Valvular Heart Disease: A focused review on Calcific Aortic Valve Stenosis and Mitral Valve Regurgitation

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Nicholas Maksim, DO
Interventional Cardiology, OhioHealth Heart and Vascular Physicians
Cardiology Fellowship Program Director, Doctors Hospital
Objectives

• 1) Etiology and Pathology
• 2) Pathophysiology
• 3) Natural History
• 4) Clinical Presentation
• 5) Key physical exam findings
• 6) Management
Compare to normal AV
Etiology and Pathology

- Valvular AS has 3 principal causes:
  - 1) Degenerative AS of a tri-leaflet valve
  - 2) Bicuspid valve with calcification
  - 3) Rheumatic disease (typically accompanied by MS)
- Calcific disease progresses from base of cusps to leaflets
- Rheumatic disease results in fusion of leaflet commissures with scarring and eventual calcification of the cusps
Etiology and Pathology

• AS is an active disease process characterized by:
  
• 1) Lipid accumulation

• 2) Inflammation and calcification with many similarities to atherosclerosis

• **Ultimately leads to leaflet calcification, decreased leaflet mobility and decreased effective valve area**
Calcific Aortic Stenosis: Disease Progression
Pathophysiology

- Obstruction usually develops gradually (decades)
- LV adapts to increased afterload via concentric hypertrophy while maintaining normal chamber volume
- Relative increase in wall thickness counters the high intracavitary systolic pressure
- **Result = No change in wall stress**
- If hypertrophic response is inadequate, results in increased wall stress and decreased LVEF
- Important to distinguish from underlying primary CM
- Low volume/mass ratio and decreased chamber compliance = Elevated LVEDP
- Atrial ‘kick’ important in ventricular filling without increasing mLAP or pulmonary venous pressure
Pathophysiology

- **Development of concentric hypertrophy is appropriate and beneficial adaptation to compensate for high intracavitary pressures**
- Adverse consequences:
  - 1) Decreased coronary blood flow per gram of muscle
  - 2) Limited coronary vasodilator reserve (even in absence of epicardial CAD)
Pathophysiology of Aortic Stenosis
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## Grading of severity of AS

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
<th>Aortic Sclerosis</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic jet velocity (m/s)</td>
<td>&lt;2.6 m/s</td>
<td>2.6–3.0</td>
<td>3–4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Mean gradient (mm Hg)</td>
<td>—</td>
<td>&lt;20 (30*)</td>
<td>20–40</td>
<td>&gt;40 (50*)</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>—</td>
<td>&gt;1.5</td>
<td>1.0–1.5</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Indexed AVA (cm²/m²)</td>
<td>—</td>
<td>&gt;0.85</td>
<td>0.60–0.85</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Velocity ratio</td>
<td>—</td>
<td>&gt;0.50</td>
<td>0.25–0.50</td>
<td>&lt;0.25</td>
</tr>
</tbody>
</table>
Clinical Presentation

- Cardinal manifestations:
  - 1) Exertional dyspnea
  - 2) Angina pectoris
  - 3) Syncope

- After onset of Sx, average survival 2-3 years with increased incidence of SCD

- Impaired platelet function and decreased levels of VonWillebrand factor in pts with severe AS leading to:
  - 1) Ecchymosis or epistaxis
  - 2) GI bleeding often associated with angiodysplasia of the ascending colon
  - May cause embolization to other organs
Natural History

• Prolonged latent period during which morbidity and mortality are low

• Average rate of progression once moderate AS present:
  1) Increase in jet velocity of 0.3 m/sec/yr
  2) Increase in mean pressure gradient of 7 mmHg/yr
  3) Decrease in valve area of 0.1cm²/yr

• As contraction of the LV becomes progressively more isometric, the LV pressure pulse exhibits a rounded summit

• Doppler velocity curve exhibits a progressively later systolic peak
1 / 3 / 5 year MORTALITY IN PARTNER 1B (“standard therapy”):
50.7% / 80.9% / 93.6% (confirms historical data)

**Median 12 month survival 50%**

Latent period
(increasing obstruction, myocardial overload)
Natural History: Aortic Sclerosis

- Irregular valve thickening without obstruction
- Present in 25% of adults >65yo
- RF: Age, Sex, HTN, smoking, LDL and Lp(a) levels, DM
- CV Health Study:
  - Aortic sclerosis on echo in pts without CAD associated with adverse clinical outcomes
  - 50% increased risk of MI and CV death compared to controls with normal aortic valves
  - ?? Mechanism
### Table 6. Stages of Valvular AS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of AS</td>
<td>- Bicuspid aortic valve (or other congenital valve anomaly) &lt;br&gt; - Aortic valve sclerosis</td>
<td>Aortic $V_{max} &lt; 2$ m/s</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Progressive AS</td>
<td>- Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or &lt;br&gt; - Rheumatic valve changes with commissural fusion</td>
<td>Mild AS: &lt;br&gt; Aortic $V_{max} 2.0-2.9$ m/s or mean $\Delta P &lt; 20$ mm Hg &lt;br&gt; Moderate AS: &lt;br&gt; Aortic $V_{max} 3.0-3.9$ m/s or mean $\Delta P 20-39$ mm Hg</td>
<td>Early LV diastolic dysfunction may be present &lt;br&gt; Normal LV EF</td>
<td>None</td>
</tr>
<tr>
<td>C1</td>
<td>Asymptomatic severe AS</td>
<td>- Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening</td>
<td>Aortic $V_{max} &gt; 4$ m/s or mean $\Delta P &gt; 40$ mm Hg &lt;br&gt; AVA typically ≤ 1.0 cm² (or AVAI ≤ 0.6 cm²/m²) &lt;br&gt; Very severe AS is an aortic $V_{max} ≥ 5$ m/s or mean $\Delta P ≥ 60$ mm Hg</td>
<td>LV diastolic dysfunction &lt;br&gt; Mild LV hypertrophy &lt;br&gt; Normal LV EF</td>
<td>None</td>
</tr>
<tr>
<td>C2</td>
<td>Asymptomatic severe AS with LV dysfunction</td>
<td>- Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening</td>
<td>Aortic $V_{max} &gt; 4$ m/s or mean $\Delta P &gt; 40$ mm Hg &lt;br&gt; AVA typically ≤ 1.0 cm² (or AVAI ≤ 0.6 cm²/m²)</td>
<td>LV EF ≤ 50%</td>
<td>None</td>
</tr>
<tr>
<td>D1</td>
<td>Symptomatic severe high-gradient AS</td>
<td>- Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening</td>
<td>Aortic $V_{max} &gt; 4$ m/s or mean $\Delta P &gt; 40$ mm Hg &lt;br&gt; AVA typically ≤ 1.0 cm² (or AVAI ≤ 0.6 cm²/m²) but may be larger with mixed AS/AR</td>
<td>LV diastolic dysfunction &lt;br&gt; LV hypertrophy &lt;br&gt; Pulmonary hypertension may be present</td>
<td>Exercise intolerance or decreased exercise tolerance &lt;br&gt; Exertional angina &lt;br&gt; Exertional syncope or presyncope</td>
</tr>
<tr>
<td>D2</td>
<td>Symptomatic severe low-flow/low-gradient AS with reduced LV EF</td>
<td>- Severe leaflet calcification with severely reduced leaflet opening</td>
<td>AVA ≤ 1.0 cm² with resting aortic $V_{max} &lt; 4$ m/s or mean $\Delta P &lt; 40$ mm Hg &lt;br&gt; Dobutamine stress echocardiography shows AVA &lt; 1.0 cm² with $V_{max} ≥ 4$ m/s at any flow rate</td>
<td>LV diastolic dysfunction &lt;br&gt; LV hypertrophy &lt;br&gt; LV EF ≤ 50%</td>
<td>HF &lt;br&gt; Angina &lt;br&gt; Syncope or presyncope</td>
</tr>
<tr>
<td>D3</td>
<td>Symptomatic severe low-gradient AS with normal LV EF or paradoxical low-flow severe AS</td>
<td>- Severe leaflet calcification with severely reduced leaflet motion</td>
<td>AVA &lt; 1.0 cm² with aortic $V_{max} &lt; 4$ m/s or mean $\Delta P &lt; 40$ mm Hg &lt;br&gt; Indexed AVA ≤ 0.6 cm²/m² &lt;br&gt; Stroke volume index ≤ 25 mL/m² &lt;br&gt; Measured when patient is normotensive (aortic BP &lt; 140 mm Hg)</td>
<td>Increased LV relative wall thickness &lt;br&gt; Small LV chamber with low stroke volume &lt;br&gt; Restrictive diastolic filling</td>
<td>HF &lt;br&gt; Angina &lt;br&gt; Syncope or presyncope</td>
</tr>
</tbody>
</table>

AVA indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVAI, aortic valve area indexed to body surface area; BP, blood pressure; HF, heart failure; LV, left ventricular; LV EF, left ventricular ejection fraction; SP, pressure gradient; and $V_{max}$, maximum aortic velocity.
Key features on physical exam

1) Evaluation of murmur
2) Palpation of carotid upstroke
3) Assessment of S2
4) Assessment for signs of CHF
Low-flow/Low-gradient AS

- Pts with severe AS and low C.O. often present with low transvalvular pressure gradients; the elevated afterload responsible for low stroke volume
- Difficult to distinguish from pts with primary CM and only mild/moderate AS; primary contractile dysfunction is responsible for low stroke volume
- **Both situations can lead to a calculated effective valve area that can meet criteria for severe AS**
Low-flow/Low-gradient AS

- In selected pts, may be useful to determine the transvalvular gradient and to calculate valve area during low-dose pharmacological stress.
- Pts without true anatomically severe AS will exhibit an increase in the valve area and little change in gradient during an increase in stroke volume.
- In contrast, pts with severe AS will have a fixed valve area with an increase in gradient.
- Pts who fail to show an increase in stroke volume with dobutamine (‘lack of contractile reserve’) have a poor prognosis with either medical or surgical therapy.
Management: Asymptomatic patients with severe AS

- Similar outcomes to age-matched normal adults
- Therapeutic decisions are based largely on the presence of symptoms
- No medical treatments proven to prevent or delay disease process
- Small longitudinal study: event-free survival 67% at 1-year and 33% at 4 years
- <50% asymptomatic at 5 years
- **Essential component of serial exams is patient education about expected disease course and symptoms of AS**
Management: Asymptomatic patients with severe AS

- Risk of AVR exceeds any potential benefit in pts with severe AS who are truly asymptomatic with normal LV function
- Argument…..irreversible myocardial depression or fibrosis might develop during a prolonged asymptomatic stage and this may preclude an optimal surgical outcome…..NEVER been proven!
Figure 1. Indications for AVR in Patients With AS

Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D1 or C) and those with lower-gradient AS (stage D2 or D3) who do not meet the criteria for intervention.

*AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is <35 mL/m², indexed AVA is ≤0.6 cm²/m², and data are recorded when the patient is norepinephrine systolic BP ≤140 mm Hg.

AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔPmean, mean pressure gradient; and Vmax, maximum velocity.
TAVR is standard of care for aortic valve replacement in patients at high or extreme risk for surgery.
FDA APPROVED FOR:

SEVERE AORTIC STENOSIS

OR

FAILURE OF BIOPROSTHETIC
AORTIC VALVE

IN PATIENTS AT HIGH OR EXTREME
RISK FOR SURGERY
How do we define risk?

• Clinical evaluation by cardiologist and 2 CT surgeons

• STS risk calculator:
  – High: STS PROM 8%
  – Extreme: STS PROM 15% or anatomic considerations

• Many factors not taken into account in risk calculators including frailty and rehab potential
Symptomatic Aortic Valve Disease

Severe Aortic Stenosis

- Decreased aortic valve systolic opening
- Mean gradient $>40$ mmHg
- Peak velocity $>4$ m/sec
- Aortic valve area $<1.0$ cm$^2$

Failure of surgical bioprosthetic aortic valve

- Stenosis
- Insufficiency
- Combined
Edwards Sapien 3

Balloon-expandable
Self-centering
Skirt to reduce PVL

Medtronic Corevalve
Evolut-R

Self-expanding nitinol
Retrievable and
repositionable
TAVR – key parameters

• Mortality
• Performance
• Durability
• Adverse Events
  – Paravalvular leak
  – Stroke
  – Pacemaker
  – Vascular complications
TAVR – key parameters

• Mortality
• Performance
• Durability
• Adverse Events
  – Paravalvular leak
  – Stroke
  – Pacemaker
  – Vascular complications
PARTNER Trial Extreme Risk

HR 0.50, 95% CI 0.39–0.65; \( p_{\text{log-rank}} < 0.0001 \)

PARTNER Trial High Risk

Corevalve Trial High Risk

TAVR – key parameters

- Mortality
- Performance
- Durability
- Adverse Events
  - Paravalvular leak
  - Stroke
  - Pacemaker
  - Vascular complications
PARTNER 5 year data
Corevalve 2 year data

TAVR – key parameters

• Mortality
• Performance
• **Durability**
• Adverse Events
  – Paravalvular leak
  – Stroke
  – Pacemaker
  – Vascular complications
TAVR – key parameters

• Mortality
• Performance
• Durability
• Adverse Events
  – Paravalvular leak
  – Stroke
  – Pacemaker
  – Vascular complications
Causes of paravalvular leak after TAVR

1. Prosthesis-patient mismatch due to **undersizing** of the implanted device

2. Incorrect site of implantation (too low or too high)

3. Incomplete expansion of prosthesis stent frame (severe calcification)
PVL predicts mortality (PARTNER trial)

Hazard ratio, 2.11 (95% CI, 1.43–3.10)
P<0.001 by log-rank test

No. at Risk
None or trace 158
Mild to severe 160

<table>
<thead>
<tr>
<th>Months after Implantation</th>
<th>None or trace</th>
<th>Mild to severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>142</td>
<td>134</td>
</tr>
<tr>
<td>6</td>
<td>134</td>
<td>112</td>
</tr>
<tr>
<td>12</td>
<td>121</td>
<td>101</td>
</tr>
<tr>
<td>18</td>
<td>84</td>
<td>64</td>
</tr>
<tr>
<td>24</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>
PVL – Corevalve Extreme Risk Pivotal Trial

Only Severe PVL Affected Mortality

- None/Trivial (N=214)
- Mild (N=179)
- Moderate (N=40)
- Severe (N=7)

Log-rank P < 0.001

All-Cause Mortality

Months

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

0 6 12 18 24

85.7%

38.2%

35.9%

30.3%
TAVR – key parameters

- Mortality
- Performance
- Durability
- Adverse Events
  - Paravalvular leak
  - Stroke
  - Pacemaker
  - Vascular complications
30 day all stroke rate

**PARTNER I and II Trials**

<table>
<thead>
<tr>
<th>Device</th>
<th>Group</th>
<th>Neurologist evaluations (pre- and post)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAPIEN</td>
<td>Major stroke &lt; 1%</td>
</tr>
<tr>
<td>P1B (TF)</td>
<td>179</td>
<td>6.7%</td>
</tr>
<tr>
<td>P1A (Overall)</td>
<td>344</td>
<td>5.6%</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>276</td>
<td>4.1%</td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td>284</td>
<td>4.3%</td>
</tr>
<tr>
<td>S3HR (Overall)</td>
<td>583</td>
<td>1.5%</td>
</tr>
<tr>
<td>S3i (Overall)</td>
<td>1076</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Kodali SK. ACC 2015
TAVR – key parameters

• Mortality
• Performance
• Durability
• Adverse Events
  – Paravalvular leak
  – Stroke
  – Pacemaker
  – Vascular complications
Pacemaker Rates

Corevalve
- Pivotal trials: 20%
- Evolut R: 10-12%

Sapien
- THV/XT: 3-5%
- S3: 8-10%

Need for PPM has not consistently been associated with worse outcomes
TAVR – key parameters

• Mortality
• Performance
• Durability
• Adverse Events
  – Paravalvular leak
  – Stroke
  – Pacemaker
  – Vascular complications
Vascular access

- Corevalve Evolut R – 14Fr (5mm vessel)
- Sapien 3 – 14-16Fr (5.5-6mm vessel)
- Percutaneous femoral artery
- Subclavian artery as preferred alternative access site
Expansion to lower risk

• PARTNER 2 trials reported ACC 2016

• Actively enrolling: SURTAVI intermediate risk trial
  – STS 3-8 or intermediate risk by surgeon’s evaluation
  – Randomized to Corevalve versus surgery

• Upcoming trials: Low risk
  – No bottom STS score
  – Age > 65
  – Randomized to surgery
PARTNER 2A

- Sapien XT
- CT imaging not universally used

Leon MB, NEJM 2016.
Mitral Regurgitation: Primary vs Secondary

• Degenerative and functional mitral regurgitation are different diseases
  – Degenerative MR is a primary *valvular problem* and requires a *valvular solution*
  – Functional MR is a *ventricular problem* and requires treatment of the underlying cause; role of treatment of the valve is unclear
Degenerative vs Functional MR

- Normal mitral valve
- Degenerative MR caused by mitral valve prolapse
- Degenerative MR caused by flail leaflet
- Functional MR
## Causes of chronic mitral regurgitation

<table>
<thead>
<tr>
<th>Leaflet</th>
<th>Papillary muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative valve disease (mitral valve prolapse)</td>
<td>Ischemia or infarction</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Infective endocarditis (acute and chronic)</td>
<td>Left ventricular aneurysm</td>
</tr>
<tr>
<td>Systemic inflammatory disorders</td>
<td>Papillary muscle rupture</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Trauma</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>Mitral annulus</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Calcification</td>
</tr>
<tr>
<td>Ehlers-Danlos syndromes</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>Congenital</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Mitral valve clefts</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Parachute mitral valve</td>
<td>Dilation</td>
</tr>
<tr>
<td>Endocardial cushion defects</td>
<td>Connective tissue disorder</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy (systolic anterior movement of mitral valve)</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Drug-related</td>
<td>Myxomatous mitral valve disease</td>
</tr>
<tr>
<td><strong>Chordae tendineae</strong></td>
<td>Prosthetic valve</td>
</tr>
<tr>
<td>Myxomatous valve disease (mitral valve prolapse)</td>
<td>Paravalvular leak</td>
</tr>
<tr>
<td>Infective endocarditis (acute and chronic)</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Ring or strut fracture</td>
</tr>
<tr>
<td>Spontaneous rupture</td>
<td>Occluder dysfunction</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Pannus and/or thrombus formation</td>
</tr>
<tr>
<td>Trauma</td>
<td>Leaflet deterioration (tissue valves)</td>
</tr>
</tbody>
</table>
Phonocardiograms from normal and abnormal heart sounds
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

*cm: centimeter; LA: left atrium; ml: milliliter.*
Expansion to lower risk

- Symptoms in chronic MR are related to:
  - Severity
  - Rate of progression
  - PA pressures
  - Arrhythmias (AF)
  - Associated cardiac disease
Degenerative vs Functional MR
Chronic MR: Natural History

- Transition from compensated to decompensated occurs over years/decades
- Nature of this transition is elusive/poorly understood
- Occurs over years/decades

- Severity of MR
- CV response to regurgitant volume
- Etiology of MR
Chronic MR: Natural History

• Transition from compensated to decompensated is also an elusive and poorly understood pathophysiology

• May occur as a consequence of progressive increments in the regurgitant volume and/or chamber size

• Substantial and progressive ventricular enlargement:
  - Increased LV diastolic volume/pressures
  - Increased systolic wall stress
  - Decline in ejection fraction
  - Progressive atrial enlargement/arrhythmias, pulmonary hypertension, and eventually CHF symptoms
Chronic MR: Natural History

- These considerations do not identify the optimal time for mitral valve replacement or repair
- They do help to predict a poor LV response to corrective surgery and provide a picture of the options of surgical or nonsurgical treatment

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Compensated</th>
<th>Transitional</th>
<th>Decompensated</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic dimension, mm</td>
<td>&lt;63</td>
<td>65 to 68</td>
<td>&gt;70</td>
</tr>
<tr>
<td>End-systolic dimension, mm</td>
<td>&lt;42</td>
<td>44 to 45</td>
<td>&gt;47</td>
</tr>
<tr>
<td>Fractional shortening, percent</td>
<td>&gt;34</td>
<td>31 to 32</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>
Hemodynamic Stages of Mitral Regurgitation

Libby. Braunwald’s Heart Disease. 8th Ed.
### Table 13. Stages of Primary MR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| A     | At risk of MR | - Mild mitral valve prolapse with normal coaptation  
- Mild valve thickening and leaflet restriction | - No MR jet or small central jet area <20% LA on Doppler  
- Small vena contracta <0.3 cm | - None | - None |
| B     | Progressive MR | - Severe mitral valve prolapse with normal coaptation  
- Rheumatic valve changes with leaflet restriction and loss of central coaptation  
- Prior IE | - Central jet MR 20%–40% LA or late systolic eccentric jet MR  
- Vena contracta <0.7 cm  
- Regurgitant volume <50 mL  
- Regurgitant fraction <50%  
- ERO <0.40 cm²  
- Angiographic grade 1–2+ | - Mild LA enlargement  
- No LV enlargement  
- Normal pulmonary pressure | - None |
| C     | Asymptomatic severe MR | - Severe mitral valve prolapse with loss of coaptation or flail leaflet  
- Rheumatic valve changes with leaflet restriction and loss of central coaptation  
- Prior IE  
- Thickening of leaflets with radiation heart disease | - Central jet MR >40% LA or hoxystolic eccentric jet MR  
- Vena contracta ≥0.7 cm  
- Regurgitant volume ≥50 mL  
- Regurgitant fraction ≥50%  
- ERO ≥0.40 cm²  
- Angiographic grade 3–4+ | - Moderate or severe LA enlargement  
- LV enlargement  
- Pulmonary hypertension may be present at rest or with exercise  
- LVEF >60% and LVEDD <40 mm  
- LVEF ≤60% and LVEDD ≥40 mm | - None |
| D     | Symptomatic severe MR | - Severe mitral valve prolapse with loss of coaptation or flail leaflet  
- Rheumatic valve changes with leaflet restriction and loss of central coaptation  
- Prior IE  
- Thickenin of leaflets with radiation heart disease | - Central jet MR >40% LA or hoxystolic eccentric jet MR  
- Vena contracta ≥0.7 cm  
- Regurgitant volume ≥50 mL  
- Regurgitant fraction ≥50%  
- ERO ≥0.40 cm²  
- Angiographic grade 3–4+ | - Moderate or severe LA enlargement  
- LV enlargement  
- Pulmonary hypertension present  
- Exertional dyspnea | - Decreased exercise tolerance  
- Exertional dyspnea |

* Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

ERO indicates effective regurgitant orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; and MR, mitral regurgitation.
Table 14. Stages of Secondary MR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics*</th>
<th>Associated Cardiac Findings</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of MR</td>
<td>Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy</td>
<td>No MR jet or small central jet area &lt;20% LA on Doppler</td>
<td>Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities</td>
<td>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</td>
</tr>
<tr>
<td>B</td>
<td>Progressive MR</td>
<td>Regional wall motion abnormalities with mild tethering of mitral leaflet</td>
<td>ERO &lt;0.20 cm²</td>
<td>Regional wall motion abnormalities with reduced LV systolic function</td>
<td>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annular dilation with mild loss of central coaptation of the mitral leaflets</td>
<td>Regurgitant volume &lt;30 mL</td>
<td>LV dilation and systolic dysfunction due to primary myocardial disease</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe MR</td>
<td>Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet</td>
<td>ERO ≥0.20 cm²</td>
<td>Regional wall motion abnormalities with reduced LV systolic function</td>
<td>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annular dilation with severe loss of central coaptation of the mitral leaflets</td>
<td>Regurgitant volume ≥30 mL</td>
<td>LV dilation and systolic dysfunction due to primary myocardial disease</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe MR</td>
<td>Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet</td>
<td>ERO ≥0.20 cm²</td>
<td>Regional wall motion abnormalities with reduced LV systolic function</td>
<td>HF symptoms due to MR persist even after revascularization and optimization of medical therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annular dilation with severe loss of central coaptation of the mitral leaflets</td>
<td>Regurgitant volume ≥30 mL</td>
<td>LV dilation and systolic dysfunction due to primary myocardial disease</td>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regurgitant fraction ≥50%</td>
<td></td>
<td>Exertional dyspnea</td>
</tr>
</tbody>
</table>

* Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crossectional shape of the proximal convergence. 2D indicates 2-dimensional, ERO, effective regurgitant orifice; HF, heart failure; LA, left atrium; LV, left ventricular; MR, mitral regurgitation; and TTE, transthoracic echocardiogram.
Echocardiography Surveillance

- Mild MR and no evidence of LV enlargement, LV dysfunction, or pulmonary hypertension
  - Echocardiography every three to five years

- Moderate MR
  - Echocardiography every one to two years

- Severe MR
  - Echocardiography every 6 to 12 months (or sooner if symptoms occur)
Pharmacotherapy

- ACEI or ARB
- Beta blockers
- Mineralocorticoid antagonists
- Diuretics

Randomized clinical trials have shown that these therapies improve cardiac function, relieve symptoms, and enhance survival
Cardiac Resynchronization Therapy (CRT)

• CRT improves survival in selected patients with systolic HF and ventricular dyssynchrony

• CRT often improves secondary MR in patients with ventricular dyssynchrony, and CRT is recommended in patients with secondary MR who meet criteria for CRT
Figure 4. Indications for Surgery for MR

*Mitral valve repair is preferred over MVR when possible.

AF: atrial fibrillation; CAD: coronary artery disease; CRT: cardiac resynchronization therapy; ERO: effective regurgitant orifice; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; MR: mitral regurgitation; MV: mitral valve; MVR: mitral valve replacement; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; RF: regurgitant fraction; RVol: regurgitant volume; and Rx: therapy.
A Largely Untreated Patient Population

Mitral Regurgitation 2009 U.S. Prevalence

Total MR Patients\(^1,2\)

Eligible for Treatment\(^3,4\)
(MR Grade ≥3+)

Annual Incidence\(^3\)
(MR Grade ≥3+)

Annual MV Surgery\(^5\)

4,100,000

1,670,000

30,000

Untreated Large and Growing Clinical Unmet Need

14% Newly Diagnosed Each Year

Only 2% Treated Surgically

1.0 INDICATION FOR USE 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 [degenerative 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.

*Prohibitive risk: STS > 8 for replacement or > 6 for repair, porcelain aorta, frailty, hostile chest, cirrhosis, severe PAH
Everest II: Freedom from Death, MV surgery or reoperation

<table>
<thead>
<tr>
<th>Patients At Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device Group</strong></td>
<td>178 136 128 117 109 98 45</td>
</tr>
<tr>
<td><strong>Control Group</strong></td>
<td>80 75 69 63 54 49 21</td>
</tr>
</tbody>
</table>

RCT Device (n = 178)
RCT Surgery (n = 80)
Everest II: Freedom from Death
Class IIb - Transcatheter MV repair may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe primary (degenerative) MR who have a reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities.
Isolated Surgery for Functional (Secondary) MR

Solid – Med therapy
Dotted – MVR
COAPT Trial for Functional MR

- FMR ≥ 3+
- NHYA II, III, amb IV
- Max therapy (PCI, CRT, OMT)
- LVEF 20-50%
- LVESD ≤ 70mm
- Not appropriate for open MVR by heart team (CT surgery and CHF specialist)
- Hospitalization for CHF or elevated BNP
Transcatheter Mitral Valve Replacement

- Edwards
- Medtronic
- Abbott
- Boston Scientific
- Others
Transcatheter Mitral Valve Replacement

- Edwards
- Medtronic
- Abbott
- Boston Scientific
- Others

$2,000,000,000
TAVR is standard of care for aortic valve replacement in patients at high or extreme risk for surgery.