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Spectrum of Calcific Aortic Valve Disease Pathogenesis, Disease Progression, and Treatment Strategies

Rosario V. Freeman, MD, MS; Catherine M. Otto, MD

Calcific aortic valve disease is a slowly progressive disorder with a disease continuum that ranges from mild valve thickening without obstruction of blood flow, termed aortic sclerosis, to severe calcification with impaired leaflet motion, or aortic stenosis (Figure 1). In the past, this process was thought to be “degenerative” because of time-dependent wear-and-tear of the leaflets with passive calcium deposition. Now, there is compelling histopathologic and clinical data suggesting that calcific valve disease is an active disease process akin to atherosclerosis with lipoprotein deposition, chronic inflammation, and active leaflet calcification. The overlap in the clinical factors associated with calcific valve disease and atherosclerosis and the correlation between the severity of coronary artery and aortic valve calcification provide further support for a shared disease process.

Pathogenesis of Calcific Aortic Valve Disease

Anatomy of Normal Aortic Valve

The normal aortic valve comprises 3 layers. The ventricularis, on the ventricular side of the leaflet, is composed of elastin-rich fibers that are aligned in a radial direction, perpendicular to the leaflet margin. The fibrosa, on the aortic side of the leaflet, comprises primarily fibroblasts and collagen fibers arranged circumferentially, parallel to the leaflet margin. The spongiosa is a layer of loose connective tissue at the base of the leaflet, between the fibrosa and ventricularis, composed of fibroblasts, mesenchymal cells, and a mucopolysaccharide-rich matrix. These layers work in concert to provide tensile strength and pliability for decades of repetitive motion.

Early Lesion of Aortic Sclerosis

Histopathologic studies of aortic sclerosis show focal subendothelial plaque-like lesions on the aortic side of the leaflet that extend to the adjacent fibrosa layer. Similarities to atherosclerosis are present in these lesions, with prominent accumulation of “atherogenic” lipoproteins, including LDL and lipoprotein(a), evidence of LDL oxidation, an inflammatory cell infiltrate, and microscopic calcification (Figure 2).¹⁻⁵

Initiating Factors

These early aortic lesions are likely initiated by endothelial disruption due to increased mechanical or decreased shear

stress, similar to that seen in early atherosclerotic lesions. Mechanical stress of the aortic valve is highest on the aortic side of the leaflet in the flexion area, near the attachment to the aortic root. Shear stress across the endothelium of the noncoronary cusp is lower than the left and right coronary cusps because of the absence of diastolic coronary flow, which likely explains why the noncoronary cusp is often the first cusp affected. Further supporting the effects of leaflet stress as an instigating event is the discrepancy in average age at the time of presentation when tricuspid and bicuspid valves are compared, despite the identical histological appearance of lesions. Patients with bicuspid valves, which are subjected to higher mechanical stress, tend to present 2 decades younger than those with tricuspid valves.^{6,7} Nearly all patients with bicuspid valves develop significant outflow obstruction over time, whereas only a relatively small proportion of patients with a trileaflet valve progress to severe aortic stenosis.

Lipoproteins

Within each valve leaflet, focal, extracellular lipid accumulation is seen in several small areas in the subendothelial region, with displacement of the elastic lamina and extension into the adjacent fibrosa (Figure 3).¹ Apolipoproteins B, (a), and E are present in the vicinity of these lipid-rich areas, which implies that the lipids were derived from plasma lipoproteins.³ Oxidatively modified LDLs, associated with proinflammatory and growth-stimulatory properties, have been identified and are subsequently taken up by macrophages to become foam cells analogous to atherosclerotic lesions.⁴

Inflammation

Inflammatory cells are the predominant cell type in early aortic valve lesions, with T lymphocytes^{2,5} and macrophages identified.¹ Monocytes infiltrate the endothelial layer via adhesion molecules and differentiate into macrophages.⁸ Activated T lymphocytes within the subendothelium and fibrosa release cytokines, such as transforming growth factor- β 1,⁹ and interleukin- β , a proinflammatory cytokine associated with increased local production of matrix metalloproteins,¹⁰ all of which contribute to extracellular matrix formation, remodeling, and local calcification. Tenascin C, which has been involved in growth promotion, stimulation of

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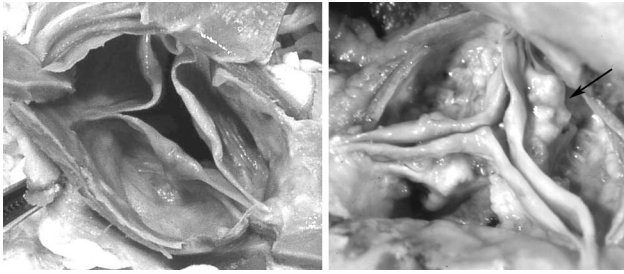


Figure 1. Gross specimen of minimally diseased aortic valve (left) and severely stenotic aortic valve (right). In the severely stenotic valve, there are prominent lipocalcific changes on aortic side of valve cusps (arrow), with sparing of commissures.

bone formation, and mineralization, is present in calcified aortic leaflets and is both coexpressed and overexpressed with matrix metalloproteinases.^{11,12}

Extracellular Matrix and ACE

ACE has been identified in aortic sclerotic lesions.¹³ Although there is evidence that some ACE may be produced locally, the majority was extracellular and colocalized with apolipoprotein B, a component of retained LDL particles, which suggests that the ACE may be “carried” into the lesion via LDL cholesterol particles. Additionally, angiotensin II, which has been associated with promotion of monocyte infiltration and enhancement of the uptake of modified LDL within atherosclerotic lesions, has been detected in early aortic sclerotic lesions, which implies that the ACE identified was active enzymatically.¹³

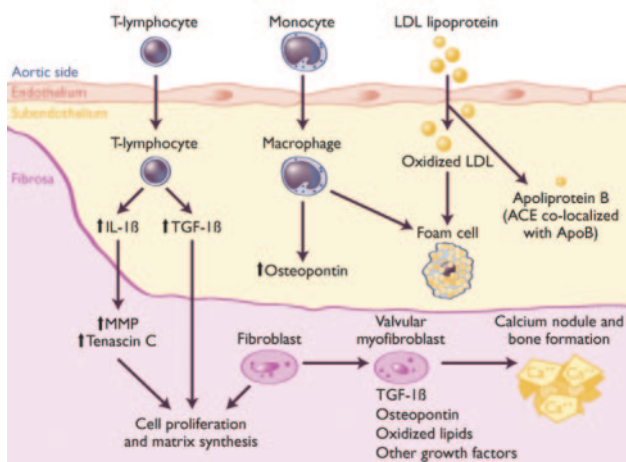


Figure 2. Potential pathways depicting calcific aortic valve disease. T lymphocytes and macrophages infiltrate endothelium and release cytokines that act on valvular fibroblasts to promote cellular proliferation and extracellular matrix remodeling. A subset of valvular fibroblasts within fibrosa layer differentiate into myofibroblasts that possess characteristics of smooth muscle cells. LDL that is taken into the subendothelial layer is oxidatively modified and taken up by macrophages to become foam cells. ACE is colocalized with apolipoprotein B (ApoB) and facilitates conversion of angiotensin II (AngII), which acts on angiotensin 1 receptors (AT-1R), expressed on valvular myofibroblasts. A subset of valvular myofibroblasts differentiate into osteoblast phenotype that is capable of promoting calcium nodule and bone formation. IL indicates interleukin; TGF, transforming growth factor; and MMP, matrix metalloproteinases.

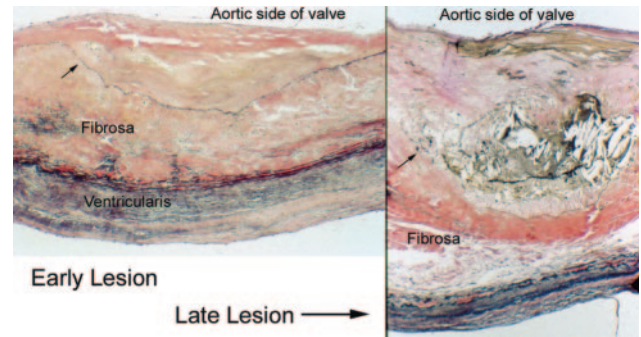


Figure 3. Examples of histological findings in early and late lesions of calcific aortic valve disease. Early lesion (left) demonstrates accumulation of cells and extracellular lipid and matrix in a subendothelial location on aortic side of leaflet, with displacement of normal subendothelial elastic lamina (arrow). In the late lesion (right), there is more prominent accumulation of lipid, cells, and extracellular matrix. Elastic lamina is displaced and fragmented (arrow). In both examples, the disease process extends into adjacent fibrosa. (Verhoeff-van Gieson stain, original magnification $\times 100$).

In the diseased aortic valve, a subset of the normal valve fibroblasts within the fibrosa layer differentiate into myofibroblasts, which possess smooth muscle cell characteristics, with expression of α -actin, vimentin, and desmin.^{1,14} In advanced aortic stenotic valve specimens, angiotensin type-1 receptors have been detected on a subset of the myofibroblasts that express α -actin, which again suggests that the ACE detected is active enzymatically.¹³ Further investigations will be required to better define the potential role for the renin-angiotensin system and causative pathways in the pathogenesis of calcific aortic valve disease.

Leaflet Calcification and End-Stage Lesions

Active calcification is prominent early in the disease process and is a major factor in the leaflet stiffness of severe stenosis.¹⁵ With aortic sclerosis, microscopic areas of calcification colocalize in areas of lipoprotein accumulation and inflammatory cell infiltration. Oxidized LDL stimulates valvular fibroblasts to release matrix vesicles, a nidus for early calcification. It has been shown that macrophages express osteopontin, a protein needed in bone formation, with the degree of mRNA expression of osteopontin corresponding to the degree and location of valvular calcification.^{16,17} A subset of valvular myofibroblasts are an osteoblast phenotype and have been associated with development of calcific nodules.^{18,19} An increased rate of calcific nodule formation by these myofibroblasts has been shown in vitro by exposure to oxidized lipids and transforming growth factor- $\beta 1$.¹⁹

As the disease progresses, active bone formation is seen. In an evaluation of 347 human aortic valves removed for aortic valve replacement, the majority (83%) had evidence of dystrophic calcification, and up to 13% contained lamellar or endochondral bone tissue with hematopoietic marrow and evidence of remodeling.²⁰ Within the specimens that contained bone tissue, there was expression of factors that promote osteogenesis, including bone morphogenic protein-2 and -4.^{20,21}

The importance of tissue calcification in the disease process is highlighted by the observation that subsets of patients with altered mineral metabolism have a higher prevalence of calcific aortic valve disease and more rapid disease progression.^{22,23} Anecdotally, it has been observed that in patients with osteoporosis or increased bone demineralization, the prevalence of any valvular calcification is higher, possibly related to increased body mineral turnover or ectopic calcification; however, this hypothesis has been examined in only a few published studies, with inconsistent results.^{24,25} Whether this association represents a true causal relationship or is just an incidental association due to the high prevalence of both disorders in the elderly is not evident at this point.

Genetic factors may be important in the development of valve leaflet calcification. In a recent case-control study of 100 patients with aortic stenosis matched for age, gender, and coronary artery disease compared with those without aortic stenosis, there was a significant difference in vitamin D receptor genotypes.²⁶ In addition, other genetic polymorphisms of interleukin-10, connective tissue growth factor, and chemokine receptor-5 appear to influence the degree of valvular calcification.²⁷ Other studies of apolipoprotein polymorphisms provide further support for a possible genetic component to valvular calcification and stenosis.^{28,29}

In addition to native aortic valves, calcific changes in bioprosthetic valves are a prominent feature of primary valve failure; however, the prevalence of calcification and bioprosthetic valve failure appears to decrease with age in contrast to native valves. In a study of 196 patients receiving a bioprosthetic aortic valve, 18 of 20 cases of primary valve failure occurred in those <65 years old.³⁰ Similarly, in another study of 653 patients who underwent aortic valve replacement, younger age was the only predictor of valve failure and need for reoperation.^{31,32} This paradox suggests that the calcific process of bioprosthetic valves is different from the process observed in native valves.³²

Relationship Between Tissue Changes and Clinical Disease

The histological changes seen in aortic sclerosis with lipoprotein accumulation, cellular infiltration, and extracellular matrix formation result in macroscopic, progressive valve thickening. As these changes progress, increasing calcification corresponds to leaflet immobility and the outflow obstruction characteristic of end-stage aortic stenosis (Figure 4).

Aortic Sclerosis

Diagnosis and Epidemiology

Aortic sclerosis is common, present in $\approx 25\%$ of people 65 to 74 years of age and in 48% of people older than 84 years.^{33–35} It is defined echocardiographically by focal areas of valve thickening, typically located in the leaflet center with commissural sparing and normal leaflet mobility. Diffuse leaflet thickening is not characteristic of aortic sclerosis; instead, it suggests normal aging changes, a different valvular pathology, or an imaging artifact. With aortic sclerosis, valvular hemodynamics are within normal limits, with an antegrade velocity across the valve <2.5 m/s. Although a systolic outflow murmur may be auscultated on physical examination

in some cases, there are no clinical symptoms reliably associated with aortic sclerosis.

Clinical Factors Associated With Aortic Sclerosis

Several studies have documented overlap in the clinical factors traditionally associated with calcific valve disease and atherosclerosis (Table 1).^{34,36–40} In the prospective, population-based Cardiovascular Health Study, which included 5621 adults over the age of 65 years, clinical factors associated with calcific aortic valve disease included older age, male gender, smoking, hypertension, and hyperlipidemia. Interestingly, the strength of these associations is comparable to that seen with atherosclerotic disease, which lends further support for a shared disease process (Table 1).⁴¹

Clinical Outcomes in Adults With Aortic Sclerosis

Although aortic sclerosis is clinically asymptomatic, its presence is associated with increased morbidity and mortality, even after controlling for the presence of coexistent cardiovascular risk factors. In the Cardiovascular Health Study, aortic sclerosis was associated with a 40% increase in the risk of myocardial infarction and a 50% increase in the risk of cardiovascular death in patients with no preexisting diagnosis of coronary artery disease at study entry.³⁵ Similarly, in a prospective study of nearly 2000 elderly patients, those with aortic sclerosis had a 1.8-times higher chance of developing a new coronary event,⁴² with other studies corroborating these findings.⁴³

The mechanism of adverse outcomes with aortic sclerosis is not entirely clear. The valve lesion itself is unlikely to be the primary cause, because valve hemodynamics are normal or near normal, and the time course supporting an association of aortic sclerosis with adverse events is short relative to the expected rates of hemodynamic progression. Furthermore, embolization of valve-associated plaque or thrombus into the coronary arteries is also unlikely, because there are no studies to suggest that the valve lesions of aortic sclerosis are unstable or associated with thrombus formation.

Rather than adverse outcomes as a consequence of the primary valvular disorder, it has been proposed that aortic sclerosis may represent a surrogate marker either for underlying atherosclerotic disease^{44,45} or some generalized systemic process, such as inflammation.^{45–48} Supporting evidence for a surrogate marker for atherosclerosis comes from the cardiac catheterization laboratory, where up to 50% of patients with severe aortic stenosis undergoing preoperative evaluation for valve replacement are diagnosed with concurrent significant coronary artery disease. Other data buttressing this theory include the overlap in genetic polymorphisms associated with both disease processes.^{28,29} However, this association alone cannot explain the adverse events observed given that not all patients with aortic stenosis develop coronary artery disease.

Recent preliminary clinical studies supporting the contention that aortic sclerosis may be a surrogate marker for a systemic inflammatory condition include links with generalized markers of inflammation such as serum homocysteine level, C-reactive protein, and endothelial dysfunction.^{45–49} One study suggested this association was reversible, with a decrease in serum C-reactive protein levels in aortic stenosis

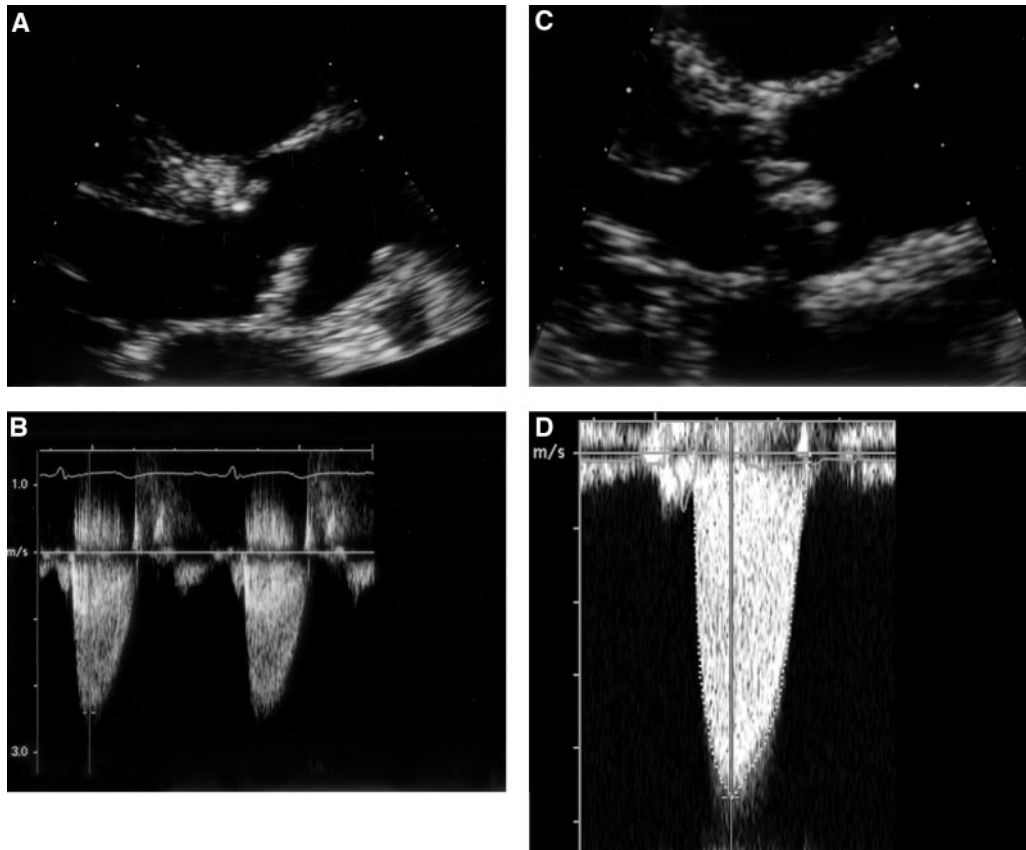


Figure 4. Echocardiographic images of aortic sclerosis (A, B) and severe aortic stenosis (C, D). Continuous wave Doppler signal from both subjects was taken from an apical window. 2D image of sclerotic aortic valve (A) shows focal leaflet thickening with mild leaflet restriction of noncoronary cusp during systole. Overall jet velocity is minimally increased at 2.4 m/s. In contrast, aortic cusps of the severely stenotic valve are thickened and calcified, with severely restricted leaflet motion during systole (C). This corresponds to jet velocity of 4.7 m/s (D).

patients after valve replacement.⁵⁰ However, more recent data are conflicting on the apparent association of inflammatory markers with calcific aortic valve disease. In a recent prospective clinical cohort study of 381 patients, several markers of inflammation, including blood counts, fibrinogen, and *Chlamydia pneumoniae* seropositivity, were not associated with aortic sclerosis after adjustment for age, gender, and smoking status.⁴⁸ Thus, despite histopathologic data that support a disease model of leaflet endothelial damage with local inflammatory changes and leaflet remodeling and the demonstration of adverse risk associated with aortic sclerosis, a confirmatory link to a systemic inflammatory state has yet to be proven definitively. Other possible explanations for the increased cardiovascular risk associated with aortic sclerosis include endothelial dysfunction, genetic polymorphisms, or some undetermined factor.

Progression of Aortic Sclerosis to Aortic Stenosis

There have been few prospective studies following rates of hemodynamic progression spanning the disease spectrum from aortic sclerosis to aortic stenosis. In the largest study to date,⁵¹ >2000 patients with aortic sclerosis were studied. In this cohort, 16% developed aortic stenosis, with mild stenosis developing in 10.5% (jet velocity 2 to 3 m/s), moderate stenosis in 3% (jet velocity 3 to 4 m/s), and severe stenosis in 2.5% (jet velocity >4 m/s). The average time interval from a diagnosis of aortic

sclerosis to progression to severe aortic stenosis was 8 years.⁵¹ Similar findings were seen in a smaller study of 400 subjects with aortic sclerosis,⁵² in which 5% of patients developed moderate aortic stenosis and 2.5% of patients developed severe aortic stenosis. Although only a small percentage of patients with aortic sclerosis progress to aortic stenosis, this proportion still represents a substantial number of patients overall, and it is likely that the number of those who progress to severe valve obstruction would increase in parallel with a longer follow-up duration. Given the adverse morbidity and mortality event rates in patients with aortic sclerosis and the significant portion who do subsequently develop aortic stenosis, these data highlight the need for close clinical follow-up and serial evaluation of patients once aortic sclerosis is identified.⁵¹

Calcific Aortic Stenosis

Epidemiology

The prevalence of calcific aortic stenosis increases with age, being present in 2% to 4% of adults over age 65 years.^{34,35} Aortic stenosis is the most common acquired valvular disorder found in developed countries. Within the United States, there are ≈50 000 aortic valve replacements performed for severe aortic stenosis annually.

Diagnostic Evaluation

The standard diagnostic evaluation of aortic stenosis includes assessment of leaflet anatomy and the extent of valvular

TABLE 1. Clinical Factors Associated With Aortic Sclerosis Compared With Coronary Heart Disease in the Framingham Cohort as Determined by Multivariate Analysis*

Risk Factor	Cardiovascular Health Study ³⁴ OR (95% CI)†	Relative Risk for CHD in Men, Based on Framingham	Relative Risk for CHD in Women, Based on Framingham	Other Supporting Studies, Reference Numbers
Increased age	2.18 (2.15, 2.2)	1.05 (1.04–1.06)	1.04 (1.03–1.06)	39, 44, 47
Male gender	2.01 (1.7, 2.5)	Men only	Women only	37, 39, 44
Smoking	1.35 (1.11, 1.7)	1.71 (1.39–2.10)	1.49 (1.13–1.97)	37, 40
Hypertension	1.23 (1.11, 1.4)	1.92 (1.42–2.59)	2.19 (1.46–3.27)	36, 38–40, 44
Elevated lipoprotein(a)	1.23 (1.14, 1.32)			
Elevated LDL	1.12 (1.03, 1.23)	1.74 (1.36–2.24)	1.68 (1.17–2.40)	
Height	0.84 (0.75, 0.93)			

CHD indicates coronary heart disease.

*The OR for the presence of aortic sclerosis and clinical factors in the Cardiovascular Health Study is compared with the relative risk of CHD in the Framingham Heart Study cohort, incorporating traditional risk factors for CHD as defined by the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure and National Cholesterol Education Program Adult Treatment Panel II guidelines.

†A total of 1417 of 5201 patients had aortic sclerosis in the Cardiovascular Health Study.

calcification by echocardiography. The severity of aortic stenosis can be measured accurately and reliably on the basis of antegrade velocity, mean pressure gradient, and continuity equation valve area. Because symptom onset does not correspond to a single value in all patients, there are no absolute breakpoints that define severity in adults; however, general guidelines are presented in Table 2. Beyond this information, echocardiography provides an assessment of left ventricular hypertrophy, diastolic dysfunction, and regional and global systolic function with calculation of ejection fraction. Other associated abnormalities also are evaluated, including aortic dilation, coexisting mitral valve disease, and pulmonary hypertension. Serial echocardiography in patients with aortic stenosis provides valuable interval information, with the timing of examination determined by the stenosis severity and any changes in physical examination or clinical status. Current clinical guidelines suggest that echocardiography is appropriate annually in patients with severe asymptomatic stenosis, every 2 years in those with moderate aortic stenosis, and every 5 years in patients with mild aortic stenosis.⁵³ Cardiac catheterization for measurement of the transvalvular gradient is reserved for the rare patient in whom echocardiography is nondiagnostic or when clinical and echocardiographic data are discrepant. Coronary angiography is usually needed before valve surgery to determine whether concurrent coronary artery bypass surgery is needed.

Beyond echocardiography, a variety of newer diagnostic methods have proved feasible for evaluating the presence and severity of calcific aortic valve disease, including electron-beam computed tomography and MRI.^{54,55} Cost-benefit analyses and comparative studies between the different diagnostic methods have yet to be performed.

Hemodynamic Progression of Valve Obstruction

Prospective studies on the rate of hemodynamic progression in patients diagnosed with aortic stenosis document an average rate of increase in aortic jet velocity of 0.3 m/s per year, with an increase in mean transaortic pressure gradient of 7 mm Hg per year and a decrease in aortic valve area

of 0.1 cm² per year.^{56–59} Although the average rate of hemodynamic progression is relatively constant between studies, there is marked individual variation, which makes prediction of hemodynamic progression in individual patients difficult.

The clinical factors associated with hemodynamic progression are not as well established as the associations with the presence of calcific valvular disease. Moreover, most of these studies are based on retrospective analyses (Table 3).^{23,60–69} As such, there is a broader list of associated factors and many discrepancies between studies.

Clinical Outcome in Asymptomatic Aortic Stenosis

Studies of the natural history of aortic stenosis have documented low overall mortality rates in patients who remain symptom free.^{70–78} Although early studies of patients with severe aortic stenosis reported sudden cardiac death rates as high as 20%, many were retrospective autopsy series and were thus limited by referral bias. Contemporary studies have documented much lower annual rates of sudden cardiac death, less than 1%, which is even lower in the absence of preceding symptoms.^{70,72,73,76,77,79}

In a study of 128 patients with asymptomatic, severe aortic stenosis, after 4 years of follow-up, fewer than 33% of the cohort remained asymptomatic, without valve replacement (Figure 5A).⁷⁷ The extent of valvular calcification was an important factor in event-free survival, with only 20% of subjects with a moderate or severely calcified valve being

TABLE 2. Guidelines for Grading Severity of Calcific Aortic Valve Disease

	Antegrade Jet Velocity, m/s	Aortic Valve Area, cm ²
Aortic sclerosis	<2.5	Normal
Mild aortic stenosis	2.5–<3.0	>1.5
Moderate aortic stenosis	3.0–<4.0	1.0–1.5
Severe aortic stenosis	>4.0	<1.0

TABLE 3. Clinical Risk Factors Associated With Hemodynamic Progression of Calcific Aortic Valve Disease

Clinical Factor	Supporting Studies, Reference Numbers
Older age	68
Male gender	64
Hypercholesterolemia	60, 66, 69
Higher body mass index	61
Smoking	60, 61, 66, 69
Elevated LDL	67
Diabetes mellitus	60
Elevated creatinine/renal failure	62–64, 66
Initial aortic valve area	63, 64, 66
Coronary artery disease	69
Left ventricular mass index	64
Calcium supplementation	62
Elevated calcium	66
Mitral annular calcification	51, 68

free of death or of symptoms that necessitated valve replacement.⁷⁷ Similarly, in 123 adults with asymptomatic aortic stenosis, fewer than 26% remained symptom free after 5 years of follow-up, which again highlights the need for close clinical follow-up to monitor for symptom onset.⁷⁶ Predictors of symptom onset in both studies included baseline jet velocity, the rate of change in jet velocity over time, the extent of valvular calcification, and functional status.^{76,77}

Aortic valve disease progression to symptom onset warranting aortic valve replacement can occur even in the absence of hemodynamically severe valvular obstruction at baseline. In a study of patients with mild or moderate aortic stenosis (jet velocity between 2.5 and 4 m/s), the likelihood of surviving without need for valve replacement was 95% at 1 year and 60% at 5 years. Peak jet velocity was an independent predictor of outcome, along with the severity of valve calcification and coexistent coronary artery disease. Importantly, in this population of aortic stenosis patients with relatively milder hemodynamic severity, 19% of the total cohort developed symptoms during the follow-up time period, with the extent of valvular calcification again a significant factor associated with either death or symptom onset that necessitated valve replacement (Figure 5B).⁷⁸ This again reinforces the need for close clinical monitoring in any patient with asymptomatic aortic stenosis, regardless of severity at initial diagnosis.

Symptom Onset in Adults With Aortic Stenosis

Although the cardinal symptoms of severe aortic stenosis are angina, congestive heart failure, and syncope, clinicians should also monitor for more subtle symptoms, such as a decrease in exercise tolerance or exertional dyspnea.⁷² Symptomatic patients with severe stenosis have a dismal prognosis if valve replacement is delayed. In one study of symptomatic patients who refused surgery, average survival was only 2 years, with a 5-year survival rate <20%.⁷¹ In another study, only 40% of patients with symptomatic, severe aortic stenosis survived 2 years, and only 12% remained event free after 5

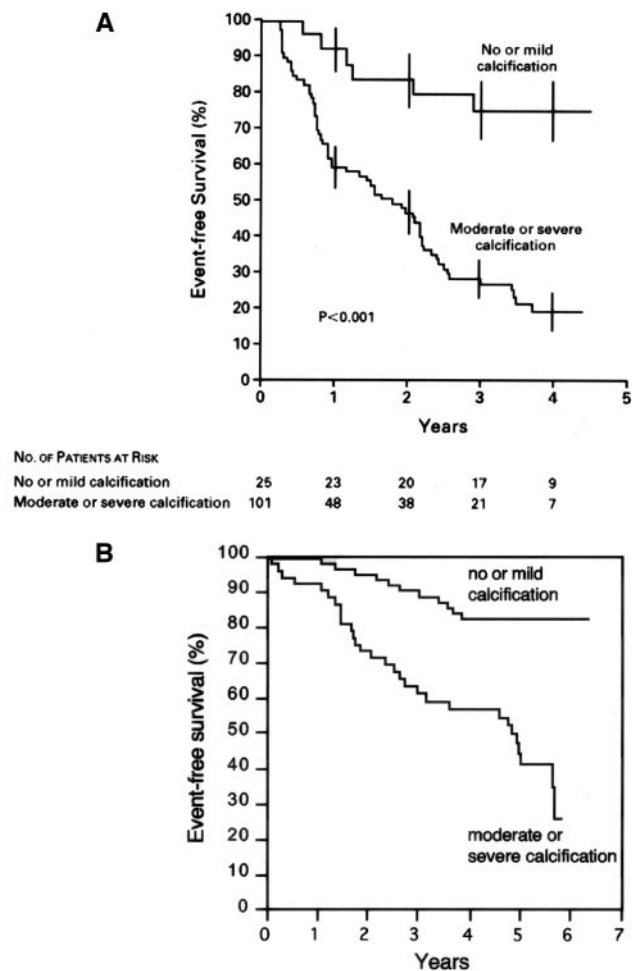


Figure 5. For patients with severe aortic stenosis (jet velocity >4.0 m/s) (A) and those with mild to moderate aortic stenosis (jet velocity 2.5 to 4.0 m/s) (B), extent of valvular calcification significantly affected event-free survival, with events defined either as death or valve replacement necessitated by symptom onset. $P=0.0001$. Reproduced with permission from (A) Rosenhek et al⁷⁷ (*The New England Journal of Medicine*; Copyright 2000 Massachusetts Medical Society; all rights reserved) and (B) Rosenhek et al⁷⁸ (*The European Heart Journal*; Copyright 2004 The European Society of Cardiology; permission from Elsevier).

years of follow-up.⁷⁰ In contrast, symptomatic patients who undergo aortic valve replacement have an age-corrected postoperative survival that is nearly normalized.⁸⁰ Therefore, current guidelines advocate surgical referral for aortic valve replacement once cardiac symptoms are present.⁵³

If symptom determination is equivocal, stress testing can be a helpful adjunct to delineate exercise tolerance and possible symptoms. Stress testing can be performed safely when monitored by an experienced physician⁷⁶ but should be ended promptly if the patient experiences symptoms or if there is a decrease or minimal increase (<20 mm Hg) in blood pressure. During stress testing of an otherwise asymptomatic individual with severe aortic stenosis, provocation of symptoms, a limited exercise tolerance, or a blunted blood pressure response to exercise should prompt consideration of surgical referral. In patients with mild aortic stenosis with provocation of symptoms, other causes should be evaluated, such as myocardial ischemia from coronary artery disease.

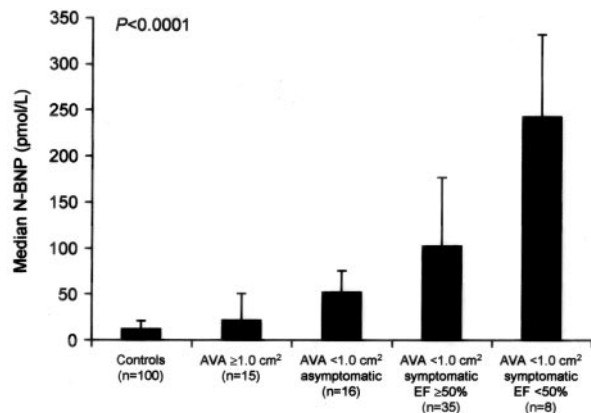


Figure 6. Association between N-BNP levels and severity of aortic stenosis. N-BNP levels in normal control subjects and in subgroups of patients with aortic stenosis by aortic valve area, symptoms, and left ventricular systolic function are shown. AVA indicates aortic valve area; EF, ejection fraction. Reproduced with permission from Gerber et al.⁸³ Copyright 2003 American Heart Association.

The most common symptom of aortic stenosis is exertional dyspnea or decreased exercise tolerance due to the inability of the heart to adequately increase stroke volume to meet increased metabolic demands. Because these symptoms are nonspecific, there has been interest in developing a more objective marker of "symptom onset" to earlier identify those who would benefit from valve replacement. Recent studies measuring serum neurohormone levels, such as brain natriuretic peptide (BNP), demonstrate an association of increased levels with disease severity.^{81,82} There is a progressive association of serum BNP with the severity of aortic stenosis and left ventricular dysfunction (Figure 6). Asymptomatic patients with more hemodynamically significant aortic valve disease had higher serum BNP levels, which suggests that BNP may represent a marker of disease severity and may potentially serve to discriminate between normal exercise tolerance and true early symptoms of heart failure.⁸³ In a study of 130 patients with severe aortic stenosis, serum BNP, N-terminal BNP, and N-terminal atrial natriuretic peptide were evaluated serially in patients for up to 1 year. All neurohormone levels increased in parallel with the severity of symptoms and ventricular dysfunction. Even those patients who claimed to be asymptomatic but had an elevation in neurohormone levels had a high likelihood of subsequently developing symptoms during follow-up.⁸⁴ Serum N-terminal BNP level was also an independent predictor of postoperative clinical outcome defined by survival and ejection fraction.⁸⁴ These preliminary data suggest that serum BNP levels may be a helpful adjunct in identification of patients with equivocal complaints at risk of rapid progression to symptom onset. Larger prospective trials will be necessary before the use of these measures on a routine basis can be advocated.

Calcific Valve Disease Versus Atherosclerosis

Despite the similarities in the histopathologic features and clinical factors associated with calcific aortic valve disease and atherosclerosis, discrepancies also exist (Table 4). For example, whereas smooth muscle cells are prominently in-

TABLE 4. Comparison of Calcific Aortic Valve Disease and Atherosclerosis

	Calcific Aortic Valve Disease	Atherosclerosis
Histopathologic features		
Lipoprotein accumulation	++++	++++
Lipid oxidation	++++	++++
Calcification	+++++	++
Inflammatory changes	++++	++++
Systemic inflammatory markers	+	++
<i>C pneumoniae</i> and other infectious agents	+	+
Genetic polymorphisms	++	+++
Prominent cell type	Fibroblast	Smooth muscle
Clinical risk factors		
Renal dysfunction	++++	++++
Smoking	+++	++++
Hypertension	++	++++
Elevated serum lipoprotein levels	+++	++++
Diabetes mellitus	+	+++++
Endothelial dysfunction	++	++++

involved in atherosclerosis, typical smooth muscle cells are not seen in diseased aortic valve leaflets, where fibroblasts and myofibroblasts, a subset of differentiated fibroblasts, are more prominent. Also, although calcific changes can be seen in atherosclerotic plaques, calcification occurs earlier and is a more prominent feature of calcific aortic valve disease, particularly in the end stages of the disease process. From a clinical standpoint, although many cohort studies have documented an overlap in many of the clinical factors associated with both diseases, such as hypercholesterolemia or hypertension, other factors conventionally associated with atherosclerosis, such as gender and diabetes, have not been as strongly linked to aortic stenosis. Last, in aortic stenosis, a large contributor of disease progression is prominent calcification with a gradual increase in leaflet thickness and outflow obstruction. In contrast, events in patients with coronary atherosclerosis are acute, related to plaque rupture with associated thrombosis and vascular occlusion. Thus, although plaque stabilization and antithrombotic treatment strategies are now a prominent feature of atherosclerosis pharmacotherapy, these approaches are less likely to be beneficial for calcific valve disease.

Treatment of Calcific Valve Disease

Surgical Intervention

Recent surgical series report operative mortality rates for aortic valve replacement as low as 1%, increasing to 9% in higher-risk patients. Long-term survival after valve replacement is 80% at 3 years, with an age-corrected survival postoperatively that is nearly normalized.⁸⁰ Significant postoperative morbidity, such as thromboembolism, hemorrhagic complications from anticoagulation, prosthetic valve dysfunction, and endocarditis, are rare and occur at a rate of 2% to 3% per year. Although percutaneous valvotomy initially provides a modest decrease in the outflow gradient, there is

TABLE 5. Potential Points on the Disease Pathway at Which Targeted Pharmacological Regimens May Affect Development and Progression of Calcific Aortic Valve Disease

Leaflet endothelial layer disruption
Activation of inflammatory cascade
Release of inflammatory cytokines
Lipoprotein accumulation and deposition
Lipid oxidation
Angiotensin-mediated effects
Tissue calcification
Osteogenesis

significant residual obstruction from leaflet thickening and annular calcification. Additionally, recurrent severe stenosis typically occurs within months, and there is no demonstrable beneficial effect on long-term clinical outcome.⁵³

Prophylactic aortic valve replacement in asymptomatic patients is not performed routinely but is considered if patients with at least moderate aortic stenosis need other cardiac surgery.⁵³ In rare instances, aortic valve replacement may be performed in asymptomatic individuals with mitigating circumstances, such as women who are contemplating pregnancy, individuals who plan activities that involve severe exertion or who live in areas remote from medical care, or individuals with a decline in left ventricular systolic function. In asymptomatic patients with a low expected operative mortality, earlier surgery might be considered if stenosis is extremely severe or if there is a high likelihood of rapid disease progression.

Currently, no pharmacological therapies have proven outcomes in symptomatic patients superior to those of aortic valve replacement. In patients with symptomatic aortic stenosis who are not candidates for aortic valve replacement, pharmacological therapy is tailored to adjunctive treatments for congestive heart failure, volume overloaded conditions, arrhythmias, and hypertension.^{85,86}

Prevention of Disease Progression

As results from studies on the pathogenesis and progression of calcific aortic valve disease emerge, targeted pharmacotherapeutic regimens to interfere with the disease pathways to either slow or halt the disease process are being proposed. Clinical implementation of pharmacological regimens will require rigorous validation in experimental models and prospective intervention trials, as well as from retrospective databases. Experimental models offer the potential to isolate individual components of the disease process and directly assess the tissue effects of specific interventions over a relatively short time frame; however, difficulty in simulating the hemodynamics and histopathology of the diseased human aortic valve lead to lack of a “natural” model. Retrospective databases offer a wealth of data from large cohorts in which clinical benefit can be inferred from associations of particular therapies and observed outcomes; however, ultimately, prospective intervention trials will be needed to establish a clear cause-and-effect benefit of any pharmacotherapeutic regimen. Potential points of action of these medical regimens are presented in Table 5. The 2 pharmacological agents currently

under the most scrutiny for potentially delaying disease progression are HMG-CoA reductase inhibitors (statins) and ACE inhibitors.

Study results indicating hypercholesterolemia plays a significant role in both calcific aortic valve disease and atherosclerosis have led to several studies investigating the association of statin use with slowed disease progression. An experimental animal model of aortic stenosis demonstrated a decrease in aortic valve area after administration of vitamin D₂ (thereby elevating serum calcium) and a cholesterol-enriched diet.⁸⁷ Additionally, in an experimental hypercholesterolemic rabbit model of early calcific aortic valve disease, there was a decrease in cellular proliferation and bone matrix production within the aortic valve after administration of atorvastatin.⁸⁸

Results from several retrospective clinical trials support an association of statin use with slowed disease progression (Table 6). In these retrospective cohorts, statins were generally prescribed by the primary care providers for conventional indications, and the association of statin use with progression of calcific valve disease was assessed. Interestingly, despite the relatively consistent slowing of disease progression in those patients receiving statin therapy, there was a relative lack of correlation with the effect on serum cholesterol levels, with some studies showing an association^{65,67,69} and others showing none.^{89–92} This inconsistency likely represents some of the limitations inherent in retrospective analyses but also suggests the possibility that statins may provide additional, pleiotropic benefits beyond cholesterol lowering. Such effects may include improvement of endothelial dysfunction, anti-thrombotic actions, plaque lesion stabilization, antioxidant effects, a reduction of the vascular inflammatory process, or some yet-unidentified benefit.⁹³ There are at least 2 prospective, randomized, placebo-controlled, multicenter studies of statin therapy to prevent disease progression under way, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study and the Aortic Stenosis Progression Observation: Measuring the Effect of Rosuvastatin (ASTRONOMER) study.⁹⁴ Until the results from these trials are available and a confirmatory, cause-and-effect relationship is established, use of statin therapy should be reserved for conventional indications.

Although there are strong proponents of ACE inhibitor use in aortic stenosis, the basis of the recommendations to date has been on the potentially favorable effect of ACE inhibitors on the remodeling and hypertrophic changes of the myocardium in aortic stenosis,⁹⁵ rather than an effect on delaying disease progression at the tissue level. In the first large, retrospective cohort study to examine use of ACE inhibitors, 134 of 211 subjects were receiving ACE inhibitors, with no significant difference in disease progression seen.⁹² However, it is premature to conclude that ACE inhibition is not beneficial. Further investigations will be needed to establish the potential benefit of ACE inhibitors on disease progression, or lack thereof. Importantly, any effect of ACE inhibition on disease progression should be explored, because 63% of the patients in this retrospective cohort were taking an ACE inhibitor, a prevalence that will likely continue in the current era and that will have a bearing on the design of future clinical trials.^{92,96}

TABLE 6. Statin Therapy in Aortic Stenosis: Retrospective Studies

Study (Year)	Total Number of Patients (% Taking Statins)	Average Follow-Up	Method of Evaluation	Results	P
Aronow et al (2001) ⁶⁵	180 (34%)	>2 y	Echocardiography	Statin use: predictor of decrease in peak transaortic gradient in multivariate model	0.001
Novaro et al (2001) ⁸⁹	174 (33%)	21 mo	Echocardiography	Nonstatin: AVA decreased 0.11 ± 0.18 cm ² /y; Statin use: AVA decreased 0.06 ± 0.16 cm ² /y	0.03
Pohle et al (2001) ⁶⁷	104 (52%)	15 mo	EBCT	Nonstatin: median AVC change 28.0%/y Statin use: median AVC change 21.5%/y	NS
Bellamy et al (2002) ⁹⁰	156 (24%)	3.7 \pm 2.3 y	Echocardiography	Nonstatin: AVA decreased 7 \pm 13%/y Statin use: AVA decreased 3 \pm 10%/y	0.04
Shavelle et al (2002) ⁹¹	65 (43%)	2.5 \pm 1.6 y	EBCT	Nonstatin: median AVC change 32.0%/y Statin use: median AVC change 12.1%/y	0.006
Rosenhek et al (2004) ⁹²	211 (39%)	2.0 \pm 1.5 y	Echocardiography	Nonstatin: jet velocity increased 0.39 ± 0.42 m/s per year Statin use: jet velocity increased 0.10 ± 0.41 m/s per year	<0.0001

AVA indicates aortic valve area; EBCT, electron-beam computed tomography; and AVC, aortic valve calcium.

Conclusions

Calcific aortic valve disease represents a disease spectrum that spans aortic sclerosis to aortic stenosis. Evidence from studies on the pathogenesis of calcific aortic valve disease supports an active disease process with lipoprotein deposition, chronic inflammation, and leaflet calcification. Given the apparent similarities with atherosclerosis, future studies on therapy for calcific aortic valve disease now include pharmacotherapies traditionally reserved for atherosclerosis, which may slow disease progression. However, studies supporting similarities between calcific aortic valve disease and atherosclerosis have produced, at best, circumstantial evidence without providing clear evidence of a direct causative pathway. Moreover, because many studies to date have concentrated on elucidating the similarities between calcific valve disease and atherosclerosis, explanatory studies explaining the observed discrepancies are lacking. Until causative pathways are identified definitively and/or these pharmacotherapeutic regimens are proven, conventional treatment of calcific aortic valve disease should be guided by conventional recommendations, which include diligent clinical follow-up to monitor for symptom onset, with surgical valve replacement once symptom onset ensues.

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KEY WORDS: aortic stenosis ■ aortic sclerosis ■ risk factors ■ valves ■ inflammation