Percutaneous mitral valve interventions – The future is here!

Amit Segev, MD, FESC
Interventional Cardiology
Chaim Sheba Medical Center, Israel

French Society of Cardiology – Israel Heart Society Joint Session
Disclosures

• Proctor – Edwards LifeSciences
• Advisory board
  – Medtronic
  – ValtechCardio
  – Pfizer, Lilly, AstraZeneca, Bayer
• Shares – Matrizyme Ltd.
Outline

• Mitral anatomy
• Mitral clip
• Novel technologies from Israel
  – Cardioband™ from ValtechCardio
  – Tiara™ from Neovasc
The mitral valve apparatus includes the annulus, the leaflets, the chordae tendineae, and papillary muscles.

The leaflets are normally asymmetric—the anterior leaflet has a larger surface area, but occupies a smaller amount of annular circumference.

Mitral valve complexity

**DISEASE**
- Mitral Apparatus
  - Leaflets
  - Annulus
  - Chordae
- Etiology
- Left Ventricle
- Physiology - difficult to measure
  - Lesion
  - Impact of therapy

**THERAPY**
- Leaflet
- Direct annulus
- Indirect annulus
- Chordae
- Chamber remodeling
- Replacement
- Combinations
Degenerative vs. Functional MR

- **Primary MR / Degenerative MR (DMR) / Organic MR**
  - Usually refers to an anatomic defect of one or more structures comprising the mitral valve apparatus—the annulus, the leaflets, the chordae tendineae, and the papillary muscles.

- **Secondary MR / Functional MR (FMR)**
  - Result of left ventricular (LV) dysfunction and dilatation, which causes otherwise normal valve components to fail and produce MR.


MR Severity is Associated with Cardiac Events Even in Asymptomatic DMR Patients

Cardiac Events: CHF, New Afib, or CV Death in Asymptomatic Degenerative MR Patients

Kaplan-Meier estimates of mean rates of cardiac events among patients with asymptomatic MR under medical management (values in parentheses are survival rates at 5 years)

P<0.01

ERO ≥40 mm² (62±8%)
ERO 20-39 mm² (40±7%)
ERO <20 mm² (15±4%)

Higher Effective Regurgitant Orifice (ERO) is predictive of greater mortality after diagnosis.

MitraClip Parts Overview

MitraClip System

- Clip Delivery System
- Delivery Catheter Handle
- Steerable Guide Handle
- Steerable Guide, Steerable Sleeve & Delivery Catheter
- Stabilizer
- MitraClip Device
Key Procedural Principles

- Less-invasive, catheter-based system
- Based on surgical repair technique of creating a double-orifice valve
- Controlled, systematic procedure, with stable hemodynamics
- Allows for precise positioning and accurate placement of the MitraClip Device and real-time efficacy assessment
- Designed to preserve the option to undergo surgery if required
- Guided by real-time transesophageal echocardiography and fluoroscopy

Clip Grasping Leaflets  Creation of Double-Orifice Valve  Vertical Coaptation of Leaflets
A Closer Look at 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
The MitraClip Procedure is Primarily Guided by Transesophageal Echo (TEE)

TEE Procedural Echo Views

**Transeptal #1**
Bi Cav (80-110°) – Proper superior-inferior tenting location

**Transeptal #2**
SAX at Base (30-60°) – Proper anterior-posterior tenting location

**Transeptal #3**
4 Chamber (0°) – Confirmation of proper height above line of coaptation

**Positioning & Trajectory #1**
Intercommisural - 2C (55-75°)
Proper medial-lateral alignment

**Positioning & Trajectory #2**
LVOT (100-160°)
Proper anterior-posterior alignment

**HEIGHT** above valve
For proper Delivery Catheter travel during grasping and adequate tension on leaflets.

**AXIAL** alignment
For proper grasping and symmetrical leaflet capture.

**PERPENDICULAR** to line of coaptation (LoC)
For symmetrical leaflet capture and adequate leaflet insertion.
The MitraClip Procedure is Primarily Guided by Transesophageal Echo (TEE)

**TEE Procedural Echo Views**

- **Clip Positioning #1**
  TG SAX (0-30°) – Clip Arms perpendicular to LoC in LA

- **Clip Positioning #2**
  Intercommissural - 2C (55-75°)
  Clip position at MR origin

- **Clip Positioning #3**
  LVOT (100-160°) – Full length of both Arms visible at 180° in LV

- **Clip Positioning #4**
  TG SAX (0-30°) – Clip Arms perpendicular to LoC in LV

- **Leaflet Coaptation Confirmation**
  TG SAX (0-30°) – Leaflet coaptation visible on both sides of Clip

- **Echocardiographic Clip “Anatomy”**
  DC Radiopaque Ring
  Gripper
  Arm
  Tip of Clip

- **Fluoroscopic Clip “Anatomy”**
EVEREST II - Randomized Controlled Trial

Study Design
- 279 Patients enrolled at 37 Sites
  - Significant MR (3+ or 4+)
  - Specific Anatomical Criteria
- MitraClip N=184
- Surgery N=95
- R 2:1
- Echocardiography Core Lab and Clinical Follow-Up

Low 30-Day MAEs Compared to Surgery

<table>
<thead>
<tr>
<th>Major Adverse Events (MAE)</th>
<th>MitraClip (N=180)</th>
<th>Surgery (N=94)</th>
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<tbody>
<tr>
<td>Death</td>
<td>2 (1.1%)</td>
<td>2 (2.1%)</td>
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<tr>
<td>Major Stroke</td>
<td>2 (1.1%)</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Re-operation of Mitral Valve</td>
<td>0</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Urgent / Emergent CV Surgery</td>
<td>4 (2.2%)</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Deep Wound Infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventilation &gt; 48 Hrs</td>
<td>0</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td>New Onset Permanent Atrial Fib</td>
<td>2 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI Complication Requiring Surgery</td>
<td>2 (1.1%)</td>
<td>0</td>
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<tr>
<td>Transfusions ≥ 2 Units</td>
<td>24 (13.3%)</td>
<td>42 (44.7%)</td>
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</table>

TOTAL % of Patients with MAE
- MitraClip: 15.0%
- Surgery: 47.9%

p<0.001; (95% CI: -20.7%, -45.0%)
EVEREST II - Randomized Controlled Trial

Effectiveness Endpoint Met and Sustained Through 2 Years

- MitraClip
  - 1 Year (N=181): 55.2%
  - 2 Years (N=172): 61.7%
  - 1 Year (N=89): 73.0%
  - 2 Years (N=83): 66.3%

- Surgery

† Between group difference at 1 year (p<0.05)
‡ Between group difference at 2 year (p<0.05)

Composite consists of freedom from: Death, Surgery for mitral-valve dysfunction, and Grade 3+ or 4+ mitral regurgitation.

EVEREST II - Randomized Controlled Trial

Clinically Significant and Sustained Reduction of MR Grade from Baseline

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<th>MitraClip</th>
<th>Surgery</th>
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<tr>
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<td>N=122 (matched pairs)</td>
<td>N=56 (matched pairs)</td>
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<tr>
<td>Baseline</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>1 Year</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>2 Years</td>
<td>1+</td>
<td>1+</td>
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Significant NYHA Functional Class Improvements

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<th>Surgery</th>
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<td>N=127 (matched pairs)</td>
<td>N=56 (matched pairs)</td>
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<tr>
<td>Baseline</td>
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<td>III</td>
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<tr>
<td>1 Year</td>
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<td>III</td>
</tr>
<tr>
<td>2 Years</td>
<td>III</td>
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CONCLUSIONS

Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes.
Percutaneous Mitral valve Devices

Already gone
- PTMA
- Monarc
- Recor RF annular remodeling
- Coapsys

Still developing
- Leaflet repair
- CS annuloplasty
- Direct annuloplasty
- Cerclage
- Mitral spacer
- Chordal replacement
- Valve replacement
Adjustable Annuloplasty Band System

- Transfemoral Adjustable Annuloplasty band system
- Direct Annuloplasty (implant anchored in supra-annular position)
- Controlled Adjustment of septo-lateral diameter
- Transvenous, transseptal
Key Advantages

- Provides the surgical gold standard Annuloplasty through a catheter
- Surgical Annuloplasty contracts the annulus and stabilizes it, Cardioband does the same
- Reduction of septo-lateral diameter
- Suitable for high-risk patients - percutaneous procedure does not require surgery, CPB and cardioplegia
Key Advantages

✓ Keeps all future options open
  – Preserves the option for percutaneous valve replacement.

✓ Image guided for optimal anatomical and physiological fit
  – Band is adjusted under echocardiography guidance for optimal Mitral regurgitation reduction.

✓ Intuitive deployment procedure
Pre-Clinical Experience

- **Chronic Animals**
  - 12 Chronic Animals
  - 90-day study
  - Full Tissue Integration

- **Acute Animal**
  - More than 50 acute animals
Proven Clinical Results

- Cardioband has been implanted surgically in 5 patients
- All completed 6 months visit.
- Accumulated implant time >60 months

<table>
<thead>
<tr>
<th>Pt. #</th>
<th>Age</th>
<th>Gender</th>
<th>Band size (mm)</th>
<th>MR post implant</th>
<th>MR 30 days</th>
<th>MR 6 Month</th>
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<tr>
<td>C101</td>
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<tr>
<td>C102</td>
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<tr>
<td>C104</td>
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<td>2+*</td>
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<tr>
<td>C201</td>
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<td>male</td>
<td>95</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* Not device related. Patient underwent reoperation - Cardioband was not explanted.
Ready for Humans – FIM expected any day now
The Tiara comprises a self-expanding frame and biological tissue leaflets fixed within this frame.
The Tiara orifice is D-shaped to match the natural shape of the mitral orifice. When implanted, the flat side of the D is positioned anteriorly to prevent impingement of the left ventricular outflow tract and aortic valve.
Tiara 3D TEE

Ventricular View      Atrial View
The team:
- 2 interventional cardiologists
- a cardiac surgeon
- an echocardiographer

Approach:
Trans-apical

Guidance: TEE and fluoroscopy

Implantation time after apical access: 5-10 min
Tiara: A Novel Catheter-Based Mitral Valve Bioprosthesis
Initial Experiments and Short-Term Pre-Clinical Results
Tiara valves were implanted successfully in 29 (81%) of 36 domestic swine with fluoroscopic and 3-dimensional TEE guidance (Fig. 1). Follow-up varied from 90 min to 96 h. Total procedure time ranged from 17 to 26 min, and the prosthesis deployment time ranged from 5 to 13 min after the apical access. In the 29 successful implantations, TEE demonstrated excellent function and alignment of the Tiara, with no LVOT obstruction, no pericardial effusion, no encroachment on the aortic valve, and no transvalvular gradients. Significant paravalvular leak was seen only in cases of either MV annulus–prosthesis mismatch or failed implantation. Macroscopic evaluation of the explanted hearts demonstrated stable and secure positioning of the valves in all planes of the mitral apparatus. There was a steady increase in the rate of successful implantation as the series progressed, with the final 12 animals in the series all undergoing successful and uneventful implantations. All 29 animals that underwent successful Tiara implantation remained hemodynamically stable throughout the implantation procedure.
Pre-Clinical Results - Tiara

- 29/36 swine under fluoro + TEE
- Procedure time
  - Total 17-26 minutes
  - From apical access – 5-13 minutes
- TEE in 29 cases - Excellent function & alignment, no LVOT obstruction, no gradient, no encroachment on AV
- 1/29 had significant para-valvular leak
- Ex-vivo- stable and secure positioning
- Learning curve – last 12/12 successful

Banai S at al, JACC 2012
Tiara Implantation
Tiara current status

- Acute animal experiments – completed
- Chronic animal experiment – completed
- Human cadaver experiment – completed
- Chronic GLP experiments – ongoing
- First in human – Oct 2013
FOR IMMEDIATE RELEASE
CONTACT: RONALD TRAHAN, APR, RONALD TRAHAN ASSOCIATES, INC., +1 508-359-4005, x108

CardiAQ™ Valve Technologies reports cardiovascular medicine milestone: first-in-human nonsurgical percutaneous implantation of a bioprosthetic mitral heart valve

IRVINE, Calif., June 14, 2012—CardiAQ Valve Technologies (CardiAQ), which has developed the world’s first self-conforming and self-anchoring technology for nonsurgical Transcatheter Mitral Valve Implantation (TMVI), today announced that the Company has achieved a cardiovascular medicine milestone: a bioprosthetic mitral heart valve was successfully implanted as a compassionate treatment into an 86-year-old male suffering from severe mitral regurgitation (MR 4+). The breakthrough TMVI procedure was performed on June 12, 2012, at The Heart Centre, Rigshospitalet University Hospital, Copenhagen, Denmark, by interventional cardiologists Lars Søndergaard, M.D., and Olaf Franzen, M.D., cardiovascular surgeon Susanne Holme, M.D., anesthesiologist Peter Bo Hansen, M.D., and echocardiographer Nikolaj Ihlemann, M.D.
Surgical Approaches to Mitral Regurgitation

Donald D. Glower, MD
Durham, North Carolina

Surgical approaches to correct mitral regurgitation have evolved over 50 years and form much of the basis for percutaneous approaches to the mitral valve. Surgical mitral repairs have been more durable with use of annuloplasty, but recurrent regurgitation not resulting in reoperation can occur. The mitral leaflets may be resected or augmented, with recent trends to preserve leaflet coaptation surfaces if possible. Mitral chords tend to be repositioned or replaced, but the relative significance of chordal involvement and ventricular deformation as contributors to the residual regurgitation is unclear.

in this age of rapidly advancing percutaneous technology that is used both by surgeons and nonsurgical interventionists, the term “surgical” could, in fact, be considered an anachronism.
Merci, Toda Raba