Aortic Stenosis
and
Transcatheter Aortic Valve Replacement

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What is the Aortic valve?

- The heart is divided into four chambers
- Each chamber is separated by a one-way valve
Aortic Valve Structure and Function

- The aortic valve separates the left ventricle (the main pumping chamber of the heart) and the aorta (the largest artery in the body).
- The aortic valve normally consists of three leaflets.
- When the left ventricle contracts, it forces blood through the aortic valve, to the aorta and then to the rest of the body.
- When the LV expands again, the aortic valve prevents the blood from returning to the ventricle.
About Aortic Stenosis

Aortic stenosis is a narrowing of the aortic valve opening that restricts normal blood flow to the entire body.
<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-Related Calcific Aortic Stenosis</td>
<td>Aortic stenosis in patients over the age of 65 is usually caused by calcific (calcium) deposits associated with aging</td>
</tr>
<tr>
<td>Infection</td>
<td>Aortic stenosis can be caused by various infections</td>
</tr>
<tr>
<td>Rheumatic Fever</td>
<td>Adults who have had rheumatic fever may also be at risk for aortic stenosis</td>
</tr>
<tr>
<td>Congenital Abnormality</td>
<td>In some cases adults may develop aortic stenosis resulting from a congenital abnormality</td>
</tr>
</tbody>
</table>
Prevalence of Aortic Stenosis

- Aortic stenosis is common and its prevalence increases with age
- Aortic stenosis is estimated to be prevalent in up to 7% of the population over the age of 65
It is estimated that in the US:
1,500,000 people have aortic stenosis
500,000 have severe aortic stenosis; and
250,000 have symptoms from severe aortic stenosis
Number of people age 65 and over, by age group, selected years 1900–2006 and projected 2010–2050

Note: Data for 2010–2050 are projections of the population.
Reference population: These data refer to the resident population.
Surgical Management: AVR

It is estimated that up to 1/3rd of patient’s who would qualify for surgical intervention on clinical grounds (symptoms and severity) are managed “conservatively” because the risk of surgery in this population is considered prohibitive.
Natural History

- Progressive and deadly if left untreated
- After onset of symptoms, average survival is 50% at 2 years and 20% at 5 years without treatment.
Symptoms of Aortic Stenosis

- Shortness of breath
- Syncope / Pre-syncope
- Angina
- Palpitations
- Sudden cardiac death
Echocardiographic Guidelines are the Gold Standard in Assessing Aortic Stenosis Severity

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m/s)</td>
<td>&lt; 3.0</td>
<td>3.0 – 4.0</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&lt; 25</td>
<td>25 – 40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>&gt; 1.5</td>
<td>1.0 - 1.5</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Valve area index (cm²/m²)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt; 0.6</td>
</tr>
</tbody>
</table>

2008 ACC/AHA Guidelines
Management

For patients with less advanced disease, follow-up echocardiography is recommended as follows, for patients with:

- Severe AS: yearly
- Moderate AS: every 3 years
- Mild AS: every 5 years

In advanced stages, valve replacement is required to correct this problem.
- There is no medical treatment to reverse aortic stenosis

Indications for valve replacement:
- Severe AS and symptoms
- Severe AS with heart dysfunction, defined by an ejection fraction < 50%
- Moderate or severe AS undergoing cardiac surgery for coronary or other valvular heart disease
Surgical Management:

Standard surgical aortic valve replacement continues to be associated with great outcomes
  • Remains the gold standard for treatment of severe aortic stenosis
Management: Transcatheter Aortic Valve Replacement

For patients who are either at high risk or deemed too sick for conventional open-heart surgery, this less invasive procedure allows the aortic valve to be replaced with a new valve while the heart is still beating.
Management: Transcatheter Aortic Valve Replacement

There are three potential access points for this less invasive procedure. Decision as to which site is utilized will be based on patient's specific anatomy.
Advantages and limits of conventional aortic valve replacement (AVR) and transcathether aortic valve replacement (TAVR)

<table>
<thead>
<tr>
<th>Conventional AVR</th>
<th>TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• easy operation</td>
<td>• less invasive, fast</td>
</tr>
<tr>
<td>• decades of evidence</td>
<td>• intubation not required*</td>
</tr>
<tr>
<td>• excellent results</td>
<td>• no extracorporal circulation</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td><strong>Limitations</strong></td>
</tr>
<tr>
<td>• invasive (sternotomy)</td>
<td>• aortic regurgitation</td>
</tr>
<tr>
<td>• intubation</td>
<td>• stroke</td>
</tr>
<tr>
<td>• use of extracorporal circulation</td>
<td>• vascular complications</td>
</tr>
<tr>
<td></td>
<td>• need for pacemaker</td>
</tr>
</tbody>
</table>
In conclusion

TAVR represents the standard of care for patients with severe symptomatic aortic stenosis who are deemed inoperable (absolute 20% reduction in mortality at 1 year)

TAVR is seen as an alternative treatment option to surgical aortic valve replacement (SAVR) in a subset of patients with high postoperative risk

Evolving / improving technologies and techniques will continue to improve safety and efficacy of this less invasive strategy (retrievable / repositionable / smaller)
Transcatheter Mitral Valve Repair for the Treatment of Mitral Regurgitation

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COR Healthcare Medical Associates
Torrance Memorial Medical Center

Agenda

The Burden of Mitral Regurgitation
Mitral Regurgitation is an Under-treated Disease
Options for Patients
Overview of Transcatheter Mitral Valve Repair

Mitral Regurgitation (MR)

MR occurs when the mitral valve fails to close completely, causing blood flow to flow backward.

Symptoms may include:
- Shortness of breath
- Heart palpitations
- Fatigue
- Lightheadedness
- Cough
- Swollen feet or ankles
- Excessive urination

See Important Safety Information Referenced Within
Mitral Regurgitation Etiologies

**Causes**

- **Degenerative MR**
  - Also known as primary or organic MR
  - Usually caused by anatomic defect of one or more structures comprising the mitral valve apparatus—annulus, leaflets, chordae tendineae, and the papillary muscles

- **Functional MR**
  - Also known as secondary MR
  - Results from left ventricular (LV) dysfunction and dilation, which causes other normal valve components to fail and results in MR

Mitral Valve Disease is Common and Increases with Age

Mitral regurgitation (MR) is the most common type of heart valve insufficiency in the US


Prevalence of Valvular Heart Disease by Age


MR Progresses to Heart Failure

MR initiates a cascade of events progressing to heart failure, then death, if untreated

Heart Failure and MR are an Economic Burden

- Estimated annual cost of heart failure is $39.2 billion
- Majority of treatment costs are due to hospital care
- Hospitalization following discharge from heart failure admission is high (25%-50% at 30 days)

Distribution of costs for heart failure treatment in the USA

- Hospital Care, 60%

Annual cost of heart failure places a large burden on health care budgets in U.S.

Moderate or greater MR is estimated to occur in 55% patients with heart failure, with the number increasing to 74% in heart failure patients.

Severe MR Leads to Increased Hospital Admissions and Lower Survival Rates

- Significantly lower survival rates experienced by patients with moderate to severe MR
- Significantly higher hospital admissions for HF experienced by patients with moderate to severe MR

A Largely Untreated Patient Population

- Mitral Regurgitation 2009 U.S. Prevalence
- Total MR Patients: 4,100,000
- Eligible for Treatment (MR Grade ≥3+): 1,670,000
- Annual Incidence (MR Grade ≥3+): 30,000
- Annual MV Surgery: Only 2% Treated Surgically

2. Markwick et al. Prognostic Implications of Moderate and Severe Mitral Regurgitation in Contemporary Care. TCT 2012
High-risk MR Patients are Not Surgical Candidates

Nearly half of MR patients not considered appropriate for mitral valve surgery.

Factors prohibiting surgery include:
- Impaired LVEF
- High operative risk
- Multiple comorbidities
- Advanced age

*High-Risk Patients* defined as any patient with an EF<35% or an age of 75+

49% High-Risk Patients
49% Surgical Candidates
2% Surgical Patients

When patients with VHD are referred for intervention in a timely manner, there is an improved outcome in preservation of ventricular function as well as enhanced survival.

MitraClip® Therapy

Filling a Treatment Gap

- Medical therapy is limited to symptom management
- MV surgery has been the only option that reliably reduces MR
- A significant gap exists between medical and surgical options
- MitraClip® therapy is a first-in-class, percutaneous option to reduce MR

INDICATION FOR USE:
Prohibitive Risk Primary MR (DMR)

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.
3. 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 (426). (Level of Evidence: B)

An RCT of percutaneous mitral valve repair using the MitraClip device versus surgical mitral repair was conducted in the United States. The clip was found to be safe but less effective than surgical repair because residual MR was more prevalent in the percutaneous group. However, the clip did reduce severity of MR, improved symptoms, and led to reverse LV remodeling. Percutaneous mitral valve repair should only be considered for patients with chronic primary MR who remain severely symptomatic with NYHA class III/IV HF symptoms despite optimal GDMT for HF and who are considered inoperable."¹

MitraClip® System Overview

Procedure Imaging:
MitraClip® Procedure is Guided by Echocardiography
PATIENT HISTORY

• 80 year old male. C/O increasing shortness of breath for 2-3 months. Presently c/o SOB walking one block, uses 3 pillows to sleep and notes his ankles are swelling.

• Past Medical History: Hypertension; CAD and previous Percutaneous Transluminal Coronary Angioplasty/Stent.

• Echocardiogram: Moderate Aortic Stenosis, Ejection Fraction 35%

• Chest Xray: interstitial edema, cardiac enlargement

YOU HAVE HEART FAILURE!!!!

NOT A DEATH SENTENCE!!!!
Heart Failure

- Complex syndrome due to any structural or functional impairment of ventricle
- Usually due to impaired LV function

Heart Failure

- Epidemiology
  - Lifetime risk
    - 20% Americans >40 years old
    - >650,000 new cases per year
  - Incidence increase with age
    - 65-69 years old 20/1,000
    - >85 years old >80/1,000
    - 5.1 million Americans clinically manifest heart failure

Heart Failure

- Heart failure increased 1994 – 2003
- Medicare population 90 to 121/1,000
- 1 in 5 Americans >65 years old by 2050
- Heart failure worse in this age group
- Problem will worsen
Heart Failure

- Leading cause of hospitalization
- 3rd leading cause of death
- Prevalence increasing
- Continuum of treatment
  - Acute episodes and hospitalization
  - Chronic management – outpatient

Heart Failure

- Outpatient care accounts for significant proportion of heart failure expenditure
- Re-hospitalization major issue

Causes of Heart Failure

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>Ischemic Heart Disease</td>
</tr>
<tr>
<td>Dysrhythmias</td>
<td>HTN</td>
</tr>
<tr>
<td>Acute papillary muscle rupture</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Valvular disorders</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Metabolic Disorders</td>
</tr>
</tbody>
</table>
ACCF/AHA Stages vs NYHA Classes

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Structural Disease</td>
<td>Structural Disease</td>
<td>Structural Disease</td>
</tr>
<tr>
<td>No symptoms</td>
<td>No symptoms</td>
<td>Current or previous symptoms</td>
<td>Refractory Symptoms</td>
</tr>
</tbody>
</table>

Asymptomatic — NYHA Class I

WHAT IS EJECTION FRACTION??!!

Systolic Dysfunction

- HFrEF: Heart Failure with reduced EF
- Defined as HF EF<40%
- Ventricle is dilated, thin-walled
- Results: Shortness of breath and fluid retention

Results:
- Shortness of breath and fluid retention
Diastolic Dysfunction

- HFrEF: Heart Failure with preserved EF
- Defined as HF EF > 50%
- Characterized by high filling pressures due to stiff or noncompliant ventricles
- Ventricle becomes thickened and concentrically hypertrophied, with a normal or small cavity

LV Dysfunction: Systolic and Diastolic

**Symptoms**
- Shortness of Breath/DOE
- Orthopnea / PND
- Weight gain with lower extremity swelling
- Coughing
- Fatigue, weakness, dizziness
- Decreased appetite
- Tachycardia/Palpitations

**Physical Findings**
- Jugular venous distention (JVD)
- S3 or S4 heart sounds
- Basilar crackles
- Ascites
- Tachycardia
- Irregular heart rhythm
- Hypertension/Hypotension

Pathophysiology of ADHF

- Neurohormonal Activation
  - SNS
  - RAAS
Heart Failure Therapy

Therapy – Chronic Heart Failure

- Diuretics
- ACEI / ARB
- Beta Blocker
- Aldosterone antagonist
- Hydralazine-Oral Nitrate

Diuretics

- Used to relieve fluid retention
- Common complication is electrolyte depletion
- High doses are associated with an increased mortality
- Some patients can be taught to adjust their diuretic dose
- Types of Diuretics:
  - Thiazides: useful in hypertensive HF patient with mild fluid retention
  - Loop diuretics: effective in the presence of renal impairment
### Loop Diuretics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Daily Dose</th>
<th>Max Total Daily Dose</th>
<th>Elimination Renal-Met</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>20-40mg qd or bid</td>
<td>600mg</td>
<td>65%R-35%M</td>
<td>4-6hrs</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 – 1.0mg qd or bid</td>
<td>10mg</td>
<td>62%R-32%M</td>
<td>6-8hrs</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10-20mg qd</td>
<td>200mg</td>
<td>20%R-80%M</td>
<td>12-16hrs</td>
</tr>
</tbody>
</table>

### Diuretic Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated.</td>
<td>1</td>
<td>C</td>
</tr>
</tbody>
</table>

### CONSENSUS

Guidelines for ACE Inhibitor

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors are recommended for all patients with HFrEF</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Angiotensin Receptor Blockers (ARBs)

- Block AT1 receptors, which bind circulating angiotensin II
- Should not be considered equivalent or superior to ACE inhibitors

ARBs Used in Clinical Trials

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Daily Dose</th>
<th>Target Dose</th>
<th>Mean Dose in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Atacand</td>
<td>4-8 mg qd</td>
<td>32 mg qd</td>
<td>24 mg/day</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozaar</td>
<td>12.5 - 25 mg qd</td>
<td>150 mg qd</td>
<td>129 mg/day</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>20-40 mg bid</td>
<td>160 mg bid</td>
<td>54 mg/day</td>
</tr>
</tbody>
</table>
Guidelines for ARBs

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs are recommended in patients with HFrEF that are ACE inhibitor intolerant</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ARBs are reasonable as alternatives to ACE inhibitors as first line therapy in HFrEF</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>

Beta Blockers

- Cardioprotective effects due to blockade of excessive SNS stimulation
- Short term effects: BBs decrease myocardial contractility
- Long-term: symptomatic improvement in patients treated with certain beta-blockers
- Improve LV function & exercise tolerance
- Improvement of symptoms of HF
- Decreased mortality and hospitalizations

Beta Blockers Used in Clinical Trials

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Dose</th>
<th>Daily Dose</th>
<th>Target Dose</th>
<th>Mean Dose in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>Zebeta</td>
<td>1.25 mg qd</td>
<td>10 mg qd</td>
<td>8.6 mg/day</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Coreg</td>
<td>3.125 mg qd</td>
<td>25 mg bid</td>
<td>37 mg/day</td>
<td></td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>Coreg</td>
<td>10 mg qd</td>
<td>80 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate CR/XL</td>
<td>Toprol XL</td>
<td>12.5 mg qd</td>
<td>200 mg qd</td>
<td>159 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- HFrEF - Heart Failure with Reduced Ejection Fraction
- ACE - Angiotensin-Converting Enzyme
- ARB - Angiotensin Receptor Blocker
- SNS - Sympathetic Nervous System
- LV - Left Ventricular
Guidelines for Beta Blockers in HFrEF

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Aldosterone Receptor Antagonists (ARAs)

- Inhibits aldosterone
- Diuretic and antihypertensive effects

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Daily Dose</th>
<th>Max Total Daily Dose</th>
<th>Elimination</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5 – 25mg qd</td>
<td>50 mg</td>
<td>Metabolic</td>
<td>48-72 hrs</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25-50 mg qd</td>
<td>100mg</td>
<td>Renal, Metabolic</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
### Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended in symptomatic patients with NYHA class II-IV who have LVEF of 35% or less</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Recommended in patients following an acute MI who have LVEF of 40% or less with symptoms of HF or history of diabetes</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Inappropriate use of ARAs may be harmful</td>
<td>III: Harm</td>
<td>B</td>
</tr>
</tbody>
</table>

### Hydralazine and Oral Nitrates
- Decreases mortality, improved functional class as compared with the use of digoxin and diuretics
- Decreases mortality, morbidity & symptoms in AA patients

**Consider if:**
- There is evidence of progression of HF despite optimal regimens that include BB, ACE (or ARBs), and aldosterone blockers, plus diuretics and possibly digoxin.
- ACE-I and ARB contraindicated (hyperkalemia, anioedema, or CrCl < 30 mL/min, OR
- Additional BP lowering needed after ACE-I and/or ARB dose maximized

### HEART FAILURIE THERAPY
- Latest and greatest:
  - Angiotensin Receptor Blocker Neprilysin Inhibitor (ARNI)
  - more effective than best HF therapy in reducing risk of CV death and HF hospitalization.
  - Ivabradine- Heart rate control in HF
Angiotensin Receptor Neprilysin Inhibitor (ARNI)

- Valsartan/Sacubitril (Entresto)
- Combination AR + NI = ARNi
- Neprilysin causes degradation of atrial and brain natriuretic peptide (ANP & BNP)
- PARADIGM- HF study
- Summary: More effective than enalapril in reducing the risk of CV death and HF hospitalization

Ivabradine

- Approved in April 2015
- Shift Trial
- Indications in Heart Failure
- Results

HEART FAILURE THERAPY

Electrical Therapies
- Implantable Cardiostim Ddefibrillator
- Cardiac Resynchronization Therapy
Mechanical Cardiac Assistance
- Left Ventricular Assist Disease
- Cardiac Transplant

Cardiac Transplant
What, if anything, did we learn today and Where do we go from here?