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72 Aortic Valve Stenosis

BRIAN R. LINDMAN, ROBERT O. BONOW, AND CATHERINE M. OTTO

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EPIDEMIOLOGY

In population-based echocardiographic studies, 1% to 2% of persons aged 65 or older and 12% of persons 75 or older had calcific aortic stenosis (AS)[1-3] (see Chapter 90). Among those older than 75, 3.4% (95% confidence interval [CI] 1.1% to 5.7%) have severe AS.[2] The prevalence of aortic valve sclerosis without stenosis, defined as irregular thickening or calcification of the aortic valve leaflets, increases with age and ranges from 9% in populations with a mean age of 54 years to 42% in populations with a mean age of 81 years.[4] The rate of progression from aortic sclerosis to stenosis is 1.8% to 1.9% per year. With the aging of the population, the number of individuals with AS is expected to increase twofold to threefold in developed countries in the coming decades.[3]

CAUSES AND ETIOLOGY

Valvular AS has three principal causes: a congenital bicuspid valve with superimposed calcification, calcification of a normal trileaflet valve, and rheumatic disease (Fig. 72.1). In a U.S. series of 933 patients undergoing aortic valve replacement (AVR) for AS, a bicuspid valve was present in more than 50%, including two thirds of those younger than 70 years and 40% of those older than 70 (see Classic References, Roberts and Ko).

In addition, AS may result from a congenital valve stenosis manifesting in infancy or childhood. Rarely, AS is caused by severe atherosclerosis of the aorta and aortic valve; this form of AS occurs most frequently in patients with severe hypercholesterolemia and is observed in children with homozygous type II hyperlipoproteinemia. Rheumatoid involvement of the valve is a rare cause of AS and results in nodular thickening of the valve leaflets and involvement of the proximal portion of the aorta. Ochronosis with alkaptonuria is another rare cause of AS.

Fixed obstruction to left ventricular (LV) outflow also may occur above the valve (supravalvular stenosis) or below the valve (discrete subvalvular stenosis) (see Fig. 16.41). Dynamic subaortic obstruction may be caused by hypertrophic cardiomyopathy (see Chapter 54).

Calcific Aortic Valve Disease

Calcific (formerly "senile" or "degenerative") aortic valve disease affecting a congenital bicuspid or normal trileaflet valve is now the most common cause of AS in adults. Aortic sclerosis, identified by either echocardiography or computed tomography (CT), is the initial stage of calcific valve disease and, even in the absence of valve obstruction or known cardiovascular disease, is associated with an increased risk of myocardial infarction (MI) and cardiovascular and all-cause mortality.[4] Epidemiologic associations have been documented between cardiovascular risk factors and calcific aortic valve disease, suggesting that treating or preventing these risk factors may lessen the risk of developing AS (Table 72.1).[1,5] Whether better control of modifiable risk factors may slow progression of AS is unknown.[6]

Bicuspid Aortic Valve Disease

Congenital malformations of the aortic valve may be unicuspid, bicuspid, or quadricuspid, or the anomaly may manifest as a dome-shaped diaphragm (see Chapter 82). Unicuspid valves typically produce severe obstruction in infancy and are the most common malformations found in fatal valvular AS in children younger than 1 year but also may be seen in young adults with an anatomy that mimics bicuspid valve disease. A congenital bicuspid aortic valve (BAV) is present in approximately 1% to 2% of the population, with a male predominance of approximately 3:1. Reflecting an underlying but complex genetic basis, a 9% prevalence of BAV has been reported in first-degree relatives of individuals with a BAV.

A BAV may be an isolated abnormality (approximately 50% of the time) or occur in the context of a genetic syndrome (e.g., Turner syndrome), alongside other congenital heart defects (e.g., hypoplastic left heart, coarctation of the aorta), or with a thoracic aortic aneurysm (most common nonvalvular manifestation).[7] The genetic etiologies of BAV are complicated and incompletely understood; several genes appear to play a role with different patterns of inheritance. Familial inheritance is complex and increased when nonvalvular abnormalities accompany a BAV.

The most prevalent anatomy for a bicuspid valve is two cusps with a right-left systolic opening, consistent with congenital fusion of the right and left coronary cusps, seen in 70% to 80% of patients (Fig. 72.2). An anterior-posterior orientation, with fusion of the right and noncoronary cusps, is less common, seen in approximately 20% to 30% of patients. Fusion of the left and noncoronary cusps is rarely seen. A prominent ridge of tissue or raphe may be present in the larger of the two cusps so that the closed valve in diastole may mimic a trileaflet valve. Echocardiographic diagnosis relies on imaging the systolic leaflet opening with only two aortic commissures, but CT is now commonly used to identify or confirm the bicuspid morphology of the valve (Fig. 72.3).

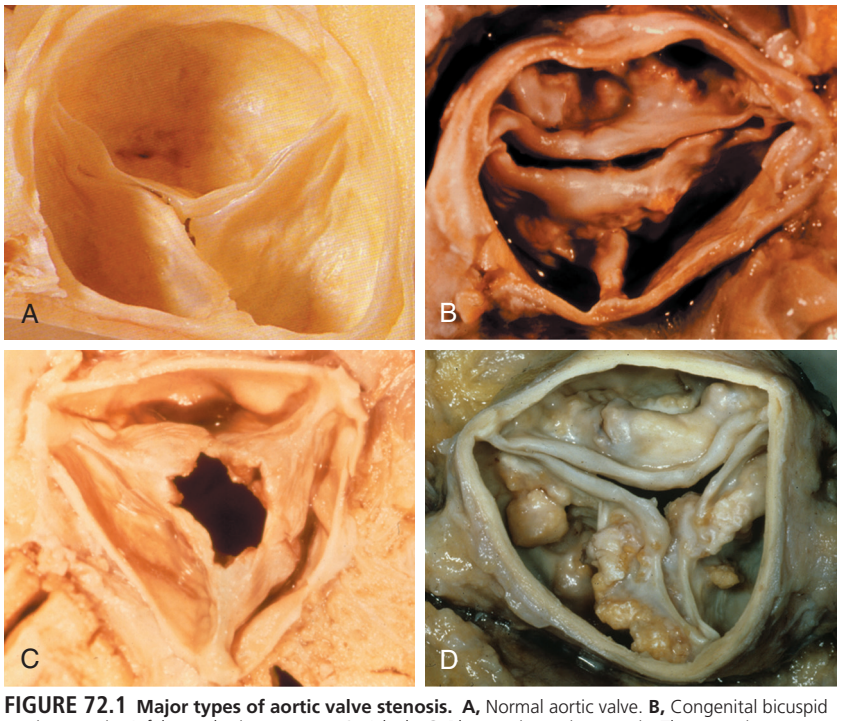


FIGURE 72.1 Major types of aortic valve stenosis. A, Normal aortic valve. **B,** Congenital bicuspid aortic stenosis. A false raphe is present at 6 o'clock. **C,** Rheumatic aortic stenosis. The commissures are fused with a fixed central orifice. **D,** Calcific aortic stenosis. (**A** from Manabe H, Yutani C, editors. *Atlas of Valvular Heart Disease.* Singapore: Churchill Livingstone; 1998:6, 131; **B-D** courtesy Dr. William C. Roberts, Baylor University Medical Center, Dallas, Tex.)

TABLE 72.1 Strength of Associations in Observational and Epidemiologic Studies of Clinical Risk Factors and Calcific Aortic Valve Disease (CAVD)

	CAVD ANALYSIS		
RISK FACTOR	CROSS-SECTIONAL	INCIDENT	PROGRESSION
Age	+++	+++	+++
Male sex	++/–	++	0
Height	++	++	0
Body mass index	++	++	0
Hypertension	++	++	0
Diabetes	+++	+++	0
Metabolic syndrome	++	++	+
Dyslipidemia	++	++	0
Smoking	++	++	+
Renal dysfunction	+	0	0
Inflammatory markers	+	0	0
Phosphorus levels	++	0	N/A
Calcium levels	0	0	N/A
Baseline calcium score	N/A	N/A	+++

+, Weak positive association; ++, modest positive association; +++, strong positive association; –, weak negative association; 0, no association seen; N/A, no/insufficient data available.
From Thanassoulis G. Clinical and genetic risk factors for calcific valve disease. In Otto CM, Bonow RO, editors. *Valvular Heart Disease: A Companion to Braunwald's Heart Disease.* 5th ed. Philadelphia: Saunders; 2021;66-78.

Unicuspid valves are distinguished from a bicuspid valve by having only one aortic commissure.

The clinical manifestations of a BAV tend to relate to the function of the aortic valve (stenosis or regurgitation), infection of the aortic valve (endocarditis), or damage to a dilated aorta related to an underlying aortopathy (dissection).[8] Often, the diagnosis is unknown until the physical examination reveals manifestations of valve dysfunction or the patient develops symptoms. The risk of aortic dissection in patients with BAV is five to nine times higher than in the general population, but the absolute risk is still quite low (see Chapter 42).[9,10]

Most bicuspid valves function normally until late in life, although a subset of patients present in childhood or adolescence with valve dysfunction. Overall, survival is no different from population estimates.[9,11] Patients with BAV also are at increased risk for endocarditis (0.4 per 100,000), accounting for approximately 1200 deaths per year in the United States. However, the most common cardiac event is need for AVR,[9] and most patients with BAV develop calcific valve stenosis later in life, typically presenting with severe AS after the age of 50 years. Although the histopathologic features of calcific stenosis of a BAV are no different from those of a trileaflet valve, the turbulent flow and increased leaflet stress caused by the abnormal architecture are postulated to result in accelerated valve changes, explaining the earlier average age at presentation in patients with a bicuspid, compared with trileaflet, stenotic valve. BAV disease accounts for greater than 50% of AVRs in the United States and is a common cause of calcific AS, even in older persons. The aortopathy associated with BAV disease often results in aortic dilation and carries an increased risk of aortic dissection. The magnitude of risk appears to vary depending on valve and aortic morphology and on a family history of aortic involvement.[12,13]

Rheumatic Aortic Stenosis

Rheumatic AS results from adhesions and fusions of the commissures and cusps and vascularization of the leaflets of the valve ring, leading to retraction and stiffening of the free borders of the cusps. Calcific nodules develop on both surfaces, and the orifice is reduced to a small, round or triangular opening (see Fig. 72.1C). As a consequence, the rheumatic valve often is regurgitant as well as stenotic. Patients with rheumatic AS invariably have rheumatic involvement of the mitral valve (see Chapter 81). With the decline in rheumatic fever in developed nations, rheumatic AS is decreasing in frequency, although it continues to be a major problem on a worldwide basis.

PATHOPHYSIOLOGY

Valve Calcification and Obstruction

Although calcific AS once was considered to represent the result of years of normal mechanical stress on an otherwise normal valve ("wear and tear"), it is now clear that active biological processes underlies the initiation and progression of calcific aortic valve disease (Fig. 72.4).[1,14-16] Differences in the biology driving the early versus later stages of calcific aortic valve disease could have important implications for medical therapies aimed at preventing, slowing, or reversing the path from aortic sclerosis to severe stenosis, both in terms of which pathways are relevant to target and when along the disease spectrum drugs targeting them are most likely to be effective.[15-17]

Normal valve leaflets comprise the fibrosa (facing the aorta), ventricularis (facing the ventricle), and spongiosa (located between the fibrosa and ventricularis). *Valve interstitial cells* (VICs) are the most predominant cell type; endothelial and smooth muscle cells are also present. Through a complex interplay of molecular events, the pliable, flexible valve becomes stiff and immobile, characterized grossly by fibrosis and calcification. The process is initiated by lipid infiltration and oxidative stress, which attract and activate inflammatory cells and promote the elaboration of cytokines (Fig. 72.5).[1] VICs undergo osteogenic reprogramming that promotes the mineralization of the extracellular matrix and the progression of fibrocalcific remodeling of the valve.

In addition to the genetic underpinnings of BAV, there is evidence indicating a genetic predisposition to valve calcification.[18] Genetic polymorphisms have been linked to the presence of calcific AS, including

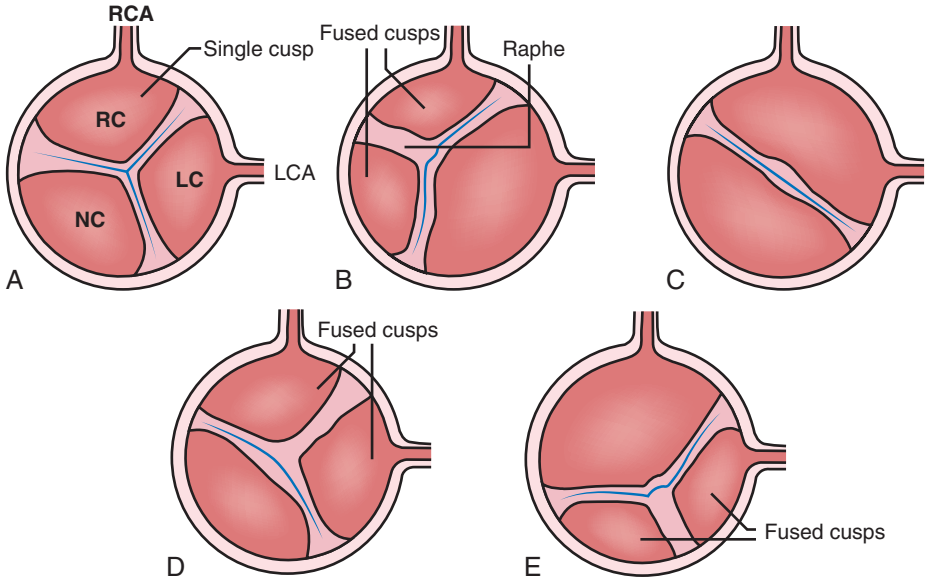


FIGURE 72.2 Comparison of tricuspid and bicuspid aortic valve structures. A, Schematic representation of a normal tricuspid aortic valve with the three cusps. *LC,* Left coronary; *LCA,* left coronary artery; *NC,* noncoronary; *RC,* right coronary; *RCA,* right coronary artery. **B,** Bicuspid valve with right noncoronary cusp fusion and one raphe (the line of union between the fused cusps). **C,** Bicuspid valve with fusion of the right and left coronary cusps and no raphe. **D,** Bicuspid valve with right-left coronary cusp fusion and one raphe. **E,** Bicuspid valve with fusion of the left and noncoronary cusps and one raphe. (From Lindman BR, et al. Calcific aortic stenosis. *Nat Rev Dis Primers.* 2016;2:16006.)

those involving the vitamin D receptor, interleukin (IL)-10 alleles, estrogen receptor, transforming growth factor (TGF)-β receptor, and the apolipoprotein E4 allele.[18] The most consistently observed genetic association is for lipoprotein(a) (Lp(a)). In a genome-wide association study (GWAS) based on a meta-analysis of data on nearly 7000 patients from three population-based cohorts, a single-nucleotide polymorphism (SNP) in Lp(a) was associated with aortic valve calcification, serum Lp(a) levels, and incident AS (hazard ratio [HR], 1.68; CI 1.32 to 2.15).[19] This association has been confirmed in several other cohorts.[20-22] Recent evidence suggests a potential link between Lp(a) and AS through lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ENPP2), also known as *autotaxin.*[23-27] Lp(a) transports both Lp-PLA_2 and autotaxin, and each of these is found in increased abundance in stenotic aortic valves.[25,26] Lp-PLA_2 transforms oxidized phospholipids species into lysophosphatidylcholine (lysoPC); in turn, autotaxin transforms lysoPC into lysophosphatidic acid (lysoPA), which appears to play a role in the osteogenic reprogramming of VICs.[26,27]

Key regulators of osteogenesis, including *BMP2* and *RUNX2,* are under the control of *NOTCH1*. Expression of BMP2 and RUNX2 are increased in diseased aortic valves. Heritable forms of calcific aortic valve disease have been linked to *NOTCH1* mutations; more recently, a role for NOTCH1 in idiopathic forms of calcific aortic valve disease was discovered.[28,29] Hypomethylation of the promoter region of long noncoding RNA *H19* led to overexpression of *H19,* which was associated with mineralized aortic valves and upregulation of *BMP2* and *RUNX2*. This was shown to be mediated by repression of *NOTCH1* as a result of *H19* preventing recruitment of p53 to the *NOTCH1* promoter. Subsequent investigations showed that cadherin 11 (*CDH11*), which is enriched in diseased aortic valves and overexpressed in VICs from *Notch1*$^{+/-}$ mice, mediates *NOTCH1*-induced calcific aortic valve disease.[30] The roles of DNA methylation and noncoding RNAs in the pathophysiology of calcific aortic valve disease have been reviewed.[31] Despite progress in elucidating pathobiology, there is no medical therapy for calcific aortic valve disease, but several potentially promising therapeutic targets have been reviewed.[15,17,32]

Over time, progressive fibrocalcific remodeling of the aortic valve leaflets makes them less pliable and obstruction to flow out of the left ventricle develops and increases. This yields a chronic pressure overload state that leads to myocardial remodeling and dysfunction and accompanying changes in the pulmonary and systemic vasculature.

Left Ventricular Response: Structure and Function

Progressive valve obstruction imposes a chronic pressure overload state that leads to numerous changes in the structure and function of the left ventricle and accompanying changes in the pulmonary and systemic vasculature.[33-35]

Hypertrophic Myocardial Remodeling. Maintenance of cardiac output in the face of an obstructed aortic valve imposes a chronic increase in LV pressure. In response, the ventricle typically undergoes hypertrophic remodeling characterized by myocyte hypertrophy and increased wall thickness (Fig. 72.6). LV remodeling may manifest as concentric remodeling, concentric hypertrophy, or eccentric hypertrophy. Based on the LaPlace law, LV remodeling reduces wall stress (afterload) and is considered one of the important compensatory mechanisms to maintain LV ejection performance, which is directly affected by afterload (see Classic References, Grossman).

Cardiac hypertrophy in response to pressure overload involves both adaptive and maladaptive processes.[36] Hypertrophic remodeling is not simply related to increased valvular afterload; several factors other than the severity of valve obstruction influence it, including sex, genetics, vascular load, and metabolic abnormalities.[37,38] Additionally, the degree to which LV hypertrophic remodeling is maladaptive versus adaptive and the resulting functional and clinical effects are not simply an issue of total LV mass and geometry; composition and energetics of the myocardium also are important.[36] Preclinical studies have demonstrated that blocking the hypertrophic response to pressure overload did not have deleterious effects on LV performance despite increased wall stress (see Classic References, Hill).

In patients with AS, several studies have now documented that increased LV hypertrophic remodeling is associated with more severe ventricular dysfunction and heart failure (HF) symptoms, as well as higher mortality.[39] In a recent study combining the largest patient numbers with the longest clinical follow-up to date, increased LV mass index before transcatheter aortic valve replacement (TAVR), particularly severe LV hypertrophy (LVH) was associated with increased mortality and rehospitalization over 5 years after the procedure.[40] Related to this, among patients with moderate or severe LVH treated with TAVR, greater LV mass index regression at 1 year is independently associated with lower death and rehospitalization rates out to 5 years.[41] Among those with moderate or severe LVH before TAVR, 39% still had severe LVH at 1 year and this degree of residual LVH was associated with a marked increase in subsequent mortality and rehospitalization rates.[41] Thus, although it may reduce wall stress, LV hypertrophic remodeling also may have longer-term deleterious effects that translate into impaired ventricular performance and worse clinical outcomes.

Myocardial Fibrosis. Although not routinely assessed in clinical practice, myocardial fibrosis is now well established as a risk factor for adverse clinical outcomes in patients with AS.[34,42-44] As a part of the hypertrophic remodeling process, diffuse and replacement myocardial fibrosis (not fibrosis from prior MI) may develop (see Chapter 19), although the incidence and extent of fibrosis are variable and unpredictable and the underlying biologic mechanisms not yet clarified (Fig. 72.7; see also Fig 72.6).[42,43,45] Diffuse fibrosis tends to regress after AVR, whereas replacement fibrosis does not.[34,45-47] Both the amount of diffuse fibrosis and the presence of replacement fibrosis are associated with subsequent mortality (Fig. 72.8).[34,42-44] Importantly, patients with severe fibrosis, despite a normal LV ejection fraction (LVEF), are more likely to have worse preoperative HF symptoms and less likely to experience improvement in symptoms midterm after AVR, compared to those with no or minimal fibrosis before valve replacement.[48]

Myocardial Ischemia. In patients with AS, the hypertrophied left ventricle, increased systolic pressure, and prolongation of ejection all elevate myocardial oxygen (O_2) consumption.[49] At the same time, even in the absence of epicardial coronary artery disease (CAD), decreased myocardial capillary density in the hypertrophied ventricle, endothelial cell loss, increased LV end-diastolic pressure (LVEDP), and a shortened diastole all serve to decrease the coronary perfusion pressure gradient and myocardial blood flow (see Chapter 36). Together, these conditions create an imbalance between myocardial O_2 supply and demand, yielding ischemia. Impaired myocardial flow reserve underlies symptoms of angina in patients with AS that is often indistinguishable from that caused by epicardial coronary obstruction.[50] Exercise or other states of increased O_2 demand may exacerbate this ischemic imbalance and

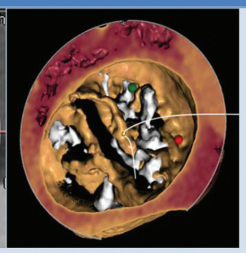
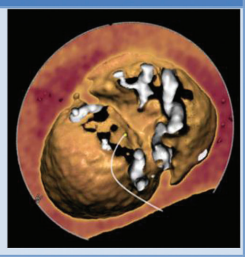
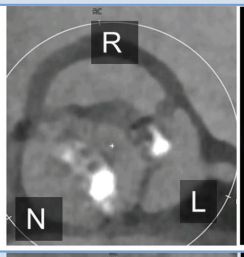
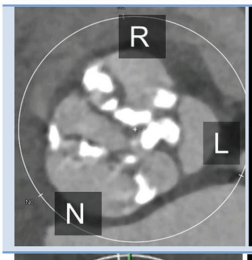
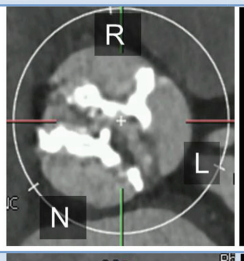
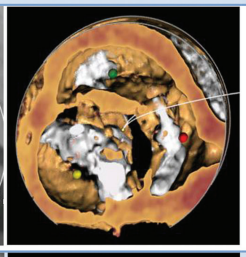
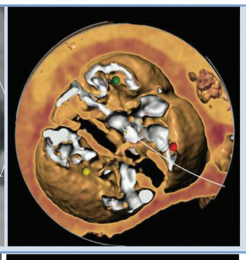
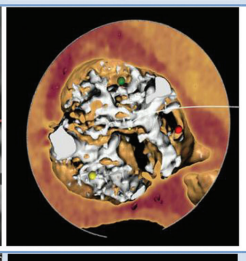
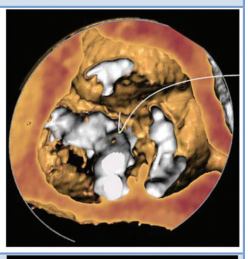
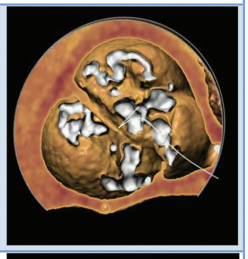
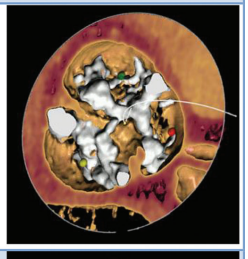
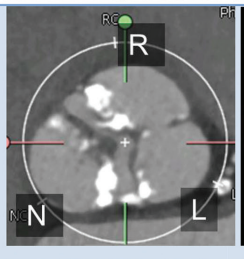
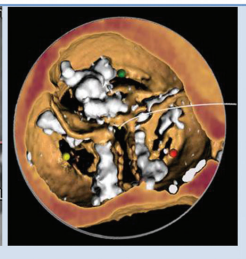
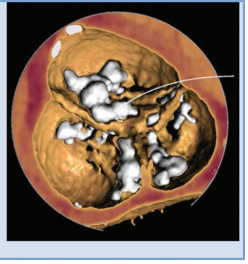
Classification	Characteristics	Double oblique transverse MPR	Volume-rendered en face view systole	Volume-rendered en face view diastole
Sievers Type 0/ bicommissural non–raphe type	• Two fairly symmetric cusps and two commissures • Each cusp has one most basal insertion point; thus there is a total of two most basal insertion points			
Sievers Type 1/ bicommissural raphe type	• Two of three cusps are conjoined by a raphe • Asymmetric cusp sizes with the cusp opposing the raphe (i.e., cusp not participating in raphe formation) being larger than in a tricuspid aortic valve • Raphe does not extend to the level of the STJ, which is the distinguishing characteristic compared to a non-opening commissure • Size of raphe and degree of calcification can vary *Upper row*: non-calcified raphe *Middle row*: Moderately calcified raphe *Lower row*: Severely calcified raphe	  	  	  
Acquired/ functional bicuspid valve (underlying tricuspid anatomy)	• Underlying tricuspid anatomy with symmetric sinus of Valsalva • Non-opening commissure due to degenerative changes (here RL commissure) • Non-opening commissure reaches STJ, which is the distinguishing factor compared to a raphe			

FIGURE 72.3 Differing morphologies and calcification patterns of bicuspid aortic valves by cardiac CT. *STJ,* Sinotubular junction. (From Blanke P, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). *JACC Cardiovasc Imaging.* 2019;12:1-24.)

provoke angina that may not be experienced at rest. Myocardial flow reserve is independently associated with aerobic exercise capacity and HF functional class in severe AS and appears to be influenced by the extent of LV hypertrophic remodeling and fibrosis, endothelial cell loss, and severity of valve obstruction.[51,52]

Left Ventricular Diastolic Function. Hypertrophic remodeling also impairs diastolic myocardial relaxation and increases stiffness, as modulated by cardiovascular and metabolic comorbidities.[53] Higher cardiomyocyte stiffness, increased myocardial fibrosis, advanced-glycation end products, and metabolic abnormalities each contribute to increased chamber stiffness and higher end-diastolic pressures.[43] Atrial contraction plays a particularly important role in filling of the left ventricle in AS because it increases LVEDP without causing a concomitant elevation of mean left atrial pressure. This "booster pump" function of the left atrium prevents the pulmonary venous and capillary pressures from rising to levels that would produce pulmonary congestion, while maintaining LVEDP at the elevated level necessary for effective contraction of the hypertrophied left ventricle. Loss of appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular (AV) dissociation, may result in rapid clinical deterioration in patients with severe AS. After relief of the pressure overload with AVR, diastolic dysfunction may revert toward normal with regression of hypertrophy, but some degree of long-term diastolic dysfunction typically persists.[53,54] Worse diastolic function before AVR and worse residual diastolic dysfunction after AVR have been associated with worse long-term outcomes.[53,54] The severity of diastolic dysfunction may also influence the clinical consequences of aortic regurgitation (AR) after TAVR.[55]

Left Ventricular Systolic Function. LV systolic function, as measured by the LVEF, generally remains preserved until late in the disease process in most patients with AS, but emerging data indicate that ejection fraction (EF) may begin to decline in patients before AS is considered severe.[1,56] What characterizes a "normal" or "preserved" EF in the setting of AS is not clear. Traditionally, it has been characterized as an EF 50% or greater, but accumulating evidence indicates that an EF <60% is associated with poor post-AVR outcomes, suggesting that the threshold indicative of impaired/

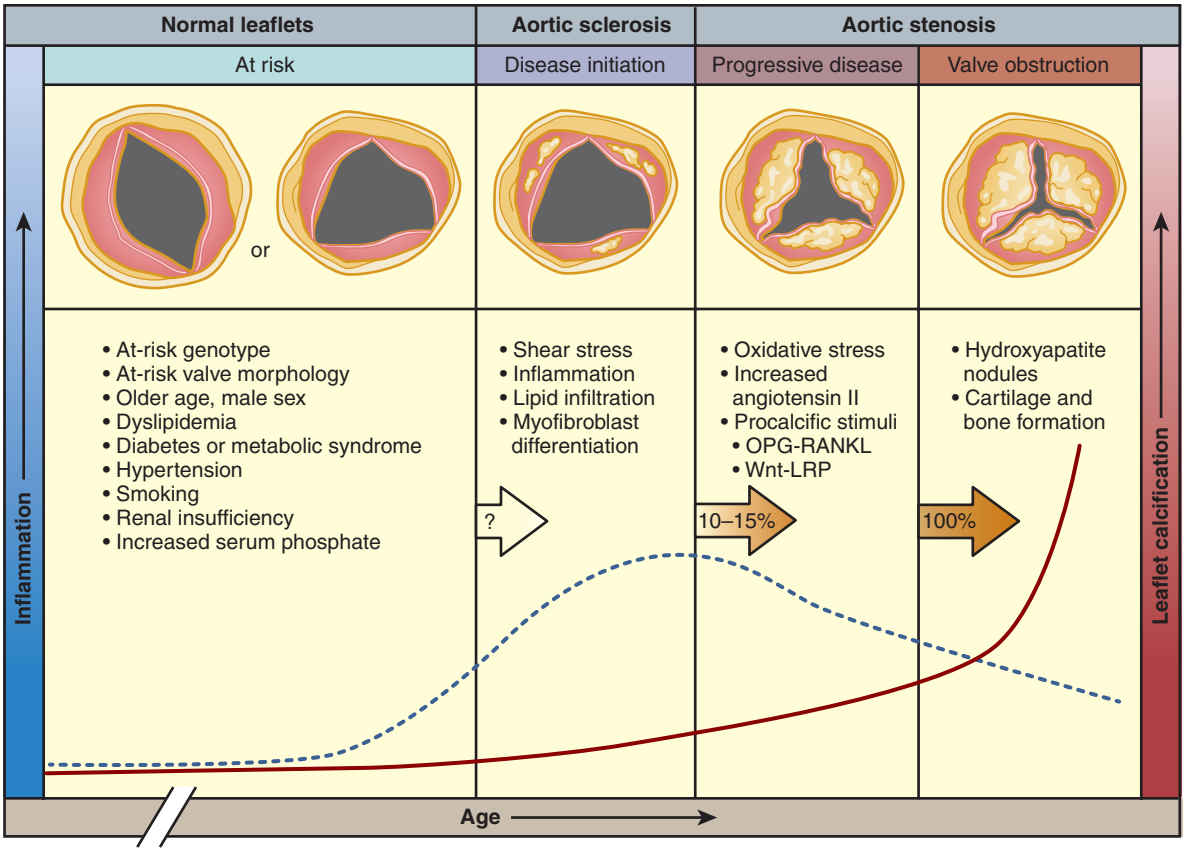


FIGURE 72.4 Disease mechanisms and time course of calcific aortic stenosis (AS): relationship among disease stage, valve anatomy, clinical risk factors, mechanisms of disease, and patient's age. Endothelial disruption with inflammation (*dashed line*) and lipid infiltration are key elements in the initiation of disease. There are few data on the prevalence of disease initiation in at-risk patients, and progressive disease develops in only a subgroup of these patients. Progressive leaflet disease, which is associated with several disease pathways, develops in approximately 10% to 15% of patients with AS. Once these disease mechanisms are activated, leaflet calcification results in severe AS in almost all patients. With end-stage disease, tissue calcification (*red line*) is the predominant tissue change, resulting in valve obstruction. Current imaging approaches are reliable only when substantial leaflet changes are present (in patients with progressive disease or valve obstruction), which limits clinical studies of interventions to prevent or slow the progression of early disease. *LRP,* Lipoprotein receptor–related protein complex; *OPG,* osteoprotegerin; *RANKL,* receptor activator of nuclear factor-κB ligand. (From Otto CM, Prendergast B. Aortic-valve stenosis: from patients at risk to severe valve obstruction. *N Engl J Med.* 2014;371:744-756.)

reduced EF in the setting of AS may need to be changed.[57-61] Before a reduction in EF occurs, more subtle systolic dysfunction can be detected as reduced longitudinal systolic strain, which is associated with worse outcomes in patients with severe AS[59,62] (see Chapter 16). The development and severity of systolic dysfunction results from a complex interplay of factors, including the severity of valve obstruction, metabolic abnormalities, vascular load, maladaptive hypertrophy (resulting in impaired contractility), ischemia, and fibrosis.[1,38,45] Eventually, a subset of patients develops overt systolic dysfunction manifested by a reduced LVEF. In these patients, systolic function usually improves after the ventricle is unloaded by AVR; the amount of recovery depends on many factors, including the degree to which systolic dysfunction was affected by afterload mismatch versus myocardial fibrosis and altered contractility.[63-65]

Pulmonary and Systemic Vasculature Response

The hypertrophied and pressure-overloaded left ventricle transmits increased pressure to the pulmonary vasculature, which leads to pulmonary hypertension in many patients with AS, becoming severe in 15% to 20%. Although patients may initially manifest pulmonary venous hypertension alone, some will go on to develop increased pulmonary vascular resistance, perhaps influenced by specific comorbidities and chronicity of pulmonary venous hypertension.[66-68] Among asymptomatic patients, exercise-induced pulmonary hypertension is associated with decreased event-free survival, and among patients undergoing TAVR or surgical AVR (SAVR), the presence and severity of pulmonary hypertension is associated with increased postoperative mortality.[67,68] Elevated pulmonary artery pressures decrease in some patients after AVR, but not all; residual pulmonary hypertension is associated with worse clinical outcomes.[69,70]

The systemic vasculature also makes an important contribution to total LV afterload.[33,66,71-73] Hemodynamic studies with agents that dilate the systemic vasculature show an acute increase in LV stroke volume, underscoring that changes in vascular properties can unload the left ventricle despite no change in the valvular obstruction[66,74] (see also Classic References, Khot). Measures of increased vascular load, including arterial stiffness, global load (integrating both valvular and vascular load), and systolic blood pressure, have been associated with adverse LV remodeling, impaired LV function, and worse clinical outcomes.[72,75] In patients with AS, characterization of systemic vascular properties is conditioned by upstream obstruction; valve replacement unmasks and induces stiffer vascular behavior (Fig. 72.9).[71] Accordingly, in patients with AS, the load on the LV is a combined load at the valvular and vascular level; increased vascular load may identify patients who benefit less from AVR and may be a target for adjunctive medical therapy to optimize outcomes.

CLINICAL PRESENTATION

The diagnosis of AS is most often made on auscultation of a murmur suggestive of AS, followed by confirmation with echocardiography. When AS is not severe and symptoms are absent, patients are reevaluated clinically and with echocardiography based on the AS severity. Generally, repeat imaging is performed every 6 to 12 months for severe AS, every 1 to 2 years for moderate AS, and every 3 to 5 years for mild AS, unless a change in signs or symptoms prompts repeat imaging sooner.[57]

Symptoms

The cardinal manifestations of acquired AS are exertional dyspnea, angina, syncope, and ultimately HF.[1,14] Many patients are diagnosed

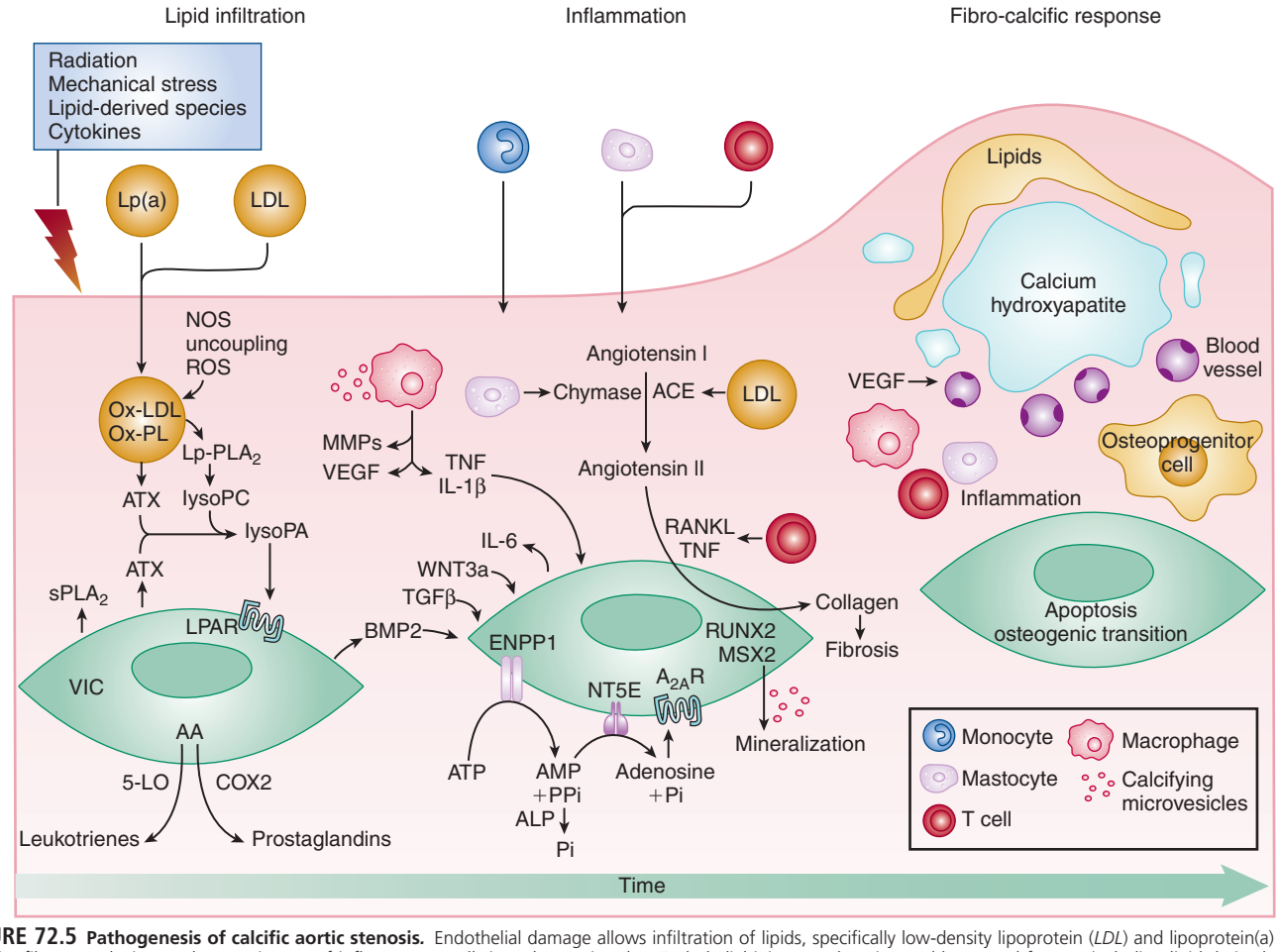


FIGURE 72.5 Pathogenesis of calcific aortic stenosis. Endothelial damage allows infiltration of lipids, specifically low-density lipoprotein (*LDL*) and lipoprotein(a) [*Lp(a)*], into the fibrosa and triggers the recruitment of inflammatory cells into the aortic valve. Endothelial injury can be triggered by several factors, including lipid-derived species, cytokines, mechanical stress, and radiation injury. The production of reactive oxygen species (*ROS*) is promoted by the uncoupling of nitric oxide synthase (*NOS*), which increases the oxidation of lipids and further intensifies the secretion of cytokines. Enzymes transported in the aortic valve by lipoproteins (i.e., LDL, Lp[a]) such as lipoprotein-associated phospholipase A_2 (*Lp-PLA*$_2$) and ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), also known as autotoxin (*ATX*), produce lysophospholipid derivatives. ATX, which is also secreted by valve interstitial cells (*VICs*), transforms lysophosphatidylcholine (*lysoPC*) into lysophosphatidic acid (*lysoPA*). Several factors, including lysoPA, the receptor activator of nuclear factor-κB ligand (*RANKL;* also known as TNFSF11), and WNT3a, promote the osteogenic transition of VIC. Arachidonic acid (*AA*) generated by cytosolic PLA_2 promotes the production of eicosanoids such as prostaglandins and leukotrienes through prostaglandin G/H synthase 2 (PTGS2; also known as cyclooxygenase 2 [*COX2*]) and 5-lipoxygenase (*5-LO*) pathways, respectively. In turn, eicosanoids promote inflammation and mineralization. Chymase and angiotensin-converting enzyme (*ACE*) promote production of angiotensin II, which increases synthesis and secretion of collagen by VIC. Because of increased production of matrix metalloproteinases (*MMPs*) and decreased synthesis of tissue inhibitors of metalloproteinases (TIMPs), disorganized fibrous tissue accumulates within the aortic valve. Microcalcification begins early in the disease, driven by microvesicles secreted by VIC and macrophages. In addition, overexpression of ectonucleotidases—ENPP1, 5′-nucleotidase ecto (*NT5E*), and alkaline phosphatase (*ALP*)—promotes both apoptosis and osteogenic-mediated mineralization. Bone morphogenetic protein 2 (*BMP2*) leads to osteogenic transdifferentiation, which is associated with the expression of bone-related transcription factors (e.g., runt-related transcription factor 2 [*RUNX2*] and homeobox protein MSX2). Osteoblast-like cells subsequently coordinate calcification of the aortic valve as part of a highly regulated process analogous to skeletal bone formation. Deposition of mineralized matrix is accompanied by fibrosis and neovascularization, which is abetted by vascular endothelial growth factor (*VEGF*). In turn, neovascularization increases the recruitment of inflammatory cells and bone marrow–derived osteoprogenitor cells. *$A_{2A}R$,* Adenosine A_{2A} receptor; *$sPLA_2$,* secreted phospholipase A_2; *LPAR,* lysophosphatidic acid receptor; *Ox-PL,* oxidized phospholipid; *Ox-LDL,* oxidized LDL; *TGFβ,* transforming growth factor beta; *TNF,* tumor necrosis factor. (From Lindman BR, et al. Calcific aortic stenosis. *Nat Rev Dis Primers*. 2016;2:16006.)

before symptom onset on the basis of the finding of a systolic murmur on physical examination, with confirmation of the diagnosis by echocardiography. Symptoms can develop at any age but typically begin at age 50 to 70 years with BAV stenosis and in those older than 70 with calcific stenosis of a trileaflet valve, although even in this age group approximately 40% of patients with AS have a congenital BAV (see Classic References, Roberts and Ko).

The most common clinical presentation in patients with a known diagnosis of AS who are followed prospectively is a gradual decrease in exercise tolerance, fatigue, or dyspnea on exertion. However, in some cases, symptom onset can be more abrupt and severe.[76] The mechanism of exertional dyspnea may be LV diastolic dysfunction, with an excessive rise in end-diastolic pressure leading to pulmonary congestion. Alternatively, exertional symptoms may be a result of the limited ability to increase cardiac output with exercise. More severe exertional dyspnea, with orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema are relatively late symptoms in patients with AS; in current practice, intervention typically is undertaken before this disease stage.

Angina is a frequent symptom of patients with severe AS, indicates myocardial ischemia, and usually resembles the angina observed in patients with CAD in that it is usually precipitated by exertion and relieved by rest (see Chapters 35 and 40). In patients without CAD, angina results from the combination of the increased O_2 needs of hypertrophied myocardium and reduction of O_2 delivery due to decreased myocardial capillary density, endothelial cell loss, and increased LVEDP, which reduce the coronary perfusion pressure gradient and impair myocardial flow reserve. In patients with CAD, angina is caused by a combination of epicardial coronary artery obstruction and the O_2 imbalance characteristic of AS. Very rarely, angina results from calcific emboli to the coronary vascular bed.

Syncope most often is caused by the reduced cerebral perfusion that occurs during exertion when arterial pressure declines because of systemic vasodilation and an inadequate increase in cardiac output related to valvular stenosis. Syncope also has been attributed to malfunction of the baroreceptor mechanism in severe AS (see Chapter 102), as well as to a vasodepressor response to a greatly elevated LV systolic pressure during exercise. Premonitory symptoms of syncope are common. Exertional hypotension also may be manifested as "graying-out spells" or dizziness on effort. Syncope at rest may be caused by transient AF with loss of the atrial contribution to LV filling,

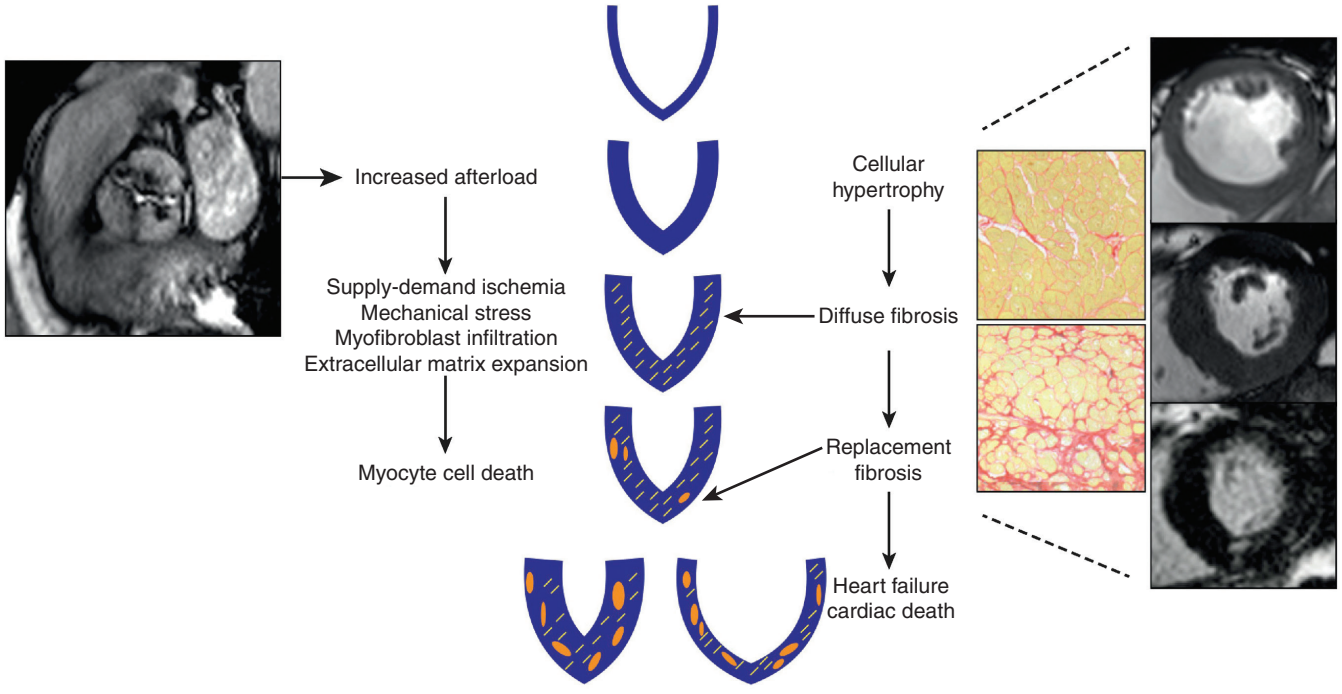


FIGURE 72.6 Hypertrophic remodeling in response to pressure overload from aortic stenosis. (From Bing R, et al. Imaging and impact of myocardial fibrosis in aortic stenosis. *JACC Cardiovasc Imaging.* 2019;12:283-296.)

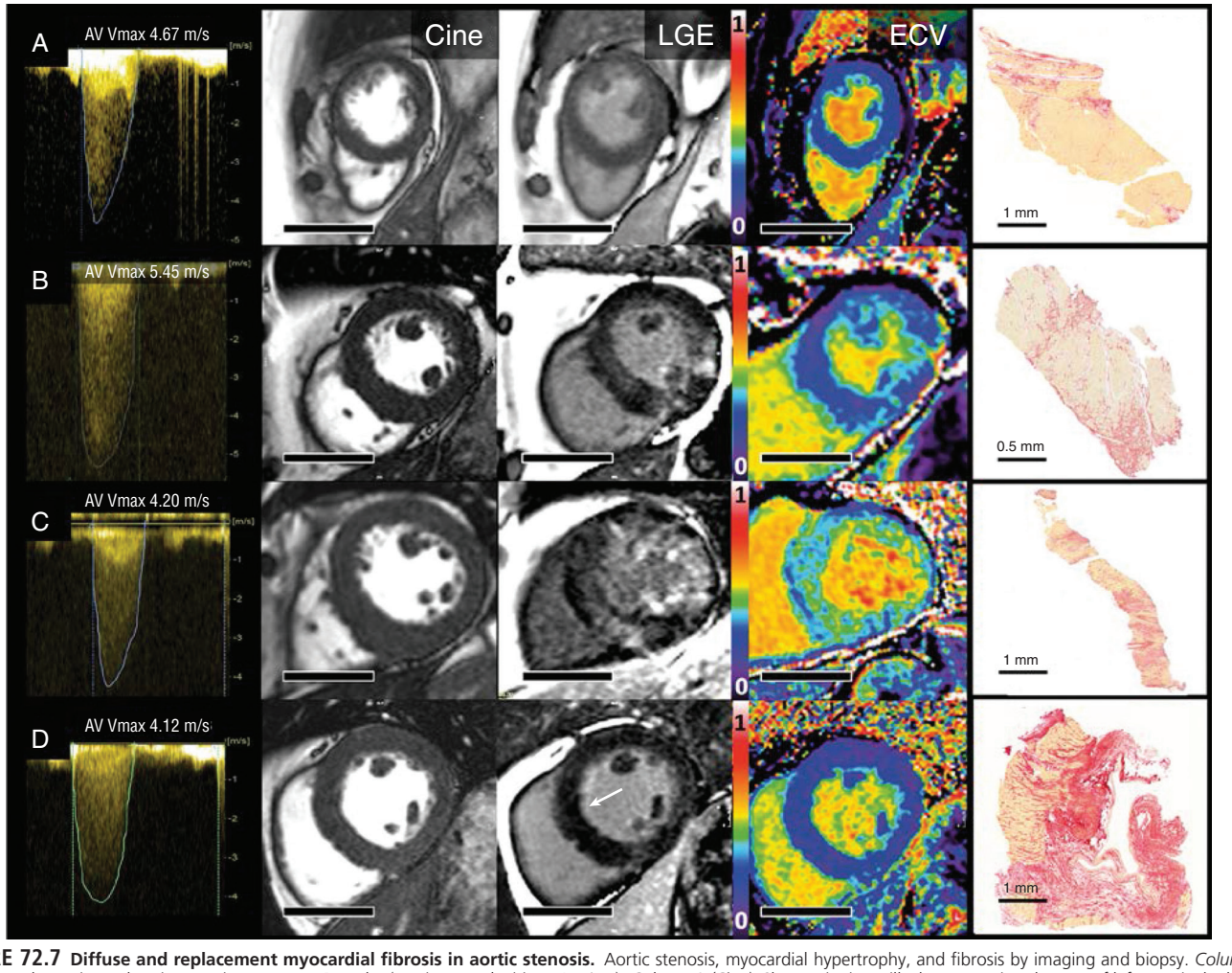


FIGURE 72.7 Diffuse and replacement myocardial fibrosis in aortic stenosis. Aortic stenosis, myocardial hypertrophy, and fibrosis by imaging and biopsy. *Column 1*, Four exemplar patients showing continuous-wave Doppler (maximum velocities >4 m/sec). *Column 2 (Cine),* Short-axis cine stills demonstrating degrees of left ventricular hypertrophy. *Column 3 (LGE),* Matching late gadolinium enhancement images. *Column 4 (ECV),* Matching extracellular volume fraction. *Column 5,* Myocardial biopsy sample stained with picrosirius red (collagen volume fraction [CVF]). Patient **A** has minimal left ventricular hypertrophy [LVH], no LGE, an ECV of 28.4% and minimal biopsy subendocardial fibrosis (CVF 4.6%). Patient **B** has concentric LVH, patchy noninfarct LGE, an ECV of 29.9%, and moderate biopsy fibrosis (CVF 19.3%). Patient **C** has concentric LVH, widespread noninfarct LGE, an ECV of 36.5%, and severe biopsy fibrosis (CVF 24.5%). Patient **D** has mild concentric LVH, subtle subendocardial LGE (*arrow*), an ECV of 24.5%, thickened endocardium, and subendocardial scarring. Scale bars (columns 2–4) equal 5 cm. (From Treibel TA, et al. Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients. *Eur Heart J.* 2018;39:699-709.)

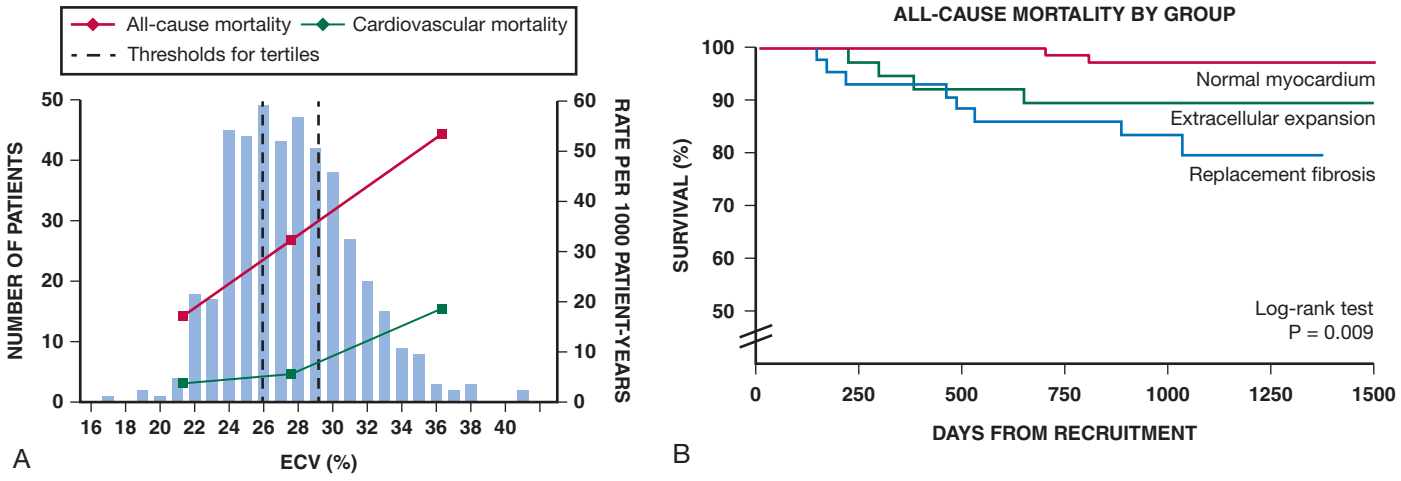


FIGURE 72.8 Myocardial fibrosis and mortality in aortic stenosis. A, Frequency distribution of magnitude of extracellular volume fraction (ECV, expressed as percent of left ventricular myocardium) in patients with aortic stenosis, and association of ECV with all-cause and cardiovascular mortality. **B,** Survival in subgroups of patients with AS defined by normal myocardium, extracellular expansion, and replacement fibrosis. (**A** from Everett RJ, et al. Extracellular myocardial volume in patients with aortic stenosis. *J Am Coll Cardiol.* 2020;75:304-316. **B** from Chin CWL, et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC Cardiovasc Imaging.* 2017;10:1320-1333.)

which causes a precipitous decline in cardiac output, or to transient AV block caused by extension of the calcification of the valve into the conduction system.

Gastrointestinal bleeding may develop in patients with severe AS, often associated with angiodysplasia (most frequently of the right colon) or other vascular malformations. This complication arises from shear stress–induced platelet aggregation with a reduction in high-molecular-weight multimers of von Willebrand factor and increases in proteolytic subunit fragments.[77] These abnormalities correlate with the severity of AS and are correctable by AVR.

An increased risk of infective endocarditis has been documented in patients with aortic valve disease, particularly in younger patients with a BAV (see Chapter 80). Cerebral emboli resulting in stroke or transient ischemic attacks may be caused by microthrombi on thickened BAVs. Calcific AS rarely may cause embolization of calcium to various organs, including the heart, kidneys, and brain.

Physical Examination

The key features of the physical examination in patients with AS are palpation of the carotid upstroke, evaluation of the systolic murmur, assessment of splitting of the second heart sound (S_2), and examination for signs of HF (see Chapters 13 and 49).

The carotid upstroke directly reflects the arterial pressure waveform. The expected finding with severe AS is a slow-rising, late-peaking, low-amplitude carotid pulse, the *parvus and tardus* carotid impulse. When present, this finding is specific for severe AS. However, many adults with AS have concurrent conditions, such as AR or systemic hypertension, that affect the arterial pressure curve and the carotid impulse. Thus, an apparently normal carotid impulse is not reliable for excluding the diagnosis of severe AS. In addition, with severe AS, radiation of the murmur to the carotid arteries may result in a palpable thrill or carotid shudder.

Auscultation

Overall, auscultation has relatively poor sensitivity and specificity for detecting AS, even among cardiologists.[78] The ejection systolic murmur of AS typically is late-peaking and heard best at the base of the heart, with radiation to the carotids. Cessation of the murmur before A_2 is helpful in differentiation from a pansystolic mitral murmur. In patients with calcified aortic valves, the systolic murmur is loudest at the base of the heart, but high-frequency components may radiate to the apex—the so-called *Gallavardin phenomenon,* in which the murmur may be so prominent that it is mistaken for the murmur of mitral regurgitation (MR). In general, a louder and later-peaking murmur indicates more severe stenosis. However, although a systolic murmur of grade 3 intensity or greater is relatively specific for severe AS, this finding is insensitive, and many patients with severe AS have only a grade 2 murmur. When the left ventricle fails and stroke volume falls, the systolic murmur of AS becomes softer; rarely, it disappears altogether.

Splitting of S_2 is helpful in excluding the diagnosis of severe AS, because normal splitting implies the aortic valve leaflets are flexible enough to create an audible closing sound (A_2). With severe AS, S_2 may be single because (1) calcification and immobility of the aortic valve make A_2 inaudible, (2) closure of the pulmonic valve (P_2) is buried in the prolonged aortic ejection murmur, or (3) prolongation of LV systole makes A_2 coincide with P_2. The intensity of the systolic murmur varies from beat to beat when the duration of diastolic filling varies, as in AF or after a premature contraction. This characteristic is helpful in differentiating AS from MR, in which the murmur usually is unaffected. The murmur of valvular AS is augmented by squatting, which increases stroke volume. It is reduced in intensity during the strain of the Valsalva maneuver and on standing, both of which reduce transvalvular flow.

Diagnostic Testing

Echocardiography

Echocardiography is the standard approach for evaluating and following patients with AS and selecting them for valve replacement (see Chapter 16). Echocardiographic imaging allows for characterization of valve anatomy, including the cause of AS (see Fig. 16.40), a qualitative impression of valve calcification (see Fig. 16.42), and sometimes allows direct imaging of the orifice area using three-dimensional imaging.[78] Echocardiographic imaging is also invaluable for the evaluation of LVH and systolic function, with calculation of EF, measurement of aortic sinus dimensions, and detection of associated AR and mitral valve disease. Longitudinal systolic strain imaging has emerged as a more sensitive measure of LV function and predicts adverse clinical events, including mortality.[59,62]

Doppler echocardiography allows measurement of indices to determine the severity of AS, including peak transvalvular jet velocity (which is used to calculate the peak transvalvular pressure gradient with the modified Bernoulli equation), mean transvalvular pressure gradient, and aortic valve area (AVA) (calculated using the continuity equation) (Fig 72.10).[79,80] Both AVA and pressure gradient calculations from Doppler data have been well validated compared with invasive

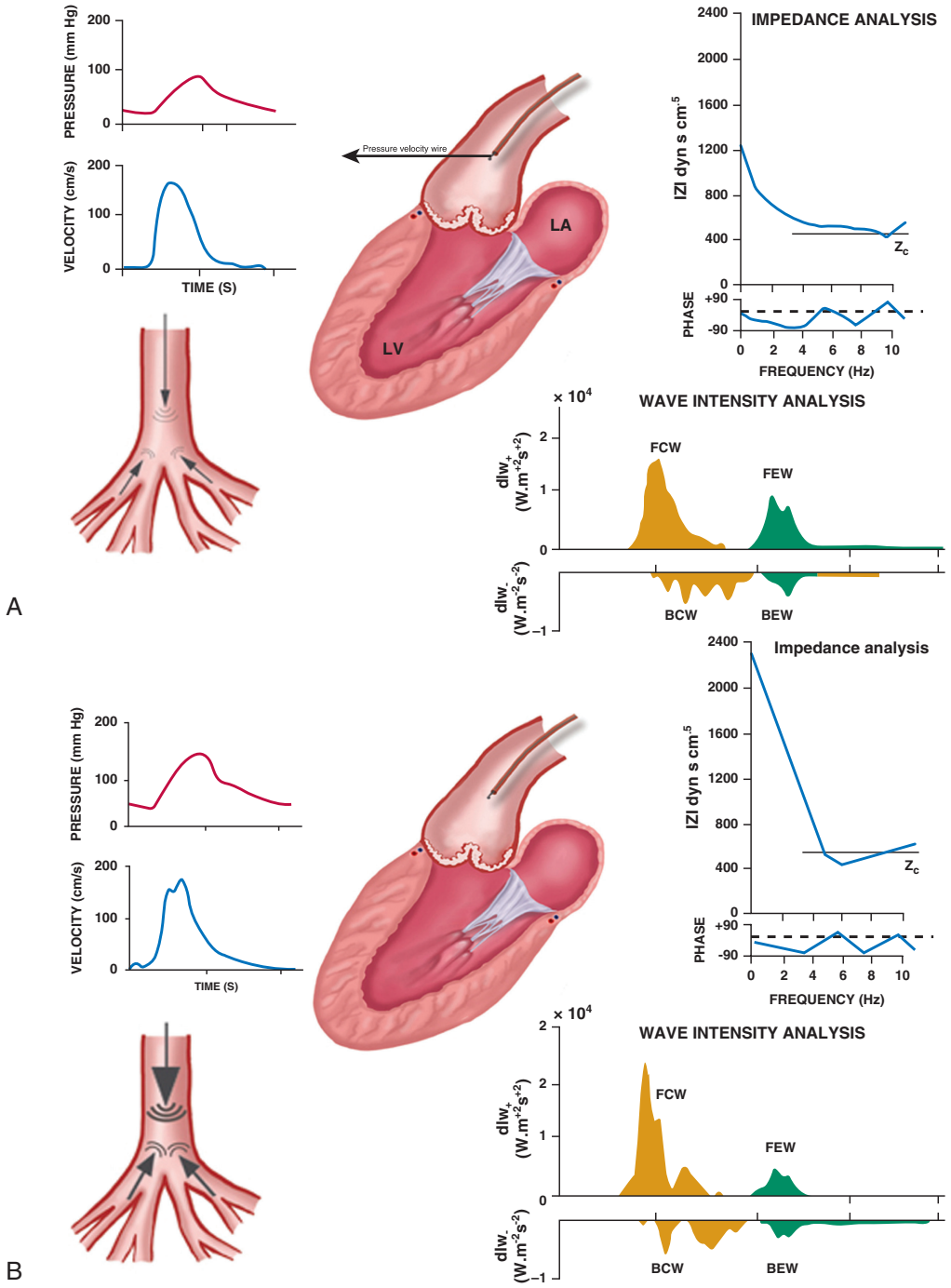


FIGURE 72.9 Aortic impedance and wave intensity analysis are shown in a patient before (A) and after (B) transcatheter aortic valve replacement (TAVR). Aortic systolic and pulse pressures increased after TAVR. Fourier decomposition of the simultaneous aortic pressure and velocity signals shows that SVR and the first three harmonic frequencies of the impedance spectrum (Z) increase after TAVR. Wave intensity analysis was used to separate total wave intensity into contributions from the forward (dIw+) and backward (dIw–) traveling waves. Compression waves (*gold*) increase pressure, and expansion waves (*green*) decrease aortic pressure. The forward compression wave (FCW) increases immediately after TAVR. *BCW,* Backward compression wave; *BEW,* backward expansion wave; *dIw,* wave intensity; *FEW,* forward expansion wave; *LA,* left atrium; *LV,* left ventricle; *SVR,* systemic vascular resistance. (From Yotti R, et al. Systemic vascular load in calcific degenerative aortic valve stenosis: insight from percutaneous valve replacement. *J Am Coll Cardiol.* 2015;65:423-433.)

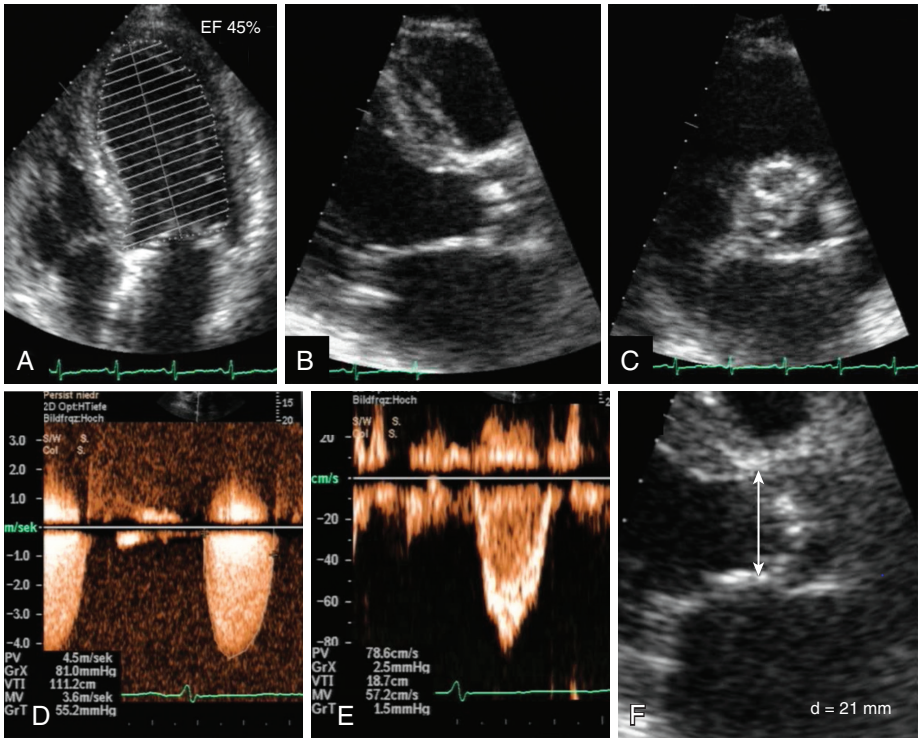


FIGURE 72.10 Assessment of aortic stenosis severity. A, The Simpson method is used to assess LV function by ejection fraction (EF). **B,** The long-axis view is used to assess the morphology, degree of calcification, and opening movement. **C,** The short axis further assesses morphology and the number of cusps. **D,** CW Doppler measures peak velocity, mean gradient, and the aortic velocity-time integral (VTI). **E,** Pulsed-wave Doppler is used to measure prestenotic velocity and the VTI in the LV outflow tract (LVOT). **F,** LVOT diameter (*d, double-headed arrow*) in zoom mode is used to calculate LVOT area. Images show a severely stenosed calcified tricuspid aortic valve with a mean gradient of 55 mm Hg, a calculated aortic valve area of 0.6 cm^2, and a reduced EF of 45%. (From Otto CM, ed. *The Practice of Clinical Echocardiography.* 6th ed. Philadelphia: Elsevier; 2022.)

hemodynamics and in terms of their ability to predict clinical outcome. However, the accuracy of these measures requires an experienced laboratory with meticulous attention to technical details. Evaluation of AS severity is affected by the presence of systemic hypertension, and reevaluation after blood pressure control may be necessary.[81] In patients with LV dysfunction and low cardiac output, assessing the severity of AS can be enhanced by assessing hemodynamic changes during dobutamine infusion (see later). In some patients, additional measures of AS severity may be necessary, such as correction for poststenotic pressure recovery or three-dimensional transesophageal echocardiography (TEE) of valve anatomy.The combination of pulsed, continuous-wave, and color flow Doppler echocardiography is helpful in detecting and determining the severity of AR (which coexists in approximately 75% of patients with predominant AS) and in estimating pulmonary artery pressure.

Exercise Stress Testing. Because patients may tailor their lifestyle to minimize symptoms or may ascribe fatigue and dyspnea to deconditioning or aging, they may not recognize early symptoms as important warning signals, although these symptoms often can be elicited by a careful history. Exercise testing may be helpful in apparently asymptomatic patients or when symptoms are vague (e.g., fatigue) to unmask symptoms or demonstrate limited exercise capacity or an abnormal blood pressure response.[57,82] Exercise stress testing should be attended by a physician and should be absolutely avoided in clearly symptomatic patients.

Cardiac Computed Tomography. The use and value of CT is rapidly expanding in patients with calcific aortic valve disease (see Chapter 20). CT is useful for evaluating aortic dilation in patients with evidence or suspicion of aortic root disease on echocardiography or chest radiography, particularly those with a bicuspid valve. Measurement of aortic dimensions at several levels, including the sinuses of Valsalva, sinotubular junction, and ascending aorta, is necessary for clinical decision making and surgical planning. CT is increasingly used to assess valve calcification to predict the rate of disease progression or, more often, when the severity of the stenosis is in doubt, particularly in those with low-flow, low-gradient AS (Fig. 72.11).[83-85] It is complementary to echocardiography in assessing valve morphology (see Fig. 20.20B) and provides valuable information on the location and extent of calcification; this can guide treatment decisions regarding transcatheter versus surgical valve replacement and, if a transcatheter approach is selected, valve choice (see Fig. 72.3).[86-89] CT is also a routine part of the preprocedural evaluation of patients undergoing SAVR or TAVR (see Chapter 74), principally to look for a porcelain aorta, as well as determine appropriate valve sizing and assess aortic and peripheral arterial anatomy for a potential transcatheter approach (see Fig. 20.23).[86] Finally, as the quality and resolution of CT have rapidly improved, a gated CT coronary angiogram (with assessment of fractional flow reserve as warranted) may be used to evaluate for CAD instead of routine invasive angiography before AVR.[90,91]

Cardiac Catheterization. In almost all patients, the echocardiographic examination provides the important hemodynamic information required for patient management. Cardiac catheterization is now recommended only when noninvasive tests are inconclusive, when clinical and echocardiographic findings are discrepant, and for coronary angiography before AVR[57] (see Chapters 21 and 22).

Other Imaging Modalities

Cardiac Magnetic Resonance Imaging. Cardiac magnetic resonance (CMR) is useful for assessing LV volume, function, and mass, especially in settings in which this information cannot be obtained readily from echocardiography (see Chapter 19).[92] CMR is also excellent for assessing aortic dimensions in patients with a bicuspid valve, particularly to avoid radiation when serial imaging is needed over many years. Given the adverse prognosis associated with the presence and severity of myocardial fibrosis, CMR with T1 mapping and late gadolinium enhancement (LGE) may be used to risk-stratify patients with AS (see Figs. 72.6 through 72.8).[34,42-47] CMR is also sometimes used instead of CT to assess valve morphology, vascular anatomy, and annular dimensions in preparation for TAVR, although CMR is not recommended for assessment of stenosis severity because of underestimation of transvalvular velocities.[92]

Positron Emission Tomography. Active uptake of ^{18}F-fluoride in the aortic valve on positron emission tomography (PET) identifies active tissue calcification and ^{18}F-fluorodeoxyglucose uptake is a marker of valvular inflammation (see Chapter 18). These tracers are associated with disease progression and predict changes in severity of aortic valve calcification on serial CT studies (Fig. 72.12).[93-95] This may become a useful surrogate end point for trials testing therapies to slow the progression of calcific aortic valve disease, but further studies are needed.

Multimodality Imaging for Cardiac Amyloidosis. Transthyretin cardiac amyloidosis (ATTR-CA) is increasingly recognized as a coexistent disease process in individuals with AS, particularly those with low-flow or low-gradient AS.[96-98] Up to 16% of patients undergoing TAVR have been identified as having ATTR-CA, which is associated with more advanced cardiac structural and functional abnormalities. Multiple imaging modalities (see Chapters 16, 18, and 19) may be helpful in assessing for ATTR-CM, including echocardiographic strain, cardiac MRI, and technetium pyrophosphate (Fig. 72.13; see also Figs. 18.34, 18.35, and 19.13).[34] Even emerging methods to assess extracellular volume with CT may be useful.[99] Although ATTR-CA in a patient with severe AS may not make TAVR futile, it may be associated with worse outcomes, and emerging therapies for ATTR-CA should be considered.[98,100] This is an evolving area that requires additional research to determine the best method(s) for screening and treatment.

DISEASE COURSE AND STAGING

The disease course for a patient with AS is characterized by (1) progressive narrowing/obstruction of the valve with its attendant consequences for myocardial and vascular remodeling/dysfunction and (2)

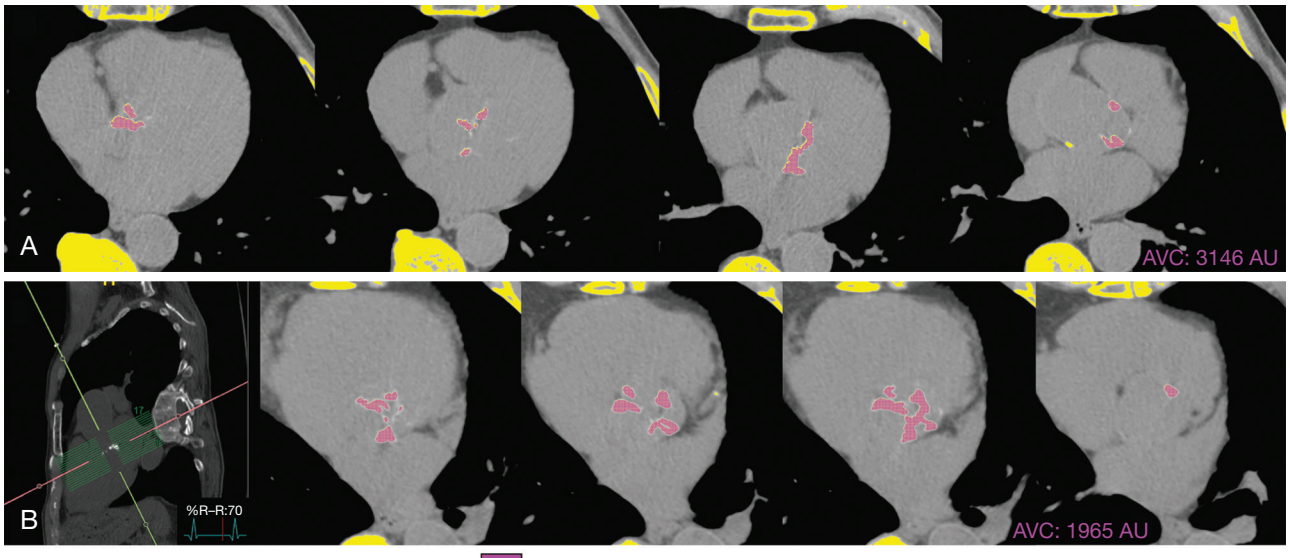


FIGURE 72.11 Aortic valve calcification quantified by cardiac CT. Multiplanar reformat images in "native" axial **(A)** and "en face" **(B)** views showing aortic valve calcification (AVC) (*pink*). Note that, with the use of the "en face" reconstructed view, the calcification score is decreased by 37% and that aortic stenosis severity would be classified as nonsevere. Thus, "en face" view measurement of aortic valve calcification must not be used to assess AVC severity. (From Pawade T, et al. Why and how to measure aortic valve calcification in patients with aortic stenosis. *JACC Cardiovasc Imaging.* 2019;12:1835-1848.)

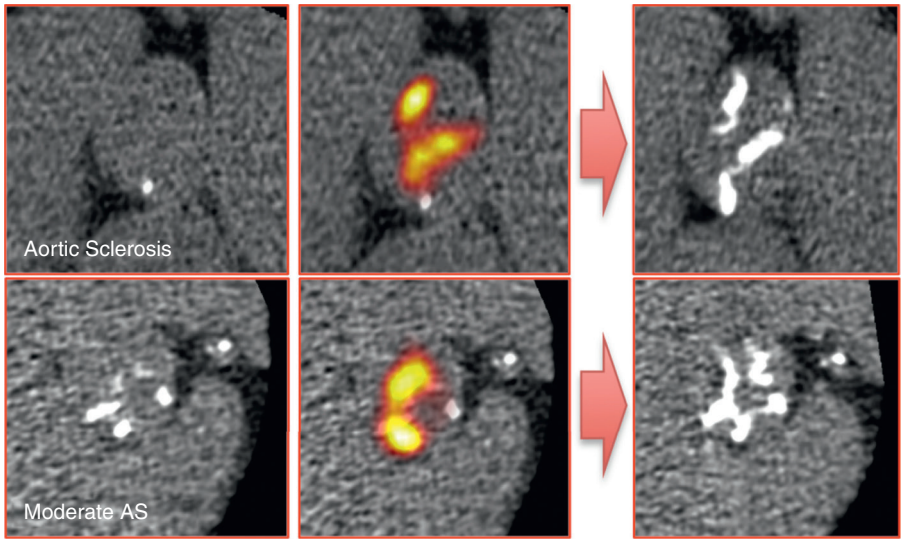


FIGURE 72.12 Valvular 18F-fluoride uptake predicts the progression of calcification in aortic stenosis. Two patients with calcific aortic valve disease. *Left,* Baseline CT images. *Middle,* Fused positron emission tomography (PET)/CT images showing increased 18F-fluoride valvular uptake (*red/yellow areas*). *Right,* Repeat CT scans after 2 years with new areas of macroscopic calcium (*white areas*) in a similar distribution to that of baseline PET uptake. (From Jenkins WS, et al. Valvular (18)F-fluoride and (18)F-fluorodeoxyglucose uptake predict disease progression and clinical outcome in patients with aortic stenosis. *J Am Coll Cardiol* 2015;66:1200-1201.)

ultimately the development of symptoms. These are reflected in the staging nomenclature of the American College of Cardiology/American Heart Association (ACC/AHA) Valvular Heart Disease Guidelines (Table 72.2).[57] Stage A includes those at risk for AS; stage B includes progressive AS (mild to moderate valve obstruction); stage C includes individuals with severe AS but no symptoms with LVEF ≥50% (C1) or with overt LV dysfunction (LVEF <50%) (C2); and stage D includes individuals with severe AS and symptoms broken down into three different subgroups (D1, D2, and D3) based on differing hemodynamics.[57]

The degree of stenosis associated with symptom onset varies among patients. Although stenosis is on average more severe in symptomatic than in asymptomatic patients, marked overlap is evident in all measures of severity between these two groups. Once AS is severe, only about 50% of patients report symptoms.[101] Markers of more rapid symptom onset include greater valve calcification, higher transvalvular gradient, more rapid increase in transvalvular gradient, and higher B-type natriuretic peptide, among others.[57]

Progressive Aortic Stenosis (Stage B; Mild to Moderate Valve Obstruction)

In adults with calcific AS, a significant burden of leaflet disease is present before obstruction to outflow develops. However, once even mild obstruction is present, hemodynamic progression occurs in almost all patients, with the interval from mild to severe obstruction ranging from less than 5 to more than 10 years. There is substantial patient-to-patient variability in the rate of progression; factors associated with more rapid hemodynamic progression include older age, more severe leaflet calcification, renal insufficiency, hypertension, obesity, metabolic syndrome, smoking, hyperlipidemia, and elevated circulating levels of Lp(a) and increased activity of Lp-PLA_2.[1,23,24,57] A greater initial increase in transvalvular gradient portends faster progression.[102] *Moderate* AS is characterized by an aortic jet velocity of 3.0 to 3.9 m/sec or mean transvalvular pressure gradient of 20 to 39 mm Hg, usually with an AVA of 1.0 to 1.5 cm^2. *Mild* AS is characterized by an aortic jet velocity of 2.0 to 2.9 m/sec or mean transvalvular pressure gradient less than 20 mm Hg, usually with aortic orifice of 1.5 to 2.0 cm^2 (see Table 72.2).[57,79]

Classification of Severe Aortic Stenosis

Criteria have been developed for characterizing severe AS; they are useful for categorizing patients, but it is important to recognize their limitations and imprecision. They should not be rigidly adhered to in isolation when determining clinical management. Clinical decisions are based on consideration of symptom status, severity of AS as determined by echocardiography, and LV systolic function. In some cases, additional measures of valve calcification by CT and hemodynamic stress with B-type natriuretic peptide (BNP) or N-terminal (NT)-pro hormone BNP (NT-proBNP) can provide important data regarding AS severity and its effect on the left ventricle. Additional factors, such as energy loss index, valvular impedance, or evaluation with changing

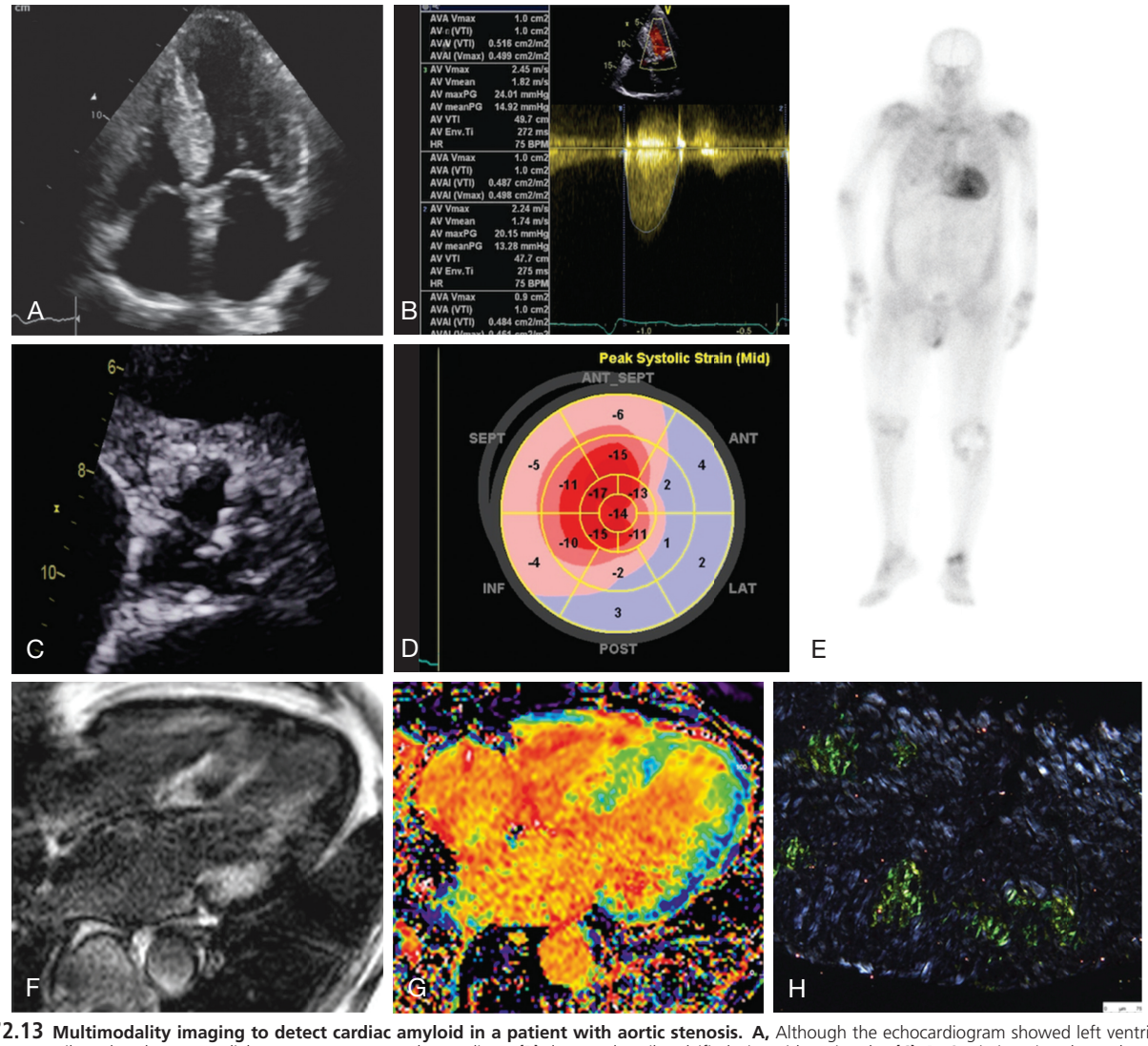


FIGURE 72.13 Multimodality imaging to detect cardiac amyloid in a patient with aortic stenosis. A, Although the echocardiogram showed left ventricular hypertrophy, this was attributed to the myocardial response to severe valve gradients **(B)** due to a heavily calcified tricuspid aortic valve **(C)**. **D,** Strain imaging showed a characteristic apical sparing. **E,** Bone scintigraphy showed Perugini grade 2 cardiac uptake. Cardiac magnetic resonance showed transmural late gadolinium enhancement with higher signal from the myocardium than from the blood pool **(F)**, and elevated native myocardial ECV **(G). H,** Diagnosis was confirmed as transthyretin amyloidosis on cardiac biopsy. (From Treibel TA, et al. Multimodality imaging markers of adverse myocardial remodeling in aortic stenosis. *JACC Cardiovasc Imaging.* 2019;12:1532-1548.)

loading conditions (e.g., dobutamine stress) or with exercise, are under investigation for evaluation of disease severity.[74,103]

The most specific definition for severe AS is a peak jet velocity of 4.0 m/sec or greater or mean gradient of 40 mm Hg or greater, usually accompanied by an AVA of 1.0 cm^2 or less (see Table 72.2 and Fig. 72.10).[57] When aortic velocity or gradient meets these criteria, severe AS is present and classified as stage C in asymptomatic patients and stage D1 in symptomatic patients. Classification of stenosis severity is more complex when AVA is 1.0 cm^2 or less, but mean pressure gradient is less than 40 mm Hg and peak jet velocity is less than 4.0 m/sec. This apparent discordance in indices of AS severity occurs because at a normal flow rate, an AVA of 1.0 corresponds to a mean gradient of 30.[104,105] This is a common clinical conundrum because over one third of patients with severe AS with an AVA of 1.0 cm^2 or less have a peak jet velocity less than 4.0 m/sec or mean gradient less than 40 mm Hg (stages D2 and D3 in Table 72.2).[104-106] Clinical judgment and expert imaging are the keys to differentiating patients with severe low-flow, low-gradient AS from those with moderate AS.

Asymptomatic Severe Aortic Stenosis (Stage C)

Stage C1 is defined as high-gradient severe AS with no symptoms and preserved systolic function (see Table 72.2). Prospective studies evaluating the rate of progression to symptomatic AS in initially asymptomatic patients are summarized in eTable 72.1. The strongest predictor of progression to symptoms is the Doppler aortic jet velocity[106] (see also Classic References, Otto). Survival free of symptoms is 84% at 2 years when aortic velocity is less than 3 m/sec, compared with only 21% when velocity is greater than 4 m/sec (Fig. 72.14A). In adults with severe AS (Doppler velocity >4 m/sec), outcome can be further predicted by the magnitude of the Doppler velocity (Fig. 72.14B), as well as by the severity of aortic valve calcification.[84] In such studies, most events consisted of the development of symptoms prompting AVR and not sudden death in otherwise asymptomatic patients. However, retrospective studies have reported cases of sudden death in apparently asymptomatic adults with severe AS.[60]

Stage C2 is defined as high-gradient severe AS with no symptoms but overt LV systolic dysfunction with an LVEF <50%. However, several recent studies indicate that an LVEF of 50% to 60% is linked to a worse prognosis among patients with severe AS.[57-61] Accordingly, an LVEF of 60% is probably a better cutoff for indicating an LVEF below which abnormal function has developed in response to pressure overload from AS; expeditious AVR even in the absence of symptoms may be warranted below this higher LVEF threshold.

Symptomatic Severe Aortic Stenosis (Stage D)

Once even mild symptoms are present, survival is poor unless outflow obstruction is relieved. Expected survival for patients with severe symptomatic AS will differ somewhat based on the age, number of comorbidities,

TABLE 72.2 Stages of Valvular Aortic Stenosis (AS)

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	At risk of AS	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis	Aortic Vmax <2 m/sec with normal leaflet motion	None	None
B	Progressive AS	Mild to moderate leaflet calcification/fibrosis of a bicuspid or trileaflet valve with some reduction in systolic motion *or* Rheumatic valve changes with commissural fusion	***Mild AS:*** Aortic Vmax 2.0-2.9 m/sec or mean ΔP <20 mm Hg ***Moderate AS:*** Aortic Vmax 3.0-3.9 m/sec or mean ΔP 20-39 mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C	Asymptomatic severe AS				
C1	Asymptomatic severe AS	Severe leaflet calcification/fibrosis or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2) Very severe AS is an aortic Vmax ≥5 m/sec, or mean ΔP ≥ 60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV systolic dysfunction	Severe leaflet calcification/fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2) but not required to define severe AS	LVEF <50%	None
D	Symptomatic severe AS				
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification/fibrosis or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec, or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2), but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow, low-gradient AS with reduced LVEF	Severe leaflet calcification/fibrosis with severely reduced leaflet motion	AVA ≤1 cm^2 with resting aortic Vmax <4 m/sec, or mean ΔP <40 mm Hg Dobutamine stress echo shows AVA ≤1 cm^2 with Vmax ≥4 m/sec at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification/fibrosis with severely reduced leaflet motion	AVA <1.0 cm^2 (AVAi <0.6 cm^2/m^2) with aortic Vmax <4 m/sec, or mean ΔP <40 mm Hg *and* stroke volume index <35 mL/m^2 Measured when patient is normotensive (systolic BP <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	HF Angina Syncope or presyncope

AVA, Aortic valve area; *AVAi*, *AVA* indexed to body surface area; *BP*, blood pressure; *HF*, heart failure; *LVEF*, left ventricular ejection fraction; *ΔP*, pressure gradient; *Vmax*, maximum aortic jet velocity.
From Otto CM, et al. 2020 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2021;77:e25-e197.

and severity of HF of the cohort examined, but average survival without AVR is only 1 to 3 years after symptom onset. Among symptomatic patients with severe AS, the outlook is poorest when the left ventricle has failed and the cardiac output and transvalvular gradient are both low. The risk of sudden death is high with symptomatic severe AS, so these patients should be promptly referred for AVR. In patients who do not undergo AVR, recurrent hospitalizations for angina and decompensated HF are common, associated with significant consumption of health care resources.[107]

Symptomatic Severe High-Gradient Aortic Stenosis (Stage D1)

Severe high-gradient AS is defined as peak jet velocity of 4.0 m/sec or greater or mean gradient of 40 mm Hg or greater, usually accompanied by an AVA of 1.0 cm^2 or less (or indexed AVA of 0.6 cm^2/m^2 or less) (see Table 72.2). Occasionally, AVA may be larger with mixed AS and AR. With alignment of all hemodynamic indices of AS severity, these patients have the clearest evidence of severe AS and warrant prompt referral for AVR.

Symptomatic Severe Low-Flow, Low-Gradient Aortic Stenosis with Reduced LVEF (Stage D2)

Classic low-flow, low-gradient AS (stage D2) is defined as AVA of 1.0 cm^2 or less with an aortic velocity less than 4.0 m/sec or mean gradient less than 40 mm Hg and LVEF less than 50% (see Table 72.2). Patients with HF symptoms and stage D2 AS often create a diagnostic dilemma for the clinician because their clinical presentation

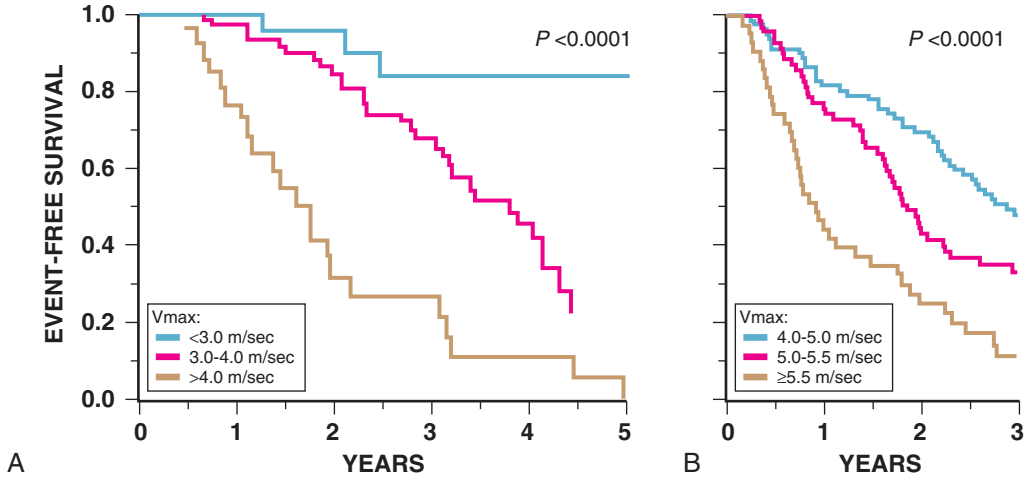


FIGURE 72.14 Event-free survival based on initial peak aortic jet velocity. A, Natural history as reflected by event-free survival in asymptomatic patients with aortic stenosis. Initial peak aortic jet velocity (Vmax) stratifies patients according to the likelihood that symptoms requiring valve replacement will develop over time. **B,** Outcomes with very severe aortic stenosis. Kaplan-Meier event-free survival rate for patients with Vmax of 4.0 m/sec or greater. In both **A** and **B,** most "events" consisted of the onset of symptoms warranting aortic valve replacement. (**A** from Otto CM, et al. A prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation.* 1997;95:2262; **B** from Rosenhek R, et al. Natural history of very severe aortic stenosis. *Circulation.* 2010;121:151.)

and hemodynamic data may be indistinguishable from those of patients with dilated cardiomyopathy and a calcified valve that is not severely stenotic.[57,83] Severe AS can be distinguished from moderate AS with primary LV dysfunction based on the changes in valve hemodynamics during transient increases in flow, usually by increasing cardiac output with dobutamine[79,83] (see Chapter 16). Severe AS is present if there is an increase in aortic velocity to at least 4 m/sec at any flow rate, with AVA that remains less than 1.0 cm^2. Dobutamine echocardiography also provides evidence of myocardial contractile reserve (increase in stroke volume >20% from baseline), which historically has been an important predictor of operative risk and survival after SAVR in these patients.[83] However, even in patients who lack contractile reserve, SAVR is associated with better survival (approximately 50% at 5 years) than medical therapy, and more recent studies in patients undergoing TAVR have shown equivalent improvement in LVEF and survival in patients with and without contractile reserve.[65,108]

Symptomatic Severe Low-Flow, Low-Gradient Aortic Stenosis with Preserved LVEF (Stage D3)

Low-flow, low-gradient AS also can occur with a normal LVEF (≥50%) (see Table 72.2), typically in elderly patients with a small, hypertrophied left ventricle or those with concurrent hypertension. This is often referred to as "paradoxical" low-flow, low-gradient AS because despite a normal EF, transaortic flow is low (stroke volume index <35 mL/m^2).[57,79,83] Distinguishing truly severe AS from moderate AS can be challenging. Measurement errors should be ruled out and small body size accounted for (an indexed AVA ≤0.6 cm^2/m^2 is consistent with severe AS).[79] Dobutamine has been used to augment flow to distinguish truly severe AS from pseudosevere AS, but is less preferred in these patients with a small, hypertrophied ventricle and marked diastolic dysfunction.[109] Evaluation of valve hemodynamics after treatment of hypertension and, increasingly, CT assessment of valve calcification can be helpful in establishing the diagnosis of severe AS and is being used to identify patients with a severely calcified valve.[57,79,83]

TREATMENT

Medical Management

Medical therapy has thus far been shown to have no effect on disease progression in patients with AS.[1,14,32] Furthermore, both observational studies and randomized clinical trials (RCTs) convincingly demonstrate that AVR is superior to medical therapy in patients with severe symptomatic AS. The risk of sudden death increases dramatically once symptoms are present, and patients should be advised to report promptly the development of any symptoms possibly related to AS. In asymptomatic patients with AS of any degree, evaluation and treatment for conventional cardiovascular risk factors is recommended in accordance with established guidelines (see Chapter 25).

Hypertension accompanies AS in many patients.[110] Because of traditional teaching that AS is a disease with fixed afterload, there often has been reluctance to treat hypertension because of concerns that vasodilation would not be offset by an increase in stroke volume. However, several studies have demonstrated that vasodilation is accompanied by increases in stroke volume, even in patients with severe AS[66] (see also Classic References, Khot). Hypertension imposes an additional load on the left ventricle and is associated with more adverse hypertrophic LV remodeling. Although treatment of hypertension may not reduce AS-related events, it should be treated because of the well-known adverse association between hypertension and vascular events and mortality.[111] Whether blood pressure targets should be the same (versus slightly higher) for patients with AS as the general population is unclear.[111] There is no one class of medicines established as the preferred treatment of hypertension in patients with AS, but because the renin-angiotensin system is upregulated in the valve and ventricle of patients with AS, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be preferentially considered. Small studies have demonstrated their safety, and some suggest a clinical benefit, but larger-scale randomized studies are needed.

Concomitant CAD is common in middle-aged and elderly patients with AS. Primary and secondary prevention guidelines should be followed, and the decision of whether to prescribe a statin medication should not be influenced by the presence of AS. RCTs testing the use of statins in patients with mild AS to more advanced disease were adequately powered and showed no improvement in mortality, time to AVR, or rate of AS progression in the treatment versus placebo groups.[15]

AF or atrial flutter develop in up to one third of older patients with AS, perhaps exacerbated by left atrial enlargement related to diastolic dysfunction. When such an arrhythmia is observed in a patient with AS, the possibility of associated mitral valvular disease should be considered. When AF occurs, the rapid ventricular rate may precipitate symptoms, and the loss of atrial contribution to LV filling and a sudden fall in cardiac output may cause serious hypotension. If this occurs, AF should be treated promptly, usually with cardioversion. New-onset AF in a previously asymptomatic patient with severe AS may be a marker of impending symptom onset. For those with AF and native valve AS, as well as those treated with a bioprosthetic valve more than 3 months ago, anticoagulation with a non–vitamin K oral anticoagulant is an effective alternative to warfarin.[57]

In patients with HF and volume overload, AVR is indicated, but diuretics may reduce congestion and provide some symptomatic relief before intervention. Patients with decompensated HF may benefit from medical therapy as a bridge to definitive therapy with AVR. Nitroprusside has been used during hemodynamic monitoring in the intensive care unit to unload the left heart, reduce congestion, and improve forward flow (see Classic References, Khot). Similarly, phosphodiesterase type 5 inhibition has been shown to provide acute improvements in pulmonary and systemic hemodynamics resulting in biventricular unloading.[66] These medications may improve the patient's hemodynamic status, allowing the AVR procedure to be performed more safely.

TABLE 72.3 Indications for Aortic Valve Replacement in Patients with Aortic Stenosis

COR	LOE	RECOMMENDATIONS
1	A	1. In adults with severe high-gradient AS (stage D1) and symptoms of exertional dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated.
1	B-NR	2. In asymptomatic patients with severe AS and an LVEF <50% (stage C2). AVR is indicated.
1	B-NR	3. In asymptomatic patients with severe AS (stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated.
1	B-NR	4. In symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF (stage D2). AVR is recommended.
1	B-NR	5. In symptomatic patients with low-flow, low-gradient severe AS with normal LVEF (stage D3), AVR is recommended if AS is the most likely cause of symptoms.
2a	B-NR	6. In apparently asymptomatic patients with severe AS (stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mm Hg from baseline to peak exercise.
2a	B-R	7. In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable.
2a	B-NR	8. In apparently asymptomatic patients with severe AS (stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide (BNP) level is greater than three times normal.
2a	B-NR	9. In asymptomatic patients with high-gradient severe AS (stage C1) and low surgical risk. AVR is reasonable when serial testing shows an increase in aortic velocity ≥0.3 m/s per year.
2b	B-NR	10. In asymptomatic patients with severe high-gradient AS (stage C1) and a progressive decrease in LVEF on at least three serial imaging studies to <60%, AVR may be considered.
2b	C-EO	11. In patients with moderate AS (stage B) who are undergoing cardiac surgery for other indications. AVR may be considered.

AS, Aortic stenosis; *AVR*, aortic valve replacement; *HF*, heart failure *LVEF*, left ventricular ejection fraction.
From Otto CM, et al. 2020 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2021;77:e25-e197.

Balloon Aortic Valvuloplasty

AVR is the procedure of choice for relief of outflow obstruction in adults with valvular AS. Balloon aortic valvuloplasty has only a modest hemodynamic effect in patients with calcific AS. It can provide short-term improvement in survival and quality of life, but these benefits are not sustained.[112] Accordingly, balloon aortic valvuloplasty is not recommended as an alternative to valve replacement for calcific AS. In selected cases, it might be reasonable as a bridge to definitive treatment with AVR in unstable patients or as a palliative procedure in patients who are not candidates for AVR.[57]

Aortic Valve Replacement

Recommendations regarding indications for and timing of AVR, type of valve used, and procedural approach require discussions within a multidisciplinary heart team and shared decision making with the patient and family.[57] Current recommendations for AVR in the 2020 revised ACC/AHA guidelines for management of valvular heart disease are shown in Table 72.3. AVR is recommended (Class I) for adults with symptomatic severe AS (stages D1, D2, and D3), even if symptoms are mild (Fig. 72.15).[57,113] AVR also is recommended (Class I) for severe AS with a LVEF less than 50% and for patients with severe asymptomatic AS who are undergoing coronary artery bypass grafting (CABG) or other forms of heart surgery. In addition, AVR is reasonable (Class IIa) for apparently asymptomatic patients with severe high-gradient AS when exercise testing provokes symptoms or a fall in blood pressure. AVR is also reasonable (Class IIa) in asymptomatic patients at low surgical risk when (1) AS is very severe (Vmax ≥5 m/sec), (2) there is rapid disease progression, or (3) BNP is greater than three times the upper limit of normal. AVR may be considered (Class IIb) when there is a progressive decrease in LVEF on at least three serial imaging studies to less than 60%.[57] Further studies are needed to determine whether other indexes of risk warrant earlier intervention in asymptomatic patients with severe AS. These include evidence of myocardial fibrosis, impaired longitudinal strain, pulmonary hypertension, and moderate or severe LVH, among others.[40,42,59,62]

The management of asymptomatic patients is the subject of ongoing study and debate.[114] A prospective observational study of initially asymptomatic Japanese patients with severe AS compared outcome in those who underwent early surgery versus a "watchful waiting" strategy.[115] With propensity matching to adjust for baseline differences between the two groups, the survival rate was significantly higher in the 291 patients with early surgery compared to the 291 initially followed conservatively. However, it is noteworthy that 31% of patients in the conservative group who developed symptoms did not undergo AVR, and this accounted for 17% of the deaths during "watchful waiting." Although this and other retrospective studies comparing prompt AVR versus medical therapy[116] are suggestive, propensity matching has its limitations. The nonperformance of AVR in many patients in the medical therapy group either initially or when criteria for AVR develop limit the value of these comparisons for informing optimal timing of AVR. Thus, the role of early AVR in asymptomatic patients can be determined only with appropriately designed RCTs.

Recently, a small trial randomized 145 asymptomatic patients with very severe AS (AVA ≤0.75 cm^2 and peak jet velocity ≥4.5 m/sec or higher or mean gradient ≥50 mm Hg or higher) to early SAVR (within 2 months of randomization) or conservative therapy with referral to SAVR when symptoms or overt LV dysfunction developed.[117] The primary end point of operative mortality or cardiovascular mortality occurred in 1% in the early surgery group and 15% in the conservative care group (HR 0.09, 95% CI 0.01 to 0.67); death from any cause occurred in 7% in the early surgery group and 21% in the conservative care group (HR 0.33, 95% CI 0.12 to 0.90). These randomized data are helpful in clarifying optimal timing of AVR in asymptomatic patients, but a couple of limitations should be considered: only younger, lower risk patients with very severe AS were included, and the small sample size with few events yielded wide confidence intervals. Several larger RCTs are under way testing the optimal timing of TAVR in asymptomatic patients; these include older, higher-risk patients and modestly less severe AS, albeit generally still high-gradient severe AS.[114] Additional RCTs are needed to

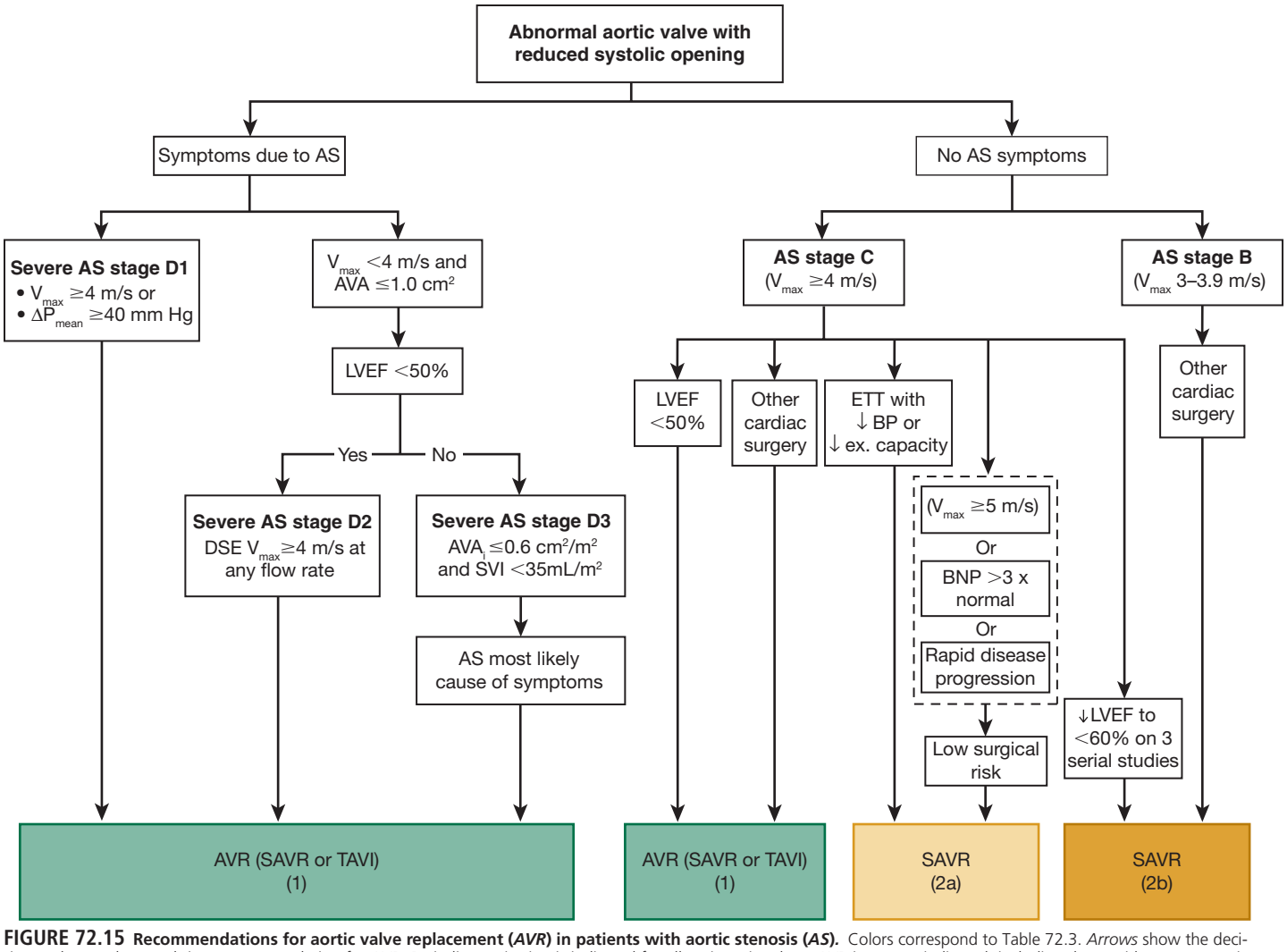


FIGURE 72.15 Recommendations for aortic valve replacement (*AVR*) in patients with aortic stenosis (*AS*). Colors correspond to Table 72.3. *Arrows* show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic (stage C) and symptomatic (stage D) AS and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention. See Fig 72.16 for choice of valve type (mechanical versus bioprosthetic [TAVI or SAVR]) when AVR is indicated. *AVA,* Aortic valve area; AVA_i, aortic valve area index; *BNP,* B-type natriuretic peptide; *BP,* blood pressure; *DSE,* dobutamine stress echocardiography; *ETT,* exercise treadmill test; *ex,* exercise; *LVEF,* left ventricular ejection fraction; ΔP_{mean}, mean systolic pressure gradient between LV and aorta; *SAVR,* surgical aortic valve replacement; *SVI,* stroke volume index; *TAVI,* transcatheter aortic valve implantation; *TAVR,* transcatheter aortic valve replacement; V_{max}, maximum velocity. (From Otto CM, et al. 2020 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2021;77:e25-197.)

clarify optimal timing of SAVR and TAVR in numerous subgroups of patients with moderate and severe AS.

In patients fulfilling current criteria for AVR, the next series of decisions revolves around a surgical or transcatheter approach. Current recommendations for SAVR or TAVR are shown in Table 72.4 and Fig. 72.16 (see also Fig. 72.15). For patients with life expectancy less than 1 year or anticipated poor quality of life not related to their AS, AVR is likely futile and palliative care is recommended.[57,118,119]

In general, AVR leads to an improvement in symptoms, quality of life, and functional capacity and lower rates of hospitalization and death. These clinical improvements are accompanied by reverse remodeling in the heart and improvements in LV function; however, cardiac recovery is variable and often incomplete with untoward consequences.[34,41,43,46,48,120]

Surgical Aortic Valve Replacement

The Society of Thoracic Surgeons (STS) 2020 update on outcomes (reporting data for the year 2018) cited an overall 30-day mortality rate of 1.9% in 25,274 patients undergoing isolated SAVR and 3.6% in 15,855 patients undergoing SAVR and CABG.[121] In patients younger than 70 with minimal comorbidities, the operative risk of mortality is less than 1% in many centers. Medicare data from the past decade indicate that the 30-day mortality after SAVR in patients aged 65 and older in the United States has decreased from 7.6% in 1999 to 4.2% in 2011, with the most marked decrease in patients aged 85 and older, in whom the 30-day mortality has decreased from 12.3% to 5.8%.[122] Therefore, advanced age should not be considered a contraindication to operation, although the majority of such patients are now treated with TAVR. Overall surgical volumes are declining as the volume of TAVR procedures steadily increases (63,361 in 2018).[121] This has the effect of also reducing SAVR mortality rates. The 30-day SAVR mortality rate also is significantly related to the number of AVR procedures performed at each hospital. Risk factors associated with a higher mortality rate include a high New York Heart Association functional class, impaired LV function, advanced age, the presence of associated CAD, and other comorbidities.

Transcatheter Aortic Valve Replacement

Over the last decade, TAVR has transformed the treatment of patients with calcific AS (see Chapter 74). Initial RCTs showed TAVR to be

TABLE 72.4 Recommendations for Choice of SAVR Versus TAVR for Patients for Whom a Bioprosthetic AVR Is Appropriate

COR	LOE	RECOMMENDATIONS
1	A	1. For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are younger than 65 years of age or have a life expectancy >20 years. SAVR is recommended.
1	A	2. For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision making about the balance between expected patient longevity and valve durability.
1	A	3. For symptomatic patients with severe AS who are older than 80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR.
1	B-NR	4. In asymptomatic patients with severe AS and an LVEF <50% who are 80 years of age or younger and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients in Recommendations 1, 2, and 3 above.
1	B-NR	5. For asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated BNP (COR 2a indications for AVR), SAVR is recommended in preference to TAVI.
1	A	6. For patients with an indication for AVR for whom a bioprosthetic valve is preferred but valve, vascular anatomy, or other factors are not suitable for transfemoral TAVI, SAVR is recommended.
1	A	7. For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life.
1	C-EO	8. For symptomatic patients with severe AS for whom predicted post-TAVI or post-SAVR survival is <12 months or for whom minimal improvement in quality of life is expected, palliative care is recommended after shared decision making, including discussion of patient preferences and values.
2b	C-EO	9. In critically ill patients with severe AS, percutaneous aortic balloon dilation may be considered as a bridge to SAVR or TAVI.

AS, Aortic stenosis; *LVEF*, left ventricular ejection fraction; *SAVR*, surgical aortic valve replacement; *TAVI,* transcatheter aortic valve implantation.
From Otto CM, et al. 2020 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2021;77:e25-e197.

superior to medical therapy (usually accompanied by balloon aortic valvuloplasty) in patients who were at prohibitive risk for surgery. Subsequently, in patients deemed high, intermediate, and low risk for surgery, TAVR was shown to be noninferior and, in some trials/subgroups, superior to SAVR.[123-127] Accordingly, TAVR is approved for the treatment of severe AS at all level of levels of risk. The most common approach to valve implantation is *transfemoral* (~95% of cases), particularly as sheath size progressively decreases. Although 5-year data on transcatheter valve durability are encouraging, longer-term data are needed particularly as we move toward treating younger, lower-risk patients.[128]

Patient Selection for TAVR or SAVR

The choice of SAVR versus TAVR should come after a decision that AVR is indicated (see Fig. 72.15). Recommendations for type of valve (mechanical versus bioprosthetic) and type of procedure (surgical versus transcatheter) are outlined in detail in Fig. 72.16. Given the complexity of issues to consider, it is recommended that these decisions occur in the environment of a multidisciplinary heart valve team of cardiac surgeons, interventional cardiologists, clinical and imaging experts in valve disease, and nurses, anesthetists, and geriatricians as needed.[57] Shared decision making with the patient and family is also essential, so that their values and preferences can be incorporated into any treatment decision.[57,129,130] As the field, experience, and technology have evolved, the choice between TAVR and SAVR has become less about patient/surgical risk (because of comorbidities) and more about age, anatomy, and accompanying coronary, valve, or aortic pathology (Table 72.5). TAVR is favored for individuals 80 years and older and those at high or extreme surgical risk, whereas SAVR is favored in those younger than 65 years of age (see Fig. 72.16). Beyond that, multiple factors should be considered to match a specific patient with the right therapy; in many cases, either TAVR or SAVR will be reasonable options. A significant area of uncertainty relates to younger patient age due to uncertainty regarding transcatheter valve durability, higher need for pacemakers after TAVR, and the anticipated need for multiple lifetime procedures if a bioprosthetic valve is implanted. Related to that is uncertainty regarding how to treat patients with BAV anatomy because of uncertainties regarding TAVR efficacy in BAVs, which are encountered more frequently in young patients, and those with a BAV were routinely excluded from the randomized trials comparing TAVR to SAVR. However, TAVR has been performed in patients with a bicuspid valve with excellent results,[1,131-133] but patient age, valve anatomy, extent and location of calcification, and associated aortopathy all influence anticipated success with TAVR and degree of clinical equipoise between the two treatment options. Randomized trials are being considered to clarify optimal management of patients with bicuspid AS.

Postprocedural Issues

Even after treatment of AS with AVR, several issues remain important for clinical management to optimize patient outcomes. As is true after other cardiovascular events, participation in *cardiac rehabilitation* after heart valve surgery is associated with lower rates of death and rehospitalization over the first postprocedure year; however, only a minority participate.[134] In the case of *structural valve degeneration and valve thrombosis,* bioprosthetic valves, both surgical and transcatheter, are prone to develop valve thrombosis and/or degenerate (e.g., calcify, pannus, leaflet tearing) over time (see Chapter 79). The incidence, consequences, and treatment implications of valve thrombosis are still being examined.[135] In some cases, there will be a marked early increase in transvalvular gradient as a result of valve thrombosis that is often responsive to treatment with anticoagulation. Ongoing surveillance with echocardiography and, as indicated, four-dimensional CT is important to detect these issues early. Although AVR improves HF symptoms and quality of life on the whole, a sizeable minority has *residual HF* after AVR, resulting in rehospitalization and less or no improvement in quality of life.[119,136,137] Accordingly, rather than simply viewing AVR as the curative "fix" for AS, treatment of HF with a reduced or preserved EF with appropriate medical therapy is critical to optimize outcomes. Some studies suggest that blood pressure targets for patients treated with AVR for AS may need to be slightly higher than for the general population, although further studies are needed to clarify this issue.[72,138]

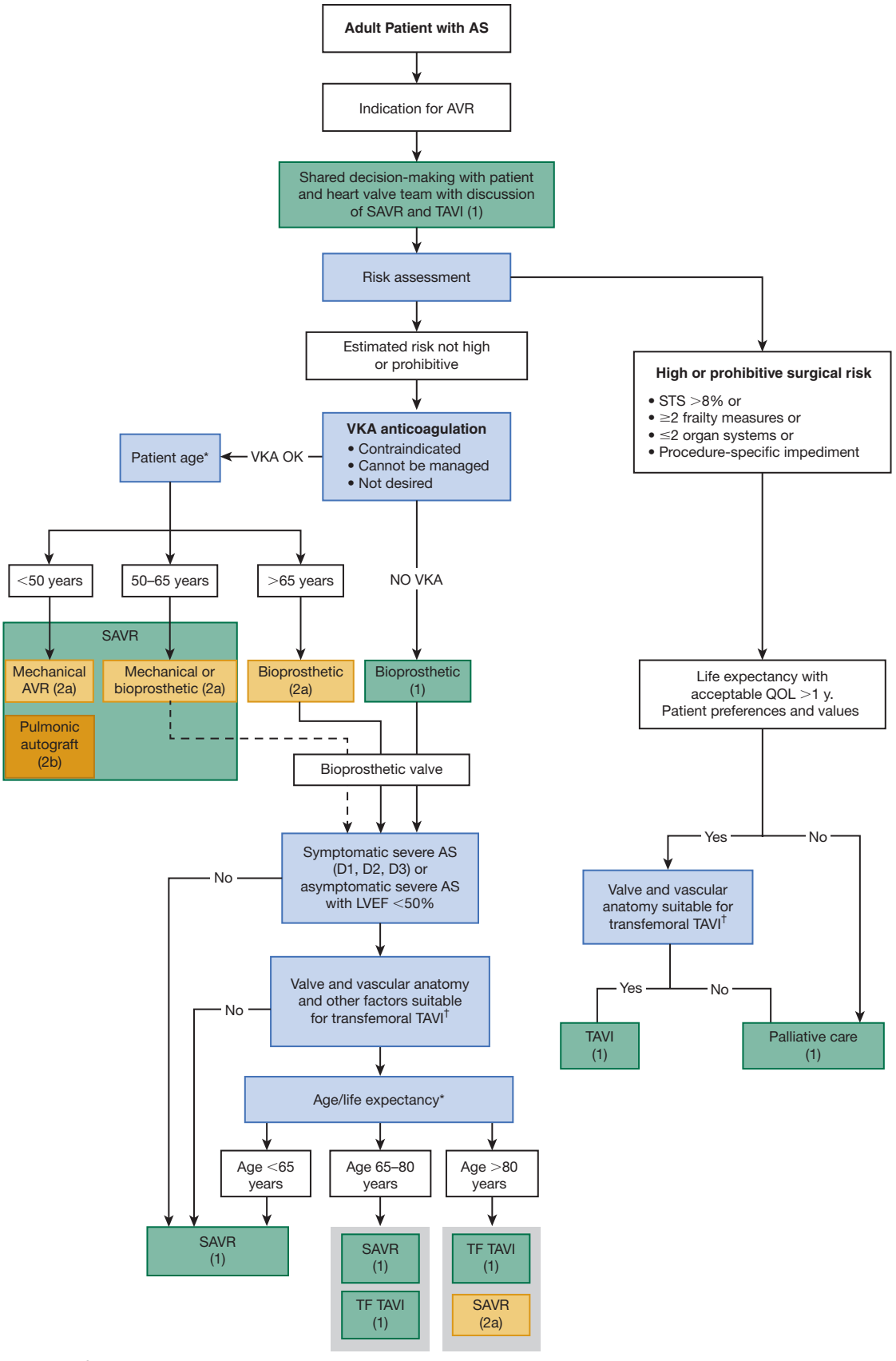


FIGURE 72.16 Selection of surgical versus transcatheter aortic valve replacement. Colors correspond to Table 72.3.*Approximate ages, based on U.S. Actuarial Life Expectancy tables, are provided for guidance. The balance between expected patient longevity and valve durability varies continuously across the age range, with more durable valves preferred for patients with a longer life expectancy. Bioprosthetic valve durability is finite (with shorter durability for younger patients), whereas mechanical valves are very durable but require lifelong anticoagulation. Long-term (20 years) data on outcomes with surgical bioprosthetic valves are available; robust data on transcatheter bioprosthetic valves extend to only 5 years, leading to uncertainty about longer-term outcomes. The decision about valve type should be individualized on the basis of patient-specific factors that might affect expected longevity.† Placement of a transcatheter valve requires vascular anatomy that allows transfemoral delivery and the absence of aortic root dilation that would require surgical replacement. Valvular anatomy must be suitable for placement of the specific prosthetic valve, including annulus size and shape, leaflet number and calcification, and coronary ostial height. *AS,* Aortic stenosis; *AVR,* aortic valve replacement; *LVEF,* left ventricular ejection fraction; *QOL,* quality of life; *SAVR,* surgical aortic valve replacement; *STS,* Society of Thoracic Surgeons; *TAVI,* transcatheter aortic valve implantation; *TF,* transfemoral; and *VKA,* vitamin K antagonist. (From Otto CM, et al. 2020 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25-197.)

TABLE 72.5 Factors to Consider for Patient Selection for Transcatheter Versus Surgical Aortic Valve Replacement

Age
Bicuspid versus tricuspid valve
Valve calcification (amount, location)
Aortic size
Annulus size
Concomitant severe mitral or tricuspid valve disease
Extent, location, and complexity of coronary disease
Severity of left ventricular dysfunction
Transfemoral vascular access

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