

Calcific Aortic Stenosis

A Review

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IMPORTANCE Calcific aortic stenosis (AS) restricts the aortic valve opening during systole due to calcification and fibrosis of either a congenital bicuspid or a normal trileaflet aortic valve. In the US, AS affects 1% to 2% of adults older than 65 years and approximately 12% of adults older than 75 years. Worldwide, AS leads to more than 100 000 deaths annually.

OBSERVATIONS Calcific AS is characterized by aortic valve leaflet lipid infiltration and inflammation with subsequent fibrosis and calcification. Symptoms due to severe AS, such as exercise intolerance, exertional dyspnea, and syncope, are associated with a 1-year mortality rate of up to 50% without aortic valve replacement. Echocardiography can detect AS and measure the severity of aortic valve dysfunction. Although progression rates vary, once aortic velocity is higher than 2 m/s, progression to severe AS occurs typically within 10 years. Severe AS is defined by an aortic velocity 4 m/s or higher, a mean gradient 40 mm Hg or higher, or a valve area less than or equal to 1.0 cm². Management of mild to moderate AS and asymptomatic severe AS consists of patient education about the typical progression of disease; clinical and echocardiographic surveillance at intervals of 3 to 5 years for mild AS, 1 to 2 years for moderate AS, and 6 to 12 months for severe AS; and treatment of hypertension, hyperlipidemia, and cigarette smoking as indicated. When a patient with severe AS develops symptoms, surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) is recommended, which restores an average life expectancy; in patients aged older than 70 years with a low surgical risk, 10-year all-cause mortality was 62.7% with TAVI and 64.0% with SAVR. TAVI is associated with decreased length of hospitalization, more rapid return to normal activities, and less pain compared with SAVR. However, evidence supporting TAVI for patients aged younger than 65 years and long-term outcomes of TAVI are less well defined than for SAVR. For patients with symptomatic severe AS, the 2020 American College of Cardiology/American Heart Association guideline recommends SAVR for individuals aged 65 years and younger, SAVR or TAVI for those aged 66 to 79 years, and TAVI for individuals aged 80 years and older or those with an estimated surgical mortality of 8% or higher.

CONCLUSIONS Calcific AS is a common chronic progressive condition among older adults and is diagnosed via echocardiography. Symptomatic patients with severe AS have a mortality rate of up to 50% after 1 year, but treatment with SAVR or TAVI reduces mortality to that of age-matched control patients. The type and timing of valve replacement should be built on evidence-based guidelines, shared decision-making, and involvement of a multidisciplinary heart valve team.

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Aortic stenosis (AS), defined as valve leaflet disease with left ventricular (LV) outflow obstruction, is most commonly caused by calcification of a congenital bicuspid or normal trileaflet valve, although AS due to rheumatic heart disease occurs in areas of the world where rheumatic fever is endemic.¹ Diagnosing AS may be challenging because symptoms of exercise intolerance, dyspnea on exertion, and dizziness occur late in the disease course and may be caused by other cardiac diseases, such as heart failure, or by pulmonary conditions, such as asthma or chronic obstructive pulmonary disease (COPD). Physical examination is not reliable for detection of AS or evaluation of AS severity.²⁻⁴ Once patients develop symptoms, severe AS is associated with an annual mortality rate as high as 50% if not treated promptly with valve replacement.⁵

Calcific AS affects approximately 12.6 million people globally and accounts for more than 100 000 deaths annually. AS is more prevalent in high-income countries compared with low- and middle-income countries.⁶ In the US, AS affects 1% to 2% of persons aged 65 years or older and 12% of those older than 75 years,⁷ with a cumulative incidence of clinically statistically significant AS of 2.88% to 3.71% in longitudinal population-based follow-up of 5795 participants (mean age, 73 years).^{8,9} In 2021, more than 40 000 surgical aortic valve replacements (SAVR) and 80 000 transcatheter aortic valve implantations (TAVI) were performed in the US.¹⁰

Methods

A PubMed search was performed for English-language articles about aortic valve stenosis published between March 1, 2014, and March 1, 2024, and was extended to March 1, 2004, in order to include important randomized clinical trials (RCTs) of treatment for AS. We prioritized inclusion of studies that were recently published and based on relevance to the generalist, rigor of study design, sample size, and length of follow-up. Of 4034 articles identified, 105 were included in this narrative review, comprised of 29 RCTs, 29 longitudinal observational studies, 17 cross-sectional studies, 16 review articles, 7 systematic reviews and meta-analyses, 6 practice guidelines, and 1 systematic review.

Discussion and Observations

Pathophysiology of AS

The normal aortic valve consists of 3 thin, pliable, semitranslucent leaflets that allow ejection of blood from the heart during systole and prevent backflow of blood during diastole. With AS, the leaflets become thickened, fibrosed, and calcified, leading to rigid leaflets characterized by high resistance to valve motion and obstruction of antegrade blood flow (Figure 1).⁷ AS increases pressure in the LV, leading to myocardial hypertrophy, diastolic dysfunction, and eventual heart failure. Symptoms from severe AS are caused by an inadequate increase in cardiac output during exercise, which may lead to cardiac ischemia (angina pectoris), decreased blood pressure (which may cause syncope), and impaired LV function with increased diastolic filling pressure (which may cause dyspnea due to pulmonary congestion).

The etiology of AS includes congenital, acquired, and metabolic causes (Table 1).¹¹⁻¹⁶ The most common predisposition is a congenital bicuspid aortic valve, which accounts for up to 50% of all aortic valve

interventions.¹⁷ Although the pathophysiology of AS has been attributed to mechanical trauma of repeated aortic valve closure, current evidence shows that AS begins as an inflammatory process involving biochemical, humoral, and genetic factors, which have many similarities to atherosclerosis, including accumulation of low-density lipoprotein and lipoprotein(a), macrophage and lymphocyte infiltration, activation of inflammatory pathways, and tissue calcification (Figure 1).¹⁸⁻²⁰

Risk Factors for AS

Risk factors for AS include the presence of a bicuspid aortic valve (present in 1%-2% of the population worldwide) and aortic sclerosis, defined as focal areas of leaflet thickening and mild calcification of a normal trileaflet valve without significant valve dysfunction. Aortic sclerosis affects approximately 25% of people older than 65 years,⁷ with an approximately 2% annual rate of progression to AS.²¹ Other factors associated with an increased risk of AS include older age, male sex, hypertension, smoking, diabetes, coronary heart disease, elevated serum lipoprotein(a) concentrations, and impaired kidney function (Box and Figure 2).²²⁻²⁴

Disease Stages

Calcific AS is a slowly progressive chronic disease and patients are asymptomatic until aortic valve obstruction is sufficiently severe to limit the normal increase in cardiac output with exercise. In patients with AS, the aortic valve leaflets are thickened and calcified with reduced systolic opening, which results in the normal aortic valve velocity of 1.0 m/s increasing progressively as valve narrowing worsens from mild (velocity, 2.0 to 2.9 m/s) to moderate (velocity, 3.0 to 3.9 m/s) and then severe valve obstruction (velocity, ≥ 4 m/s) (Figures 1 and 2). AS disease stages are defined as Stage A, when risk factors are present but valve function is normal, and Stage B, when there is mild to moderate AS (velocity, 2.0 to 3.9 m/s). In patients with AS Stage B, LV systolic function is typically normal, although diastolic dysfunction may be present, particularly in older patients.²⁵

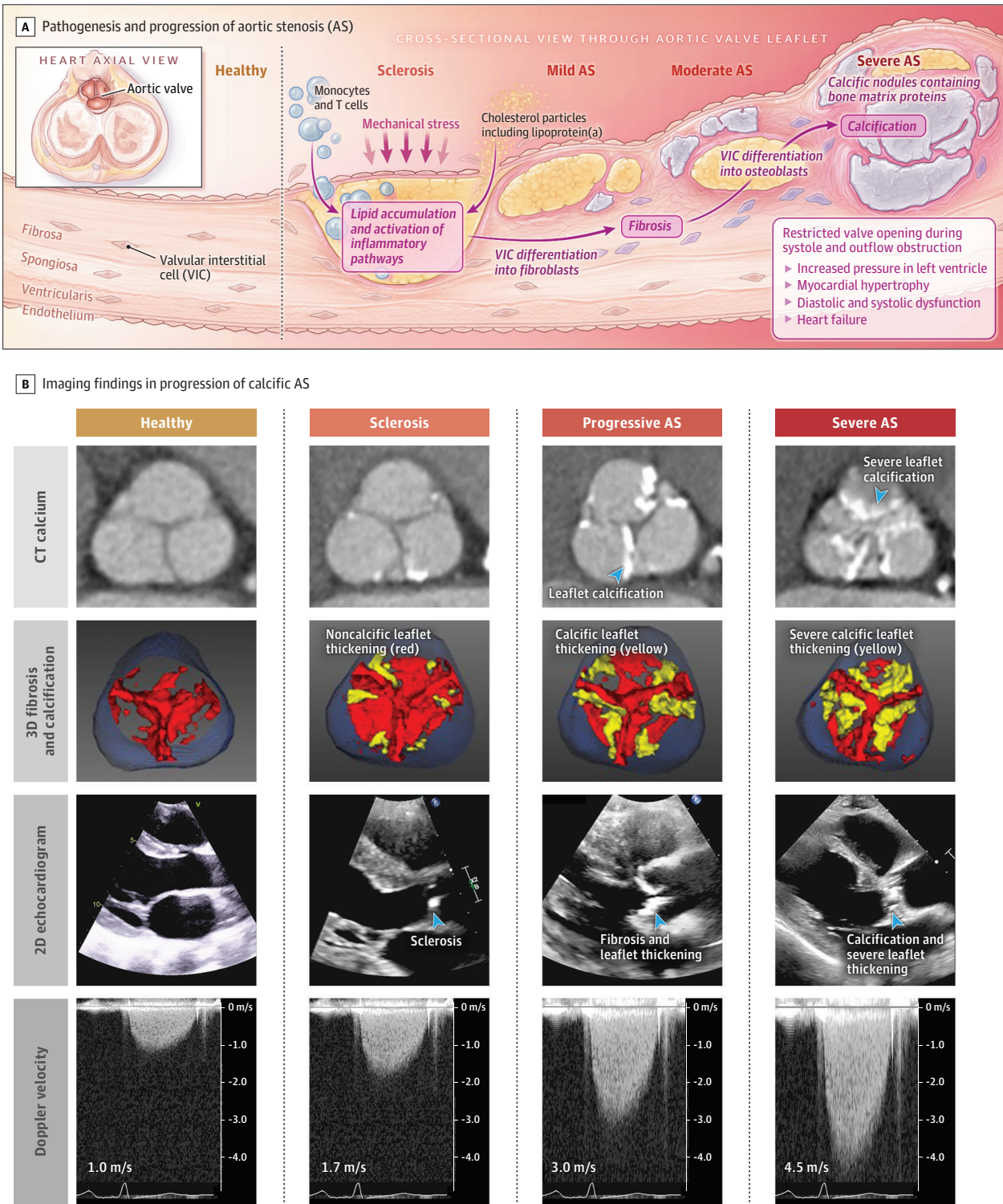
Stage C includes asymptomatic patients with severe valve obstruction with an aortic velocity 4 m/s or higher or mean gradient 40 mm Hg or higher. Typically, valve area is less than or equal to 1.0 cm² (≤ 0.6 cm²/m² indexed to body surface area) but a high velocity (≥ 4 m/s) or high mean gradient (≥ 40 mm Hg) alone meets the definition of severe AS. Subsets of stage C are very severe AS with a velocity 5 m/s or higher and stage C2 AS with an LV ejection fraction of less than 50%.²⁵

Stage D is defined as symptomatic severe AS, which can be further categorized as high-gradient severe AS with normal ventricular function (stage D1), low-gradient severe AS with a velocity less than 4 m/s but valve area less than or equal to 1.0 cm² due to LV systolic dysfunction (stage D2), and low-gradient severe AS with a small LV chamber with a normal ejection fraction (stage D3).²⁵

Progression and Clinical Presentation of AS

Once patients develop mild aortic valve obstruction with an aortic velocity greater than 2 m/s, hemodynamic progression to AS occurs in nearly all patients.²⁶ The mean (SD) rate of hemodynamic progression of AS is an annual increase in velocity of 0.16 (0.01) m/s per

Figure 1. Pathogenesis and Natural History of Calcific Aortic Stenosis



Pathogenesis of AS (A). Expansion and transdifferentiation of valvular interstitial cells lead to fibroblast and osteoblast formation, generating irregular calcific masses that contain hydroxyapatite, collagen, and other bone matrix proteins. Differentiation of activated fibroblasts into an osteoblast phenotype leads to progressive valve calcification involving several pathways, including

receptor activator of nuclear factor- κ B and its ligand, osteoprotegerin, bone morphogenetic protein 2, transforming growth factor- β , and Wnt/ β -catenin signaling.

CT indicates computed tomographic.

Table 1. Etiology and Pathogenesis of Aortic Stenosis (AS)

Category	Pathogenesis	AVR cases, % ^a	Age at presentation, y ^b	Comments
Congenital/bicuspid	Structural valvular abnormalities leading to altered biomechanical stress and injury	~50	40-50	Bicuspid aortic valve (1%-2% of the population), which can be associated with aortopathy and genetic disorders, such as Turner syndrome Rarely, unicuspid valve
Calcific/degenerative	Valvular atherosclerosis-like process	~50	>65	Risk factors: age >65 y, male sex, hypertension, cigarette smoking, hypercholesterolemia, elevated lipoprotein(a) level, autoimmune disease (eg, rheumatoid arthritis), chronic kidney disease, and diabetes ¹¹ Associated cardiovascular calcification increases the incidence and accelerates AS progression
Rheumatic valve disease	Valvular autoimmune inflammatory reaction to oropharyngeal group A streptococci infection	<5 in US and Europe	Variable	Most common cause of AS worldwide, affecting more than 40 million people, with women accounting for >80% of cases ¹ Age at presentation ranged from teenage years in countries with a high prevalence of rheumatic fever to age 50-60 y in the US and Europe Rheumatic disease typically affects the mitral valve, with aortic valve involvement in approximately 30% of patients ¹²
Iatrogenic	Chest radiotherapy	<1	NA	Radiotherapy of the chest for cancers such as lymphoma and breast cancer. However, the prevalence of iatrogenic causes of AS is declining due to more targeted radiotherapy practices
Metabolic (rare)	Homozygous familial hypercholesterolemia	Rare	NA	Marked lipid accumulation can cause aortic stenosis and supravulvular stenosis ¹³ Cumulative incidence of AS is ~18% of patients with homozygous familial hypercholesterolemia ¹⁴
	Ochronosis	Rare	NA	Alkaptonuria, which causes blue-black valvular and cartilage discoloration due to deposition of homogentisic acid, can lead to fibrosis and calcification of the aortic valve ^{15,16}

Abbreviations: AVR, aortic valve replacement; NA, not applicable.
^a Approximate percentage of patients undergoing valve replacement for severe AS in the US and Europe.
^b Age at presentation was variable and also depended on associated risk factors.

year and decrease in aortic valve area of 0.08 (0.21) cm² per year.^{27,28} However, progression of AS varies among patients and may accelerate as stenosis becomes more severe.

Despite normal valve function for many decades, nearly all patients with a congenital bicuspid aortic valve eventually require valve intervention, although often not until age 60 to 80 years.²⁹ In patients undergoing aortic valve replacement for severe AS, a congenital bicuspid valve accounts for more than 80% of patients younger than 60 years and approximately 50% of those older than 60 years.¹⁷

For patients with mild or moderate AS, symptoms are unlikely to be due to AS when LV function is normal, and many patients with severe AS remain asymptomatic for years until AS becomes more severe. The most common initial symptoms of AS are reduced exercise tolerance or exertional dyspnea, which also may be caused by other conditions such as heart failure, asthma, COPD, or deconditioning. End-stage symptoms of AS (heart failure and syncope) are currently uncommon among patients with known AS who are undergoing periodic clinical and echocardiographic surveillance.³⁰⁻³²

Assessment and Diagnosis

Clinical Assessment

Diagnosing AS may be challenging, particularly in asymptomatic patients. Physical examination findings of a loud, late-peaking systolic murmur radiating to the carotid artery, a single quiet second heart sound, and a delayed and diminished (“parvus and tardus”) carotid upstroke (Table 2)^{2-4,25,33} are specific but occur with severe disease, making them relatively insensitive for diagnosis earlier in the

Box. Commonly Asked Questions About Aortic Stenosis (AS)

What are the risk factors for AS?

Risk factors for calcific AS include a congenital bicuspid aortic valve, older age (65 years or older), male sex, hypertension, diabetes, coronary heart disease, elevated serum lipoprotein(a) concentrations, impaired kidney function, and cigarette smoking.

How is AS diagnosed?

Echocardiography is the definitive test to diagnose AS and assess its severity. Echocardiography is recommended for adults older than 65 years with symptoms of exercise intolerance, exertional dyspnea, and syncope, and for individuals with a bicuspid aortic valve or with other risk factors for aortic valve calcification, such as hypertension and impaired kidney function.

How is AS treated?

Adults with asymptomatic AS should receive periodic clinical and echocardiographic monitoring; treatment of hypertension, hyperlipidemia, and cigarette smoking as indicated; optimal dental hygiene; and education about the prognosis and progression of AS. The only effective therapies for symptomatic AS are surgical aortic valve replacement or transcatheter aortic valve implantation.

disease course. Among 123 patients with moderate to severe AS, 64% had a grade 3 out of 6 systolic murmur and 19% had a grade 1 or 2 murmur.³ Among 251 individuals undergoing echocardiography in a primary care practice, auscultation of a cardiac murmur by a primary care clinician had a sensitivity of 44% and specificity of

Figure 2. Aortic Stenosis Risk Factors, Symptoms, and Management Strategies

Risk and symptom progression in aortic stenosis (AS) and after aortic valve replacement (AVR)					
Risk factors and symptoms	STAGE A		STAGE B	STAGES C AND D	AFTER AVR
	At risk for AS	Aortic sclerosis	Progressive AS	Severe AS	Prosthetic valve
	Genetic risk factors - Lipoprotein(a) Anatomical risk factors - Congenital bicuspid aortic valve Clinical attributes - Older age (≥65 y) - Male sex - Hypertension - Diabetes - Hyperlipidemia - Metabolic syndrome Healthy aortic valve	Characteristics - Asymptomatic - Murmur may be present - Echocardiogram findings of areas of leaflet thickening and calcification (Figure 1) - Maximum antegrade transaortic velocity (V_{max}) <2 m/s Aortic valve sclerosis	Mild AS - Asymptomatic - V_{max} <3 m/s on echocardiogram Moderate AS - Asymptomatic - V_{max} = 3–4 m/s on echocardiogram Mild and moderate AS - Normal left ventricular (LV) systolic function - LV hypertrophy and diastolic dysfunction Progressive AS	Characteristics - Symptomatic or asymptomatic - V_{max} ≥4 m/s on echocardiogram - High mortality without early aortic valve replacement if symptomatic High V_{max} due to severe valve narrowing Severe AS Some patients with severe AS may present with reduced LV ejection fraction or lower V_{max} due to LV systolic dysfunction or small LV chamber	Characteristics - Embolic risk with all valve types - Risk of heart block (may require pacemaker) - Bioprosthetic valve degeneration (around 10 y) - Risk of endocarditis Mechanical valve (surgical) Bioprosthetic valve (surgical) Bioprosthetic valve (transcatheter)
Management	▶ Cardiovascular disease (CVD) risk factor evaluation and management ▶ Patient education about disease progression to ensure early symptom reporting ▶ Periodic imaging for bicuspid aortic valve	▶ CVD risk factor evaluation and management ▶ Patient education ▶ Repeat echocardiogram in 3–5 y	▶ Cardiology referral ▶ Treatment of risk factors and periodic imaging (echocardiogram every 3–5 y for mild AS and 1–2 y for moderate AS) ▶ Optimal dental hygiene	▶ Coordinate care between primary care physician and cardiology ▶ Periodic imaging and echocardiogram every 6–12 mo ▶ Consideration of surgical or transcatheter valve replacement if symptomatic ▶ Discussion of timeline for AVR or palliative care	▶ Management of antithrombotic medications ▶ Optimal dental hygiene and antibiotic prophylaxis to avoid endocarditis ▶ Periodic imaging

Clinical risk factors for AS are similar to atherosclerotic risk factors. Patients at risk of AS may develop aortic sclerosis, shown by focal calcification of the aortic valve on echocardiographic long-axis view. A subset of 25% of adults older than 65 years with aortic sclerosis develop progressive AS, illustrated by a

high-velocity transaortic Doppler signal (Figure 1B). In symptomatic patients with severe AS due to fibrotic and calcified valve leaflets, SAVR or TAVI prolongs survival and reduces symptoms and cardiac hospitalizations.

69% for any valvular heart disease, and diagnostic accuracy did not improve when auscultation was performed by a cardiologist.²

Echocardiography

Transthoracic echocardiography is the most helpful imaging study to diagnose and monitor AS. Echocardiography is used to visualize valve anatomy and provide accurate measures of hemodynamic severity, LV hypertrophy, and systolic and diastolic function, and assess for associated conditions, such as aortic dilatation, mitral valve disease, and elevated pulmonary pressures (Figure 1).^{25,34} For patients with AS, repeat echocardiography is recommended at intervals of 3 to 5 years for mild AS, 1 to 2 years for moderate AS, and every 6 to 12 months for severe AS.

Computed Tomographic Imaging

Computed tomographic (CT) imaging can quantify leaflet calcification and define AS severity (Figure 1). CT imaging prior to aortic valve replacement is helpful to define specific anatomic factors, such as annulus size, coronary ostial position, and vascular access, which affect the feasibility of a transcatheter approach.³⁵

Cardiology Referral

Cardiology referral should be considered for patients with aortic valve leaflet thickening and an antegrade velocity 2 m/s or higher and for those with a bicuspid aortic valve. Prompt cardiology evaluation

Table 2. Diagnosis of Aortic Stenosis (AS)

	Key elements	Clinical utility	Comments
Clinical history	Decreased exercise tolerance Dyspnea on exertion Exertional dizziness or syncope Exertional chest pain	Low sensitivity for diagnosis Not specific, as these symptoms have many other causes Symptoms are present only late in the disease course	Classic symptoms of heart failure, syncope, and angina are uncommon except with end-stage severe AS
Physical examination	Systolic murmur at cardiac base Murmur radiates to carotid arteries Late-peaking systolic murmur Single quiet S ₂ Diminished and slow carotid upstroke	Systolic murmur most often grade 3/6, but 20% have a softer murmur ³ Sensitivity of murmur for diagnosis of any valve disease is <50% ^{2,4} Specificity of murmur for any valve disease is approximately 70% ^{2,4} Distinguishing the origin of the cardiac murmur by examination is not accurate; echocardiogram is recommended	A diminished and delayed carotid upstroke is a specific finding (100%) for severe AS but lacks sensitivity (12%) ³ Carotid upstroke may be brisk despite severe AS due to atherosclerosis and arterial stiffening A single S ₂ may be difficult to appreciate Murmur may radiate to the cardiac apex in older patients
Echocardiography	Valve leaflets thickened and calcified Reduced leaflet mobility or bicuspid valve Hemodynamics include aortic maximum velocity, mean transaortic gradient, and valve area	Aortic sclerosis is a marker of increased atherosclerotic risk and can progress to AS An aortic velocity >2 m/s warrants cardiology evaluation and periodic echocardiographic imaging Severe AS is present when aortic velocity is ≥4 m/s, valve area ≤1.0 cm ² , or mean gradient ≥40 mm Hg ²⁵ Severe AS might be present when aortic velocity is 3–4 m/s; further cardiology evaluation is needed	AS severity is rarely underestimated on echocardiography due to technical limitations AS severity may be underestimated if the patient is hypertensive during echocardiography; repeat evaluation after blood pressure control is recommended ²⁵ Point-of-care ultrasound may identify a thickened, immobile aortic valve or LV hypertrophy, which should prompt more complete cardiac imaging and Doppler echocardiogram
CT imaging	CT valve calcium score CT imaging of annular size and shape, coronary ostial position, and vascular access routes	CT valve calcium score >1300 in women and >2000 in men indicates severe AS ^{25a} CT imaging needed for planning aortic valve intervention	Not used routinely for patient monitoring Data most useful when performed by radiologists in context of a heart valve team
Stress testing	Exercise treadmill stress testing Low-dose dobutamine stress echocardiography	Exercise stress testing to measure exercise capacity and blood pressure response to exercise Dobutamine stress to distinguish severe AS from moderate AS when LV ejection fraction is reduced	Avoid exercise testing if symptoms are present due to risk of complications, such as syncope or cardiac arrest Exercise capacity often limited for other reasons; consider cardiopulmonary exercise testing in selected patients Dobutamine stress testing for AS requires expertise and is not routinely recommended
Serum biomarkers	Serum BNP	Serum BNP can be followed annually Serum BNP >3 times the upper limit of normal in a patient with severe AS is indicative of cardiac decompensation ³³	BNP might be elevated for other reasons, such as heart failure or atrial fibrillation Serial changes in BNP over time are more useful than a single measurement
Emerging approaches	Artificial intelligence ECG analysis Focused point-of-care imaging Automated echocardiography interpretation Other biomarkers such as hs-TnT and lipoprotein(a)	Preliminary data only, not integrated into clinical practice	Role of screening will depend on larger studies, including cost-benefit analyses

Abbreviations: BNP, B-type natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; hs-TnT, high-sensitivity troponin T; LV, left ventricular.
^a The CT calcium score is measured in Agatston units with a normal valve having a value of 0. CT calcium is most useful for low-flow, low-gradient AS when severity is uncertain, with these thresholds defining severe AS. CT scores are not useful serially to follow disease progression.

(within 1 month) is appropriate for individuals with (1) severe AS, (2) an abnormal aortic valve and any degree of AS who have symptoms that may be due to AS, (3) any degree of AS and an LV ejection fraction less than 60%, or (4) combined moderate AS and aortic regurgitation.^{25,36,37}

Management

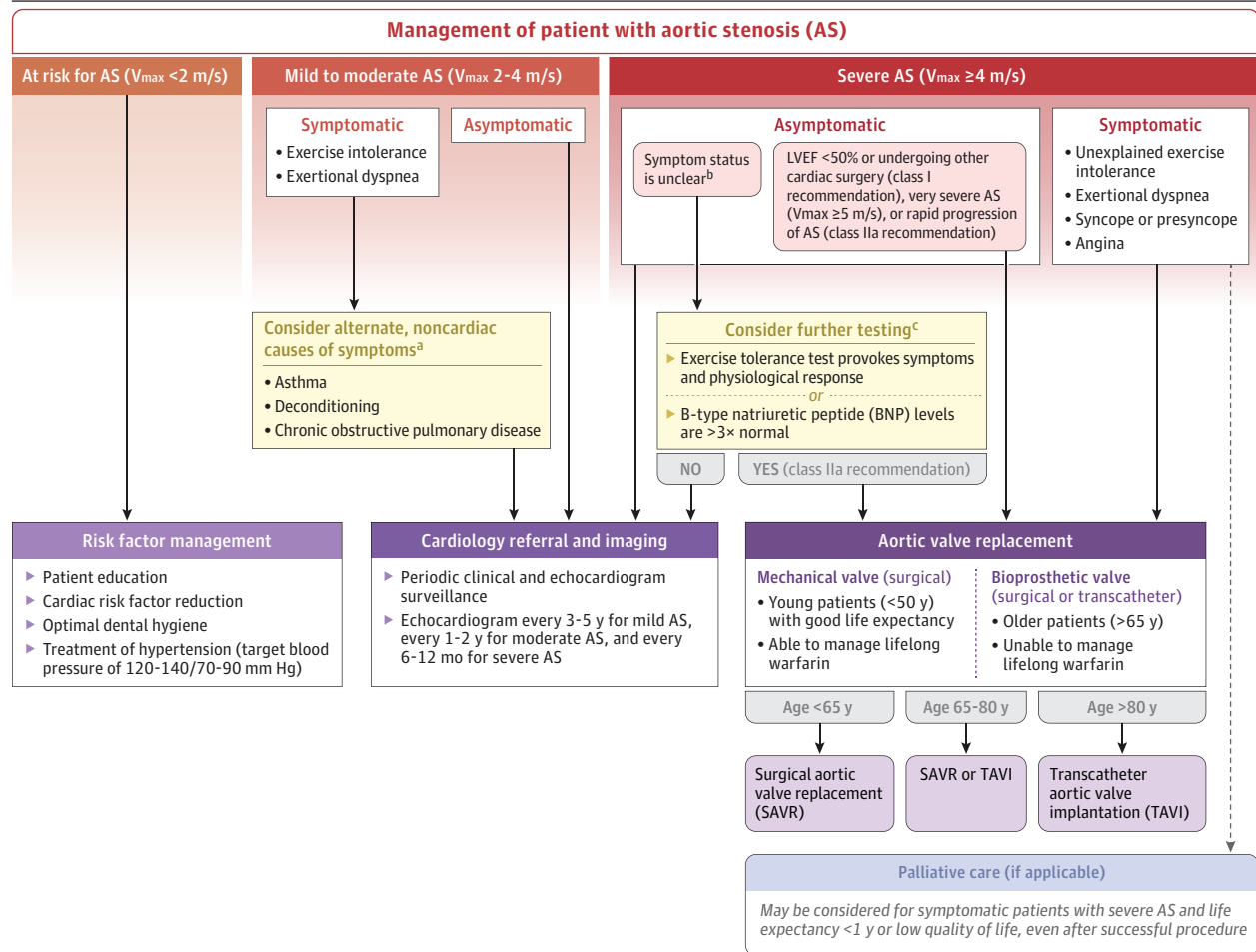
For patients diagnosed with AS, education about the expected disease course is important to facilitate prompt reporting of early symptoms that might be due to AS and to optimize timing of aortic valve intervention. In addition, cardiovascular risk factor modification, including smoking cessation if indicated and treatment of comorbid

conditions, such as hypertension or atrial fibrillation, and periodic echocardiographic surveillance allows patient engagement and participation in shared decision-making about interventions for AS (Figures 2 and 3).

Medical Therapies for AS

For patients with calcific AS, risk factors for atherosclerosis should be managed based on recommendations for patients without AS to reduce the risk of concurrent coronary disease when valve intervention becomes necessary. Because hypertension and kidney failure are associated with more rapid AS progression through increased afterload and augmented valvular calcification, clinical management should focus on guideline-directed medical therapy to reduce blood pressure and optimize kidney function.

Figure 3. Flowchart for Management of Aortic Stenosis



^aAdditional testing may be needed to exclude the possibility of low-flow, low-gradient AS.

^bDue to insidious onset, patients may attribute symptoms to normal aging or other conditions.

^cFurther testing considerations include American Heart Association/American College of Cardiology class IIa recommendations, where valve interventions should only be considered and are not mandated.

LVEF indicates left ventricular ejection fraction.

Hypertension affects 30% to 79% of patients with AS, and in a study of 5.4 million patients in the UK, each 20-mm Hg increase in systolic blood pressure was associated with a 41% higher risk of AS (hazard ratio [HR], 1.41 [95% CI, 1.38-1.45]) over a median follow-up of 9.2 years (absolute rates not available).²⁴ Hypertension is associated with a 2-fold higher rate of valve calcification.³⁸ A study of 338 patients with AS reported an annual mean (SD) change in aortic velocity of 0.26 (0.23) m/s per year in those with hypertension compared with 0.17 (0.20) m/s per year in those without hypertension.³⁹ First-line antihypertensive medications for patients with AS are not well-established, but small RCTs and observational population-based data indicate that angiotensin converting enzyme inhibitors or receptor blockers are safe and well-tolerated, and β -blockers are a reasonable alternative or additional treatment option.^{25,36,38-48}

Patients with aortic stenosis are at increased risk of developing infective endocarditis. A study of 83 453 patients with aortic or

mitral valve disorders reported a cumulative 10-year rate of infective endocarditis of 0.9%, which is 8.75-fold higher than in the general population.⁴⁹ Maintaining optimal dental hygiene, including dental cleanings every 6 months, is recommended for all patients with valvular heart disease.⁵⁰ However, routine antibiotic prophylaxis before dental treatment is not indicated for patients with AS who have not undergone aortic valve replacement.²⁵

Currently, there are no medical therapies that slow progression of AS (eTable in the Supplement).^{28,43,51-59} RCTs that included 2407 patients with established AS showed no effect of statin lipid-lowering therapy on AS progression or the need for valve replacement. Similarly, in RCTs, medications targeting calcification, such as bisphosphonates and denosumab, have been ineffective in slowing AS progression.^{27,28,51-59} Genome-wide association studies have suggested that lipoprotein(a) is associated with incident cases of AS⁶⁰ and high serum lipoprotein(a) concentrations are associated with more rapid progression of AS, but currently there are no

published data to support using medications targeting lipoprotein(a) in patients with AS.^{61,62}

Indications for Aortic Valve Replacement

Current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines strongly recommend prompt SAVR or TAVI in adults with symptoms due to severe AS (Figure 3).^{25,36} This recommendation is based on the high mortality rate associated with severe symptomatic AS, which was 50.7% at 1 year with standard medical care vs 30.7% with TAVI in the PARTNER RCT of 358 patients with AS who were not candidates for aortic valve surgery (HR [death with TAVI vs medical care], 0.55 [95% CI, 0.40-0.74]; $P < .001$).⁵ However, a palliative care approach may be more appropriate for patients with limited life expectancy (defined as less than 1 year) or those whose quality of life is unlikely to improve even after valve replacement, such as those with severe dementia or other substantial comorbidities.⁶³

Observational studies suggest that severe AS is undertreated in the US. In a 2022 cohort study that included 10 795 patients with severe AS on echocardiography, 6105 patients had a potential indication for aortic valve replacement, but only 2977 (48%) underwent SAVR or TAVI.⁶⁴ Among patients with symptomatic high-gradient AS and normal ventricular function, the 2-year survival rate was 97% in those who underwent aortic valve replacement vs 85% in those who did not undergo valve replacement (adjusted HR, 0.42 [95% CI, 0.29-0.61]).⁶⁴ The AHA's Target: Aortic Stenosis initiative is developing patient care pathways to ensure that all individuals with an ACC/AHA class 1 guideline recommendation for valve replacement are treated appropriately within 90 days.⁶⁵

The 2020 ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease stated that for asymptomatic patients with severe AS, aortic valve replacement is: (1) recommended when LV ejection fraction is less than 50% or when patients are undergoing cardiac surgery for other reasons; (2) reasonable when exercise testing shows a decrease in blood pressure or reduced exercise capacity; and (3) reasonable if aortic velocity is 5 m/s or higher, serum B-type natriuretic peptide (BNP) level is more than 3 times the normal limit, or aortic velocity increases more than 0.3 m/s per year.^{25,36} Management of patients with severe AS who do not meet any of these criteria is less clear. An observational cohort study of 622 asymptomatic patients with severe AS suggested that with careful follow-up, the risk of sudden death was low (<1% per year).^{66,67} Thus, current ACC/AHA and ESC guidelines^{25,36} recommend expectant management of asymptomatic patients with severe AS with clinical and echocardiographic follow-up every 6 to 12 months until development of AS symptoms or LV systolic dysfunction (Figure 3). Recently, this approach has been questioned^{68,69} because of widespread availability of TAVI, increased awareness of the long-term effect of severe AS on LV diastolic function,^{70,71} and registry data showing a lower risk of death and heart failure hospitalization in asymptomatic patients with severe AS who underwent SAVR compared with a conservative management strategy.⁷² In addition, a randomized study of 145 asymptomatic patients with very severe AS, defined as an aortic valve area of less than or equal to 0.75 cm² with an aortic jet velocity 4.5 m/s or higher or a mean transaortic gradient of 50 mm Hg or less

reported lower all-cause mortality at a median follow-up of 6.2 years in those who underwent SAVR within 2 months after randomization vs those who underwent SAVR at symptom onset (7% vs 21%; HR, 0.33 [95% CI, 0.12-0.90]).⁷³ However, these patients had a mean aortic velocity of 5 m/s, indicating that most already met ACC/AHA criteria for valve replacement. Another study of 157 asymptomatic patients with severe AS reported that those randomized to early surgery, defined as within 8 weeks after randomization, had a lower incidence of the composite primary outcome (all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure) compared with those who underwent valve replacement at symptom onset (17% vs 33% at 30 months; HR, 0.46 [95% CI, 0.23-0.90]).⁷⁴ Currently, routine aortic valve replacement in asymptomatic patients with severe AS is not advised, pending results of ongoing larger clinical trials.

Aortic valve replacement is not recommended for patients with moderate AS. In these patients, symptoms such as exertional dyspnea or decreased exercise tolerance are unlikely to be due to AS and instead are likely caused by conditions such as pulmonary disease (eg, asthma, COPD, interstitial lung disease), anemia, heart block, or arrhythmia, such as atrial fibrillation. However, some patients with apparently moderate AS may have severe AS with a lower gradient than expected because forward stroke volume is low (≤ 35 mL/m²) due to LV systolic dysfunction (Stage D2 AS) or a small ventricle (Stage D3 AS). When the aortic valve is heavily calcified or valve area is greater than or equal to 1.0 cm² despite only a moderate gradient, it is important to consider the diagnosis of low-flow, low-gradient severe AS because these patients benefit from valve replacement.^{25,36} In addition, for patients with moderate AS who are undergoing cardiac surgery for another reason, SAVR may be appropriate because progression to severe AS is inevitable.^{25,36}

Selection of Prosthetic Valve Type

Factors to consider when selecting the prosthetic aortic valve include the patient's age, life expectancy, appropriate valve size, contraindications to long-term anticoagulation, and patient preferences. Choice of prosthetic aortic valve should be based on a shared decision-making process between patients and clinicians with expertise in cardiology and cardiac surgery.⁷⁵ Bioprosthetic valves, typically derived from porcine heart valves or bovine pericardium, undergo tissue degeneration between 10 and 20 years after implantation and may require repeat valve replacement. Mechanical aortic valves, typically composed of pyrolytic carbon, are durable and rarely require replacement. However, mechanical aortic valves require surgical placement and lifelong anticoagulation with a vitamin K antagonist, which is associated with an increased risk of bleeding and requires monitoring of blood anticoagulant levels. Direct oral anticoagulant medications are contraindicated in patients with mechanical heart valves. RCTs have reported that dabigatran use was associated with increased rates of thromboembolic and bleeding complications compared with a vitamin K antagonist,⁷⁵ and apixaban was less effective for prevention of aortic valve thrombosis or thromboembolism compared with a vitamin K antagonist.⁷⁶

SAVR vs TAVI | Bioprosthetic valve replacement can be performed using a surgical or transcatheter approach (Table 3).^{77-79,81-90} Several large randomized trials have compared SAVR with TAVI in

Table 3. Outcomes in Randomized Clinical Trials of Surgical Aortic Valve Replacement (SAVR) vs Transcatheter Aortic Valve Implantation (TAVI) in Symptomatic Adults With Severe Aortic Stenosis^a

	Patient characteristics ^b	
Mean age, y	High- and intermediate-risk patients: ⁷⁷⁻⁸⁰ approximately 80-84 ⁸¹ Low-risk patients: ⁸²⁻⁸⁵ approximately 73-81 ⁸¹	
Sex distribution	High- and intermediate-risk patients: ⁷⁷⁻⁸⁰ 55% male (2922/5272); 45% female (2350/5272) Low-risk patients and any risk category: ⁸²⁻⁸⁵ 62% male (2209/3546); 38% female (1337/3546)	
Race	White: 94% (1748/1863) ^c	
Outcomes	SAVR	TAVI
Survival	30 d: 97.5% ⁸⁶ 1 y: 90.6%, ⁸¹ 90.5% ⁸⁶ 5 y: 56.8% ^{86d}	30 d: 97.8% ⁸⁶ 1 y: 91.8%, ⁸¹ 91.6% ⁸⁶ 5 y: 52.0% ^{86d}
Adverse events at 30 d ⁸⁵⁻⁸⁹	Postoperative AF (~33%) Major bleeding (~20%) Permanent pacemaker (~6%-7%) Acute kidney injury (~4%) Stroke (~2%-4%)	Postprocedural AF (~10%) Permanent pacemaker (~11%-15%) Major bleeding (~6%-8%) Stroke (~2%-3%) Moderate to severe paravalvular regurgitation (~2.5%) Acute kidney injury (~2%)
Adverse events >30 d ⁸⁵⁻⁸⁹	Structural deterioration of bioprosthetic valves (~6% at 10 y, 18% at 15 y, and 48% at 20 y) Thromboembolic complications (~1% per y with either bioprosthetic or mechanical valve) Major bleeding (~1% per y with mechanical valve) Infective endocarditis (~0.5%-1% at 1 y and 2% at 5 y); risk is higher for bioprosthetic vs mechanical valves	Structural deterioration, moderate or severe (~15% at 10 y) Stroke (5% at 1 y) Valve reintervention (~4% at 10 y) Infective endocarditis (~0.5%-1% at 1 y, 3% at 5 y, and 7% at 10 y)
Other considerations in clinical decision-making		
	Mechanical surgical valve recommended in younger patients (aged <50 y) without contraindications to vitamin K antagonist anticoagulation Preferred option if CABG, aortic root replacement, or other valve surgery is indicated Frailty, prior cardiac surgery, excessive aortic calcification, and other factors indicating high surgical risk may make SAVR less appropriate	May be only option in patients with very high surgical risk and preferred option in patients with high surgical risk TAVI may not be feasible for individuals with unsuitable transfemoral access, unfavorable valve anatomy, severe calcification, and low coronary ostia
Patient considerations		
	Longer postoperative hospitalization Postoperative pain and surgical scar Longer recovery to normal activities after hospitalization Longer-term (20 y) data on bioprosthetic surgical aortic valve durability at all patient ages Potential option of transcatheter valve-in-valve procedure if needed in the future	Shorter hospitalization Less pain and no scar Short time to resumption of normal activity Valve durability data with TAVI is similar to SAVR at 10 y in adults aged older than 70 y with inadequate data in younger patients Scant data on outcomes with a repeat procedure

Abbreviation: CABG, coronary artery bypass grafting.

^c Race data as reported in 2 trials (UK TAVI⁸⁵ and PARTNER-3).⁸³^a Data and recommendations are assembled and generalized from multiple sources. Individual papers and meta-analyses as referenced in the text.^d Five-year survival data based on study cohorts with a high or intermediate surgical risk.^b Aggregate data on demographics from cited randomized comparisons of surgical vs transcatheter aortic valve replacement.

patients with AS who had a high estimated surgical mortality risk (>8%), followed by studies in those with moderate (3%-8%) and low mortality risk (<3%).^{77-80,83,84} The mean age of participants in these trials was mid-80s in the high-risk group, approximately 80 in the moderate risk group, and mid-70s for low-risk patients. There are few published data about TAVI in adults younger than age 65 years or about potential differences in outcomes based on sex.

A study that randomized 699 high-risk patients with severe AS to TAVI or SAVR reported no statistically significant difference in 1-year mortality (24.2% vs 26.5%).⁷⁷ In this study, at 30 days, major vascular complications, such as aortic dissection or vascular access site injury requiring intervention, were statistically significantly more frequent with TAVI (11.0% vs 3.2%; $P < .001$), but SAVR was associated with statistically significantly higher rates of major

bleeding (19.5% vs 9.3%; $P < .001$) and new-onset atrial fibrillation (16% vs 8.6%; $P = .01$) compared with TAVI.⁷⁷ In patients at low surgical risk (<3% estimated surgical mortality risk), a 2023 meta-analysis of 8 RCTs that included 8698 patients reported that the risk of death or disabling stroke at 1 year was lower in patients who underwent TAVI compared with SAVR (relative risk, 0.68 [95% CI, 0.50 to 0.92]; $P = .01$).⁸¹

TAVI typically requires a 1- to 2-day hospitalization, with a return to normal activities within 1 week. In contrast, patients undergoing SAVR typically have a 1-week hospitalization and 6 weeks of limited activity with gradual recovery to baseline functional status over 3 to 6 months. Compared with SAVR, TAVI has a lower 30-day risk of postprocedural atrial fibrillation (10% vs 33%) and major bleeding.⁸⁵⁻⁸⁹ However, patients undergoing TAVI have a higher risk

of residual paraprosthetic aortic regurgitation and are more likely to require permanent pacemaker placement at 30 days than those with SAVR (15% vs 6%).⁸⁶ Data on durability of bioprosthetic transcatheter aortic valves are available up to 10 years in small numbers of patients older than age 70 years, compared with more than 20 years of follow-up data in larger patient cohorts of all ages for surgically placed aortic bioprosthetic valves⁹¹⁻⁹⁴ (see Bioprosthetic Valve Degeneration and Dysfunction below).

The 2020 ACC/AHA and 2021 ESC guidelines recommend transfemoral TAVI for patients with symptomatic AS who are unable to undergo surgery or have a high estimated surgical mortality risk (>8%).^{25,36} ACC/AHA guidelines recommend SAVR for adults younger than 65 years, with a mechanical valve preferred over a bioprosthetic valve in those younger than 50 years based on expected years of remaining life and valve durability.^{25,36} TAVI is recommended for individuals aged 80 years and older in ACC/AHA guidelines and 75 years and older in ESC guidelines. US guidelines suggest that either TAVI or SAVR is appropriate for those aged 65 to 80 years regardless of surgical risk. In contrast, ESC guidelines recommend SAVR in patients younger than age 75 years who are at low surgical risk (<4%) with shared decision-making for either SAVR or TAVI only in those at intermediate surgical risk.³⁶ In addition to these age-based recommendations, specific patient factors (such as the suitability of valve anatomy and vascular access, comorbidities, frailty, and individual preferences), local experience and availability of an experienced TAVI team should be considered when making decisions about the type of aortic valve replacement (Figure 3).

Prognosis

Aortic valve replacement decreases mortality, relieves symptoms due to AS, and results in regression of LV hypertrophy and improvement in LV systolic function. However, replacement of a native valve with a prosthetic valve requires long-term management, including lifelong antithrombotic therapy for patients with a mechanical aortic valve, endocarditis prevention, and monitoring for valve deterioration and dysfunction.

Bioprosthetic Valve Deterioration and Dysfunction

In a systematic review of observational studies of patients undergoing SAVR with a bioprosthetic valve, freedom from structural valve deterioration was 94.0% at 10 years, 81.7% at 15 years, and 52% at 20 years.⁸⁸ Surgically implanted bioprosthetic valves have more rapid deterioration in younger patients compared with older patients.⁹⁴

Valve durability for bioprosthetic TAVI valves is similar to surgically implanted valves in older adults at a follow-up duration of 5 to 10 years. In 783 propensity-matched patients at intermediate surgical risk randomized to SAVR vs TAVI, the rate of bioprosthetic valve failure at 5 years was 0.63% with TAVI compared with 0.37% with SAVR per 100 exposure-years ($P = .22$).⁹⁵ In a study of 280 symptomatic patients at low surgical risk older than age 70 years with severe AS randomized to TAVI vs SAVR, the risk of moderate to severe structural valve deterioration was similar 10 years after implantation (TAVI, 15.4% and SAVR, 20.8%; HR, 0.7 [95% CI, 0.4-1.3]; $P = .30$).⁹⁰ When repeat valve surgery is necessary, mortality

and morbidity typically are twice the risk of the original surgery depending on patient age and comorbidities.⁹⁶ A valve-in-valve procedure, in which a transcatheter valve is implanted within a poorly functioning surgical bioprosthetic valve, may be considered for selected patients, although long-term outcome data are not currently available.⁹⁷

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis, which occurs at a rate of 0.3% to 1.2% per patient-year, is associated with increased rates of adverse outcomes, such as valve dysfunction, heart failure, embolic stroke, and death.^{94,95,98} Prosthetic valve endocarditis is associated with a mortality rate of 20% or higher compared with 5% or lower in patients with native valve endocarditis.^{94,95} ACC/AHA and ESC guidelines recommend antibiotic prophylaxis for all patients with a prosthetic valve when undergoing dental procedures, including routine cleanings.^{99,100}

Persistent AS Symptoms

For some patients, symptoms of dyspnea and exercise intolerance persist following aortic valve replacement, which may be caused by suboptimal hemodynamics of prosthetic valves compared with normal native valves.³⁰⁻³² Implanting a small prosthetic valve in a patient with a small annulus can lead to a high residual valve gradient, termed patient-prosthesis mismatch. Even in the absence of this mismatch, AS symptoms may persist due to persistent LV hypertrophy, diastolic dysfunction, irreversible LV fibrosis, and systolic dysfunction.¹⁰¹

Permanent Pacemaker Requirement

Complete heart block requiring a permanent pacemaker occurs in about 6% of patients after SAVR, likely due to disruption of the bundle of His during surgery and up to 15% of patients after TAVI likely because the calcified aortic valve and its annulus are displaced into the septum during implantation of the bioprosthetic valve.^{81,86,102} Heart block typically occurs immediately or within days of the procedure but can also occur weeks or months later. Potential complications of a permanent pacemaker include device or lead infection and tricuspid valve dysfunction due to the pacemaker lead position.

Limitations

This review has several limitations. First, it is not a systematic review and the quality of the included studies was not formally evaluated. Second, some relevant studies may have been missed. Third, this review does not cover some topics related to epidemiology, diagnosis, treatment, and complications related to AS.

Conclusions

Calcific AS is a common chronic progressive condition among adults older than 65 years and is diagnosed via echocardiography. Symptomatic patients with severe AS have a mortality rate of up to 50% after 1 year, but treatment with SAVR or TAVI reduces mortality to that of age-matched control patients. The type and timing of valve replacement should be built on evidence-based professional society guidelines, shared decision-making, and involvement of a multidisciplinary heart valve team.

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