America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more-developed nations and frequently causes serious symptoms in patients younger than 20 years of age. This accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 15 million to 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).

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 with age for both men and women. Important left-sided valve disease may affect as many as 12–13% of adults older than the age of 75. 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).

The incidence of infective endocarditis (Chap. 155) 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 associated with an increase in incidence rates. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation.

Bicuspid aortic valve 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. Management decisions and outcome differences based on age, gender, race, and geography require educational efforts across all levels of providers.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 51e and 267; of electrocardiography (ECG) in Chap. 268; of echocardiography and other noninvasive imaging techniques in Chap. 270e; and of cardiac catheterization and angiography in Chap. 272.

TABLE 283-1 MAJOR CAUSES OF AORTIC VALVE DISEASE

Valve Lesion	Etiologies
Aortic stenosis	Congenital (bicuspid, unicuspid)
	Degenerative calcific
	Rheumatic fever
	Radiation
Aortic regurgitation	Valvular
	Congenital (bicuspid)
	Endocarditis
	Rheumatic fever
	Myxomatous (prolapse)
	Traumatic
	Syphilis
	Ankylosing spondylitis
	Root disease
	Aortic dissection
	Cystic medial degeneration
	Marfan's syndrome
	Bicuspid aortic valve
	Nonsyndromic familial aneurysm
	Aortitis
	Hypertension

AORTIC STENOSIS

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

ETIOLOGY AND PATHOGENESIS

(Table 283-1) AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (bicuspid aortic valve), chronic (trileaflet) deterioration, or previous rheumatic inflammation. A pathologic study of specimens removed at the time of aortic valve replacement for AS 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. 283-1). Eventually, 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 older than age 65. Approximately 30% of persons older than 65 years exhibit aortic valve sclerosis, whereas 2% exhibit frank stenosis.

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 the 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. 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 approximately 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 independent of the hemodynamic severity of the valve lesion and is a risk factor 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.