MAYO CLINIC

Management of Patients With Aortic Valve Stenosis

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Abstract

With increased life expectancy and aging of the population, aortic stenosis is now one of the most common valvular heart diseases. Early recognition and management of aortic stenosis are of paramount importance because untreated symptomatic severe disease is universally fatal. The advent of transcather aortic valve replacement technologies provides exciting avenues of care to patients with this disease in whom traditional surgical procedures could not be performed or were associated with high risk. This review for clinicians offers an overview of aortic stenosis and updated information on the current status of various treatment strategies. An electronic literature search of PubMed, MEDLINE, EMBASE, and Scopus was performed from conception July 1, 2016, through November 30, 2017, using the terms *aortic stenosis*, *aortic valve replacement*, *transcatheter aortic valve replacement (TAVR)*, *transcatheter aortic valve insertion (TAVI)*, *surgical aortic valve replacement*, *aortic stenosis flow-gradient patterns*, *low-flow aortic valve stenosis*, *natural history*, *stress testing*, *pathophysiology*, *bicuspid aortic valve*, and *congenital aortic valve disease*.

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As life expectancy and the aging population increase, aortic stenosis (AS) has become one of the most common valvular heart diseases. Early recognition and management are imperative because untreated symptomatic severe AS is universally fatal. New transcather aortic valve replacement (TAVR) technologies have extended care to elderly patients whose options were previously limited. To provide an overview of AS and updated information on current treatment strategies, we performed an electronic literature search of PubMed, MEDLINE, EMBASE, and Scopus from conception through November 30, 2017, using the terms *aortic stenosis*, *aortic valve replacement*, *transcatheter aortic valve replacement*, *transcatheter aortic valve insertion*, *surgical aortic valve replacement*, *aortic stenosis flow-gradient patterns*, *low-flow aortic valve stenosis*, *natural history*, *stress testing*, *pathophysiology*, *bicuspid aortic valve*, and *congenital aortic valve disease*.

PREVALENCE OF AORTIC VALVE STENOSIS

An estimated 4.2 to 5.6 million adults in the United States have some form of clinically important valve disease.[1] There were approximately 40 million persons aged 65 and older in 2010, but this number is expected to be 55 million in 2020 and 72 million in 2030.[2] Because the common forms of valve diseases are linked to aging, this demographic shift will increase the number of patients with AS.

The Helsinki Aging Study, an echocardiographic screening study, provided further evidence of increased calcification and degeneration of the aortic valve with increasing age.[3] Some degree of valvular calcification was noted in 75% of people aged 85 to 86 years. The prevalence of critical aortic valve stenosis increased with age from between 1% and 2% in persons aged 75 to 76 years to 6% in those aged 85 to 86 years. Similarly, the Euro Heart Survey on Valvular Heart Disease prospectively surveyed 5001 individuals from 92 centers in 25 countries.[4] Among incident native left-sided valve disease, AS was the most frequent (1197 of 2779 patients [43.1%]) and was severe in a substantial number of affected individuals (809 of the 1197 patients [67.6%]).

A study of 16,501 adults from the National Heart, Lung, and Blood Institute–funded population-based studies and 11,911 adults undergoing clinically indicated echocardiography in Olmsted County, Minnesota,[1,2] also revealed increasing prevalence of AS with increasing age (Figure 1). The prevalence of

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moderate or severe AS was age dependent and increased from a low of 0.02% to 0.1% in individuals aged 18 to 44 years to a high of 2.8% to 4.6% in patients 75 years or older enrolled in the National Heart, Lung, and Blood Institute–based and Olmsted County studies, respectively.

RISK FACTORS FOR DEVELOPMENT OF AORTIC VALVE STENOSIS

A normal aortic valve is tricuspid. However, up to 2% of individuals in the general population are born with a congenitally abnormal bicuspid aortic valve or, rarely, a unicuspid or quadricuspid aortic valve. A unicuspid or bicuspid valve is predisposed to development of calcific AS because of underlying abnormal valve geometry and mechanical stress.[5,6] A bicuspid aortic valve is responsible for AS in the majority of individuals up to the seventh decade of life,[7] after which tricuspid aortic valve stenosis is more common. The earlier in life AS occurs, the higher the likelihood of underlying congenital aortic valve disease.[8] Risk factors associated with the development of AS are similar to those for atherosclerosis and are more common in tricuspid than bicuspid aortic valve stenosis given the congenital predisposition of a bicuspid valve for development of stenosis.[9,10] Quadricuspid aortic valve stenosis is rare.[11]

Calcific aortic valve stenosis was traditionally considered a senile or degenerative process, but active inflammation has been reported in the early lesion of aortic valve sclerosis that progresses to calcific stenosis.[12] Calcific AS is considered an active disease process characterized by inflammation, atherosclerosis, calcium deposition, and ossification, with marked differences noted in tissue and clinical factors responsible for disease initiation and progression.[13] Elevated serum lipid levels and markers of inflammation are associated with aortic valve sclerosis (the early lesion of AS) but not with progression of aortic valve disease.[14-16] Transformation at the tissue level from early to progressive disease probably explains the lack of a substantial effect of statins on progression of AS, as reported by the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) randomized trial.[17] In patients with mild to moderate asymptomatic AS, incident aortic valve replacement (AVR) did not differ in patients receiving statin therapy vs placebo; during a median follow-up of 52.2 months in 1873 patients with mild to moderate AS, AVR occurred in 333 patients (35.3%) receiving statin therapy and in 355 patients (38.2%) in the placebo group (hazard ratio [HR] in the simvastatin-ezetimibe group, 0.96; 95% CI, 0.83-1.12; P=.59). Similar results (no reduction in progression of AS with statins) were reported by the Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin (ASTRONOMER) trial that randomized 269 asymptomatic patients with mild to moderate AS with no clinical indications of lipid lowering to 40 mg of rosuvastatin or placebo.[18] A meta-analysis of 4 studies also found no benefit of statins on progression of AS.[19]

ARTICLE HIGHLIGHTS

- There are new guidelines related to the clinical and echocardiographic assessment and classification of aortic valve stenosis.
- Treatment of aortic valve stenosis has undergone a radical change with the advent of transcatheter aortic valve replacement.
- There are new guidelines related to candidacy for transcatheter aortic valve replacement vs surgical aortic valve replacement.
- A "heart team" approach is recommended in the evaluation and management of patients with aortic valve stenosis.

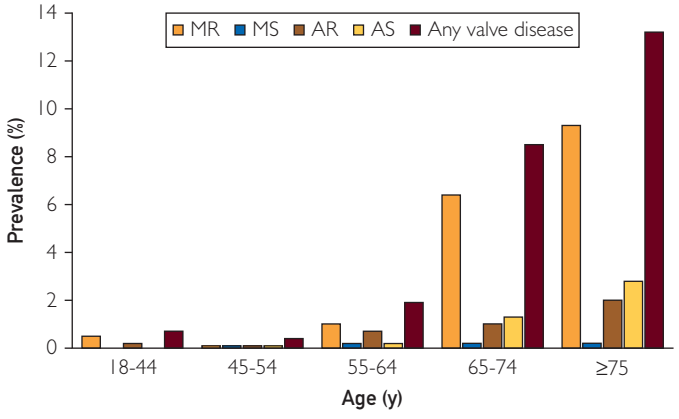

FIGURE 1. Prevalence of valvular heart disease in the general population. AR = aortic regurgitation; AS = aortic stenosis; MR = mitral regurgitation; MS = mitral stenosis. From *Lancet*,[1] with permission from Elsevier.

Aortic valve sclerosis is common among older adults and shares epidemiological and histopathologic similarities to atherosclerosis. In the Multi-Ethnic Study of Atherosclerosis (MESA),[13] incident aortic valve sclerosis and its progression was quantified from 5880 participants (aged 45-84 years). The incident rate (mean, 1.7% per year) increased with age and risk factors including older age, body mass index, current smoking, and use of lipid-lowering and antihypertensive medications. Among 5621 participants aged 65 years or older in the Cardiovascular Health Study (CHS) in whom baseline and 5-year (mean) follow-up echocardiographic studies were available, approximately 9% of patients with aortic valve sclerosis had progression to AS.[16] Increasing age and higher levels of low-density lipoprotein cholesterol were associated with incident aortic valve sclerosis in participants with normal aortic valves at baseline, and male sex was associated with a 32% excess risk. A recent study reported that risk factors of hypertension, diabetes, and hyperlipidemia accounted for about 30% of the incidence of severe AS in an unselected population of older adults.[20]

Bicuspid Aortic Valve

Bicuspid aortic valve is the most common congenital heart disease, with prevalence estimates ranging between 0.5% and 2%.[21] Larson and Edwards[22] found 293 bicuspid aortic valves (1.37%) among 21,417 autopsies. There was a predominance of males (male to female ratio, 3:1). The clinical manifestations usually vary from presentation in infancy to asymptomatic valve/aortic disease in adulthood, symptom manifestations related to the aortic valve (stenosis/incompetence), aortopathy (aneurysm/dissection), or acquired complications such as infective endocarditis.[23,24] Aortic stenosis is the most common sequela of bicuspid aortic valve. In patients with bicuspid aortic valve undergoing AVR for severe AS, 60% are younger than 70 years.[8,23,25]

Among 212 asymptomatic community residents from Olmsted County, Minnesota (age, 32±20 years; 65% male), with bicuspid aortic valve and 20-year follow-up, 24%±4%, 5%±2%, and 27%±4% required aortic valve, ascending aorta, or any cardiovascular surgical procedure, and 40% incurred a cardiovascular medical or surgical event.[26]

Other Risk Factors

Familial clustering in patients with bicuspid and tricuspid AS suggests a genetic component; 9.1% of first-degree relatives of those with bicuspid valve will have the condition, and among those with bicuspid valve, 36.7% will have at least one additional family member with the condition.[27] A recent French study identified clusters and larger families affected by calcified tricuspid AS.[28] In another study, investigators identified a family of European-American descent spanning 5 generations with 11 cases of congenital heart disease, and in 8 cases, an abnormal aortic valve was the only cardiac malformation; 6 had bicuspid aortic valve and 7 had development of calcific AS, including 3 in the setting of a trileaflet valve.[29]

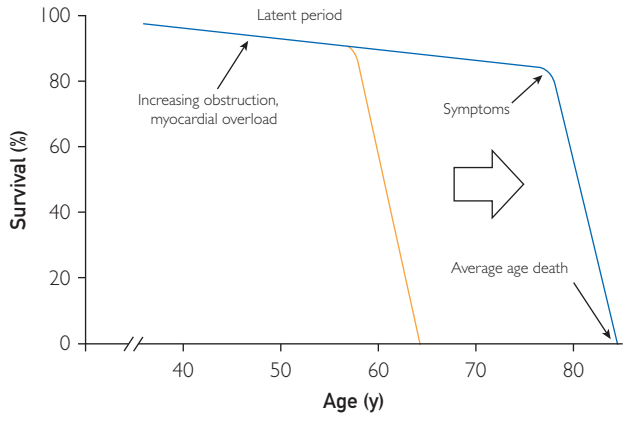

FIGURE 2. The natural history of aortic stenosis. From *Circulation*[40], with permission.

NATURAL HISTORY OF AORTIC VALVE STENOSIS

The natural history of AS is characterized by a relatively benign course in patients with asymptomatic disease but a rapid downhill course with the onset of symptoms.[30-38] The symptomatic demarcation conceptualized by Ross and Braunwald[39] to occur in middle age has shifted to the right (due to a decline in rheumatic heart disease—related AS in younger patients), with development of symptoms in the seventh through ninth decade

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heralding poor survival unless timely valve replacement is performed (Figure 2).[40]

The progression of aortic valve disease and the need for eventual AVR varies considerably. In general, progression from aortic valve sclerosis to valve obstruction is seen in approximately 10% to 15% of patients over a period of 2 to 5 years[13,16]; however, progression is universal and valve replacement is eventually required once mild valve obstruction is identified. On average in the SEAS trial, the annualized change in the mean peak aortic jet velocity was 0.15 meters per second per year, mean transaortic pressure gradient increased by 2.7±0.1 mm Hg, and annualized reduction in the aortic valve area of 0.03±0.01 cm^2 per year was seen among patients with mild to moderate aortic valve stenosis (Table 1).[17] Variability in progression of aortic valve disease and lack of correlation between severity and symptoms does not allow precision estimates for future events but helps guide patient counseling and follow-up strategies.

STAGES OF AORTIC VALVE STENOSIS

Stages of AS, similar to stages of heart failure, have been proposed by the current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines to acknowledge the continuum of AS from those at risk for development of AS (stage A) to progressive mild to moderate AS (stage B), to severe AS without symptoms and with normal left ventricular ejection fraction (LVEF) of 50% or higher (stage C), and severe AS with symptoms and/or reduced LVEF of less than 50% (stage D). Stage D is further subdivided into stage D1 (symptomatic severe high gradient AS), stage D2 symptomatic severe low-gradient AS with LVEF of less than 50%, and stage D3 (symptomatic severe low-flow, low-gradient AS with LVEF ≥50%) (Table 2).[42] Recognition of the different stages of AS is useful in the management of the disease because each stage is linked to a recommendation for continued surveillance or AVR. Surgical AVR or transcatheter AVR (TAVR) is indicated primarily for stage D AS with some exceptions for stage C disease (see "Exercise Stress Testing in Severe Aortic Valve Stenosis" section).

TABLE 1. Annual Progression of Aortic Stenosis (Rule of 3)

Increase in peak aortic jet velocity (m/s)	(0.3/2) 0.15
Increase in transaortic pressure gradient (mmHg)	~3
Reduction in aortic valve area (cm^2)	0.3

From *N Engl J Med*,[41] with permission from the Massachusetts Medical Society.

SYMPTOMS IN AORTIC VALVE STENOSIS

The cardinal symptoms of severe AS are exertion-related angina, congestive heart failure (reduced exercise tolerance), presyncope, or syncope. Dyspnea is due to either increased left ventricular filling pressure or inability to increase cardiac output with exercise. In most patients, symptoms appear with normal LVEF; however, in some patients there is a reduction in systolic myocardial function and inability of the left ventricle to develop pressure and shorten against a load (afterload mismatch) before the onset of symptoms.[43,44] Consequently, with left ventricular dysfunction and reductions in stroke volume and cardiac output, signs and symptoms of congestive heart failure appear. Reduction in cerebral perfusion results in dizziness and syncope and can caused by exercise-induced vasodilatation with a backdrop of fixed cardiac output, baroreceptor dysfunction, bradyarrhythmias, or uncommon atrial or ventricular arrhythmias.[45] Effort-related angina is more common in patients with concomitant coronary artery disease (CAD) but is also reported by patients without CAD and thus has a low positive predictive value for underlying CAD.[46] Angina can be caused by increased myocardial oxygen demand due to myocardial hypertrophy, compression of intramyocardial coronary arteries, impaired coronary flow reserve, and/or reduced diastolic coronary perfusion time during tachycardia. Earlier series reported significant CAD in 25% to 50% of patients and that it was a function of age.[47-49] Surgical series have found that in the age group 61 to 70 years, 40% of patients require concomitant coronary artery bypass grafting (CABG), whereas in patients older than 80 years, more than 65% require

TABLE 2. Disease Stages in Patients With Aortic Valve Stenosis[a,b]

Stage	Description	Definition	Outcomes	Management
A	At risk	Aortic valve sclerosis or bicuspid valve; V_{max} of <2 m/s	Associated with a 50% increase in the risk of myocardial infarction and cardiovascular death over 5 y	Assessment of cardiovascular risk factors and primary prevention
B	Progressive	Mild to moderate calcification or rheumatic changes with reduced leaflet motion, V_{max} of 2-3.9 m/s or mean transaortic pressure gradient of 20-39 mm Hg	Hemodynamic progression in most patients	Assessment of cardiovascular risk factors and primary prevention; periodic clinical and echocardiographic monitoring; patient education about disease progression and outcomes
C1	Asymptomatic, severe aortic stenosis with normal left ventricular function	Severe calcification or rheumatic changes with reduced leaflet motion; V_{max} of ≥4 m/s or mean transaortic pressure gradient of ≥40 mm Hg with ejection fraction ≥50%	Symptom onset in 50%-80% of patients within 3 y; low risk of sudden death; variability in severity at symptom onset; symptom onset >50% of patients with very severe aortic stenosis (V_{max} of >5 m/s) within 2 y	Frequent clinical monitoring (≤6 mo) and echocardiographic monitoring (≤12 mo) for symptoms onset and disease progression; consider treadmill exercise testing or testing serum levels of brain natriuretic peptide; AVR is reasonable with asymptomatic very severe aortic stenosis
C2	Asymptomatic, severe aortic stenosis with ejection fraction <50%	Severe calcification or rheumatic changes with reduced leaflet motion; V_{max} of ≥4 m/s or mean transaortic pressure gradient of ≥40 mm Hg with ejection fraction <50%	If other causes of left ventricular dysfunction are absent, the ejection fraction is likely to normalize after AVR	AVR is recommended to preserve left ventricular function
D1	Symptomatic, severe, high-gradient aortic stenosis	Severe calcification or rheumatic changes with reduced leaflet motion; V_{max} of ≥4 m/s or mean transaortic pressure gradient of ≥40 mm Hg	Mortality is 50% at 1 y, 70%-80% at 2 y without AVR	Prompt AVR is the only effective therapy
D2	Symptomatic, severe, low-gradient aortic stenosis with ejection fraction <50%	Severe calcification or rheumatic changes with reduced leaflet motion; baseline AVA of ≤1 cm^2 with V_{max} of <4 m/s with ejection fraction of <50%; V_{max} of ≥4 m/s with AVA of ≤1 cm^2 at any flow rate on low-dose dobutamine stress testing	Mortality at 2 y is about 20% with medical therapy, as compared to 40% with AVR; operative mortality is higher and survival lower in patients without contractile reserve	AVR is reasonable if severe aortic stenosis is present; the ejection fraction is likely to improve after AVR, even in patients without contractile reserve
D3	Symptomatic, severe, low-flow, low-gradient aortic stenosis with normal ejection fraction	Severe calcification or rheumatic changes with reduced leaflet motion; baseline AVA of ≤1 cm^2 and V_{max} of <4 m/s with ejection fraction of ≥50%; indexed AVA of ≤0.6 cm^2/m^2 with stroke volume index of <35 mL/m^2 when patient is normotensive	Mortality at 2 y is 50%-70% without AVR	AVR is reasonable in symptomatic patients if evaluation indicates the presence of severe aortic stenosis and there is no other cause for symptoms

[a]AVA = aortic valve area; AVR = aortic valve replacement; V_{max} = aortic maximum velocity.

[b]Echocardiography is diagnostic for evaluation of the severity of aortic stenosis in nearly all patients. However, these measurements require considerable technical expertise and adequate image quality, so the underestimation of the severity of aortic stenosis should be considered if the echocardiographic data are discrepant with clinical findings. Additional evaluation by repeated echocardiography at specialist heart valve center, cardiac catheterization, or other imaging method may be needed in some patients.

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concomitant CABG.[50-52] The prevalence of significant CAD in the TAVR population ranges from 40% to 75%.[53-57] In the Placement of Aortic Transcatheter Valves (PARTNER) 2 trial, CAD was seen in 69.7% of patients assigned to TAVR,[58] and, similarly, CAD was found in 69.2% of patients in the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial.[59]

Correlation between onset of symptoms and severity of stenosis is not robust. The onset of symptoms may be early with coexistent aortic regurgitation or delayed in some patients even with critical stenosis. However, symptoms generally appear in patients with normal ejection fraction when the AS is severe (see "Echocardiography" section).and can be vague, such as tiredness or fatigue. In symptomatic patients, event-free survival is only 30% to 50% at 2 years, underscoring the need for frequent monitoring for progression (Figure 3).[32,33] Sudden death, an important consideration and a complication of severe AS, is more common in patients with symptomatic AS[30] but can occur without preceding symptoms at a rate of 1% per year.[31]

Patients with moderate AS may exhibit similar symptoms, but other etiologies for these symptoms should be carefully considered before attributing symptoms to AS. For example, dyspnea can be a symptom of deconditioning, cardiomyopathy, chronic lung disease, anemia, renal failure, or coexisting CAD. Similarly, angina can be a manifestation of CAD; arrhythmias and heart block in the elderly can lead to presyncope and syncope. However, once a diagnosis of severe AS is firmly established, careful attention should be paid to even mild cardiac symptoms because symptom onset is associated with an average survival without valve replacement of only 2 to 3 years and there is an increased risk of sudden death.[30,39]

PHYSICAL EXAMINATION FINDINGS IN AORTIC VALVE STENOSIS

Three classic physical examination findings, when present, support the diagnosis of advanced AS: mid to late systolic murmur intensity, low volume and rate of increase of carotid upstroke (pulsus parvus et tardus), and reduced intensity of the second heart sound (Table 3).[60,61] A clinical prediction rule that also included maximum murmur intensity at the right second intercostal space with radiation to the right carotid artery predicted the presence of echocardiography-confirmed moderate to severe AS if 3 of 4 criteria were present and the absence of murmur at the second right intercostal space ruled out significant AS (negative likelihood ratio, 0.05-0.10).[61] In elderly patients with vascular disease, a softer murmur intensity and normal carotid upstroke do not rule out a diagnosis of severe AS. The only finding that reliably rules out severe AS is the normally split second heart sound.

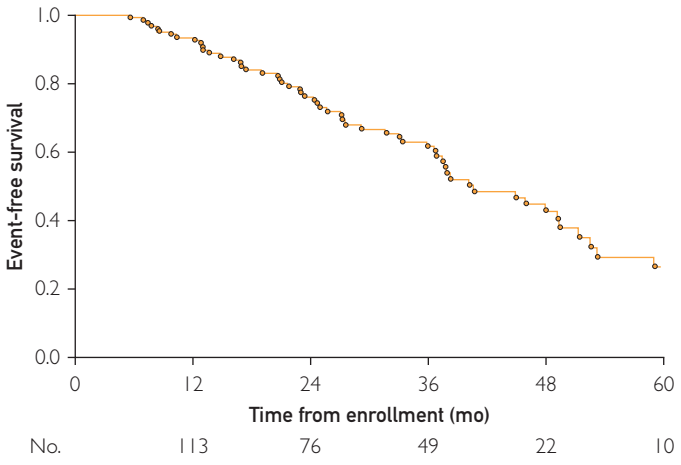

FIGURE 3. Survival without aortic valve replacement in 123 patients with initially asymptomatic valvular aortic stenosis. From *Circulation*[32], with permission.

DIAGNOSIS AND EVALUATION OF AORTIC VALVE STENOSIS

An aortic valve area of 1 cm^2 or less is considered severe AS (normal, 3-4 cm^2), and the hemodynamic severity of AS is best characterized by transaortic peak velocity of 4 m/s or

TABLE 3. Physical Diagnostic Features of Severe Aortic Stenosis

- Mid to late peaking of ejection systolic murmur
- Reduced intensity of second heart sound
- Maximum murmur intensity at the second right intercostal space
- Low volume and rate of increase of carotid upstroke (pulsus parvus et tardus)

more or mean gradient of 40 mm Hg or more. Greater importance is attached to the peak velocity and mean gradient and if the hemodynamic threshold for severe AS is met, then severe AS is considered to be present regardless of aortic valve area. Recent recommendations on the echocardiographic assessment of AS from the European Association of Cardiovascular Imaging and the American Society of Echocardiography recognize the importance of the entity of low-gradient AS when the aortic valve area is small ($\leq$1 cm^2) but the hemodynamics are discordant with a peak velocity of less than 4 m/s or a mean gradient of less than 40 mm Hg.[62] Reasons for discordance include measurement error, elevated blood pressure at the time of echocardiography, or low forward flow (stroke volume index <35 mL/m^2) because flow influences gradient. Flow gradient patterns in AS can be categorized as normal flow—high gradient, low flow—high gradient, normal flow—low gradient, and low flow—low gradient, with preserved ($\geq$50%) or reduced (<50%) LVEF. The high-gradient pattern categories indicate classic severe AS; patients with the low flow—low gradient pattern appear to have worse outcomes with medical management than those with classic AS; and patients with the normal flow—low gradient pattern have clinical outcomes more similar to those with moderate AS.[62] These flow-gradient AS categories are in line with the AHA/ACC guideline on the management of patients with valve disease and are part of the continuum in the stages of AS (Table 2).[42]

Echocardiography

The primary test for diagnosis and management decisions in patients with AS is echocardiography. A transthoracic echocardiogram delineates aortic valve anatomy (number of cusps, extent of calcification, leaflet excursion), valve hemodynamics to confirm severity, its consequences on left ventricle function, pulmonary hypertension, concomitant valvular heart disease, and ascending root dilation.[63] Transthoracic echocardiography is indicated in patients with signs or symptoms of AS or a bicuspid aortic valve for accurate diagnosis of the cause, hemodynamic severity, left ventricular size, and systolic function and for determining prognosis and timing of valve intervention (class I, level of evidence B).[42]

Doppler echocardiography uses the Bernoulli principle to evaluate maximum instantaneous pressure gradient (ΔP) across the aortic valve ($\Delta P = 4 \times [V_{AV}]^2$, where V_{AV} represents stenotic jet velocity across the aortic valve). The stenotic jet velocity is also used to calculate aortic valve area (AVA) from the continuity equation: $AVA = (A_{OT} \times VTI_{OT}) \div VTI_{AV}$, where A_{OT} and VTI_{OT} represent area and velocity time integral at the outflow tract, respectively, and VTI_{AV} is the aortic valve velocity time integral.[62]

Low-dose dobutamine stress echocardiography is appropriate for patients with low-gradient AS (stage D_2) (ie, calculated valve area $\leq$1.0 cm^2 and aortic velocity <4 m/s or mean gradient <40 mm Hg with reduced LVEF <50%) and is a class IIa (level of evidence B) recommendation in the ACC/AHA-European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines.[42] Severe AS on low-dose dobutamine stress testing is defined as a maximum velocity of 4.0 m/s or more with a valve area of 1.0 cm^2 or less at any point during the test. In the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study, projected effective orifice area (EOA_{proj}) at normal transvalvular flow rate (250 mL/s) was used to differentiate true from pseudostenosis and correctly classified 83% patients as compared with standard echocardiographic parameters.[64] Patients whose stroke volume does not increase by 20% or more with low-dose dobutamine infusion are often said to have a "lack of contractile reserve" or "lack of flow reserve."[65] These patients appear to be at particularly high risk of operative mortality if AVR is attempted.

Cardiac Catheterization

Cardiac catheterization is recommended when there is discordance between the clinical and echocardiographic evaluations, when noninvasive data are nondiagnostic, or when coronary angiography needs to be obtained as a part of the work-up or treatment. According to the AHA/ACC guideline for the management of patients with valvular heart disease, coronary angiography is indicated before valve intervention in patients with symptoms of angina,

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objective evidence of ischemia, decreased left ventricular systolic function, history of CAD, or coronary risk factors (including age >40 years in men and postmenopausal status in women) (level of evidence C). Additionally, catheterization with dobutamine infusion may be used in patients with low-flow, low-gradient AS and left ventricular dysfunction.[42]

Pressure difference across the aortic valve is measured by using double-lumen fluid-filled catheters for simultaneous left ventricular and aortic pressure measurements. Pullback gradients are inaccurate for diagnostic purposes. Cardiac output assessment is done by either Fick or thermodilution methods, and aortic valve area is calculated by Gorlin or simplified Hakki equation (Aortic Valve Area [cm^2] = Cardiac Output [l/min]/ Square Root of Peak-to-Peak Gradient Across the Aortic Valve).

Role of Other Imaging Modalities

Cardiac magnetic resonance imaging can evaluate valve anatomy and flow characteristics across the stenotic valve, calculate valve area, and estimate left ventricular function and severity of concomitant aortic regurgitation.[66,67] This technique has shown promise but is not widely available. Cardiac computed tomography is useful for quantitation of valve calcification. A calcium score of less than 700 Agatston units (AU) excludes severe AS with a high negative predictive value, and a score of more than 2000 AU suggests severe AS. In one study, a threshold of 1651 AU provided a sensitivity of 80%, specificity of 87%, negative predictive value of 88%, and a positive predictive value of 70% for severe AS vs nonsevere AS.[68] Computed tomography is also helpful in the evaluation of patients undergoing TAVR for measurement of annulus area, annulus circumference, and the annular to coronary ostial distance.

Exercise Stress Testing in Severe Aortic Valve Stenosis

Exercise testing is safe and can be useful in asymptomatic patients for further risk stratification. Approximately 25% to 30% of patients with asymptomatic severe AS experience exercise-limiting symptoms during stress testing and have a worse outcome than those with a normal exercise stress test result.[69] Exercise stress testing is contraindicated and should not be preformed in patients who have symptomatic AS and/or have reduced LVEF of less than 50%. In essence, exercise stress testing is reserved for patients with asymptomatic severe AS and normal LVEF of 50% or greater. Poor exercise capacity, abnormal blood pressure response to exercise (<20 mm Hg increase or hypotension), or exercise-induced arrhythmias are important prognostic findings in patients with severe AS. Exercise testing is safe when performed under close electrocardiographic and blood pressure monitoring. In one series, 37% of asymptomatic patients seen as outpatients had exercise-limiting symptoms during graded treadmill exercise.[70] In a multivariate analysis, only the development of symptoms during stress testing was found to predict spontaneous symptom onset within 12 months (odds ratio, 7.7; 95% CI, 2.79-21.39; $P<.001$). Abnormal blood pressure response or ST-segment abnormalities with exercise were associated with poor 2-year symptom-free survival (19% vs 85%).[71]

The additive value of Doppler echocardiography has been reported in studies showing prognostic value in identifying, during exercise, an increase in the mean gradient across the aortic valve of 18 mm Hg or more, pulmonary hypertension (pressure >60 mm Hg), or a decrease or lack of improvement in LVEF.[69]

An abnormal cardiopulmonary exercise stress test result showing low peak oxygen consumption (<85% predicted) has also been reported to unmask symptoms in asymptomatic patients and identify those at high risk for development of symptoms or needing AVR sooner.[72,73]

TREATMENT OVERVIEW

The only effective treatment for severe AS is AVR. Although helpful in ameliorating symptoms in the short term, medical therapy and balloon valvuloplasty by themselves do not change the poor prognosis and natural history of severe AS.

A multidisciplinary "heart valve team" is increasingly emphasized for evaluation and management of patients with severe AS.[42] Current guidelines encourage the integration of the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) score,

TABLE 4. Risk Assessment for Aortic Valve Intervention

Variable	Low risk (must meet ALL criteria in this column)	Intermediate risk (any 1 criterion in this column)	High risk (any 1 criterion in this column)	Prohibitive risk (any 1 criterion in this column)
STS-PROM score	<4% **AND**	4%-8% **OR**	>8% **OR**	Predictive risk with surgery of death or major morbidity (all-cause) >50% at 1 y **OR**
Frailty	None **AND**	1 Index (mild) **OR**	≥2 Indices (moderate to severe) **OR**	
Major organ system compromise that will not be improved postoperatively	None **AND**	1 Organ system **OR**	No more than 2 organ systems **OR**	≥3 Organ systems **OR**
Procedure-specific impediment	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Possible procedure-specific impediment

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

frailty score, major organ system compromise that will not be improved postoperatively, and procedure-specific impediments in deciding treatment options for patients with severe AS (Table 4). This classification system can identify patients at low, intermediate, or high risk or those in whom aortic vale replacement would be futile. The surgical or transcatheter treatment is considered futile if life expectancy is less than 1 year or the chance of "survival with benefit" (defined as improvement in heart failure or angina class of ≥1, improvement in quality of life or life expectancy) is less than 25% at 2 years.[42] In the inoperable cohort of the PARTNER trial, patients with an STS-PROM score greater than 15% derived no survival benefit compared with medically managed patients with severe AS.[74] Arnold et al[75] proposed a score to predict poor clinical outcomes at 6 months (Kansas City Cardiomyopathy Questionnaire score <45 or a decrease of ≥10 points from baseline) and found that 35% of patients meeting these criteria treated with TAVR had poor outcomes.

MEDICAL TREATMENT

Hypertension

Hypertension results in serially increased afterload and is associated with higher rates of mortality and ischemic cardiovascular events. Hypertension is common in patients with AS, and its treatment should follow the contemporary guidelines. Hypertensive patients (n=1340) with asymptomatic AS in the SEAS study had a 56% higher rate of ischemic cardiovascular events and a 2-fold increased mortality rate (both $P<.01$) compared with normotensive patients with AS, although no impact on progression of AS was demonstrated.[17] Systemic hypertension in low-gradient severe AS with preserved ejection fraction (stage D3) is associated with increased left ventricular filling pressures and pulmonary hypertension, and treatment of hypertension with vasodilator therapy results in salutary symptom improvement.[76] General guidelines for antihypertensive therapy include initiation with low dose and gentle upward titration, use of angiotensin-converting enzyme inhibitors, β-blockers in patients with concomitant CAD, and avoidance of diuretics to prevent hypotension due to a decrease in cardiac output.

Lipid-Lowering Therapy

Three randomized trials failed to demonstrate usefulness of statins to prevent progression of calcific AS.[17,18,77] In a randomized, double-blind controlled trial, a combination of simvastatin and ezetimibe in 1873 patients with mild to moderate AS did not reduce primary outcomes of cardiovascular death, AVR, nonfatal myocardial infarction, hospitalization for unstable angina, heart failure,

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CABG, percutaneous coronary intervention, and nonhemorrhagic stroke during a median follow-up of 52.2 months (333 patients [35.3%] in the simvastatin-ezetimibe group and 355 [38.2%] in the placebo group [HR, 0.96; 95% CI, 0.84-1.18; P=.97]).[17] However, fewer patients in the drug group had ischemic cardiovascular events than in the placebo group (HR, 0.78; 95% CI, 0.63-0.97; P=.02). Current AHA/ACC guidelines do not recommend statins to prevent hemodynamic progression of AS; however, statins are important for patients with associated CAD to lower ischemic end points.

Vasodilator Therapy

Vasodilator therapy is a cornerstone in the management of patients with left ventricular dysfunction but was historically contraindicated in patients with severe AS. It was previously believed that cardiac output across a fixed stenotic aortic valve and vasodilatation from vasodilator therapy would reduce the systemic vascular resistance without compensatory increase in the cardiac output that will result in severe hypotension. However, smaller studies have documented beneficial effects of vasodilatation in asymptomatic patients with severe AS. More recently, the Use of Nitroprusside in Left Ventricular Dysfunction and Obstructive Aortic Valve Disease (UNLOAD) Study investigated the use of nitroprusside, an intravenous vasodilator, in critically ill patients with congestive heart failure (ejection fraction ≤35%), depressed cardiac index (≤2.2 L/min per square meter), and severe AS (aortic valve area ≤1.0 cm^2).[78] At baseline, the mean (±SD) ejection fraction was 0.21±0.08, aortic valve area was 0.6±0.2 cm^2, and peak and mean gradients were 65±37 mm Hg and 39±23 mm Hg, respectively. The cardiac index increased to 2.52 from a baseline of 1.6 L/min per square meter after 24 hours of nitroprusside infusion. Nitroprusside was well tolerated. These studies suggest the usefulness of this therapy as a bridge in patients who present with severe AS and severe congestive heart failure, indicating that afterload reduction may be used to stabilize the patient before valve replacement or switching to oral vasodilators in patients who choose not to undergo surgery. During nitroprusside infusion, invasive monitoring of left ventricular filling pressures, cardiac output, and systemic vascular resistance is paramount because tenuous hemodynamic status can lead to a sudden decline in systemic vascular resistance and cardiac output across the obstructed aortic valve. Treatment of hypertension with vasodilator therapy results in a beneficial reduction in left ventricular afterload and filling pressures and improvement in pulmonary hypertension in patients with low-gradient, severe AS.[76]

Aortic Balloon Valvuloplasty

Percutaneous aortic balloon valvoplasty is essentially a balloon inflation across the aortic valve to reduce the severity of AS. The mechanism by which reduction in aortic valve gradient and improvement in symptoms with valvuloplasty occurs is yet unknown, but fracture of the calcific deposits, separation of commissures, or stretching of the aortic annulus may play a part.[79] Its current role is mainly as a part of the TAVR procedure or sometimes as a bridge to more definitive therapy.[80] Despite successful balloon inflation, the procedure is limited by the following problems. First, following balloon valvuloplasty, the aortic valve remains severely stenotic because the area rarely exceeds 1.0 cm^2.[81] Early studies reported decreases in the mean and peak aortic valve gradient from 55±21 and 65±28 mm Hg to 29±13 and 31±18 mm Hg, respectively, and the aortic valve area increased from 0.5±0.2 cm^2 to 0.8±0.3 cm^2.[82] Second, the procedure is associated with serious vascular complications in 10% to 20% of patients.[82,83] Other complications include left ventricular perforation, death, stroke, myocardial infarction, and severe aortic regurgitation. Following aortic balloon valvuloplasty, long-term event-free survival is poor and resembles the natural history of untreated severe AS. In a study with 99% 6-year follow-up, the probability of event-free (death, AVR, or repeated balloon valvuloplasty) survival at 1, 2, and 3 years after valvuloplasty was 40%, 19%, and 6%, respectively.[81] The National Heart, Lung, and Blood Institute Balloon Valvuloplasty Registry reported immediate and 30-day follow-up results on 674 patients who underwent aortic balloon valvuloplasty.[82] Ninety-two (14%)

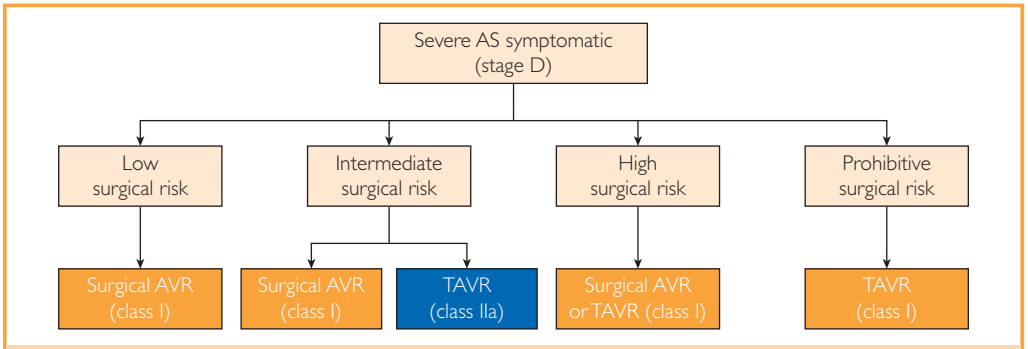

FIGURE 4. Updated guidelines for transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (aortic valve replacement). AS = aortic stenosis.

had died by 30 days, most from cardiovascular-related causes. Thirty-day mortality predictors included New York Heart Association class IV heart failure, serum urea nitrogen level less than 30 mg/dL, use of antiarrhythmic drugs, and cardiac output of less than 3 L/min. However, short-term improvement in survival and functional status was noted in patients with reasonably preserved ejection fraction.[82]

In a National Inpatient Sample study,[81] time trends between 1998 and 2010 revealed a 158% increase in the rate of percutaneous balloon valvuloplasty with a 23% reduction in in-hospital mortality, from 11.5% in 1998-1999 to 8.8% in 2009-2010 ($P<.01$). This study also demonstrated an influence of operator and hospital volume on outcomes.

In a more recent National Inpatient Sample study examining percutaneous balloon valvuloplasty between 2004-2013,[84] aortic balloon valvuloplasty vs TAVR was associated with similar rates of in-hospital mortality (2.9% vs 3.5%; $P=.6$), clinical stroke (1.6% vs 3.1%; $P=.10$), and vascular complications (8.2% vs 10.9%; $P=.14$), although aortic balloon valvuloplasty was associated with lower rates of pacemaker implantation (2.9% vs 8.0%; $P<.001$) and blood transfusion (12.8% vs 22.9%; $P<.001$).

AORTIC VALVE REPLACEMENT

Indications and Timing of Replacement

Asymptomatic Patients. Patients with asymptomatic AS have low rates of sudden death (<1% annually)[31] and therefore require only periodic monitoring for progression of disease or development of symptoms, which is inevitable in these patients (Figure 4). In a large study of 622 adults with severe, asymptomatic AS (peak velocity ≥4 m/s), the probability of remaining free of cardiac symptoms without surgical intervention was 82%, 67%, and 33% and event-free survival rates (death and free of valve surgery) were 80%, 63%, and 25% at 1, 2, and 5 years, respectively.[31] Similar results were reported from other observational studies.[32] Moderate or severe aortic valve calcification, peak aortic velocity, and progression of peak aortic velocity have been correlated with mortality and need for AVR.[31,33]

Asymptomatic severe AS is divided into 2 categories, C1 (normal ejection fraction) and C2 (reduced ejection fraction). Patients with C2 disease benefit from AVR. Depressed ejection fraction is the result of afterload mismatch that improves following AVR or CAD and prior myocardial infarction. Aortic valve replacement is also recommended in asymptomatic patients with severe AS who are undergoing cardiac surgery for other indications such as CABG (class I indication) and in asymptomatic low-risk patients with very severe AS (aortic velocity ≥5 m/s or mean pressure gradient ≥60 mm Hg) because these patients have more rapid progression of AS and symptom onset is inevitable (class IIa indication).

Aortic valve replacement is reasonable for patients with moderate AS with aortic velocity (3-3.9 m/s) and mean pressure gradient (20-39 mm Hg) who are undergoing cardiac

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surgery for other reasons (class IIa indication). Aortic valve replacement is also reasonable in asymptomatic patients with severe AS who have calcified, severe (aortic velocity 4-4.9 m/s or mean gradient 40-59 mm Hg) in whom the exercise test demonstrates reduced exercise tolerance (60%-80% of age- and sex-matched controls) or an abnormal blood pressure response to exercise (failure to increase by at least 20 mm Hg) (class IIa).

A recent pooled analysis and data from retrospective studies confirmed an approximately 3.5-fold higher rate of all-cause death with watchful waiting as compared with AVR.[58] Taniguchi et al[85] reported that at a mean follow-up of 2 years, more than 40% of patients had a class I indication for AVR but did not undergo valve replacement, possibly because of their higher-risk status or increased operative risk. These new findings are relevant because approximately half of patients with severe AS are asymptomatic at initial presentation.[30,86]

Symptomatic Patients. Aortic valve replacement is recommended in symptomatic patients with severe AS (class I indication).[42] Aortic valve replacement is recommended with the onset of symptoms and should not be delayed because of symptom improvement with medical therapy. Early symptoms are shortness of breath or reduction in exercise tolerance. Other symptoms such as syncope, angina (typically in patients with concomitant CAD), and heart failure are less common in current clinical practice because they typically develop later. All symptomatic patients, irrespective of age, should be offered AVR unless a serious comorbid condition limits life expectancy or quality of life (Table 4). Current ACC/AHA guidelines outline indications for AVR (Figure 4).

Low-flow, low-gradient, symptomatic AS (stage D3) poses a special diagnostic and therapeutic challenge. Among 971 patients in the PARTNER trial (inoperable and high-risk cohorts), low flow (stroke volume index $\leq$35 mL/m^2) was observed in 530 (55%), low ejection fraction (<50%) in 225 (23%), and low ejection fraction, low flow, and low mean aortic valve gradient (<40 mm Hg) in 147 (15%).[87] Aortic valve replacement is recommended (class IIa) in the setting of a calcified aortic valve, resting valve area of 1 cm^2 or less, aortic velocity less than 4 m/s or mean gradient less than 40 mm Hg, and ejection fraction less than 50% and in patients whose low-dose dobutamine stress study demonstrates an increase in the velocity and gradient to the severe range with a concurrent aortic valve area of 1 cm^2 or less. It is important to have clinical, hemodynamic, and anatomic correlation and record the data when the patient is normotensive. The ejection fraction typically increases following valve replacement, especially in patients with afterload mismatch.[88] In some patients with poor contractile reserve, the decision to operate should be individualized because surgical AVR is associated with high risk, and TAVR may be a better option.

Low-flow, low-gradient AS with preserved LVEF occurs in 5% to 25% of patients with severe AS.[65] The treatment of these patients is still controversial because some studies suggest that even asymptomatic patients with low-flow, low-gradient severe AS and a normal LVEF have a poor prognosis[24,45,89-92] and might benefit from AVR (class IIa) while others suggest that many of these patients have only moderate stenosis and their outcomes are similar to moderate AS with normal flow across the aortic valve.[93,94] Both case-control and prospective studies suggest that outcomes are worse in symptomatic patients with low-flow, low-gradient AS and a normal LVEF compared with patients with high-gradient severe AS. Although no randomized clinical trials have been performed, a post hoc subset analysis of a randomized clinical trial suggests that survival may be improved with TAVR or AVR vs medical management in symptomatic patients with low-flow severe AS.[87]

The clinical approach in such patients, as highlighted by the current guidelines, is as follows. In patients with low-flow, low-gradient severe AS with preserved LVEF, severe AS is unlikely if aortic velocity is less than 3.0 m/s or mean pressure gradient is less than 20 mm Hg. Various steps should be undertaken to ensure an accurate diagnosis, including recording and measuring data accurately, repeating measurements in hypertensive patients once they become

TABLE 5. Outcomes Associated With Aortic Valve Replacement[a,b]

Variable	PARTNER[102]		PARTNER[87]		PARTNER[103]		CoreValve[104]		SURTAVI[59]	
	Inoperable, TAVR	Inoperable, standard treatment	High-risk, TAVR	High-risk, surgery	Intermediate risk, TAVR	Intermediate risk, surgery	High-risk, TAVR	High-risk, surgery	Intermediate risk, TAVR	Intermediate risk, surgery
30-Day all-cause mortality	5%	2.8%	3.4%	6.5%	3.9%	4.1%	…	…	2.2%	1.7%
1-Year outcomes										
Mortality	30.7%	49.7%[c]	24.2%	26.8%	12.3%	12.9%	14.2%	19.1%[c]	6.7%	6.8%
Pacemaker	4.5%	7.8%	5.7%	5.0%	9.9%	8.9%	22.3%	11.3%[c]	25.9%	6.6%
Any stroke	10.6%	4.5%[c]	8.3%	4.3%[c]	8%	8.1%	8.8%	12.6%	5.4%	6.9%
Vascular complications	32.4%	7.3%[c]	18.0%	4.8%	8.4%	5.3%[c]	6.2%	2.0%[c]	6.0%	1.1%
Major bleed	22.3%	11.2%	14.7%	25.7%[c]	15.2%	45.5%	29.5%	36.7%[c]	12.2%	9.3%
Acute kidney injury (creatinine >3 mg/dL)[d]	1.1%	2.8%	3.9%	2.7%	3.4%	5.0%	6.0	15.1%[c]	1.7%	4.4%
Atrial fibrillation	0.6%	1.7%	12.1%	17.1%	10.1%	27.2%	15.9%	32.7%	12.9%	43.4%

[a]CoreValve = U.S. CoreValve High Risk Study; PARTNER = Placement of Aortic Transcatheter Valves; TAVR = transcatheter aortic valve replacement; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation; ellipses indicate data not available.

[b]The major complications for SURTAVI are reported for 30 days.

[c]Indicates significant difference.

[d]To convert creatinine value to μmol/L, multiply by 88.4.

normotensive, measuring aortic valve area indexed to body size ($\leq$0.6 cm^2/m^2 suggests severe AS), and evaluating degree of valve calcification.[62,95,96]

Choice of Intervention

Aortic valve replacement is indicated for survival benefit, improvement in symptoms, and improvement in left ventricular systolic function in patients with severe, symptomatic AS. The choice of intervention (surgical vs transcatheter) rests on risk of operation, frailty, and comorbid conditions (Table 4, Figure 4). Surgical AVR is considered primarily in low- or intermediate-risk patients and in patients with severe multivessel CAD. All patients should be evaluated by a multidisciplinary heart valve team, and suitability of a surgical vs a transcatheter approach should be determined. A transcatheter approach (TAVR) is considered primarily in patients with prohibitive, high or intermediate surgical risk based on current guidelines.[97] No valve replacement is recommended for patients with life expectancy of less than 1 year.[42]

TRANSCATHETER AORTIC VALVE REPLACEMENT

The worldwide TAVR experience has been dominated by 2 kinds of transcather heart valves, the balloon-expandable valve (Edwards SAPIEN, Edwards Lifesciences) and the self-expandable valve (CoreValve, Medtronic) (Table 5).[98-100] In Germany, TAVR has surpassed surgical AVR as definitive treatment of AS,[101] and in the United States, approximately 30% of valve replacements are via TAVR.[100] Both valves have undergone improvements in design and deployment and are now in their third generation.

Inoperable, High- and Intermediate-Risk Patients

The PARTNER trial[102] randomized 358 patients with severe AS considered unsuitable for aortic valve surgery (prohibitive risk with predictive 1-year mortality or major morbidity >50%, disease affecting 3 or more major organ systems that are unlikely to improve after valve replacement, or anatomic features

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such as prior radiation or porcelain aorta that preclude or increase the risk from surgery) to standard therapy (including balloon valvuloplasty) or TAVR with a balloon-expandable bovine pericardial valve. Two-year all-cause mortality was lower with TAVR (43.3% vs 68.0%; HR, 0.58; 95% CI, 0.36-0.92; P=.02). However, a significant increase in the rate of major stroke (5.1% vs 1.0%; P=.06) and major vascular complications (16.2% vs 1.1%; P<.001) were noted in patients treated with TAVR.

Transcatheter AVR was also studied in high-risk (operative complications or death of at least 15% by 30 days on the basis of coexisting conditions) patients with severe AS, and 699 patients were randomized to surgical replacement or TAVR (transfemoral or transapical approach).[87] All-cause 30-day and 1-year mortality was 3.4% vs 6.5% (P=.07) and 24.2% vs 26.8% (P=.44), respectively, in patients who underwent TAVR or surgical AVR. The rates of 30-day and 1-year major stroke (3.8% vs 2.1%, P=.20 and 5.1% vs 2.4%, P=.07, respectively) were higher in patients who underwent TAVR compared with surgical replacement. Major vascular complications at 30 days were also noted to be higher in patients with TAVR (11% vs 3.2%; P<.001). In contrast, higher rates of major bleeds (19.5% vs 9.3%; P<.001) and new-onset atrial fibrillation (16% vs 8.6%; P=.006) were noted in patients with surgical AVR as compared with TAVR.[105]

More recently, a randomized trial (PARTNER 2, cohort A) randomized 2032 intermediate-risk patients with severe AS (30-day mortality risk between 4% and 8% based on a risk model developed from the STS) to TAVR or surgical AVR.[103] All-cause mortality or disabling stroke rates were similar (6.1% vs 8.0%; P=.11). At 2 years, the Kaplan-Meier event rates were 19.3% in the TAVR group and 21.1% in the surgery group (HR, 0.89; 95% CI, 0.73-1.09; P=.25). The transfemoral access had lower rates of primary end points than surgery (HR, 0.79; 95% CI, 0.62-1.00; P=.05). The percutaneous approach resulted in larger AVAs and lower rates of acute kidney injury, severe bleeding, and new-onset atrial fibrillation whereas surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation.

Transcatheter AVR using a self-expanding transcatheter aortic valve has also been compared with surgical AVR in 795 high-risk (30-day mortality risk ≥15% and the risk of death or irreversible complication within 30 days <50%) patients.[104] The primary end point (all-cause death at 1 year) was significantly lower in the TAVR group compared with the surgical group (14.2% vs 19.1%; P<.001 for noninferiority; P=.04 for superiority). Exploratory analyses suggested a reduction in the rates of major adverse cardiovascular and cerebrovascular events (P=.03) with no increase in the risk of stroke.

Intermediate-risk (STS predicted risk, 4.5%±1.6%) patients were also studied with implantation of a self-expanding prosthesis in the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial in which 1660 patients were randomized to TAVR or surgical AVR.[59] At 24 months, the primary end point of all-cause death or disabling stroke was seen in 12.6% in the TAVR group and 14.0% in the surgery group. The need for pacemaker and residual aortic regurgitation was higher with TAVR, and surgery was associated with higher rates of acute kidney injury, atrial fibrillation, and transfusion requirements.

Current AHA/ACC guidelines recommend TAVR either as the primary intervention or as an alternative to surgical AVR in patients with prohibitive operative risk, high operative risk, and intermediate operative risk.[97]

Prospective registry data are consistent with the randomized trial data and document the efficacy of TAVR in an unselected population. Among 7710 patients (1559 inoperable, 6151 high-risk) undergoing balloon-expandable TAVR at US centers in the STS/ACC Transcatheter Valve Therapy Registry, the device implantation success rate was 92%, in-hospital mortality was 5.5%, and the stroke rate was 2.0%.[88] The OBSERVANT (Observational Study of Effectiveness of SAVR-TAVI Procedures for Severe Aortic Stenosis Treatment) trial enrolled 7618 patients (5707 surgical and 1911 TAVR). The 1-year mortality (13.6% vs 13.8%; HR. 0.99; 95% CI, 0.72-1.35; P=.936),

rehospitalization rate, and major adverse cardiac and cerebrovascular events of propensity-matched low- to intermediate-risk patients (n=1300) were comparable.[106]

Low-Risk Patients

In a small study of 355 propensity-matched pairs of patients with low operative risk (EuroSCORE [European System for Cardiac Operative Risk Evaluation], <4%), 3-year survival was higher in patients who underwent surgical AVR compared with TAVR (83.4% vs 72%; *P*=.0015).[107] In the NOTION (Nordic Aortic Valve Intervention) trial, 280 low-risk patients (STS-PROM score, ~3%) were randomized to surgery or transcatheter valve replacement.[65] In the intention-to-treat population, the primary end point (1-year all-cause death/myocardial infarction/stroke) was similar (13.1% vs 16.3%; *P*=.43) for TAVR and surgical AVR, respectively. The results of this randomized trial were congruent with propensity-matched studies showing no difference in all-cause mortality between TAVR and surgical AVR at 30 days and 1 year. Similar to the high-risk population, low-risk patients treated with TAVR had higher rates of aortic regurgitation and conduction abnormalities requiring pacemaker implantation, whereas surgically treated patients had higher rates of major or life-threatening bleeding, shock, acute kidney injury, and atrial fibrillation at 30 days.

The ongoing PARTNER III trial (ClinicalTrials.gov Identifier: NCT02675114) is enrolling 1200 patients aged 65 years or older with severe, calcific AS and STS risk of less than 4%; the trial will randomize low-risk patients to surgical AVR or TAVR and will study 1-year composite of death, stroke, or rehospitalization. A similar trial using the Medtronic CoreValve Evolut R (ClinicalTrials.gov Identifier: NCT02701283) is being performed in low-risk patients. Until the safety and efficacy of TAVR can be demonstrated in low-risk patients, surgical AVR remains is the treatment of choice.

Balloon-Expandable vs Self-Expanding Transcatheter Heart Valves

The CHOICE (Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve vs Edwards SAPIEN XT) randomized clinical trial compared balloon-expandable vs self-expanding transfemoral TAVR in 241 high-risk patients at 5 centers in Germany.[108] The primary end point of device success was higher in the balloon-expandable valve group (relative risk, 1.24; 95% CI, 1.12-1.37; *P*<.001). This result was attributed to significantly lower rates of severe aortic paravalvular regurgitation (4.1% vs 18.3%; relative risk, 0.23; 95% CI, 0.09-0.58; *P*<.001) and less frequent need to implant more than 1 valve (0.8% vs 5.8%; *P*=.03) in patients treated with a balloon-expandable valve. Thirty-day cardiovascular mortality, bleeding, and vascular complication rates were similar, but the incidence of new permanent pacemaker was higher among patients treated with self-expanding valves (37.6% vs 17.3%; *P*=.001).

Paravalvular Aortic Regurgitation. The incidence of significant paravalvular aortic regurgitation is higher with TAVR than with surgical AVR, especially with self-expanding stents compared with a balloon-expandable strategy. A recent meta-analysis of 45 studies (self-expanding, n=5261; balloon-expandable, n=7279) demonstrated higher rates of moderate or severe aortic regurgitation in patients treated with self-expanding valves (16% vs 9.1%; *P*=.005).[109] The prognostic significance of higher incidence of aortic regurgitation is yet unclear. The procedural mortality in the UK-TAVI (United Kingdom Transcatheter Aortic Valve Implantation) and FRANCE-2 (French Aortic National CoreValve and Edwards) registries was noted to be similar whether the patients were treated with self- or balloon-expandable TAVRs.[110,111] In the FRANCE-2 registry, 1-year mortality was increased in patients with grade 2 or higher regurgitation (HR, 2.49; 95% CI, 1.91-3.25). It is plausible that aortic regurgitation seen immediately after implantation of the self-expanding valves continues to decline over time. Third-generation transcatheter heart valve improvements in design, deployment, and retrievability are in part aimed at reducing incident paravalvular regurgitation.

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Permanent Pacemaker Implantation. Thirty-day permanent pacemaker implantation rate was 4.3% among those undergoing balloon-expandable TAVRs versus 25.1% for self-expanding TAVRs.[112] Most permanent pacemakers are implanted during index hospital admission (97.1%; median time to implant, 3 days). The high incidence of pacemaker implantation, especially after self-expanding TAVRs, is likely due to design differences in stents with the lower portion of the valve (skirt) positioned lower into the left ventricular outflow tract. Notably, the conduction system is located in the membranous septum of the outflow tract and is susceptible to compression, ischemia, or trauma during deployment.[113] Predictors of permanent pacemaker implantation include right bundle branch block, left anterior fascicular block, smaller left ventricular outflow diameter, large annulus to outflow diameter ratio, depth of implantation, and oversizing the prosthesis.[114] Urena et al studied 1556 patients who underwent TAVR, and at a mean follow-up of 22 months, no difference in mortality or heart failure was noted in the groups that received pacemaker compared with patients who did not.[115] In contrast, in the US STS/ACC Transcatheter Valve Therapy Registry, permanent pacemaker implantation was associated with increased mortality (24.1% vs 19.6%; HR, 1.31; 95% CI, 1.09-1.58) and a composite of mortality or heart failure admission (37.3% vs 28.5%; HR, 1.33; 95% CI, 1.13-1.56) at 1 year.[112] Also, a retrospective study by Nazif et al[116] from the PARTNER trial and registry data showed that a new pacemaker is required in 8.8% of patients, and at 1 year these patients had higher repeat hospitalization and mortality (23.9% vs 18.2%; P=.05) or repeat hospitalization alone (42.0% vs 32.6%; P=.007).

The current approach to permanent pacemaker implantation includes keeping the temporary pacemaker for up to 24 hours and then removing it if postprocedure electrocardiography shows no new development of bundle branch or atrioventricular block. In contrast, development of high-grade atrioventricular block (Mobitz type II, second degree or complete heart block) merits permanent pacemaker implantation. Patients with first-degree atrioventricular or left bundle branch block require prolonged monitoring.

Transcather Heart Valve Durability

Durability of the first balloon-expandable Edwards SAPIEN valve was shown to be excellent up to 5 years, with rare structural deterioration of the valve requiring reintervention in only 5 of 2795 patients.[117] Indications for reinterevntion included stenosis (1 patient), valve thrombosis (1 patient), and prosthetic regurgitation (3 patients).[117] Overall, there was a slight trend in transcather valve hemodynamic deterioration and increasing valve regurgitation that did not differ from surgical AVR, and the conclusion from the analysis was that transcatheter valves had excellent durability similar to surgical prostheses.[117] Excellent 5-year durability has also been shown in patients who received the self-expandable CoreValve.[118-120] Collection of long-term 10-year transcatheter heart valve durability data is ongoing.[121] Reassuringly, both the SAPIEN and CoreValve transcatheter heart valves have approved indications to treat failed aortic valve bioprostheses (surgical or transcatheter), also termed the *aortic valve-in-valve procedure*.[122,123]

FUTURE DIRECTIONS

Presently, repositioning of the valve is restricted in patients with a balloon-expandable valve, but self-expanding valves and newer valve-stent designs allow the valve to be repositioned and retrieved before complete deployment. The benefit of the new designs on paravalvular leak, superior sustained valve function, and noninterference with the conduction system remains to be seen. One-year outcomes of 120 high-risk patients enrolled in the REPRISE II (Repositionable Percutaneous Placement of Stenotic Aortic Valve Through Implantation of Lotus Valve System—Evaluation of Safety and Performance) study demonstrated favorable valve performance and sustained hemodynamic and clinical benefit at 1 year, but the risk of permanent pacemaker implantation was high (31.9%).[124]

More studies are needed to explore novel predictors of progression of AS and find newer therapeutic targets to slow or stall the worsening of AS. The results thus far with statins

and bisphosphonates have been disappointing. The current population trends favor the elderly, and with increased life expectancy, we expect an epidemic of patients with severe AS. With the aging of population, some of these patients will be at higher risk for surgical AVR, especially in the setting of frailty and comorbidities potentially involving multiple organ systems. Future iterations of the TAVR may extend the current indications to the lower-risk group, which currently constitutes 80% of all AS patients. More research is needed to prevent AS or stop or reverse its progression. Also, racial disparities in care need to be addressed to ensure equitable application of resources.[125]

CONCLUSION

Aortic stenosis is common and expected to increase in prevalence with the aging population. The majority of patients up to the seventh decade of life have an underlying bicuspid aortic valve as the main cause of aortic valve stenosis, and older patients have degenerative remodeling of a tricuspid valve as the cause of AS. In addition to aging, clinical risk factors for the development of AS are similar to those for atherosclerosis and include hypertension, hyperlipidemia, and diabetes. Atherosclerotic risk factors are more prevalent in tricuspid aortic valve stenosis than bicuspid aortic valve stenosis because of the congenital predisposition of a bicuspid valve to develop stenosis. Medications to treat underlying cardiovascular risk factors and symptoms do not alter the poor prognosis of severe AS, and the only effective therapy is AVR. Transcatheter AVR has emerged as an alternative to surgical AVR in patients who have tricuspid aortic valve stenosis and are at intermediate, high, or prohibitive risk for open heart surgery. The transcatheter heart valves have proved durable up to 5 years, and data regarding longer-term durability is pending. Studies are ongoing examining the efficacy of TAVR in low-risk groups with severe AS, in patients with moderate AS associated with reduced LVEF (<50%), and in patients with severe AS from bicuspid aortic valve stenosis.

Abbreviations and Acronyms: **ACC** = American College of Cardiology; **AHA** = American Heart Association; **AS** = aortic stenosis; **AU** = Agatston unit; **AVA** = aortic valve area; **AVR** = aortic valve replacement; **CABG** = coronary artery bypass grafting; **CAD** = coronary artery disease; **HR** = hazard ratio; **LVEF** = left ventricular ejection fraction; **PARTNER** = Placement of Aortic Transcatheter Valves; **PROM** = Predicted Risk of Mortality; **SEAS** = Simvastatin and Ezetimibe in Aortic Stenosis; **STS** = Society of Thoracic Surgeons; **TAVR** = transcatheter aortic valve replacement

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