Chapter 256: Aortic Valve Disease

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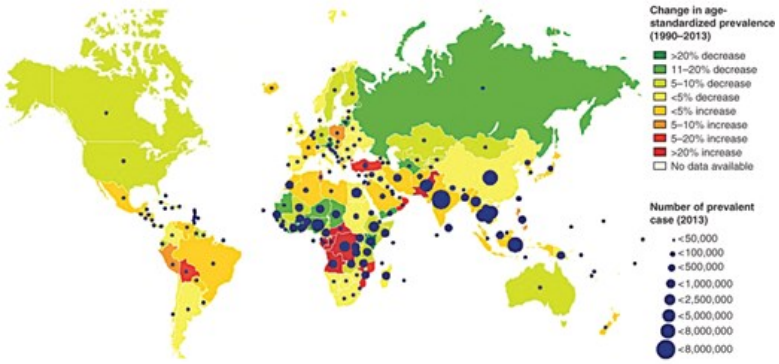
GLOBAL BURDEN OF VALVULAR HEART DISEASE

Primary valvular heart disease ranks well below coronary heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health. Nevertheless, it can cause significant morbidity and lead to premature death. Rheumatic fever **(Chap. 352)** is the dominant cause of valvular heart disease in developing and low-income countries. Its prevalence has been estimated to range from as low as 1 per 100,000 school-age children in Costa Rica to as high as 150 per 100,000 in China **(Fig. 256-1)**. Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some developing countries. Prevalence and mortality rates vary among communities even within the same country as a function of overcrowding and the availability of medical resources and population-wide programs for detection and treatment of group A streptococcal pharyngitis. In economically deprived areas, tropical and subtropical climates (particularly on the Indian subcontinent and in Southeast Asia), Central America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more-developed nations and frequently causes serious symptoms in patients aged <20 years. This accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 15–20 million people live with rheumatic heart disease worldwide, an estimated prevalence characterized by 300,000 new cases and 233,000 case fatalities per year, with the highest mortality rates reported from Southeast Asia (~7.6 per 100,000). In the United States, rheumatic heart disease accounted for 20,000 hospital admissions in 2010 and 3281 deaths in 2014.

FIGURE 256-1

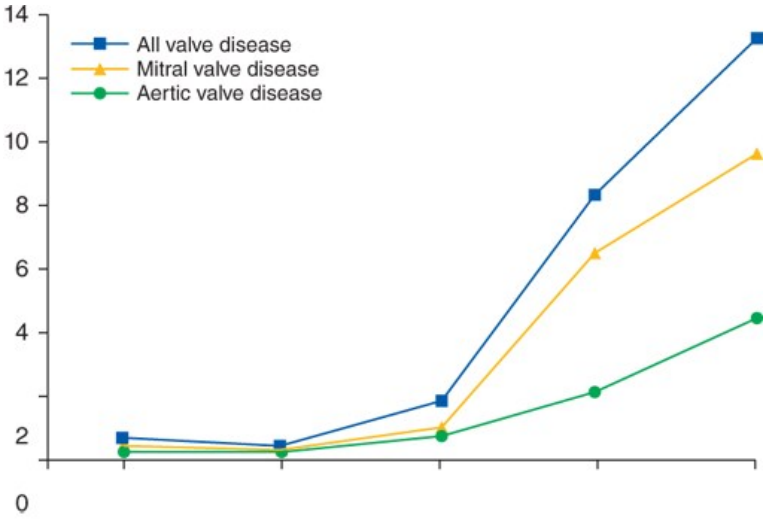
The global burden of rheumatic heart disease. This world map provides a snapshot of both the change in prevalence of rheumatic heart disease cases between 1990 and 2013 (upper right legend) and the estimated number of rheumatic heart disease cases per country (lower right legend). Regions in which the disease is highly prevalent include sub-Saharan Africa, India, China, and Southeast Asia. *(From JR Carapetis et al: Nat Rev Dis Primers 2:15084, 2016.)*



Although there have been recent reports of isolated outbreaks of streptococcal infection in North America, valve disease in high-income countries is dominated by degenerative or inflammatory processes that lead to valve thickening, calcification, and dysfunction. The prevalence of valvular heart disease increases significantly with age for both men and women. Important left-sided valve disease may affect as many as 12–13% of adults aged >75 years **(Fig. 256-2)**. Severe aortic stenosis (AS) is estimated to affect 3.5% of the population aged >75 years. In the United States, there were 85,000 hospital discharges with valvular heart disease in 2010, and the vast majority of these were related to surgical procedures for heart valve disease (mostly involving the aortic and mitral valves).

FIGURE 256-2

The burden of moderate or severe mitral and aortic valve disease in the United States. Prevalence estimates are derived from three population-based studies comprising a total of 11,911 individuals: The Coronary Artery Risk Development in Young Adults (CARDIA), the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS). *(From VT Nkomo et al: Lancet 368:1005, 2006.)*



The incidence of infective endocarditis **(Chap. 123)** has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, and the growing epidemic of diabetes. The more restricted use of antibiotic prophylaxis since 2007 has thus far not been convincingly associated with an increase in incidence rates for infective endocarditis cases attributable to oropharyngeal pathogens. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation. Rates of valve surgery during the acute phase of infective endocarditis increased significantly in U.S. hospitals over the decade from 2000 to 2010.

Bicuspid aortic valve (BAV) disease affects as many as 0.5–1.4% of the general population, with an associated incidence of aortopathy involving root or ascending aortic aneurysm disease or coarctation. An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction. The global burden of valvular heart disease is expected to progress.

As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented, especially for those patients with rheumatic heart disease in low- and middle-income countries. Management decisions and outcome differences based on age, gender, race, and geography require educational efforts across all levels of providers and prioritization of resources.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 38** and **234**; of electrocardiography (ECG) in **Chap. 235**; of echocardiography and other noninvasive imaging techniques in **Chap. 236**; and of cardiac catheterization and angiography in **Chap. 237**.

AORTIC STENOSIS

Aortic stenosis (AS) occurs in about one-fourth of all patients with chronic valvular heart disease; ~80% of adult patients with symptomatic, valvular AS are male.

ETIOLOGY AND PATHOGENESIS

AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (BAV), chronic (trileaflet) deterioration, or previous rheumatic inflammation **(Table 256-1)** . A pathologic study of specimens removed at the time of aortic valve

replacement for AS in adults showed that 53% were bicuspid and 4% unicuspid. The process of aortic valve deterioration and calcification is not a passive one, but rather one that shares many features with vascular atherosclerosis, including endothelial dysfunction, lipid accumulation, inflammatory cell activation, cytokine release, and upregulation of several signaling pathways **(Fig. 256-3)**. Eventually, a fibrocalcific response is established wherein collagen is deposited and valvular myofibroblasts differentiate phenotypically into osteoblasts and actively produce bone matrix proteins that allow for the deposition of calcium hydroxyapatite crystals. Genetic polymorphisms involving the vitamin D receptor, the estrogen receptor in postmenopausal women, interleukin 10, and apolipoprotein E4 have been linked to the development of calcific AS, and a strong familial clustering of cases has been reported from western France. Several traditional atherosclerotic risk factors have also been associated with the development and progression of calcific AS, including low-density lipoprotein (LDL) cholesterol, lipoprotein a (Lp[a]), diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. The presence of aortic valve sclerosis (focal thickening and calcification of the leaflets not severe enough to cause obstruction) is associated with an excess risk of cardiovascular death and myocardial infarction (MI) among persons aged >65. Approximately 30% of persons aged >65 years exhibit some degree of aortic valve sclerosis. Rate and extent of progression to valve obstruction (stenosis) vary among individual patients.

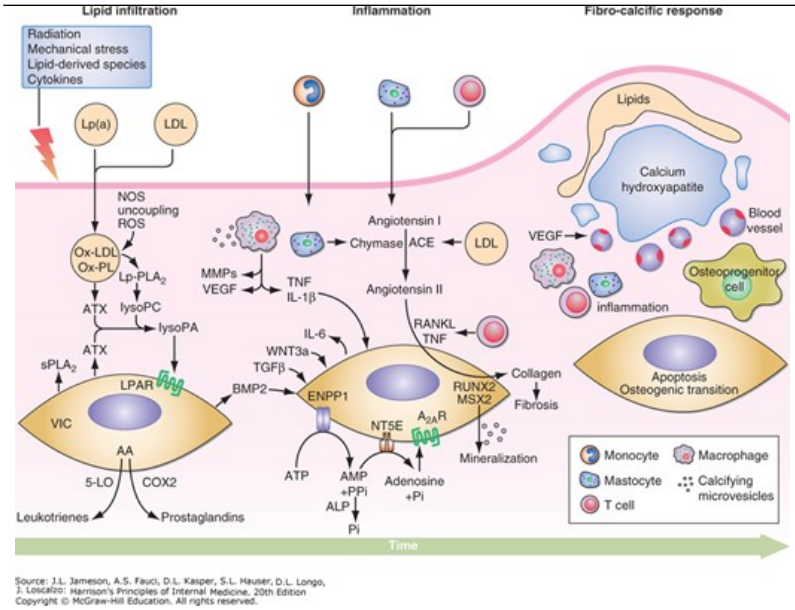
TABLE 256-1

Major Causes of Aortic Stenosis

Valve Lesion	Etiologies
Aortic stenosis	Congenital (bicuspid, unicuspid)
	Degenerative calcific
	Rheumatic fever
	Radiation

FIGURE 256-3

Pathogenesis of calcific aortic stenosis. Lipid and inflammatory cell infiltration occurs across damaged endothelium. A cascade of events follows that leads eventually to formation of disorganized collagen (fibrosis) and calcium hydroxyapatite (bone) deposition. Valvular interstitial cells (VIC) are critical participants in this active process. AA, arachidonic acid; ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; ApoB, apolipoprotein B; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ATX, autotaxin; A2AR, adenosine A2A receptor; BMP, bone morphogenetic protein; COX2, cyclo-oxygenase2; ENPP, ectonucleotide pyrophosphatase/phosphodiesterase; IL, interleukin; 5-LO, 5-lipoxygenase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPAR, lysophosphatidic acid receptor; Lp-PLA2, lipoprotein-associated phospholipase A2; lysoPA, lysophosphatidic acid; lysoPC, lysophosphatidylcholine; MMP, matrix metalloproteinase; NOS, nitric oxide synthase; Ox-PL, oxidized phospholipid; Ox-LDL, oxidized LDL; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; RUNX2, runt-related transcription factor 2; sPLA2, secreted PLA2; TGFβ, transforming growth factor-β; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIC, valvular interstitial cell. *(From B Lindman et al: Nat Rev Dis Primers 2:16006, 2016.)*



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Rheumatic disease of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid-appearing valve. This condition, in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time obstruction to left ventricular (LV) outflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine the etiology of the underlying process. Rheumatic AS is almost always associated with involvement of the mitral valve and with aortic regurgitation (AR). Mediastinal radiation can also result in late scarring, fibrosis, and calcification of the leaflets with AS.

BICUSPID AORTIC VALVE DISEASE

A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner's syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is ~10%. A single gene defect to explain the majority of cases has not been identified, although a mutation in the *NOTCH1* gene has been described in some families. Abnormalities in endothelial nitric oxide synthase and NKX2.5 have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independently of the hemodynamic severity of the valve lesion, but directional shear forces dictated by the anatomic configuration of the valve may influence its expression. For example, enlargement of the ascending aorta along its greater curvature is most often associated with right-left cusp fusion, the most common bicuspid variant. Patients with BAV disease are at risk for aneurysm formation and/or dissection. A BAV can be a component of more complex congenital heart disease with or without other left heart obstructing lesions, as seen in Shone's complex.

OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

In addition to valvular AS, three other lesions may be responsible for obstruction to LV outflow: *hypertrophic obstructive cardiomyopathy* **(Chap. 254)**, *discrete fibromuscular/membranous subaortic stenosis*, and *supravalvular AS* **(Chap. 264)**. The causes of LV outflow obstruction can be differentiated on the basis of the cardiac examination and Doppler echocardiographic findings.

PATHOPHYSIOLOGY

The obstruction to LV outflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilation and reduction of stroke volume. However, in some patients, the obstruction may be present at birth and/or increase gradually over the course of many years, and LV contractile performance is maintained by the presence of concentric LV hypertrophy. Initially, this serves as an adaptive mechanism because it reduces toward normal the systolic stress developed by the myocardium, as predicted by the Laplace relation ($S = Pr/h$, where S = systolic wall stress, P = pressure, r = radius, and h = wall thickness). A large transaortic valve pressure gradient may exist for many years without a reduction in cardiac output (CO) or the development of LV dilation. Ultimately, however, excessive hypertrophy becomes

maladaptive, LV systolic function declines because of afterload mismatch, abnormalities of diastolic function progress, and irreversible myocardial fibrosis develops.

A mean systolic pressure gradient >40 mmHg with a normal CO or an effective aortic orifice area of ~<1 cm^2 (or ~<0.6 cm^2/m^2 body surface area in a normal-sized adult)—i.e., less than approximately one-third of the normal orifice area—is generally considered to represent severe obstruction to LV outflow. The elevated LV end-diastolic pressure observed in many patients with severe AS and preserved ejection fraction (EF) signifies the presence of diminished compliance of the hypertrophied LV. Although the CO at rest is within normal limits in most patients with severe AS, it usually fails to rise normally during exercise. Loss of an appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may cause rapid progression of symptoms. Late in the course, contractile function deteriorates because of afterload excess, the CO and LV–aortic pressure gradient decline, and the mean left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures rise. LV performance can be further compromised by superimposed epicardial coronary artery disease (CAD). Stroke volume (and thus CO) can also be reduced in patients with significant hypertrophy and a small LV cavity despite a normal EF. Low-flow, low-gradient AS (with either reduced or normal LV systolic function) is both a diagnostic and therapeutic challenge.

The hypertrophied LV causes an increase in myocardial oxygen requirements. In addition, even in the absence of obstructive CAD, coronary blood flow is impaired to the extent that ischemia can be precipitated under conditions of excess demand. Capillary density is reduced relative to wall thickness, compressive forces are increased, and the elevated LV end-diastolic pressure reduces the coronary driving pressure. The subendocardium is especially vulnerable to ischemia by this mechanism.

SYMPTOMS

AS is rarely of clinical importance until the valve orifice has narrowed to ~1 cm^2. Even severe AS may exist for many years without producing any symptoms because of the ability of the hypertrophied LV to generate the elevated intraventricular pressures required to maintain a normal stroke volume. Once symptoms occur, valve replacement is indicated.

Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades. Adult patients with BAV disease, however, develop significant valve dysfunction and symptoms one to two decades sooner. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often, there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities and reduced effort tolerance. *Dyspnea* results primarily from elevation of the pulmonary capillary pressure caused by elevations of LV diastolic pressures secondary to impaired relaxation and reduced LV compliance. *Angina pectoris* usually develops somewhat later and reflects an imbalance between the augmented myocardial oxygen requirements and reduced oxygen availability. CAD may or may not be present, although its coexistence is common among AS patients age >65. *Exertional syncope* may result from a decline in arterial pressure caused by vasodilation in the exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixed CO, or from a sudden fall in CO produced by an arrhythmia.

Because the CO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, cachexia, and other clinical manifestations of a low CO are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV failure and systemic venous hypertension, hepatomegaly, AF, and tricuspid regurgitation (TR) are usually late findings in patients with isolated severe AS.

When AS and mitral stenosis (MS) coexist, the reduction in flow (CO) induced by MS lowers the pressure gradient across the aortic valve and, thereby, masks many of the clinical findings produced by AS. The transaortic pressure gradient can be increased in patients with concomitant AR due to higher aortic valve flow rates.

PHYSICAL FINDINGS

The rhythm is generally regular until late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. Hypertension occurs commonly among older adults with AS. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. The carotid arterial pulse rises slowly to a delayed peak (*pulsus parvus et tardus*). A thrill or anacrotic “shudder” may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the *a* wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the

bulging, hypertrophied interventricular septum.

The LV impulse is sometimes displaced laterally in the later stages of the disease. A double apical impulse (with a palpable S_4) may be recognized, particularly with the patient in the left lateral recumbent position. A systolic thrill may be present at the base of the heart to the right of the sternum when leaning forward or in the suprasternal notch.

Auscultation

An early systolic ejection sound is frequently audible in children, adolescents, and young adults with congenital BAV disease. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxical splitting of S_2 **(Chap. 234)**. The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves, and calcification diminishes the intensity of this sound. Frequently, an S_4 is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an S_3 generally occurs late in the course, when the LV dilates and its systolic function becomes severely compromised.

The murmur of AS is characteristically an ejection (mid) systolic murmur that commences shortly after the S_1, increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure. It is characteristically low-pitched, rough and rasping in character, and loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally it is transmitted downward and to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR) (Gallavardin effect). In almost all patients with severe obstruction and preserved CO, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure and low CO in whom the stroke volume and, therefore, the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

LABORATORY EXAMINATION

ECG

In most patients with severe AS, there is LV hypertrophy. In advanced cases, ST-segment depression and T-wave inversion (LV “strain”) in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the ECG and the hemodynamic severity of obstruction, and the absence of ECG signs of LV hypertrophy does not exclude severe obstruction. Systemic hypertension can coexist and also contribute to the development of hypertrophy.

Echocardiogram

The key findings on TTE are thickening, calcification, and reduced systolic opening of the valve leaflets and LV hypertrophy. Eccentric closure of the aortic valve cusps is characteristic of congenitally bicuspid valves. TEE imaging can display the obstructed orifice extremely well, but it is not routinely required for accurate characterization of AS. The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity. Severe AS is defined by a valve area <1 cm^2, whereas moderate AS is defined by a valve area of 1–1.5 cm^2 and mild AS by a valve area of 1.5–2 cm^2. Aortic valve sclerosis, conversely, is accompanied by a jet velocity of <2.5 m/s (peak gradient <25 mmHg). LV dilation and reduced systolic shortening reflect impairment of LV function. There is increasing experience with the use of longitudinal strain and strain rate to characterize earlier changes in LV systolic function, well before a decline in EF can be appreciated. Doppler indices of impaired diastolic function are frequently seen.

Echocardiography is useful for identifying coexisting valvular abnormalities, differentiating valvular AS from other forms of LV outflow obstruction, and measuring the aortic root and proximal ascending aortic dimensions. These aortic measurements are particularly important for patients with BAV disease. Dobutamine stress echocardiography is useful for the evaluation of patients with AS and severe LV systolic dysfunction (low-flow, low-gradient, severe AS with reduced EF), in whom the severity of the AS can often be difficult to judge. Patients with severe AS (i.e., valve area <1 cm^2) with a relatively low mean gradient (<40 mmHg) despite a normal EF (low-flow, low-gradient, severe AS with normal EF) are often hypertensive, and efforts to control their systemic blood pressure should be optimized before Doppler echocardiography is repeated. The use of dobutamine stress echocardiography in this setting is under investigation. When there is continued uncertainty regarding the severity of AS in patients with reduced CO,

quantitative analysis of the amount of aortic valve calcium with chest computed tomography (CT) may be helpful. There is increasing use of chest CT to assess aortic valve morphology and function. It has become the imaging method of choice to plan for transcatheter aortic valve replacement (TAVR).

Chest X-Ray

The chest x-ray may show no or little overall cardiac enlargement for many years. Hypertrophy without dilation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view. A dilated proximal ascending aorta may be seen along the upper right heart border in the frontal view. Aortic valve calcification may be discernible in the lateral view, but it is usually readily apparent on fluoroscopic examination or by echocardiography; the absence of valvular calcification on fluoroscopy in an adult suggests that severe valvular AS is *not* present. In later stages of the disease, as the LV dilates, there is increasing roentgenographic evidence of LV enlargement, pulmonary congestion, and enlargement of the LA, PA, and right-sided heart chambers.

Catheterization

Right- and left-sided heart catheterization for invasive assessment of AS is performed infrequently but can be useful when there is a discrepancy between the clinical and noninvasive findings. Concern has been raised that attempts to cross the aortic valve for measurement of LV pressures are associated with a risk of cerebral embolization. Catheterization is also useful in three distinct categories of patients: (1) *patients with multivalvular disease*, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment; (2) *young, asymptomatic patients with noncalcific congenital AS*, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is present, even in the absence of symptoms; and (3) *patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve* but rather at the sub- or supravalvular level.

Coronary angiography is indicated to screen for CAD in appropriate patients with severe AS who are being considered for surgical or transcatheter valve replacement. The incidence of significant CAD for which bypass grafting is indicated at the time of surgical aortic valve replacement (SAVR) exceeds 50% among adult patients.

NATURAL HISTORY

Death in patients with severe AS occurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients before surgical treatment became widely available, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; congestive heart failure, 1.5–2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Among adults dying with valvular AS, sudden death, which presumably resulted from an arrhythmia, occurred in 10–20%; however, most sudden deaths occurred in patients who had previously been symptomatic. Sudden death as the first manifestation of severe AS is very uncommon (~1% per year) in asymptomatic adult patients. Calcific AS is a progressive disease, with an annual reduction in valve area averaging 0.1 cm^2 and annual increases in the peak jet velocity and mean valve gradient averaging 0.3 m/s and 7 mmHg, respectively (**Table 256-2**).

TABLE 256-2

Mortality Rates after Aortic Valve Surgery[a]

Operation	Number	Unadjusted Operative Mortality (%)
AVR (isolated)	21,921	2.2
AVR + CAB	13,000	4.0
AVR + MVR	1349	8.0

[a]Data are for the first three quarters of calendar year 2015 during which 1033 sites reported a total of 210,421 procedures. Data (accessed March 9, 2017) are available from the Society of Thoracic Surgeons at *http://www.sts.org/sites/default/files/documents/2015Harvest4_ExecutiveSummary.pdf*.

Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass; MVR, mitral valve replacement.

TREATMENT

TREATMENT

Aortic Stenosis

(Fig. 256-4)

MEDICAL TREATMENT

In patients with severe AS (valve area <1 cm^2), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage. Care must be taken to avoid dehydration and hypovolemia to protect against a significant reduction in CO. Medications used for the treatment of hypertension or CAD, including beta blockers and angiotensin-converting enzyme (ACE) inhibitors, are generally safe for asymptomatic patients with preserved LV systolic function. Nitroglycerin is helpful in relieving angina pectoris in patients with CAD. Retrospective studies suggested that patients with degenerative calcific AS who receive HMG-CoA reductase inhibitors ("statins") exhibit slower progression of leaflet calcification and aortic valve area reduction than those who do not. However, randomized prospective studies with either high-dose atorvastatin or combination simvastatin/ezetimibe have failed to show a measurable effect on valve-related outcomes. The use of statin medications should be driven by considerations regarding primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. ACE inhibitors have not been studied prospectively for AS-related outcomes. The need for endocarditis prophylaxis is restricted to AS patients with a prior history of endocarditis.

SURGICAL TREATMENT

Asymptomatic patients with calcific AS and severe obstruction should be followed carefully for the development of symptoms and by serial echocardiograms for evidence of deteriorating LV function. Operation is indicated in patients with severe AS (valve area <1 cm^2 or 0.6 cm^2/m^2 body surface area) who are symptomatic, those who exhibit LV systolic dysfunction (EF <50%), and those with BAV disease and an aneurysmal root or ascending aorta (maximal dimension >5.5 cm). Operation for aneurysm disease is recommended at smaller aortic diameters (4.5–5.0 cm) for patients with a family history of an aortic catastrophe and for patients who exhibit rapid aneurysm growth (>0.5 cm/year). Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting surgery should also have AVR. In patients without heart failure, the operative risk of SAVR (including patients with AS or AR) is ~2% (Table 256-2) but increases as a function of age and the need for concomitant aortic surgery or coronary revascularization with bypass grafting. The indications for SAVR in the asymptomatic patient have been the subject of intense debate, as surgical outcomes in selected patients have continued to improve. Relative indications for which surgery can be considered include an abnormal response to treadmill exercise; rapid progression of AS, especially when urgent access to medical care might be compromised; very severe AS, defined by an aortic valve jet velocity >5 m/s or mean gradient >60 mmHg and low operative risk; and excessive LV hypertrophy in the absence of systemic hypertension. Exercise testing can be safely performed in asymptomatic patients, as many as one-third of

whom will show signs of functional impairment. A randomized controlled trial (RCT) of SAVR versus active surveillance in patients with asymptomatic severe AS is in the planning stages.

Operation should be carried out promptly (1–3 months) after symptom onset. In patients with low-flow, low-gradient severe AS with reduced LVEF, the perioperative mortality risk is high (15–20%), and evidence of myocardial disease may persist even when the operation is technically successful. Long-term postoperative survival correlates with preoperative LV function. Nonetheless, in view of the even worse prognosis of such patients when they are treated medically, there is usually little choice but to advise valve replacement, especially in patients in whom contractile reserve can be demonstrated by dobutamine stress echocardiography (defined by a ≥20% increase in stroke volume after dobutamine challenge). Patients in this high surgical risk group may benefit from TAVR, (see below), but data from RCTs in this population are lacking. The treatment of patients with low-flow, low-gradient severe AS with normal LVEF is also difficult. Outcomes appear to be better with surgery compared with conservative medical care for symptomatic patients with this type of "paradoxical" low-flow AS, but more research is needed to guide therapeutic decision making. In patients in whom severe AS and CAD coexist, relief of the AS and revascularization may sometimes result in striking clinical and hemodynamic improvement (Table 256-2).

Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to SAVR for AS. The perioperative mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. Assessment of frailty is a critical component of preprocedural evaluation. Treatment decisions for AS patients who are not at low operative risk should be made by a multidisciplinary heart team with representation from general cardiology, interventional cardiology, imaging, cardiac surgery, and other allied specialties as needed, including geriatrics. The 10-year survival rate of older adult patients with AVR is ~60%. Recommendations regarding the type of valve prosthesis (tissue or mechanical) must weigh the trade-offs between durability and thromboembolism/bleeding and are heavily influenced by patient age and preferences. Bioprostheses are favored for patients age >65 years. Shared decision making with younger patients must be individualized. Approximately 30% of bioprosthetic valves evidence primary valve failure in 10 years, requiring re-replacement, and an approximately equal percentage of patients with mechanical prostheses develop hemorrhagic complications as a consequence of treatment with vitamin K antagonists. Homograft AVR is usually reserved for patients with aortic valve endocarditis.

The Ross procedure involves replacement of the diseased aortic valve with the autologous pulmonic valve and implantation of a homograft in the native pulmonic position. Its use has declined considerably in the United States because of the technical complexity of the procedure and the incidence of late postoperative aortic root dilation and autograft failure with AR. There is also a low incidence of pulmonary homograft stenosis.

PERCUTANEOUS AORTIC BALLOON VALVULOPLASTY (PABV)

This procedure is preferable to operation in many children and young adults with congenital, noncalcific AS **(Chap. 264)**. It is not commonly used as definitive therapy in adults with severe calcific AS because of a very high restenosis rate (80% within 1 year) and the risk of procedural complications, but on occasion, it has been used successfully as a "bridge to operation" in patients with severe LV dysfunction and shock who are too ill to tolerate surgery. It is performed routinely as part of the TAVR procedure (see below).

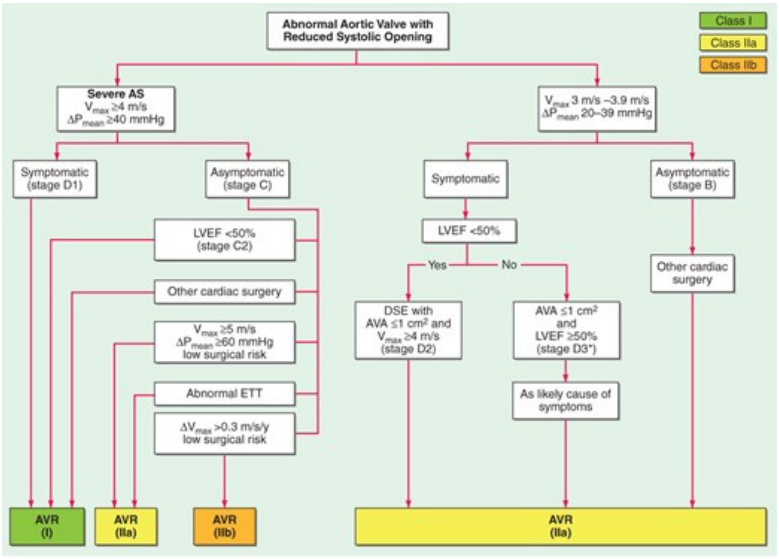
TRANSCATHETER AORTIC VALVE REPLACEMENT

TAVR for treatment of AS has been performed with increasing frequency in prohibitive-, high-, and intermediate surgical-risk adult patients worldwide using one of two available systems, a balloon-expandable valve and a self-expanding valve, both of which incorporate a pericardial prosthesis **(Fig. 256-5)**. Newer valve platforms are under investigation. Nearly 25,000 U.S. patients underwent TAVR in 2015 across more than 415 centers. TAVR is most frequently performed via the transfemoral route, although trans-LV apical, subclavian, carotid, and ascending aortic routes have been used. Aortic balloon valvuloplasty under rapid RV pacing is performed as a first step to create an orifice of sufficient size for the prosthesis. Procedural success rates exceed 90%. Among elderly patients with severe AS who are considered inoperable (i.e., prohibitive surgical risk), 1- and 2-year survival rates are significantly higher with TAVR compared with medical therapy (including PABV) **(Fig. 256-6)**. One- and 2-year survival rates are essentially equal for high-surgical-risk patients treated with TAVR or SAVR **(Fig. 256-7)**. Last, the 2-year rate of death or disabling stroke is lower in intermediate surgical risk patients who undergo transfemoral TAVR compared with SAVR **(Fig. 256-8)**. TAVR is associated with an early hazard for stroke and a higher incidence of postprocedural, paravalvular AR, a risk factor for mortality over the next 2 years. The rate of postprocedural heart block requiring permanent pacemaker (~10%) is significantly more common after TAVR. Valve performance characteristics are excellent over 5 years; longer-term durability assessment is ongoing, but results at 5 years are acceptable. Overall outcomes with this transformative technology have been very favorable and have allowed the extension of AVR to groups of patients previously considered at high or prohibitive risk

for conventional surgery. Nevertheless, some patients are not candidates for this procedure because their comorbidity profile and frailty would make its undertaking inappropriate. The heart team is specifically charged with making challenging decisions of this nature. The use of these devices for the treatment of patients with structural deterioration of bioprosthetic aortic valves ("valve-in-valve"), as an alternative to reoperative valve replacement, has been approved. Presently, patients with BAV are not candidates for TAVR.

FIGURE 256-4

Management strategy for patients with aortic stenosis. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. The class designations refer to the American Heart Association/American College of Cardiology methodology for treatment recommendations. Class I recommendations should be performed or are indicated; Class IIa recommendations are considered reasonable to perform; Class IIb recommendations may be considered. The stages refer to the stages of progression of the disease. At disease stage A, risk factors are present for the development of valve dysfunction; stage B refers to progressive, mild-moderate, asymptomatic valve disease; stage C disease is severe in nature but clinically asymptomatic; stage C1 characterizes asymptomatic patients with severe valve disease but compensated ventricular function; stage C2 refers to asymptomatic, severe disease with ventricular decompensation; stage D refers to severe, symptomatic valve disease. With aortic stenosis, stage D1 refers to symptomatic patients with severe aortic stenosis and a high valve gradient (>40 mmHg mean gradient); stage D2 comprises patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and low left ventricular ejection fraction; and stage D3 characterizes patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and preserved left ventricular ejection fraction (paradoxical, low-flow, low-gradient severe aortic stenosis). AS, aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; V_{max}, maximum velocity. *(Adapted from RA Nishimura et al: J Am Coll Cardiol 70:252, 2017.)*



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

FIGURE 256-5

Balloon-expandable (***A***) and self-expanding (***B***) valves for transcatheter aortic valve replacement (TAVR). B, inflated balloon; N, nose cone; V, valve. *(Part A, courtesy of Edwards Lifesciences, Irvine, CA; with permission. NovaFlex+ is a trademark of Edwards Lifesciences Corporation. Part B, © Medtronic, Inc. 2015. Medtronic CoreValve Transcatheter Aortic Valve. CoreValve is a registered trademark of Medtronic, Inc.)*

Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

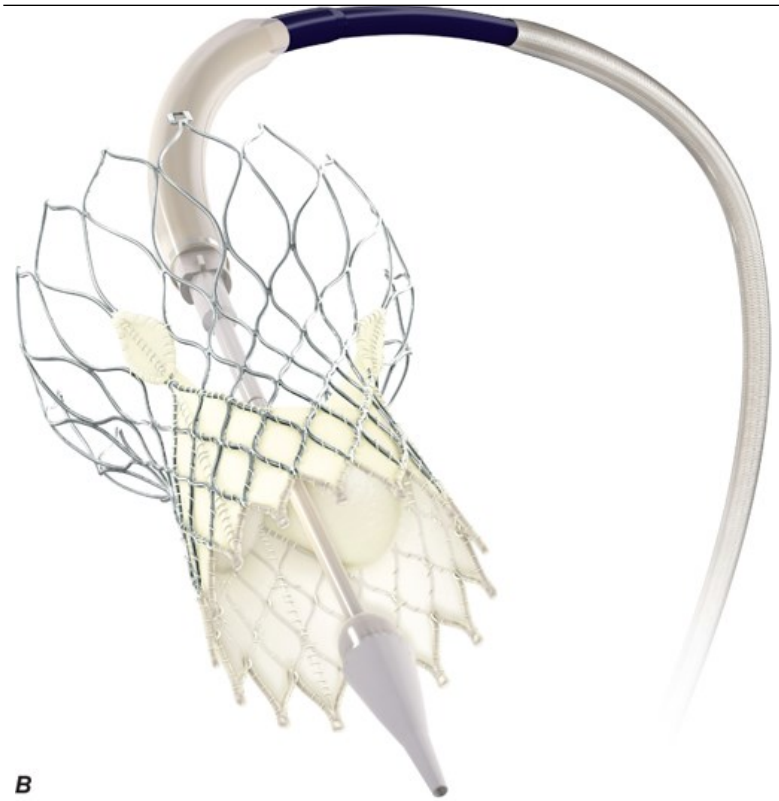
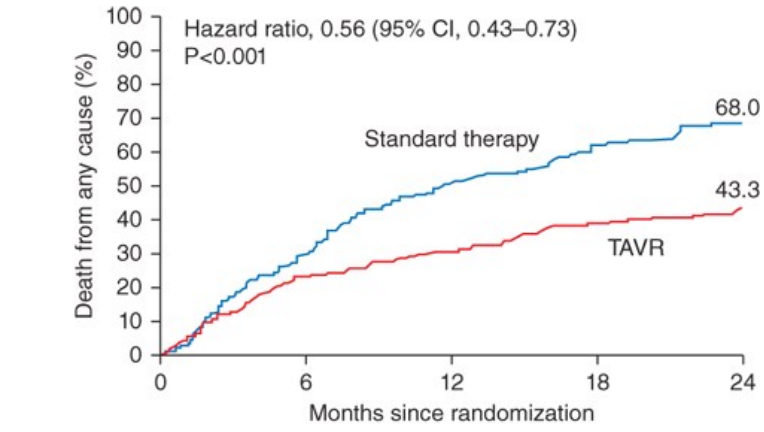


FIGURE 256-6

Twenty-four-month outcomes following transcatheter aortic valve replacement (TAVR) for inoperable patients in the PARTNER I trial (cohort B). CI, confidence interval. *(Adapted from RR Makkar et al: N Engl J Med 366:1696, 2012; with permission.)*



No. at Risk

TAVR	179	138	124	110	83
Standard therapy	179	121	85	62	42

FIGURE 256-7

Five-year mortality rates following transcatheter (TAVR) or surgical aortic valve replacement (SAVR) for high-surgical-risk patients (cohort A) in the PARTNER I trial. Mortality rates in this AS patient cohort are similar for TAVR and SAVR. CI, confidence interval. *(Adapted from MJ Mack et al: Lancet 2015; 385:2477–2484.)*

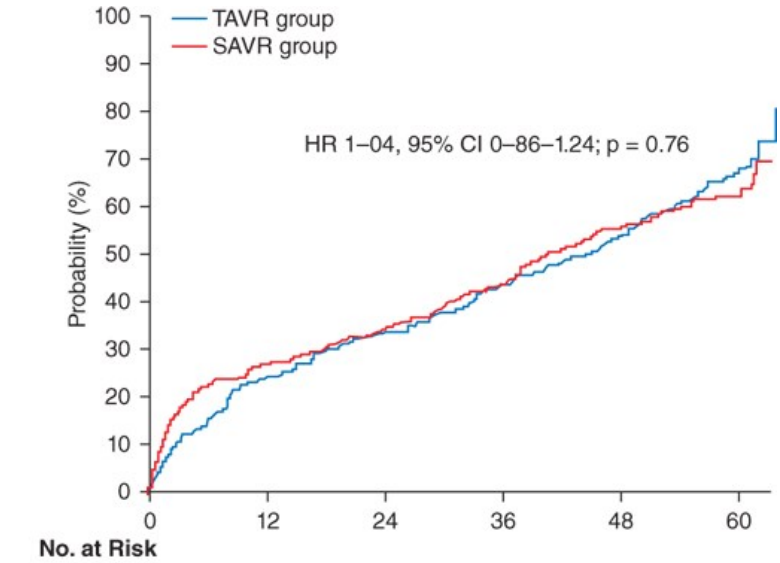
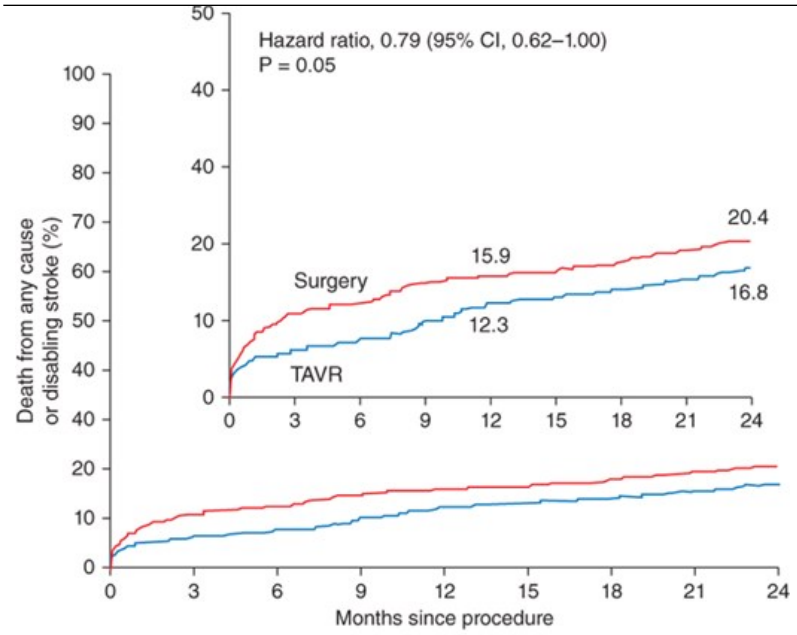


FIGURE 256-8

Rates of death from any cause or disabling stroke for intermediate surgical risk as patients undergoing surgical aortic valve replacement (SAVR) or transfemoral transcatheter aortic valve replacement (TAVR). In this intention-to-treat analysis, transfemoral TAVR proved superior to SAVR. *(Adapted from MB Leon et al: N Engl J Med 374:1609, 2016.)*



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

FURTHER READING

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Nishimura RA et al: 2017 AHA/ACC Focused Update of the 2014 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 Clinical Practice Guidelines. J Am Coll Cardiol 70:252, 2017.