEDIATE SURGICAL RISK
• MITRAL VALVE SURGICAL REPAIR VS MITRACLIP
• INCLUSION: AGE >75, OR >65 WITH RISK
TREATMENT OPTIONS:
MITRAL REPAIR VS REPLACEMENT

Leaflet Repair
Annuloplasty
Chordal Replacement

Harpoon

Surgical

Pascal
Cardioband
NeoChord

MitraClip

MitraCerclage

Mitraalign

Carillon

Tendyne

Tiara

MVValve

Valve Replacement

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Courtesy of E Grube
Andersen Stent-Valve 1989

The valve was constructed of a handmade wire frame to which was sewn a porcine valve.

FIRST IN PIG; May 1, 1989
Figure 7. First-in-Man implantation (Rouen, April 16th, 2002). A—The complex antegrade transseptal route used for TAVR. B—View of the transcatheter valve in place within the native calcified valve and hemodynamic result (no gradient). C—The patient immediately after valve implantation and D 8 days later.
COMMERCIALLY AVAILABLE TMVR DEVICES

MitraClip
- Primary (Degenerative) MR
- Prohibitive surgical risk
- 10/24/2013
- Secondary (Functional) MR
- All surgical risk
- 3/14/2019

SAPIEN 3:
- Mitral Valve-In-Valve
- High or greater surgical risk
- 6/5/2017
MITRAL VALVE-IN-VALVE OPTION
All-Cause Mortality According to TMVR

Log-rank p < 0.001

- Valve-in-MAC (n=58) 62.8%
- Valve-in-Ring (n=141) 30.6%
- Valve-in-Valve (n=322) 14.0%

Days: 0, 90, 180, 270, 360

Yoon SH, EHJ 2018;40:441
TRANSCATHETER MITRAL VALVE REPLACEMENT

- Neovasc Tiara (February)
- CardiAQ (May)
- Twelve (November)
- CardiAQ (June)
- Caisson (June)

2012

CardiAQ (June)

- Edwards Fortis (March)
- Tendyne (October)
- Navigate (November)
- HighLife (January)

2014

2015

2016

Courtesy of E Grube
TMVR

• Devices in Randomized Controlled Trials in US

1. Tendyne (Abbott)
   – SUMMIT

2. Intrepid (Medtronic)
   – APOLLO
MITRAL REGURGITATION IN THE US

- Most PRIMARY MR patients are better served with surgical repair
- Most SECONDARY MR patients are best treated with optimal or guideline-directed medical therapy.
- Interventional population is unknown
THANK YOU