JAMA | Review

Calcific Aortic Stenosis
A Review

Catherine M. Otto, MD; David E. Newby, MD; Graham S. Hillis, MBChB, PhD

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 cm^2. 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.

Multimedia

Supplemental content

CME at jamacmelookup.com

Author Affiliations: Division of Cardiology, University of Washington School of Medicine, Seattle (Otto); University of Edinburgh, British Heart Foundation Centre of Research Excellence, Royal Infirmary, Edinburgh, United Kingdom (Newby); Department of Cardiology, Royal Perth Hospital and Medical School, University of Western Australia, Perth (Hillis).

Corresponding Author: Catherine M. Otto, MD, Division of Cardiology, University of Washington School of Medicine, 1959 NE Pacific St, HSB AA522, Seattle, WA 98195 (cmotto@u.washington.edu).

Section Editor: Kristin Walter, MD, Deputy Editor.

JAMA. doi:10.1001/jama.2024.16477
Published online November 11, 2024.

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]

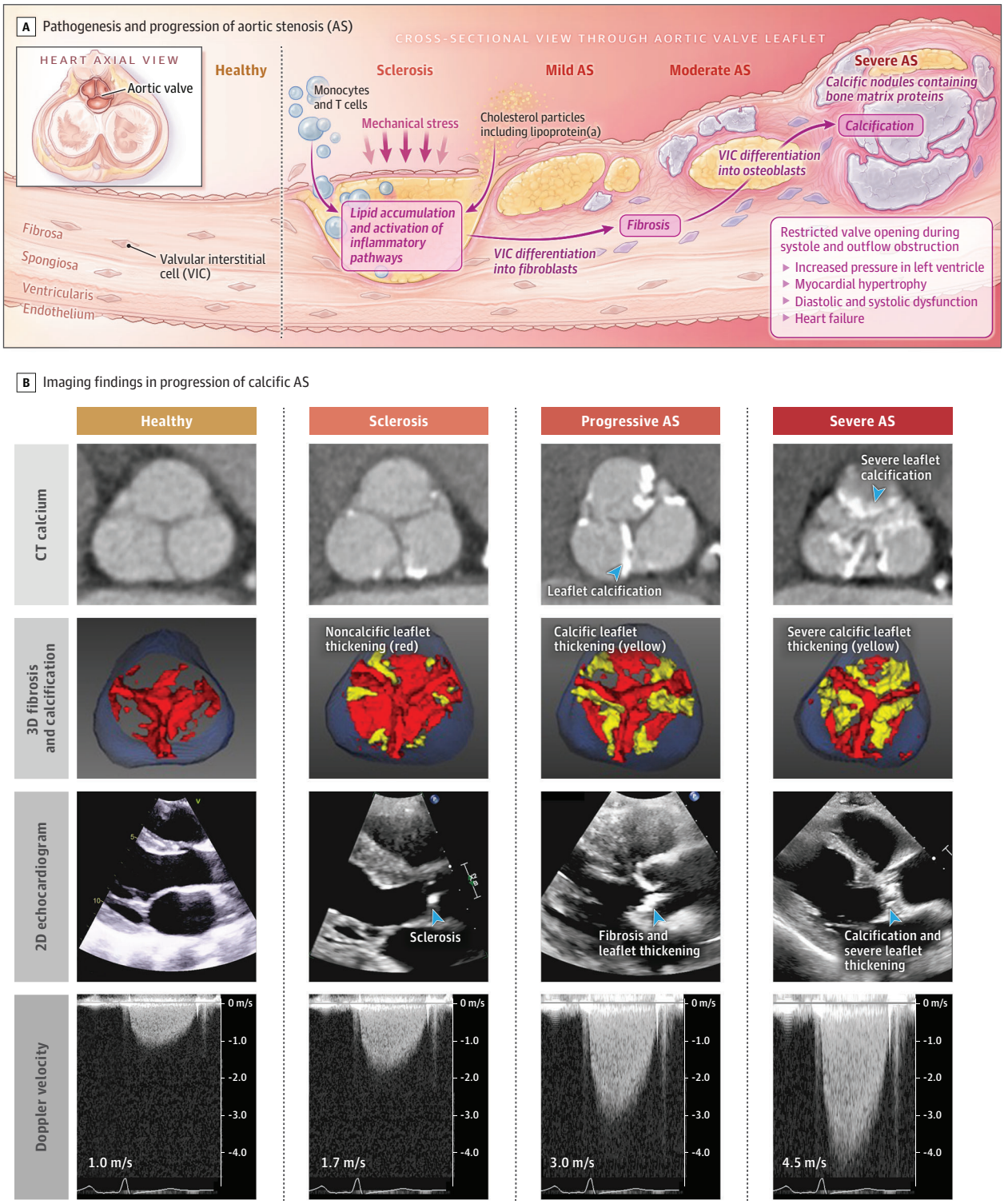
Stage C includes asymptomatic patients with severe valve obstruction with an aortic velocity 4 m/s or higher or mean gradient 40 mm Hg or higher. Typically, valve area is less than or equal to 1.0 cm^2 (≤0.6 cm^2/m^2 indexed to body surface area) but a high velocity (≥4 m/s) or high mean gradient (≥40 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 cm^2 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-κB 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 supravalvular 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.

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.

year and decrease in aortic valve area of 0.08 (0.21) cm^2 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]

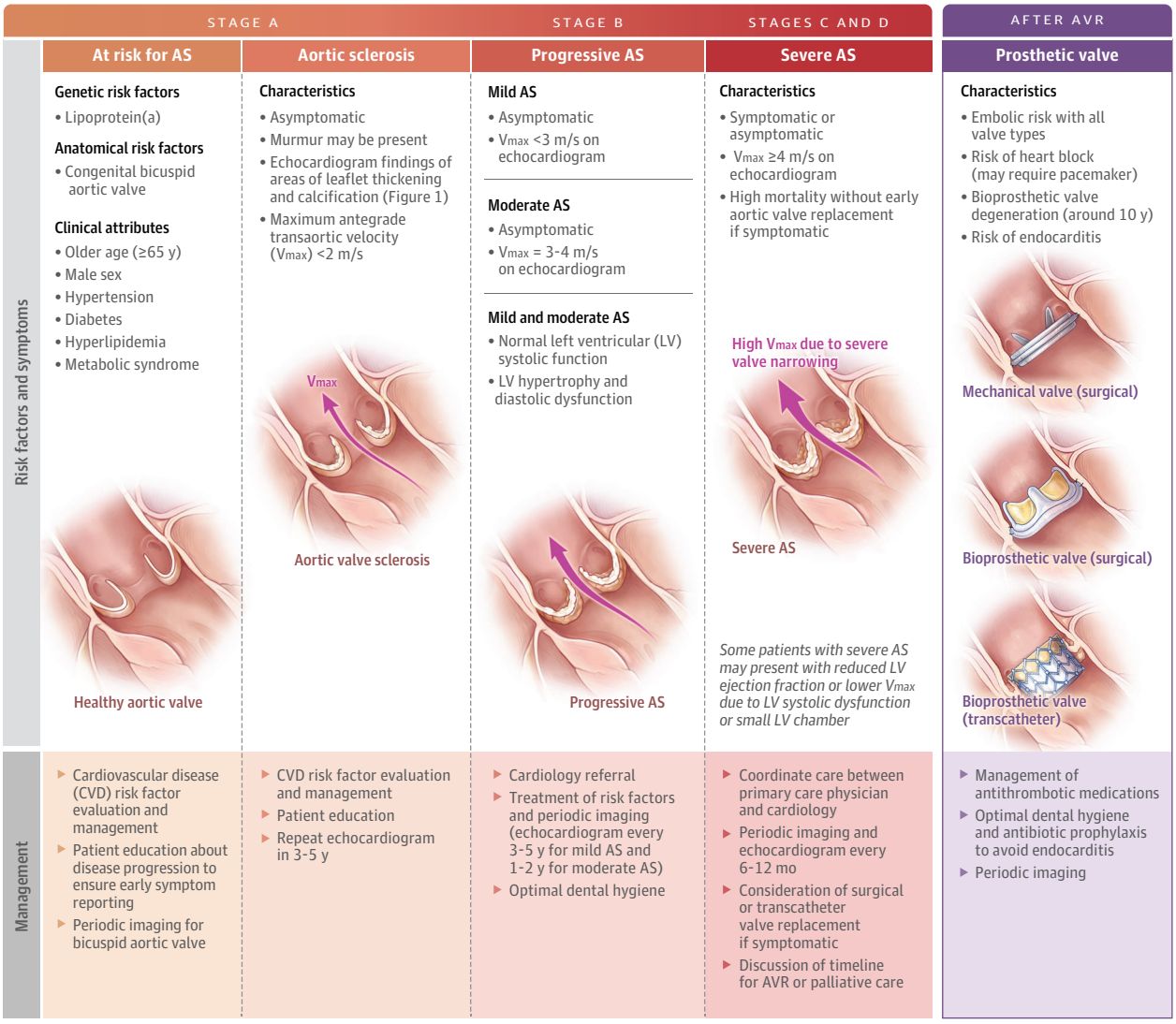
For patients with mild or moderate AS, symptoms are unlikely to be due to AS when LV function is normal, and many patients with severe AS remain asymptomatic for years until AS becomes more severe. The most common initial symptoms of AS are reduced exercise tolerance or exertional dyspnea, which also 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 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



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]

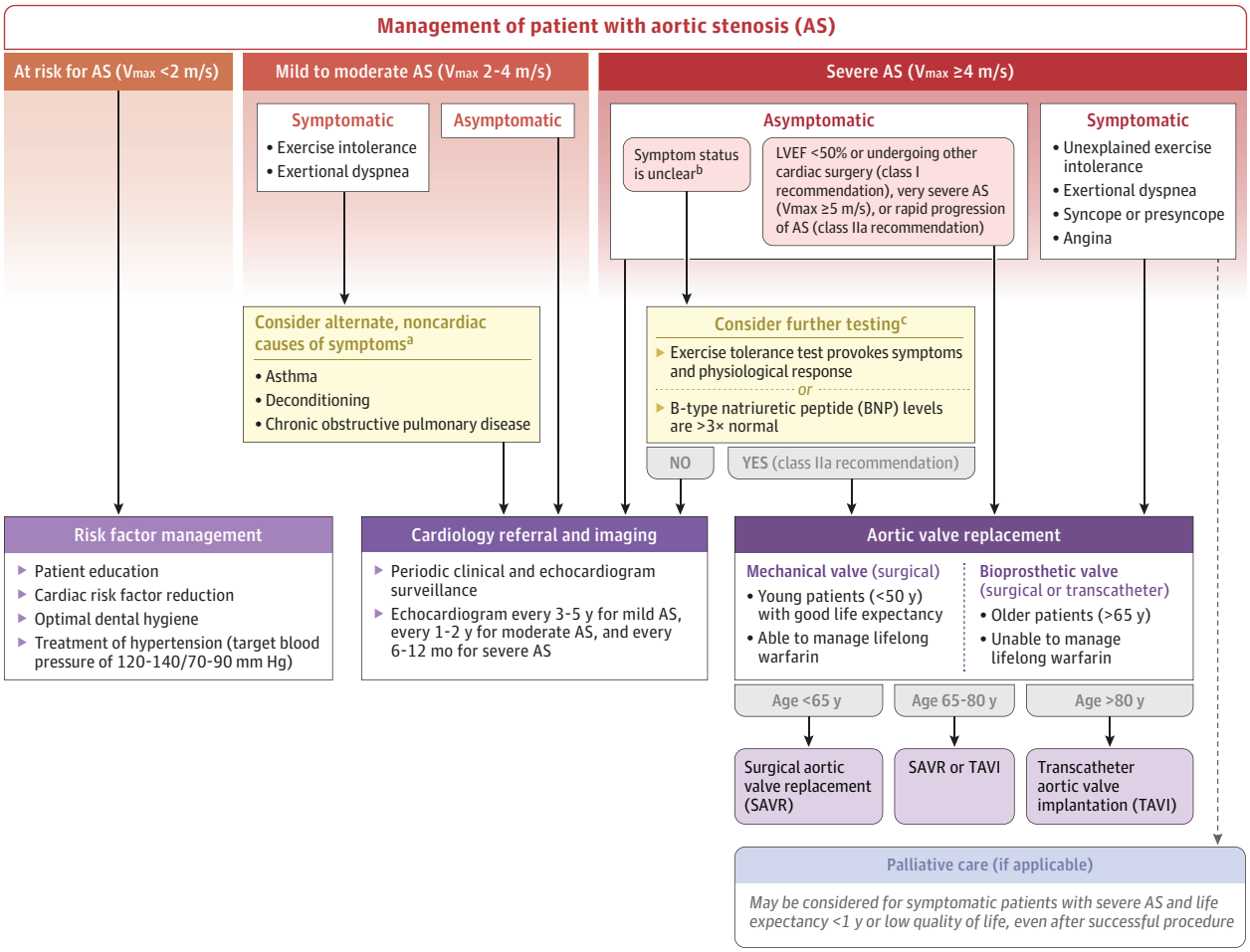
Management

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



[a]Additional testing may be needed to exclude the possibility of low-flow, low-gradient AS.

[b]Due to insidious onset, patients may attribute symptoms to normal aging or other conditions.

[c]Further 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 AS[60] 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 cm^2 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 ($\leq$35 mL/m^2) 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 cm^2 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.

[a] Data and recommendations are assembled and generalized from multiple sources. Individual papers and meta-analyses as referenced in the text.

[b] Aggregate data on demographics from cited randomized comparisons of surgical vs transcatheter aortic valve replacement.

[c] Race data as reported in 2 trials (UK TAVI[85] and PARTNER-3).[83]

[d] Five-year survival data based on study cohorts with a high or intermediate surgical risk.

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 valves[91-94] (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.

ARTICLE INFORMATION

Accepted for Publication: July 29, 2024.

Published Online: November 11, 2024. doi:10.1001/jama.2024.16477

Conflict of Interest Disclosures: Dr Hillis reported receiving research grants from the Australian Medical Research Future Fund and the British Heart Foundation for the Early valve replacement in severe ASYmptomatic Aortic Stenosis (EASY-AS) trial during the conduct of the study. No other disclosures were reported.

Funding/Support: Dr Newby is supported by the British Heart Foundation (CH/09/002, RE/18/5/34216, and RG/F/22/110093). Dr Hillis is supported by a WA Health Research Excellence Award.

Role of the Funder/Sponsor: The British Heart Foundation had no role in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med*. 2017;377(8):713-722. doi:10.1056/NEJMoa1603693

2. Gardezi SKM, Myerson SG, Chambers J, et al. Cardiac auscultation poorly predicts the presence of valvular heart disease in asymptomatic primary care patients. *Heart*. 2018;104(22):1832-1835. doi:10.1136/heartjnl-2018-313082

3. Munt B, Legget ME, Kraft CD, et al. Physical examination in valvular aortic stenosis: correlation with stenosis severity and prediction of clinical outcome. *Am Heart J*. 1999;137(2):298-306. doi:10.1053/hj.1999.v137.95496

4. Nascimento BR, Beaton AZ, Nunes MCP, et al; PROVAR+ (Programa de RastreamentO da VAlvopatia Reumática and Other Cardiovascular Diseases) investigators. Integration of echocardiographic screening by non-physicians with remote reading in primary care. *Heart*. 2019;105(4):283-290. doi:10.1136/heartjnl-2018-313593

5. Leon MB, Smith CR, Mack M, et al; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597-1607. doi:10.1056/NEJMoa1008232

6. Yadgir S, Johnson CO, Aboyans V, et al; Global Burden of Disease Study 2017 Nonrheumatic Valve Disease Collaborators. Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990-2017. *Circulation*. 2020;141(21):1670-1680. doi:10.1161/CIRCULATIONAHA.119.043391

7. Lindman BR, Clavel MA, Mathieu P, et al. Calcific aortic stenosis. *Nat Rev Dis Primers*. 2016;2:16006. doi:10.1038/nrdp.2016.6

8. Owens DS, Bartz TM, Buzkova P, et al. Cumulative burden of clinically significant aortic stenosis in community-dwelling older adults. *Heart*. 2021;107(18):1493-1502. doi:10.1136/heartjnl-2021-319025

9. d'Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people. *Eur Heart J*. 2016;37(47):3515-3522. doi:10.1093/eurheartj/ehw229

10. Kim KM, Arghami A, Habib R, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2022 update on outcomes and research. *Ann Thorac Surg*. 2023;115(3):566-574. doi:10.1016/j.athoracsur.2022.12.033

11. Movahed MR, Timmerman B, Hashemzadeh M. Independent association of aortic stenosis with many known cardiovascular risk factors and many inflammatory diseases. *Arch Cardiovasc Dis*. 2023;116(10):467-473. doi:10.1016/j.acvd.2023.07.008

12. Coffey S, Roberts-Thomson R, Brown A, et al. Global epidemiology of valvular heart disease. *Nat Rev Cardiol*. 2021;18(12):853-864. doi:10.1038/s41569-021-00570-z

13. Mundal LJ, Hovland A, Igland J, et al. Association of low-density lipoprotein cholesterol with risk of aortic valve stenosis in familial hypercholesterolemia. *JAMA Cardiol*. 2019;4(11):1156-1159. doi:10.1001/jamacardio.2019.3903

14. Mulder JWCM, Tromp TR, Al-Khnifsawi M, et al; Homozygous Familial Hypercholesterolemia International Clinical Collaborators. Sex differences in diagnosis, treatment, and cardiovascular outcomes in homozygous familial hypercholesterolemia. *JAMA Cardiol*. 2024;9(4):313-322. doi:10.1001/jamacardio.2023.5597

15. Ranganath LR, Heseltine T, Khedr M, Fisher MF. Evaluating the aortic stenosis phenotype before and after the effect of homogentisic acid lowering therapy: analysis of a large cohort of eighty-one alkaptonuria patients. *Mol Genet Metab*. 2021;133(3):324-331. doi:10.1016/j.ymgme.2021.05.007

16. Bernardini G, Braconi D, Zatkova A, et al. Alkaptonuria. *Nat Rev Dis Primers*. 2024;10(1):16. doi:10.1038/s41572-024-00498-x

17. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*. 2005;111(7):920-925. doi:10.1161/01.CIR.0000155623.48408.C5

18. Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. *J Am Coll Cardiol*. 2015;66(5):561-577. doi:10.1016/j.jacc.2015.05.066

19. Goody PR, Hosen MR, Christmann D, et al. Aortic valve stenosis: from basic mechanisms to novel therapeutic targets. *Arterioscler Thromb Vasc Biol*. 2020;40(4):885-900. doi:10.1161/ATVBAHA.119.313067

20. Small AM, Yutzey KE, Binstadt BA, et al; American Heart Association Council on Genomic and Precision Medicine Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation and Council on Cardiovascular and Stroke Nursing. Unraveling the mechanisms of valvular heart disease to identify medical therapy targets. *Circulation*. 2024. doi:10.1161/CIR.0000000000001254

21. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2014;63(25 Pt A):2852-2861. doi:10.1016/j.jacc.2014.04.018

22. Massera D, Bartz TM, Biggs ML, et al. Traditional and novel risk factors for incident aortic stenosis in community-dwelling older adults. *Heart*. 2023;110(1):57-64. doi:10.1136/heartjnl-2023-322709

23. Nazarzadeh M, Pinho-Gomes AC, Bidel Z, et al. Plasma lipids and risk of aortic valve stenosis: a Mendelian randomization study. *Eur Heart J*. 2020;41(40):3913-3920. doi:10.1093/eurheartj/ehaa070

24. Rahimi K, Mohseni H, Kiran A, et al. Elevated blood pressure and risk of aortic valve disease: a cohort analysis of 5.4 million UK adults. *Eur Heart J*. 2018;39(39):3596-3603. doi:10.1093/eurheartj/ehy486

25. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143(5):e72-e227.doi:10.1161/CIR.0000000000000923

26. Willner N, Prosperi-Porta G, Lau L, et al. Aortic stenosis progression: a systematic review and meta-analysis. *JACC Cardiovasc Imaging*. 2023;16(3):314-328. doi:10.1016/j.jcmg.2022.10.009

27. Rossebø AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359(13):1343-1356. doi:10.1056/NEJMoa0804602

28. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J; ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the Aortic Stenosis Progression Observation. *Circulation*. 2010;121(2):306-314. doi:10.1161/CIRCULATIONAHA.109.900027

29. Yang LT, Ye Z, Wajih Ullah M, et al. Bicuspid aortic valve: long-term morbidity and mortality. *Eur Heart J*. 2023;44(43):4549-4562. doi:10.1093/eurheartj/ehad477

30. San Román JA, Ybarra-Falcón C, García-Gómez M, et al. Recurrence of syncope after valve replacement in severe aortic stenosis. *Heart*. 2023;109(21):1631-1638. doi:10.1136/heartjnl-2023-322859

31. Ben-Shoshan J, Zahler D, Margolis G, et al. Relation of clinical presentation of aortic stenosis and survival following transcatheter aortic valve implantation. *Am J Cardiol*. 2019;123(6):961-966. doi:10.1016/j.amjcard.2018.12.009

32. San Román JA, Ybarra-Falcón C, García-Gómez M, et al. Evolution and prognostic significance of patient-reported symptoms after intervention in severe aortic stenosis. *Mayo Clin Proc*. 2024;99(3):400-410. doi:10.1016/j.mayocp.2023.09.024

33. Nakatsuma K, Taniguchi T, Morimoto T, et al; CURRENT AS Registry Investigators. B-type natriuretic peptide in patients with asymptomatic severe aortic stenosis. *Heart*. 2019;105(5):384-390.doi:10.1136/heartjnl-2018-313746

34. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of

Echocardiography. *J Am Soc Echocardiogr*. 2017;30(4):372-392. doi:10.1016/j.echo.2017.02.009

35. Geers J, Bing R. Computed tomographic imaging of patients with native and prosthetic aortic valve stenosis. *Heart*. 2023;109(17):1327-1337. doi:10.1136/heartjnl-2022-321660

36. Vahanian A, Beyersdorf F, Praz F, et al; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632. doi:10.1093/eurheartj/ehab395

37. Lindman BR, Fonarow GC, Myers G, et al. Target aortic stenosis: a national initiative to improve quality of care and outcomes for patients with aortic stenosis. *Circ Cardiovasc Qual Outcomes*. 2023;16(6):e009712. doi:10.1161/CIRCOUTCOMES.122.009712

38. Tastet L, Capoulade R, Clavel MA, et al. Systolic hypertension and progression of aortic valve calcification in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2017;18(1):70-78. doi:10.1093/ehjci/jew013

39. Capoulade R, Clavel MA, Mathieu P, et al. Impact of hypertension and renin-angiotensin system inhibitors in aortic stenosis. *Eur J Clin Invest*. 2013;43(12):1262-1272. doi:10.1111/eci.12169

40. Rieck AE, Cramariuc D, Boman K, et al. Hypertension in aortic stenosis: implications for left ventricular structure and cardiovascular events. *Hypertension*. 2012;60(1):90-97. doi:10.1161/HYPERTENSIONAHA.112.194878

41. Nadir MA, Wei L, Elder DH, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *J Am Coll Cardiol*. 2011;58(6):570-576. doi:10.1016/j.jacc.2011.01.063

42. Dalsgaard M, Iversen K, Kjaergaard J, et al. Short-term hemodynamic effect of angiotensin-converting enzyme inhibition in patients with severe aortic stenosis. *Am Heart J*. 2014;167(2):226-234. doi:10.1016/j.ahj.2013.11.002

43. Bull S, Loudon M, Francis JM, et al. A prospective, double-blind, randomized controlled trial of the angiotensin-converting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). *Eur Heart J Cardiovasc Imaging*. 2015;16(8):834-841. doi:10.1093/ehjci/jev043

44. Mancusi C, Gerdts E, De Simone G, et al. Impact of isolated systolic hypertension on normalization of left ventricular structure during antihypertensive treatment (the LIFE study). *Blood Press*. 2014;23(4):206-212. doi:10.3109/08037051.2013.858482

45. Bang CN, Greve AM, Køber L, et al. Renin-angiotensin system inhibition is not associated with increased sudden cardiac death, cardiovascular mortality or all-cause mortality in patients with aortic stenosis. *Int J Cardiol*. 2014;175(3):492-498. doi:10.1016/j.ijcard.2014.06.013

46. Rossi A, Temporelli PL, Cicoira M, et al. Beta-blockers can improve survival in medically-treated patients with severe symptomatic aortic stenosis. *Int J Cardiol*. 2015;190:15-17. doi:10.1016/j.ijcard.2015.04.083

47. Hansson NH, Sörensen J, Harms HJ, et al. Metoprolol reduces hemodynamic and metabolic overload in asymptomatic aortic valve stenosis patients: a randomized trial. *Circ Cardiovasc Imaging*. 2017;10(10):e006557. doi:10.1161/CIRCIMAGING.117.006557

48. Bang CN, Greve AM, Rossebø AB, et al. Antihypertensive treatment with β-blockade in patients with asymptomatic aortic stenosis and association with cardiovascular events. *J Am Heart Assoc*. 2017;6(12):e006709. doi:10.1161/JAHA.117.006709

49. Østergaard L, Valeur N, Wang A, et al. Incidence of infective endocarditis in patients considered at moderate risk. *Eur Heart J*. 2019;40(17):1355-1361. doi:10.1093/eurheartj/ehy629

50. Duval X, Delahaye F, Alla F, et al; AEPEI Study Group. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications. *J Am Coll Cardiol*. 2012;59(22):1968-1976. doi:10.1016/j.jacc.2012.02.029

51. Chockalingam A, Venkatesan S, Subramaniam T, et al; Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS). *Am Heart J*. 2004;147(4):E19. doi:10.1016/j.ahj.2003.10.017

52. Cowell SJ, Newby DE, Prescott RJ, et al; Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med*. 2005;352(23):2389-2397. doi:10.1056/NEJMoa043876

53. Dichtl W, Alber HF, Feuchtner GM, et al. Prognosis and risk factors in patients with asymptomatic aortic stenosis and their modulation by atorvastatin (20 mg). *Am J Cardiol*. 2008;102b(6):743-748. doi:10.1016/j.amjcard.2008.04.060

54. van der Linde D, Yap SC, van Dijk AP, et al. Effects of rosuvastatin on progression of stenosis in adult patients with congenital aortic stenosis (PROCAS Trial). *Am J Cardiol*. 2011;108(2):265-271. doi:10.1016/j.amjcard.2011.03.032

55. Pawade TA, Doris MK, Bing R, et al. Effect of denosumab or alendronic acid on the progression of aortic stenosis: a double-blind randomized controlled trial. *Circulation*. 2021;143(25):2418-2427. doi:10.1161/CIRCULATIONAHA.121.053708

56. Brandenburg VM, Reinartz S, Kaesler N, et al. Slower progress of aortic valve calcification with vitamin K supplementation. *Circulation*. 2017;135(21):2081-2083. doi:10.1161/CIRCULATIONAHA.116.027011

57. Diederichsen ACP, Lindholt JS, Möller S, et al. Vitamin K2 and D in patients with aortic valve calcification: a randomized double-blinded clinical trial. *Circulation*. 2022;145(18):1387-1397. doi:10.1161/CIRCULATIONAHA.121.057008

58. Stewart RA, Kerr AJ, Cowan BR, et al; ZEST Study Investigators. A randomized trial of the aldosterone-receptor antagonist eplerenone in asymptomatic moderate-severe aortic stenosis. *Am Heart J*. 2008;156(2):348-355. doi:10.1016/j.ahj.2008.03.012

59. Helske-Suihko S, Laine M, Lommi J, et al. Is blockade of the renin-angiotensin system able to reverse the structural and functional remodeling of the left ventricle in severe aortic stenosis? *J Cardiovasc Pharmacol*. 2015;65(3):233-240. doi:10.1097/FJC.0000000000000182

60. Thanassoulis G, Campbell CY, Owens DS, et al; CHARGE Extracoronary Calcium Working Group. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368(6):503-512. doi:10.1056/NEJMoa1109034

61. Zheng KH, Tsimikas S, Pawade T, et al. Lipoprotein(a) and oxidized phospholipids promote valve calcification in patients with aortic stenosis. *J Am Coll Cardiol*. 2019;73(17):2150-2162. doi:10.1016/j.jacc.2019.01.070

62. Kaiser Y, Singh SS, Zheng KH, et al. Lipoprotein(a) is robustly associated with aortic valve calcium. *Heart*. 2021;107(17):1422-1428. doi:10.1136/heartjnl-2021-319044

63. Nishimura RA, O'Gara PT, Bavaria JE, et al. 2019 AATS/ACC/ASE/SCAI/STS expert consensus systems of care document: a proposal to optimize care for patients with valvular heart disease: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2019;73(20):2609-2635. doi:10.1016/j.jacc.2018.10.007

64. Li SX, Patel NK, Flannery LD, et al. Trends in utilization of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol*. 2022;79(9):864-877. doi:10.1016/j.jacc.2021.11.060

65. Généreux P, Schwartz A, Oldemeyer B, et al. Design and rationale of the evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis. *Am Heart J*. 2024;268:94-103. doi:10.1016/j.ahj.2023.11.019

66. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111(24):3290-3295. doi:10.1161/CIRCULATIONAHA.104.495903

67. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J*. 2020;41(45):4349-4356. doi:10.1093/eurheartj/ehaa485

68. Hillis GS, McCann GP, Newby DE. Is asymptomatic severe aortic stenosis still a waiting game? *Circulation*. 2022;145(12):874-876. doi:10.1161/CIRCULATIONAHA.121.058598

69. Lindman BR, Dweck MR, Lancellotti P, et al. Management of asymptomatic severe aortic stenosis: evolving concepts in timing of valve replacement. *JACC Cardiovasc Imaging*. 2020;13(2 Pt 1):481-493. doi:10.1016/j.jcmg.2019.01.036

70. Musa TA, Treibel TA, Vassiliou VS, et al. Myocardial scar and mortality in severe aortic stenosis. *Circulation*. 2018;138(18):1935-1947. doi:10.1161/CIRCULATIONAHA.117.032839

71. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol*. 2012;60(19):1854-1863. doi:10.1016/j.jacc.2012.02.093

72. Taniguchi T, Morimoto T, Shiomi H, et al; CURRENT AS Registry Investigators. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66(25):2827-2838. doi:10.1016/j.jacc.2015.10.001

73. Kang DH, Park SJ, Lee SA, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382(2):111-119. doi:10.1056/NEJMoa1912846

74. Banovic M, Putnik S, Penicka M, et al; AVATAR Trial Investigators. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation*. 2022; 145(9):648-658. doi:10.1161/CIRCULATIONAHA.121.057639

75. Coylewright M. Implementing shared decision-making for patients with aortic stenosis with longer life expectancy. *JAMA Cardiol*. 2023;8 (8):715-716. doi:10.1001/jamacardio.2023.1459

76. Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214. doi:10.1056/NEJMoa1300615

77. Smith CR, Leon MB, Mack MJ, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187-2198. doi:10.1056/NEJMoa1103510

78. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;371 (10):967-968. doi:10.1056/NEJMc1408396

79. Reardon MJ, Van Mieghem NM, Popma JJ, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321-1331. doi:10.1056/NEJMoa1700456

80. Leon MB, Smith CR, Mack MJ, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609-1620. doi:10.1056/NEJMoa1514616

81. Ahmad Y, Howard JP, Arnold AD, et al. Transcatheter versus surgical aortic valve replacement in lower-risk and higher-risk patients: a meta-analysis of randomized trials. *Eur Heart J*. 2023;44(10):836-852. doi:10.1093/eurheartj/ehac642

82. Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the All-Comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65(20):2184-2194. doi:10.1016/j.jacc.2015.03.014

83. Mack MJ, Leon MB, Thourani VH, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380(18):1695-1705. doi:10.1056/NEJMoa1814052

84. Popma JJ, Deeb GM, Yakubov SJ, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380 (18):1706-1715. doi:10.1056/NEJMoa1816885

85. Toff WD, Hildick-Smith D, Kovac J, et al; UK TAVI Trial Investigators. Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic stenosis: a randomized clinical trial. *JAMA*. 2022;327(19):1875-1887. doi:10.1001/jama.2022.5776

86. Swift SL, Puehler T, Misso K, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis. *BMJ Open*. 2021;11(12): e054222. doi:10.1136/bmjopen-2021-054222

87. Desai ND, O'Brien SM, Cohen DJ, et al. Composite metric for benchmarking site performance in transcatheter aortic valve replacement: results from the STS/ACC TVT Registry. *Circulation*. 2021;144(3):186-194. doi:10.1161/CIRCULATIONAHA.120.051456

88. Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ*. 2016;354:i5065. doi:10.1136/bmj.i5065

89. Korteland NM, Etnel JRG, Arabkhani B, et al. Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation. *Eur Heart J*. 2017;38(45):3370-3377. doi:10.1093/eurheartj/ehx199

90. Thyregod HGH, Jørgensen TH, Ihlemann N, et al. Transcatheter or surgical aortic valve implantation: 10-year outcomes of the NOTION trial. *Eur Heart J*. 2024;45(13):1116-1124. doi:10.1093/eurheartj/ehae043

91. Bagur R, Pibarot P, Otto CM. Importance of the valve durability-life expectancy ratio in selection of a prosthetic aortic valve. *Heart*. 2017;103(22): 1756-1759. doi:10.1136/heartjnl-2017-312348

92. Oyetunji SO, Otto CM. Transcatheter aortic valve implantation or replacement? Valve durability in the context of patient life expectancy. *Eur Heart J*. 2021;42(30):2920-2923. doi:10.1093/eurheartj/ehab393

93. Rashedi N, Otto CM. Treatment of severe aortic valve stenosis: impact of patient sex and life expectancy on treatment choice. *Eur Cardiol*. 2022; 17:e25. doi:10.15420/ecr.2022.31

94. Bourguignon T, El Khoury R, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards Perimount aortic valve in patients aged 60 or younger. *Ann Thorac Surg*. 2015;100(3):853-859. doi:10.1016/j.athoracsur.2015.03.105

95. Madhavan MV, Kodali SK, Thourani VH, et al. Outcomes of SAPIEN 3 transcatheter aortic valve replacement compared with surgical valve replacement in intermediate-risk patients. *J Am Coll Cardiol*. 2023;82(2):109-123. doi:10.1016/j.jacc.2023.04.049

96. Kaneko T, Vassileva CM, Englum B, et al. Contemporary outcomes of repeat aortic valve replacement: a benchmark for transcatheter valve-in-valve procedures. *Ann Thorac Surg*. 2015; 100(4):1298-1304. doi:10.1016/j.athoracsur.2015.04.062

97. Raschpichler M, de Waha S, Holzhey D, et al. Valve-in-valve transcatheter aortic valve replacement versus redo surgical aortic valve replacement for failed surgical aortic bioprostheses: a systematic review and meta-analysis. *J Am Heart Assoc*. 2022;11(24):e7965. doi:10.1161/JAHA.121.024848

98. Monaci C, Nair AN, Gilukara SS, et al. Clinical profiles and outcomes of prosthesis-specific infective endocarditis subsequent to transcatheter versus surgical aortic valve replacement: a systematic review and meta-analysis. *Cureus*. 2024;16(4):e59398. doi:10.7759/cureus.59398

99. Wilson WR, Gewitz M, Lockhart PB, et al; American Heart Association Young Hearts Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular and Stroke Nursing; and the Council on Quality of Care and Outcomes Research. Prevention of viridans group streptococcal infective endocarditis: a scientific statement from the American Heart Association. *Circulation*. 2021;143(20):e963-e978. doi:10.1161/CIR.0000000000000969

100. Wilson W, Taubert KA, Gewitz M, et al; American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Quality of Care and Outcomes Research Interdisciplinary Working Group; American Dental Association. Prevention of infective endocarditis: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *J Am Dent Assoc*. 2007;138(6):739-745, 747-760. doi:10.14219/jada.archive.2007.0262

101. Lindman BR, Liu Q, Cupps BP, et al. Heterogeneity of systolic dysfunction in patients with severe aortic stenosis and preserved ejection fraction. *J Card Surg*. 2017;32(8):454-461. doi:10.1111/jocs.13183

102. Siontis GCM, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J*. 2019;40(38):3143-3153. doi:10.1093/eurheartj/ehz275