

## REVIEW ARTICLE

John A. Jarcho, M.D., *Editor*

## Aortic-Valve Stenosis — From Patients at Risk to Severe Valve Obstruction

Catherine M. Otto, M.D., and Bernard Prendergast, D.M.

From the Division of Cardiology, Department of Medicine, University of Washington School of Medicine, Seattle (C.M.O.); and the Department of Cardiology, John Radcliffe Hospital, Oxford, United Kingdom (B.P.). Address reprint requests to Dr. Otto at the Division of Cardiology, University of Washington, 1959 N.E. Pacific St., Box 356422, Seattle, WA 98195, or at [cmotto@u.washington.edu](mailto:cmotto@u.washington.edu).

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**V**ALVULAR AORTIC STENOSIS IS A PROGRESSIVE DISEASE IN WHICH THE END stage is characterized by obstruction of left ventricular outflow, resulting in inadequate cardiac output, decreased exercise capacity, heart failure, and death from cardiovascular causes. The prevalence of aortic stenosis is only about 0.2% among adults between the ages of 50 and 59 years but increases to 9.8% in octogenarians, with an overall prevalence of 2.8% in adults older than 75 years of age.<sup>1,2</sup> Although mortality is not increased when aortic stenosis is asymptomatic, the rate of death is more than 50% at 2 years for patients with symptomatic disease unless aortic-valve replacement is performed promptly.<sup>3,4</sup>

A total of 65,000 aortic-valve replacements were performed in the United States in 2010, primarily for aortic stenosis; 70% of these procedures were performed in patients older than 65 years of age, contributing to the high cost of health care in our aging population.<sup>5</sup> Currently, there are no medical therapies to prevent or slow the progression of the disease. Instead, improving patient outcomes depends on identifying those at risk for valve disease, accurately measuring the severity of stenosis, managing any concurrent disease, and ensuring the appropriate timing and type of aortic-valve replacement.<sup>6,7</sup>

## STAGES OF DISEASE

The spectrum of aortic stenosis starts with the risk of leaflet changes and progresses from early lesions to valve obstruction, which is initially mild to moderate but eventually becomes severe, without or with clinical symptoms.<sup>6</sup> The severity of aortic stenosis is best characterized by integration of information concerning valve anatomy, hemodynamics, symptoms, and the left ventricular response to pressure overload (Table 1 and Fig. 1; and interactive graphic, available with the full text of this article at NEJM.org). Commonly used indexes of the severity of stenosis include the maximum transvalvular velocity and the mean transaortic pressure gradient. These measures remain relatively normal early in the disease course, and symptoms are unusual until the maximum transvalvular velocity is more than four times the normal velocity (i.e., increased to 4.0 m per second). However, patients with concurrent left ventricular systolic dysfunction may have severe valve obstruction with a low velocity and pressure gradient but a small aortic-valve area. Rarely, patients may have severe low-gradient aortic stenosis even with a normal left ventricular ejection fraction.

## RISK OF AORTIC STENOSIS

Anatomical, genetic, and clinical factors all contribute to the pathogenesis of aortic stenosis. Calcification occurs in many patients with a normal trileaflet aortic valve, but the presence of a congenital bicuspid valve accounts for 60% of the patients



An interactive graphic showing echocardiographic evaluation of aortic-valve stenosis is available at NEJM.org

**Table 1. Disease Stages in Patients with Aortic-Valve Stenosis.\***

Stage	Description	Definition†	Outcomes	Management
A	At risk	Aortic-valve sclerosis or bicuspid valve; $V_{\max}$ of <2 m/sec	Associated with a 50% increase in the risk of myocardial infarction and cardiovascular death over 5 yr	Assessment of cardiovascular risk factors and primary prevention
B	Progressive	Mild-to-moderate calcification or rheumatic changes with reduced leaflet motion; $V_{\max}$ of 2 to 3.9 m/sec or mean transaortic pressure gradient of 20 to 39 mm Hg	Hemodynamic progression in most patients	Assessment of cardiovascular risk factors and primary prevention; periodic clinical and echocardiographic monitoring; patient education about disease progression and outcomes
C1	Asymptomatic, severe aortic stenosis with normal left ventricular function	Severe calcification or rheumatic changes with reduced leaflet motion; $V_{\max}$ of $\geq 4$ m/sec or mean transaortic pressure gradient of $\geq 40$ mm Hg with an ejection fraction of $\geq 50\%$	Symptom onset in 50 to 80% of patients within 3 yr; low risk of sudden death; variability in severity at symptom onset; symptom onset in >50% of patients with very severe aortic stenosis ( $V_{\max}$ of >5 m/sec) within 2 yr	Frequent clinical monitoring ( $\leq 6$ mo) and echocardiographic monitoring ( $\leq 12$ mo) for symptom onset and disease progression; consider treadmill exercise testing or testing serum levels of brain natriuretic peptide; AVR is reasonable with asymptomatic very severe aortic stenosis
C2	Asymptomatic, severe aortic stenosis with ejection fraction <50%	Severe calcification or rheumatic changes with reduced leaflet motion; $V_{\max}$ of $\geq 4$ m/sec or mean transaortic pressure gradient of $\geq 40$ mm Hg with an ejection fraction <50%	If other causes of left ventricular dysfunction are absent, the ejection fraction is likely to normalize after AVR	AVR is recommended to preserve left ventricular function
D1	Symptomatic, severe, high-gradient aortic stenosis	Severe calcification or rheumatic changes with reduced leaflet motion; $V_{\max}$ of $\geq 4$ m/sec or mean transaortic pressure gradient of $\geq 40$ mm Hg	Mortality is 50% at 1 yr, 70 to 80% at 2 yr without AVR	Prompt AVR is the only effective therapy
D2	Symptomatic, severe, low-gradient aortic stenosis with ejection fraction <50%	Severe calcification or rheumatic changes with reduced leaflet motion; baseline AVA of $\leq 1$ cm <sup>2</sup> with $V_{\max}$ of <4 m/sec with an ejection fraction of <50%; $V_{\max}$ of $\geq 4$ m/sec with AVA of $\leq 1$ cm <sup>2</sup> at any flow rate on low-dose dobutamine stress testing	Mortality at 2 yr is about 80% with medical therapy, as compared with 40% with AVR; operative mortality is higher and survival lower in patients without contractile reserve	AVR is reasonable if severe aortic stenosis is present; the ejection fraction is likely to improve after AVR, even in patients without contractile reserve
D3	Symptomatic, severe, low-flow, low-gradient aortic stenosis with normal ejection fraction	Severe calcification or rheumatic changes with reduced leaflet motion; baseline AVA of $\leq 1$ cm <sup>2</sup> and $V_{\max}$ of <4 m/sec with an ejection fraction of $\geq 50\%$ ; indexed AVA of $\leq 0.6$ cm <sup>2</sup> /m <sup>2</sup> with stroke volume index of <35 ml/m <sup>2</sup> when patient is normotensive	Mortality at 2 yr is 50 to 70% without AVR	AVR is reasonable in symptomatic patients if evaluation indicates the presence of severe aortic stenosis and there is no other cause for symptoms

\* AVA denotes aortic-valve area, AVR aortic-valve replacement, and  $V_{\max}$  aortic maximum velocity.

† Echocardiography is diagnostic for the evaluation of the severity of aortic stenosis in nearly all patients. However, these measurements require considerable technical expertise and adequate image quality, so the underestimation of the severity of aortic stenosis should be considered if the echocardiographic data are discrepant with clinical findings. Additional evaluation by repeat echocardiography at a specialist heart-valve center, cardiac catheterization, or other imaging method may be needed in some patients.

younger than 70 years of age who undergo valve replacement for severe aortic stenosis and for 40% of those 70 years of age or older.<sup>8,9</sup> Bicuspid aortic-valve disease is present in 1 to 2% of the U.S. population, and nearly all affected persons require aortic-valve replacement during their lifetimes.<sup>9-12</sup> Although rheumatic heart disease, which can cause aortic stenosis in association with rheumatic mitral-valve disease, is now rare in the United States and Europe, the condition remains prevalent in underdeveloped countries, where improvement in primary prevention (treatment of streptococcal throat infections) is needed.<sup>13,14</sup>

A genetic component in calcific aortic stenosis is suggested by familial clustering of patients with bicuspid aortic valves in a pattern suggesting autosomal dominant inheritance with variable penetrance. A specific gene abnormality has not been identified, and only about one third of families have more than one affected family member.<sup>15</sup> Familial clustering has also been reported for calcific trileaflet aortic stenosis, with several generations of patients descended from a single ancestor.<sup>16</sup> In a few families with congenital aortic-valve abnormalities and valve calcification, a mutation in *NOTCH1* has been documented.<sup>17</sup> In a genomewide linkage meta-analysis of three large population-based studies, a specific lipoprotein(a) polymorphism was shown to be associated with elevated serum levels of lipoprotein(a), aortic-valve calcification, and incident aortic stenosis.<sup>18</sup>

Clinical factors associated with calcific valve disease mirror those associated with coronary atherosclerosis, and coronary artery disease is common among adults with aortic stenosis.<sup>2</sup>

Population-based studies have shown associations between calcific valve disease and older age, male sex, elevated serum levels of low-density lipoprotein (LDL) cholesterol and lipoprotein(a), hypertension, smoking, diabetes, and the metabolic syndrome.<sup>19,20</sup>

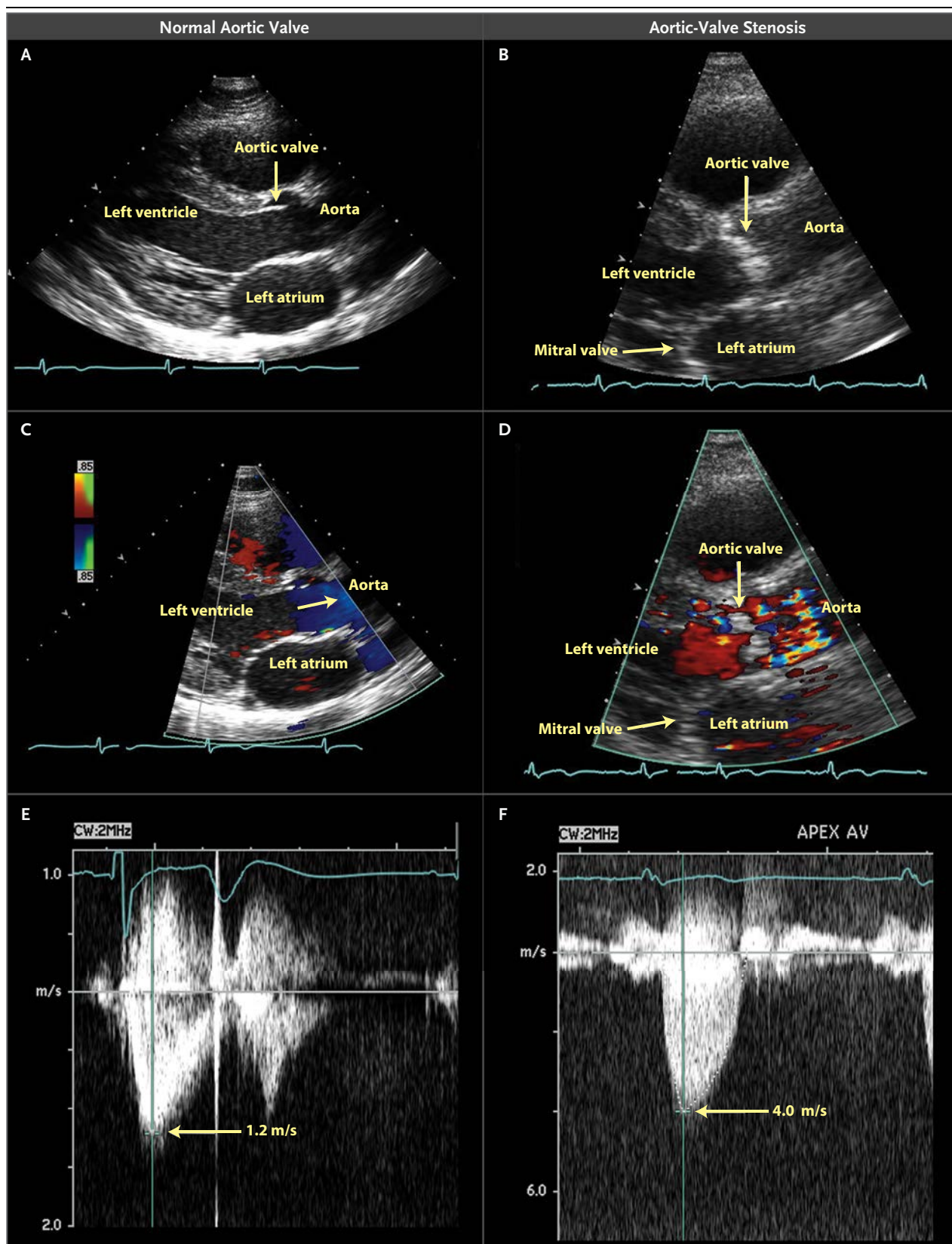
Specific populations at increased risk for aortic stenosis include patients with a history of mediastinal irradiation, renal failure, familial hypercholesterolemia, or disorders of calcium metabolism.<sup>21</sup> The role of subtle differences in calcium metabolism has received increased attention, with one study showing a close relationship between serum phosphate levels and calcific aortic-valve disease.<sup>22</sup>

#### DISEASE PREVENTION

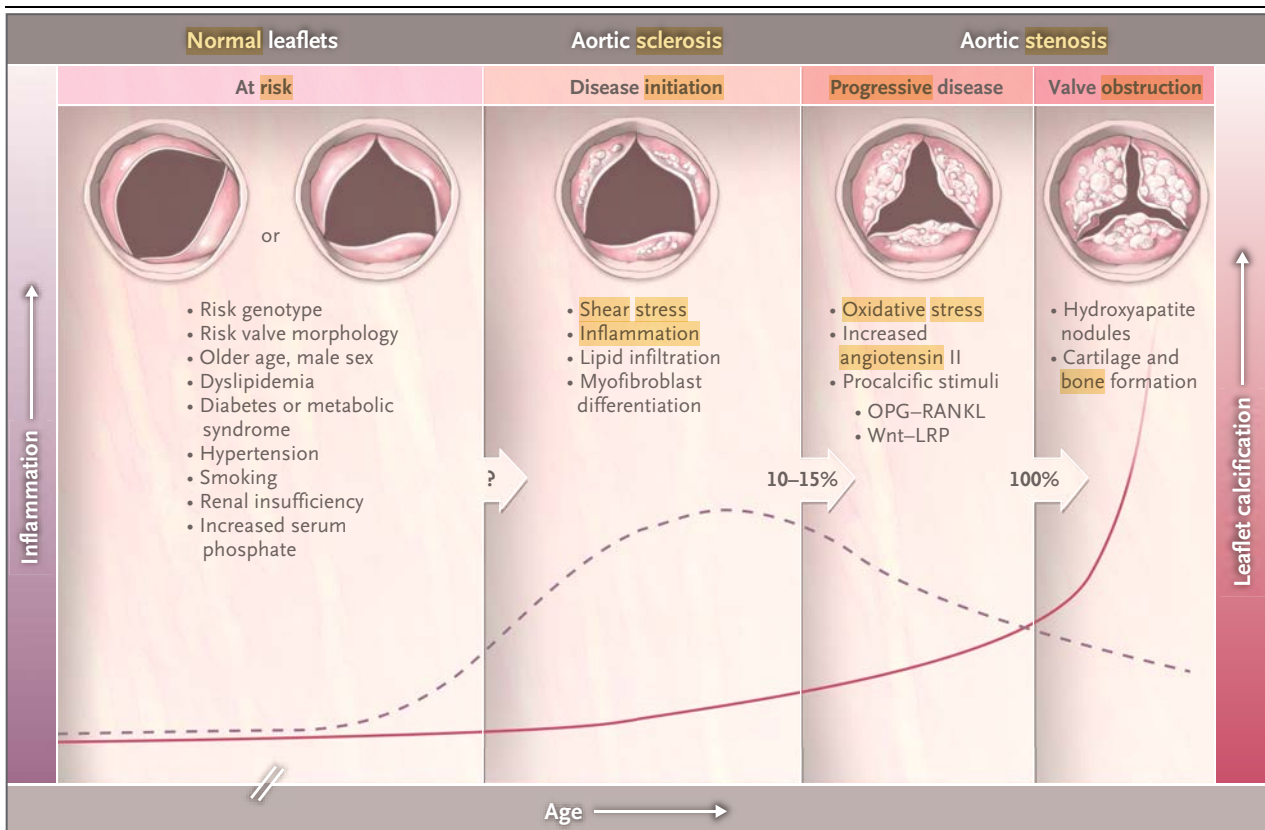
Calcific aortic stenosis is due to an active disease process at the cellular and molecular levels<sup>23,24</sup> (Fig. 2). Differences between disease initiation and progression that are observed at the tissue level are also seen in studies showing that clinical factors associated with the early stage of the disease process differ from those associated with progression. For example, although elevated serum lipid levels are associated with aortic-valve sclerosis, there is no convincing evidence that elevated serum LDL levels are associated with more rapid disease progression.<sup>20</sup> Similarly, systemic markers of inflammation are not associated with progression of aortic-valve disease.<sup>25</sup> Transformation at the tissue level from early to progressive disease probably explains why prospective, randomized clinical trials of lipid-lowering

**Figure 1 (facing page). Echocardiographic Evaluation of Aortic-Valve Stenosis.**

Panel A shows a long-axis, two-dimensional echocardiographic view of a normal aortic valve, in which the thin valve leaflets are seen in the open position, parallel to the walls of the aorta, in mid-systole. The left ventricle is normal in size and wall thickness, the mitral valve is closed, and the left atrium is not enlarged. Panel B shows the corresponding view of a stenotic aortic valve, in which the calcified, thickened, and relatively immobile leaflets are seen in systole as a bright white band that obstructs left ventricular outflow. The mitral valve is closed in systole. The left ventricle shows increased wall thickness, and the left atrium is enlarged. Panel C shows color Doppler imaging of a normal aortic valve with unobstructed flow across the aortic valve shown in blue during systole. Panel D shows the corresponding image of a stenotic aortic valve with normal flow proximal to the aortic valve (in red) with a mixture of colors in the aorta, reflecting the increase in velocity and pressure drop across the valve. Panel E shows a continuous-wave Doppler recording of normal antegrade flow across the aortic valve, obtained with the transducer at the left ventricular apex. The vertical axis shows the velocity in meters per second (m/s) with aortic flow, which is directed away from the transducer, shown below the baseline. The electrocardiogram (ECG) is shown in blue at the top of the image with standard ECG timing markers at 0.2 seconds (minor tick marks) and 1.0 second (major tick marks). The flow velocity profile seen during systole is normal, with a triangular shape (early peaking) and a maximum velocity of 1.2 m per second. The signals in diastole represent normal mitral inflow signals. Panel F shows a corresponding recording of high-velocity flow across a stenotic aortic valve. The vertical axis shows a scale up to 6 m per second for flow directed away from the transducer. The aortic-stenosis velocity profile shows a high-velocity pattern (typically 4 m per second or higher) with a peak in mid-systole and a more rounded shape than normal flow. This patient has little aortic regurgitation, which would be seen in diastole if present.







**Figure 2. Disease Mechanisms and Time Course of Calcific Aortic Stenosis.**

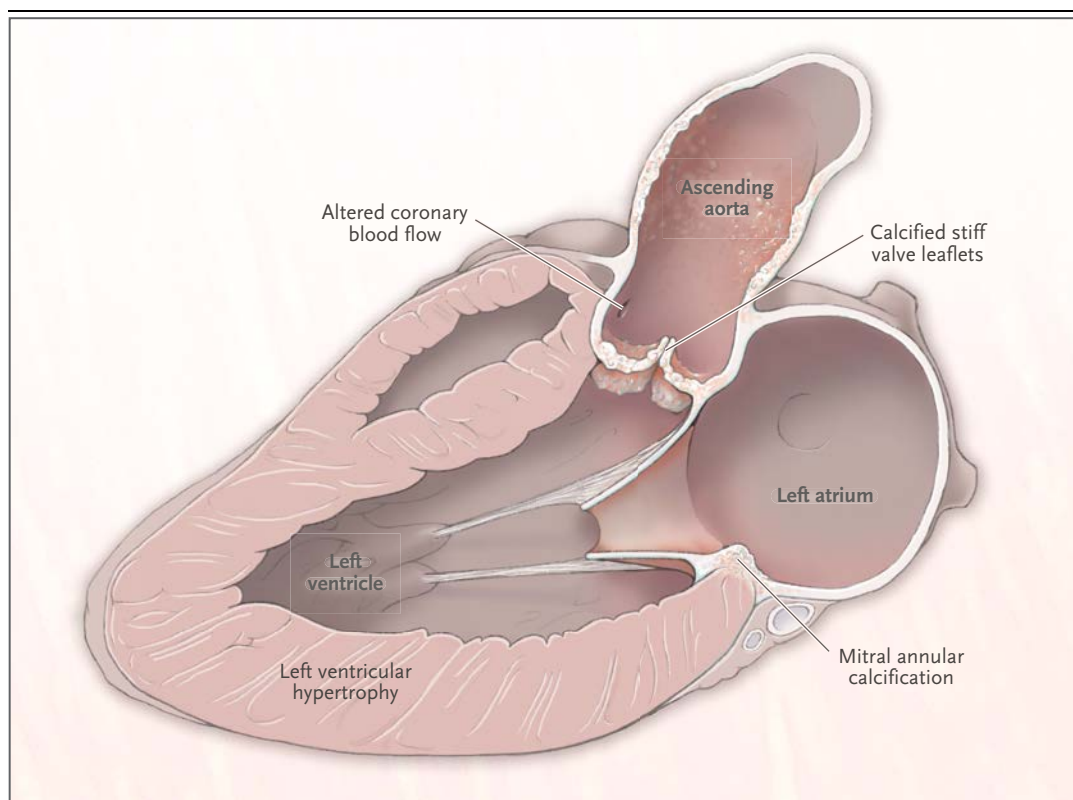
Shown is the relationship among disease stage, valve anatomy, clinical risk factors, mechanisms of disease, and the age of the patient. Endothelial disruption with inflammation (dashed line) and lipid infiltration are key elements in the initiation of disease. There are few data on the prevalence of 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 aortic sclerosis. Once these disease mechanisms are activated, leaflet calcification results in severe aortic stenosis in nearly 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 denotes lipoprotein receptor–related protein complex, OPG osteoprotegerin, and RANKL receptor activator of nuclear factor  $\kappa$ B ligand.

therapy in adults with mild-to-moderate aortic stenosis showed no significant effect on disease progression or aortic-valve events.<sup>26,27</sup>

Once leaflet disease is present, hemodynamic progression is associated with older age, male sex, the severity of stenosis, and the degree of leaflet calcification. Progression from aortic sclerosis to valve obstruction occurs in only about 10 to 15% of patients over a period of 2 to 5 years.<sup>20,25</sup> Once even mild valve obstruction is present, progressive stenosis occurs in nearly all patients, and most of them eventually require valve replacement.<sup>27–31</sup> On average, the maximum transvalvular velocity increases by 0.1 to 0.3 m per second per year, with the mean gradient increasing by 3 to 10 mm Hg per year and the

valve area decreasing by 0.1 cm<sup>2</sup> per year.<sup>28</sup> These average values are somewhat helpful in counseling patients but do not allow precise prediction of when aortic-valve replacement will be needed, because hemodynamic progression varies widely among patients and often accelerates as stenosis becomes more severe.<sup>1</sup> The degree of aortic stenosis associated with the onset of symptoms also differs among patients, with some patients remaining asymptomatic for several years despite hemodynamically severe disease.

Increased understanding of the specific disease pathways involved in calcific valve disease, the clinical and genetic associations with aortic stenosis, and the observed natural variation in disease progression all suggest that medical



**Figure 3. Anatomical Changes Associated with Aortic Stenosis.**

Aortic-valve stenosis is associated with left ventricular hypertrophy, diastolic dysfunction, and decreased longitudinal shortening, although the ejection fraction remains normal in most patients. Left atrial enlargement is common owing to elevated left ventricular filling pressures. Calcification is often seen in the ascending aorta and mitral annulus, as well as on the valve leaflets. Mitral annular calcification is often accompanied by mild-to-moderate mitral regurgitation and can extend onto the leaflets, causing obstruction to left ventricular inflow. Patients with a severely calcified, rigid, and fragile (“porcelain”) ascending aorta have better outcomes with transcatheter aortic-valve replacement than with surgical replacement. Coronary blood-flow patterns are abnormal owing to an increased left ventricular mass and a reduced diastolic pressure gradient.

therapy might prevent or delay disease progression. In addition to lifestyle and pharmacologic interventions to reduce cardiovascular risk, treatment might be targeted to specific cellular and molecular pathways at various time points in the disease process, including pathways involved in oxidative stress, the renin–angiotensin system, and triggers of abnormal tissue calcification.<sup>24,32,33</sup> However, at present no medical therapies have been shown to prevent disease progression.

#### AORTIC STENOSIS AS A SYSTEMIC DISEASE

Several lines of evidence suggest that aortic stenosis is not simply a mechanical problem limited to the valve leaflets. The disease affects the upstream left ventricle and the downstream systemic vas-

culature, as well as the valve itself<sup>34</sup> (Fig. 3). Anatomically, abnormal tissue calcification affects the entire cardiovascular system, not just the aortic valve. In addition, dilatation of the ascending aorta is common and may need to be addressed at the time of valve replacement. The association between aortic stenosis and aortic dilatation is complicated by the phenotypic overlap between calcific aortic stenosis and congenital bicuspid-valve disease. Patients with bicuspid aortic valves, as compared with those with trileaflet aortic valves, have larger aortic diameters<sup>35,36</sup> and an increased long-term risk of aortic dissection, with estimates of 3.1 cases per 10,000 patient-years, for an age-adjusted relative risk of 8.4.<sup>11,35,37</sup>

In some patients with aortic stenosis, angiodysplastic gastrointestinal bleeding is seen in association with an acquired deficiency of von

Willebrand factor multimers, a condition known as Heyde's syndrome.<sup>38</sup> Unfolding of the von Willebrand multimers owing to abnormal shear stress as blood passes through the narrow valve results in cleavage by a specific plasma metalloproteinase. Low levels of von Willebrand factor also affect platelet function and may confer a predisposition to angiogenesis; these abnormalities typically normalize after valve replacement.<sup>39</sup> Clinically, there is a complex interplay between increased bleeding and thrombotic events, with some studies showing enhanced thrombin formation and platelet activation.<sup>40</sup>

Rheumatic aortic stenosis is usually accompanied by mitral-valve disease and is more likely than calcific disease to manifest as mixed stenosis and regurgitation of both valves, rather than as an isolated single-valve lesion, a factor that can complicate decision making.<sup>13</sup> In addition, rheumatic-valve disease is often associated with tricuspid-valve involvement, pulmonary hypertension, and right-heart dysfunction.

Adverse cardiovascular outcomes are seen with aortic-valve calcification even in the absence of valve obstruction. In the Cardiovascular Health Study (CHS), the presence of aortic sclerosis in adults older than 65 years of age without known coronary artery disease was associated with a 52% increase in the risk of death from cardiovascular causes and a 40% increase in the risk of myocardial infarction over the course of 5 years, even when the analysis was corrected for known cardiovascular risk factors.<sup>41</sup> In the higher-risk population in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, aortic-valve sclerosis in patients without known cardiovascular disease was associated with a doubling of cardiovascular risk.<sup>42</sup> In a population similar to the CHS cohort, the Multi-Ethnic Study of Atherosclerosis (MESA) showed that aortic-valve calcification was associated with a 50% increase in the risk of cardiovascular events.<sup>20</sup> Similarly, in the Heinz Nixdorf Recall Study, the degree of aortic-valve calcification provided additive value to Framingham Heart Study risk factors for the prediction of cardiovascular events.<sup>43</sup> Further studies are needed to explore whether aortic sclerosis is a marker of coronary artery disease or whether it reflects a shared underlying risk factor, such as systemic inflammation.

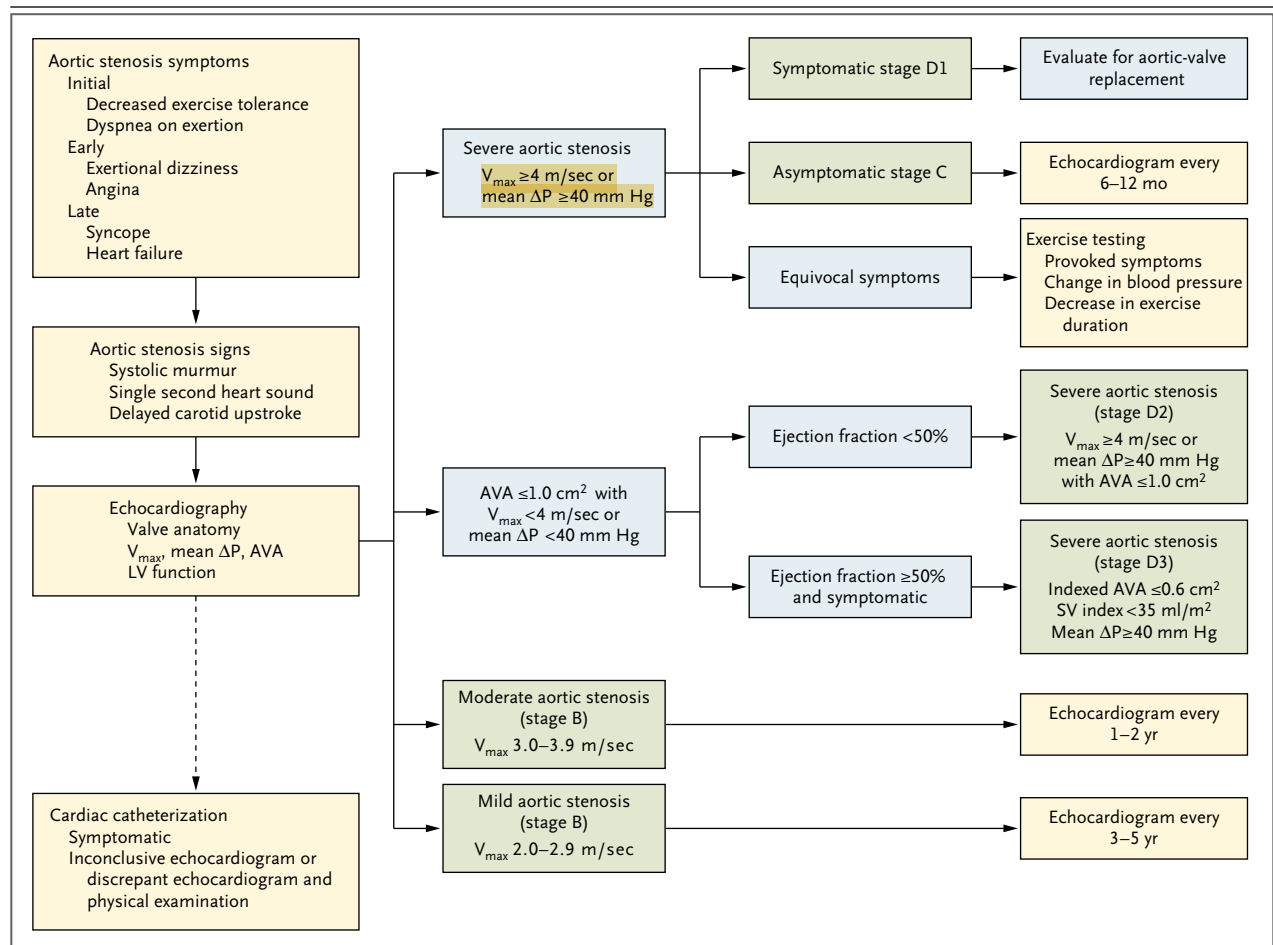
## TIMING OF AORTIC-VALVE REPLACEMENT

Clinical outcomes in adults with aortic stenosis are determined primarily by clinical symptoms, the severity of valve obstruction, and the left ventricular response to pressure overload. Assessment of patients and management decisions should take all three of these factors into account.<sup>6,7</sup>

The presence or absence of symptoms is the key element in decision making (Fig. 4). There is robust evidence that aortic-valve replacement prolongs life in patients with symptomatic severe aortic stenosis, regardless of the type or severity of symptoms or the response to medical therapy.<sup>3,4,44,45</sup> However, accurate measures of the severity of stenosis are needed to ensure that valve obstruction — rather than concurrent coronary, pulmonary, or systemic disease or other conditions — is the cause of symptoms. In a patient with typical symptoms, a maximum transvalvular velocity of 4 m per second or greater, in conjunction with calcified immobile valve leaflets, confirms the diagnosis of severe aortic stenosis.<sup>6,28,30,46</sup> With symptomatic, severe, high-gradient aortic stenosis, calculation of the valve area or indexed valve area does not improve the identification of patients who will benefit from valve replacement (Fig. 5).<sup>47</sup>

In contrast, in asymptomatic patients with aortic stenosis and normal left ventricular systolic function, the usefulness of measures of severity is in identifying patients who will soon become symptomatic, thus indicating the need for frequent follow-up and consideration of elective intervention. Intervention is not needed until symptoms supervene, because the risk of sudden death is less than the risk of intervention, even when valve obstruction is severe.<sup>31,48</sup> With very severe aortic stenosis, the rate of symptom onset is so high that elective valve replacement may be reasonable in selected cases.<sup>49-51</sup>

Given the importance of symptom onset in clinical decision making, primary care physicians and cardiologists need to be alert to the presence of a systolic murmur in older adults with exertional dyspnea, chest pain, or dizziness. In the case of apparently asymptomatic patients with severe aortic stenosis, detailed questions should be asked about levels of physi-



**Figure 4. Diagnostic Approach to the Treatment of Suspected Aortic Stenosis.**

Shown is a diagnostic algorithm for the treatment of patients with suspected aortic stenosis. The classic triad of symptoms of aortic stenosis — angina, dyspnea, and syncope — occurs late in the disease process. With improved diagnosis and prospective management, the most common presenting symptoms currently are decreased exercise tolerance and exertional dyspnea. Although a loud systolic murmur with a palpable thrill is specific for severe aortic stenosis, a softer murmur does not exclude severe aortic stenosis. Other clues that suggest severe aortic stenosis include a single second heart sound or a delayed and diminished carotid upstroke (“parvus and tardus”), although the sensitivity and specificity of these findings are suboptimal. Thus, echocardiography is appropriate to evaluate for aortic stenosis in any patient (particularly older adults, given the disease demographics) with a systolic murmur and symptoms that might be due to aortic stenosis. On the basis of echocardiographic findings, the severity of aortic stenosis is categorized into stages, as shown. In stage D3 disease, echocardiographic or catheterization measurements should be obtained when the patient is normotensive, because hypertension can alter hemodynamics, resulting in either overestimation or underestimation of severity. In addition, other potential causes of symptoms should be ruled out or treated before aortic-valve replacement is considered in patients with apparently severe aortic stenosis who have a low gradient and normal ejection fraction. Such patients often have a small aortic annulus, so the anticipated hemodynamics of the prosthetic valve should also be considered to avoid patient–prosthesis mismatch if aortic-valve replacement is performed. AVA denotes aortic-valve area, LV left ventricle, ΔP transaortic pressure gradient, SV stroke volume, and  $V_{\max}$  aortic maximum velocity.

cal activity, because many patients unconsciously limit activities to avoid symptoms as valve obstruction slowly worsens. When the clinical history is unclear, standard treadmill exercise testing is helpful to detect provoked symptoms,

ensure that blood pressure rises appropriately, and measure exercise capacity objectively.<sup>52,53</sup>

Evaluation of the severity of stenosis is more difficult when the valve appears to be calcified with only a **moderately** elevated transvalvular



velocity (3 to 4 m per second) or mean transaortic pressure gradient (20 to 40 mm Hg), but the calculated valve area is less than 1.0 cm<sup>2</sup>. This situation, termed low-flow, low-gradient aortic stenosis, occurs most often in patients with a reduced left ventricular ejection fraction (<50%). These patients may have severe aortic stenosis with afterload mismatch causing left ventricular dysfunction, in which case valve replacement will prolong survival and improve the ejection fraction. Alternatively, valve obstruction may only be moderate, with the apparently small valve area caused by primary dysfunction of the myocardium. Low-dose dobutamine stress echocardiography is a useful additional test in such patients. During stress testing, a transvalvular velocity that increases to 4 m per second or higher with the valve area remaining less than 1.0 cm<sup>2</sup> is consistent with severe aortic stenosis. Conversely, a transvalvular velocity of less than 4 m per second or an increase in valve area is consistent with only moderate valve obstruction, and evaluation for other causes of left ventricular dysfunction and medical therapy for heart failure are appropriate.<sup>54-56</sup>

Diagnosis of low-flow, low-gradient, severe aortic stenosis with a normal left ventricular ejection fraction is particularly challenging. Because transvalvular velocity is less than 4 m per second, diagnosing this condition depends on indexing the valve area and volume flow rate to the body-surface area. In symptomatic patients with a calcified aortic valve and decreased leaflet mobility, an indexed valve area of 0.6 cm<sup>2</sup> per square meter of body-surface area and a stroke volume index of less than 35 ml per square meter are consistent with a diagnosis of severe aortic stenosis. This situation is seen most often in elderly women with left ventricular hypertrophy, small

ventricular volumes, diastolic dysfunction, and reduced longitudinal shortening.<sup>57,58</sup>

#### SELECTION OF VALVE-REPLACEMENT PROCEDURE

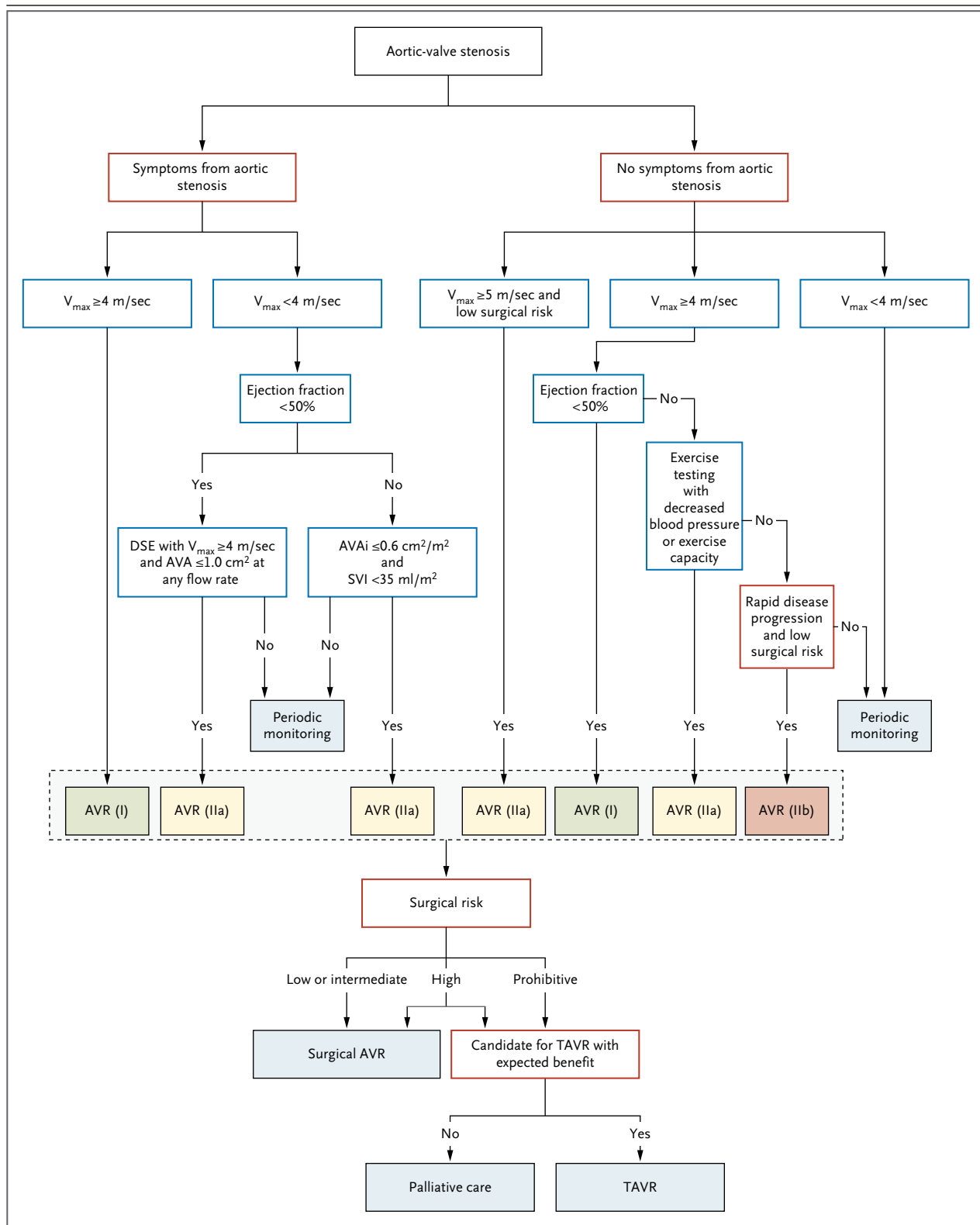
The goals of intervention in aortic stenosis are to relieve symptoms, enhance exercise capacity and quality of life, and prolong life expectancy. Indirect physiological benefits include improvement in left ventricular function and regression of left ventricular hypertrophy. Aortic-valve replacement should be considered, regardless of the patient's age at presentation, if overall life expectancy is greater than 1 year and there is a likelihood of survival of more than 25% with improved symptoms at 2 years after the procedure.

The determination of procedural risk and the correct choice of intervention for an individual patient require a multifactorial approach, including assessments of coexisting coronary artery disease, other valve lesions, and noncardiac conditions; frailty; results of invasive and noninvasive anatomical testing; and overall life expectancy.<sup>6,59</sup> These assessments are best performed by a multidisciplinary group of clinicians, including valve experts, imaging specialists, interventional cardiologists, cardiac surgeons and anesthesiologists, and physicians with experience in the care and assessment of the elderly. Such a group, termed a "heart team," can develop an individualized risk-benefit analysis of the available options for aortic-valve replacement. Patients and their families should also be involved in a shared decision-making process that reflects the preferences and values of the patient.

Surgical aortic-valve replacement remains the standard approach, except in the case of inoperable conditions and procedures with a high esti-

#### Figure 5 (facing page). Indications for Aortic-Valve Replacement (AVR).

Shown are recommendations from the 2014 guidelines of the American College of Cardiology and the American Heart Association for the treatment of patients with valvular heart disease.<sup>6</sup> Clinical factors are shown in open red boxes, imaging findings in open blue boxes, overall treatment recommendations in solid blue boxes, and AVR recommendations in other solid boxes (green for class I, yellow for class IIa, and brown for class IIb recommendations). The decision as to whether AVR is indicated is made before consideration of the choice of AVR type, as indicated by the placement of the AVR recommendations in a dashed black box. If the estimated surgical risk is low to intermediate, surgical AVR is recommended. If the surgical risk is high, transcatheter AVR (TAVR) should also be evaluated. When surgical risk is prohibitive, TAVR is recommended, with palliative care as an option in patients who will not benefit from intervention because of coexisting conditions, frailty, impaired mental status, or low functional status. AVAi denotes aortic-valve area indexed to body-surface area, DSE dobutamine stress echocardiography, SVI stroke volume index, and V<sub>max</sub> aortic maximum velocity.



mated surgical mortality.<sup>60</sup> Overall 30-day surgical mortality is less than 3% for isolated aortic-valve replacement and approximately 4.5% for aortic-valve replacement with coronary-artery bypass grafting. After recovery from successful aortic-valve replacement, the rate of overall survival is similar to that among age-matched adults without aortic stenosis.

The primary consideration in the choice of valve type is the risk of reoperation when a bioprosthetic valve is used versus the risk associated with warfarin anticoagulation when a mechanical valve is used. Mechanical valves are appropriate for patients younger than 60 years of age who have no contraindication to anticoagulation, because of the long-term durability of these prostheses. An exception is women of childbearing age, in whom a bioprosthetic valve is preferred, given the risks of anticoagulation and thromboembolism during pregnancy. In patients older than 70 years of age, bioprostheses are favored because valve durability increases with age and the risks of anticoagulation are avoided.<sup>61</sup> In patients between 60 and 70 years of age, the choice of valve is based on patients' preferences and values after a shared discussion between the patient and the surgeon.

Transcatheter aortic-valve replacement (TAVR) is recommended in patients with symptomatic severe aortic stenosis who have a prohibitive surgical risk, which is defined as a predicted risk of death or major complication with surgery of more than 50% at 1 year, a medical condition involving three other major organ systems that is not likely to be improved postoperatively, or a severe impediment to surgery, such as a heavily calcified, fragile ("porcelain") aorta. In a prospective, randomized clinical trial, TAVR provided a reduction in 2-year all-cause mortality from 68% without TAVR to 43.4% with TAVR, as well as improved symptomatic status and quality of life.<sup>3</sup>

TAVR is also a reasonable alternative to surgical aortic-valve replacement in patients with symptomatic severe aortic stenosis who are at high risk but are suitable candidates for surgery. Randomized studies have shown that the clinical outcomes in such patients are similar with surgical aortic-valve replacement and TAVR, with 1-year rates of death of 26.8% and 24.2%, respectively, with equivalence maintained at 3-year follow-up.<sup>4</sup> The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score can be used to estimate the risk of death

within 30 days after surgery, but other measurements also affect procedural risk. High risk is currently defined as an STS-PROM score of more than 8%, moderate-to-severe frailty, irreversible disease of more than two other organ systems, or possible impediments to a surgical approach.<sup>6</sup>

In randomized trials,<sup>62,63</sup> several types of complications occurred more frequently during the 30-day postoperative period among patients undergoing TAVR than among those undergoing surgical aortic-valve replacement. These complications included stroke (with rates of 4.9 to 5.5% with TAVR vs. 2.4 to 6.2% with surgery), major vascular complications (5.9 to 11% with TAVR vs. 1.7 to 3.2% with surgery), moderate-to-severe paravalvular aortic regurgitation (10.0 to 12.2% with TAVR vs. 0.9 to 1.3% with surgery), and the need for new pacemaker implantation (3.8 to 19.8% with TAVR vs. 3.6 to 7.1% with surgery). There is evidence that the adverse-event rates associated with TAVR are decreasing.<sup>64</sup> The threshold for choosing TAVR versus surgical aortic-valve replacement is likely to shift as technological developments and increasing clinical experience lead to reductions in complication rates, particularly residual paravalvular leak, which may be associated with an adverse long-term outcome.

Balloon aortic-valve dilation provides only limited hemodynamic benefit, which is offset by the substantial risk of procedural complications and a high probability of recurrent stenosis within 6 months.<sup>65</sup> Balloon aortic dilation is now restricted to occasional patients presenting with hemodynamic compromise, as a bridge to TAVR or surgery.<sup>6</sup>

A further important function of the multidisciplinary approach to the selection of treatment is the avoidance of expensive, high-risk, and ultimately futile procedures in patients who will derive little symptomatic benefit or improvement in quality of life. Examples include patients with a very limited life expectancy, irreversible left ventricular impairment, severe pulmonary disease, impaired mobility as a result of neurologic or musculoskeletal disease, advanced dementia, or other systemic diseases. Specialist palliative care should be available for these patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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