Compendium

Circulation Research Compendium on Aortic Valve Disease:

Introduction to the Compendium
Introduction to Aortic Stenosis
Hemodynamic and Cellular Response Feedback in Calcific Aortic Valve Disease
Molecular and Cellular Aspects of Calcific Aortic Valve Disease
Fibrocalcific Aortic Valve Disease
Current Management of Calcific Aortic Stenosis

Donald Heistad & Linda Demer, Editors

Current Management of Calcific Aortic Stenosis

Brian R. Lindman, Robert O. Bonow, Catherine M. Otto

Abstract: Calcific aortic stenosis is a progressive disease with no effective medical therapy that ultimately requires aortic valve replacement (AVR) for severe valve obstruction. Echocardiography is the primary diagnostic approach to define valve anatomy, measure aortic stenosis severity, and evaluate the left ventricular response to chronic pressure overload. In asymptomatic patients, markers of disease progression include the degree of leaflet calcification, hemodynamic severity of stenosis, adverse left ventricular remodeling, reduced left ventricular longitudinal strain, myocardial fibrosis, and pulmonary hypertension. The onset of symptoms portends a predictably high mortality rate unless AVR is performed. In symptomatic patients, AVR improves symptoms, improves survival, and, in patients with left ventricular dysfunction, improves systolic function. Poor outcomes after AVR are associated with low-flow low-gradient aortic stenosis, severe ventricular fibrosis, oxygen-dependent lung disease, frailty, advanced renal dysfunction, and a high comorbidity score. However, in most patients with severe symptoms, AVR is lifesaving. Bioprosthetic valves are recommended for patients aged >65 years. Transcatheter AVR is now available for patients with severe comorbidities, is recommended in patients who are deemed inoperable, and is a reasonable alternative to surgical AVR in high-risk patients. (Circ Res. 2013;113:223-237.)

Key Words: aortic valve stenosis ■ heart failure ■ heart valve diseases ■ heart valve prosthesis ■ hypertrophy, left ventricular

The prevalence of calcific aortic valve disease approaches 25% of all adults aged >65 years. Most of these patients have only mild focal valve thickening, or aortic valve sclerosis, with normal valve function, but a significant number, ranging from 2% to 5% of all older adults, have significant aortic stenosis (AS) with obstruction to left ventricular (LV) outflow. Aortic sclerosis progresses to mild AS in <15% of patients over 2 to 7 years. However, once even mild valve obstruction is present, hemodynamic progression is common, leading to severe symptomatic AS that requires aortic valve replacement (AVR). An increasing number of older adults with calcific AS will be seen during the next few decades given worldwide demographics of an aging population.

Diagnosis

Clinical Presentation

The initial diagnosis of calcific AS typically is based on detection of a systolic murmur followed by echocardiographic confirmation; in some cases, AS is first recognized on echocardiography requested for other indications. Most patients are diagnosed long before the onset of symptoms and are followed prospectively on a regular basis until AVR is indicated. Others present with symptoms, including exertional dyspnea, heart failure, angina or syncope, and require intervention soon after diagnosis. A smaller subset of patients presents with advanced disease with critical valve obstruction resulting in severe LV systolic dysfunction because of the high afterload imposed by the stenotic valve.

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Valve Anatomy

Transthoracic echocardiography is the primary diagnostic modality for evaluating aortic valve anatomy, AS severity, and the LV response to chronic pressure overload. A congenital bicuspid valve is diagnosed accurately when short axis 2-dimensional (2D) or 3D images show 2 leaflets in systole; diastolic images are unreliable as a bicuspid valve with a raphe in 1 leaflet may be mistaken for a trileaflet valve and vice versa. Determination of the number of valve leaflets is more problematic once significant calcification is present.9 Rheumatic AS is distinguished by commissural fusion and mitral valve involvement.

Hemodynamic Severity

Standard measures of AS severity are the maximum velocity ($V_{\text{max}}$) across the stenotic valve, the mean transaortic pressure gradient ($\Delta P_{\text{mean}}$) calculated with the Bernoulli equation, and the functional aortic valve area (AVA) calculated with the continuity equation (Table 1; Figure 1). Echocardiographic $\Delta P_{\text{mean}}$ and AVA calculations have been well validated against invasive measurements and are now the clinical standard of care.8,10 AVA calculation is especially important when transaortic volume flow rate is higher than normal (as with coexisting aortic regurgitation) or lower than normal (as with LV dysfunction or a small normally functioning left ventricle) because transaortic velocities and gradients vary with volume flow rate. In patients with mixed stenosis and regurgitation, the diagnosis of severe valve disease will be evident on the basis of a high transaortic gradient. However, with a low transaortic flow rate, severe AS might be missed if only velocity or pressure gradient data are considered.

Some clinicians index AVA to body size to account for expected smaller valve areas in smaller patients. However, indexing AVA to body size may not be appropriate in overweight or obese patients. Instead, the ratio of LV outflow to aortic velocity may be useful because this ratio is, in effect, indexed to the patient’s own LV outflow tract size. A normal ratio is close to 1.0 with a ratio of 0.25 indicating a valve area 25% of normal. Direct planimetry of AVA is sometimes possible, particularly with transesophageal or 3D imaging, but overall accuracy of this approach is limited because of the nonplanar anatomy of the stenotic valve and calcification-related acoustic shadowing and reverberations.

Cardiac magnetic resonance (CMR) imaging is useful when echocardiographic data are suboptimal or conflicting with clinical assessment of AS severity. CMR can distinguish between bicuspid or trileaflet valve anatomy and provide accurate assessment of peak jet velocity. CMR is also valuable for assessing aortic root and ascending aortic anatomy in patients with a bicuspid valve.

### Table 1. Classification of Aortic Stenosis Severity

<table>
<thead>
<tr>
<th>Valve Anatomy</th>
<th>Aortic Velocity, m/s</th>
<th>Mean Gradient, mm Hg</th>
<th>Aortic Valve Area, cm²</th>
<th>Other Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic sclerosis</td>
<td>Focal leaflet thickening with normal leaflet motion</td>
<td>$&lt;2.5$</td>
<td>$&lt;10$</td>
<td>3–4</td>
</tr>
<tr>
<td>Mild AS</td>
<td>Mild leaflet thickening with mildly reduced motion</td>
<td>2.5–3</td>
<td>10–20</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Moderate AS</td>
<td>Mild to moderate Ca++ with moderately reduced leaflet motion</td>
<td>3–4</td>
<td>20–40</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>Severe AS</td>
<td>Moderate to severe Ca++ with little leaflet motion</td>
<td>$&gt;4$</td>
<td>$&gt;40$</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Low-output low-gradient severe AS with reduced EF</td>
<td>Severe valve Ca++, reduced leaflet motion</td>
<td>Rest</td>
<td>3–4</td>
<td>20–40</td>
</tr>
<tr>
<td>Low-output low-gradient severe AS with normal EF</td>
<td>Severe valve Ca++, reduced leaflet motion</td>
<td>Dobutamine stress</td>
<td>$&gt;4$</td>
<td>$&gt;40$</td>
</tr>
<tr>
<td>Critical AS</td>
<td>Severe Ca++ with immobile leaflets</td>
<td>$&gt;5$</td>
<td>$&gt;60$</td>
<td>&lt;0.6</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; AVA, aortic valve area; EF, ejection fraction; and LVH, left ventricular hypertrophy.
Computed tomographic (CT) imaging provides an alternate approach for planimetry of valve area and provides quantitative measures of valve calcification. In patients undergoing transcatheter AVR (TAVR), multimodality imaging includes CT assessment of aortic annulus size and shape, leaflet length, and the annular to coronary ostial distance.

Diagnostic cardiac catheterization is rarely needed for adults with AS but should be considered when echocardiographic and other noninvasive data are nondiagnostic or when there are discrepancies between noninvasive findings and other clinical data. When transaortic pressure measurements are made during catheterization, the phenomenon of pressure recovery—a higher pressure in the aorta distal to the valve than in the valve orifice itself—may create confusion if not recognized because Doppler measures the gradient at the orifice level. Pressure recovery is most likely to be seen in patients with a small aorta and systolic doming of a congenitally stenotic valve.

**LV Response to Chronic Pressure Overload**

LV volumes, mass, and systolic function can be measured using 2D or 3D quantitative echocardiography. AS results in increased LV systolic pressure, leading to increased myocardial cell mass and interstitial fibrosis. In compensated disease, this increase in LV wall thickness allows wall stress to remain relatively normal with a normal ejection fraction (EF) and normal cardiac output. Reduced left ventricular ejection fraction or cardiac output occurs only in end-stage disease and usually is preceded by clinical symptoms, although LV diastolic dysfunction occurs earlier in the disease course (Figure 2). Metabolic abnormalities adversely affect hypertrophic LV remodeling and LV function in patients with AS.

**Other Diagnostic Considerations**

**Aortic Dilation Associated With AS**

Dilation of the aortic sinuses and ascending aorta frequently accompanies calcific AS, particularly in those with bicuspid aortic valve disease. Aortic dilation is not primarily because of abnormal valve hemodynamics—in bicuspid valve patients there likely are underlying genetic factors leading to abnormal cell signaling in the aortic wall and in those with a trileaflet valve, atherosclerotic risk factors, including hypertension.

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**Figure 1. Diagnostic imaging of aortic stenosis.** Transvalvular mean and peak gradients and the aortic valve velocity time integral (VTI) are obtained by continuous wave Doppler across the aortic valve (A). The left ventricular (LV) outflow tract VTI is obtained from pulse wave Doppler in the LV outflow tract (B) and used along with the aortic valve VTI to calculate the aortic valve area (AVA) by the continuity equation. The valve morphology, opening, and calcification can be seen clearly on transesophageal echocardiographic imaging (C) and the amount of calcification in the valve leaflets quantified by computed tomography (D). LVCI indicates left ventricular cardiac index; LVCO, left ventricular cardiac output; LVOT, left ventricular outflow tract; and LSV, left ventricular stroke volume.
play a role. CT or CMR imaging of the aorta is recommended in bicuspid valve patients unless the ascending aorta distal to the sinotubular junction is well visualized on echocardiography. Additional imaging is also appropriate in adults with calcific trileaflet AS if echocardiography shows an aortic diameter >4 cm.15

Coronary Artery Disease Associated With AS

Significant coronary artery disease (CAD) is present in ≈50% of adults with severe symptomatic AS. Unfortunately, stress testing with perfusion imaging or echocardiography has a low accuracy for diagnosis of CAD and is contraindicated if any cardiac symptoms are present, so that coronary angiography is recommended when CAD is a concern.15 CT coronary angiography may be a reasonable alternative to invasive coronary angiography in some cases, particularly in younger patients.

Definition of Severe AS

Clinical Implications

With progressive calcific AS, LV outflow obstruction eventually results in clinical symptoms particularly with exercise, because of inadequate forward output and/or increased LV filling pressures caused by hypertrophic LV remodeling. Symptom onset portends a high mortality rate unless outflow obstruction is relieved by AVR.8 However, the exact degree of valve obstruction associated with symptom onset is variable among patients. Thus, it is challenging to define severe AS using any single numeric value; instead, hemodynamic measures must be considered in the context of symptoms, valve anatomy, and the LV response to chronic pressure overload.

Even so, it is useful to provide a hemodynamic definition for severe AS to guide decision making in 2 clinical situations (Figure 3): (1) the asymptomatic patient with AS at high risk for adverse outcomes and progressive disease who might benefit from preemptive AVR before symptom onset; and (2) the patient with symptoms possibly because of AS to determine whether symptoms are caused by valve obstruction so that AVR would be beneficial.
Hemodynamically Severe AS

Current definitions of severe AS are based on prospective studies showing that the $V_{\text{max}}$ is the strongest predictor of symptom onset and clinical outcomes (Figure 4). In adults with calcific AS and a $V_{\text{max}} >4$ m/s, 70% to 80% develop symptoms requiring AVR within 2 years compared with symptom onset in 25% to 35% of those with a $V_{\text{max}}$ between 3 and 4 m/s and only 15% of those with a $V_{\text{max}} <3$ m/s.6,7,16–18 Higher $V_{\text{max}}$ values (>5 or 5.5 m/s) are associated with even higher rates of symptom onset.19 Measurement of energy loss index accounts for pressure recovery and predicts clinical events in patients with asymptomatic AS.20 In symptomatic patients, other studies have shown that a $V_{\text{max}} >4$ or <3 m/s reliably identifies those who do or do not require AVR.21 Thus, a $V_{\text{max}} >4$ m/s, corresponding to a mean gradient >40 mm Hg, is generally considered severe AS, and a $V_{\text{max}} <3$ m/s, corresponding to a mean gradient of 20 mm Hg, denotes mild AS.

Although recommended in all AS patients, calculation of AVA is essential when $V_{\text{max}}$ is between 3 and 4 m/s (Figure 5). Most of these patients have moderate AS with an AVA between 1.0 and 1.5 cm², but some have severe AS with an AVA <1.0 cm² in the setting of a low transaortic volume flow rate.

Low Flow, Low Gradient, and Low EF

In the symptomatic adult with AS who also has a low transaortic volume flow rate, the definition of severe AS is particularly problematic. When left ventricular ejection fraction is reduced (<50%), heart failure symptoms may be because of primary LV dysfunction, valve obstruction, or their combination. Dobutamine stress echocardiography is helpful in this situation—specifically in patients with an EF <50%, and a small calculated AVA, despite a $V_{\text{max}} <4$ m/s—to separate patients with moderate AS and primary LV dysfunction from those with severe AS and a low EF because of afterload mismatch. AVR will not be helpful in relieving symptoms in the former patients, but will be lifesaving in the latter patients. Dobutamine is infused at incremental doses with the goal of increasing transaortic flow rate to the normal range. Severe AS is present if $V_{\text{max}}$ increases to >4 m/s and AVA remains <1.0 cm² at a normal flow rate; these patients benefit from AVR. Those with an increase in AVA to >1.0 cm² or with a maximum $V_{\text{max}} <4$ m/s have moderate AS and medical therapy is appropriate. Lack of contractile reserve, defined as an increase in transaortic stroke volume or EF of <20% with dobutamine infusion, is associated with high cardiovascular mortality regardless of treatment,22,23 although outcomes seem to be somewhat better with AVR than with medical therapy24 (see Risk Stratification section).

Low-Flow, Low-Gradient, and Preserved EF

Recent studies suggest that between 10% and 35% of adults with symptomatic AS present with paradoxical low flow and low gradient, despite a normal EF. These patients have a calculated AVA <1 cm², a $V_{\text{max}}$ between 3 and 4 m/s (mean gradient, 20–40 mm Hg), and a transaortic stroke volume <35 mL/m², despite an EF >50%.25–27 This occurs in patients with increased LV hypertrophy, small chamber volumes, reduced longitudinal systolic function, and increased vascular afterload.27 A firm diagnosis of severe AS is challenging in these patients. Many of these patients have only moderate AS,28 a small body size, or the AVA calculation is erroneous. Some investigators recommend reclassifying AS severity on the basis of transaortic volume flow rate along with pressure gradient.25,26 However, further studies are needed to clarify whether this classification system will aid in the clinical management of asymptomatic patients. In symptomatic patients with a small AVA, preserved EF, and lower aortic gradients, identifying patients who might benefit from AVR is aided by evaluation of severity of valve calcification, ensuring that echocardiographic measurements are made accurately and when normotensive, and careful assessment of other possible causes of symptoms. The use of stress echocardiography may help identify patients with truly severe AS.29

Risk Stratification of the Asymptomatic Patient

The primary clinical marker for recommending AVR is the development of symptoms. However, additional diagnostic risk

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**Figure 4. Outcomes for patients with aortic stenosis (AS) by jet velocity.** A, Kaplan–Meier plot for survival free of symptoms of AS by peak aortic velocity <3.50 m/s, 3.50 to 4.00 cm/s, and >4.00 cm/s (log-rank P<0.0001) in a study of 183 initially asymptomatic adults with moderate to severe AS and normal left ventricular (LV) systolic function. Reprinted from Stewart et al37 with permission of the publisher. B, Kaplan–Meier event-free survival curves according to maximum aortic velocity in 163 initially asymptomatic AS patients with a normal LV ejection fraction and an indexed aortic valve area of ≤0.6 cm²/m². The mean±SD survival rates at 2 and 4 years are indicated. Reprinted from Lancellotti et al46 with permission of the publisher. Copyright © 2010, BMJ Publishing Group Ltd.
stratification can complement symptom assessment and guide management decisions about timing of AVR by predicting the rate of disease progression and event-free survival (Table 2).

**Symptom Onset**

**Exercise Testing**

Although the classical symptoms of AS—angina, heart failure, and syncope—are not subtle, they are late manifestations of disease. In the current era, the most common early symptom is simply exertional dyspnea. Patients who are knowledgeable about the disease process are reliable in promptly reporting a change in status, but symptom onset may be insidious and decline in exercise tolerance may be ascribed to normal aging changes or physical deconditioning. In adults with severe AS and uncertain symptoms, particularly in older and sedentary individuals, exercise testing offers a more objective assessment of functional capacity and symptom status than patient self-report. In apparently asymptomatic individuals, treadmill exercise testing is safe and helpful in risk stratification. An abnormal exercise test is defined as the development of symptoms (angina, dyspnea, and presyncope), decreased exercise tolerance, or an inadequate increase in systolic blood pressure (<20 mm Hg). However, interpreting whether limiting symptoms on treadmill testing are truly cardiac in origin is not an exact science in patients who are elderly, overweight, and deconditioned.

Exercise echocardiography may provide more objective prognostic indicators, based on the concept that more severely stenotic, rigid valve leaflets will limit the ability to increase cardiac output with exercise. With a small, fixed valve area, the rise in pressure gradient or velocity with exercise is greater following the mathematical relationship between flow rate and velocity across a flow limiting orifice. Accordingly, in patients with severe asymptomatic AS, a larger increase in mean transvalvular gradient with exercise independently predicts reduced event-free survival, even in those with a normal exercise test. Exercise-induced pulmonary hypertension (>60 mm Hg) may provide further incremental prognostic value to the rest and exercise aortic valve gradients.

**B-Type Natriuretic Peptide**

Elevated levels of B-type natriuretic peptide (BNP) in asymptomatic patients predict symptom onset and postoperative survival, functional status, and LV function, although the precise cutoff values vary between studies. Additional study of the role of BNP levels in clinical decision making is needed, but in elderly patients in whom the cause of dyspnea is unclear, BNP levels are helpful in determining whether symptoms are because of cardiac or noncardiac causes. Similarly, in the apparently asymptomatic elderly patient with severe AS, an elevated BNP level suggests early clinical decompensation. A risk score comprising BNP, $V_{max}$, and sex has been proposed.

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**Figure 5. Approach to the diagnosis of aortic stenosis (AS).** A subset of patients presents with low flow, low gradient severe AS with preserved ejection fraction, characterized by a stroke volume index <35 mL/m² and usually accompanied by left ventricular hypertrophy (LVH), a very calcified valve, small LV chamber, and reduced longitudinal systolic strain. See text for details. Surgical aortic valve replacement (AVR) is appropriate in most patients. Transcatheter AVR is recommended in inoperable patients and may be reasonable in patients with high surgical risk. 2D indicates 2-dimensional; AVA, aortic valve area; AR, aortic regurgitation; DSE, dobutamine stress echocardiography; ETT, exercise treadmill testing; LV, left ventricular; LVEF, left ventricular ejection fraction; and PA pulmonary artery.
as a means to incorporate biomarker and hemodynamic data into clinical decision making, but further prospective studies of this concept are needed.

**Valve Anatomy**

**Valve Calcification**

In patients with severe asymptomatic AS, increased valve calcification is associated with reduced event-free survival. Rosenhek et al reported that only 20% of patients with asymptomatic severe AS with moderate or severe valve calcification were free of death or symptoms at 3 years. Quantification of aortic valve calcification by CT correlates with AS severity and also provides independent prognostic information beyond echocardiographic indices of AS severity. CT assessment of valve calcification may also be useful in distinguishing truly severe from moderate AS in patients with a low flow state, but further studies are needed.

**Hemodynamic Severity**

**Transvalvular Velocity, Gradients, and Stroke Volume**

$V_{\text{max}}$, and rate of change in $V_{\text{max}}$ over time are independent predictors of clinical events in patients with severe asymptomatic AS and may help guide decisions about timing of AVR. Event-free survival of patients with $V_{\text{max}} >5$ m/s was 64%, 36%, and 25%, at 1, 2, and 3 years, respectively. Patients with $V_{\text{max}} >5.5$ m/s developed more severe symptoms, with half presenting with New York Heart Association class III or IV symptoms. Among patients with severe asymptomatic AS with moderate to severe valve calcification and a rapid increase of $V_{\text{max}} (>0.3$ m/s in a year), there is a high likelihood of death or onset of symptoms.

Recent studies have highlighted the adverse prognosis of patients with paradoxical low flow and low gradient AS, but these studies included both symptomatic and asymptomatic patients. Importantly, they highlight the potentially adverse consequences of not referring a symptomatic patient with AVA $<1.0$ cm$^2$ to surgery because of uncertainty about AS severity caused by the lower transvalvular gradient. The impact of low flow and low gradients on outcomes in asymptomatic patients with AVA $<1.0$ cm$^2$ remains controversial with conflicting results in clinical studies. This represents an area in need of further investigation.

**Valvuloarterial Impedance**

Increased global LV load or valvuloarterial impedance ($Z_{va}$), measured as the ratio of systolic blood pressure plus mean transvalvular gradient to the stroke volume index [(SBP+MG)/SVI], integrates both valvular and vascular afterload. Although $Z_{va}$ is a useful index for understanding pathophysiology and the effects of increased vascular load in patients with AS, it does not yet have a clear role in clinical decision making about timing of AVR. Increased $Z_{va}$ in adults with AS is associated with impaired LV systolic function, worse overall survival in symptomatic patients, and lower event-free survival rates in asymptomatic patients. However, when the increase in $Z_{va}$ in a given patient is because of more increased blood pressure and vascular stiffness (in the setting of moderate AS), the clinical response to the increased $Z_{va}$ should be aggressive blood pressure control rather than expedited AVR. The use of $Z_{va}$ (beyond established indices of AS severity) as a guide to timing of AVR requires further study.

**LV Response to Chronic Pressure Overload**

**Hypertrophic LV Remodeling**

Although LV hypertrophy can decrease wall stress, several studies have demonstrated the adverse impact of greater degrees of hypertrophic remodeling in patients with AS. Cioffi et al showed that in asymptomatic patients with severe AS and inappropriately high LV mass—LV mass exceeding 10% of predicted based on height, sex, and stroke work—was associated with 56% and 29% event-free survival at 1 and 3 years, respectively, and was an independent predictor of an adverse outcome. Increased LV mass and concentric geometry are associated with increased perioperative complications (eg, low output syndrome) and mortality, as well as worse long-term outcomes.

**LV Longitudinal Strain**

More sensitive indices of systolic function can demonstrate LV dysfunction, despite a normal EF. Reduced longitudinal strain is associated with increased myocardial fibrosis and predicts an abnormal exercise test and increased cardiac events in follow-up. Lancellotti et al showed that longitudinal strain $\leq 15.9\%$ is associated with a 2-year event-free survival of 29%.

**Table 2. Risk Stratification of Patients with Severe AS**

<table>
<thead>
<tr>
<th>Asymptomatic Patients*</th>
<th>Symptomatic Patients†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal exercise test</td>
<td>Lack of contractile reserve in patients with low flow, low gradient, low EF AS</td>
</tr>
<tr>
<td>Elevated BNP</td>
<td>Very low mean gradient (&lt;20 mmHg)</td>
</tr>
<tr>
<td>Moderate to severe valve calcification</td>
<td>Very elevated BNP</td>
</tr>
<tr>
<td>Very high aortic velocity (≥5 or 5.5 m/s)</td>
<td>Severe ventricular fibrosis</td>
</tr>
<tr>
<td>Rapid increase in aortic velocity</td>
<td>O₂-dependent lung disease</td>
</tr>
<tr>
<td>Increased hypertrophic LV remodeling</td>
<td>Frailty</td>
</tr>
<tr>
<td>Reduced LV longitudinal systolic strain</td>
<td>Advanced renal dysfunction</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>Very high STS score</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
</tbody>
</table>

*AS indicates aortic stenosis; BNP, B-type natriuretic peptide; EF, ejection fraction; LV, left ventricular; and STS, Society of Thoracic Surgeons.
†Markers of increased rate of disease progression and decreased event-free survival.
*Marks of increased risk and potential futility in patients undergoing valve intervention.
Myocardial Fibrosis
Myocardial fibrosis is associated with an adverse prognosis. Increased midwall fibrosis (unrelated to previous myocardial infarction) is an independent predictor of mortality in patients with moderate and severe AS. Increased fibrosis is also associated with lower transvalvular gradients and less improvement in LV function after AVR. In addition to visually apparent fibrosis, CMR is capable of quantifying the extent of interstitial fibrosis. Whether an earlier operative strategy in asymptomatic patients with evidence of LV fibrosis will improve outcomes requires further study.

Pulmonary Hypertension
Long-standing AS may result in increased pulmonary venous pressure, most likely because of diastolic dysfunction, and increased pulmonary vascular resistance. Among adults with severe AS, pulmonary hypertension is present in ≤65% and characterized as severe in 15% to 20% of patients. The presence of pulmonary hypertension is associated with worse heart failure symptoms, increased mortality with medical management, and increased perioperative and late mortality in patients undergoing surgical or transcatheter AVR. Pulmonary hypertension with exercise impacts adversely on event-free survival in asymptomatic patients with severe AS in accord with its association with symptom onset in patients with asymptomatic mitral valve disease.

Medical Therapy
In patients with calcific AS, there are currently no medical therapies that delay the progression of disease. However, medical therapy plays an important role in the treatment of common comorbidities in patients with AS.

Medical Therapy for AS: Valve, Ventricle, and Vasculature
Although LV outflow obstruction at the valve level is the sine qua non of AS, increased vascular afterload (because of increased stiffness and resistance) exerts an additional load on the left ventricle. In fact, hypertrophic LV remodeling and dysfunction in response to this combined valvular and vascular chronic pressure overload drive much of the morbidity and mortality of AS. As such, potential targets for medical therapy to improve clinical outcomes in patients with AS include the valve, ventricle, and vasculature.

It is now clear that there is an active biology that leads to stiffening and calcification of the valve leaflets. Despite significant optimism that statins may help slow the progression of AS based on retrospective studies, prospective randomized trials have consistently shown that statins do not slow progression of disease or reduce aortic valve events in patients with mild to severe AS. Angiotensin-converting enzyme (ACE) and angiotensin 2 are upregulated in diseased aortic valves, but retrospective studies have shown conflicting results on the impact of ACE inhibitors on disease progression. Angiotensin receptor blockers (ARBs) may provide superior inhibition of the renin–angiotensin system in the leaflets; however, prospective studies are needed to determine the effectiveness of renin–angiotensin system inhibition on the progression of calcific AS. Ongoing efforts to elucidate the valvular biology should identify other therapeutic targets.

Hypertrophic LV remodeling that occurs because of chronic pressure overload leads to impaired coronary vasodilator reserve, LV dysfunction, and heart failure symptoms. No therapies are particularly effective for retarding and reversing this maladaptive remodeling in patients with AS. However, the renin–angiotensin system is upregulated in the pressure overloaded and failing heart, and preclinical studies of pressure overload show that ACE inhibition attenuates (or reverses) hypertrophic remodeling and LV dysfunction. Small clinical studies have demonstrated that ACE/ARB medications are tolerated in patients with AS and even have favorable effects on symptoms and functional capacity in symptomatic patients awaiting surgery. A recent retrospective study showed that ACE/ARB medications were associated with improved survival and lower risk of cardiovascular events in patients with AS. Larger, prospective studies are needed to evaluate the impact of renin–angiotensin system inhibition on clinical outcomes in patients with AS and the mechanisms for these potential effects.

Hypertension
Because calcific AS is a disease of the elderly, concomitant hypertension is very common. In relatively young cohorts, the prevalence of hypertension was 30% to 40%, compared with 75% or higher in studies that included older patients undergoing transcatheter AVR. There has been an underappreciation of the prevalence of hypertension in AS patients and reluctance to treat it adequately because of traditional teaching that AS is a disease with a fixed afterload and an emphasis on avoidance of vasodilators. However, it is misleading to think of AS as a disease with fixed afterload. Indeed, increased vascular afterload serves as an additional load on the left ventricle and is associated with increased hypertrophic remodeling and LV dysfunction in patients with AS. Increased global LV load, measured as the Zd, also portends a worse outcome. As such, it is important to recognize and treat hypertension in patients with AS. Uncontrolled hypertension may also mask the severity of AS so that AS severity should be re-evaluated after blood pressure control. There are no long-term prospective data supporting any specific antihypertensive agent, but given their potential favorable effects on hypertrophic LV remodeling, ACE/ARB medications may be considered preferentially.

Atrial Fibrillation
AS patients may become quite symptomatic with atrial fibrillation, particularly when the ventricular response is fast because the atrial contribution to ventricular diastolic filling is particularly important in a small, hypertrophied ventricle with concomitant diastolic dysfunction. Rate and rhythm control as indicated by the clinical scenario is important, as is anticoagulation in accordance with management guidelines. The onset of atrial fibrillation in an otherwise asymptomatic patient with severe AS may be an early marker of symptom onset.
Coronary Artery Disease
CAD is common in patients with AS, and guidelines for primary and secondary prevention should be followed. These include the use of aspirin, statins, β-blockers, ACE inhibitors, and aldosterone antagonists as indicated. Although nitrates may be used for anginal symptoms, an excessive decrease in preload and afterload should be avoided.

Heart Failure
In patients with severe AS, initial symptoms of heart failure usually occur in the setting of preserved EF. Symptomatic patients require AVR, although diuretics are often used preoperatively to decrease congestion and provide symptomatic relief. AVR is also indicated in patients with severe AS and a reduced left ventricular ejection fraction, regardless of whether LV dysfunction is because of chronic pressure overload or primary myocardial disease. However, some patients present with heart failure symptoms in the setting of only mild or moderate AS and primary LV dysfunction. These patients should be treated with standard heart failure therapies, including β-blockers, ACE inhibitors/ARBs, aldosterone antagonists, nitrates/hydralazine, and diuretics as clinically indicated.

 Decompensated Heart Failure
Patients with severe AS may present with advanced heart failure symptoms characterized by pulmonary congestion, pulmonary hypertension, afterload mismatch, and reduced cardiac output. Although AVR is indicated, these patients are at considerable surgical risk. In high-risk surgical patients, balloon valvuloplasty can modestly reduce AS severity, albeit temporarily. Alternatively, systemic vascular resistance may be targeted to unload the heart. In this regard, nitroprusside has been shown to decrease wedge pressure and improve cardiac output by decreasing systemic vascular resistance and increasing LV contractility, which may stabilize patients with low output. Recently, a single dose of sildenafil has been shown to unload both right and left ventricles in patients with severe AS and advanced heart failure by reducing pulmonary and systemic vascular afterload. These preliminary results raise the possibility that medical therapy may serve as a stabilizing bridge to definitive AVR in high-risk patients with advanced heart failure symptoms and low output.

Aortic Valve Replacement
AVR has transformed the outlook of patients with AS. Numerous studies have confirmed the concept of Ross and Braunwald that the onset of symptoms heralds a predictable decline in survival, with roughly 50% of patients dying within the next 3 to 5 years. AVR clearly is indicated in patients with symptomatic severe AS, and surgery in such patients improves symptoms and increases life expectancy. In patients with LV systolic dysfunction, reduction in afterload after AVR significantly improves, and often normalizes, left ventricular ejection fraction, which also translates into improved survival. As noted previously, some patients with severe AS have heart failure and LV systolic dysfunction with low stroke volume and low aortic valve gradient. In these patients, determination of AS severity and the presence of LV contractile reserve with dobutamine infusion are very helpful for operative risk stratification and identifying those for whom AVR will likely improve outcome.

AVR for treatment of AS represents 50% of all operations for valvular heart disease in North America, with an increasing use of bioprosthetic valves compared with mechanical valves. Isolated AVR can now be accomplished with a mini-sternotomy, although a full sternotomy is often required if extensive concomitant coronary artery bypass grafting is required. Bioprosthetic valves are generally recommended for patients aged >65 years because of greater durability in older individuals, but there is also greater usage in younger patients because of lifestyle considerations and lack of necessity of chronic anticoagulation. There are no definitive data favoring one bioprosthetic valve (porcine heterograft, bovine pericardial heterograft, or homograft) compared with another. The Ross operation (replacement of the aortic valve with the pulmonary autograft and replacement of the pulmonic valve with a homograft) is an alternative for adolescents and young adults, including women who wish to become pregnant. Because of complexity of the Ross procedure, it is not favored by the majority of surgeons, although in centers with expertise in this operation, outcomes are excellent.

The operative mortality associated with AVR is dependent on both patient risk factors and the skill and experience of the surgical team. Comorbidities associated with higher 30-day mortality include age, LV dysfunction, concomitant CAD, previous coronary artery bypass grafting, renal insufficiency, and chronic pulmonary disease. A number of readily available risk scores, including the EuroSCORE, the Society of Thoracic Surgeons (STS) risk calculator, and the valve-specific risk calculator of Ambler et al, provide an estimate of surgical risk, although none of these scores is optimal because other important variables, such as frailty and cognitive capacity, are not included. These same factors impact long-term survival after AVR.

The mortality associated with AVR has decreased dramatically during the past 2 decades, and 30-day mortality in the STS database is currently under 3% for isolated AVR and under 4.5% for combined AVR plus coronary artery bypass grafting, despite increasing age and comorbidities of those undergoing surgery. However, among more elderly patients, the risks are considerably higher, and a large dataset of 142,488 patients enrolled in Medicare indicates that the average in-hospital mortality for AVR is 8.8%. Importantly, the hospital mortality in the Medicare study was twice as high in hospitals in the lowest decile of surgical volume compared with hospitals in the highest decile of surgical volume (13.0% versus 6.0%). As these data were risk adjusted, they suggest that higher volume centers place greater attention to quality of care and thus provide better outcomes. In carefully selected patients undergoing surgery in experienced centers, the operative morbidity and mortality are low even in the elderly.

The indications for AVR are clear in symptomatic patients, but are much less clear and remain the subject of debate in asymptomatic patients. Although the current evidence-based guidelines recommend a watchful waiting approach for most asymptomatic patients, numerous studies have shown that patients with severe AS have a high likelihood...
of developing symptoms and requiring surgery within 3 to 5 years, and other series have reported that asymptomatic patients with severe AS are also at risk of death when managed without surgery. As the operative risk of AVR is low in experienced centers, there is ongoing interest in identifying high-risk asymptomatic patients who might benefit from early, preemptive AVR rather than a watchful waiting approach, as noted previously.

However, there is also evidence that many symptomatic patients who fulfill clear class I indications for AVR are not referred for surgery appropriately in Europe and the United States, with as many as 30% of symptomatic patients not undergoing AVR, despite definite indications. Although this treatment gap might be explained by the reluctance of internists and cardiologists to recommend surgery in elderly patients with many comorbidities, even low-risk symptomatic patients are often not referred for surgery. Bach et al reported that 22% of symptomatic patients with severe AS and an operative mortality risk <10% as estimated by the EuroSCORE were not referred for surgery. It is widely understood that the EuroSCORE overestimates actual observed operative mortality, and these were indeed relatively low-risk patients for surgery. The mortality of the symptomatic patients in that series who did not undergo AVR was 53% at 36 months, in keeping with the concept of Ross and Braunwald of 40 years ago that severe symptomatic AS has a dismal prognosis.

Transcatheter AVR

In elderly, higher risk individuals, age and comorbidities do conspire to increase the risk of surgical AVR, and it is this target population in whom transcatheter AVR (TAVR) has become an exciting treatment option. Developed >10 years ago and now performed in more than 40,000 patients worldwide, TAVR has been the subject of numerous reports in the medical literature in recent years, with large national and international registries and the landmark Placement of Transcatheter Aortic Valves (PARTNER) trial—a prospective randomized trial investigating the role of TAVR in high-risk patients with severe AS. PARTNER B investigated the impact of TAVR on the outcome of symptomatic patients who were considered to have a prohibitive operative risk when assessed by a team of both surgeons and cardiologists, randomizing 358 patients to TAVR versus standard care. In this very high-risk population, TAVR resulted in a 39% reduction in mortality at 1 year (30.7% versus 50.7%) compared with the results of standard therapy, which included percutaneous balloon valvuloplasty in many patients. The mortality benefit with TAVR persisted at 2 years (43.3% with TAVR and 68.0% with standard therapy; Figure 6). On the basis of these results, TAVR was approved by the Food and Drug Administration in late 2011 for inoperable patients and, more recently, for very high risk patients. It is noteworthy that the risk of stroke was higher in the TAVR group compared with standard therapy, with overall rates of 13.8% versus 5.5% at 2 years, and it is important to have this discussion with patients as part of the decision-making process.

PARTNER A investigated the impact of TAVR on the outcome of symptomatic patients who were considered high-risk candidates for surgical AVR with an STS score estimated 30-day mortality of ≥10%. In this arm of the trial, in which 699 patients were randomized to TAVR or surgical AVR, TAVR was found to be noninferior to surgery in terms of late mortality at 1 year (24.2% versus 26.8%) and 2 years (33.9% versus 35.0%; Figure 6). As a result of these findings, TAVR was approved by the Food and Drug Administration for high-risk surgical candidates in June 2012.

In making the decision for TAVR or surgical AVR in high-risk surgical candidates, one has to balance the increased risk of bleeding and atrial fibrillation with surgery against the increased risk of stroke and vascular damage with TAVR. The risk of stroke continues to increase with TAVR compared with surgical AVR over the course of time, which is presumably the result of vascular damage during device implantation or thromboembolic material from the native calcified valve tissue that remains exposed to the circulation. Both stroke and vascular damage have been linked to higher mortality rates after TAVR. In addition, other complications that occur at higher frequency with TAVR than with surgical AVR, including complete heart block, left bundle-branch block, and paravalvular regurgitation, have also been linked to higher long-term mortality after TAVR. Although one would anticipate that the sudden volume load associated with moderate to severe paravalvular regurgitation would be poorly tolerated in a hypertrophied left ventricle that had previously adapted to chronic pressure overload, even mild regurgitation has been associated with a significant increase in long-term mortality. Whereas moderate to severe regurgitation after TAVR is relatively uncommon (occurring in 8%–12% of patients), mild regurgitation developed in 43% of patients in PARTNER A. Possible mechanisms for paravalvular regurgitation include malposition, undersizing, underexpansion, and malapposition of the prosthesis. In addition, aggressive dilatation of the valve during deployment to prevent paravalvular regurgitation increases the risk of stroke and can produce central regurgitation through the valve leaflets themselves, contributing to the total regurgitant volume.

In its current state of the art, TAVR represents a transformative technology with the potential to improve symptoms and prolong life in patients who previously had no surgical options. There are several ethical and cost-effectiveness issues that will need to be addressed, including methods to identify patients who have such severe comorbid illness that even TAVR will not result in improved outcome. Clinical safety and efficacy must temper consumer enthusiasm for TAVR, as surgical AVR represents the standard with proven safety and durability for the majority of patients. One of the remarkable findings of the PARTNER A trial is that the surgical mortality was much lower than anticipated (8.0% actual mortality in those who received surgical AVR compared with average estimated surgical mortality of 11.8%), which is the result of the development of highly skilled heart valve teams in the trial. Whether this can be achieved in expanding the access of TAVR to the community is uncertain. Thus, the broad application of TAVR will present challenges in patient selection, cost effectiveness, and the need for dedicated expert heart valve centers.
Hybrid Approaches to AS and CAD

Several heart valve centers have developed programs to address management of higher risk patients with AS who have concomitant CAD. To minimize cardiopulmonary bypass times during open heart surgery, such approaches include percutaneous coronary intervention immediately before surgical AVR or TAVR. Hybrid operating rooms permitting the full range of interventional and surgical options are being implemented in a growing number of institutions.

Risk Stratification of the Symptomatic Patient

Although AVR is indicated for symptomatic severe AS, some patients present late in the disease course with severely advanced disease or have such extensive comorbidities that AVR is unlikely to improve survival and quality of life. In these patients, additional risk stratification may be needed to clarify the risk–benefit ratio of AVR. With the recent introduction of TAVR, it will become increasingly important to recognize when there is so little potential benefit to the patients that valve replacement would be futile.

Dobutamine Echocardiogram

In patients with low flow, low gradient AS, and reduced EF, dobutamine echocardiography both confirms the presence of truly severe AS and provides an evaluation of LV contractile reserve. Although operative mortality is substantially increased in AS patients without contractile reserve, long-term survival may be improved by AVR. However, the subset of patients with a very low resting transvalvular mean gradient (<20 mm Hg) has a particularly poor prognosis, suggesting futility of AVR. TA VR may provide better outcomes than surgical AVR in patients with severe LV dysfunction, but further studies are needed.

B-Type Natriuretic Peptide

Although most attention has been focused on the use of BNP as a risk stratification tool in the asymptomatic patient, in symptomatic patients with low flow, low gradient AS, and a reduced EF a very elevated BNP is associated with a markedly decreased 1-year survival after AVR. Even after adjusting for EuroScore, an elevated BNP predicts mortality in patients referred for AVR. Further studies are needed on the relationship between a very high BNP and adverse clinical outcomes to determine whether there are cutoffs above which a favorable clinical result is unlikely.

Myocardial Fibrosis

Weidemann et al showed that patients with severe AS and severe ventricular fibrosis (without CAD and with a preserved...
mean EF) are more likely to have worse preoperative symptoms and less improvement in symptoms after AVR, whereas those with none or minimal fibrosis generally improved. In patients with concomitant severe LV dysfunction and CAD, it is possible that assessment of fibrosis (because of prior infarction and pressure overload from AS) may indicate whether ventricular recovery and symptomatic improvement are likely after AVR.

Severe Pulmonary Disease

Patients with severe AS who have O₂-dependent chronic obstructive pulmonary disease have a poor prognosis. Among patients considered inoperable with O₂-dependent chronic obstructive pulmonary disease, 1-year mortality was not significantly better with TAVR than standard therapy, and at 2 years O₂-dependent chronic obstructive pulmonary disease was an independent risk factor for mortality in those who received TAVR. This deleterious impact on survival has been demonstrated in other TAVR cohorts. Nonetheless, in these patients, there is a quality of life benefit of TAVR at 12 months compared with standard therapy, although that benefit may not be observed early after treatment. Although not a contraindication to AVR, severe chronic obstructive pulmonary disease is an important comorbidity to consider when assessing the likelihood of clinical improvement.

Frailty

Frailty likely influences both procedural risk and likelihood of clinical improvement after AVR. Qualitative assessment of frailty has long been incorporated into the clinical evaluation of patients considered for AVR, commonly referred to as the eyeball test. Only more recently have attempts been made to measure frailty quantitatively. Atilalo et al recently demonstrated that a 5-m walk time of ≥6 s was an independent predictor of death or major morbidity after cardiac surgery after adjusting for STS risk score. Further studies validating objective measures of frailty and determining the impact of frailty on clinical outcomes are needed.

Renal Dysfunction

Although not a contraindication to AVR, more severe renal impairment is consistently an independent risk factor for mortality in surgical AVR and TAVR patients. The risk of TAVR will be lower than surgical AVR in patients with significant renal impairment requires further study.

Very High STS Scores

The STS score provides an integrated, global snapshot of patient risk as it estimates the risk of mortality and serious morbidity for various cardiac surgeries based on numerous individual cardiac and noncardiac clinical characteristics. Although not perfect, the STS score is perhaps that most accurate risk algorithm for predicting mortality in patients undergoing AVR. The 2-year results of the PARTNER B trial of inoperable patients demonstrated that TAVR provides no mortality benefit compared with standard therapy in those with the highest estimated operative risk (STS score ≥15%; Figure 6). However, in these same very high-risk patients TAVR does seem to improve quality of life compared with standard therapy at 6 and 12 months. Further studies are needed to develop risk algorithms specifically designed for patients with AS (which also integrate important features, such as frailty, currently missing from risk algorithms) and to clarify which cut points may identify individuals who are too sick to benefit from valve replacement.

Disclosures

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