Multi-disciplinary Approach to Mitral Disease

Kendra J. Grubb, M.D., M.H.A., F.A.C.C
Assistant Professor, Cardiothoracic Surgery
Surgical Director, Structural Heart & Valve Center
Emory University
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Review of Mitral Regurgitation
Mitral Regurgitation (MR)

- Mitral valve fails to close
  - Blood flows backward into the left atrium and pulmonary veins
  - Chronic LV overload
  - LV remodeling and dilation
  - Pulmonary hypertension
  - Heart failure

- Severity scale 1+ (mild) to 4+ (severe)
Mitral Regurgitation (MR)

• Two Etiologies:
  - Primary = Degenerative – mitral valve leaflet pathology
    • Prolapse, flail, chord or leaflet restriction
  - Secondary = Functional – normal valve with ventricular pathology
    • Papillary muscle displacement
    • Mitral valve tethering
    • Annular dilation
Mitral Regurgitation (MR)

<table>
<thead>
<tr>
<th>Grade</th>
<th>R Vol (ml)</th>
<th>RF(%)</th>
<th>ERO (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;20</td>
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<tr>
<td>2+</td>
<td>30-44</td>
<td>30-39</td>
<td>20-29</td>
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<tr>
<td>3+</td>
<td>45-59</td>
<td>40-49</td>
<td>30-39</td>
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<tr>
<td>4+</td>
<td>≥60</td>
<td>≥50</td>
<td>≥40</td>
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Mitral Regurgitation (MR)

Repair or Replacement indicated for symptomatic patients with moderate or severe MR

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Mitral Regurgitation (MR)

Table 1. Echocardiographic Assessment of Mitral Regurgitation Severity (ASE Guidelines20)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Regurgitation fraction (%)</td>
<td>&lt; 30</td>
<td>30-50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Regurgitation volume (ml)</td>
<td>&lt; 30</td>
<td>30-60</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Vena contracta (cm)</td>
<td>&lt; 0.3</td>
<td>0.3-0.7</td>
<td>&gt; 0.7</td>
</tr>
<tr>
<td>Regurgitation orifice area (cm²)</td>
<td>&lt; 0.2</td>
<td>0.2-0.4</td>
<td>&gt; 0.4</td>
</tr>
<tr>
<td>Jet area (% of LA area)</td>
<td>&lt; 20 %</td>
<td>20% to 40%</td>
<td>&gt; 40%</td>
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cm: centimeter; LA: left atrium; ml: milliliter.
Mitral Regurgitation

MR is the most frequent valve disease in the United States\textsuperscript{4,5}

NEARLY 1 IN 10 PEOPLE AGE 75 AND OLDER HAVE MODERATE OR SEVERE MR\textsuperscript{4,5}

(In comparison, 1 in 20 are affected by aortic valve disease.)
Mitral Regurgitation

- Approximately 4 million people have significant mitral valve insufficiency
  - Annual incidence of 250,000
  - Approximately 50,000 of these patients undergo surgery each year in the United States
Mitral Regurgitation is a High-Risk Diagnosis and Undertreated

- Only 2% of the estimated 1.7 million patients with MR >3+ were treated with surgery in 2009
  - Up to 50% deemed “Too High Risk” and never referred to a surgeon
  - Denied Surgery (49% of patients sent to a surgeon)
    - Low EF
    - Multiple comorbidities
    - Advanced age

(Diagram of the cycle of mitral regurgitation showing increasing risk over time)
Mitral Regurgitation (MR)

Primary MR
- Severe MR
  - Vena contracta ≥0.7 cm
  - RVol ≥60 mL
  - RF ≥50%
  - ERO ≥0.4 cm²
  - LV dilation

  - Symptomatic (stage D)
    - LVEF >30%
      - NO
      - YES
        - MV Surgery* (IIb)
  - Asymptomatic (stage C)
    - LVEF 30% to ≤60% or LVEDD ≥40 mm (stage C2)
    - LVEF >60% and LVEDD ≤40 mm (stage C1)
      - New onset AF or PASP >50 mm Hg (stage C1)
        - Likelihood of successful repair >95% and Expected mortality <1%
          - YES
          - NO
    - MV Repair (IIa)
    - Periodic Monitoring

Secondary MR
- Progressive MR (stage B)
  - Vena contracta <0.7 cm
  - RVol <60 mL
  - RF <50%
  - ERO <0.4 cm²

  - CAD Rx
  - HF Rx
  - Consider CRT

  - Symptomatic severe MR (stage D)
  - Asymptomatic severe MR (stage C)
  - Progressive MR (stage B)

Periodic Monitoring

Emory Heart & Vascular Center
Mitral Valve Surgery

- Risk of Death
- Risk of Stroke
- Prolonged Ventilation
- Renal Failure
- Need for Blood Transfusion
Minimally Invasive Mitral Valve Surgery
Minimally Invasive Mitral Valve Surgery
Minimally Invasive Mitral Valve Surgery

- Same Risks
- Decreased blood loss
- Decreased time in the ICU
- Faster return to work/activity
Surgery for Degenerative Mitral Regurgitation (MR)

- Damaged segment of mitral valve
- Segment removed
- Cut edges sutured together
- Annuloplasty band
Surgery for Degenerative Mitral Regurgitation (MR)

- Correct the leaflet pathology
- Often curative
- Decreased risk of thromboembolism
- No need for anticoagulation
- Excellent durability
  - 46% twenty-year survival
  - Reduced incidence of reoperation
Surgery for Functional Mitral Regurgitation (MR)

- Ventricular pathology
- Medical management and resynchronization therapy are first line

- Question if surgical correction of FMR in the setting of a failing LV is beneficial
  - Repair = high recurrence
  - Repair or replace = no survival advantage
Percutaneous Mitral Valve Repair
EVEREST (I, II)

- The purpose of these studies was to evaluate the safety and efficacy of isolated leaflet repair using the MitraClip device in patients with functional MR (FMR).

FDA Approved for Degenerative MR 2013
MitraClip

• Edge-to-Edge repair based on the Alfieri stitch
• Beating heart procedure
  • No cardiopulmonary bypass
• Allows real-time reduction of MR
• Able to reposition clip or place a second clip
• Limited hospital stay 1-2 days
MitraClip Edge to Edge Repair

Over 50,000 Implants Worldwide
Reduction in MR severity

Immediate improvement in MR severity was reported at discharge, and was sustained at 1 year.¹⁺

Mitral Regurgitation Grade

<table>
<thead>
<tr>
<th>Percent Patients (%)</th>
<th>Baseline (N=124)</th>
<th>Dischargeᵃ (N=123)</th>
<th>1 Year (N=84)</th>
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<td>4+</td>
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ᵃ30-day MR severity was used if discharge MR was unavailable.

83% MR ≤ 2+ at 1 Year
Improvement in New York Heart Association (NYHA) Functional Class

Reverse LV remodeling resulted in improvements in heart failure symptoms, with immediate (30 days) and sustained (1 year) improvement in NYHA class.¹,‡

NYHA Functional Class

87% NYHA Class I or II at 1 Year

<table>
<thead>
<tr>
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<th>Baseline (N=127)</th>
<th>30 Days (N=113)</th>
<th>1 Year (N=84)</th>
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<tbody>
<tr>
<td>Percent Patients (%)</td>
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<td>100</td>
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MitraClip 1-year Rehospitalization

**Hospitalizations for Heart Failure**

- **0.67** Hospitalization Rate per Patient Year 1 Year Prior to MitraClip (N = 127)
- **0.18** Hospitalization Rate per Patient Year 1 Year Post Discharge (N = 120)

73% Reduction
MitraClip 5-Year Follow up

- No difference in mortality between MitraClip or Surgery
MitraClip 5-Year Follow up

- No difference in mortality between MitraClip or Surgery
- Majority of MitraClip failures occurred in the first 6 months
- LV remodeling was demonstrated despite less reduction of MR by MitraClip

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*Kaplan-Meier curves depict (A) freedom from the composite of death, mitral valve (MV) surgery, or reoperation, (B) freedom from death, (C) freedom from MV surgery or reoperation, and (D) landmark analysis of freedom from MV surgery or reoperation beyond 6 months after percutaneous repair or surgery. Although patients undergoing percutaneous repair may be initially required surgery for mitral valve regurgitation during the first year after treatment, compared to low rates of surgery for MV dysfunction with either percutaneous or surgical therapy were seen between 1- and 5-year follow-up.RCT = randomized clinical trial.
MitralClip 5-Year Follow up

- For high-risk patients treated with MitraClip, inferior efficacy of MR reduction was not associated with increased mortality.
STS/ACC TVT Registry date – presented at ACC 2017
- 2,952 patients, 250 sites in US, average STS PROM 6.1%
  - Acute procedural success 91.8%
    - MR Grade 2 or less, without death
  - In-hospital mortality 2.7%
  - Average LOS 2 days
    - 85.9% discharge to home
MitraClip Commercial Experience

STS/ACC TVT Registry date – presented at ACC 2017

- 25.9% Mortality at 1 year
- 20.2% Hospitalization for heart failure
  - 37.9% Heart Failure or Death
- Patients with postprocedure grade 3+ MR, 1-year mortality was 48.9%
  - 29.2% with grade 2
  - 21.7% with grade 0/1
MitraClip Commercial Experience

- Functional MR
  - Rate of death was higher compared with degenerative
    - 31.2% vs 24.7%
  - Cumulative endpoint of death/heart-failure hospitalization
    - 49.0% vs 35.7%
- Patient with tricuspid regurgitation were at highest risk of death at 1 year (38.5% vs 23%, p<0.001)
Future Percutaneous Repair

- Percutaneous MV Repair – attempt to mimic surgical repair
- Annuloplasty
  - Direct annuloplasty
  - Indirect annuloplasty
- Artificial chords
- Left ventricular remodeling devices
Indirect Annuloplasty

- Carillon (Cardiac Dimension, Inc.) – mitral contouring system
  - Coronary sinus band to reduce the size of the posterior annulus
Indirect Annuloplasty

- Carillon (Cardiac Dimension, Inc.) – mitral contouring system
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- Technically simple cannulation of the coronary sinus
- High rate of complications
  - Variable anatomy
  - Circumflex coronary artery compression
  - Coronary sinus rupture
Direct Annuloplasty

- Cardioband (Edwards LifeSciences)
  - Transvenous-transseptal technology with circumferential annular cinching from the atrial side of the mitral annulus
Direct Annuloplasty

- Mitralign (Mitralign Inc)
  - Retrograde femoral technology for secondary MR, plication of the posterior annulus with pledgets
Direct Annuloplasty

• Accucinch (Guided Delivery Systems – now Ancora Heart)
  • Sub-valvular percutaneous band, prompting remodeling of the basal LV and papillary approximation
Direct Annuloplasty

Guided Delivery Systems – now Ancora Heart - Accucinch Annuloplasty

Nebraska Heart
Dr. Nagaraj
A New Era Begins – Transcatheter Mitral Valve Replacement (TMVR)
CardiAQ – Edwards Lifescience

- 2012 - First TMVR to be implanted percutaneously in a human
Tendyne – Tendyne Inc, Abbott
Tiara – Neovasc Inc
Intrepid (formerly Twelve) - Medtronic
TMVR in US trials

- Percutaneous platforms
- Self-expanding nitinol frames
- Bioprosthetic valve leaflets
- Most designed to be implanted via left mini-thoracotomy and Transapical
  - CardiAQ has a transfemoral-transseptal delivery option
Edwards LifeSciences Announces First Human Implants With Mitral Transcatheter Valve System

- February 2014:
- Heart Team at St. Thomas' Hospital, London – The FORTIS valve
Early TMVR Results

- Low survival, high complication rate
  - Edwards paused enrollment in preliminary clinical trail of Fortis
  - HeartWare International dropped plans to acquire Valtech Cardio
    – Cardioband is unlikely to deliver solid profits
- EuroIntervention Sept 2015 – Summary of 4 TMVR
  - 30-day mortality 38-50%
- TCT 2015 - Tendyne (Abbott), Twelve (Medtronic), Tiara (Neovasc), Fortis and CardiAQ (Edwards LifeSciences)
  - 30-day mortality 25-38.5%
Early Results for Transcatheter Mitral Valve Replacement Reveal Complications and Challenges for the Long Road Ahead - Feb 2016
Tendyne – Tendyne Holding, LLC, Abbott Vascular

- Largest clinical experience
- Fully repositionable and retrievable
- Global Feasibility Study
  - 30 patients
  - 93% Successful implantation
  - No death, strokes, or MI
  - 30 day – 86.6% free of CV mortality, stroke, and device malfunction
TAVR in Mitral Stenosis or Failed Valve

- 20-35% of patients will require reoperation within 10 years of mitral valve repair or replacement
  - Average STS PROM for reoperative surgery 5-12% in registry
TAVR in Mitral Stenosis or Failed Valve
TAVR in Mitral Stenosis or Failed Valve

- Transapical TAVR in annuloplasty ring or failed bioprosthetic valve is feasible
- S3 can also be implanted via a transeptal approach
TMVR Results

- TAVR in Mitral – Mitral Annulus Calcification (MAC) Global registry
  - 81 patients SapienXT/S3 in the mitral position
  - 21 died (25.9%) within 30 days
    - 2 LVOT obstruction, 2 LV perforations, 2 strokes, 1 complete AV block, 1 MI
- Better patient selection, improved awareness of the hazards, and design innovations may be helping to bring the rates down, but the path has been a bumpy one!
Conclusions

• There is an unmet clinical need for mechanical treatment of mitral regurgitation
• Percutaneous mitral valve therapies are evolving
• A one-size-fits-all device is unlikely – it’s not like TAVR
• We may rethink our objective for MV repair in high-risk patients – reduction in MR by 1 grade leading to LV remodeling and improved quality of life may be our ultimate goal
Conclusions

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• The Heart Team is challenged to raise awareness of the disease process and promote early referral for surgical discussion or enrollment in clinical trials
THANK YOU!