

AORTIC STENOSIS: CHANGING DISEASE CONCEPTS

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Aortic stenosis (AS) occurs in almost 10% of adults over age 80 years with a mortality about 50% at 2 years unless outflow obstruction is relieved by aortic valve replacement (AVR). Development of AS is associated with anatomic, clinical and genetic risk factors including a bicuspid valve in 50%; clinical factors that include older age, hypertension, smoking, diabetes and elevated serum lipoprotein(a) [Lp(a)] levels; and genetic factors such as a polymorphism in the Lp(a) locus. Early stages of AS are characterized by focal areas of leaflet thickening and calcification. The rate of hemodynamic progression is variable but eventual severe AS is inevitable once even mild valve obstruction is present. There is no specific medical therapy to prevent leaflet calcification. Basic principles of medical therapy for asymptomatic AS are patient education, periodic echocardiographic and clinical monitoring, standard cardiac risk factor evaluation and modification and treatment of hypertension or other comorbid conditions. When severe AS is present, a careful evaluation for symptoms is needed, often with an exercise test to document symptom status and cardiac reserve. In symptomatic patients with severe AS, AVR improves survival and relieves symptoms. In asymptomatic patients with severe AS, AVR also is appropriate if ejection fraction is < 50%, disease progression is rapid or AS is very severe (aortic velocity > 5 m/s). The choice of surgical or transcatheter AVR depends on the estimated surgical risk plus other factors such as frailty, other organ system disease and procedural specific impediments.

KEY WORDS: Aortic stenosis · Valve replacement · Echocardiography.

INTRODUCTION

Aortic stenosis (AS) is the most common type of valvular heart disease. Aortic valve disease spans a disease spectrum that begins with mild fibrocalcific leaflet changes, termed aortic sclerosis, which is associated with a 50% increased risk of adverse cardiovascular events, even with normal leaflet opening.¹⁾ Aortic sclerosis often progresses to more severe leaflet calcification with the end stage of disease characterized by obstruction of left ventricular (LV) outflow resulting in the inability to adequately increase cardiac output with exertion. Once even mild symptoms are present, failure to relieve LV outflow obstruction leads to heart failure and death, with a mortality as high as 50% over 2 years.²⁾ Although the prevalence of AS is only about 0.2% among adults aged 50 and 59 years, it is as high as 9.8% in those 80 years or older, with an overall prevalence of 2.8% in adults over 75 years of age.^{3,4)} Several population-based studies have shown a significant association between age and calcific aortic valve disease. Therefore it is likely that the

prevalence of aortic valve stenosis will increase even further with the demographic change toward an elderly population in developed countries.

The 2014 American Heart Association and American College of Cardiology (AHA/ACC) Valve Guidelines introduced a new classification of AS with four stages, defined by combining information about patient symptoms, leaflet anatomy, valve hemodynamics, and LV function (Table 1). This patient centered approach allows close alignment between disease stage and treatment recommendations.⁵⁾ In addition, these guidelines emphasize the Heart Valve Team approach, with an integrative decision making approach by valve experts, imaging specialists, cardiothoracic surgeons and interventional cardiologists. Valve centers of excellence with high surgical/interventional volumes and low complication rates also participate in outcomes registries, implement quality improvement processes and ensure adherence to guidelines.⁶⁾

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Table 1. Stage of aortic valve stenosis

Stage	Symptoms and severity	Aortic valve anatomy and hemodynamics
A	At risk of AS	Examples: aortic sclerosis or congenital bicuspid valve
B	Progressive AS (mild-moderate)	Mild AS: abnormal valve with V_{max} 2–2.9 m/s, mean $\Delta P < 20$ mm Hg Moderate AS: abnormal valve with reduced leaflet motion and V_{max} 3–3.9 m/s, mean $\Delta P < 20$ –40 mm Hg
C	Asymptomatic severe AS	Calcified and thickened leaflets with limited mobility and $V_{max} \geq 4.0$ m/s or mean $\Delta P \geq 40$ mm Hg (AVA usually < 1.0 cm ²) C1: normal LV systolic function C2: LV EF $< 50\%$ Very severe $V_{max} \geq 5.0$ m/s, mean $\Delta P \geq 60$ mm Hg
D	Symptomatic severe AS	Severely thickened and calcified aortic valve leaflets with reduced systolic opening with: D1: high gradient severe AS: $V_{max} \geq 4.0$ m/s or mean $\Delta P \geq 40$ mm Hg (AVA usually < 1.0 cm ² but not needed for diagnosis) D2: low-flow low-gradient severe AS (low EF): LV EF $< 50\%$ with a resting AVA < 1.0 cm ² and V_{max} 3 to 4 m/s. On low dose DSE there is a $V_{max} \geq 4.0$ m/s with an AVA < 1.0 cm ² at any flow rate D3: low-flow low-gradient severe AS (normal EF): V_{max} 3 to 4 m/s, AVA < 1.0 cm ² , indexed AVA < 0.6 cm ² /m ² , and indexed SV < 35 mL/m ² , all measured when patient is normotensive

ΔP : mean gradient, AS: aortic stenosis, AVA: aortic valve area, DSE: dobutamine stress echocardiography (maximum dose 20 mcg/mg/min), EF: ejection fraction, LV: left ventricular, SV: stroke volume, V_{max} : maximum aortic velocity

STAGES OF DISEASE

Stage A disease is defined as the patient at risk of developing AS who is currently asymptomatic without valve obstruction; for example a young patient with a normally functioning bicuspid valve or an older adult with aortic valve sclerosis. Stage B disease is present if there is evidence of progressive leaflet calcification and thickening with reduced leaflet motion resulting mild to moderate valve obstruction. In patients with stage A and stage B disease, standard cardiac risk factor evaluation and reduction, including treatment of hypertension, is particularly important although these patients do not benefit from aortic valve replacement (AVR).⁶⁾ In addition, periodic monitoring is recommended for evaluation of progressive valve obstruction and patient symptoms. When severe valve obstruction is present, the most important distinction is between asymptomatic (stage C) and symptomatic (stage D) disease with sub-classifications for LV dysfunction (stage C2) and for low-gradient severe AS (stage D2 or D3).

Severe AS is defined as calcified and thickened valve leaflets with reduced systolic opening and an antegrade velocity across the valve of 4.0 m/s or higher, equivalent to a mean systolic transaortic pressure gradient of 40 mm Hg or higher.^{7,8)} Typically, aortic valve area (AVA) is 1.0 cm² or less although this is not required for diagnosis of severe AS because a high velocity or gradient alone is predictive of clinical outcome regardless of valve area. Asymptomatic patients with severe AS and an LV ejection fraction of 50% or higher (stage C1) are distinguished from those with LV systolic dysfunction (stage C2) because outcomes and treatment recommendations are different for these subsets of disease.

In the symptomatic patient with AS, a velocity of 4.0 m/s or higher or mean gradient of 40 mm Hg or higher is consistent with high-gradient severe AS (stage D1). The goal is simply

to establish whether AS is severe enough to cause symptoms. Again, valve area typically is 1.0 cm² or less but may be larger in patients with mixed stenosis and regurgitation or a large body size; in any case, severe aortic valve disease is present and relief of valve obstruction will improve clinical outcome.

In symptomatic patients with a calcified valve with reduced leaflet opening and a small valve area (≤ 1.0 cm²) but a low transvalvular velocity (< 4 m/s) and mean systolic gradient (< 40 mm Hg), the possibility of low-flow low-gradient severe AS must be considered. In the setting of LV systolic dysfunction (ejection fraction $< 50\%$), a low-dose (maximum 20 mcg/m²/min) dobutamine stress echocardiogram showing an increase in aortic velocity to 4 m/s or higher with valve area remaining less than 1.0 cm² is consistent with low-flow low gradient severe AS (stage D2), rather than moderate AS with concurrent primary myocardial disease.

Diagnosis is more challenging in the symptomatic patient with possible low-flow low-gradient severe AS when LV systolic function is normal. Stress echocardiography has not been shown to be useful in this subset of patients.

Typically, low-flow low gradient severe AS with normal LV ejection fraction (stage D3) is diagnosed in older patients, predominantly women, with a heavily calcified valve, an indexed AVA < 0.6 cm² and a small hypertrophied LV resulting in a stroke volume index less than 35 mL/m². It is critical that measurements of AS severity be confirmed when the patient is normotensive because valve hemodynamics are affected by concurrent hypertension. Stage D3 severe AS is a diagnosis of exclusion and should be made only if all other possible causes for the patient symptoms have been fully evaluated and treated.

RISK FACTORS FOR CALCIFIC AORTIC VALVE DISEASE

Pathogenesis of AS is determined by clinical factors, genetics

and valve anatomy. Calcification occurs in many patients with a normal trileaflet aortic valve, however presence of bileaflet anatomy accounts for 60% of AVRs under the age of 70 and 40% of those 70 years or older.^{9,10} Bicuspid aortic valve disease is present in 1–2% of the United States population and nearly all will require AVR during their lifetime.^{11,12} Rheumatic heart disease remains prevalent in underdeveloped countries, where improvement in primary prevention is needed. Specifically prevention and treatment of streptococcal pharyngitis prevents rheumatic fever and rheumatic valve disease.

Bicuspid aortic valve disease appears to be inherited in an autosomal dominant pattern, with variable penetrance, in some families. However, a specific single gene abnormality has not yet been identified.¹³ Familial inheritance patterns have also been reported for calcific valve disease in patients without a congenital bicuspid valve.¹⁴ In a large genome wide association study a specific polymorphism in lipoprotein(a) [Lp(a) locus rs10455872] has been shown to be associated with elevated serum levels of Lp(a) as well with incident AS [hazard ratio (HR) per allele, 1.68; 95% confidence interval (CI), 1.32 to 2.15] and AVR (HR, 1.54; 95% CI, 1.05 to 2.27).¹⁵ In a separate cohort, the same Lp(a) polymorphism was associated with elevated serum Lp(a) levels and with incident AS, further supporting a genetic component in risk of AS.¹⁶ In a prospective validation study the Lp(a) risk genotypes also were associated with elevated serum Lp(a) levels and increased risk of AS, with a serum Lp(a) level > 90 mg/dL predicting a threefold increased risk of AS.¹⁷

Clinical factors associated with the development of calcific valve disease are similar to those associated with atherosclerosis and coronary artery disease (Table 2). In population-based studies prevalent calcific valve disease was associated with older age, male gender, elevated serum low-density lipoprotein (LDL) and Lp(a) levels, hypertension, smoking, diabetes and metabolic syndrome.^{4,18,19} A Mendelian randomization study design using community-based cohorts confirmed that serum LDL levels are associated with aortic valve calcification and AS (HR per mmol/L, 1.51; 95% CI, 1.07–2.14; $p = 0.02$).²⁰ Patients with a history of disorders of calcium metabolism, renal failure, or mediastinal radiation also are at increased risk of AS.²¹

Progression from aortic sclerosis, defined as focal areas of valve calcification and leaflet thickening, to hemodynamically significant valve obstruction occurs in 10 to 15% of patients over 2 to 5 years. However, factors associated with disease progression differ from those associated with initiation of disease suggesting differences in the disease process at the tissue level. In contrast to prevalent aortic valve disease, the only identified factors associated with disease progression are older age, male gender, stenosis severity, and the degree of leaflet calcification.^{19,22}

HEMODYNAMIC PROGRESSION OF AS

Once even mild AS is present, defined as an aortic velocity of

Table 2. General summary of strength of associations seen in observational and epidemiologic studies of clinical risk factors and calcific aortic valve disease

	CAVD analyses		
	Cross-sectional	Incident	Progression
Age	+++	+++	+++
Male gender	++/-	++	0
Height	++	++	0
BMI	++	++	0
Hypertension	++	++	0
Diabetes	+++	+++	0
Metabolic syndrome	++	++	+
Dyslipidemia	++	++	0
Smoking	++	++	+
Renal dysfunction	+	0	0
Inflammatory markers	+	0	0
Phosphorus	++	0	n/a
Calcium levels	0	0	n/a
Baseline calcium score	n/a	n/a	+++

BMI: body mass index, CAVD: calcific aortic valve disease, +: weak positive association, ++: modest positive association, +++: strong positive association, -: weak negative association, 0: no association seen, n/a: insufficient data available. From Owens DS, O'Brien KD. *Clinical and genetic risk factors for calcific valve disease*. In: Otto CM, Bonow RO, editors. *Valvular heart disease: a companion to Braunwald's heart disease*. 4th ed. Philadelphia: Elsevier; 2014. Chapter 4, page 54, Table 4-1

2 m/s or higher, progressive stenosis occurs in nearly all patients and most will require AVR over their lifetime. Overall the average rate of hemodynamic progression in adults with mild to moderate AS is an increase in trans-aortic velocity of 0.3 m/s per year, an increase in mean gradient 7 mm Hg per year and a decrease in valve area of 0.1 cm² per year.⁷ However, the rate of hemodynamic progression varies significantly between patients with progression tending to be more rapid in older patients and those with more severe valve calcification. Interestingly, the degree of valve obstruction leading to onset of symptoms also varies significantly among patients. Thus, these two factors—heterogeneity in the rate of hemodynamic progression and variability in onset of clinical symptoms mandate periodic clinical and echocardiographic evaluation for patients with asymptomatic mild to moderate AS.

Once severe valve obstruction is present, the most important distinction is between asymptomatic (stage C) and symptomatic (stage D) disease. Most patients who are educated about the disease course will recognize and report early symptoms of AS, most often dyspnea on exertion or simply a decline in exercise capacity. Once even mild symptoms due to severe AS are present, clinical outcomes are very poor unless outflow obstruction is relieved by AVR. The classic symptoms of angina, heart failure or syncope are typically the later manifestation of disease and now are seen only in patients who were not receiving medical care, failed to report early symptoms or had an inap-

appropriate surgical delay. In those with symptomatic severe AS, the only effective treatment is surgical AVR (SAVR) or transcatheter AVR (TAVR), resulting in improved survival and reduced symptoms. If symptom status is unclear, standard treadmill exercise testing may be helpful to document exercise capacity, ensure symptoms are not provoked by exercise and to measure the blood pressure response to exertion. An elevated serum B-natriuretic peptide levels may suggest early or incipient symptoms in the patient with an equivocal clinical history.²³⁾²⁴⁾

Asymptomatic patients with hemodynamically severe AS are classified as stage C disease. The definition of “severe AS” in the guidelines was chosen to ensure that all symptomatic patients are promptly referred for valve replacement. However, many patients with numbers consistent with “severe AS” remain asymptomatic for several years and the rate of disease progression is quite variable. Survival during this asymptomatic phase is similar to age-matched control group with low risk of sudden death (< 1% per year) in retrospective series, a risk that may be even lower when patients are followed prospectively. The goals in clinical management of stage C disease are to: 1) identify any high-risk patients, 2) provide patient education and followup to ensure early symptom recognition, 3) treat comorbid conditions, and 4) optimize the timing of valve replacement. In adults with moderate to severe AS, all patients will develop symptoms due to hemodynamic progression with an event free survival of 75% to 80% at 2 years in those with velocity of less than 3.0 m/s compared to 35% to 50% in those with jet velocity of more than 4.0 m/s.⁷⁾

MEDICAL THERAPY

Despite experimental models suggesting benefit with lipid-lowering therapy in preventing disease progression in calcific AS, multiple large randomized clinical trials failed to show benefit in changing hemodynamic severity or clinical outcomes.²⁵⁾²⁶⁾ Therefore, statin therapy is not indicated for prevention of progression of AS in patients with mild to moderate calcific valve disease, unless there is concurrent coronary artery disease. Hopefully, ongoing research will identify novel disease mechanisms that might allow therapy targeted towards pathways to reduce inflammation, oxidative stress and abnormal tissue calcification.

However, cardiovascular lifestyle and pharmacologic risk factor modifications are important in adults with any degree of calcific aortic valve disease. Standard cardiovascular risk factors, including smoking, hypertension, diabetes, obesity and hyperlipidemia, should be evaluated and treated according to current guidelines. Many patients with AS will receive lipid-lowering therapy for standard indications, although not specifically to prevent AS progression. Patients with AS should be encouraged to follow a heart-healthy diet and to exercise regularly. With mild-moderate AS, exercise restrictions are not needed; asymptomatic patients with severe AS should be advised to avoid strenuous activities or competitive sports.

Hypertension is common in patients with AS. This adds to

the total LV pressure overload in combination with the valve obstruction. Despite the concerns that antihypertensive medications may cause excessive peripheral vasodilation resulting in hypotension, this concern has not been supported in clinical practice. In fact, hypertension was associated with 56% higher rate of ischemic cardiovascular events and 2 fold increase in mortality over 4.3 years in a prospective study of 1616 adults with mild to moderate AS.²⁷⁾ Standard therapy for hypertension is appropriate in adults with AS although medications should be started at low doses with slow titration to achieve blood pressure control. It may be prudent to avoid diuretics when LV size is small. In theory, angiotensin pathway inhibitors might have beneficial for LV remodeling effects and beta blockers might be more beneficial in patients with concurrent coronary artery disease. However, there is no data on clinical outcomes with specific antihypertensive regimens in AS patients.

In symptomatic severe AS, medical therapy does not prolong life and AVR is the only effective treatment. In patients presenting with cardiogenic shock due to decompensated severe AS, there has been limited experience using vasodilator therapy with close hemodynamic monitoring to stabilize patients prior to SAVR or TAVR.²⁸⁾ In symptomatic patients with severe AS who refuse AVR or in whom AVR would be futile, palliative therapy with standard medical therapy to relieve symptoms of heart failure or angina is appropriate.

INDICATIONS FOR AVR

The new staging system (stage A to D) emphasizes a patient centered approach, where defining disease severity allows alignment of treatment recommendations with disease stages (Table 3). A constellation of symptoms, valve anatomy and hemodynamics should be considered when a patient is being considered for valve replacement. Recommendations for AVR are classified as a strong recommendation termed Class I, or a weaker recommendation classified as Class IIa (AVR is reasonable) or IIb (AVR may be considered) in the American Heart Association/American College of Cardiology and in the European Society of Cardiology guidelines (Table 3).

SYMPTOMATIC PATIENTS WITH SEVERE AS

STAGE D1

In patients with severe AS, the key factor in clinical decision-making is development of symptoms. Once symptoms occur, the rate of death is more than 50% at 2 years for patients unless aortic valve is performed promptly. In the absence of serious comorbid conditions that may limit life expectancy, AVR is indicated in all symptomatic patients with severe AS and should be promptly performed at the onset of symptoms.²⁾⁶⁾²⁹⁻³¹⁾

STAGE D2

Low-gradient AS with LV dysfunction has poorer outcomes

Table 3. AHA/ACC recommendations for timing and choice of valve replacement for aortic valve stenosis

Indications for timing of valve replacement	Class (LOE)
Disease stage	
Class I: AVR is indicated in patients with:	
D1 Severe high-gradient AS with symptoms by history (or on exercise testing)	I (B)
C2 Severe asymptomatic AS with an LVEF < 50%	I (B)
C or D Severe asymptomatic AS in patients undergoing other cardiac surgery	I (B)
Class IIa: AVR is reasonable in patients with:	
C1 Asymptomatic very severe AS (aortic velocity ≥ 5 m/s) and low surgical risk	IIa (B)
C1 Asymptomatic severe AS and decreased exercise tolerance or an exercise fall in BP	IIa (B)
D2 Symptomatic low-flow/low-gradient severe AS with reduced LVEF	IIa (B)
D3 Symptomatic low-flow/low-gradient severe AS who are normotensive and have an LVEF $\geq 50\%$ if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	IIa (C)
B Moderate AS (aortic velocity 3.0–3.9 m/s) if undergoing other cardiac surgery	IIa (C)
Class IIb: AVR may be considered in patients with:	
C1 Asymptomatic severe AS with rapid disease progression and low surgical risk	IIb (C)
Choice of type of valve replacement	
Class I: Surgical AVR or TAVR is recommended	
Surgical AVR in patients who meet an indication for AVR with low or intermediate surgical risk	I (A)
Members of a Heart Valve Team should collaborate to provide optimal patient care For patients in whom TAVR or high-risk surgical AVR is being considered	I (C)
TAVR in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 months	I (B)
Class IIa: TAVR is a reasonable alternative to surgical AVR	
In patients who meet an indication for AVR for severe AS and who have high surgical risk	IIa (B)
Class IIb: Percutaneous aortic balloon dilation may be considered	
As a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS (or before urgent noncardiac surgery in ESC guidelines)	IIb (C)
Class III: TAVR is not recommended	
In patients in whom the existing comorbidities would preclude the expected benefit from correction of AS	III (B) No benefit

AHA/ACC: 2014 American Heart Association and American College of Cardiology Guidelines, AS: aortic stenosis, AVR: aortic valve replacement, either surgical or transcatheter, BP: blood pressure, ESC: 2012 European Society of Cardiology guidelines, LOE: level of evidence, LVEF: left ventricular ejection fraction, TAVR: transcatheter AVR. Adapted from Nishimura et al.⁶⁾

after AVR compared to high gradient severe AS with normal LV systolic function.³²⁾ However, survival is higher in patients undergoing AVR compared to those treated medically.³³⁾ Thus, AVR is reasonable for symptomatic patients with low-flow low gradient severe AS with reduced LV ejection fraction, after confirmation of the diagnosis by low dose dobutamine stress echocardiography (Fig. 1). If LV systolic dysfunction is due to outflow obstruction and afterload mismatch, LV systolic function should normalize after AVR. However, even if the low ejection fraction is related to a primary cardiomyopathy or coronary disease, ejection fraction still should improve after AVR due to the decreased total LV afterload, if significant valve obstruction was present. On average, LV ejection fraction increases by 10 points after relief of severe AS.

STAGE D3

The prevalence of low-flow low-gradient severe AS with preserved LV ejection fraction is controversial but a reasonable

estimate is between 5% and 25% of patients with severe AS. Many patients with apparent low-flow low-gradient AS with normal ejection fraction simply have moderate AS with clinical outcomes paralleling those for other patients with moderate AS.³⁴⁾ A second source of confusion arises when diagnostic data is suboptimal with measurement error accounting for an erroneous diagnosis of severe AS. In addition, it is important to measure AS severity when the patient is normotensive, to exclude other causes for AS symptoms and to take patient body size into consideration. Finally, patient-prosthesis mismatch should be avoided by comparing the expected hemodynamics after valve replacement to those of the native diseased valve.³⁵⁾

In patients with a confirmed diagnosis of severe low-output low-gradient severe AS, it is likely that AVR will improve survival and decrease symptoms. In a prospective observational study of 260 patients with symptomatic low-gradient severe AS with preserved ejection fraction, medical therapy was associated with 2-fold greater all-cause mortality than AVR over

mean 28 ± 24 months of followup.³⁶⁾ Similarly, based on an echocardiographic database of 1704 consecutive patients with severe AS, AVR was associated with a 69% mortality reduced in patients with low-flow low-gradient severe AS with normal ejection fraction.³⁷⁾

ASYMPTOMATIC PATIENTS WITH SEVERE AS

STAGE C1

The rate of symptom onset with severe AS is higher in patients with more severe AS. In asymptomatic patients with an

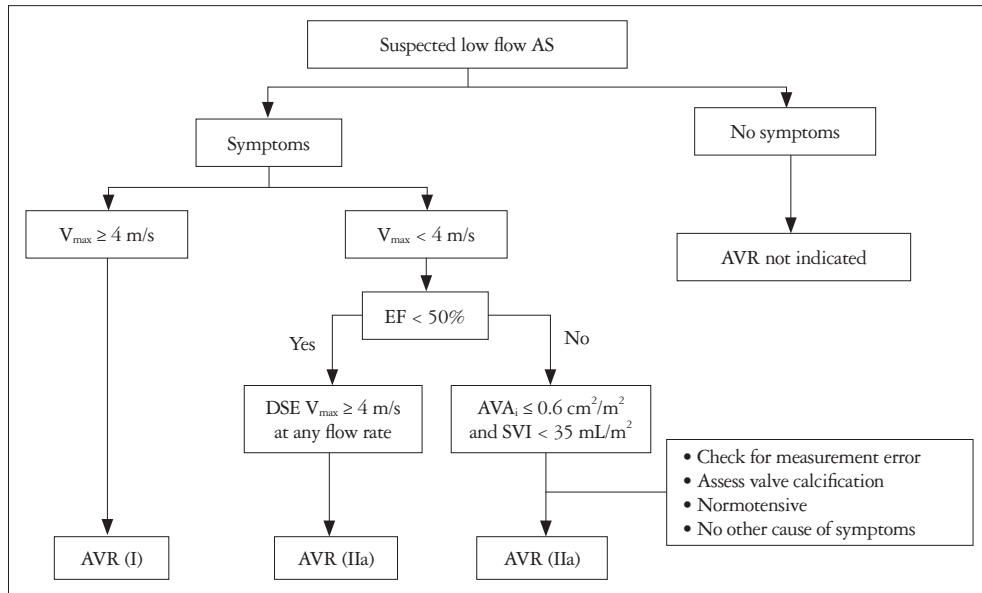


Fig. 1. Evaluation and management of the patient with low-flow low-gradient aortic stenosis. The AHA/ACC class recommendation (I, IIa, or IIb) is shown in parentheses corresponding to Table 3. AHA/ACC: 2014 American Heart Association and American College of Cardiology Guidelines, AS: aortic stenosis, AVA: aortic valve area, AVR: aortic valve replacement which may be either surgical or transcatheter, DSE: dobutamine stress echocardiography (low dose), EF: ejection fraction, SVI: stroke volume indexed to body size, V_{max} : maximum aortic velocity.

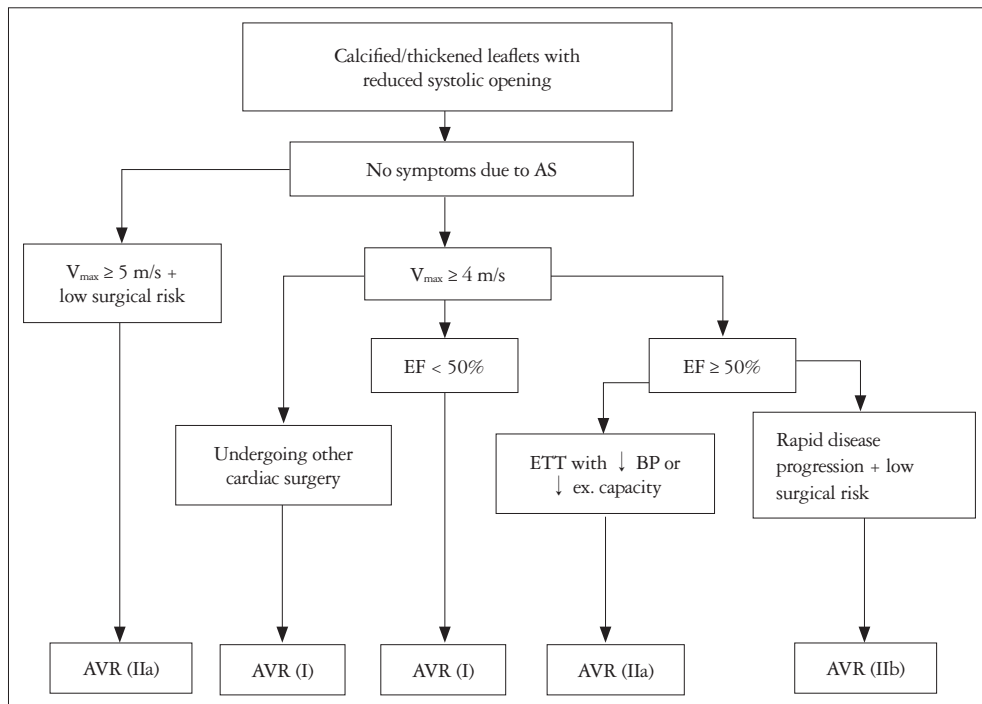


Fig. 2. Timing of aortic valve replacement in adults with asymptomatic aortic stenosis. The AHA/ACC class recommendation (I, IIa, or IIb) is shown in parentheses corresponding to Table 3. AHA/ACC: 2014 American Heart Association and American College of Cardiology Guidelines, AS: aortic stenosis, AVR: aortic valve replacement which may be either surgical or transcatheter, BP: blood pressure, EF: ejection fraction, ETT: exercise treadmill test, ex: exercise, V_{max} : maximum aortic velocity.

Table 4. Randomized controlled clinical trials of aortic valve replacement for aortic stenosis

Study	Study groups (n)	Patient population	Major endpoints	Other results
PARTNER cohort A (high-surgical risk) ⁽²⁴⁾⁽³⁵⁾⁽⁴⁶⁾	TAVR (balloon expandable Edwards-Sapien valve) in 348 vs. SAVR in 351	Severe symptomatic calcific AS defined as AVA < 0.8 cm ² plus a mean $\Delta P \geq 40$ mm Hg or $V_{max} \geq 4.0$ m/s with NYHA class II–IV symptoms	All cause death (intention to treat analysis): TAVR SAVR <i>p</i> -value	Stroke or TIA at 2 y: TAVR 11.2% vs. SAVR 6.5% (<i>p</i> = 0.05)
	Mean age 84 yrs Men 57% Mean STS-PROM score 11.7%	High surgical risk defined as $\geq 15\%$ risk of death by 30 d after the procedure. An STS score $\geq 10\%$ was used for guidance with an actual mean STS score of $11.8 \pm 3.3\%$ Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF < 20%, aortic annulus < 18 or > 25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	30 d 3.4% 6.5% 0.07 1 y* 24.2% 26.8% 0.44 2 y 33.9% 35.0% 0.78 5 y 67.8% 62.4% 0.76	Major vascular complications at 30 d: TAVR 11.0% vs. SAVR 3.2% (<i>p</i> < 0.001) Major bleeding at 30 d: TAVR 9.3% vs. SAVR 19.5% (<i>p</i> < 0.001) New-onset AF at 30 d: TAVR 8.6% vs. SAVR 16.0% (<i>p</i> = 0.006)
PARTNER cohort B (inoperable) ⁽³⁰⁾⁽³¹⁾⁽⁴⁴⁾	TAVR in 179 vs. medical therapy in 179 [including BAV in 150 (84%)]	Severe symptomatic calcific AS defined as AVA < 0.8 cm ² plus a mean $\Delta P \geq 40$ mm Hg or $V_{max} \geq 4.0$ m/s with NYHA class II–IV symptoms	All-cause death at 2 y: TAVR 43.3% vs. standard therapy 68% HR: with TAVR, 0.58 (95% CI: 0.36–0.92; <i>p</i> = 0.02)	Cardiac symptoms (NYHA class III or IV) were present in 25.2% of survivors at 1 y after TAVR vs. 58% with standard therapy (<i>p</i> < 0.001)
	Mean age 83 yrs Female 54% Mean STS-PROM score 11.7%	Inoperable due to coexisting conditions with predicted $\geq 50\%$ risk of death within 30 d of intervention or a serious irreversible condition Significant CAD, LVEF < 20%, aortic annulus < 18 or > 25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	Repeat hospitalization: TAVR 55% vs. 72.5% standard therapy (<i>p</i> < 0.001) Survival benefit of TAVR stratified by STS score: STS score HR 95% CI <i>p</i> -value < 5% 0.37 0.13–1.01 0.04 5–14.9% 0.58 0.41–0.81 0.002 $\geq 15\%$ 0.77 0.46–1.28 0.31	Major stroke rate at 30 d, was 5.0% with TAVR vs. 1.1% with standard therapy (<i>p</i> = 0.06) and remained high at 2 y 13.8% with TAVR vs. 5.5% (<i>p</i> = 0.01) Major vascular complications occurred in 16.2% with TAVR vs. 1.1% with standard therapy (<i>p</i> < 0.001)
Core Valve Study ⁽⁴⁷⁾	TAVR with self-expanding Core Valve prosthesis in 390 vs. SAVR in 357	Severe symptomatic calcific AS defined as AVA ≤ 0.8 cm ² , or indexed AVA ≤ 0.5 cm ² /m ² and either a mean $\Delta P > 40$ mm Hg or $V_{max} > 4.0$ m/s with NYHA class II–IV symptoms	All-cause death at 1 y: TAVR 14.2% vs. SAVR 19.1% (<i>p</i> < 0.001 for non inferiority and <i>p</i> = 0.04 for superiority)	Major vascular complications at 1 y: TAVR 6.2% vs. SAVR 2.0% (<i>p</i> = 0.004)
	Mean age 83.2 yrs Men 52.7% Mean STS-PROM score 7.4%	High surgical risk defined as $\geq 15\%$ risk of death by 30 d after the procedure and a risk or death or irreversible complications < 50% within 30 days of procedure Exclusions were valve sizing mismatch, inadequate access vessels, bicuspid aortic valve, significant CAD, or compliance issues	Major bleeding at 1 y: TAVR 29.5% vs. SAVR 36.7% (<i>p</i> = 0.03) Acute kidney injury: TAVR 6.0% vs. SAVR 15.1% (<i>p</i> < 0.001) Permanent pacemaker implantation: TAVR 22.3% vs. SAVR 11.3% (<i>p</i> < 0.001) New-onset AF at 1 y: TAVR 15.9% vs. SAVR 32.7% (<i>p</i> < 0.001)	
NOTION (severe symptomatic AS with low surgical risk) ⁽⁴⁸⁾	TAVR with self-expanding Core Valve prosthesis in 145 vs. SAVR in 135	Severe symptomatic calcific AS in patients over age 70 years with no significant coronary disease. Severe AS defined as AVA < 1.0 cm ² or indexed AVA ≤ 0.6 cm ² /m ² plus a mean $\Delta P > 40$ mm Hg or $V_{max} > 4.0$ m/s with NYHA class II–IV symptoms	Composite endpoint: death from any cause, stroke, or myocardial infarction at 1 year TAVR 13.1% vs. SAVR 16.3% (-3.2% absolute difference, <i>p</i> = 0.43 for superiority)	Major vascular complications at 30 d: TAVR 5.6% vs. SAVR 1.5% (<i>p</i> = 0.10)
	Mean age 79.12 yrs Men 53.2% STS-PROM score < 4 in 81.8%	Also include asymptomatic severe AS (<i>n</i> = 10) if severe LV hypertrophy, decreasing LVEF or new onset AF present Exclusions were expected survival < 1 yr, other severe valve disease, significant coronary disease, previous cardiac surgery, MI or stroke within 30 days, severe renal or pulmonary disease	Major bleeding at 30 d: TAVR 29.5% vs. SAVR 36.7% (<i>p</i> = 0.03) Acute kidney injury: TAVR 0.7% vs. SAVR 6.7% (<i>p</i> = 0.01) Permanent pacemaker implantation at 30 d: TAVR 34.13% vs. SAVR 1.6% (<i>p</i> < 0.001) New-onset or worsening AF at 30 d: TAVR 16.9% vs. SAVR 57.8% (<i>p</i> < 0.001)	

AF: atrial fibrillation, AMI: acute myocardial infarction, AR: aortic regurgitation, AS: aortic stenosis, AVA: aortic valve area, CAD: coronary artery disease, CI: confidence interval, HR: hazard ratio, LVEF: left ventricular ejection fraction, MI: myocardial infarction, MR: mitral regurgitation, NYHA: New York Heart Association, ΔP : mean transaortic pressure gradient, STS-PROM: Society of Thoracic Surgeons-Predicted Risk Of Mortality, pt(s): patient(s), SAVR: surgical aortic valve replacement, STS: Society of Thoracic Surgeons, TAVR: transcatheter aortic valve replacement, TIA: transient ischemic attack, V_{max} : aortic valve maximum velocity, BAV: balloon aortic valvotomy

aortic velocity of 5.0 m/s or greater, the rate of symptom onset is 50% at 2 years.³⁸⁾ Therefore, if surgical risk is low (< 1%), it is reasonable to consider elective AVR in this group of patients, even in the absence of symptoms (Fig. 2).³⁹⁾

Asymptomatic patients with severe AS who demonstrate decreased exercise tolerance or a failure of systolic blood pressure to increase by at least 20 mm Hg on exercise testing have a rate of symptom onset of 60–80% within one to two years. Patients with rapid progression of disease, defined as increase in aortic velocity of 0.3 m per second per year or greater also are at high risk of imminent symptom onset. In both these patients groups, AVR is appropriate as indicated in Table 3.

STAGE C2

The presence of a low LV ejection fraction in a patient with severe AS is an indication for AVR because it is likely that severe AS is the cause of LV systolic dysfunction. In patients with severe AS and a low ejection fraction, survival is higher, symptoms are reduced and LV ejection fraction is higher in those undergoing SAVR compared to those treated with medical therapy.⁴⁰⁾⁴¹⁾

STAGE B

In asymptomatic adults with progressive (mild-moderate) AS, there is no evidence that AVR improves long-term outcomes. The risk of valve replacement (and the risks of a prosthetic valve) are higher than the risk of sudden death, which is estimated at < 1% per year even with severe AS in asymptomatic adults.⁴²⁾ An exception to this approach is the patient with moderate AS who is undergoing other cardiac surgery. In this setting, AVR is recommended when severe AS is present and is reasonable if moderate AS is present because AS is progressive, with symptom onset likely within 5 years, and the risk of reoperative SAVR is high.⁶⁾ It is possible that this recommendation will be modified in the future as TAVR becomes an acceptable alternative to SAVR.

CHOICE OF INTERVENTION

In the patient with AS, there are two separate decisions regarding valve replacement. First, decide if AVR is indicated for relief of valve obstruction. Then, if AVR is appropriate, begin to think about the choice between SAVR and TAVR. The factors influencing the choice of AVR type include estimated surgical risk, comorbid conditions, patient frailty, technical impediments to either SAVR or TAVR, patient age and expected longevity as well as patient preferences and values.

Current procedural risk estimates for cardiac surgical procedures include the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons Predicted Risk Of Mortality (STS-PROM) score. These scoring systems assess the patient's risk of operative mortality and morbidity based on demographic factors, clinical variables, and the planned procedure. Evaluation of patients being con-

sidered for surgical vs. transcatheter approach is challenging as these risk scores are based on surgical (not transcatheter) outcome date, are not specific for valve disease, do not include all relevant variables (such as frailty) and do not consider structural impediments to surgery or a transcatheter approach. For example, structural impediments to SAVR include chest wall adhesions or a porcelain aorta whereas structural impediments to TAVR include poor vascular access or an aortic annulus too small or too large for currently available TAVR prosthetic valves. Thus, the Heart Valve Team bases the choice of SAVR vs. TAVR on integration of all these factors.

SAVR

SAVR remains the standard approach for patients with a low to intermediate surgical risk (STS-PROM score < 8%). SAVR benefits include survival advantage, improvement in symptoms and LV systolic function. Overall 30 day surgical mortality post aortic-valve replacement is 3% for isolated AVR. After recovery from successful AVR, the rate of overall survival is similar to that among age-matched adults without AS.⁴³⁾

TAVR

TAVR is the procedure of choice risk when the risk of surgery is prohibitive and expected survival after the procedure is at least one year (Table 4). These patients have a very high mortality at 5 years even with TAVR (73%) but survival, symptoms and quality of life all were improved in the PARTNER cohort B randomized controlled clinical trial of TAVR (2 year mortality 43.4%) compared to medical therapy (2 year survival 68%).³⁰⁾³¹⁾⁴⁴⁾

TAVR also is a reasonable alternative to SAVR in high risk patients. Currently, high surgical risk is defined as STS-PROM score of more than 8% or moderate to severe frailty or irreversible disease of more than 2 other organ systems not likely to improve after intervention. In the Placement of Aortic Transcatheter Valves (PARTNER) cohort A study; high risk patients with severe symptomatic AS were randomized to TAVR vs. SAVR. Long-term results of the PARTNER cohort A study showed similar long-term clinical outcomes between TAVR and SAVR. This study utilized the balloon expandable Sapien-Edwards valve. At 5 years, the mortality rate was 67.8% in the TAVR arm compared with 62.4% in the surgical arm (HR 1.04, 95% CI 0.86–1.24, $p = 0.76$). Echocardiography after TAVR showed durable hemodynamic benefit (AVA 1.52 cm² at 5 years, mean gradient 10.6 mm Hg at 5 years) with no evidence of structural valve deterioration.²⁾⁴⁵⁾⁴⁶⁾

In the randomized controlled clinical trial of the self-expanding Core Valve, the primary endpoint of death at one year was no different in the 390 patients randomized to TAVR (14.2%) compared to those randomized to SAVR (19.1%, $p < 0.001$ for non-inferiority) providing further confirmation that TAVR is a reasonable alternative to SAVR in high risk patients.⁴⁷⁾

Complications of TAVR differ from those with SAVR. The

risk of stroke was higher with TAVR compared to SAVR in early studies but now ranges from 2% to 6% with either approach. As might be expected, major vascular complications at 30 days are more common with TAVR (5.9–11%) compared to SAVR (1.7% to 3.2%). Paravalvular aortic regurgitation after TAVR has been associated with poor outcomes and it is hoped that refinements in valve design will reduce or eliminate this technical problem. Finally, the need for permanent pacer implantation after TAVR (3.8–19.8% with TAVR vs. 3.6–7.1% with SAVR) continues to be an issue, particularly with the self-expanding transcatheter valve.⁴⁷⁾

Most recently the Nordic Aortic Valve Intervention (NOTION) study,⁴⁸⁾ suggests that TAVR might be extended to lower-risk older patients who require AVR for severe AS. In a prospective randomized clinical trial, TAVR with the self-expanding prosthesis was compared to SAVR in patients over age 70 years (n = 280) with 81% of patients with a low surgical risk score (STS-PROM < 4). The first report from this study showed no significant difference in the primary composite endpoint that was death from any cause, stroke, or myocardial infarction at 1 year (13.1% for TAVR vs. 16.3% for SAVR, $p = 0.43$ for superiority).⁴⁸⁾

The choice of TAVR vs. SAVR will undergo continued change over the next decade as further data is published as the long-term durability of these valves is established. The 5-year results are encouraging but the higher risk period for bioprosthetic valves is in the 10 to 20 year time frame, data we will not have for some time to come.

PALLIATIVE CARE

The task of balancing the risks and benefits of TAVR depends on an accurate assessment of prognosis of survival, morbidity and expected quality of life. Baseline clinical risk factors associated with poor outcomes after TAVR include advanced age, frailty, smoking, chronic obstructive pulmonary disease, liver disease, prior stroke or other systemic conditions. Ideally a validated model that predicts long-term outcomes after TAVR would help guide this analysis. However until development of such ideal model, surgical risk scores can be used to evaluate those who may benefit from TAVR (Table 4). TAVR is not recommended in patients with a life expectancy < 1 year even with a successful procedure or in patients with comorbidities that preclude significant symptomatic benefit from relief of AS.²⁾ In this setting, appropriate palliative care should be offered as it provides the best quality of life for these patients.

BALLOON AORTIC DILATION

Balloon aortic valve dilation provides modest hemodynamic benefits, which does not outweigh the risk of the procedure including stroke, aortic regurgitation and a high probability of recurrence of AS within 6 months.⁴⁹⁾ Currently this procedure is only recommended for stabilization before TAVR or surgery in patients presenting with hemodynamic instability due to se-

vere AS.⁶⁾

CONCLUSIONS

In summary, the 2014 AHA/ACC Valve Guidelines provide a new framework of thinking about aortic valve disease, which aligns disease severity with recommendations for intervention. An integrative approach that considers clinical factors, valve anatomy, hemodynamics and LV function in addition to the patient preference and overall condition now is recommended and the importance of the Heart Valve Team in the diagnosis and treatment of disease is reaffirmed. With the publication of randomized controlled clinical trials data, refinements in valve design, and reductions in procedural complications, we will see a gradual shift towards from surgical towards transcatheter valve replacement when intervention for AS is required. In the future, intervention is likely to move even earlier in the disease course if transcatheter bioprosthetic valves demonstrate long-term durability. However until further data is available, SAVR remains the recommended treatment of severe symptomatic AS in those with low surgical risks because of the known durability of surgical prosthetic valves.

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